TABLE 3.—REGISTRANTS REQUESTING VOLUNTARY CANCELLATION AND/OR AMENDMENT TO TERMINATE USES

EPA Company No.	Company name and address
000363	Coopers Creek Chemical Corp., 884 River Road, West Conshohocken, PA 19428–2699
003008	Osmose Inc., 980 Ellicott Street, Buffalo, NY 14209–2398
061468	Koppers Inc., 436 Seventh Avenue, Pittsburgh, PA 15219–1800
061470	Rutgers Chemicals, 10611 Harwin Drive, Suite 402, Houston, TX 77036
061483	KMG-Bernuth, Inc., 10611 Harwin Drive, Suite 402, Houston, TX 77036–1534
073408	Railworks Wood Products, 2525 Prairieton Road, Terre Haute, IN 47802

III. What is the Agency's Authority for Taking this Action?

Section 6(f)(1) of FIFRA provides that a registrant of a pesticide product may at any time request that any of its pesticide registrations be canceled or amended to terminate uses. FIFRA further provides that, before acting on the request, EPA must publish a notice of receipt of any such request in the **Federal Register**, and provide a 30–day public comment period. Thereafter, the Administrator may approve such a request.

IV. Procedures for Withdrawal of Request

Registrants who choose to withdraw a request for voluntary cancellation or amendment to terminate uses must submit such withdrawal in writing to the person listed under **FOR FURTHER INFORMATION CONTACT**. The Agency will consider withdrawal requests received on or before December 26, 2003. This written withdrawal of the request for cancellation or amendment to terminate uses will apply only to the applicable FIFRA section 6(f)(1) request listed in this notice. If the product(s) have been subject to a previous cancellation or use termination action, the effective date of cancellation and all other provisions of any earlier cancellation or use termination order are controlling. The withdrawal request must also include a commitment to pay any reregistration fees that are due, and to fulfill any applicable unsatisfied data requirements.

V. Provisions for Disposition of Existing Stocks

Existing stocks are those stocks of registered pesticide products which are currently in the United States and which have been packaged, labeled, and released for shipment prior to the effective date of the cancellation action. Unless the provisions of an earlier order apply, existing stocks already in the hands of dealers or users can be distributed, sold, or used legally until they are exhausted, provided that such further sale and use comply with the EPA-approved label and labeling of the affected product. Exception to these general rules will be made in specific cases when more stringent restrictions on sale, distribution, or use of the products or their ingredients have already been imposed, as in a Special Review action, or where the Agency has identified significant potential risk concerns associated with a particular chemical. This is in accordance with the Agency's statement of policy as set forth in the **Federal Register** of June 26, 1991 (56 FR 29362) (FRL–3846–4).

1. *Creosote*. The registrants of affected creosote products have requested that the voluntary product cancellations and/or use terminations become effective December 31, 2004, with no provision for existing stocks.

2. *ACC*. The effective date of cancellation will be the date of the cancellation order. Osmose stated in its request that its affected product (EPA Reg. No. 3008–60) is no longer being manufactured or distributed by them and that, therefore, there is no need for a time period for the depletion of existing stocks.

List of Subjects

Environmental Protection, Creosote, Acid Copper Chromate, Pesticides and Pests.

Dated: November 20, 2003.

Frank Sanders,

Director, Antimicrobials Division, Office of Pesticide Programs.

[FR Doc. 03–29591 Filed 11–25–03; 8:45 am]

BILLING CODE 6560–50–S

ENVIRONMENTAL PROTECTION AGENCY

[OPP–2003–0364; FRL–7333–8]

Sodium thiosulfate; Notice of Filing a Pesticide Petition to Amend a Tolerance for a Certain Pesticide Chemical in or on Food

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice announces the amendment of a pesticide petition proposing the establishment of regulations for residues of a certain pesticide chemical in or on various food commodities.

DATES: Comments, identified by docket ID number OPP–2003–0364, must be received on or before December 26, 2003.

ADDRESSES: Comments may be submitted electronically, by mail, or through hand delivery/courier. Follow the detailed instructions as provided in Unit I. of the **SUPPLEMENTARY INFORMATION**.

FOR FURTHER INFORMATION CONTACT: Princess Campbell, Registration Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (703) 308–8033 ; e-mail address: *campbell.princess@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. Potentially affected entities may include, but are not limited to:

- Crop production (NAICS 111)
- Animal production (NAICS 112)
- Food manufacturing (NAICS 311)
- Pesticide manufacturing (NAICS 32532)

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Get Copies of this Document and Other Related Information?

1. *Docket*. EPA has established an official public docket for this action under docket identification (ID) number OPP–2003–0364. The official public docket consists of the documents specifically referenced in this action, any public comments received, and other information related to this action. Although a part of the official docket, the public docket does not include Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. The official public docket is the collection of materials that is available for public viewing at the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Hwy., Arlington, VA. This docket facility is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The docket telephone number is (703) 305–5805.

