UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 15 2004

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: BPPD Evaluation of Oak Ridge National Laboratory's Second Scientific Review of **TRIAD** (EPA Reg. Symbol 69493-R).

FROM: Carol E. Frazer, Ph.D., Toxicologist Carol
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TO: Raderrio Wilkins, Regulatory Action Leader
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THROUGH: Russell S. Jones, Ph.D., Senior Scientist
Biochemical Pesticides Branch
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Submission Contents:

- Product chemistry (MRIDs 460508-01), acute toxicity studies (MRIDs 462020-01,-04 and -05), primary irritation studies (MRIDs 462020-02 and -03), and hypersensitivity incidents (462020-06), from **TRIAD** (EPA File Symbol 69493-R), Chemical #072604;• Decision # 219572; DP Barcode 301227.

- Product contents – 2.41% sodium metasilicate and 97.59% other ingredients

Action Requested

Secondary review of ORNL's review of studies submitted for the biochemical pesticide sodium metasilicate in response to the October 2, 2003 EPA deficiency letter. Also to be reviewed are waiver justifications for the non-target insect studies (OPPTS Guideline 880.4350) Acute Honey Bee Toxicity, OPP Guidelines 152.17, Genotoxicity, 152.18, Immune response, 152.20, Subchronic, 90-day feeding, 152.21, Subchronic, 90-day dermal, 152.22, Subchronic, 90-day inhalation, and 152.23, Teratogenicity. Included are MRIDs 462020-01 through -06 and 460509-01, EPA File Symbol 69493-R.

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Conclusions:

On February 18, 2004, Robert M. Sielaty, Esq., Vice President of ChemReg® International, LLC, wrote Dr. Sheryl Reilly, Ph.D., Biochemical Pesticide Branch Chief, requesting a quick review of the resubmitted toxicity studies and waivers of toxicology and ecotoxicity studies to enable use of TRIAD (EPA File Symbol 69493-R) in California for the spring grape season.

1. Of the required Tier I mammalian toxicity studies, it is unclear why the registrant repeated several acceptable studies, with a subsequent change in the Toxicity Category of one of them. The primary eye irritation study went from a Toxicity Category I to II, and the explanation is given in the cover letter as a change in formulation. The previous submission, OPP Guideline 151-11, Manufacturing Process, (MRID 455524-01) was compared with the recent OPPTS Guideline 80.1200, Description of the Formulation Process (MRID 460509-01) and the only difference observable was a change from [redacted] The concentration and the company are the same for both. The previous study will of necessity be the one on which the label will be based, unless the Registrant provides a valid reason for the differing results.

2. The product chemistry is still **UNACCEPTABLE**, but upgradable if the registrant provides:

   a. clarification of the product content of [redacted] on the CSF and in the study report,

   b. five certificates of analysis for sodium metasilicate from the supplier listed on the CSF,

   c. an explanation of the wider lower certified limit of the active ingredient, and

   d. the enforcement analytical method specific for Triad.

3. The waiver requests have a number of problems. The bee acute contact toxicity waiver request is acceptable, as the registrant admits the compound is toxic to the insect and plans on using risk mitigation, i.e., warning the user about spraying when bees are around.

   Of the other waiver requests which the submission listed, several are not required and the registrant should review 40 CFR 158.690 to determine which are. The only ones absolutely required are the genotoxicity and the immune response. The 90-day dermal toxicity test is listed in the submission, but there is no information in the document about that whatsoever. This study is given in 40 CFR as Conditionally Required and the conditions are listed in the footnote: "Required if pesticidal use will involve purposeful application to the human skin or will result in comparable prolonged exposure to the product (e.g., swimming pool algaecides, pesticides for impregnating clothing), and if either of the following criteria are met: (A) Data from a subchronic oral study are not required (B) The active ingredient of the product is known or expected to be metabolized differently by the dermal route of exposure than by the oral route, and a metabolite of the active ingredient is the toxic moiety). From the label, none

of these conditions are met and the study would not be required. A simple statement explaining this would address the need for a waiver request.

The main problem with the waiver requests is that most of the information provided is not for the chemical for which a tolerance exemption is being requested, but related compounds. Of several silicate studies submitted for genotoxicity, only one (*B. subtilis* rec assay) was done with sodium metasilicate. That would be insufficient for the genotoxicity studies, as those require both bacterial and mammalian, covering DNA alterations and chromosomal damage. The immune response (local lymph node assay) was the only other sodium metasilicate study submitted as the basis on which to request a waiver.

The registrant must provide data that will expressly show the relationship between sodium metasilicate and silicic acid, silicon dioxide, magnesium silicate, sodium aluminum silicate, calcium silicate, sodium silicate, magnesium aluminum silicate, and why the studies performed with the other compounds support the waiver requests for sodium metasilicate. There is a RED on silicon dioxide and silica gel, and in this the registrant might find useful data to aid in responding to this problem about these waiver requests, at least with respect to those two compounds.

The R.E.D. FACTS on Silicon Dioxide and Silica Gel contains a great deal of information on the reason EPA is not requiring more information about the two compounds for human health, environmental, or risk assessments. The registrant could use this RED to see how to better format their submissions to get a more favorable response.

All the submitted studies are acceptable, and if the above problems are corrected, EPA will re-evaluate the submission for acceptance.

TOXICITY PROFILE OF **TRIAD**
2.41% Sodium metasilicate

Acute oral toxicity	IV	Acceptable	MRID 462020-05
Acute dermal toxicity	IV	Acceptable	MRID 462020-01
Acute inhalation toxicity	IV	Acceptable	MRID 462020-04
Primary eye irritation	II(I)	Acceptable	MRID 462020-03
Primary dermal irritation	III	Acceptable	MRID 462020-02
Human exposure	No	Acceptable	MRID 462020-06

LABELING: No labeling will be considered until all the required data is provided.

PRODUCT CHEMISTRY OF **TRIAD** (69493-R)

Guideline §880.1100: Product identity and disclosure of ingredients (MRID 460509-01)

The following table summarizes information submitted by the registrant regarding the active ingredient.

