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

MAY 12 2000

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

BRIEFING MEMORANDUM

SUBJECT: **18 Month Time-Limited Registration**
"AlphaSan RC 5000" (EPA File Symbol 11631-E)
New Active Ingredient -- Silver Sodium Hydrogen Zirconium Phosphate

FROM: Frank Sanders, Division Director
Antimicrobials Division

TO: Marcia Mulkey, Director
Office of Pesticide Programs

The purpose of this memorandum is to recommend your concurrence on the 18 month, time-limited registration for the End-Use product **"AlphaSan RC 5000"**, containing the new active ingredient complex **"Silver Sodium Hydrogen Zirconium Phosphate".** Based on our review of the application, I have concluded that this new chemical can be registered without causing undue adverse effects to man and the environment.

INTRODUCTION

In June 1998, Milliken Chemical of Spartanburg, S.C. submitted an application for registering this new active ingredient. The chemical is intended to suppress the growth of bacteria, algae, fungi, mold and mildew in **non-food contact** treated articles. It is used by adding it to various plastics, fibers, coatings, adhesives, sealants and building materials that go into the manufacture of a wide variety of treated articles. Silver is the main antimicrobial component, and it makes up 3.8 % of the 99.9% complex by weight. Even though silver is the main antimicrobial component, we are considering the entire silver sodium hydrogen zirconium phosphate complex (at 3.8% silver), as the new active ingredient.

Existing Silver Data Base Not Applicable --The Agency found that the existing silver data base is not applicable for registering this chemical because of the unique structure and properties of the silver sodium hydrogen zirconium phosphate complex. Therefore, in support of using this new active ingredient, Milliken Chemical submitted a full set of product chemistry studies, a full set of six acute toxicology studies, a 90-day oral feeding study, two fish studies (only one required), a daphnia study, and a mutagenicity battery.

A slight variant of this new chemical, which differs only in that it contains 10% silver, was used to conduct the submitted developmental toxicology and avian studies, as well as for a

solubility versus pH study (to satisfy the hydrolysis data requirement). Data generated using the 10% silver variant is determined to be applicable for AlphaSan RC 5000 because silver is the more toxic component of the complex. AlphaSan RC 5000, which contains 3.8 % silver, is therefore not expected to be any more toxic than the variant complex containing10% silver.

Reasons For 18 Month Time Limited Registration--With the exception of the fish, daphnia, acute oral and dermal studies, all other data are acceptable. There will be an 18 month time-limited restriction on this registration to allow Milliken Chemical time to submit acceptable fish and daphnia studies. These studies, along with the accepted avian oral study, are required only to generate information for the "Environmental Hazards" label warnings about the potential hazards from transport, use, storage, or spill of the product. During the interim, the most stringent and comprehensive "Environmental Hazards" labeling statements will be placed on the label. These statements can be relaxed later if the outstanding data warrants it.

The acute oral and dermal studies have been reviewed and are sufficient to characterize the chemical. The Agency however requires submission of individual animal data, for these two studies, only to verify clinical observations and necropsy statements made in the original reports. In fact, these missing animal data were submitted May 2, 2000 and are under review. If found acceptable, the acute oral and dermal studies would be upgraded.

Our Conclusion -- It is our opinion that the data submitted to the Agency for this chemical, and found to be acceptable, are adequate to support the registration of the this end use product. Registration for this product can proceed without the immediate need for the fish and daphnia data, because the most stringent "Environmental Hazards" statements will be placed on the label.

BACKGROUND

This new end-use antimicrobial powder, is intended to be added to various plastics, fibers, coatings, adhesives, sealants and building materials that go into the manufacture of a wide variety of **non-food contact** "Treated Articles". The active ingredient is intended to suppress the growth of bacteria, algae, fungi, mold and mildew in the treated article. Treated articles with pesticide claims that extend beyond protection of the article will need to be registered. The product is intended to be used up to 2% by weight, in the finished treated article.

This new active ingredient is a synthetic inorganic polymer. Under a scanning electron microscope, it resembles cube shaped crystals, with an average particle size of about one micron (about the size of an average bacterium). It consists of a three dimensional, repeating framework of sodium hydrogen zirconium phosphate, with many equally spaced cavities containing silver. Silver provides the main antimicrobial properties, while the framework matrix acts to distribute silver evenly (without clumping or pooling), throughout substances to which the product is added.