2. *Electronic access*. You may access this **Federal Register** document electronically through the EPA Internet under the ''**Federal Register**'' listings at *http://www.epa.gov/fedrgstr/*.

An electronic version of the public docket is available through EPA's electronic public docket and comment system, EPA Dockets. You may use EPA Dockets at *http://www.epa.gov/edocket/* to submit or view public comments, access the index listing of the contents of the official public docket, and to access those documents in the public docket that are available electronically. Although not all docket materials may be available electronically, you may still access any of the publicly available docket materials through the docket facility identified in Unit I.B.1. Once in the system, select ''search,'' then key in the appropriate docket ID number.

Certain types of information will not be placed in the EPA Dockets. Information claimed as CBI and other information whose disclosure is restricted by statute, which is not included in the official public docket, will not be available for public viewing in EPA's electronic public docket. EPA's policy is that copyrighted material will not be placed in EPA's electronic public docket but will be available only in printed, paper form in the official public docket. To the extent feasible, publicly available docket materials will be made available in EPA's electronic public docket. When a document is selected from the index list in EPA Dockets, the system will identify whether the document is available for viewing in EPA's electronic public docket. Although not all docket materials may be available electronically, you may still access any of the publicly available docket materials through the docket facility identified in Unit I.B. EPA intends to work towards providing electronic access to all of the publicly available docket materials through EPA's electronic public docket.

For public commenters, it is important to note that EPA's policy is that public comments, whether submitted electronically or in paper, will be made available for public viewing in EPA's electronic public docket as EPA receives them and without change, unless the comment contains copyrighted material, CBI, or other information whose disclosure is restricted by statute. When EPA identifies a comment containing copyrighted material, EPA will provide a reference to that material in the version of the comment that is placed in EPA's electronic public docket. The entire printed comment, including the copyrighted material, will be available in the public docket.

Public comments submitted on computer disks that are mailed or delivered to the docket will be transferred to EPA's electronic public docket. Public comments that are mailed or delivered to the docket will be scanned and placed in EPA's electronic public docket. Where practical, physical objects will be photographed, and the photograph will be placed in EPA's electronic public docket along with a brief description written by the docket staff.

C. How and To Whom Do I Submit Comments?

You may submit comments electronically, by mail, or through hand delivery/courier. To ensure proper receipt by EPA, identify the appropriate docket ID number in the subject line on the first page of your comment. Please ensure that your comments are submitted within the specified comment period. Comments received after the close of the comment period will be marked ''late.'' EPA is not required to consider these late comments. If you wish to submit CBI or information that is otherwise protected by statute, please follow the instructions in Unit I.D. Do not use EPA Dockets or e-mail to submit CBI or information protected by statute.

1. *Electronically*. If you submit an electronic comment as prescribed in this unit, EPA recommends that you include your name, mailing address, and an e-mail address or other contact information in the body of your comment. Also include this contact information on the outside of any disk or CD ROM you submit, and in any cover letter accompanying the disk or CD ROM. This ensures that you can be identified as the submitter of the comment and allows EPA to contact you in case EPA cannot read your comment due to technical difficulties or needs further information on the substance of your comment. EPA's policy is that EPA will not edit your comment, and any identifying or contact information provided in the body of a comment will be included as part of the comment that is placed in the official public docket, and made available in EPA's electronic public docket. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment.

i. *EPA Dockets*. Your use of EPA's electronic public docket to submit comments to EPA electronically is EPA's preferred method for receiving comments. Go directly to EPA Dockets at *http://www.epa.gov/edocket/*, and follow the online instructions for submitting comments. Once in the system, select ''search,'' and then key in docket ID number OPP–2003–0364. The system is an ''anonymous access'' system, which means EPA will not know your identity, e-mail address, or other contact information unless you provide it in the body of your comment.

ii. *E-mail*. Comments may be sent by e-mail to *opp-docket@epa.gov*, Attention: Docket ID Number OPP–2003–0364. In contrast to EPA's electronic public docket, EPA's e-mail system is not an ''anonymous access'' system. If you send an e-mail comment directly to the docket without going through EPA's electronic public docket, EPA's e-mail system automatically captures your e-mail address. E-mail addresses that are automatically captured by EPA's e-mail system are included as part of the comment that is placed in the official public docket, and made available in EPA's electronic public docket.

iii. *Disk or CD ROM*. You may submit comments on a disk or CD ROM that

you mail to the mailing address identified in Unit I.C.2. These electronic submissions will be accepted in WordPerfect or ASCII file format. Avoid the use of special characters and any form of encryption.

