# Overview Of The
# Zinc Pyrithione Preliminary Risk Assessment,
## June 2, 2004

## *Introduction*

This document summarizes EPA's preliminary human health and ecological risk findings and conclusions for the antimicrobial pesticide **Zinc Pyrithione** (also referred to in these assessments as Zinc Omadine® or Zinc 2-pyridinethiol-1-oxide), as presented fully in the following ten documents:

1. Zinc Pyrithione (Zinc Omadine®): AD Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document, Antimicrobials Division, D301376, 4/21/04, Deborah Smegal.

2. Zinc Pyrithione (Zinc Omadine®) - Revised Toxicology Endpoint Selection Report – Revised to address Registrant Error Comments, Antimicrobials Division, 4/1/04,Timothy F. McMahon, Ph.D., Senior Toxicologist.

3. Zinc Pyrithione (Zinc Omadine®): Toxicology Science Chapter For the Reregistration Eligibility Decision Document, PC Code 088002, Case 3030, Barcode: D301369, Antimicrobials Division, 4/1/04, Timothy F. McMahon, Ph.D., Senior Toxicologist.

4. Zinc Pyrithione (Zinc Omadine®): Occupational and Residential Exposure Assessment for the RED Document. Chemical No. 088002. Case No. 2480. DP Barcode: D301370, Antimicrobials Division 4/20/04, Doreen Aviado, Biologist/Deborah Smegal, Toxicologist/Risk Assessor.

5. Residue Chemistry Science Chapter for Zinc 2-pyridinethiol-1-oxide, Antimicrobials Division A. Najm Shamim, Ph.D., Chemist, no date.

6. Environmental Fate Science Chapter on Zinc Pyrithione (Zinc Omadine®) For Reregistration Eligibility Document (RED), Antimicrobials Division, D301372, 4/14/04, A. Najm Shamim, Ph.D., Chemist.

7. Revised Environmental Modeling for Zinc Omadine (Zinc pyrithione)
Antimicrobials Division, D301373, 4/22/04, Siroos Mostaghimi, Ph.D., Senior Scientist.

8. Zinc Pyrithione Ecological Hazard and Environmental Risk Characterization Chapter for the Reregistration Eligibility Decision (RED) Document (D301371), Antimicrobials Division 4/15/04, Kathryn Montague, M.S., Biologist.

9. Zinc Omadine–Report of the Hazard Identification Assessment Review Committee, 3/19/99, Tim McMahon.

10. Zinc Omadine – Report of the FQPA Safety Factor Committee, 8/7/01, Brenda Tarplee.

The purpose of this overview summary is to assist the reader by identifying the key features and findings of these risk assessments and conclusions reached in the assessments. This standard overview format was developed in response to comments and requests from the public which indicated that prior risk assessments for other chemicals were difficult to understand and too lengthy, and that it was not easy to compare the assessments for different chemicals due to the use of different formats.

Risks summarized in this document are those that result only from the use of zinc pyrithione. The Food Quality Protection Act 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 mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. Although it is possible that zinc pyrithione may express toxicity through a common mechanism with other compounds, at this time, the Agency does not have sufficient reliable information to make this determination. Consequently, the risks summarized herein are only for zinc pyrithione. If EPA identifies other substances that share a common mechanism of toxicity with zinc pyrithione, aggregate exposure assessments will be performed on each chemical, followed by a cumulative risk assessment.

Once the risk assessments are available to the public, there will be an opportunity for the public to view them and to comment on them. Public comments may be submitted to the OPP electronic docket at: www.epa.gov/edocket under the docket number OPP-2004-0147. Meetings with stakeholders (e.g., registrants, distributors, etc.) are planned to discuss the identified risks and to solicit input on risk mitigation strategies. This feedback will be used to complete the Reregistration Eligibility Decision (RED) document, which will include the resultant risk management decisions. The Agency plans to conduct a closure conference call with interested stakeholders to discuss the final regulatory decisions presented in the RED.

The Agency changed the reregistration case name for this chemical from "Omadine Salts" to "Zinc Pyrithione" to accurately reflect the sole active ingredient in this case. Previously, the Omadine Salts case contained two active ingredients (ie., Zinc Omadine and tert-Butylamine 2-pyridinethiol-1-oxide). The rationale for changing the case name is that: Omadine is a registered trade name and the Agency prefers not to use trade names as titles of documents; the plural "Salts" in the case name indicates multiple actives but there is only one chemical being considered (ie., zinc pyrithione); harmonize the case name with the sole active ingredient; and the second chemical previously listed in this case (ie., tert-Butylamine 2-pyridinethiol-1-oxide; PC

code 088005) has no active registered products, and is no longer a registered active ingredient.

## *Use Profile*

- **Antimicrobial:** Zinc pyrithione is used as an industrial preservative to prevent microbial degradation and deterioration, and to maintain the integrity of manufacturing precursor materials and finished manufactured articles. It is considered to have bacteriostat, fungistat, mildewstat, and algaestat properties.

  It is registered for the following indirect **food/drinking water** contact applications: Incorporation into food packaging adhesives, incorporation into articles made from, or coated with, FDA approved food contact polymers including food processing equipment, conveyor belts, utensils, and storage containers.