Typical **non-food contact** finished treated articles that are intended to incorporate this new active ingredient include (this is a partial listing to show the wide scope of intended uses): automobile parts, shower curtains, mats, tape, non-food packaging, waste containers, gaskets, brush bristles and handles, sponges, mops, vacuum cleaner bags, indoor and outdoor furniture,

umbrellas, coats, aprons, socks, inner linings for jackets, gloves, helmets, tubing, wire insulation, counter tops, fabrics, conveyor belts, footwear, sports equipment, mattress cover pads and filling, pillow covers, curtains, draperies, carpets, mops, towels, bags, cushion pads, sleeping bags, auto parts, ropes, tents, awnings, toilets, sinks, counter tops, flooring, floor coverings, tiles, house siding, footwear including boots/sporting equipment, ceramics, roof shingles, stucco, furniture, cat litter, drainage and sewerage pipe, etc.

The following boldfaced restriction statement will be required on the front page of the proposed label, as well as in five other locations, **"This product is not approved for any food contact or human drinking water contact uses".**

TYPES AND METHODS OF APPLICATIONS

This end use product is intended to be added to the treated article manufacturing process as a powder or from a variety of liquid or solid dispersions. It will be added into, or applied to the surface of polymers (eg., plastics, etc.) and other materials, which will then be incorporated into finished treated articles at a maximum of 2%, by weight.

SCIENTIFIC FINDINGS

PRODUCT CHEMISTRY

All product chemistry data required by Guideline Series 61, 62, and 63 have been submitted, and are acceptable.

ECOLOGICAL EFFECTS

Avian oral study – Using the 10% silver containing variant on bobwhite quail, the acute oral LD50 is greater than 2000 ppm. The study is acceptable.

Fish/Daphnia Studies -- The submitted rainbow trout, bluegill sunfish, and daphnia studies are rated invalid due mainly to the unacceptable variations in the concentration of this low solubility product that the organisms experienced. However, these data, along with the accepted avian oral data, are required only to generate information for the "Environmental Hazards" label warnings about the potential hazards from transport, use, storage, or spill of the product. Registration for this product can proceed without the immediate need for these data because the most stringent "Environmental Hazards" statements will be placed on the label. During the time-limited registration, both submission and acceptance of these invalid studies within 1.5 years will be required. The "Environmental Hazards" labeling can be relaxed later if the data warrants it.

Environmental Fate – This study is acceptable. A hydrolysis study is the only environmental fate data requirement. However, because of the special nature of this chemical, a study determining water solubility as a function of pH, is accepted in lieu of hydrolysis. This study showed that silver solubility decreases as pH increases. For example, at pH 5, the maximum solubility was 30 ppm, and at pH 9 it was 2.7 ppm. The study also showed that the metals zirconium and silver do have a tendency to leach out from the active ingredient, although zirconium leaches into the aqueous system far less in quantity than does silver in acidic to neutral

conditions.

HUMAN HEALTH EFFECTS

Residue Chemistry – There are no food contact uses intended for this.

Acute Toxicity– Four of the six acute studies are acceptable, with the exception that Milliken Chemicals must submit (now submitted and under review) individual animal data for the acute oral and acute dermal studies. These data are needed so that EPA can verify clinical observations and necropsy statements made in the reports. Until then, the oral and dermal studies are considered upgradable. The chemical is relatively non-toxic with all categories being a IV, except for one category III.

		Toxicity Category
Acute Oral	LD_{50} (rat) both sexes >5000 mg/kg	IV
Acute Dermal	LD_{50} (rat) both sexes > 2000 mg/kg	IV
Acute Inhalation	LC50 (rat) both sexes >5.18 mg/L	IV
Primary Eye Irritation	Rabbits, slight irritant	III
Primary Skin Irritation	Not a dermal irritant	IV
Dermal Sensitization	Not a dermal sensitizer	N/A

Subchronic Toxicity – This study is acceptable. Using this 3.8% silver containing product in a 90-day oral feeding study in rats, the systemic LOAEL was greater than 1000mg/kg/day, and the systemic NOAEL was greater than, or equal to1000 mg/kg/day. No differences in macroscopic or microscopic findings, that could be attributed to treatment, were noted in the high-dose treatment groups, when compared to the corresponding controls.