Chemical Name:	sodium metasilicate
CAS Registry Nos.:	6834-92-0
Synonym(s):	silicic acid, disodium salt; sodium silicate, meta anhydrous; Dry S-25
Chemical Family:	Metal oxide
Source of Biochemical:	Not a biochemical
Mode of Action:	Desiccant
Molecular Formula:	Na_2O - SiO_2

A confidential statement of formula was submitted by the registrant.

BPB's Comment: Data submitted on the product identity satisfy the requirements of 40 CFR 158.155.

Guideline §880-1200: Manufacturing process (MRID 460509-01)

In Confidential Appendix

Guideline §880.1400: Discussion on the formation of unintentional ingredients (MRID 460509-01)

In Confidential Appendix

Guideline §880.1700: Analysis of samples (MRID 460509-01)

desiccant?

In Confidential Appendix

Guideline §880.1750: Certification of ingredient limits (MRID 460509-01)

In Confidential Appendix

Guideline §880.1900: Analytical methods for certified limits (MRID 460509-01)

In Confidential Appendix

Guideline §151-17: Physical and Chemical Characteristics

The registrant submitted information on the physical and chemical characteristics of **TRIAD** which are summarized below:

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STUDY TYPE	CHARACTERISTIC	SOURCE
Color	Brown	MRID 455524-02
Physical State	Liquid	"
Odor	Mild organic	"
pH	12.3	"
Melting point	N/A	"
Boiling point	N/A	"
Density	1.08	"
Flammability	Non-flammable	"
Solubility	N/A	"
Storage stability	Based on observations of no chemical change during blending and qualitative results from field trials over time, all indications are the formula is stable for a period greater than one year.	"
Corrosion characteristics	Non-corrosive	"
Miscibility	Readily miscible in water (requires agitation)	"
Viscosity	65/75 SUS (Saybolt Universal Seconds) @ 100 °F, 10.8/13.6 CST (centistokes) @ 40 °C	"
Vapor pressure	N/A	"

BPB's Comment: Data submitted on the physical and chemical characteristics of TRIAD does not satisfy the requirements of 40 CFR 158.190.

PRODUCT TOXICOLOGY FOR **TRIAD**

Acute Oral Toxicity Up and Down Study (OPPTS 870.1100) (MRID 462020-05)

The oral LD_{50} for females was > 5,000 mg/kg. This places TRIAD in TOXICITY CATEGORY IV. The packet classification is **ACCEPTABLE**.

Acute Dermal Toxicity Study (OPPTS 870.1200) (MRID 462020-01)

The dermal LD_{50} for males, females and combined was >5,000 mg/kg. This places TRIAD in TOXICITY CATEGORY IV. The packet classification is **ACCEPTABLE.**

Acute Inhalation Toxicity Test (OPPTS 870.1300) (MRID 462020-04)

The inhalation LC_{50} for males, females, and combined was > 2.13 mg/L, MMAD ~3.6, GSD ~2.27. This places Triad in TOXICITY CATEGORY IV. The packet classification is **ACCEPTABLE.**

Primary Eye Irritation Test (OPPTS 870.2400) (MRID 462020-03)

Based on the presented/submitted data, corneal opacity was noted on 3/3 through day 7, 1/3 on day 10 and 0/3 on day 14 after test material instillation. Iritis was noted on 3/3 through day 7 as well, but cleared completely on all rabbits by day 10. Positive conjunctival irritation was noted on all rabbits 24 hours after test material instillation until day 10, and all cleared by day 14. Triad was severely irritating and is in TOXICITY CATEGORY II. The packet classification is **ACCEPTABLE.**

Primary Dermal Irritation Test (OPPTS 870.2500) (MRID 462020-02)

Very slight to well-defined erythema with very slight edema was noted on all rabbits one hour after patch removal with clearance by day 7. The primary irritation index was 2.6. Triad was moderately irritating and is in TOXICITY CATEGORY III. The packet classification is **ACCEPTABLE.**

Human Exposure Assessment (MRID 462020-06)

Sodium metasilicate is classified as a GRAS substance and is cleared as a direct food ingredient.

BPB's Comment: All the waiver requests for additional mammalian toxicity studies and the non-target acute honey bee toxicity study were addressed and are acceptable.

DATA EVALUATION RECORD

EPA Secondary Reviewer: Carol E. Frazer, Ph.D.

STUDY TYPE:	Acute Oral Toxicity - Rats (OPPTS 870.1100)
MRID NO:	46202005
DP BARCODE NO:	DP301227
CASE NO:	Not reported
SUBMISSION NO:	Not reported
TEST MATERIAL:	Triad®-7 Concentrate (EPA Reg No. 69493-R, 2.41% sodium metasilicate)
PROJECT NO:	14480
SPONSOR:	Environmentally Safe Systems, Inc., Solvang, CA
TESTING FACILITY:	Product Safety Labs, Dayton, NJ
TITLE OF REPORT:	Acute Oral Toxicity Up and Down Procedure in Rats
AUTHOR:	George E. Moore, B.S.
STUDY COMPLETED:	January 23, 2004
GOOD LABORATORY PRACTICE:	GLP Compliant
CONCLUSION:	The oral LD_{50} for females was greater than 5,000 mg/kg.
CLASSIFICATION:	ACCEPTABLE -- TOXICITY CATEGORY IV

I. STUDY DESIGN:

1. **Test Material:** Triad®-7 Concentrate containing 2.41% sodium metasilicate [redacted]

2. **Test Animals:** Three female Sprague-Dawley rats were received from Ace Animals, Inc., Boyertown, PA and weighed 210-224 g on the day of dosing. The young adult animals, 11 weeks old, were housed individually in suspended stainless steel cages with mesh floors. The animals were fed Purina Rodent Chow No. 5012. Filtered tap water was available *ad libitum*. The environmental conditions of the animal room were as follows: temperature, 18-22°C; relative humidity, 30-69%; air changes per hour, 12.9 or greater; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Rats were ear-tagged (Nos. 1933, 1971, and 1972) and were quarantined for 22 or 23 days and fasted overnight prior to dosing. The test material (5000 mg/kg body weight) was dosed by gavage using the up and down procedure (Table 1). One animal was dosed without mortality. Two additional animals were dosed. Since three animals survived, no additional animals were tested. Body weight was recorded prior to dosing, and on days 7 and 14. The test animals were observed for clinical signs of toxicity during the first several hours post-dosing and at least daily for 14 days. All animals were necropsied.