  It is registered for the following **non-food/non-drinking water** contact applications: Dry film preservation of joint compounds; glazing compounds; wood fillers; flooring adhesives; caulks; sealants; grouts; patching compounds; paints and coatings for residential, architectural, industrial and non-marine applications; dry wall; gypsum; pearlite; plaster-like or mineral based building materials used in the manufacture of ceilings, ceiling tile, walls, and partitions.

  Control of mildew and bacteria in styrene butadiene rubber and thermoplastic resin used in the manufacture of a wide variety of products such as carpet fibers; carpet backings; rubber or rubber-backed bath mats; foam underlay for carpets; synthetic, non-leather materials; foam stuffing for cushions and mattresses; wire and cable insulation; vinyl, linoleum, tile and other synthetic floor coverings; wall coverings; plastic furniture; athletic flooring and mats; mattress liners, covers or ticking; molding; mats; gaskets; weather stripping; coated fabrics for furniture cushions, boat covers, tents; tarpaulins and awnings; rubber gloves (non-surgical); garbage bags, cans, and other refuse containers; bathtub appliques; garden hose; pipe (non-potable water); ductwork; air filters; air filtration components and media for industrial, hospital, residential, and commercial heating and cooling; conveyor belts; shower curtains; sponge or fiber mops; household use sponges; toilet brush receptacles; toothbrush receptacles (non-bristle contact); scrub brushes (non-medical); sink mats and drain boards; storage containers; soap dish holders; towel bars; components of uppers in footwear.

  In-can preservation of latex emulsions, clay, pigment and guar gum slurries used in the manufacture of adhesives, caulks, patching compounds, sealants and grouts.

  Control of mildew and other fungal growth in non-food contact polymer systems to include incorporation into PVC, polyolefins, polystyrene, nylon, thermoplastic elastomers, and acrylonitrile butadiene styrene used in the manufacture of plastic screens for tents,

decks, porches, floor coverings, vinyl wall coverings, coated fabrics, swimming pool liners, shower curtains, marine upholstery, tarpaulins, roofing membranes, automotive, pond and ditch liners, wire and cable, plastisol coatings used to form a liquid vinyl material to coat screens or mesh materials for enclosures, refrigerator gaskets.

Control of bacterial and fungal growth on laundered products in industrial settings (not intended for residential, commercial, or institutional settings).

In addition, it is conditionally registered until 6/30/05 as an antifouling agent for boat paints to control the growth of slime, algae, and marine fouling organism such as barnacles and tubeworms below the water line of recreational and commercial boat hulls in fresh, salt, or brackish water. This use is conditionally registered pending receipt of acceptable confirmatory data listed in this document's "Summary of Pending Confirmatory Data".

The chemical is also used as the active ingredient of anti-dandruff shampoos, but this is a non-pesticidal use regulated by FDA.

- **Formulations:** Powder, liquid or aqueous dispersion for incorporation into treated articles and/or their precursor materials, and into ready-to-use antifoulant boat bottom paints.

- **Method of Application:** The end use products are added during the manufacturing process of the treated articles and treated article precursor materials. Zinc pyrithione formulations are added usually by metering pump if they are liquids, and by open pouring if they are the powder. They are added at a point where thorough mixing will take place. The antifoulant paints are applied by brush, roller, and by spraying (airless).

- **Use Rates:** The dosages below are based on using the product containing 95% active ingredient concentration. End use products with lower concentrations of active ingredient use higher product application rates that produce the same concentration of active ingredient.

**Food contact clearances/incorporation rates –**
**(A)** On July 18, 1995, zinc pyrithione (95%) received FDA approval for use in preservation of food packaging adhesives, at a maximum use concentration of 1000 ppm, at use temperatures up to 120 degrees Fahrenheit, and subject to Good Manufacturing Practices, including the conditions specified in 21 CFR 175.105 (a) and (b).

**(B)** On December 16, 1994, zinc pyrithione received FDA approval for incorporation into FDA approved polymers listed in 21 CFR, Parts 174 through 186 (inclusive), or in the FDA's "Food Contact Substance Notification System." It is restricted to use applications at or below room temperature. It is not approved for the incorporation into any food

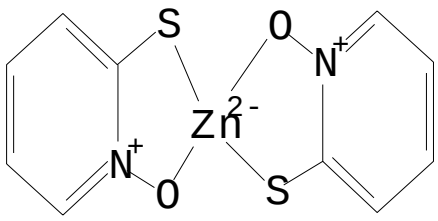
contact substance other than approved and listed FDA food contact polymers at 750 to 1000 ppm of the 95% product (0.75 to 1.0 lb) per 1000 lbs of food contact polymer.

**Non-food contact incorporation rates**
Incorporation rates using the 95% zinc pyrithione article product, range between 750 - 5000 ppm/1000 pounds of material to be treated (i.e., 0.75 – 5.0 lb/1000 lb material). Incorporation rates using the 5% zinc pyrithione product, range between 10,000 - 44,000 ppm/1000 pounds of material to be treated (i.e., 10.0 – 44.4 lb/1000 lb material).

