
# Reregistration Eligibility Decision (RED) for Azadioxabicyclooctane

## September 30, 2005

United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7510C)

EPA 739-R-05-010
September 2005

# Reregistration Eligibility Decision for Azadioxabicyclooctane

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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

**CERTIFIED MAIL**

Dear Registrant:

This is to inform you that the Environmental Protection Agency (hereafter referred to as EPA or the Agency) has completed its review of the available data and public comments received related to the preliminary risk assessments for the antimicrobial preservative referred to as azadioxabicyclooctane. The enclosed Reregistration Eligibility Decision (RED) document was approved on September 30, 2005. Public comments and additional data received were considered in this decision.

Based on its review, EPA is now publishing its Reregistration Eligibility Decision (RED) and risk management decision for azadioxabicyclooctane and its associated human health and environmental risks. A Notice of Availability will be published in the *Federal Register* announcing the publication of the RED.

The RED and supporting risk assessments for azadioxabicyclooctane are available to the public in EPA's Pesticide Docket **OPP-2005-0186** at: http://www.epa.gov/edockets.

The azadioxabicyclooctane RED was developed through EPA's public participation process, published in the Federal Register on July 20, 2005, which provides opportunities for public involvement in the Agency's pesticide reassessment and reregistration programs. Developed in partnership with USDA and with input from EPA's advisory committees and others, the public participation process encourages robust public involvement starting early and continuing throughout the pesticide risk assessment and risk mitigation decision making process. The public participation process encompasses full, modified, and streamlined versions that enable the Agency to tailor the level of review to the level of refinement of the risk assessments, as well as to the amount of use, risk, public concern, and complexity associated with each pesticide. Using the public participation process, EPA is attaining its strong commitment to both involve the public and meet statutory deadlines.

Please note that the azadioxabicyclooctane risk assessment and the attached RED document concern only this particular pesticide. This RED presents the Agency's conclusions on the dietary, drinking water, occupational and ecological risks posed by exposure to azadioxabicyclooctane alone. This document also contains both generic and product-specific data that the Agency intends to require in Data Call-Ins (DCIs). Note that DCIs, with all pertinent instructions, will be sent to registrants at a later date. Additionally, for product-specific

DCIs, the first set of required responses will be due 90 days from the receipt of the DCI letter. The second set of required responses will be due eight months from the receipt of the DCI letter.

As part of the RED, the Agency has determined that azadioxabicyclooctane will be eligible for reregistration provided that all the conditions identified in this document are satisfied, including implementation of the risk mitigation measures outlined in Section IV of the document. Sections IV and V of this RED document describe labeling amendments for end-use products and data requirements necessary to implement these mitigation measures. Instructions for registrants on submitting the revised labeling can be found in the set of instructions for product-specific data that accompanies this document.

Should a registrant fail to implement any of the risk mitigation measures outlined in this document, the Agency will continue to have concerns about the risks posed by azadioxabicyclooctane. Where the Agency has identified any unreasonable adverse effect to human health and the environment, the Agency may at any time initiate appropriate regulatory action to address this concern. At that time, any affected person(s) may challenge the Agency's action.

If you have questions on this document or the label changes necessary for reregistration, please contact the Chemical Review Manager, Tom Luminello, at (703) 308-8075. For questions about product reregistration and/or the Product Specific DCI that accompanies this document, please contact Marshall Swindell at (703) 308-6341.

Sincerely,

Frank T. Sanders
Director,
Antimicrobials Division

**REREGISTRATION ELIGIBILITY**
**DECISION**
**for**
**AZADIOXABICYCLOOCTANE**
**List C**
**CASE 3023**

Approved By:

Frank T. Sanders
Director,
Antimicrobials Division
Date

Attachment

**Table of Contents**

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## GLOSSARY OF TERMS AND ABBREVIATIONS

| | |
|---|---|
| a.i. | Active Ingredient |
| aPAD | Acute Population Adjusted Dose |
| ADTC | Antimicrobials Division Toxicology Endpoint Selection Committee |
| APHIS | Animal and Plant Health Inspection Service |
| ARTF | Agricultural Re-entry Task Force |
| BCF | Bioconcentration Factor |
| CDC | Centers for Disease Control |
| CDPR | California Department of Pesticide Regulation |
| CFR | Code of Federal Regulations |
| ChEI | Cholinesterase Inhibition |
| CMBS | Carbamate Market Basket Survey |
| cPAD | Chronic Population Adjusted Dose |
| CSFII | USDA Continuing Surveys for Food Intake by Individuals |
| CWS | Community Water System |
| DCI | Data Call-In |
| DEEM | Dietary Exposure Evaluation Model |
| DL | Double layer clothing {i.e., coveralls over SL} |
| DWLOC | Drinking Water Level of Comparison |
| EC | Emulsifiable Concentrate Formulation |
| EDSP | Endocrine Disruptor Screening Program |
| EDSTAC | Endocrine Disruptor Screening and Testing Advisory Committee |
| EEC | Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem. |
| EP | End-Use Product |
| EPA | U.S. Environmental Protection Agency |
| EXAMS | Tier II Surface Water Computer Model |
| FDA | Food and Drug Administration |
| FFDCA | Federal Food, Drug, and Cosmetic Act |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FOB | Functional Observation Battery |
| FQPA | Food Quality Protection Act |
| FR | Federal Register |
| GL | With gloves |
| GPS | Global Positioning System |
| HIARC | Hazard Identification Assessment Review Committee |
| IDFS | Incident Data System |
| IGR | Insect Growth Regulator |
| IPM | Integrated Pest Management |
| RED | Reregistration Eligibility Decision |
| LADD | Lifetime Average Daily Dose |
| $LC_{50}$ | Median Lethal Concentration. Statistically derived concentration of a substance expected to cause death in 50% of test animals, usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm. |
| LCO | Lawn Care Operator |

| | |
|---|---|
| $LD_{50}$ | Median Lethal Dose. Statistically derived single dose causing death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation), expressed as a weight of substance per unit weight of animal, e.g., mg/kg. |
| LOAEC | Lowest Observed Adverse Effect Concentration |
| LOAEL | Lowest Observed Adverse Effect Level |
| LOC | Level of Concern |
| LOEC | Lowest Observed Effect Concentration |
| mg/kg/day | Milligram Per Kilogram Per Day |
| MOE | Margin of Exposure |
| MP | Manufacturing-Use Product |
| MRID | Master Record Identification (number). EPA's system of recording and tracking studies submitted. |
| MRL | Maximum Residue Level |
| N/A | Not Applicable |
| NASS | National Agricultural Statistical Service |
| NAWQA | USGS National Water Quality Assessment |
| NG | No Gloves |
| NMFS | National Marine Fisheries Service |
| NOAEC | No Observed Adverse Effect Concentration |
| NOAEL | No Observed Adverse Effect Level |
| NPIC | National Pesticide Information Center |
| NR | No respirator |
| OPP | EPA Office of Pesticide Programs |
| ORETF | Outdoor Residential Exposure Task Force |
| PAD | Population Adjusted Dose |
| PCA | Percent Crop Area |
| PDCI | Product Specific Data Call-In |
| PDP | USDA Pesticide Data Program |
| PF10 | Protections factor 10 respirator |
| PF5 | Protection factor 5 respirator |
| PHED | Pesticide Handler's Exposure Data |
| PHI | Pre-harvest Interval |
| ppb | Parts Per Billion |
| PPE | Personal Protective Equipment |
| PRZM | Pesticide Root Zone Model |
| RBC | Red Blood Cell |
| RED | Reregistration Eligibility Decision |
| REI | Restricted Entry Interval |
| RfD | Reference Dose |
| RPA | Reasonable and Prudent Alternatives |
| RPM | Reasonable and Prudent Measures |
| RQ | Risk Quotient |
| RTU | (Ready-to-use) |
| RUP | Restricted Use Pesticide |
| SCI-GROW | Tier I Ground Water Computer Model |
| SF | Safety Factor |
| SL | Single layer clothing |
| SLN | Special Local Need (Registrations Under Section 24C of FIFRA) |

| | |
|---|---|
| STORET | Storage and Retrieval |
| TEP | Typical End-Use Product |
| TGAI | Technical Grade Active Ingredient |
| TRAC | Tolerance Reassessment Advisory Committee |
| TTRS | Transferable Turf Residues |
| UF | Uncertainty Factor |
| USDA | United States Department of Agriculture |
| USFWS | United States Fish and Wildlife Service |
| USGS | United States Geological Survey |
| WPS | Worker Protection Standard |

## EXECUTIVE SUMMARY

The Environmental Protection Agency (hereafter referred to as EPA or the Agency) has completed its review of public comments on the human health and environmental risk assessments for azadioxabicyclooctane and is issuing its risk management decision. The Agency has decided that azadioxabicyclooctane is eligible for reregistration provided all measures outlined in this document are implemented. Azadioxabicyclooctane consists of an equilibrium mixture of three chemicals (**I:** 5-hydroxymethoxymethyl-1-aza-3,7-dioxabicyclo(3,3,0)octane; **II:** 5-hydroxymethyl-1-aza-3,7-dioxabicyclo(3,3,0)octane; **III:** 5-hydroxypoly(methylene-oxy)methyl-1-aza-3,7-dioxabicyclo(3,3,0)octane). These chemicals cannot be divided into components for individual testing and the three of them will be referred to as azadioxabicyclooctane in this Reregistration Eligibilty Decision. This mixture is registered as a preservative for antimicrobial control in the following use sites: oil recovery drilling muds and flooding fluids; industrial adhesives and coatings (natural based and synthetic); latex and polymer emulsions; metalworking cutting fluids; latex paints; paper coatings; caulks and sealants; inks; pigment dispersion and pigment slurry; and textile fiber finishes that are not intended as clothing. Azadioxabicyclooctane has been cleared by the US Food and Drug Administration (US FDA) for use as an antibacterial preservative in paper and paperboard products that are limited to dry food contact only in 21CFR 176.180 as well as a component in paper adhesives in 21CFR 175.105.

### *Overall Risk Summary*

The Agency's human heath risk assessment indicates no risks of concern for dietary or drinking water exposures. Acute and chronic dietary risk estimates are below the Agency's level of concern for the general U.S. population and all population subgroups.

Azadioxabicyclooctane is not likely to contaminate surface and ground waters based on its use patterns. Thus, a drinking water assessment was not conducted.

Residential risks for handlers were calculated for short- and intermediate-term dermal and inhalation exposures. All exposure and risk estimates for residential handler scenarios are below the Agency's level of concern with the exception of the risks associated with application of paint using an airless sprayer at the maximum application rate. Based on the use patterns of azadioxabicyclooctane there are no potential dermal post application exposures to assess. Inhalation post application exposures are expected to be minimal because the paint is dry and the vapor pressure of azadioxabicyclooctane is negligible.

For the occupational handler dermal and inhalation risk assessment, the short- and intermediate- term risks calculated were above target MOEs for all scenarios. Post-application exposure is expected to be minimal based on the use patterns of this chemical with the exception of metal working fluids. Occupational risks from post-application exposure were calculated for long-term dermal and inhalation exposures to machinists resulting from metal working fluid use. Risks of concern were identified for this use pattern at the maximum application rate of 0.3% product by weight of material treated.

The indoor uses of azadioxabicyclooctane are not likely to pose risk to fish, wildlife or plants due to the low likelihood of exposure and the low toxicity of the compound. The offshore oil production use drilling fluid treatment and flooding fluid treatment is considered unlikely to adversely affect aquatic organisms due to the low toxicity and large dilution factor. The Agency assumes that the waste streams occurring from terrestrial oil production are actively managed under local environmental regulations to prevent adverse ecological effects.

***Dietary Risk***

The Agency has conducted a dietary exposure and risk assessment for use of azadioxabicyclooctane as a preservative in paper coatings and paper adhesives each of which may end in indirect food contact scenarios. For both the acute and chronic dietary exposure, the risk is highest for children (12% of the acute PAD and 39.6% chronic PAD). For an adult, the acute and chronic dietary exposures are 5.1% and 17% of the acute and chronic PADs respectively. All dietary exposures calculated are below the Agency's level of concern (100% of aPAD or cPAD) for non-cancer risk. A dietary cancer risk assessment could not be performed as there are no carcinogenicity data for azadioxabicyclooctane.

***Drinking Water Risk***

None of the uses associated with azadioxabicyclooctane are expected to impact either surface or ground water resources. Therefore, no drinking water assessment was performed.

***Residential Handler Risk***

Residential risks for handlers were calculated for short- and intermediate-term dermal and inhalation exposures. All exposure and risk estimates for residential handler scenarios are below the Agency's level of concern with the exception of the risks associated with application of paint using an airless sprayer at the maximum application rate.

***Aggregate Risk***

The aggregate short-term risk assessment is designed to provide estimates of risk likely to result from exposures to the pesticide or pesticide residues in food, water, and from residential (or other non-occupation) pesticide uses. For adults, the aggregate assessment includes dietary (oral) and residential inhalation exposures from painting. An assessment was not conducted for children since there are no residential exposures expected for this subgroup.

Since exposures to residential handlers for the paint scenario are of concern at the highest application rate, short-term aggregate risks are also of concern.

***Occupational Risk***

The short- and intermediate-term exposure scenarios identified for occupational workers are the liquid pour and liquid pump applications of this chemical when it is used as a preservative for the label-specified materials. There are also occupational painter scenarios (which result from the chemical being incorporated as a preservative into paints) that involve the

methods of applications of airless painting and brush painting. **A**ll exposure and risk estimates for occupational handler scenarios are below the Agency's level of concern. Therefore, no risk mitigation measures are required for these handler scenarios.

For azadioaxabicyclootane, exposures are expected to be minimal except for the metal working fluid scenario. Occupational risks from post-application exposure were calculated for long-term dermal and inhalation exposures to machinists resulting from metal working fluid use. Risks of concern were identified for this use pattern at the maximum application rate of 0.3% product by weight of material treated.

***Ecological Risk***

The indoor uses of azadioxabicyclooctane are not likely to pose risk to fish, wildlife or plants due to the low likelihood of exposure and the low toxicity of the compound. Most uses of azadioxabicyclooctane are indoor uses, with little chance of exposure to the environment. The oil production uses do occur outdoors; however, the Agency does not have an available model for estimating exposure from those uses. The risk from offshore oil drilling uses of azadioxabicyclooctane was previously addressed (Agency review July 14, 1983), and the application of 500-2000 ppm drilling fluid treatment or 100-1000 ppm flooding fluid treatment was considered "unlikely to adversely affect aquatic organisms due to the low toxicity and large dilution factor." Discharge of waste streams occurring from terrestrial oil recovery operations would be regulated at the local level in order to prevent undue environmental exposure.