Developmental Toxicity – This study is acceptable. Using the variant containing 10% silver, the developmental NOAEL was greater than, or equal to1000 mg/kg/day, and the LOAEL was greater than 1000 mg/kg/day. The maternal NOAEL was greater than, or equal to 1000 mg/kg/day, and the maternal LOAEL was greater than 1000 mg/kg/day. There were no treatment related deaths, and no clinical signs of toxicity. Maternal or developmental effects were not observed. Body weight gain, food consumption, and reproductive parameters were not affected by treatment. External, visceral, and skeletal fetal examinations revealed no treatment-related effects.

Chronic Toxicity– EPA determined that for non-food water uses, no chronic data are required.

Mutagenicity -- These three studies are acceptable.

In the reverse gene mutation assay in bacteria, there was no evidence of an increase in

mutant colonies over background in the presence or absence of S9 activation.

In the mammalian cell gene mutation assay using mouse lymphoma cells, there was no evidence of a biologically relevant increase in induced mutant colonies over background.

In the mouse none marrow micro nucleus assay, there was no significant increase in the frequency of micro nucleated polychromatic erythrocytes in bone marrow after any treatment time.

HUMAN HEALTH RISK ASSESSMENT

The available toxicology data for this product, including a developmental study using the variant containing 10% silver, show no systemic toxicity at doses up to and including a limit dose (ie., 1000 mg/kg/day) in both the 90 day oral toxicity study, and the developmental study. Mutagenicity data shows a negative response in the submitted studies, and acute toxicity studies are in the III and IV range.

The Agency is not concerned with setting endpoints for risk assessment when systemic effect levels in experimental studies (ie., subchronic oral, developmental) are above the limit dose, as this is an indication of the relative low-toxicity of the chemical. Occupational exposure exists, but the post-application exposure will be minimal due to the products incorporation into treated articles. Because the Agency is not concerned with setting end points for risk assessment, no further occupational or residential risk assessment for this chemical is required at this time.

FQPA RISK ASSESSMENT

There are no current food or food-contact uses at this time for "Silver Sodium Hydrogen Zirconium Phosphate". Thus, no FQPA risk assessment is needed at this time.

I recommend that "AlphaSan RC 5000", containing the new active ingredient **"Silver Sodium Hydrogen Zirconium Phosphate"**, which contains 3.8% silver by weight, receive an 18 month, time-limited registration. Continuing the registration past 18 months is contingent on finding the recently submitted individual animal data for the acute oral and dermal studies acceptable, and on Milliken Chemical submitting one acceptable rainbow trout and daphnia study. No tolerances/exemptions are required because this is a non-food contact registration action.

CONCUR: Susan B. Hazen (Signature) 5/19/2000 (Date)

NON-CONCUR: _____ (Signature) _____ (Date)

PESTICIDE FACT SHEET

Name of Chemical: **"Silver Sodium Hydrogen Zirconium Phosphate"**
Reason of Issuance: **18 Month Time-Limited Registration, New Active Ingredient**
Date Issued:

DESCRIPTION OF CHEMICAL

This new active ingredient is a synthetic inorganic polymer. Under a scanning electron microscopic, it resembles cube shaped crystals, with an average particle size of about one micron (about the size of an average bacterium). It consists of a three dimensional, repeating framework of sodium hydrogen zirconium phosphate, with many equally spaced cavities containing silver. Silver (at 3.8% by weight) provides the main antimicrobial properties, while the framework matrix acts to distribute silver evenly (without clumping or pooling), throughout substances to which the product is added. Even though silver is the main antimicrobial component, we are considering the entire silver sodium hydrogen zirconium phosphate 99.9% complex (with 3.8% silver), as the new active ingredient.

Generic Name:	"Silver Sodium Hydrogen Zirconium Phosphate"
Common Name:	None
Trade Name(s):	None
Common End Use Product Name:	"Antimicrobial AlphaSan RC 5000"
Chemical Abstract Number (CAS):	None, registrant will apply for a number
EPA Chemical Code:	072560
Year of Initial Registration:	2000
Pesticide Type:	Antimicrobial, Indoor; for incorporation into treated articles
Chemical Family:	Synthetic inorganic polymer
U.S. Producer:	Produced in Japan by Toagosei Company Limited for the U.S. Registrant, Milliken Chemical, Spartanburg SC

USE PATTERNS AND FORMULATION

This End-Use antimicrobial chemical is intended to be added as a powder, liquid, or solid dispersion into, or on the surface of various plastics, fibers, coatings, adhesives, sealants and building materials. These materials then are used to manufacture a wide variety of **non-food contact,** finished treated articles. The product can be added up to 2% by weight in finished

treated articles. The active ingredient is used to suppress the growth of bacteria, algae, fungi, mold and mildew in the treated article. Treated articles with pesticide claims that extend beyond protection of the article, will of course need to be registered.