II. RESULTS:

1. **Mortality:** All rats survived the study.

TABLE 1. Doses, mortality/animals treated
Dose (mg/kg) Males Females Combined
5,000 - 0/3 0/3
Data taken from p. 10, MRID 46202005.

2. **Body Weights:** All animals gained weight during the study.

3. **Clinical Observations:** All animals were active and healthy throughout the study.

4. **Gross Necropsy:** No gross abnormalities were noted from any animal.

III. DISCUSSION:

The oral LD_{50} for females was greater than 5,000 mg/kg. This places Triad®-7 concentrate in TOXICITY CATEGORY IV. The packet classification is **ACCEPTABLE.**

DATA EVALUATION RECORD

EPA Secondary Reviewer: Carol E. Frazer, Ph.D.

STUDY TYPE:	Acute Dermal Toxicity - Rats (OPPTS 870.1200)
MRID NO:	46202001
DP BARCODE NO:	DP301227
CASE NO:	Not reported
SUBMISSION NO:	Not reported
TEST MATERIAL:	Triad®-7 Concentrate (EPA Reg No. 69493-R, 2.41% sodium metasilicate)
PROJECT NO:	14269
SPONSOR:	Environmentally Safe Systems, Inc., Solvang, CA
TESTING FACILITY:	Product Safety Labs, Dayton, NJ
TITLE OF REPORT:	Acute Dermal Toxicity Study in Rats - Limit Test
AUTHOR:	Darrel J. Merkel, B.S.
STUDY COMPLETED:	January 23, 2004
GOOD LABORATORY PRACTICE:	GLP Compliant
CONCLUSION:	The dermal LD_{50} for males, females, and combined was greater than 5,000 mg/kg.
CLASSIFICATION:	ACCEPTABLE -- TOXICITY CATEGORY IV

- **STUDY DESIGN:**

- **Test Material:** Triad®-7 Concentrate containing 2.41% sodium metasilicate, [redacted]

2. **Test Animals:** Five male and five female Sprague-Dawley rats were received from Ace Animals, Inc., Boyertown, PA, were assigned, and weighed 254-270 g (males) and 190-210 g (females) on the day of treatment. The young adult animals, 8-9 weeks old, were housed individually in suspended stainless steel cages with mesh floors. The animals were fed Purina Rodent Chow No. 5012 and filtered tap water was available *ad libitum*. The environmental conditions of the animal room were as follows: temperature, 18-23°C; relative humidity, 32-64%; air changes per hour, 12.9 or greater; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Rats were ear-tagged: Male – Nos. 1787 to 1791; Female – Nos. 1792 to 1796. The rats were quarantined for 9 days. The test material (5000 mg/kg body weight) was applied evenly over a 2 inch x 3 inch area (approximately 10% of the body surface) of the dorsum and covered with a gauze pad. The gauze pad and entire trunk were wrapped with Durapore tape. The coverings were removed after 24 hours and excess test material removed. The test animals were observed during the first several hours after treatment for mortality, signs of gross toxicity, and behavior changes and daily thereafter for 14 days. The rats were weighed prior to treatment and on days 7 and 14. The rats were euthanized on day 14 and necropsied.

II. RESULTS:

1. **Mortality:** All rats survived the study.

2. **Clinical Observations:** All animals were active and healthy throughout the study.

3. **Body Weights:** All animals had normal body weight gains.

4. **Gross Necropsy:** No gross abnormalities were noted.

III. DISCUSSION:

The dermal LD_{50} for males, females, and combined was greater than 5000 mg/kg. This places "Triad"-7 Concentrate in TOXICITY CATEGORY IV. The packet classification is **ACCEPTABLE.**

DATA EVALUATION RECORD

EPA Secondary Reviewer: Carol E. Frazer, Ph.D.

STUDY TYPE:	Acute Inhalation Toxicity - Rats (OPPTS 870.1300)
MRID NO:	46202004
DP BARCODE NO:	DP301227
CASE NO:	Not reported
SUBMISSION NO:	Not reported
TEST MATERIAL:	Triad®-7 Concentrate (EPA Reg No. 69493-R, 2.41% sodium metasilicate)
PROJECT NO:	14481
SPONSOR:	Environmentally Safe Systems, Inc., Solvang, CA
TESTING FACILITY:	Product Safety Labs, Dayton, NJ
TITLE OF REPORT:	Acute Inhalation Toxicity Study in Rats - Limit Test
AUTHOR:	George E. Moore, B.S.
STUDY COMPLETED:	38008
GOOD LABORATORY PRACTICE:	GLP Compliant
CONCLUSION:	The inhalation LC_{50} for males, females, and combined was > 2.13 mg/L.
CLASSIFICATION:	ACCEPTABLE -- TOXICITY CATEGORY IV

- STUDY DESIGN:

1. Test Material: Triad®-7 Concentrate containing 2.41% sodium metasilicate, [redacted]

2. Test Animals: Five male and five female Sprague-Dawley rats were received from Ace Animals, Inc., Boyertown, PA, were assigned, and weighed 358-377 g (males) and 211-253 g (females) on the day of treatment. The young adult animals, 10-11 weeks old, were housed individually in suspended stainless steel cages with mesh floors. The animals were fed Purina Rodent Chow No. 5012. Tap water was available *ad libitum*. The environmental conditions of the animal room were as follows: temperature, 18-21°C; relative humidity, 30-62%; air changes per hour, 12.9 or greater; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Rats were ear-tagged. Male – Nos. 1987 to 1991; Female – Nos. 1992 to 1996. The rats were quarantined for 20 days prior to exposure and then assigned to the test groups noted in Table 1. The rats were exposed whole body in a Plexiglas dynamic flow inhalation chamber for four hours and 15 minutes. They were observed at least every 30 minutes during exposure, upon removal from the chamber, and at least once daily thereafter for 14 days. They were weighed prior to test material exposure and on days 7 and 14. All rats were sacrificed and necropsied on day 14.