***Regulatory Decision***

The Agency has completed its review and has determined that the data are sufficient to support reregistration of all supported products containing azadioxabicyclooctane. The Agency is issuing this RED for azadioxabicyclooctane, as announced in a Notice of Availability published in the *Federal Register*. This RED document includes guidance and time frames for making any necessary label changes for products containing azadioxabicyclooctane.

***Summary of Mitigation Measures***

The Agency has determined that azadioxabicyclooctane is eligible for reregistration provided the mitigation measures described in this document and the label changes included in Table 13 in Section V of the RED are implemented.

<u>Residential:</u>

To reduce residential exposure, the Agency has determined that the following mitigation and label changes for specific scenarios are appropriate and required for reregistration eligibility:

- Reduce the maximum application rate for paint uses to 0.4% product by weight of material treated.

Occupational:

To reduce post-application exposure, the Agency has determined that the following mitigation and label changes for specific scenarios are appropriate and required for reregistration eligibility:

- Reduce the maximum application rate for paint uses to 0.2% product by weight of material treated.

***Data Requirements***

Confirmatory data is required to complete the reregistration of azadioxabicyclooctane as outlined in Section V of this document. A complete list of data gaps is presented in Appendix B (Table of Generic Data Requirements) as well as in Appendix E (the Generic Data Call-In) at the end of this document.

## I. Introduction

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was amended in 1988 to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984 and amended again by the Pesticide Registration Improvement Act of 2003 to set time frames for the issuance of Reregistration Eligibility Decisions. The amended Act calls for the development and submission of data to support the reregistration of an active ingredient, as well as a review of all submitted data by the U.S. Environmental Protection Agency (EPA or the Agency). Reregistration involves a thorough review of the scientific database underlying a pesticide's registration. The purpose of the Agency's review is to reassess the potential hazards arising from the currently registered uses of the pesticide; to determine the need for additional data on health and environmental effects; and to determine whether or not the pesticide meets the "no unreasonable adverse effects" criteria of FIFRA.

On August 3, 1996, the Food Quality Protection Act of 1996 (FQPA) was signed into law. This Act amends FIFRA to require tolerance reassessment. The Agency has decided that, for those chemicals that have tolerances and are undergoing reregistration, the tolerance reassessment will be initiated through this reregistration process. The Act also requires that by 2006, EPA must review all tolerances in effect on the day before the date of the enactment of the FQPA. FQPA also amends the Federal Food, Drug, and Cosmetic Act (FFDCA) to require a safety finding in tolerance reassessment based on factors including consideration of cumulative effects of chemicals with a common mechanism of toxicity. This document presents the Agency's revised human health and ecological risk assessments; and the Reregistration Eligibility Decision (RED) for azadioxabicyclooctane.

Azadioxabicyclooctane is a materials preservative registered for use on oil recovery drilling muds and flooding fluids; industrial adhesives and coatings (natural based and synthetic); latex and polymer emulsions; metalworking cutting fluids; latex paints; paper coatings; caulks and sealants; inks; pigment dispersion and pigment slurry; and textile fiber finishes that are not intended as clothing.

The Agency has concluded that the FQPA safety factor should be retained at 10X**.** The toxicology database is not complete with respect to assessing the increased susceptibility to infants and children as required by FQPA for azadioxabicyclooctane. There is an absence of adequate developmental toxicity data and an absence of reproductive toxicity data for this chemical. There is one prenatal dermal developmental toxicity study available for azadioxabicyclooctane. While the developmental study showed no evidence of susceptibility of offspring, the dermal route of administration is not a good indicator of potential effects from oral exposures and the available data do not examine potential reproductive effects of the chemical.

Risks summarized in this document are those that result only from the use of the active ingredient azadioxabicyclooctane. The Food Quality Protection Act (FQPA) requires that the Agency consider available information concerning the cumulative effects of a particular pesticide's residues and other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common toxic mechanism could lead to the same adverse health effect that would occur at a higher level of exposure to any

of the substances individually. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for azadioxabicyclooctane and any other substances. Azadioxabicyclooctane does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that azadioxabicyclooctane has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative.

This document presents the Agency's decision regarding the reregistration eligibility of the registered uses of azadioxabicyclooctane. In an effort to simplify the RED, the information presented herein is summarized from more detailed information which can be found in the technical supporting documents for azadioxabicyclooctane referenced in this RED. The risk assessments and related addenda are not included in this document, but are available in the Public Docket at http://www.epa.gov/edocket.

This document consists of six sections. Section I is the introduction. Section II provides a chemical overview, a profile of the use and usage of azadioxabicyclooctane, and its regulatory history. Section III, Summary of azadioxabicyclooctane Risk Assessment, gives an overview of the human health and environmental assessments, based on the data available to the Agency. Section IV, Risk Management, Reregistration, and Tolerance Reassessment Decision, presents the reregistration eligibility and risk management decisions. Section V, What Registrants Need To Do, summarizes the necessary label changes based on the risk mitigation measures outlined in Section IV. Finally, the Appendices list all use patterns eligible for reregistration, bibliographic information, related documents and how to access them, and Data Call-In (DCI) information.

## II. Chemical Overview

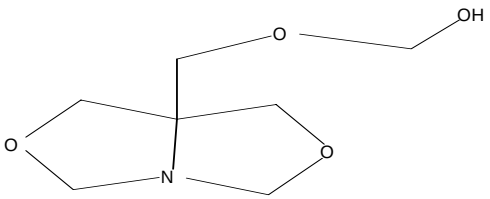
### A. Regulatory History

Azadioxabicyclooctane has been registered since October 30, 1975. The registration and all data to support reregistration were transferred from Tenneco Chemicals on December 22, 1982 to Nuodex Inc. The Nuosept 95 product was purchased by International Specialty Products on March 26, 2002. There are currently two products registered with azadioxabicyclooctane as the active ingredient (one technical product and one end-use-product).

### B. Chemical Identification

#### 1. Technical Azadioxabicyclooctane

59720-422

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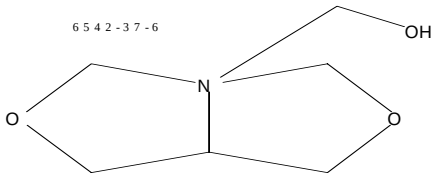


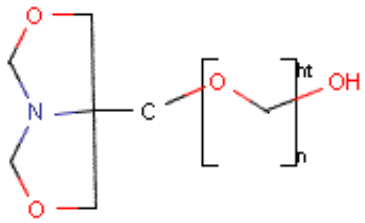


Azadioxabicyclooctane is an equilibrium reaction mixture of three Azadioxabicyclooctanes in a 50% aqueous solution.

**Common name:** Azadioxabicyclooctane

**Chemical names:** 5-Hydroxymethoxymethyl-1-aza-3,7-dioxabicyclo(3,3,0)octane;
5-Hydroxymethyl-1-aza-3,7-dioxabicyclo(3,3,0)octane;
5-Hydroxypoly(methylene-oxy)*methyl-1-aza-3, 7-dioxabicyclo(3.3.0)octane ***(74%C2, 21%C3, 4%C4, 1%C5)**

**CAS Registry No.:** 107001: 59720-42-2
107002: 6542-37-6
107003: 56709-13-8

**OPP Chemical Code:** 107001, 107002, 107003

**Case Number:** 3023

**Chemical Family:** Bicyclic Oxazolidine

**Empirical formula:** $C_7H_{13}O_4N$

**Molecular weight:** 170.5

**Trade name:** Nuosept 95 Preservative

**Basic manufacturer:** International Specialty Products

Technical azadioxabicyclooctane is in the form of a liquid and is clear yellow in color. The solubility of azadioxabicyclooctane in organic solvents range from 0.2 g/100 g at 25$^{o}$C (Hexane) to 28.0 g/100 g at 25$^{o}$C (Ethyl ether). Azadioxabicyclooctane has a vapor pressure of 20.44 mm Hg at 90 $^{o}$C and <2.1 x $10^{-5}$ mm Hg at 20$^{o}$C.

## C. Use Profile

The following is information on the currently registered uses of azadioxabicyclooctane and an overview of use sites and application methods. A detailed table of the uses of azadioxabicyclooctane eligible for reregistration is contained in Appendix A.

**Type of Pesticide:** Preservative

**Summary of Use:**

Food: Paper coatings and paper adhesives.

Non-Food: Adhesives (natural and synthetic), caulks, metalworking fluids, drilling muds and flooding fluids, paper coatings, latex emulsions, wax emulsions. Latex paint, inks, pigment dispersion, pigment slurry, sealants, textile fiber finishes.

Residential: Paints and caulks.

**Target Pests:** Used to control slime forming bacteria and fungi.

**Formulation Types**: The end-use product is a liquid.

**Method and Rates of Application**:

Equipment: Open pour, liquid pump.

Application Rates: 0.05 to 0.5 percent by weight.

Timing: Added to water phase or post addition during manufacturing process.

## III. Summary of Azadioxabicyclooctane Risk Assessments

The purpose of this summary is to assist the reader by identifying the key features and findings of these risk assessments, and to help the reader better understand the conclusions reached in the assessments. The human health and ecological risk assessment documents and supporting information listed in Appendix C were used to formulate the safety finding and regulatory decision for azadioxabicyclooctane. While the risk assessments and related addenda are not included in this document, they are available from the OPP Public Docket and may also be accessed on the Agency's website at http://epa.gov/dockets. Hard copies of these documents may be found in the OPP public docket under docket number OPP-2005-0186. The OPP public docket is located in Room 119, Crystal Mall II, 1801 S. Bell Street, Arlington, VA, and is open Monday through Friday, excluding Federal holidays, from 8:30 a.m. to 4:00 p.m.

### A. Human Health Risk Assessment

#### 1. Toxicity of Azadioxabicyclooctane

A brief overview of the toxicity studies used for determining endpoints in the dietary risk assessments are outlined in Table 2. Further details on the toxicity of azadioxabicyclooctane can be found in the azadioxabicyclooctane docket and include, "AD Preliminary Risk Assessment for the Reregistration Eligibility Decision" dated September 28, 2005; and "Report of the Antimicrobials Division Toxicology Endpoint Selection Committee", dated April 20, 2005. These documents are available on the Agency's website in the EPA Docket at http://www/epa.gov/edockets.

The Agency has reviewed all toxicity studies submitted for azadioxabicyclooctane and has determined that the toxicological database is sufficient for reregistration. Major features of the toxicology profile are presented below. The acute oral and dermal toxicities of azadioxabicyclooctane are low. The acute inhalation toxicity showed a median lethal dose range of between 0.441 mg/L and 0.819 mg/L in males, and between 0.819 mg/L and 1.397 mg/L in females, with epistaxis, labored breathing, rales, and rhinorrhea in all dose groups. Corneal opacity was observed in the primary eye irritation study resulting in a Toxicity Category I classification. Moderate dermal irritation effects were noted in the primary dermal irritation study, leading to a Toxicity category III classification.

**Table 1. Acute Toxicity Profile for Azadioxabicyclooctane**

| Guideline Number | Study Type/ Test substance (% a.i.) | MRID Number/ Citation | Results | Toxicity Category |
|---|---|---|---|---|
| 870.1100 (§81-1) | Acute Oral- Rat Nuosept® 95 (50% a.i.) | MRID 41641601 | $LD_{50}$ = 1940 mg/kg/day | III |
| 870.1200 (§81-2) | Acute Dermal- Rabbit Nuosept® 95 (50% a.i.) | MRID 41671801 | $LD_{50}$ > 2000 mg / kg | III |
| 870.1300 (§81-3) | Acute Inhalation- Rat Nuosept® 95 (50% a.i.) | MRID 42650901 | Combined $LC_{50}$ >0.441 mg/L< 0.819 mg/L | II |

| Guideline Number | Study Type/ Test substance (% a.i.) | MRID Number/ Citation | Results | Toxicity Category |
|---|---|---|---|---|
| 870.2400 (§81-4) | Primary Eye Irritation- Rabbit Nuosept® 95 (50% a.i.) | MRID 41641602 | Corrosive | I |
| 870.2500 (§81-5) | Primary Dermal Irritation- Rabbit Nuosept® 95 (50% a.i.) | MRID 41641603 | Moderate irritant | III |
| 870.2600 (§81-6) | Dermal Sensitization | NA | Assumed Sensitizer | no data available |

The doses and toxicological endpoints selected for the dietary exposure scenarios are summarized in Table 2.

**Table 2. Toxicological Endpoints for Azadioxabicyclooctane (Dietary)**

| Exposure Scenario | Dose Used in Risk Assessment, UF | Special FQPA SF* and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| Acute Dietary (gen. pop.) | NOAEL = **10.6** mg/kg/day<br>UF = **100** | FQPA SF = **10x**<br>**aPAD** = acute RfD / FQPA SF<br>= **0.01** mg/kg/day | **90 day oral toxicity in rats**<br>NOAEL = **10.6** mg/kg/day based on **decreased water consumption at 56.5 mg/kg/day in males.** |
| Acute Dietary (females 13+) | NOAEL = **10.6** mg/kg/day<br>UF = **100** | FQPA SF = **10x**<br>**aPAD** = acute RfD / FQPA SF<br>= **0.01** mg/kg/day | **90 day oral toxicity in rats**<br>NOAEL = **10.6** mg/kg/day based on **decreased water consumption at 56.5 mg/kg/day in males.** |
| Chronic Dietary (All populations) | NOAEL = **10.6** mg/kg/day<br>UF = **300** | FQPA SF = **10x**<br>**cPAD** = chronic RfD / FQPA SF<br>= **0.003** mg/kg/day | **90 day oral toxicity in rats**<br>NOAEL = **10.6** mg/kg/day based on **decreased water consumption at 56.5 mg/kg/day in males.** |
| Cancer (oral) | | | No cancer data available |

Notes:
UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern

From the available repeat dose toxicity studies, there was no evidence of neurotoxicity of azadioxabicyclooctane. There are no reproductive toxicity data available for azadioxabicyclooctane.

In a dermal developmental toxicity study there was clear evidence of maternal dermal effects (e.g. erythema, scabbing, edema) in all treatment groups. The LOAEL for maternal dermal toxicity is 100 mg/kg/day (based on severe dermal irritation); a NOAEL could not be established. The systemic maternal toxicity NOAEL is greater than or equal to 1000 mg/kg/day. There were no other embryotoxic or fetotoxic effects observed in this study. The developmental NOAEL is greater than or equal to 1000 mg/kg/day.

Carcinogenicity Classification

There are no lifetime carcinogenicity studies available for azadioxabicyclooctane.