Typical **non-food** contact finished treated articles that are intended to incorporate this new active ingredient include (this is a partial listing to show wide scope of intended uses): automobile parts, shower curtains, mats, tape, non-food packaging, waste containers, gaskets, brush bristles and handles, sponges, mops, vacuum cleaner bags, indoor and outdoor furniture, umbrellas, coats, aprons, socks, inner linings for jackets, gloves, helmets, tubing, wire insulation, counter tops, fabrics, conveyor belts, footwear, sports equipment, mattress cover pads and filling, pillow covers, curtains, draperies, carpets, mops, towels, bags, cushion pads, sleeping bags, auto parts, ropes, tents, awnings, toilets, sinks, counter tops, flooring, floor coverings, tiles, house siding, footwear including boots/sporting equipment, ceramics, roof shingles, stucco, furniture, cat litter, drainage and sewerage pipe, etc.

The following boldfaced restriction statement will be required on the front page of the proposed label, as well as in five other locations, **"This product is not approved for any food contact or human drinking water contact uses".**

SCIENCE FINDINGS

Even though silver is the main active species, the Agency found that the existing silver data base is not directly applicable because of the unique structure and properties of this new inorganic polymer. In support of using this active ingredient containing 3.8% silver, Milliken Chemical submitted a full set of product chemistry studies, a full set of acute toxicology studies, a 90-day oral feeding study, two fish studies (only one required), a daphnia study, and a mutagenicity battery of studies.

A manufacturing variant of this new chemical, which differs only in that it contains 10% silver, was used to conduct the submitted developmental toxicology and avian studies, as well as for a solubility versus pH study (to satisfy the hydrolysis data requirement), and for residue chemistry via a food packaging migration study. Data generated using the 10% silver variant are determined to be applicable for variants which only differ by containing less silver. This is because silver is the more toxic component of the complex. Variants containing less than10% silver are therefore not expected to be more toxic than the10% silver variant itself.

Physical and Chemical Characteristics

The submitted product chemistry data satisfies all product chemistry guidelines required by Guideline Series 830.

Color:	White
Physical State:	Solid; fluffy fine powder

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Odor:	Odorless
Melting Point:	>1300 Degrees C
Boiling Point:	N/A, based on melting point it's a solid at >1300 C
Density; Bulk Density	3.0 g/cu.cm (packed); 0.2 g/ cu cm (unpacked fluff)
Solubility:	Not directly measurable. In terms of silver ions, solubility ranges from 30 ppm at pH 5, to 2.7 ppm at pH 9.
Vapor Pressure:	Not applicable
Dissociation Constant:	$<1 \times 10^{-13}$
Water Partition Coefficient:	Not applicable
pH:	Not applicable
Stability:	Stability shown over a 22 month study
Oxidizing or Reducing Action:	Not applicable based on its chemistry
Flammability:	Not Flammable
Explodability:	Not Explosive
Viscosity:	Not Applicable
Miscibility:	Not Applicable
Corrosion Characteristics:	Not corrosive based on its chemistry
Dielectric Breakdown Voltage:	Not Applicable

Ecological Effects

Avian oral study – This study is acceptable. Using the 10% silver containing variant on bobwhite quail, the acute oral LD50 is greater than 2000 ppm.

Fish/Daphnia Studies -- The submitted rainbow trout, bluegill sunfish, and daphnia studies were rated invalid due mainly to the unacceptable variations in the concentration of this low solubility product that the organisms experienced. However, these data, along with the accepted avian oral study, are required only to generate the "Environmental Hazards" label

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warnings about the potential hazards from transport, use, storage, or spill of the product. During the 18 month time-limited registration, both submission and acceptance of these data will be required. In the interim, the most stringent and comprehensive "Environmental Hazards" labeling statements will be placed on the label. These statements can be relaxed later only if the outstanding fish/daphnia data shows it is warranted.