2. *By mail*. Send your comments to: Public Information and Records Integrity Branch (PIRIB) (7502C), Office of Pesticide Programs (OPP), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC20460–0001, Attention: Docket ID Number OPP–2003–0364.

3. *By hand delivery or courier*. Deliver your comments to: Public Information and Records Integrity Branch (PIRIB), Office of Pesticide Programs (OPP), Environmental Protection Agency, Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Hwy., Arlington, VA, Attention: Docket ID Number OPP–2003–0364. Such deliveries are only accepted during the docket's normal hours of operation as identified in Unit I.B.1.

D. How Should I Submit CBI to the Agency?

Do not submit information that you consider to be CBI electronically through EPA's electronic public docket or by e-mail. You may claim information that you submit to EPA as CBI by marking any part or all of that information as CBI (if you submit CBI on disk or CD ROM, mark the outside of the disk or CD ROM as CBI and then identify electronically within the disk or CD ROM the specific information that is CBI). Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

In addition to one complete version of the comment that includes any information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket and EPA's electronic public docket. If you submit the copy that does not contain CBI on disk or CD ROM, mark the outside of the disk or CD ROM clearly that it does not contain CBI. Information not marked as CBI will be included in the public docket and EPA's electronic public docket without prior notice. If you have any questions about CBI or the procedures for claiming CBI, please consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

E. What Should I Consider as I Prepare My Comments for EPA?

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.

2. Describe any assumptions that you used.

3. Provide copies of any technical information and/or data you used that support your views.

4. If you estimate potential burden or costs, explain how you arrived at the estimate that you provide.

5. Provide specific examples to illustrate your concerns.

6. Make sure to submit your comments by the deadline in this notice.

7. To ensure proper receipt by EPA, be sure to identify the docket ID number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and **Federal Register** citation.

II. What Action is the Agency Taking?

EPA has received a pesticide petition as follows proposing the establishment and/or amendment of regulations for residues of a certain pesticide chemical in or on various food commodities under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a. EPA has determined that this petition contains data or information regarding the elements set forth in FFDCA section 408(d)(2); however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data support granting of the petition. Additional data may be needed before EPA rules on the petition.

List of Subjects

Environmental protection, Agricultural commodities, Feed additives, Food additives, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: November 13, 2003.

Debra Edwards,

Director, Registration Division, Office of Pesticide Programs.

Summary of Petition

The petitioner summary of the pesticide petition is printed below as required by FFDCA section 408(d)(3). The summary of the petition was prepared by the petitioner and represents the view of the petitioner. The summary may have been edited by EPA if the terminology used was unclear, the summary contained extraneous material, or the summary unintentionally made the reader conclude that the findings reflected EPA's position and not the position of the petitioner. The petition summary announces the availability of a description of the analytical methods available to EPA for the detection and measurement of the pesticide chemical residues or an explanation of why no such method is needed.

EDEN Bioscience Corporation

PP OE6177

EPA has received a pesticide petition (PP OE6177) from EDEN Bioscience Corporation, 3830 Monte Villa Parkway, Bothell WA 98021–6942 proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180 by amending the current exemption from the requirement of a tolerance for the inert ingredient sodium thiosulfate in or on all food crops. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

In the **Federal Register** of September 6, 2000 (65 FR 54015) (FRL–6738–4), EPA issued a notice pursuant to section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), announcing the filing of a tolerance petition (PP OE6177) by EDEN Bioscience. This notice included a summary of the petition prepared by the petitioner and this summary contained conclusions and arguments to support its conclusion that the petition complied with the Food Quality Protection Act (FQPA) of 1996. This petition requested that 40 CFR part 180 be amended by establishing an exemption from the requirement of a tolerance for residues of the inert ingredient sodium thiosulfate in or on all food crops. The final rule exempted the inert ingredient sodium thiosulfate from requirement of a tolerance when it comprises no more than 6% of the formulated product and when used on growing crops or on raw agricultural commodities after harvest. EPA published a final rule establishing a tolerance exemption in the **Federal Register** on December 21, 2001 (66 FR 65850) (FRL–6811–6) amending 40 CFR 180.1001(c). Research by EDEN Bioscience Corporation indicates that higher levels of sodium thiosulfate are needed in certain situations, such as the use of very high water volumes with products containing a low percentage of active ingredient. Therefore, EDEN proposes to amend this exemption to permit the use of sodium thiosulfate in a pesticide formulated product with no numerical limitation when used on growing crops or on raw agricultural commodities after harvest.

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 Na_2S_{23} (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: $Na_2S_2O3 + 4Cl_2 + 5H_2O = 2NaHSO_4 + 8HCl$ and $Na_2S_2O3 + 2HCl = 2NaCl + H_2O + S + SO_2$.

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 $LD_{50} > 5{,}000$ 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 Bioscence 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

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 LD_{50} 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 osmolarity. 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.

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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