Mutagenicity

Azadioxabicyclooctane has been tested for mutagenic activity in several assays. Although the data suggest largely negative responses, the lack of test article characterization (especially in light of positive responses observed in two studies) points to the need for proper test article characterization before an adequate conclusion can be made about the mutagenicity of azadioxabicyclooctane.

Endocrine Disruption Potential

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupting Screening Program (EDSP) have been developed, azadioxabicyclooctane may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

### 2. FQPA Safety Factor

The FQPA Safety Factor (as required by the Food Quality Protection Act of 1996) is intended to provide an additional 10-fold safety factor (10X), to protect for special sensitivity in infants and children to specific pesticide residues in food, drinking water, or residential exposures, or to compensate for an incomplete database for certain exposure pathways. The FQPA Safety Factor has been retained (i.e., remains 10X) for azadioxabicyclooctane based on the very limited developmental and reproductive toxicity databases.

The toxicology database for azadioxabicyclooctane with respect to assessing sensitivity of infants and children is not complete. There is only one study, a developmental toxicity study in rats conducted by the dermal route, available for this chemical. While the developmental study showed no evidence of susceptibility of offspring to this chemical, the route of administration is not a good indicator of potential effects from oral exposures.

### 3. Population Adjusted Dose (PAD)

Dietary risk is characterized in terms of the Population Adjusted Dose (PAD), which reflects the reference dose (RfD), either acute or chronic, that has been adjusted to account for the FQPA Safety Factor (SF). This calculation is performed for each population subgroup. A risk estimate that is less than 100% of the acute or chronic PAD is not of concern.

#### a. Acute PAD

Acute dietary risk for azadioxacyclooctane is assessed by comparing acute dietary exposure estimates (in mg/kg/day) to the acute Population Adjusted Dose (aPAD). Acute dietary risk is expressed as a percent of the aPAD. The aPAD is the acute reference dose (0.1 mg/kg/day) modified by the FQPA safety factor. The acute reference dose was derived from a 90-day oral toxicity study in rats in which both the NOAEL (10.6 mg/kg/day) and the LOAEL (56.5 mg/kg/day) were determined. The azadioxacyclooctane aPAD is 0.01 mg/kg/day based on a reference dose of 0.1 mg/kg/day, and incorporating the FQPA safety factor of 10X for the overall U.S. population or any population subgroups.

#### b. Chronic PAD

Chronic dietary risk for azadioxacyclooctane is assessed by comparing chronic dietary exposure estimates (in mg/kg/day) to the chronic Population Adjusted Dose (cPAD). Chronic dietary risk is expressed as a percent of the cPAD. The cPAD is the chronic reference dose (0.03 mg/kg/day) modified by the FQPA safety factor. The cPAD was derived from a 90-day oral toxicity study in rats in which both the NOAEL (10.6 mg/kg/day) and the LOAEL (56.5 mg/kg/day) were determined. However, no chronic studies were available necessitating the use of an additional 3X uncertainty factor. The azadioxacyclooctane cPAD is 0.003 mg/kg/day based on a reference dose of 0.03 mg/kg/day, which includes the incorporation of the FQPA safety factor (10X) for the overall U.S. population or any population subgroups**.**

### 4. Exposure Assumptions

The use of antimicrobial chemicals on paper coatings and paper adhesives may result in pesticide residues in human food. The Agency must determine the risk to human health that may occur from exposure to these chemicals.

Potential dietary exposures to the active ingredient, azadioxabicyclooctane, from its uses as paper coating and paper adhesive preservatives were assessed. Azadioxabicyclooctane has been cleared by the US Food and Drug Administration (US FDA) for use as an antibacterial preservative in paper and paperboard products contacting dry food only in 21CFR176.180 as well as, a component in paper adhesives in 21CFR175.105.

US FDA has estimated a Cumulative Dietary Concentration of 12 ppb and a Cumulative Dietary Exposure Intake (CEDI) of 0.006 mg/kg/day for azadioxabicyclooctane (http://www.cfsan.fda.gov/~dms/opa-tedi.html) however, the Agency does not have the specific details (i.e., application rates or residue migration potential) used by US FDA in their review of this petition. Furthermore, no residue data have been submitted to the Agency in support of the

azadioxabicyclooctane indirect food contact uses. Therefore, a screening-level assessment has been conducted using the US FDA's Center for Food Safety & Applied Nutrition's (CFSAN) approach as presented in "Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations" dated April 2002. The Agency calculated "worst-case" dietary concentration values using the labeled maximum application rate for the paper coating preservative use (0.25% or 2500 ppm of the paper coating) (EPA Reg. No. 1529-28), US FDA's default assumptions for preservation of paper adhesives, and EPA's standard values for body weights.

Since azadioxabicyclooctane can be used as a preservative in paper coatings and adhesives, the dietary exposures resulting from both uses must be added together because both the coatings and adhesives could be used together within one paper product.

### 5. Dietary (Food) Risk Assessment

Generally, a dietary risk estimate that is less than 100% of the acute or chronic PAD does not exceed the Agency's risk concerns. A summary of acute and chronic risk estimates are shown in Table 3.

#### a. Acute Dietary Risk

An acute dietary risk assessment was conducted for azadioxabicyclooctane food uses. The result of the combined assessment for coatings and adhesives showed the risk estimates to be ≤12.0% of the aPAD for all population subgroups and therefore are not of concern.

#### b. Chronic (Non-cancer) Dietary Risk

A chronic dietary risk assessment was conducted for azadioxabicyclooctane food uses. The risk analysis assumes daily exposure from paper coatings and adhesives. The result of the combined assessment for coatings and adhesives showed the risk estimates to be ≤39.6% of the cPAD for all population subgroups and therefore are not of concern.

**Table 3: Acute and Chronic Dietary Exposure and Risk**

| Use | Daily Dietary Dose (mg/kg bw/day) | % aPAD | %cPAD |
|---|---|---|---|
| Paper Coating Preservative | 0.00021 (adult)<br>0.0005 (child) | 2.1% (adult)<br>5% (child) | 7.0% (adult)<br>16.6% (child) |
| Paper Adhesive Preservative | 0.00030 (adult)<br>0.00070 (child) | 3% (adult)<br>7% (child) | 10% (adult)<br>23% (child) |
| Combined | 0.00051 (adult)<br>0.0012 (child) | 5.1% (adult)<br>12% (child) | 17% (adult)<br>39.6% (child) |

### c. Dietary Risk from Drinking Water

Azadioxabicyclooctane is not likely to contaminate surface and ground waters based on its use patterns. Therefore, a drinking water assessment was not conducted.

## 6. Residential Exposure

Residential exposure assessment considers all potential pesticide exposure, other than exposure due to residues in food or in drinking water. Exposure may occur during painting or caulking. Each route of exposure (oral, dermal, inhalation) is assessed, where appropriate, and risk is expressed as a Margin of Exposure (MOE), which is the ratio of estimated exposure to an appropriate NOAEL. Based on its use patterns, azadioxabicyclooctane has been assessed for the residential mixing/loading/applicator (or "handler") exposure for applications by homeowners painting. For azadioxabicyclooctane there are no potential dermal post application exposures to assess. As for inhalation post application exposures, these are expected to be minimal because the paint is dry and the vapor pressure of azadioxabicyclooctane is negligible.

### a. Toxicity

The toxicological endpoints and associated uncertainty factors used for assessing the non-dietary risks for azadioxabicyclooctane are listed in Table 4.

A MOE greater than or equal to 3,000 is considered adequately protective for the residential exposure assessment for the inhalation route of exposure. The MOE of 3,000 includes 10x for interspecies extrapolation, 10x for intraspecies variation, 3x for a lack of histopathology data and the 10x FQPA factor. The FQPA 10x hazard based safety factor was retained based on the lack of developmental and reproductive toxicity data for azadioxabicyclooctane, but was not applied to children's risk assessments for residential exposure as residential exposures to children are not expected from the uses.

For the dermal route of exposure, a MOE greater than or equal to 300 is considered adequately protective for the residential exposure assessment. The MOE of 300 includes 10x for interspecies extrapolation, 10x for intraspecies variation and 3x for lack of a NOAEL.

A MOE greater than or equal to 3,000 is considered adequately protective for the long-term occupational exposure assessment for the dermal route of exposure. The MOE of 3000 includes 10x for interspecies extrapolation, 10x for intraspecies variation and 3x for lack of a NOAEL and 3x for the lack of a chronic endpoint.

**Table 4: Toxicity Endpoints Selected for Assessing Occupational and Residential Risk for Azadioxabicyclooctane**

| Exposure Scenario | Dose Used in Risk Assessment, UF | Special FQPA SF* and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| Dermal (all | Dermal LOAEL = | Occupational MOE = | Co-critical studies: |

| Exposure Scenario | Dose Used in Risk Assessment, UF | Special FQPA SF* and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| durations) | **100** mg/kg/day | 300 (ST and IT) = 3000 (LT) Residential MOE = 300 (ST and IT) | **21-day dermal toxicity in rabbits** LOAEL = 100 mg/kg/day (severe dermal effects) **developmental toxicity in rats** LOAEL = **100** mg/kg/day (severe dermal effects) |
| Inhalation (all durations ) | NOAEL= **10.6** mg/kg/day (inhalation absorption rate = 100%) | Occupational MOE = 300 Residential MOE = 3000 | **90 day oral toxicity in rats** NOAEL = **10.6** mg/kg/day based on **decreased water consumption at 56.5 mg/kg/day in males.** |
| Cancer | | | No cancer data available |

Notes: ST= short-term, IT = intermediate–term, LT= long-term

b. **Residential Handler**

**i. Exposure Scenarios, Data and Assumptions**

Residential exposure may occur for azadioxabicyclooctane during application as a paint or caulk. A number of assumptions, or estimates, such as adult body weight and area treated per application, are made by the Agency for residential risk assessment. Also, note that residential handlers are sometimes addressed somewhat differently than occupational handlers in that homeowners are assumed to complete all elements of an application (mix/load/apply) without the use of personal protective equipment.

The quantitative exposure/risk assessment developed for residential handlers is based on these scenarios:

(1) painting using a brush or roller,
(2) painting using an airless sprayer

Based on end-use product application methods and use amounts, it is assumed that exposures while applying paints will be equal to or greater than exposures that may occur when an individual uses any of the other end use products (i.e., caulks, inks, sealants). Therefore, residential handler exposures were assessed for the application of paint, as this scenario represents maximum possible exposure to the chemical.

Brush/Roller

The dermal and inhalation unit exposures for this application method were obtained from

the Agency's Residential SOPs. The dermal unit exposure is representative of the handler a tee-shirt and shorts while applying the paint with a brush and without gloves because this is a residential use site. The inhalation unit exposure is representative of a painter applying paint with a brush. The maximum application rate is 0.5% product by weight of material being treated. The application rates on the label do not account for the product containing only 50% a.i., so the maximum application results in exposure to 0.25% a.i. by weight of the material treated.

For this scenario, the painter is expected to handle 2 gallons of paint per day. This is from the AD Residential SOPs (1997 & 2001) in which this value is the 90$^{th}$ percentile value of 8 gallons of latex paint used per year divided by the mean frequency of 4 painting events per year. The density of paint is assumed to be 10 lb/gallon, so that the value of 2 gallons is equivalent to 20 pounds of paint.

Airless Sprayer

The dermal and inhalation unit exposures for this application method were obtained from the Agency's Residential SOPs. The dermal unit exposure is representative of the handler wearing a tee-shirt and shorts while performing an ungloved airless spray application. The inhalation unit exposure is representative of a painter applying a material with an airless sprayer. For this scenario, the painter is expected to handle 15 gallons of paint per day. This is from the Agency's SOP's in which this value is based on coverage of 200ft$^2$/gal and a house size being 40' x 30' x 20' (surface area of 2,800ft$^2$). The density of paint is assumed to be 10 lbs/gallon, so that the value of 15 gallons is equivalent to 150 lbs of paint.

### ii. Residential Handler Risk Estimates

Based on toxicological criteria and potential for exposure, the Agency has conducted dermal and inhalation exposure assessments. As noted previously, MOEs greater than or equal to 3,000 for the inhalation route of exposure and 300 for dermal exposure are considered adequately protective for the residential exposure assessment.

A summary of the residential handler exposures and risk are presented on Table 5. For residential handlers that handle products containing azadioxabicyclooctane, short-term, and intermediate-term MOEs were below the target MOEs for painting using an airless sprayer at the maximum application rate and thus are of concern. MOEs do not exceed the Agency's level of concern for the painting using a brush or roller or for painting using an airless sprayer at the minimum application rate.

**Table 5: Estimates of Exposures and Risks to Residential Handlers of Azadioxabicyclooctane (Short -Term Duration)**

| Exposure Scenario | Method of Application | Application rate (% a.i. by weight of material being treated = % product by weight of material treated x 50% a.i.) | Daily Dose (mg a.i./kg per day) | | MOE | |
|---|---|---|---|---|---|---|
| | | | Dermal Dose | Inhalation Dose | Dermal (target = 300) | Inhalation (target = 3000) |
| Paints | Brush/Roller | 0.25% (max) | 0.1643 | 0.0002 | 609 | 53,000 |
| | Airless Sprayer | 0.25% (max) | 0.4232 | 0.004446 | 236 | 2.400 |
| | Airless Sprayer | 0.05% (min)[i] | 0.0846 | 0.000889 | 1,181 | 12,000 |

### c. Residential Post-Application

Residential post application exposures occur when bystanders contact areas in which the antimicrobial end use product has recently been applied. For azadioxabicyclooctane there are no potential dermal post application exposures to assess. As for inhalation post application exposures, these are expected to be minimal because the paint is dry and the vapor pressure of azadioxabicyclooctane is negligible.

## 6. Aggregate Risk

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require "that there is a reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure will typically include exposures from food, drinking water, residential uses of a pesticide, and other non-occupational sources of exposure. Since no drinking water estimates were developed for azadioxabicyclooctane, aggregate assessments include exposure to food and as a result of residential uses only.

Typically, aggregate risk assessments are conducted for acute (1 day), short-term (1-30 days), intermediate-term (1-6 months) and chronic (6 months to lifetime) exposures. However, acute and chronic aggregate assessments were not conducted because there are no significant impacts to drinking water sources, nor are there long-term residential uses. Thus, only short- and intermediate-term aggregate assessments were conducted. Oral and inhalation exposure and risk estimates were combined for the aggregate risk assessment because these endpoints are based on the same toxicity study and effects of concern. Dermal exposures were not aggregated with the oral or inhalation exposures due to different toxicological endpoints for oral and dermal exposures.