Environmental Fate --This study is acceptable. A hydrolysis study is the only environmental fate data requirement. However, because of the special nature of this chemical, a study determining water solubility as a function of pH, is accepted in lieu of hydrolysis. This study showed that silver solubility decreases as pH increases. For example, at pH 5, the maximum solubility was 30 ppm, and at pH 9 it was 2.7 ppm. The study also showed that the metals zirconium and silver do have a tendency to leach out from the active ingredient, although zirconium leaches into the aqueous system far less in quantity than does silver in acidic to neutral conditions.

HUMAN HEALTH EFFECTS

Residue Chemistry

There are no food contact uses intended for this product registration, therefore, no residue data are needed.

End-Use Acute Toxicology Profile

Four of the six acute studies are acceptable, with the exception that Milliken Chemicals must submit individual animal data for the acute oral and acute dermal studies, so that EPA can verify clinical observations and necropsy statements made in the reports. Milliken Chemical submitted this missing information on May 2, 2000 and it is now under review. The oral and dermal studies are currently considered supplemental but upgradable. They are, however, sufficient to accurately characterize the toxicity of the chemical. As shown, the chemical is relatively non-toxic with all categories being a IV, except for one category III.

		Toxicity Category
Acute Oral	LD_{50} (rat) both sexes >5000 mg/kg	IV
Acute Dermal	LD_{50} (rat) both sexes > 2000 mg/kg	IV
Acute Inhalation	LC50 (rat) both sexes >5.18 mg/L	IV
Primary Eye Irritation	Rabbits, slight irritant	III
Primary Skin Irritation	Not a dermal irritant	IV
Dermal Sensitization	Not a dermal sensitizer	N/A

Subchronic Toxicity

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90 Day Oral Toxicity In Rats – This study is acceptable. Using this 3.8% silver containing product, the systemic LOAEL was greater than 1000 mg/kg/day, and the systemic NOAEL was greater than, or equal to1000 mg/kg/day. No differences in macroscopic or microscopic findings, that could be attributed to treatment, were noted in the high-dose treatment groups, when compared to the corresponding controls.

Developmental Toxicity

This study is acceptable. Using the variant containing 10% silver, the developmental NOAEL was greater than, or equal to1000 mg/kg/day, and the LOAEL was greater than 1000 mg/kg/day. The maternal NOAEL was greater than, or equal to 1000 mg/kg/day, and the maternal LOAEL was greater than 1000 mg/kg/day. There were no treatment related deaths, and no clinical signs of toxicity. Maternal or developmental effects were not observed. Body weight gain, food consumption, and reproductive parameters were not affected by treatment. External, visceral, and skeletal fetal examinations revealed no treatment-related effects.

Chronic Toxicity

EPA determined that for this non-food use application, no chronic data are required.

Mutagenicity

The following three submitted studies are acceptable.

In the reverse gene mutation assay in bacteria, there was no evidence of an increase in mutant colonies over background in the presence or absence of S9 activation.

In the mammalian cell gene mutation assay using mouse lymphoma cells, there was no evidence of a biologically relevant increase in induced mutant colonies over background.

In the mouse none marrow micronucleus assay, there was no significant increase in the frequency of micro nucleated polychromatic erythrocytes in bone marrow after any treatment time.

HUMAN HEALTH RISK ASSESSMENT

The available toxicology data for this product, including a developmental study using the variant containing 10 % silver, indicate no systemic toxicity at doses up to and including a limit dose (ie., 1000 mg/kg/day) in both the 90 day oral toxicity study, and the developmental study. Mutagenicity data shows a negative response in the submitted studies, and acute toxicity studies are in the III and IV range.

The Agency is not concerned with setting endpoints for risk assessment when systemic effect levels in experimental studies (ie., subchronic oral, developmental) are above the limit dose, as this is an indication of the relative low toxicity of the chemical. Occupational exposure exists, but the post-application exposure will be minimal due to the products incorporation into treated articles. Because the Agency is not concerned with setting end points for risk assessment,

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no further occupational/residential risk assessment for this chemical is required at this time.

FQPA RISK ASSESSMENT

There are no current food or food-contact uses at this time for "Silver Sodium Hydrogen Zirconium Phosphate". Thus, no FQPA risk assessment is needed at this time.

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