

A. Residue Chemistry

1. *Plant metabolism.* Due to the breakdown of sodium thiosulfate in chlorinated water to sodium chloride, water, sulfur, and sulfate prior to application to plants, there is no plant metabolism of the parent compound. All of the breakdown products are considered to be plant nutrients.

Sodium thiosulfate pentahydrate (CAS 10102-17-7) is an odorless crystalline substance with a molecular weight of 248.18. The molecular formula is $\text{Na}_2\text{S}_2\text{O}_3$ (Na 29.08%, O 30.36%, S 40.56%). It has a pKa of 1.6, is soluble in water (42%; by weight at 0°C) and insoluble in alcohol. The aqueous solution is practically neutral with a pH range of 6.5-8.0. In aqueous solution sodium thiosulfate slowly decomposes to its molecular constituents. Sodium thiosulfate pentahydrate has a melting point of 48°C when heated rapidly. It loses all its water at 100°C and decomposes at higher temperatures. When sodium thiosulfate is used to remove chlorine from an aqueous solution it follows the equations: $\text{Na}_2\text{S}_2\text{O}_3 + 4\text{Cl}_2 + 5\text{H}_2\text{O} = 2\text{NaHSO}_4 + 8\text{HCl}$ and $\text{Na}_2\text{S}_2\text{O}_3 + 2\text{HCl} = 2\text{NaCl} + \text{H}_2\text{O} + \text{S} + \text{SO}_2$.

2. *Analytical method.* Analysis of sodium thiosulfate can be accomplished through a variety of methods. Some researchers have employed a gas chromatographic (GC) analytical method using a C18 column and 420-E fluorescence detector for determining elution of thiosulfate in plasma and urine. Other researchers have reported using a high performance liquid chromatographic (HPLC) method used to determine thiosulfate concentrations in plasma and urine. Medical researchers have also described the use of a clinical nephelometer to determine sulfate and thiosulfate concentrations in plasma and urine.

3. *Magnitude of residues.* 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.

B. Toxicological Profile

Sodium thiosulfate has been safely used for over 100 years as a therapeutic agent; medical uses of sodium thiosulfate have been well documented since 1895. In humans it is employed as an antidote for acute cyanide poisoning; as a chemoprotectant against carboplatin and cisplatin induced ototoxicity; to prevent cyanide poisoning from treatment with sodium nitroprusside, nitrile compounds and laetrile; to reduce calcinosis; and is used topically to treat acne and pityriasis

versicolor (tinea versicolor, a type of ringworm). Recent studies have shown that sodium thiosulfate may be effective in reducing some chemically induced cancers. In veterinary medicine it is used to treat or prevent cyanide poisoning; as a "general detoxifier" to treat bloat; and when applied dermally to treat ringworm and mange. Sodium thiosulfate is also being used experimentally to increase food utilization in livestock.

Sodium thiosulfate is present at 8% in lotion formulations to treat acne. Other lotions, containing 25% sodium thiosulfate, are used for treating ringworm and may be applied twice daily to affected and susceptible skin for at least a week to many months until complete control is achieved. Sodium thiosulfate (12%) is also mixed with a sterile solution of 0.5% potassium ferricyanide to treat silver nitrate burns.

Sodium thiosulfate is used to treat drinking water where there is concern with high levels of chlorine, chloroform or other reactive species, especially in drinking water produced by desalination plants. It is also used as a dechlorinator in aquariums and aquaculture, and in a number of manufacturing processes that require the removal of chlorine or other reactive species.

Sodium thiosulfate is classified in the Code of Federal Regulations, U.S. Food and Drug Administration, title 21, part 184, as a Direct Food Substance Affirmed As Generally Recognized As Safe (§ 184.1807) and title 21, part 582 as a Substance Generally Recognized As Safe, (§ 582.6807). According to § 184.1807, sodium thiosulfate is used as a formulation aid and a reducing agent. It is used in alcoholic beverages and table salt at levels not to exceed good manufacturing practice, currently 0.00005% in alcoholic beverages and 0.1% in table salt. Section 582.6807 authorizes the use of sodium thiosulfate as a sequestrant in salt with a tolerance of 0.1%.

1. *Acute toxicity.* Sodium thiosulfate exhibits a low order of acute toxicity. In an acute oral toxicity study of sodium thiosulfate in the rat, an $\text{LD}_{50} > 5,000$ milligrams/kilograms (mg/kg) was established, which places this material in Toxicity Category IV. Sodium thiosulfate is not well absorbed through the intestinal tract at high doses. Sodium thiosulfate is low in acute toxicity but may cause irritation of the gastrointestinal tract and purging if large quantities are ingested. Sodium thiosulfate has been used as a topical treatment for a variety of ailments for numerous years. Sodium thiosulfate is available in various lotion formulations

such as Komed™, an acne medication containing 8% sodium thiosulfate together with 2% salicylic acid, 25% isopropyl alcohol and other ingredients. Tinver™ and Versiclear™, are lotions used for tinea versicolor (ringworm). Both lotions contain 25% sodium thiosulfate, 1% salicylic acid and 10% isopropyl alcohol. It is recommended that the lotions be applied twice daily to affected and susceptible skin for at least a week to many months until complete control of tinea versicolor is achieved. Sodium thiosulfate (12%) is also mixed with a sterile solution of 0.5% potassium ferricyanide to treat silver nitrate burns. No adverse effects are expected when sodium thiosulfate is used topically. There is little information available on inhalation toxicity of sodium thiosulfate, but as with all dust or crystalline compounds, breathing product dust or mist may irritate the respiratory tract. Product labeling calls for mixers to wear a dust mask, thus precluding inhalation of dust when sodium thiosulfate is present as part of the product formulation. Eden Bioscience Corporation believes that the use of sodium thiosulfate as proposed is not expected to pose an inhalation hazard since it is already incorporated into the formulation at low to moderate concentrations (1 to 25%), or will be added in tablet form. Once the sodium thiosulfate either in tablet form or in the formulated end product is mixed with water, it breaks down into sodium chloride, water, sulfur and sulfate, which eliminates further possibility of inhalation exposure to the parent compound.

Although intravenous (IV) exposure to sodium thiosulfate is irrelevant to concerns with its proposed use, information from IV studies and therapeutic uses provides further data on the safety of sodium thiosulfate. Sodium thiosulfate is considered to be essentially a nontoxic drug, although nausea and vomiting have been described with rapid IV administration of antidotal doses to normal adult human volunteers. The standard dose of sodium thiosulfate for treatment of cyanide poisoning in humans is an IV administration of 50 milliliters (mL) of a 250 mg/mL (25%) solution. Patients also have been administered 50 mL of a 50% sodium thiosulfate solution without adverse effects. Sodium thiosulfate administered IV at 150–200 mg/kg over a period of 15 minutes, is part of the therapy to treat suspected cyanide toxicity from administration of sodium nitroprusside.

The lethal dose of sodium thiosulfate when given at intravenous doses to rats is greater than 2.5 g/kg. The IV LD_{50} in