### a. Short-Term Aggregate Risk

The aggregate short-term risk assessment is designed to provide estimates of risk likely to result from exposures to the pesticide or pesticide residues in food, water, and from residential

(or other non-occupation) pesticide uses. For adults, the aggregate assessment includes dietary (oral) and residential inhalation exposures from painting. An assessment was not conducted for children since there are no residential exposures expected for this subgroup.

Since exposures to residential handlers for the paint scenario are of concern at the highest application rate short-term aggregate risks are also of concern.

### 7. Occupational Exposure and Risk

Workers can be exposed to a pesticide through mixing, loading, and/or applying a pesticide, or re-entering treated sites. Occupational handlers of azadioxabicyclooctane include workers in a variety of occupational settings. Additionally, postapplication exposures are likely to occur in these settings. The representative scenarios selected for assessment were evaluated using maximum application rates as recommended on the product labels for azadioxabicyclooctane.

Occupational risk is assessed for exposure at the time of application (termed "handler" exposure) and is assessed for exposure following application, or post-application exposure. Application parameters are generally defined by the physical nature of the formulation (e.g., formula and packaging), by the equipment required to deliver the chemical to the use site, and by the application rate.

Occupational risk for all of these potentially exposed populations is measured by a Margin of Exposure (MOE) which determines how close the occupational exposure comes to a No Observed Adverse Effect Level (NOAEL) from toxicological studies. In the case for azadioxabicyclooctane, MOEs greater than 300 for dermal and inhalation exposures are not of concern to the Agency for short- and intermediate-term exposures. MOEs greater than 1000 for dermal and inhalation exposures are not of concern to the Agency for long-term exposures. For workers entering a treated site, MOEs are calculated for each day after application to determine the minimum length of time required before workers can safely re-enter.

#### a. Occupational Toxicity

Table 4 provides a listing of the toxicological endpoints used in the occupational risk assessment for azadioxabicyclooctane.

#### b. Occupational Handler Exposure

The Agency has determined that there is potential ~~for~~ dermal and inhalation worker exposure to azadioxabicyclooctane at various use sites when used as a preservative consistent with existing labeling. There are also occupational painter scenarios associated with its use as a preservative in paints. Painting methods evaluated include application with an airless sprayer and a brush. To assess handler risks, the Agency used surrogate unit exposure data from both the Pesticide Handlers Exposure Database (PHED) and proprietary data from the Chemical Manufacturers (CMA) antimicrobial exposure study.

### c. Occupational Handler Risk Summary

For the occupational handler dermal and inhalation risk assessment, the short- and intermediate- term risks calculated were above the target MOEs for all scenarios (i.e., dermal and inhalation >300). However, the inhalation MOE for the airless sprayer paint scenario falls below the MOE of 1,000, when the additional 10X route-to-route extrapolation uncertainty factor is applied. In such cases, an inhalation study would be required to confirm these findings. A summary of the results of the occupational handler assessment is provided in Table 6.

**Table 6: Short and Intermediate Term Azadioxabicyclooctane Exposures and MOEs Associated with Occupational Handlers**

| Substrate Treated/Handled through Exposure Scenario | Method of Application | Application rate (% a.i. by weight of material being treated) | Quantity Handled/Treated per day (unit as indicated) | Daily Dose (mg a.i./kg per day) | | MOE[r] | |
|---|---|---|---|---|---|---|---|
| | | | | Dermal Dose | Inhalation Dose | Dermal (target ST/IT MOE = 300) | Inhalation (target MOE = 300) |
| Latex Paint (Latex Emulsions)[s] | Liquid Pour (preservation) | 0.25 (max) | 19,100 lbs (2,000 gallons) | 0.0921 | 0.00236 | 1,100 | 4,500 |
| | Liquid Pump (preservation) | 0.25 (max) | 191,000 lbs (20,000 gallons) | 0.0429 | 0.00275 | 2,300 | 3,800 |
| | Airless spraying (end user) | 0.25 (max) | 500 lbs (50 gallons) | 0.25 | 0.0148 | 400 | 720 |
| | Airless spraying (end user) | 0.05 (min) | 500 lbs (50 gallons) | 0.05 | 0.00296 | 2,000 | 3,600 |
| | Brush Painting (end user) | 0.25 (max) | 50 lbs (5 gallons) | 0.0429 | 0.0005 | 2,300 | 21,000 |
| Metalworking cutting fluids (preservation) | Liquid Pour | 0.15 (max) | 2,865 lbs (300 gallons) | 0.0113 | 0.000524 | 8,900 | 20,000 |
| | Liquid Pump | 0.15 (max) | 2,865 lbs(300 gallons) | 0.0192 | 0.000214 | 5,200 | 50,000 |
| Paper Coating (preservation) | Liquid Pump | 0.25 (max) | 9,550 lbs (1000 gallons) | 0.0015 | 0.000090 | 65,000 | 120,000 |
| Drilling Muds (end user) | Liquid Pour | 0.25 (max) | 46.7 lbs(5.6 gal (ST)) | 0.0002 | 0.000006 | 440,000 | 1.8 x 106 |
| Flooding Fluids (end-user) | | | 23.3 lbs(2.8 gal (IT)) | 0.0001 | 0.000003 | 890,000 | 3.7 x 106 |

**a:** The maximum application rate of 0.5% product ( 0.25% a.i). by weight of material treated generates an MOE of concern, whereas using materials treated at the minimum application rates specified in the table, an MOE that is not of concern is generated. All of these uses in Table 6.2 were assessed at this rate, except for metalworking fluids. This treatment was label specified to be 0.3 % product (0.15% a.i.) by weight of the fluid treated.
**b,c :** CMA preservative liquid pour, gloved values for dermal and inhalation are 0.135 mg/lb a.i. and 0.00346 mg/lb a.i., respectively.
**d,e :** CMA preservative liquid pump, gloved values for dermal and inhalation are 0.00629 mg/lb a.i. and 0.000403 mg/lb a.i., respectively.
**f, g :** PHED unit exposure values for a handler wearing gloves and applying paint using an airless sprayer were used, so that the dermal and inhalation values were 14 mg/lb a.i. and 0.830 mg/lb a.i., respectively.
**h, i :** PHED paintbrush application scenario, gloved values for dermal and inhalation are 24 mg/lb a.i. and 0.28 mg/lb a.i., respectively.
**j, k :** CMA MWF liquid pour, gloved values for dermal and inhalation are 0.184 mg/lb a.i. and 0.00854 mg/lb a.i., respectively
**l, m :** CMA MWF liquid pump, gloved values for dermal and inhalation are 0.312 mg/lb a.i. and 0.00348 mg/lb a.i., respectively
**n, o :** CMA liquid pump for pulp and paper, gloved values for dermal and inhalation are 0.0045 mg/lb a.i. and 0.00027 mg/lb a.i., respectively.

**p:** For the quantity handled, it is explained in the MOE discussion following, which addresses each scenario individually
**q:** Daily Dose (mg a.i./kg per day) = Daily Dose (mg a.i./kg per day) = Unit Exposure (mg/lb a.i.) x rate x amount handled x (1/ body weight (kg))
**r:** MOE = Toxicity Endpoint (mg/kg/day) / Daily Dose (mg/kg/day); where dermal NOAEL = 100 mg/kg/day and the inhalation LOAEL = 10.6 mg/kg/day
**s:** Latex paints are representative for adhesives, caulks, ink dispersions, pigment dispersions, pigment slurries, wax emulsions, textiles, and sealants.
**t**: There is a chemical metering application (i.e. liquid pump) for drilling muds and flooding fluid uses. However, this was not assessed because appropriate unit exposure values are not available. This is further discussed in the End User discussion later in the document.

### d. Occupational Post-application

Occupational painter post-application exposures result when bystanders contact areas in which the antimicrobial end-use product has been recently applied. For azadioxabicyclooctane, exposures are expected to be minimal except for the metal working fluid scenario.

*Metalworking Fluids:*

There is a potential for dermal and inhalation exposure when a worker handles treated metalworking fluids. This route of exposure occurs after the chemical has been incorporated into the metal working fluid and a machinist is using/handling this treated end-product. The MOEs are in Table 7 for this exposure scenario. A screening-level long-term dermal exposure estimate was derived using the 2-hand immersion model from ChemSTEER. The model is available at www.epa.gov/opptintr/exposure/docs/chemsteer.htm

**Table 7. Post Application Risks to Machinists from Metal Working Fluid Use**

| Substrate Treated/Handled through Exposure Scenario | Method of Application | Application Rate (% a.i. by weight of material being treated) | Daily Dose | | Long Term MOE | |
|---|---|---|---|---|---|---|
| | | | Dermal Dose | Inhalation Dose | Dermal | Inhalation |
| Metalworking cutting fluids | Liquid Pour Liquid Pump | 0.15 | 0.1854 | 0.00107 | 540 | 9900 |
| | Liquid Pour Liquid Pump | 0.05 | 0.0618 | 0.000357 | 1,600 | 30,000 |

At the maximum application rate (0.3% product by weight of material to be treated, 0.15% a.i.) permitted for metalworking fluids (MWF), there is concern with the dermal exposure to the worker. The target MOE for long-term exposure is 1,000, and at the maximum rate, the MOE is 540, which is a concern. However, when the worker comes into contact with fluid that has been treated at the minimum application rate (0.1% product by weight of material to be treated, 0.05% a.i.), the MOE is 1,600 which is not of concern since it is greater than 1,000.

## B. Environmental Risk Assessment

A summary of the Agency's environmental risk assessment is presented below. The following risk characterization is intended to describe the magnitude of the estimated environmental risks for azadioxabicyclooctane use sites and any associated uncertainties.

### 1. Environmental Fate and Transport

The environmental fate assessment for azadioxabicyclooctane is based on U.S. EPA's Estimation Programs Interface (EPI) Suite. EPI Suite provides estimations of physical/chemical

properties and environmental fate properties. Azadioxabicyclooctane is a mixture of three acetals (components a, b and c). EPI Suite lacks estimation of the third of the three isomers (component C).

Under abiotic conditions, the mixture of these acetals is hydrolytically unstable with half-lives of 0.347 days at pH 5, 1.74 days at pH 7 and approximately 15 days at pH 9. It is, therefore, not likely to be persistent in water.

Components A and B of the mixture are likely to volatilize into the atmosphere as their vapor pressures vary between 0.0004 to 0.003 mm Hg. Component C is likely to have less volatility as the side chain of $CH_2O$ groups are added into the structure. Estimated half lives in the atmosphere for components A and B are 1.2 and 1.4 hours. Hence, these two chemicals are not likely to persist in the atmosphere.

Estimated log Kows of components A and B respectively are -2.23 and -1.55 (very highly miscible in water and show no tendency for dissolving organic solvents); therefore, the mixture is not likely to bioaccumulate in aquatic organisms.

MITI linear biodegradability (modified linear biodegradation method) for components A and B indicates a fast biodegradation is highly probable in soils and water. These compounds do not likely pose a concern for surface and ground water contamination.

**2. Ecological Risk**

Azadioxabicyclooctane demonstrates low toxicity to birds and mammals and slight toxicity to freshwater aquatic organisms. All submitted ecological toxicity studies were conducted with the formulated product Nuosept® 95. Although conducted using a formulated product and not the TGAI, the submitted studies for avian acute, avian subacute, freshwater invertebrates and estuarine/marine organisms are considered adequate to support the registered uses of azadioxabicyclooctane, as Nuosept® 95 is the only end-use product. A summary of submitted data is provided below.

The indoor uses of azadioxabicyclooctane are not likely to pose risk to fish, wildlife or plants due to the low likelihood of exposure and the low toxicity of the compound. Most uses of azadioxabicyclooctane are indoor uses, with little chance of exposure to the environment. The oil production uses do occur outdoors; however, the Agency does not have an available model for estimating exposure from those uses. The risk from offshore oil drilling uses of azadioxabicyclooctane was previously addressed (Agency review July 14, 1983), and the application of 500-2000 ppm drilling fluid treatment or 100-1000 ppm flooding fluid treatment was considered “unlikely to adversely affect aquatic organisms due to the low toxicity and large dilution factor." Discharge of waste streams occurring from terrestrial oil recovery operations would be regulated at the local level in order to prevent undue environmental exposure.

**Table 8. Acute Oral Toxicity of Nuosept® 95 to Birds**

| Species | % Active Ingredient (ai) | Endpoint (mg /kg product) | Toxicity Category | Reference |
|---|---|---|---|---|
| Mallard duck (*Anas platyrhynchos*) | 107001 24.5% 107002 17.7% 107003 7.8% | $LD_{50}$ > 2,510<br><br>NOEL = 2510 (mortality) | Practically non-toxic | Beavers, 1983 (ACC # 250533) |

**Table 9. Subacute Dietary Toxicity of Nuosept® 95 to Birds**

| Species | % Active Ingredient (ai) | Endpoint (ppm) | Toxicity Category | Reference |
|---|---|---|---|---|
| Bobwhite quail (*Colinus virginianus*) | 50% | $LC_{50}$ >5,200 a.i. (>10,400 product) NOEC 1541 ppm a.i. (3082 ppm product) | Practically non-toxic | Hakin et al., 1990 (MRID 416848-01) |
| Bobwhite quail (*Colinus virginianus*) | not reported | LC50 > 10,000 ppm product NOEC 10,000 ppm | Practically non-toxic | Truslow Farms, 1974. (ACC#24878) |
| Mallard duck (*Anas platyrhynchos*) | not reported | LC50 > 10,000 ppm product NOEC 10,000 ppm | Practically non-toxic | Truslow Farms, 1974. (ACC#24878) |

NOAEC= No-observable adverse effect concentration

**Table 10. Acute Toxicity of Nuosept® 95 to Fish**

| Species | % Active Ingredient (a.i.) | Endpoints (ppm product) | Toxicity Category | Reference |
|---|---|---|---|---|
| Rainbow trout (*Oncorhynchus mykiss*) | not reported | $LC_{50}$ = 240<br>NOEC = 87 | practically non- toxic | Bentley and Sleight, 1974 (ACC #247878; MRID 930500-15) |
| Bluegill (*Lepomis macrochirus*) | not reported | $LC_{50}$ = 163<br>NOEC = 87 | practically non-toxic | Bently and Bevier, 1974 (ACC#247878; MRID 930500-15) |
| Sheepshead minnow (*Cyprinodon variegatus*) | PC code %<br>107001<br>24.5%<br>107002<br>17.7%<br>107003<br>7.8% | $LC_{50}$ = 440 ppm<br>NOEC = 250 ppm | practically non-toxic | Ward,1983. (ACC# 250533) |

**Table 11. Acute Toxicity of Nuosept® 95 to Invertebrates**

| Species | % Active Ingredient (ai) | Endpoints (ppm product) | Toxicity Category | Reference |
|---|---|---|---|---|
| Eastern oyster (*Crassostrea virginica*) | PC Code %<br>107001<br>24.5%<br>107002<br>17.7%<br>107003<br>7.8% | $EC_{50}$ = 42<br>NOEC =25 | slightly toxic | Ward, 1983. (ACC#250533) |
| Mysid (*Americamysis bahia*) | 107001<br>24.5%<br>107002<br>17.7%<br>107003<br>7.8% | LC50 = 88 ppm<br>NOEC < 50 ppm\ | slightly toxic | Ward, 1983. ACC#250533 |
| Water flea (*Daphnia magna*) | 107001<br>24.5%<br>107002<br>17.7%<br>107003<br>7.8% | $EC_{50}$ = 77<br>NOEC = 7.7 | slightly toxic | Suprenant, 1983 (ACC# 250533/MRID #930500-16) |

### 3. Listed Species Consideration

#### a. The Endangered Species Act

Section 7 of the Endangered Species Act, 16 U.S.C. Section 1536(a)(2), requires all federal agencies to consult with the National Marine Fisheries Service (NMFS) for marine and anadromous listed species, or the United States Fish and Wildlife Services (FWS) for listed wildlife and freshwater organisms, if they are proposing an "action" that may affect listed species or their designated habitat. Each federal agency is required under the Act to insure that any action they authorize, fund, or carry out is not likely to jeopardize the continued existence of a listed species or result in the destruction or adverse modification of designated critical habitat. To jeopardize the continued existence of a listed species means "to engage in an action that reasonably would be expected, directly or indirectly, to reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of the species." 50 C.F.R. § 402.02.