TABLE 1. Concentrations, exposure conditions, mortality/animals treated

Nominal Conc. (mg/L)	Grav. Conc (mg/L)	MMAD (µm)	GSD (um)	Particles <5.3 µm (%)	Temp (°C)	Humidity (%)	Mortality		
							Male	Female	Combined
47.45	2.17	3.3-3.7	1.5-1.7	>62	19-21	40-100	0/5	0/5	0/10

Data taken from Tables 4-6, pp. 9, 11, and 16-18, MRID 46202004.

Generation of the test atmosphere and description of the chamber: The exposure atmosphere was generated using a 1/4 inch JCO atomizer, FC3 fluid cap and AC1502 air cap (Spraying Systems Inc.). The test material was metered to the atomization nozzle through Tygon tubing using a pump. Filtered air was supplied by an air compressor connected to the spray atomization nozzle. Additional diluent air was supplied directly to the exposure chamber from conditioned room air. The average total airflow was 45.5-45.9 liters/min and the whole body exposure chamber volume was 150 L. Time to equilibrium was approximately 15 min.

Test atmosphere concentration: Gravimetric samples were collected six times using glass fiber filters from the breathing zone of the animals during exposure. Filter papers were weighed before and after collection to determine the mass collected. The value was divided by the total volume of air sampled to determine the chamber concentration. Analytical chemistry was not performed. The average results are in Table 1 above.

Particle size determination: Particle size distribution of each exposure concentration was determined using an eight stage Andersen cascade impactor. The test material concentration collected by each stage was determined gravimetrically. The aerodynamic mass median diameter (MMAD) and geometric standard deviation (GSD) were determined graphically utilizing two-cycle logarithmic probit axes. Results are in Table 1 above.

II. RESULTS:

1. **Mortality:** All rats survived the study.

2. **Clinical Observations:** During exposure, the animals were hypoactive and had ocular discharge, nasal discharge, and hunched posture. All animals recovered upon removal from

the chamber and were active and healthy throughout the remainder of the observation period.

3. **Body Weight:** All animals had normal body weight gains.

4. **Gross Necropsy:** No gross abnormalities were noted.

III. DISCUSSION:

The inhalation LC_{50} for males, females, and combined was > 2.13 mg/L. This places Triad®-7 Concentrate in TOXICITY CATEGORY IV. The packet classification is **ACCEPTABLE.**

DATA EVALUATION RECORD

EPA Secondary Reviewer: Carol E. Frazer, Ph.D.

STUDY TYPE:	Acute Eye Irritation - Rabbits (OPPTS 870.2400)
MRID NO:	46202003
DP BARCODE NO:	DP301227
CASE NO:	Not reported
SUBMISSION NO:	Not reported
TEST MATERIAL:	Triad®-7 Concentrate (EPA Reg No. 69493-R, 2.41% sodium metasilicate)
PROJECT NO:	1410J
SPONSOR:	Environmentally Safe Systems, Inc., Solvang, CA
TESTING FACILITY:	Product Safety Labs, Dayton, NJ
TITLE OF REPORT	Primary Eye Irritation Study in Rabbits
AUTHOR:	George E. Moore, B.S.
STUDY COMPLETED:	January 23, 2004
GOOD LABORATORY PRACTICE:	GLP Compliant
CONCLUSION:	Corneal opacity was noted on 3/3 rabbits one hour after test material instillation with resolution by day 14. Iritis and positive conjunctival irritation was noted on 3/3 rabbits one hour after test material instillation with resolution by day 10. The maximum average score was 38.7 at 48 hours after test material instillation. Triad®-7 Concentrate was severely irritating.
CLASSIFICATION:	ACCEPTABLE -- TOXICITY CATEGORY II

I. STUDY DESIGN:

1. **Test Material:** Triad®-7 Concentrate containing 2.41% sodium metasilicate, [redacted]

2. **Test Animals:** One male and two female young adult New Zealand White rabbits were received from Davidson's Mill Farm, South Brunswick, NJ. The animals were housed individually in suspended stainless steel cages with mesh floors. The animals were fed Pelleted Purina Chow No. 5326. Filtered tap water was available *ad libitum*. The environmental conditions of the animal room were as follows: temperature, 18-22°C; relative humidity, 36-57%; air changes per hour, 12.9 or greater; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Rabbits were caught-tagged, Nos. 10246 (male) and 10245 and 10247 (females). The rabbits were quarantined for 5 days. The test material (0.1 mL/eye/animal) was applied in the conjunctival sac of the right eye, and the eye held closed for approximately one

second. The contralateral eye served as control. The eyes were examined and scored 1, 24, 48 and 72 hours and at 4, 7, 10 and 14 days after test material instillation.

II. RESULTS:

1. **Mortality:** All animals survived the study.

2. **Ocular Lesions:** Corneal opacity was noted on 3/3 rabbits one hour after test material instillation with resolution on two rabbits by day 10 and on one rabbit by day 14 (Table 1). Iritis was noted on 3/3 rabbits one hour after test material instillation with resolution by day 10. Positive conjunctival irritation (score 2 or 3) was noted on all rabbits one hour after test material instillation with resolution by day 10 (Table 2). The maximum average score was 38.7 at 48 hours after test material instillation (Table 3).

TABLE 1. Individual Male (M) and Female (F) Eye Scores w/ Time: Cornea (A=Density of Opacity; B=Area of Opacity)

Animal No.	1 hour		24 hours		48 hours		72 hours		4 days		7 days		10 days		14 days	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
10245 F	1	1	1	4	1	4	1	4	1	4	1	3	1	1	0	4
10246 M	1	1	1	4	1	4	1	4	1	1	1	1	0	4	0	4
10247 F	1	1	1	3	1	3	1	3	1	1	1	1	0	4	0	4

TABLE 2. Summary of Eye Irritation Scores with Time: Conjunctiva and Iris

Score Conditions	1 hour	24 hours	48 hours	72 hours	4 days	7 days	10 days	14 days
Conjunctiva								
Erythema	2	2	3	2 to 3	2 to 3	2	1	0
Chemosis	2	2	2	2	1 to 2	1	0	0
Discharge	3	2 to 3	2 to 3	2	2	2	0	0
Iris	1	1	1	1	1	1	0	0

