

mice is 1.19 g/kg, while the median lethal dose in dogs is 3 g/kg. The lethal dose injected into the flank of rabbits was estimated to be 4 g/kg. The main toxic effects from IV administration of sodium thiosulfate appear to be osmotic, which result from the rapid sodium load together with acid-base disturbances. Osmotic and acid-base disturbances have not been observed at lower doses or from dermal or oral administration of sodium thiosulfate.

Information from intraperitoneal (IP) studies provide further support that sodium thiosulfate has relatively low acute toxicity. Sodium thiosulfate protects the auditory system from the major ototoxic effects of cisplatin and reduces other overt signs of systemic toxicity.

Hamsters receiving IP injections of sodium thiosulfate at 1,600 mg/kg every other day until five injections were completed showed no ill effects from sodium thiosulfate. When sodium thiosulfate was injected in hamsters in combination with cisplatin (a chemotherapeutic agent that has been shown to cause ototoxicity), sodium thiosulfate provided amelioration over a broad hearing range, as well as providing protection from cisplatin induced gastrointestinal necrosis and nephrotoxicity. Similarly, in a study where guinea pigs treated with cisplatin, cisplatin and sodium thiosulfate, saline or sodium thiosulfate only (1,600 mg/kg/day for 8 days), there were no signs of toxicity in any of the guinea pigs treated with sodium thiosulfate only. There were no effects on body weight (bwt) or auditory brainstem response and animals treated with cisplatin and sodium thiosulfate, had improved hearing and lost less weight than animals treated with cisplatin only.

Sodium thiosulfate has been shown to be an effective antidote in mice exposed to acrylonitrile. Mice were given IP injections of sodium thiosulfate at 400 mg/kg from 10 to 30 minutes prior to acrylonitrile administration at the LD₅₀ dose level of 60 mg/kg. All mice appeared normal after prophylactic treatment with sodium thiosulfate and showed no ill effects from subsequent acrylonitrile exposure. Animals treated with sodium thiosulfate only, showed no evidence of toxicity.

Aquated cisplatin has a higher uptake by tumors than that of cisplatin, but aquated cisplatin is also more nephrotoxic. Subcutaneous injection of sodium thiosulfate (1,000 mg/kg) five minutes before IP administration of aquated cisplatin to B6D2F1 mice resulted in reduced aquated cisplatin-induced nephrotoxicity.

2. *Genotoxicity.* Sodium thiosulfate is not genotoxic and is regularly used in cell culture mediums as a source of sulfur. Sodium thiosulfate does not cause cell death or reduce the rate of growth in a wide variety of bacteria. Sodium thiosulfate is non-mutagenic to *Salmonella typhimurium* and can reduce the mutagenic effects induced by other chemicals. Sodium thiosulfate does not increase the rate of sister chromatid exchanges (SCEs) or chromosomal aberrations in human lymphocytes. Sodium thiosulfate has been shown to reduce the number of SCEs in human lymphocytes and Chinese hamster (CH) lung cells when administered simultaneously with known SCE inducers. When sodium thiosulfate at concentrations up to 5 X 10⁻² M was added to untreated human cells, there was no effect at all on the cells. *In vitro* studies with sodium thiosulfate and LX-1 small-cell lung carcinoma cells found that sodium thiosulfate concentrations of 10 mg/kg and above were toxic to LX-1 cells, presumably due to high osmolality. However, lower concentrations of sodium thiosulfate had no effect on cell growth. Sodium thiosulfate has also been shown to inhibit cisplatin-induced mutagenesis in somatic tissue of *Drosophila*.

3. *Reproductive and developmental toxicity.* Sodium thiosulfate is not considered to be a reproductive or developmental toxicant due to its rapid breakdown in the body to normal constituents, (i.e. thiosulfate is a normal constituent of blood and is utilized by mitochondrial enzyme rhodanase, a.k.a. thiosulfate sulfurtransferase, as a sulfur donor). In addition, remaining thiosulfate is rapidly hydrolyzed by water into sodium chloride, water, sulfur and sulfate, which are all compounds readily used by living organisms. Teratology studies conducted in two species established that the administration of 550 mg/kg sodium thiosulfate for 13 days in the mouse and of 580 mg/kg sodium thiosulfate for 10 days in the rabbit had no effect on nidation or on maternal or fetal survival in either species. Use of sodium nitroprusside for the treatment of hypertensive emergencies in pregnancy has been hampered by concern for the possibility of cyanide poisoning in both the mother and fetus. Coinfusion of sodium thiosulfate with nitroprusside in gravid ewes prevented fetal and maternal cyanide toxicity. Physicians are currently treating some pregnant women with IV administration of sodium thiosulfate and sodium nitroprusside.

4. *Subchronic toxicity.* No studies that fall into the usual subchronic category were found. However, data from chronic and acute studies provide adequate information as to the non-toxicity of sodium thiosulfate. It should be noted that Versiclear™ Lotion containing 25% sodium thiosulfate and 1% salicylic acid in propylene glycol is recommended for subchronic treatment of tinea versicolor in humans. In a series of studies of various therapeutics for cyanide poisoning in sheep, up to 660 mg/kg of sodium thiosulfate was administered in distilled water via stomach tube directly to the rumen of ewes that had been treated with lethal doses of sodium cyanide (7.6 mg/kg). All ewes treated with 660 mg/kg sodium thiosulfate survived. Ewes receiving 66.7 mg/kg sodium thiosulfate still exhibited severe signs of cyanide poisoning and subsequently died. Based on this study, it is recommended that cyanide toxicity in ruminants should be treated with high doses of sodium thiosulfate (500 mg/kg or more) and repeated as needed, since sodium thiosulfate is rapidly cleared from the body and sustained release of free cyanide from the rumen is possible.

An evaluation of 41 potential chemopreventive agents using the inhibition of carcinogen-induced aberrant crypt foci (ACF) in the rat colon as the measure of efficacy found that sodium thiosulfate was one of 18 agents that significantly reduced the incidence of ACF.

5. *Chronic toxicity.* Long term treatment of patients with a variety of illnesses has shown that ingestion of low levels of sodium thiosulfate is a non-toxic and safe therapeutic agent. A patient with renal tubular acidosis I was treated for 9 years with sodium thiosulfate, 15–20 mmol daily (orally), to control nephrocalcinosis. During this time period, there were no treatment-related adverse effects, nephrocalcinosis did not worsen, and renal function improved. Thirty-four patients received daily oral doses of sodium thiosulfate (10 mmol twice daily with meals) for 3 to 4 years in the treatment of recurrent calcium urinary lithiasis. Sodium thiosulfate was well tolerated by all patients for over 4 years with no apparent toxic or side effects. It was also found that the patients only absorbed 20–25% of the oral dose, excreting four to five mmol as urinary thiosulfate. Higher oral dose levels of sodium thiosulfate resulted in watery stools in some patients so higher oral dose levels were not used in this clinical trial.

Three patients undergoing maintenance hemodialysis for more than 4 years developed calcified masses.