To facilitate compliance with the requirements of the Endangered Species Act subsection (a)(2) the Environmental Protection Agency, Office of Pesticide Programs has established procedures to evaluate whether a proposed registration action may directly or indirectly reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of any listed species (U.S. EPA 2004). After the Agency's screening-level risk assessment is performed, if any of the Agency's Listed Species LOC Criteria are exceeded for either direct or indirect effects, a determination is made to identify if any listed or candidate species may co-occur in the area of the proposed pesticide use. If determined that listed or candidate species may be present in the proposed use areas, further biological assessment is undertaken. The extent to which listed species may be at risk then determines the need for the development of a more comprehensive consultation package as required by the Endangered Species Act.

For certain use categories, the Agency assumes there will be minimal environmental exposure, and only a minimal toxicity data set is required (Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs U.S. Environmental Protection Agency - Endangered and Threatened Species Effects Determinations, 1/23/04, Appendix A, Section II B, pg.81). Chemicals in these categories therefore do not undergo a full screening-level risk assessment, and are considered to fall under a "no effect" determination. Due to the low likelihood of exposure and low toxicity of azadioxabicyclooctane, the indoor uses of the compound are not likely to adversely affect listed species. Likewise, offshore oil production use of azadioxabicyclooctane is considered unlikely to adversely affect listed species due to the low toxicity of the compound and the large dilution factor in offshore operations. Therefore, the Agency expects no effects to listed species or critical habitat and therefore makes a "No Effect" determination for this chemical.

#### b. General Risk Mitigation

Azadioxabicyclooctane end-use products (EPs) may also contain other registered pesticides. Although the Agency is not proposing any mitigation measures for products

containing azadioxabicyclooctane specific to federally listed species, the Agency needs to address potential risks from other end-use products. Therefore, the Agency requires that users adopt all listed species risk mitigation measures for all active ingredients in the product. If a product contains multiple active ingredients with conflicting listed species risk mitigation measures, the more stringent measure(s) should be adopted.

## IV. Risk Management, Reregistration, and Tolerance Reassessment Decision

### A. Determination of Reregistration Eligibility

Section 4(g)(2)(A) of FIFRA calls for the Agency to determine, after submission of relevant data concerning an active ingredient, whether or not products containing the active ingredient are eligible for reregistration. The Agency has previously identified and required the submission of the generic (i.e., active ingredient-specific) data required to support reregistration of products containing azadioxabicyclooctane as an active ingredient. The Agency has completed its review of these generic data, and has determined that the data are sufficient to support reregistration of all supported products containing azadioxabicyclooctane.

The Agency has completed its assessment of the dietary, occupational, drinking water, and ecological risks associated with the use of pesticide products containing the active ingredient azadioxabicyclooctane. Based on a review of these data and on public comments on the Agency's assessments for the active ingredient azadioxabicyclooctane, the Agency has sufficient information on the human health and ecological effects of azadioxabicyclooctane to make decisions as part of the tolerance reassessment process under FFDCA and reregistration process under FIFRA, as amended by FQPA. The Agency has determined that all azadioxabicyclooctane containing products are eligible for reregistration provided that: (i) current data gaps and confirmatory data needs are addressed; (ii) the risk mitigation measures outlined in this document are adopted; and (iii) label amendments are made to reflect these measures. Label changes are described in Section V. Appendix A summarizes the uses of azadioxabicyclooctane that are eligible for reregistration. Appendix B identifies the generic data requirements that the Agency reviewed as part of its determination of reregistration eligibility of azadioxabicyclooctane, and lists the submitted studies that the Agency found acceptable. Data gaps are identified as generic data requirements that have not been satisfied with acceptable data.

Based on its evaluation of azadioxabicyclooctane, the Agency has determined that azadioxabicyclooctane products, unless labeled and used as specified in this document, would present risks inconsistent with FIFRA. Accordingly, should a registrant fail to implement any of the risk mitigation measures identified in this document, the Agency may take regulatory action to address the risk concerns from the use of azadioxabicyclooctane. If all changes outlined in this document are incorporated into the product labels, then all current risks for azadioxabicyclooctane will be substantially mitigated for the purposes of this determination.

### B. Public Comments and Responses

Through the Agency's public participation process, EPA worked with stakeholders and the public to reach the regulatory decisions for azadioxabicyclooctane. During the public comment period on the risk assessments, which closed on September 19, 2005, the Agency received comments from the registrant, International Speciality Products. These comments in their entirety are available in the public docket, http://docket.epa.gov/edkpub/index.jsp, (OPP-2005-0186). These comment have been considered in the writing of this RED.

The registrant also submitted comments to the Agency during Phase 1, the error only comment period. The Agency's responses to these comments are incorporated into the revised chapters and are available in the public docket.

## C. Regulatory Position

### 1. Food Quality Protection Act Findings

#### a. "Risk Cup" Determination

As part of the FQPA tolerance reassessment process, EPA assessed the risks associated with azadioxabicyclooctane. An aggregate assessment was conducted for exposures through food, drinking water and residential use. The Agency has determined that the human health risks from these combined exposures are within acceptable levels with the mitigation contained in this document. In reaching this determination, EPA has considered the available information on the special sensitivity of infants and children, as well as aggregate exposure from food, water and residential use.

#### b. Determination of Safety to U.S. Population

As part of the FQPA tolerance reassessment process, EPA assessed the risks associated with azadioxabicyclooctane. The Agency has determined that there is a reasonable certainty no harm will result to the general population or any subgroup from the use of azadioxabicyclooctane with amendments and changes as specified in this document. In reaching this conclusion, the Agency has considered all available information on the toxicity, use practices and exposure scenarios, and the environmental behavior of azadioxabicyclooctane. Both the acute dietary (food alone) and chronic dietary risks from azadioxabicyclooctane are not of concern. Azadioxabicyclooctane is not likely to contaminate surface and ground waters based on its use patterns. Thus, a drinking water assessment was not conducted.

Because the Agency has concerns for residential handler risks for the paint scenario short- and intermediate-term aggregate risk assessments were not conducted for azadioxabicyclooctane since this use alone exceeds the Agency's level of concern.

#### c. Determination of Safety to Infants and Children

EPA has determined that the established tolerances for azadioxabicyclooctane, with amendments and changes as specified in this document, meet the safety standards under the FQPA amendments to section 408(b)(2)(C) of the FFDCA, that there is a reasonable certainty of no harm for infants and children. The safety determination for infants and children considers factors of the toxicity, use practices, and environmental behavior noted above for the general population, but also takes into account the possibility of increased dietary exposure due to the specific consumption patterns of infants and children, as well as the possibility of increased susceptibility to the toxic effects of azadioxabicyclooctane residues in this population subgroup.

A Special FQPA Safety Factor is necessary to protect the safety of infants and children. In determining whether or not infants and children are particularly susceptible to toxic effects

from azadioxabicyclooctane residues, the Agency considered the completeness of the database for developmental and reproductive effects, the nature of the effects observed, and other information. The FQPA Safety Factor has been retained (i.e., remains 10X) for azadioxabicyclooctane based on the very limited developmental and reproductive toxicity databases.

### d. Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that EPA include evaluations of potential effects in wildlife. For pesticides, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the EDSP have been developed, azadioxabicyclooctane may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

### e. Cumulative Risks

Risks summarized in this document are those that result only from the use of azadioxabicyclooctane. The Food Quality Protection Act (FQPA) requires that the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common toxic mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the substances individually. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for azadioxabicyclooctane. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

## D. Regulatory Rationale

The Agency has determined that azadioxabicyclooctane is eligible for reregistration provided that additional required data confirm this decision and that the risk mitigation measures outlined in this document are adopted, and label amendments are made to reflect these measures.

The following is a summary of the rationale for managing risks associated with the use of azadioxabicyclooctane. Where labeling revisions are warranted, specific language is set forth in the summary tables of Section V of this document.

### 1. Human Health Risk Management

#### a. Dietary (Food) Risk Mitigation

For all supported uses, the acute and chronic dietary exposure estimates are below the Agency's level of concern. Therefore, no risk mitigation measures are required to address exposure to azadioxabicyclooctane residues in food.

#### b. Drinking Water Risk Mitigation

Azadioxabicyclooctane is not likely to contaminate surface and ground waters based on its use patterns. Thus, a drinking water assessment was not conducted. Therefore, no risk mitigation measures are required to address azadioxabicyclooctane exposure from drinking water.

#### c. Residential Risk Mitigation

Residential risks for handlers were calculated for short- and intermediate-term dermal and inhalation exposures. Risks of concern were identified for the application of paints using an airless sprayer at the maximum application rate of 0.5% product by weight of material treated. All other exposure and risk estimates for residential handler scenarios are below the Agency's level of concern.

To reduce residential exposure, the Agency has determined that the following mitigation and label change for specific scenarios is appropriate and required for reregistration eligibility:

- Reduce the maximum application rate for paint uses to 0.4% product by weight of material treated.

#### d. Occupational Risk Mitigation

##### i. Handler Exposure

Occupational risks from handler and applicator exposures were calculated for short-term and intermediate-term dermal and inhalation exposures. All exposure and risk estimates for

occupational handler scenarios are below the Agency's level of concern. Therefore, no risk mitigation measures are required for these handler scenarios.

#### ii. Post-Application Risk Mitigation

Occupational risks from post-application exposure were calculated for long-term dermal and inhalation exposures to machinists resulting from metal working fluid use. Risks of concern were identified for this use pattern at the maximum application rate of 0.3% product by weight of material treated.

To reduce post-application exposure, the Agency has determined that the following mitigation and label change for specific scenarios is appropriate and required for reregistration eligibility:

- Reduce the maximum application rate for paint uses to 0.2% product by weight of material treated

### 2. Environmental Risk Management

As the uses of azadioxabicyclooctane considered in this RED make it unlikely that any appreciable exposure to terrestrial or aquatic organisms would occur, no risk mitigation measures are required to address environmental exposure to azadioxabicyclooctane.

### 3. Other Labeling Requirements

In order to be eligible for reregistration, various use and safety information will be included in the labeling of all end-use products containing azadioxabicyclooctane. For the specific labeling statements and a list of outstanding data, refer to Section V of this RED document.

### 4. Threatened and Endangered Species Considerations

#### a. The Endangered Species Program

The Agency has developed the Endangered Species Protection Program to identify pesticides whose use may cause adverse impacts on endangered and threatened species, and to implement mitigation measures that address these impacts. The Endangered Species Act requires federal agencies to ensure that their actions are not likely to jeopardize listed species or adversely modify designated critical habitat. To analyze the potential of registered pesticide uses to affect any particular species, EPA puts basic toxicity and exposure data developed for risk assessments into context for individual listed species and their locations by evaluating important ecological parameters, pesticide use information, the geographic relationship between specific pesticide uses and species locations, and biological requirements and behavioral aspects of the particular species. A determination that there is a likelihood of potential impact to a listed species may result in limitations on use of the pesticide, other measures to mitigate any potential impact, or consultations with the Fish and Wildlife Service and/or the National Marine Fisheries Service as necessary.

Due to the low likelihood of exposure and low toxicity of azadioxabicyclooctane, the indoor uses of the compound are not likely to adversely affect listed species. Likewise, offshore oil production use of azadioxabicyclooctane is considered unlikely to adversely affect listed species due to the low toxicity of the compound and the large dilution factor in offshore operations. Therefore, the Agency expects no effects to listed species or critical habitat and therefore makes a "No Effect" determination for this chemical.

### b. General Risk Mitigation

Azadioxabicyclooctane end use products (EPs) may also contain other registered pesticides. Although the Agency is not proposing any mitigation measures for products containing azadioxabicyclooctane specific to federally listed threatened and endangered species, the Agency needs to address potential risks from other end-use products. Therefore, the Agency requires that users adopt all threatened and endangered species risk mitigation measures for all active ingredients in the product. If a product contains multiple active ingredients with conflicting threatened and endangered species risk mitigation measures, the more stringent measure(s) should be adopted.

## V. What Registrants Need to Do

The Agency has determined that azadioxabicyclooctane is eligible for reregistration provided that: (i) additional data that the Agency intends to require confirm this decision; and (ii) the risk mitigation measures outlined in this document are adopted, and (iii) label amendments are made to reflect these measures. To implement the risk mitigation measures, the registrants must amend their product labeling to incorporate the label statements set forth in the Label Changes Summary Table in Section B below (Table 13). The additional data requirements that the Agency intends to obtain will include, among other things, submission of the following:

For azadioxabicyclooctane technical grade active ingredient products, the registrant needs to submit the following items:

**Within 90 days from receipt of the generic data call in (DCI):**

1. Completed response forms to the generic DCI (i.e., DCI response form and requirements status and registrant's response form); and,

2. Submit any time extension and/or waiver requests with a full written justification.

**Within the time limit specified in the generic DCI:**

1. Cite any existing generic data which address data requirements or submit new generic data responding to the DCI.

Please contact Tom Luminello at (703) 308-8075 with questions regarding generic reregistration.