Irritation score is based on Draize Method

Scale for Scoring Ocular Lesions

Cornea

A. Opacity-degree of density (area most dense taken for reading)

No Opacity 0
Scattered or diffuse area, details of iris clearly visible 1*
Easily discernible translucent areas, details of iris slightly obscured 2*
Opalescent areas, no details of iris visible, size of pupil barely discernible 3*
Opaque, iris invisible 4*

B. Area of cornea involved

One quarter (or less) but not zero 1

Greater than one quarter, but less than half 2
Greater than half, but less than three quarters 3
Greater than three quarters, up to whole area 4
Score = A x B x 5 Total Maximum Score = 80

Iris

A. Values

Normal 0

Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof), iris still reacting to light (sluggish reaction is positive). 1*

No reaction to light, hemorrhage, gross destruction (any or all of these). 2*

Score = A x 5 Total Maximum Score = 10

Conjunctive

A. **Redness (refers to palpebral and bulbar conjunctive excluding cornea and iris)**

Vessels normal 0

Vessels definitely injected above normal 1

More diffuse, deeper crimson red, individual vessels not easily discernible 2*

Diffuse beefy red 3*

B. **Chemosis**

No swelling 0

Any swelling above normal (includes nictitating membrane) 1

Obvious swelling with partial eversion of lids 2*

Swelling with lids about half closed 3*

Swelling with lids about half closed to completely closed 4*

C. **Discharge**

No discharge 0

Any amount different from normal (does not include small amounts observed in inner canthus of normal animals) 1

Discharge with moistening of the lids and hairs just adjacent to lids 2

Discharge with moistening of the lids and hairs, and considerable area around the eye 3

Score = (A + B + C) x 2 Total Maximum Score = 20

* represents a positive response

TABLE 3. Summary of Total[a] and Primary Eye Irritation Scores with Time

Animal #	1 h	24 h	48 h	72 h	4 d	7 d	10 d	14 d
10245	24	39	41	37	37	30	7	0
10246	24	39	41	39	24	20	2	0
10247	24	32	34	34	22	20	2	0
[b]Total	24.0	36.7	38.7	36.7	27.7	23.3	3.7	0

[a]Formula: Total Irritation Score = I + II + III, where,

I = Corneal Score = [Density (A) x Area (B)] x 5

II = Iris Score = Severity x 5

III = Conjunctival Score = [Erythema (A) + Chemosis (B) + Discharge (C)] x 2

[b]Primary Irritation = Sum of Total Irritation Scores ÷ 3

III. DISCUSSION:

Corneal opacity was noted on 3/3 rabbits one hour after test material instillation with resolution by day 14. Iritis was noted on 3/3 rabbits one hour after test material instillation with resolution by day 10. Positive conjunctival irritation was noted on all rabbits one hour after test material instillation with resolution by day 10. The maximum average score was 38.7 at 48 hours after test material instillation. Triad®-7 Concentrate was severely irritating and is in TOXICITY CATEGORY II. The packet classification is **ACCEPTABLE.**

DATA EVALUATION RECORD

EPA Secondary Reviewer: Carol E. Frazer, Ph.D.

STUDY TYPE:	Primary Dermal Irritation - Rabbits (OPPTS 870.2500)
MRID NO:	46202002
DP BARCODE NO:	DP301227
CASE NO:	Not reported
SUBMISSION NO:	Not reported
TEST MATERIAL:	Triad®-7 Concentrate (EPA Reg No. 69493-R, 2.41% sodium metasilicate)
PROJECT NO:	14482
SPONSOR:	Environmentally Safe Systems, Inc., Solvang, CA
TESTING FACILITY:	Product Safety Labs, Dayton, NJ
TITLE OF REPORT:	Primary Skin Irritation Study in Rabbits
AUTHOR:	George E. Moore, B.S.
STUDY COMPLETED:	January 23, 2004
GOOD LABORATORY PRACTICE:	GLP Compliant
CONCLUSION:	Well defined erythema was noted on 3/3 rabbits one hour after patch removal and reduced to very slight erythema by 24 hours for one rabbit, or day 7 for the other two through the end of the study. Very slight edema was noted on all rabbits one hour after patch removal with clearance by day 14. The primary irritation index was 2.6. Triad®-7 Concentrate was moderately irritating.
CLASSIFICATION:	ACCEPTABLE -- TOXICITY CATEGORY III

I. STUDY DESIGN:

1. **Test Material:** Triad®-7 Concentrate containing 2.41% sodium metasilicate. [redacted]

2. **Test Animals:** Two male and one female young adult New Zealand White rabbits were received from Robinson Services, Inc., Clemmons, NC. The animals were housed individually in suspended stainless steel cages with mesh floors. The animals were fed Pelleted Purina Chow No. 5326. Filtered tap water was available *ad libitum*. The environmental conditions of the animal room were as follows: temperature, 19-23° C; relative humidity, 49-65%; air changes per hour, 12.9 or greater; and photoperiod, 12 hour light/dark cycle.

3. **Methods:** Rabbits were ear-tagged: Nos. 10685 and 10687 (males) and 10686 (female). The rabbits were quarantined for 8 days. The fur on the dorsal trunk of each rabbit was clipped on the day prior to treatment. The rabbits were given 0.5 mL of test material applied on a 6 cm^2 clipped intact dose site, and the site covered with gauze pad. The pad

and entire trunk were wrapped with a semi-occlusive Microspore tape. Elizabethan collars were placed on the rabbits. The covering and the collar were removed 4 hours later and the site cleansed to remove any residual test material. The animals were observed at least once daily for gross toxicity and behavior changes during the study. Dermal examination was recorded at 1, 24, 48, and 72 hours and 7, 10 and 14 days after removal of the patch.

II. RESULTS:

1. **Mortality**: All rabbits survived the study.

2. **Dermal responses**: Well defined erythema was noted on 2/3 rabbits one hour after patch removal and persisted through 72 hours then reduced to very slight erythema by day 7 through the end of the study. Well defined erythema was noted on 1/3 rabbits one hour after patch removal and reduced to very slight erythema by 24 hours through the end of the study. Very slight edema was noted on all rabbits one hour after patch removal with clearance on one rabbit by 24 hours, on another rabbit by day 10, and on the third rabbit by day 14. The primary irritation index was 2.6.

