

To reduce the symptoms, each patient was given 20 mmol of sodium thiosulfate IV at the end of each hemodialysis for the next 6 to 12 months. A considerable regression of calcified masses with concurrent clinical improvement was observed in two of the patients while the third patient showed a softening in the mass but no regression in size due to encapsulation prior to starting sodium thiosulfate treatment. For all patients, there were no new calcified masses observed during sodium thiosulfate treatment, sodium thiosulfate was well tolerated, and no apparent side effects were observed.

6. *Animal metabolism.* Thiosulfate is a normal constituent of mammalian urine. In humans, urinary thiosulfate excretion averages approximately 30 mole per 24 hours, which is less than 1% of the total urinary sulfur load. Sodium thiosulfate is not well absorbed when administered orally as it is broken down in the acidic gastric juices to form sulfite and sulphur. Research has shown that 20–25% of a chronic low level dose is excreted in the urine as urinary thiosulfate.

When sodium thiosulfate is given intravenously, it is distributed throughout the extracellular fluid and renal excretion occurs by glomerular filtration and secretion. The serum half-life of thiosulfate in humans (after bolus injections) is around 15 to 20 minutes. When sodium thiosulfate is administered during sodium nitroprusside therapy, the plasma half life of thiosulfate is reported to be as short as 15 minutes to as long as 3 hours. Depending on the dosage, around 10 to 50% of exogenous thiosulfate is eliminated unchanged via the kidneys. Endogenous levels of plasma and urinary thiosulfate concentrations, determined from healthy volunteers are 1.13 ± 0.11 milligrams/deciliter (mg/dL) and 0.28 ± 0.02 mg/dL, respectively. Clearance of endogenous thiosulfate in normal males was 0.26 ± 0.04 mL/min, with net excretion accounting for only 0.17% of the filtered load. The majority of endogenous thiosulfate is actively reabsorbed and endogenous levels are regulated by the kidney through secretion into and reabsorption out of tubules.

Sodium thiosulfate is known to be a strong diuretic. Following IV administration of sodium thiosulfate, peak thiosulfate concentrations were obtained 5 minutes after injection. The half-life of the distribution phase was 23 minutes while that of the elimination phase was 182 minutes. Urine concentration, clearance and rate of thiosulfate excretion increased

markedly after injection. Total excretion was $42.6 \pm 3.5\%$ of the injected dose at 180 minute. Total excretion increased to only $47.4 \pm 2.4\%$ at 18 hours after injection. Sodium thiosulfate kinetics were also studied in patients undergoing cancer treatment. Sodium thiosulfate was eliminated from the plasma by first-order kinetics. On the average approximately 28% of the dose was recovered unchanged in the urine. In these patients, 95% of the total recoverable thiosulfate was excreted within 4 hours after termination of infusion. When sodium thiosulfate is coadministered with cisplatin (a chemotherapeutic agent that often causes nephrotoxicity), inactive mobile metabolites of cisplatin are formed by a direct reaction between cisplatin and sodium thiosulfate in the systemic circulation, which results in a reduction in the amount of cisplatin in the kidney. The strong diuretic action of sodium thiosulfate also increases elimination of both compounds, thus minimizing the time the remaining cisplatin is in the kidneys.

Sodium thiosulfate has been used to estimate extracellular water in cattle and was found to reach equilibrium with extracellular water in 5 to 10 minutes after infusion. Sodium thiosulfate was cleared from venous blood in a two part fashion: First, it was cleared from the plasma into the interstitial fluid, then secondly through renal clearance from the extracellular water. A first-order clearance of the sodium thiosulfate was demonstrated 15 to 20 minutes after infusion. When combined with urea, sodium thiosulfate gave reasonable estimates of empty body water, extracellular water, intracellular water and lean body mass. No adverse effects were noted in any of the steers.

7. *Metabolite toxicology.* None of the metabolites of sodium thiosulfate are considered to be of toxicological significance. Thiosulfate is a normal body constituent as are the other breakdown products from the reaction of sodium thiosulfate in chlorinated water: Sodium chloride, water, sulfur and sulfate.

8. *Endocrine disruption.* Sodium thiosulfate does not affect the endocrine system, except as a detoxifying agent of compounds that have been shown to adversely affect the endocrine system (i.e. chlorine and other reactant species).

C. Aggregate Exposure

1. *Dietary exposure.* The proposed use of sodium thiosulfate to remove chlorine and other reactive species from tank water ensures that there is no dietary exposure to sodium thiosulfate. Due to the breakdown of sodium

thiosulfate in water to sodium chloride, water, sulfur and sulfate, there are no residues of sodium thiosulfate applied to the plants and thus there are no residues in food.

i. *Food.* The proposed use will not result in any dietary exposure beyond what is currently present in salt and alcohol.

ii. *Drinking water.* There is no exposure to sodium thiosulfate through drinking water. Any sodium thiosulfate that gets into water is quickly broken down to the following non-toxic compounds: Sodium chloride, water, sulfur and sulfate.

2. *Non-dietary exposure.* The only anticipated human exposure to non-dietary sources of sodium thiosulfate would be through medical treatment, occupational exposure, or aquaculture (hobbyists).

D. Cumulative Effects

Studies have shown that excess sodium thiosulfate beyond endogenous levels of thiosulfate is rapidly cleared from the body and there are no cumulative effects. It should also be noted that with the exception of possible occupational exposure of the mixer/loader/applicator, the proposed uses of sodium thiosulfate will not result in exposure to any other persons or any non-target organisms.

E. Safety Determination

1. *U.S. population.* EDEN Bioscience Corporation believes that the use of sodium thiosulfate as an adjuvant added to tank mixes does not pose a safety concern for the U.S. population due to the non-toxic nature of the compound and the absence of exposure.

2. *Infants and children.* Infants and children will not be exposed to sodium thiosulfate from its use as an adjuvant in conjunction with formulated products.

F. International Tolerances

There are no known international tolerances for sodium thiosulfate.

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