By US mail:
Document Processing Desk (DCI/AD)
Tom Luminello
US EPA (7510C)
1200 Pennsylvania Ave., NW
Washington, DC 20460

By express or courier service:
Document Processing Desk (DCI/AD)
Tom Luminello
Office of Pesticide Programs (7510C)
Room 266A, Crystal Mall 2
1801 S. Bell Street
Arlington, VA 22202

For end use products containing the active ingredient azadioxabicyclooctane, the registrant needs to submit the following items for each product.

**Within 90 days from the receipt of the product-specific data call-in (PDCI)**:

1. Completed response forms to the PDCI (PDCI response form and requirements status and registrant's response form); and,

2. Submit any time extension or waiver requests with a full written justification.

**Within eight months from the receipt of the PDCI:**

1. Two copies of the confidential statement of formula (CSF) (EPA Form 8570-4);

2. A completed original application for reregistration (EPA Form 8570-1). Indicate on the form that it is an "application for reregistration";

3. Five copies of the draft label incorporating all label amendments outlined in Table 13 of this document;

4. A completed form certifying compliance with data compensation requirements (EPA Form 8570-34);

5. If applicable, a completed form certifying compliance with cost share offer requirements (EPA Form 8570-32); and,

6. The product-specific data responding to the PDCI.

Please contact Marshall Swindell at (703) 308-6341 with questions regarding product reregistration and/or the PDCI. All materials submitted in response to the PDCI should be addressed as follows:

By US mail:
Document Processing Desk (PM-31)
Marshall Swindell
US EPA (7510C)
1200 Pennsylvania Ave., NW
Washington, DC 20460

By express or courier service:
Document Processing Desk (PM-31)
Marshall Swindell
Office of Pesticide Programs (7510C)
Room 266A, Crystal Mall 2
1801 South Bell Street
Arlington, VA 22202

## A. Manufacturing Use Products

### 1. Additional Generic Data Requirements

The generic database supporting the reregistration of azadioxabicyclooctane has been reviewed and determined to be substantially complete. However, the following additional data requirements have been identified by the Agency as confirmatory data requirements. A generic data call-in will be issued at a later date. The 90-day inhalation study is being required to confirm the Agency's conclusions on residential risks.

EPA requires that the registrant submit carcinogenicity data for azadioxabicyclooctane to support the metal working fluid use. Conversely, the registrant may claim that a carcinogenicity study would not be required for the metalworking fluid use if the use is for "enclosed metalworking systems". Under this scenario, it has been determined that certain toxicology data requirements including carcinogenicity testing would be held in reserve pending review of worker exposure in such enclosed systems.

The Agency has established an interim two-tiered system for toxicology testing requirements. Tier I toxicology data requirements would apply to all indirect food additives that result in residue concentrations ranging from 0-200ppb which applied to azadioxabicyclooctane. The requirements would consist of an acute toxicity testing battery, subchronic toxicity study in the rodent, a developmental toxicity study in the rat, and a mutagenicity testing battery. The Agency also conducts a literature search and can also conduct a Structural Activity Relationship analysis (SAR) if appropriate. The Agency also will hold in reserve a two-generation reproduction toxicity study in the rat and a subchronic toxicity studies in a non-rodent which would become data requirements if the Agency's evaluation of the Tier 1 data warranted. A 2-generation reproduction study and a subchronic toxicity study in a non-rodent species are being held in reserve for azadioxabicyclooctane.

Tier II studies would be triggered by the presence of significant (i.e. >200ppb) residues in food or evidence of significant toxicity from the Tier I data set, which may include developmental / reproductive, or other systemic toxicity such as presence of neoplastic growth or significant target organ toxicity. In such cases, chronic toxicity and carcinogenicity testing would be required.

The risk assessment noted deficiencies in the surrogate dermal and inhalation exposure data available from the Chemical Manufacturers Association (CMA) data base. Therefore, the Agency is requiring confirmatory data to support the uses assessed with the CMA exposure data within this risk assessment. The risk assessment also noted that many of the use parameters (e.g., amount handled and duration of use) were based on professional judgments. Therefore, descriptions of human activities associated with the uses assessed are required as confirmatory.

**Table 12. Confirmatory Data Requirements for Reregistration**

| Guideline Study Name | New OPPTS Guideline No. | Old Guideline No. |
|---|---|---|
| Skin Sensitization | 870.2600 | 81-6 |
| 90-Day Inhalation Toxicity Study-Rat | 870.3465 | 82-4 |
| Freshwater Fish Acute Toxicity with a warmwater species, preferably Bluegill sunfish, using TGAI | 850.1075 | 72-1 |
| Indoor Inhalation Exposure and Applicator Exposure Monitoring Data Reporting | 875.1400 and 875.1600 | 234 and 236 |
| Indoor Dermal Exposure and Applicator Exposure Monitoring Data Reporting | 875.1200 and 875.1600 | 233 and 236 |
| Descriptions of Human Activity | 875.2800 | 133-1 |
| Carcinogenicity | 870.4200 | 83-2 |
| **Studies Held in Reserve** | | |
| 2-Generation Reproduction | 870.3800 | 83-4 |
| 90-Day Oral Toxicity in Non-Rodents | 870.3150 | 82-1 |

### 2. Labeling for Technical and Manufacturing Use Products

To ensure compliance with FIFRA, technical and manufacturing use product (MP) labeling should be revised to comply with all current EPA regulations, PR Notices and applicable policies. The Technical and MP labeling should bear the labeling contained in Table 13, Label Changes Summary Table.

## B. End-Use Products

### 1. Additional Product-Specific Data Requirements

Section 4(g)(2)(B) of FIFRA calls for the Agency to obtain any needed product-specific data regarding the pesticide after a determination of eligibility has been made. The Registrant must review previous data submissions to ensure that they meet current EPA acceptance criteria and if not, commit to conduct new studies. If a registrant believes that previously submitted data meet current testing standards, then the study MRID numbers should be cited according to the instructions in the Requirement Status and Registrants Response Form provided for each product.

A product-specific data call-in, outlining specific data requirements, will follow this RED at a later date.

### 2. Labeling for End-Use Products

Labeling changes are necessary to implement measures outlined in Section IV above. Specific language to incorporate these changes is specified in Table 13.

Registrants may generally distribute and sell products bearing old labels/labeling for 26 months from the date of the issuance of this Reregistration Eligibility Decision document.

Persons other than the registrant may generally distribute or sell such products for 52 months from the approval of labels reflecting the mitigation described in this RED. However, existing stocks time frames will be established case-by-case, depending on the number of products involved, the number of label changes, and other factors. Refer to "Existing Stocks of Pesticide Products; Statement of Policy," *Federal Register*, Volume 56, No. 123, June 26, 1991.

### a. Label Changes Summary Table

In order to be eligible for reregistration, amend all product labels to incorporate the risk mitigation measures outlined in Section IV. The following table describes how language on the labels should be amended.

**Table 13. Labeling Changes Summary Table**

| Summary of Labeling Changes for Azadioxabicyclooctane | | |
|---|---|---|
| Description | Amended Labeling Language | Placement on Label |
| Reduce rate for paint applications | Maximum rate for paint applications is 0.4% product by weight of material treated | Directions for Use |
| Reduce rate for metal working fluids applications | Maximum rate for metal working fluids applications is 0.2% product by weight of material treated | Directions for Use |

# VI. APPENDICES

**Appendix A. Table of Use Patterns for Azadioxabicyclooctane**

| Use Site | Formulation | Method of Application | Application Rate (Range)[a] | Use Limitations |
|---|---|---|---|---|
| **Industrial and Manufacturing Facilities** | | | | |
| Adhesives (natural-based) | 1529-28 | Open pour | 0.2 – 0.5 % by weight of formulation | Add to water phase or post addition. |
| Adhesives (synthetic) | 1529-28 | Open pour | 0.1 – 0.5 % by weight of formulation | Add to water phase or post addition. |
| Caulks | 1529-28 | Open pour | 0.1 – 0.5 % by weight of formulation | Add to water phase during manufacture. |
| Drilling Muds | 1529-28 | Open pour | 0.05 – 0.2 % by weight of formulation | Add to water phase or post addition. |
| Flooding Fluids | 1529-28 | Open pour | 0.01 – 0.1 % by weight of formulation | Post addition. |
| Latex Emulsion | 1529-28 | Open pour | 0.05 – 0.3 % by weight of formulation | Post addition. |
| Wax Emulsion | 1529-28 | Open pour | 0.05 – 0.3 % by weight of formulation | Post addition. |
| Latex Paint | 1529-28 | Open pour | 0.1 – 0.5 % by weight of formulation | Add at any point during manufacture. |

[a] The optimum amount of Nuosept 95 Preservative required for adequate preservation is best determined by conducting a series of test loadings and making adjustments. The maximum level permitted for metal-working fluids is 0.3%. The maximum level permitted for all other applications is 0.5%

| Use Site | Formulation | Method of Application | Application Rate (Range)[a] | Use Limitations |
|---|---|---|---|---|
| Inks | 1529-28 | Open pour | 0.1 – 0.5 % by weight of formulation | Post addition. |
| Paper Coatings | 1529-28 | Open pour | 0.1 – 0.5 % by weight of formulation | **Must be limited to contact with dry food.**<br>Add to water phase or post addition. |
| Pigment Dispersion | 1529-28 | Open pour | 0.1 – 0.3 % by weight of formulation | Add at any point during manufacture. |
| Pigment Slurry | 1529-28 | Open pour | 0.05 – 0.1 % by weight of formulation | Add to water phase or post addition. |
| Sealants | 1529-28 | Open pour | 0.1 – 0.5 % by weight of formulation | Add to water phase during manufacture. |
| Metalworking Fluids | 1529-28 | Open pour | 0.1 – 0.3 % by weight of formulation | Add to water phase during manufacture and service. |
| Textile Fiber Finish | 1529-28 | Open pour | 0.05 – 0.1 % by weight of formulation | **For use on fibers that are not in direct contact with skin.**<br>Add at any point during manufacture. |

[a] The optimum amount of Nuosept 95 Preservative required for adequate preservation is best determined by conducting a series of test loadings and making adjustments. The maximum level permitted for metal-working fluids is 0.3%. The maximum level permitted for all other applications is 0.5%.

**APPENDIX B: Azadioxabicyclooctane (Case 3023)**

Appendix B lists the **generic** (not product specific) data requirements which support the re-registration of azadioxabicyclooctane. These requirements apply to azadioxabicyclooctane in all products, including data requirements for which a technical grade active ingredient is the test substance. The data table is organized in the following formats:

1. **Data Requirement** (Columns 1 and 2). The data requirements are listed by Guideline Number. The first column lists the new Part 158 Guideline numbers, and the second column lists the old Part 158 Guideline numbers. Each Guideline Number has an associated test protocol set forth in the Pesticide Assessment Guidance, which are available on the EPA website.

2. **Guideline Description** (Column 3). Identifies the guideline type.

3. **Use Pattern** (Column 4). This column indicates the standard Antimicrobial Division use patterns categories for which the generic (not product specific) data requirements apply. The number designations are used in Appendix B.

   **(1) Agricultural premises and equipment**
   **(2) Food handling/ storage establishments premises and equipment**
   **(3) Commercial, institutional and industrial premises and equipment**
   **(4) Residential and public access premises**
   **(5) Medical premises and equipment**
   **(6) Human water systems**
   **(7) Materials preservatives**
   **(8) Industrial processes and water systems**
   **(9) Antifouling coatings**
   **(10) Wood preservatives**
   **(11) Swimming pools**
   **(12) Aquatic areas**

3. **Bibliographic Citation** (Column 5). If the Agency has data in its files to support a specific generic Guideline requirement, this column will identity each study by a "Master Record Identification (MRID) number. The listed studies are considered "valid" and acceptable for satisfying the Guideline requirement. Refer to the Bibliography appendix for a complete citation of each study.

| DATA REQUIREMENT | | | | CITATION(S) |
|---|---|---|---|---|
| **New Guideline Number** | **Old Guideline Number** | **Study Title** | **Use Pattern** | **MRID Number** |
| **PRODUCT CHEMISTRY** | | | | |
| 830.1550 | 61-1 | Product Identity and Composition | All | 42734301, 41671601, 41671602,41671603 |
| 830.1600<br>830.1620<br>830.1650 | 61-2a | Starting Materials and Manufacturing Process | All | 42734301, 41671601, 41671602,41671603 |
| 830.1670 | 61-2b | Formation of Impurities | All | 42734301, 41671601, 41671602,41671603 |
| 830.1700 | 62-1 | Preliminary Analysis | All | 42734301, 41671601, 41671602,41671603 |
| 830.1750 | 62-2 | Certification of Limits | All | 42740801, 41671601, 41671602,41671603 |
| 830.1800 | 62-3 | Analytical Method | All | 42740801, 41671601, 41671602,41671603 |
| 830.6302 | 63-2 | Color | All | 42734301, 41671601, 41671602,41671603 |
| 830.6303 | 63-3 | Physical State | All | 42734301, 41671601, 41671602,41671603 |
| 830.6304 | 63-4 | Odor | All | 42734301, 41671601, 41671602,41671603 |
| 830.7050 | None | UV/Visible Absorption | All | 42734301, 41671601, 41671602,41671603 |
| 830.7200 | 63-5 | Melting Point | All | 42734301, 41671601, 41671602,41671603 |
| 830.7220 | 63-6 | Boiling Point | All | 42734301, 41671601, 41671602,41671603 |
| 830.7300 | 63-7 | Density | All | 42734301, 41671601, 41671602,41671603 |
| 830.7840<br>830.7860 | 63-8 | Solubility | All | 42734301, 41671601, 41671602,41671603 |
| 830.7950 | 63-9 | Vapor Pressure | All | 42734301, 41671601, 41671602,41671603 |
| 830.7370 | 63-10 | Dissociation Constant in Water | All | 42734301, 41671601, 41671602,41671603 |