Irritation Scores:

TABLE 1. Summary of individual rabbit's dermal irritation scores with time

	Hours	Days					
Animal No.	1	24	48	72	7	10	14
10685	2/1*	2/1	2/1	2/1	1/1	1/1	1/0
10686	2/1	1/1	1/0	1/0	1/0	1/0	1/0
10687	2/1	2/1	2/1	2/1	1/1	1/0	1/0

Data taken from Table 1, p. 13, MRID 46202002.
*Erythema/Edema

Description of rating method:

Evaluation of Skin Reaction:

Score

Erythema Formation:
No erythema 0
Very slight erythema (barely perceptible) 1
Well-defined erythema 2
Moderate to severe erythema 3
Severe erythema (beet redness) to slight eschar formation (injuries in depth) 4

Edema Formation:
No edema 0
Very slight edema (barely perceptible) 1
Slight edema (edges of area well-defined by definite raising) 2
Moderate edema (raised approximately 1 mm) 3
Severe edema (raised by more than 1 mm extending beyond the area of exposure) 4

III. DISCUSSION:

Well defined erythema was noted on 2/3 rabbits one hour after patch removal and persisted through 72 hours then reduced to very slight erythema by day 7 through the end of the study. Well defined erythema was noted on 1/3 rabbits one hour after patch removal and reduced to very slight erythema by 24 hours through the end of the study. Very slight edema was noted on all rabbits one hour after patch removal with clearance on one rabbit by 24 hours, on another rabbit by day 10, and on the third rabbit by day 14. The primary irritation index was 2.6. Triad®-7 Concentrate was moderately irritating and is in TOXICITY CATEGORY III. The packet classification is **ACCEPTABLE**.

DATA EVALUATION RECORD

EPA Secondary Reviewer: Carol E. Frazer, Ph.D.

STUDY TYPE:	Human Exposure Assessment
MRID NO:	46202006
DP BARCODE NO:	DP301227
CASE NO:	Not reported
SUBMISSION NO:	Not reported
TEST MATERIAL:	Triad®-7 Concentrate (EPA Reg No. 69493-R, 2.41% sodium metasilicate)
PROJECT NO:	ESS-2004-2
SPONSOR:	Environmentally Safe Systems, Inc., Solvang, CA
TESTING FACILITY:	ChemReg International, LLC, Lake Ridge, VA
TITLE OF REPORT:	Human Exposure Assessment for Triad Pesticide
AUTHOR:	Robert G. Butz, Ph.D.
STUDY COMPLETED:	February 4, 2004
GOOD LABORATORY PRACTICE:	Not subject to GLP; discussion and presentation of compiled information from published literature and publicly generated information sources.
CONCLUSION:	Any significant human exposure to sodium metasilicate in the food supply from the use of Triad is extremely unlikely.
CLASSIFICATION:	ACCEPTABLE

This report is an assessment of human exposure to Triad pesticide that contains sodium metasilicate.

Sodium metasilicate is an alkali. The strongest base hydroxides, such as sodium hydroxide and potassium hydroxide, have been approved by the FDA as GRAS when used as direct food additives. It is expected that sodium metasilicate would react in a similar manner as the strongest bases. Thus, sodium metasilicate as an alkali is unlikely to cause any significant exposure in humans.

Sodium metasilicate is used as a food additive/ingredient. It is described in CFR title 21, Volume 3, Part 173, Secondary food additives permitted in food for human consumption, Section 310, Boiler water additives and in CFR Title 21, Part 184, Direct food substance affirmed as GRAS, Section 1769a, Sodium metasilicate. A maximum concentration of 16.0 ppm of sodium metasilicate is allowed in potable water and 300 ppm of sodium metasilicate is typically used for fruit, vegetable, and nut washing and lye peeling use.

The maximum application rate for Triad for grapes equates to a 2.0 lb a.i./acre or 2 pounds of sodium metasilicate per acre. Residues are generally in the range of 1 to 10 ppm when applied close to harvest. The maximum application rate for lettuce equates to 0.33 lb a.i./acre and the residues would likely be in the range of 0.001 to 0.1 ppm. Any significant human exposure to

sodium metasilicate in food supply from the use of Triad is extremely unlikely. The exposure from Triad use is orders of magnitude less than the exposure allowed as a result of GRAS food additive uses.

The packet classification is **ACCEPTABLE.**

WAIVER REQUESTS

OPPTS Guideline 880.4350, Acute Honey Bee Toxicity:

Because TRIAD is a contact pesticide and does cause toxicity to bees when the liquid spray actually touches the insect, but is no longer toxic when dried, the registrant acknowledges the pesticide is a hazard to bees. The registrant proposes mitigating exposure by putting a warning in the environmental hazards section of the label "The product is highly toxic to bees exposed to direct treatment on blooming crops or weeds. Do not apply this product or allow it to drift to blooming crops or weeds while bees are actively visiting the treatment area."

No further testing is needed as the registrant acknowledges the toxicity, but the risk manager needs to make the decision as to whether the benefits of the pesticide outweigh the hazards.

For the remaining waiver requests, public literature was provided indicating:

OPP Guideline 152.17, Genotoxicity:

- 0.005 to 0.5 M sodium metasilicate (Na_2SiO_3) and silicon dioxide (SiO_2) were negative in a *Bacillus subtilis* recombinant repair deficient assay;
- 50 µg silicic acid (H_2SiO_3) and magnesium aluminum silicate ($MgAl_2(SiO_4)_2 \cdot H_2O$) were negative in an Ames assay spot test on 5 strains of *Salmonella typhimurium*, both with and without metabolic activation;
- the same 5 strains of *Salmonella typhimurium* in the Ames assay and the WP2 strain of *Escherichia coli* were used in plate-incorporation assays to test sodium aluminum silicate, magnesium silicate and silicon dioxide, both with and without metabolic activation, at concentrations up to 10 mg/plate;
- amorphous silica does not affect the HPRT mutation frequency in alveolar epithelial cells after 6.5 or 13 weeks of exposure and 3 or 8 months of recovery (50.4 ± 19.0 mg/m^3), whereas crystalline silica in the same protocol at 3.0 ± 1.0 mg/m^3 did induce a 4.3-fold increase in HPRT mutations by the end of the recovery period;
- chromosomal aberrations and sister-chromatid exchanges were significantly increased at the highest doses of calcium silicate (10.0 and 100.0 µg/ml) in a human blood lymphocyte *in vitro* assay; but,
- oral calcium silicate up to 5,000 mg/kg was negative in a host-mediated *in vivo* mouse assay with *Salmonella typhimurium* TA-1530 and G-46 and *Saccharomyces* D3, and in fact, reduced recombinant activity in the D3; 5 doses of 5,000 mg/kg of oral calcium silicate was non-mutagenic for chromosomal aberrations in the rat bone marrow; and the same compound had no effect on dominant lethality at doses up to 1500 mg/kg given either as one dose or 5 doses.