| DATA REQUIREMENT | | | | CITATION(S) |
|---|---|---|---|---|
| **New Guideline Number** | **Old Guideline Number** | **Study Title** | **Use Pattern** | **MRID Number** |
| 830.7550<br>830.7560<br>830.7570 | 63-11 | Partition Coefficient (Octanol/Water) | All | 42734301, 41671601, 41671602,41671603 |
| 830.7000 | 63-12 | pH | All | 42734301, 41671601, 41671602,41671603 |
| 830.6313 | 63-13 | Stability | All | 42734301, 41671601, 41671602,41671603 |
| 830.6314 | 63-14 | Oxidizing/Reducing Action | All | 42734301, 41671601, 41671602,41671603 |
| 830.6315 | 63-15 | Flammability | All | 42734301, 41671601, 41671602,41671603 |
| 830.6316 | 63-16 | Explodability | All | 42734301, 41671601, 41671602,41671603 |
| 830.6317 | 63-17 | Storage Stability | All | 42734301, 41671601, 41671602,41671603 |
| 830.7100 | 63-18 | Viscosity | All | 42734301, 41671601, 41671602,41671603 |
| 830.6319 | 63-19 | Miscibility | All | 42734301, 41671601, 41671602,41671603 |
| 830.6320 | 63-20 | Corrosion Characteristics | All | 42734301, 41671601, 41671602,41671603 |
| **ECOLOGICAL EFFECTS** | | | | |
| 850.2100 | 71-1 | Avian Acute Oral Toxicity Test (Mallard Duck) | All | 129008 |
| 850.2200 | 71-2 | Avian Dietary Toxicity (Bobwhite Quail) | | 4164801,112791 |
| 850.2200 | 71-2b | Avian Dietary Toxicity (Mallard Duck) | | 112792 |
| 850.1075 | 72-1a | Fish Acute Toxicity – Freshwater (Blue Gill) | All | 109246 |
| 850.1075 | 72-1c | Fish Acute Toxicity – Freshwater (Rainbow Trout) | | 109246 |
| 850.1010 | 72-2 | Acute Aquatic Invertebrate Toxicity (Daphnid) | | 129009 |
| 850.1025 | 72-3B | Estuarine/Marine Toxicity - Mollusk | | 129012 |
| | | | | |
| | | | | |
| **TOXICOLOGY** | | | | |

| DATA REQUIREMENT | | | | CITATION(S) |
|---|---|---|---|---|
| **New Guideline Number** | **Old Guideline Number** | **Study Title** | **Use Pattern** | **MRID Number** |
| 870.1100 | 81-1 | Acute Oral - Rat | All | 41641601 |
| 870.1200 | 81-2 | Acute Dermal - Rabbit | All | 41671801 |
| 870.1300 | 81-3 | Acute Inhalation - Rat | All | 42650901 |
| 870.2400 | 81-4 | Primary Eye Irritation - Rabbit | All | 41641602 |
| 870.2500 | 81-5 | Primary Dermal Irritation - Rabbit | All | 41641603 |
| 870.2600 | 81-6 | Dermal Sensitization | All | 41641604 |
| 870.3100 | 82-1a | 90-Day Feeding-Rodent | All | 41641606 |
| 870.3200 | 82-2 | 21/28-Day Dermal Toxicity - Rat | All | 41641605 |
| 870.3250 | 82-3 | 90-day Dermal Toxicity - Rodent | All | |
| 870.3465 | 82-4 | 28/90-Day Inhalation - Rat | All | DG |
| 870.4200 | 83-2 | Carcinogenicty | | DG |
| 870.3700 | 83-3 | Developmental Toxicity -Rat | All | 41537501 |
| 870.3700a | 83-3a | Prenatal Developmental in Rodents | All | 41699001 |
| 870.3700b | 83-3b | Developmental Toxicity -Rabbit | | |
| 870.5265 | 84-2 | Bacterial Reverse Mutation Assay | All | |
| 870.5395 | 84-2 | Micronucleus Assay | All | |
| 870.5450 | 84-2 | Dominant Lethal Rat | | |
| 870.5500 | 84-2 | Bacterial DNA Damager or Repair | | 93050019 |
| 870.5550 | 84-2 | Unscheduled DNA Synthesis Assay | | 42711001 |
| | | ***Reserved Studies*** | | |

| DATA REQUIREMENT | | | | CITATION(S) |
|---|---|---|---|---|
| **New Guideline Number** | **Old Guideline Number** | **Study Title** | **Use Pattern** | **MRID Number** |
| 870.3800 | 83-4 | 2 Generation Repro | | DG, reserved study |
| 870.3150 | 82-1b | 90-Day Oral Subchronic in Non-Rodent | | DG, reserved study |
| | | ***Other Genotoxic Studies*** | | |
| Non-Guideline | 84-4 | In Vitro Cell Transformation Assay | | 93050022, 93050024, 93050025 |
| **OCCUPATIONAL/RESIDENTIAL EXPOSURE** | | | | |
| 875.2800 | 133-1 | Descriptions of Human Activity | All | DG |
| 875.1200<br>875.1600 | 233/236 | Dermal Indoor Exposure | All | DG |
| 875.1400<br>875.1600 | 234/236 | Inhalation Indoor Exposure | All | DG |
| **ENVIRONMENTAL FATE** | | | | |
| 835.2120 | 161-1 | Hydrolysis | All | 43067001 |
| **OTHER DATA REQUIREMENTS** | | | | |
| | | | | |
| | | | | |

## Appendix C. Technical Support Documents

Additional documentation in support of this RED is maintained in the OPP docket, located in room 119, Crystal Mall #2, 1801 S. Bell St., Arlington, VA 22202. It is open Monday through Friday, excluding legal holidays, from 8:30 AM to 4:00 PM.

The docket initially contained preliminary risk assessments and related documents as of July 20, 2005. Sixty days later the first public comment period closed. The EPA then considered comments and revised the risk assessments.

All documents, in hard copy form, may be viewed in the OPP docket room or downloaded or viewed via the Internet at the following site: http://www.epa.gov/edockets

These documents include:

1. Azadioxabicyclooctane: AD Preliminary Risk Assessment for the Reregistration Eligibility Decision Document, July12, 2005

2. Azadioxabicyclooctane: Dietary Exposures and Risks from Antimicrobial Indirect Food Contact Uses, July 7, 2005

3. Azadioxabicyclooctane: Occupational and Residential Exposure Chapter for RED, July, 7, 2005

4. Azadioxabicyclooctane: Environmental Fate Assessment of Nuosept 95 for RED, March 1, 2005

5. Azadioxabicyclooctane: Product Chemistry Science Chapter for RED, April 6, 2005

6. Azadioxabicyclooctane: Report of the Antimicrobials Division Toxicology Endpoint Selection Committee, May 25, 2005

7. Azadioxabicyclooctane: Ecological Hazard and Environmental Risk Assessment for 5-hydroxymethoxymethyl-1-aza-3, 7-dioxabicyclooctanes (Aza), May 17, 2005

8. Epidemiology Assessment based on Incident Reports, May 19, 2005

9. Hazard Characterization

## Appendix D: Generic Data Requirements and Studies Used to Make the Reregistration Decision (Bibliography)

1. MRID Studies


| MRID# | Citation |
|---|---|
| 109246 | Bentley, R. (1974) Acute Toxicity of Nuosept 95 to Bluegill (Lepomis macrochirus) and Rainbow Trout (Salmo gairdneri). (Unpublished study received Jul 19, 1982 under 92-35; prepared by Bionomics EG & G, Inc., submitted by Tenneco Chemical, Inc., Piscataway, N.J.; CDL:247878-A) |
| 112791 | Fink, R. (1974) Final Report: Eight-day Dietary LC50--Bobwhite Quail: Nuosept 95: Project No. 122-101. (Unpublished study received Jul 19, 1982 under 92-35; prepared by Truslow Farms, Inc., submitted by Tenneco Chemical, Inc., Piscataway, NJ; CDL: 247878-B) |
| 112792 | Fink, R. (1974) Final Report: Eight-day Dietary LC50--Mallard Ducks: Nuosept 95: Project No. 122-102. (Unpublished study received Jul 19, 1982 under 92-35; prepared by Truslow Farms, Inc., submitted by Tenneco Chemical, Inc., Piscataway, NJ; CDL: 247878-C) |
| 129008 | Beavers, J.; Jaber, M.; Joiner, G.; et al. (1983) Acute Oral LD50-- Mallard Duck: Nuosept 95: Project No. 122-105. Final rept. (Unpublished study received Jun 23, 1983 under 1100-82; prepared by Wildlife International Ltd., submitted by Nuodex, Inc., Piscataway, NJ; CDL:250533-A) |
| 129009 | LeBlanc, G.; Surprenant, D. (1983) Acute Toxicity of Nuosept 95 to the Water Flea ...: Report #BW-83-2-1366. (Unpublished study received Jun 23, 1983 under 1100-82; prepared by EG & G Bionomics, submitted by Nuodex, Inc., Piscataway, NJ; CDL:250533-B) |
| 129010 | Ward, G.; Hodgson, J. (1983) Acute Toxicity of Nuosept 95 to Sheepshead Minnows ...: Report No. BP-83-5-56. (Unpublished study received Jun 23, 1983 under 1100-82; prepared by EG & G Bionomics, submitted by Nuodex, Inc., Piscataway, NJ; CDL: 250533-C) |
| 129011 | Ward, G.; Hodgson, J. (1983) Acute Toxicity of Nuosept 95 to Mysid Shrimp ...: Report No. BP-83-3-41. (Unpublished study received Jun 23, 1983 under 1100-82; prepared by EG & G Bionomics, submitted by Nuodex, Inc., Piscataway, NJ, CDL:250533-D) |

129012 Ward, G.; Hodgson, J. (1983) Acute Toxicity of Nuosept 95 to Embryos-larvae of Eastern Oysters ...: Report No. BP-83-6-64. (Unpublished study received Jun 23, 1983 under 1100-82; prepared by EG & G Bionomics, submitted by Nuodex, Inc., Piscataway, NJ; CDL:250533-E)

41537501 Smith, J.; Masters, R.; John, D.; et al. (1990) A Study of the Effect of Nuosept 95 on Pregnancy of the Rat: Report No. NDX 3/ 88962. Unpublished study prepared by Huntingdon Research Centre Ltd. 122 p.

41641601 Dilley, J. (1990) Acute Oral Toxicity of Nuosept 95 in Rats: Interim Progress Report: Lab Project Number: LSC-8470. Unpublished study prepared by SRI International. 11 p.

41641602 Hershman, R. (1984) Summary of Results of a Primary Eye Irritation Study, Rabbit: Lab Project Number: 84-3988A. Unpublished study prepared by Biosearch Inc. 9 p.

41641603 Unwin, S. (1983) Primary Dermal Irritation Test on Nuosept 95 in New Zealand White Albino Rabbits: Final Report: Lab Project Number: 7808-E/1. Unpublished study prepared by Midwest Research Institute. 11 p.

41641605 Elliot, P.; Street, A.; Gibson, W.; et al. (1985) Twenty-One Day Dermal Toxicity Study in Rabbits with Nuosept 95/Nuosept C: Lab Project Number: NDX 1-84955-SB. Unpublished study prepared by Huntingdon Research Centre. 103 p.

41641606 Sasmore, D.; Tyson, C. (1980) Effect of Nuosept 95 in Rats: 90-Day Toxicity Study-Contains Dose Range Study for Dominant Lethal Study: Final Report: Lab Project Number: LSC-8654. Unpublished study prepared by SRI Int. 72 p.

41671801 Liggett, M.; McRae, L. (1990) Acute Dermal Toxicity to Rabbits of Nuosept 95: Final Report: Lab Project Number: 90591D/NDX 8/AC. Unpublished study prepared by Huntingdon Research Centre Ltd. 14 p.

41684801 Hakin, B.; Rodgers, M.; Anderson, A.; et al. (1990) Nuosept 95: LC- 50 to Bobwhite Quail: Lab Project Number: NDX9/901288. Unpublished study prepared by Huntingdon Research Centre Ltd. 30 p.

41699001 Hodgson, J. (1988) A Study of the Effect of Nuosept 95 on Pregnancy of the Rat: Lab Project Number: HRC NDX 3/88962. Unpublished study prepared by Huntingdon Research Centre, Ltd. 122 p.

41728601 O'Loughlin, K. (1990) Measurement of Micronuclei in Bone Marrow Erythrocytes of Swiss-Webster Mice Following Two Treatments with Nuosept 95: Lab Project Number: 1556-C01-90. Unpublished study prepared by SRI International. 36 p.

42587501 Popendorf, W.; Selim, M.; Kross, B. (1992) Chemical Manufacturers Association Antimicrobial Exposure Assessment Study: Second Replacement to MRID 41761201: Lab Project Number: Q626. Unpublished study prepared by The University of Iowa. 316 p.

42650901 Cholakis, J.; Sprinz, H. (1983) Acute Inhalation Toxicity of Nuosept 95 in Sprague-Dewley Rats: Lab Project Number: 7808-E(1). Unpublished study prepared by Midwest Research Institute. 25 p.

42711001 Hamilton, C. (1993) Measurement of Unscheduled DNA Synthesis in Male Fischer-344 Rat Hepatocytes Following In-Vivo Treatment with Nuosept 95: Lab Project Number: LSC 4084-U01-92. Unpublished study prepared by SRI International. 24 p.

42720801 Rush, D. (1993) Efficacy/Phytotoxicity Studies Performed with Monocarbamide Dihydrogensulfate: Lab Project Number: RE-P-GA-10: RE-P-GA-4: RE-FC-GA-2. Unpublished study prepared by Unocal Agriproducts. 123 p.

42734301 Mahoney, D. (1993) Product Identity (Confidential Statement of Formula): Nuosept 95 Preservative: Upgrade to MRID 41671601. Unpublished study prepared by Huls America, Inc. 6 p.

42740801 Mahoney, D. (1993) Nuosept 95: Certification of Limits (Gas Chromatogram): Final Report. Unpublished study prepared by Huls America, Inc. 7 p.

43060701 Hauswirth, J.; Davis, C. (1993) PrimaryDermal Irritation of M-Pede Insecticide in Rabbits. Unpublished study prepared by Mycogen Corp. 6 p.

43067001 Cross, J. (1993) Aqueous Hydrolysis of Nuosept 95: Lab Project Number: 211S01. Unpublished study prepared by EPL Bio-Analytical Services, Inc. 120 p.

93050015 Bentley, R.; Sleight, B. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00109246. Acute Toxicity of Nuosept 95 Preservative to Bluegill and Rainbow Trout. Prepared by EG&G, Inc. 13 p.

93050016 LeBlanc, G. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00129009. Acute Toxicity of NUOSEPT 95 to the Water Flea (Daphnia magna): Project No. BW-83-2-1366. Prepared by EG&G, Bionomics. 18 p.

93050017 Haworth, S. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00088956. Salmonella/Mammalian-Microsome Plate Incorporation Mutagenesis Assay: Project No. 601-257-1. Prepared by EG&G Mason Research Institute. 20 p.

93050018 Lee, C.; Van Goethem, D. (1990) Huls America, Inc. Phase 3 Reformat of MRID

00088974. Mutagenicity Studies on NUOSEPT 95 Salmonella/Microsome Test: Project No. 4754-B. Prepared by Midwest Research Institute. 14 p.

93050019 Haworth, S. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00088957. Bacterial DNA Damage/Repair Suspension Assay: Project No. 026-601-257-6. Prepared by EG&G Mason Research Institute. 17 p.

93050020 Metz, F.; Van Goethem, D. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00088958. Bacterial DNA Repair Assay of NUOSEPT 95: Project No. 4822-B. Prepared by Midwest Research Institute. 13 p.

93050021 Myhr, B. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00088959. Evaluation of NUOSEPT 95 in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay: Project No. 20991. Prepared by Litton Bionetics. 21 p.

93050022 Thilager, A. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00088960. An Evaluation of Carcinogenic Potential of NUOSEPT 95 Employing the C3H/10T 1/2 Cell Transformation Assay: Project No. 601-257-8. Prepared by EG&G Mason Research Institute. 23 p.

93050023 Schechtman, L. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00088961. Activity of T 1597 in an vitro Mammalian Cell Transformation Assay in the Absence of Exogenous Metabolic Activation: Project No. T 1597.122. Prepared by Microbiological Associates. 22 p.

93050024 Thilager, A. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00088962. An Evaluation of Carcinogenic Potential of R-1162 (NUOSEPT 95) Employing C3H/1OT 1/2 Cell Transformation System: Project No. 026-205-435-8. Prepared by EG&G Mason Research Institute. 24 p.

93050025 Thilagar, A. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00088963. An Evaluation of Carcinogenic Potential of R-1143 (NUOSEPT 95) Employing C3H/10T 1/2 Cell Transformation System: Project No. 026-205-437-8. Prepared by EG&G Mason Research Institute. 24 p.

93050026 Jorgenson, T. (1990) Huls America, Inc. Phase 3 Reformat of MRID 00088953. Dominant Lethal Study of NUOSEPT 95: Project No. LSC-8654. Prepared by SRI International. 81 p.

2. Open Literature

PHED Surrogate Exposure Guide. 1997. Estimates of Worker Exposure from the Pesticide Handler Exposure Database Version 1.1. May 1997.

3. Website References

Environmental Protection Agency (EPA), 2002. ECOTOX User Guide: ECOTOXicology Database System. Version 3.0. http://www.epa.gov/ecotox/.

Environmental Protection Agency (EPA), 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs U.S. Environmental Protection Agency - Endangered and Threatened Species Effects Determinations, Appendix A, Section IIB, pg.81. US Environmental Protection Agency. January 24, 2004. http://www.epa.gov/oppfead1/endanger/consultation/ecorisk-overview.pdf.

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Food and Drug Administration (US FDA), Center for Food Safety & Applied Nutrition (CFSAN). 2002. Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations. April 2002. http://www.cfsan.fda.gov/~dms/opa2pmnc.html.

Food and Drug Administration (US FDA), Center for Food Safety & Applied Nutrition (CFSAN). 2005. CEDI/ADI Table: Publicly Available Database of Cumulative Estimated Daily Intakes and Acceptable Daily Intakes. May 2005. http://www.cfsan.fda.gov/~dms/opa-tedi.html.

4. Supporting Documents

Cinalli, Christina, et al., 1992. A Laboratory Method to Determine the Retention of Liquids on the Surface of Hands. Prepared for Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA Contract No. 68-02-4254. September 1992.

Environmental Protection Agency (EPA), 1997a. Standard Operating Procedures (SOPs) for Residential Exposure Assessments. Health Effects Division, Office of Pesticide Programs.

Environmental Protection Agency (EPA), 1997b. The Use of Models for Estimating Exposure and Risk of Antimicrobials in Metalworking Fluids. Memorandum from Winston Dang.

Environmental Protection Agency (EPA), 1999. Evaluation of the Chemical Manufacturers Association Antimicrobial Exposure Assessment Study (Amended on December 8, 1992). Memorandum from Siroos Mostaghimi, Ph.D., Environmental Engineer to Julie Fairfax, PM #36. November 4, 1999.

Environmental Protection Agency (EPA), 2000. Options for Revising CEB's Model for Screening Level Estimates of Dermal Exposure. Chemical Engineering Branch: Economics, Exposure, and Technology Division, Office of Pollution Prevention and Toxics. June 2000.

Environmental Protection Agency (EPA), 2001. Standard Operating Procedures (SOPs) for Residential Exposure Assessments. Office of Pesticide Programs.

Environmental Protection Agency, 2005. Summary of Antimicrobial Standard Operating Procedure (SOP) Assumptions for Residential and Occupational Exposure Assessments, January 2005.

## Appendix E. Generic Data Call-In

## Appendix F. Product Specific Data Call-In

## Appendix G. Batching of Azadioxabicyclooctane Products for Meeting Acute Toxicity Data Requirements for Reregistration

In an effort to reduce the time, resources and number of animals needed to fulfill the acute toxicity data requirements for reregistration of products containing azadioxabicyclooctane as the active ingredient, the Agency has batched products which can be considered similar for purposes of acute toxicity. Factors considered in the sorting process include each product's active and inert ingredients (identity, percent composition and biological activity), type of formulation (e.g., emulsifiable concentrate, aerosol, wettable powder, granular, etc.), and labeling (e.g., signal word, use classification, precautionary labeling, etc.). Note that the Agency is not describing batched products as "substantially similar" since some products within a batch may not be considered chemically similar or have identical use patterns.

Using available information, batching has been accomplished by the process described in the preceding paragraph. Not with-standing the batching process, the Agency reserves the right to require, at any time, acute toxicity data for an individual product should the need arise.

Registrants of products within a batch may choose to cooperatively generate, submit or cite a single battery of six acute toxicological studies to represent all the products within that batch. It is the registrants' option to participate in the process with all other registrants, only some of the other registrants, or only their own products within a batch, or to generate all the required acute toxicological studies for each of their own products. If a registrant chooses to generate the data for a batch, he/she must use one of the products within the batch as the test material. If a registrant chooses to rely upon previously submitted acute toxicity data, he/she may do so provided that the data base is complete and valid by today's standards (see acceptance criteria attached), the formulation tested is considered by EPA to be similar for acute toxicity, and the formulation has not been significantly altered since submission and acceptance of the acute toxicity data. Regardless of whether new data is generated or existing data is referenced, registrants must clearly identify the test material by EPA Registration Number. If more than one confidential statement of formula (CSF) exists for a product, the registrant must indicate the formulation actually tested by identifying the corresponding CSF.

In deciding how to meet the product specific data requirements, registrants must follow the directions given in the Data Call-In Notice and its attachments appended to the RED. The DCI Notice contains two response forms which are to be completed and submitted to the Agency within 90 days of receipt. The first form, "Data Call-In Response," asks whether the registrant will meet the data requirements for each product. The second form, "Requirements Status and Registrant's Response," lists the product specific data required for each product, including the standard six acute toxicity tests. A registrant who wishes to participate in a batch must decide whether he/she will provide the data or depend on someone else to do so. If a registrant supplies the data to support a batch of products, he/she must select one of the following options: Developing Data (Option 1), Submitting an Existing Study (Option 4), Upgrading an Existing Study (Option 5) or Citing an Existing Study (Option 6). If a registrant depends on another's data, he/she must choose among: Cost Sharing (Option 2), Offers to Cost Share (Option 3) or

Citing an Existing Study (Option 6). If a registrant does not want to participate in a batch, the choices are Options 1, 4, 5 or 6. However, a registrant should know that choosing not to participate in a batch does not preclude other registrants in the batch from citing his/her studies and offering to cost share (Option 3) those studies.

Two products were found which contain azadioxabicyclooctane as the active ingredient. These products have been placed into one batch in accordance with the active and inert ingredients and type of formulation.

NOTE: The technical acute toxicity values included in this document are for informational purposes only. The data supporting these values may or may not meet the current acceptance criteria.

| Batch 1 | EPA Registration Number | Percentage Active Ingredient |
|---|---|---|
| | 1528-28 | 50.0 |
| | 1528-49 | 50.0 |

## Appendix H. List of All Registrants Sent the Data Call-In

International Specialty Products

## Appendix I. List of Available Related Documents and Electronically Available Forms

Pesticide Registration Forms are available at the following EPA internet site: http://www.epa.gov/opprd001/forms/.

Pesticide Registration Forms (These forms are in PDF format and require the Acrobat reader)

**Instructions**

1. Print out and complete the forms. (Note: Form numbers that are bolded can be filled out on your computer then printed.)

2. The completed form(s) should be submitted in hardcopy in accord with the existing policy.

3. Mail the forms, along with any additional documents necessary to comply with EPA regulations covering your request, to the address below for the Document Processing Desk.

DO NOT fax or e-mail any form containing 'Confidential Business Information' or 'Sensitive Information.'

If you have any problems accessing these forms, please contact Nicole Williams at (703) 308-5551 or by e-mail at williams.nicole@epamail.epa.gov.

The following Agency Pesticide Registration Forms are currently available via the internet at the following locations:

| | | |
|---|---|---|
| 8570-1 | Application for Pesticide Registration/Amendment | http://www.epa.gov/opprd001/forms/8570-1.pdf |
| 8570-4 | Confidential Statement of Formula | http://www.epa.gov/opprd001/forms/8570-4.pdf |
| 8570-5 | Notice of Supplemental Registration of Distribution of a Registered Pesticide Product | http://www.epa.gov/opprd001/forms/8570-5.pdf |
| 8570-17 | Application for an Experimental Use Permit | http://www.epa.gov/opprd001/forms/8570-17.pdf |
| 8570-25 | Application for/Notification of State Registration of a Pesticide To Meet a Special Local Need | http://www.epa.gov/opprd001/forms/8570-25.pdf |
| 8570-27 | Formulator's Exemption Statement | http://www.epa.gov/opprd001/forms/8570-27.pdf |
| 8570-28 | Certification of Compliance with Data Gap Procedures | http://www.epa.gov/opprd001/forms/8570-28.pdf |
| 8570-30 | Pesticide Registration Maintenance Fee Filing | http://www.epa.gov/opprd001/forms/8570-30.pdf |
| 8570-32 | Certification of Attempt to Enter into an Agreement with other Registrants for Development of Data | http://www.epa.gov/opprd001/forms/8570-32.pdf |
| 8570-34 | Certification with Respect to Citations of Data (in PR Notice 98-5) | http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf |
| 8570-35 | Data Matrix (in PR Notice 98-5) | http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf |
| 8570-36 | Summary of the Physical/Chemical Properties (in PR Notice 98-1) | http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf |
| 8570-37 | Self-Certification Statement for the Physical/Chemical Properties (in PR Notice 98-1) | http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf |

**Pesticide Registration Kit**
www.epa.gov/pesticides/registrationkit/.

Dear Registrant:

For your convenience, we have assembled an online registration kit that contains the following pertinent forms and information needed to register a pesticide product with the U.S. Environmental Protection Agency's Office of Pesticide Programs (OPP):

1. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA) as Amended by the Food Quality Protection Act (FQPA) of 1996.

2. Pesticide Registration (PR) Notices

    a. 83-3 Label Improvement Program—Storage and Disposal Statements

    b. 84-1 Clarification of Label Improvement Program

    c. 86-5 Standard Format for Data Submitted under FIFRA

    d. 87-1 Label Improvement Program for Pesticides Applied through Irrigation Systems (Chemigation)

    e. 87-6 Inert Ingredients in Pesticide Products Policy Statement

    f. 90-1 Inert Ingredients in Pesticide Products; Revised Policy Statement

    g. 95-2 Notifications, Non-notifications, and Minor Formulation Amendments

    h. 98-1 Self Certification of Product Chemistry Data with Attachments. (This document is in PDF format and requires the Acrobat reader.)

    Other PR Notices can be found at http://www.epa.gov/opppmsd1/PR_Notices.

3. Pesticide Product Registration Application Forms (These forms are in PDF format and will require the Acrobat reader.)

    a. EPA Form No. 8570-1, Application for Pesticide Registration/Amendment

    b. EPA Form No. 8570-4, Confidential Statement of Formula

    c. EPA Form No. 8570-27, Formulator's Exemption Statement

    d. EPA Form No. 8570-34, Certification with Respect to Citations of Data

    e. EPA Form No. 8570-35, Data Matrix

4. General Pesticide Information (Some of these forms are in PDF format and will require the Acrobat reader.)

    a. Registration Division Personnel Contact List

    b. Biopesticides and Pollution Prevention Division (BPPD) Contacts

    c. Antimicrobials Division Organizational Structure/Contact List

    d. 53 F.R. 5952, Pesticide Registration Procedures; Pesticide Data Requirements (PDF format)

    e. 40 CFR Part 156, Labeling Requirements for Pesticides and Devices (PDF format)

    f. 40 CFR Part 158, Data Requirements for Registration (PDF format)

    g. 50 F.R. 48833, Disclosure of Reviews of Pesticide Data (November 27, 1985)

Before submitting your application for registration, you may wish to consult some additional sources of information. These include:

1. The Office of Pesticide Programs' Web Site.

2. The booklet "General Information on Applying for Registration of Pesticides in the United States", PB92-221811, available through the National Technical Information Service (NTIS) at the following address:

    National Technical Information Service (NTIS)
    5285 Port Royal Road
    Springfield, VA. 22161

The telephone number for NTIS is (703) 605-6000. Please note that EPA is currently in the process of updating this booklet to reflect the changes in the registration program resulting from the passage of the FQPA and the reorganization of the Office of Pesticide Programs. We anticipate that this publication will become available during the Fall of 1998. Their Web site is www.NTIS.gov.

3. The National Pesticide Information Retrieval System (NPIRS) of Purdue University's Center for Environmental and Regulatory Information Systems. This service does charge a fee for subscriptions and custom searches. You can contact NPIRS by telephone at (765) 494-6614 or through their Web site.

4. The National Pesticide Telecommunications Network (NPTN) can provide information on active ingredients, uses, toxicology, and chemistry of pesticides. You can contact NPTN by telephone at (800) 858-7378 or through their Web site: ace.orst.edu/info/nptn.

The Agency will return a notice of receipt of an application for registration or amended registration, experimental use permit, or amendment to a petition if the applicant or petitioner encloses with his submission a stamped, self-addressed postcard. The postcard must contain the following entries to be completed by OPP:

Date of receipt
EPA identifying number
Product Manager assignment

Other identifying information may be included by the applicant to link the acknowledgment of receipt to the specific application submitted. EPA will stamp the date of receipt and provide the EPA identifying File Symbol or petition number for the new submission. The identifying number should be used whenever you contact the Agency concerning an application for registration, experimental use permit, or tolerance petition.
To assist us in ensuring that all data you have submitted for the chemical are properly coded and assigned to your company, please include a list of all synonyms, common and trade names, company experimental codes, and other names which identify the chemical (including "blind" codes used when a sample was submitted for testing by commercial or academic facilities). Please provide a CAS number if one has been assigned.