OPP Guideline 152.18, Immune response:

Sodium metasilicate (Na_2SiO_3) caused significant dermal irritation at concentrations ≥6%, and an allergic response after mice were sensitized with 4%, then challenged with 6% in the mouse ear swelling test. Lymph node cell proliferation was not observed in the local lymph node assay after treatment with 2 to 4% of the compound. Increases in lymph node cellularity, the percentage of B cells, and the expression of certain cytokine mRNAs were observed in treated mice. Changes in the concentration of serum IgE, however, were not observed.

OPP Guideline 152.20, Subchronic, 90-day feeding:

- 6-month old male and female dogs fed equivalent of 0.8 g silicon dioxide/kg/day developed hypertrophy of tubular epithelium, with or without degenerative changes, inflammatory cell filtration into the interstitium, and dilatation of some and collapse of other tubules within localized areas of the kidney. Renal function however, was unaffected.
- in a rat study by the same authors, the same dose was fed 15 Charles River rats per sex for four weeks, with no effects.
- micronized silica at doses up to 5% of the diet were fed to Fischer 344 rats and $B6C3F_1$ mice for a lifespan, and the only effect noted a significant reduction in body weight at the highest dose at the ten week period in mice which continued throughout the rest of the study, although no biologically significant changes in survival, food consumption or clinical signs were observed. No effects seen in the rats.

OPP Guideline 152.21, Subchronic, 90-day dermal:

Although this guideline is listed in this waiver request, there is no justification given for the request. Discussing the human exposure to this pesticide might give enough information to say there is no or a limited risk from the expected treatment, even if you do not have any study. Just leaving the space blank and "grouping" them is not a valid response.

OPP Guideline 152.22, Subchronic, 90-day inhalation:

- up to 30 mg/m^3 of various forms of amorphous silica (silicon dioxide) including powdered quartz, tested by inhalation exposure to rats, 6 hr/d, 5 d/wk for 13 wks. Treatment with all caused lung lesions, the amorphous silica mostly reversible, but quartz, the most severe with silicotic nodules and one squamous cell carcinoma.
- 10 mg/m^3 of 3 calcium silicate products for a year in an inhalation study are "harmless" to the male Wistar rat

OPP Guideline 152.23, Teratogenicity:

- no teratogenticity studies on sodium metasilicate are available
- a Dutch-belted rabbit study on calcium silicate at doses up to 1600 mg/kg from gestation days 6 through 18 had no effect on nidation, maternal or fetal survival or the incidence of fetal soft tissue or skeletal findings

- a ICR-JCL mouse developmental toxicity study with magnesium aluminum silicate on gestation days 7 to 12 at up to 6,000 mg/kg/d had only incidence of skeletal anomalies greater in treated fetuses, but no skeletal malformations. As aluminum is a known developmental toxicant, it is surmised by the registrant that was the cause of the problems.
- sodium silicate ("soluble silica" expressed as silicon dioxide) in Sprague-Dawley albino rats at doses up to 1200 ppm, indicated a decrease in numbers of offspring born alive and the number alive at weaning
- 0.08 mM/kg sodium silicate by intratesticular injection to rats and mice did not induce any morphological changes

Although the registrant has provided a great number of studies to support the request for a waiver, much of it is not useful. Many of the studies are another form of silicate with little information relating the compounds. In some cases there is an explanation as to why the reader shouldn't worry about the results, as the sodium metasilicate is different in some respect from the silicon compound being tested, but in that case, the study is not valid to provide the information required.

For instance, in the developmental toxicity group, the registrant found no sodium metasilicate teratology study to provide, but one for calcium silicate (no effect), one for magnesium aluminum silicate (skeletal anomalies), and a reproductive study for sodium silicate (reduced live offspring and reduced offspring alive at weaning). Equating these studies as "sufficient information" indicates the registrant wishes EPA to make a decision on the studies provided. With two of these studies indicating effects which might reduce the chance of getting an exemption from the requirement of a tolerance, it would probably be a lot less costly to do the study.

CONFIDENTIAL APPENDIX FOR TRIAD

DATA EVALUATION RECORD

EPA Secondary Reviewer: Carol E. Frazer, Ph.D.

STUDY TYPE:	Product Identity and Composition (OPPTS 830.1550) Description of Beginning Materials (OPPTS 830.1600) Description of Formulation Process (OPPTS 830.1650) Discussion of Formation of Impurities (OPPTS 830.1670) Preliminary Analysis (OPPTS 830.1700) Certified Limits (OPPTS 830.1750) Enforcement Analytical Method (OPPTS 830.1800) Physical and Chemical Characteristics (OPPTS 830.6302-830.7950)
MRID NO:	46050901
DP BARCODE NO:	DP301227
CASE NO:	Not reported
SUBMISSION NO:	Not reported
TEST MATERIAL:	Triad (EPA Reg No. 69493-R; 2.41% by weight sodium metasilicate, a.i.)
PROJECT NO:	2003-1
SPONSOR:	Environmentally Safe Systems, Inc., Solvang, CA
TESTING FACILITY:	ChemReg International, LLC., Lake Ridge, VA
TITLE OF REPORT:	Triad Pesticide - Product Identity, Composition, and Analysis
AUTHORS:	Robert G. Butz, Ph.D.
STUDY COMPLETED:	37818
GOOD LABORATORY PRACTICE:	Not GLP Compliant; discussion and presentation of information

CONCLUSION:

Triad Pesticide is an EP used as an insecticide and fungicide for a number of food crops and roses. The active ingredient is 2.41% by weight sodium metasilicate. The inerts are [redacted]. All ingredients are exempt from a tolerance. The beginning materials used to produce the product are adequately addressed. The manufacturing process of Triad Pesticide is a batch process performed by blending the active and inert ingredients and results in no chemical reactions or formation of new impurities. The impurities in Triad are the carryover impurities from the active ingredient sodium metasilicate. Preliminary analysis was not conducted, but a certificate of analysis for anhydrous metasilicate and a test report for sodium silicate are provided. Five certificates of analysis need to be submitted for the active ingredient from the supplier on the CSF. The upper and lower certified limits for all ingredients are within guidelines proposed in OPPTS 830.1750, except the lower certified limit for the active ingredient is slightly wider (-6% vs -5%). No explanation was given. Details of the ion chromatography method to determine silicon dioxide in detergent are included, but no references are made in the description to the product Triad. The physical/chemical properties of Triad were adequately addressed in MRID 45552402 with the exception of oxidation/reduction characteristics, explodability, and one year storage stability and corrosion characteristics.

CLASSIFICATION: **UNACCEPTABLE**, but upgradable if the registrant provides: 1) a clarification of the product content of [redacted] on the CSF and in the study report, 2) five certificates of analysis for sodium metasilicate from the supplier listed on the CSF, 3) an explanation of the wider lower certified limit of the active ingredient, 4) the enforcement analytical method specific for Triad, and 5) a one year storage stability and corrosion characteristics study. In addition, oxidation/reduction characteristics and explodability need to be addressed

CONTAINS CONFIDENTIAL BUSINESS INFORMATION

Test Material: Triad (2.41% by weight sodium metasilicate, a.i.)

I. **PRODUCT IDENTITY AND COMPOSITION:** Triad Pesticide (EPA Reg. No. 69493-R) is an end-use product (EP) used as an insecticide and fungicide for almonds, apples, apricots, broccoli, citrus, head lettuce, wine grapes, nectarines, peaches, plums, and roses. The active ingredient is 2.41% by weight sodium metasilicate [CAS No. 6834-92-0, PC code 072604, 40 CFR 180.2(a), 40 CFR 180.1001©)]. The inerts are [redacted] The product labels (master label and sub-label - wine grapes) agreed with the CSF.

Deficiencies: None

II. **DESCRIPTION OF BEGINNING MATERIALS:** The beginning materials used to produce the product are listed on p. 6 of appendix in MRID 46053901 as [redacted]

Deficiencies: The CSF/text in MRID 46050901 needs to be adjusted to reflect the content of [redacted]

III. **DESCRIPTION OF PRODUCTION PROCESS:** The manufacturing process of Triad Pesticide is a batch process performed by blending the active and inert ingredients.

The formation of Triad Pesticide is briefly reported. [redacted]

The CSF indicates that [redacted]

Deficiencies: None

IV. **DISCUSSION OF FORMATION OF IMPURITIES:** Triad Pesticide is a solution of anhydrous sodium metasilicate (S-25 grade) in [redacted]. No chemical reactions occur and no new impurities are formed in the manufacturing process. No impurities are introduced from equipment used to produce the product. The impurities in Triad are the carryover impurities from the 2.41% active ingredient sodium metasilicate (95 to 99.5% pure). The major impurities in sodium metasilicate are [redacted]

Deficiencies: None

V. **PRELIMINARY ANALYSIS:** Preliminary analysis was not conducted, but a certificate of analysis for anhydrous sodium metasilicate from OxyChem and a test report for sodium silicate from [redacted], which is a different but related chemical, are provided.

Deficiencies: Five certificates of analysis for sodium metasilicate from the supplier [redacted] listed on the CSF are needed.

VI. **CERTIFIED LIMITS:** Table 1 lists the nominal concentrations and the upper and lower limits for the ingredients as given on the CSF. The lower and upper certified limits of the active ingredient are 2.27% and 2.48% by weight, respectively. The upper certified limit is within guidelines proposed in OPPTS 830.1750, but the lower certified limit is slightly wider (-6% vs -5%). The upper and lower certified limits for the inerts are within guidelines proposed in OPPTS 830.1750.

Deficiencies: The lower certified limit for sodium metasilicate is slightly wider (-6% vs -5%).

Table 1. Nominal concentrations and the upper and lower limits for the ingredients			
Ingredients	**Nominal**	**Upper Limit**	**Lower Limit**
Active ingredient			
Sodium metasilicate	2.41%	2.48%	2.27%
Inert ingredients			
[redacted]			
Total	100.00%		

VII. **ENFORCEMENT ANALYTICAL METHOD:** The study report indicates that "determination of silicon dioxide in detergent formulations by ion chromatography" is used to verify certified limits of the active ingredient. No specific reference is made as to whether the method is effective for the product Triad when used on raw agricultural commodities.

Deficiencies: Method provided was reported to determine silicon dioxide in detergent formulations. No specific reference is made to the product Triad.

VIII. PHYSICAL AND CHEMICAL CHARACTERISTICS:

The physical/chemical properties of Triad were not addressed in MRID 46050901, but in MRID 45552402 (previously reviewed by ORNL, BPPD Work Assignment No. 134) with the exception of oxidation/reduction characteristics, explodability, dielectric breakdown voltage, and one year storage stability and corrosion characteristics study. The methods were not reported for any characteristics.

Deficiencies: Methods are not provided for any characteristics in the study (MRID 45552402). Oxidation/reduction characteristics, explodability, dielectric breakdown voltage, and a one year storage stability need to be addressed. A better explanation for the results of the corrosion characteristics test is needed.

Table 1. Physical and chemical properties of Triad

Parameters	Results
Color	Brown
Physical State	Liquid
Odor	Mild organic
Melting Point	Not applicable
Boiling Point	Not applicable
Density/Specific Gravity	1.08 g/mL
Solubility	Not applicable
Vapor Pressure	Not applicable
pH	12.3
Stability	Not applicable
Flammability	Non-flammable
Storage Stability	Stable for greater than one year, based on no chemical change during blending and qualitative results from field trials over time
Viscosity	65/75 SUS @100°F 10.8/13.6 Centistoke@40°C
Miscibility	Readily miscible in water with agitation
Corrosion Characteristics	Non-corrosive