- **Annual Poundage:** Total zinc pyrithione production for pesticidal purposes (including antifoulants) in the U.S. was about 241,000 pounds in 2003, calculated as pure active ingredient. Use of zinc pyrithione for non-pesticidal, FDA regulated applications (i.e., control of dandruff, seborrheic dermatitis, and psoriasis) accounted for the vast majority of total chemical production (> million pounds/year).

- **Technical Registrant:** Arch Chemicals, Inc.

- **Chemical structural formula representation**




## *Hazard*

The toxicology database for zinc pyrithione is adequate for the current registered uses, but uncertainty factors were applied for lack of adequate characterization of neurotoxicity of zinc pyrithione. Acute and sub-chronic neurotoxicity data will be requested as confirmatory data to properly characterize the dose-response relationship that exists for this aspect of zinc pyrithione toxicity. Developmental neurotoxicity data requirements are held in "reserve", pending the results of the requested acute and subchronic neurotoxicity studies.

The toxicology database for zinc pyrithione indicates that by the oral route, zinc pyrithione is moderately toxic (LD50 is 267 mg/kg; Toxicity Category II) but that acute toxicity by the dermal route is not as significant (LD50 > 2000 mg/kg; Toxicity Category III). Acute toxicity by the inhalation route is also relatively low (>0.61 mg/L; Toxicity Category III). Zinc pyrithione is

a severe eye irritant (Toxicity category I) but does not appear to demonstrate significant dermal irritation (Toxicity category IV). Zinc pyrithione does not demonstrate dermal sensitization potential.

Repeated dose (13 weeks) toxicity studies indicate that by the dermal route, zinc pyrithione is relatively non-toxic (decreased food consumption, decreased body weight gain, decreased food efficiency at the limit dose of 1000 mg/kg/day), but by the oral route, toxicity is significantly greater (increased relative organ weights, clinical toxicity, and hindlimb weakness at 3.75 mg/kg/day).

In both oral developmental studies in rats and rabbits, there was no quantitative evidence of increased susceptibility [i.e., maternal and developmental no-observed-adverse effect levels (NOAELs) were the same]. There was however, qualitative evidence of increased susceptibility (i.e., fetal effects such as skeletal effects, and a decreased number of viable fetuses were considered to be more severe in the presence of minimal maternal toxicity).

Significant nervous system deficits following either acute or subchronic oral administration are observed with zinc pyrithione. Intravenous administration of 5 mg/kg zinc pyrithione to female Yorkshire pigs produced cholinergic effects lasting for 30-60 minutes post- dose (HED document 003933). Increased salivation was reported immediately after dosing in the rat developmental toxicity study at a dose of 3 mg/kg/day (MRID # 42827904). Subchronic administration of zinc pyrithione at 3.75 mg/kg/day has been shown to produce hindlimb weakness (HED document no. 003933). Peripheral neuropathy in the form of axonal degeneration has been observed. Neurotoxicity studies are thus triggered 'for cause' in order to properly characterize the effects of zinc pyrithione on nervous system structure and function as well as a more adequate identification of the neurotoxic dose-response in adults.

Studies with zinc pyrithione were not available to assess chronic toxicity and carcinogenicity for this chemical. One two year rat study is available from the 1950's for zinc pyrithione, however, this study had several deficiencies including: small sample size (n=10/sex/dose), inadequate histopathological evaluation, no dietary analyses of dose levels administered, no clinical chemistry analysis, no food consumption data, clinical signs were not recorded and only 3 out of 10 male control rats survived (Larson 1958). Two chronic toxicity and carcinogenicity studies are available for sodium pyrithione: one oral rat gavage study and a mouse dermal study. These two cancer studies for sodium pyrithione showed no evidence of carcinogenicity, but the dermal study did not achieve the maximum tolerated dose. Therefore, sodium pyrithione was classified as a Group D (not classifiable as to carcinogenicity) carcinogen by the Health Effects Division Carcinogenicity Peer Review Committee.

The available evidence for gene mutations using the Ames Salmonella test system suggests that zinc pyrithione is negative for mutations in this system. In a Chinese hamster ovary forward gene mutation assay, zinc pyrithione failed to induce a mutagenic response at doses which included cytotoxicity. In an *in vivo* micronucleus assay in mice, there was no evidence of a

positive effect. Therefore, the data indicate that zinc pyrithione is negative for mutagenic effects.

## *Human Health Risk Assessment*

**TOXICITY ENDPOINTS**

The toxicity endpoints used in this document to assess potential risks include acute and chronic dietary reference doses (RfDs), and short-, intermediate- and/or long-term incidental oral, dermal and inhalation doses, are listed in Table 1 below. The EPA Health Effects Division's (HED) Hazard Identification Assessment Review Committee (HIARC) selected these toxicity endpoints in 1999, which were upheld by the Antimicrobials Division's endpoint selection committee (ADTC) in 2004.

**Acute and Chronic RfDs**: Because zinc pyrithione causes adverse developmental effects, the HIARC identified two acute dietary acute RfDs, one for females of child bearing age (13-50 years) and one for the general population. The acute RfDs are 0.0016 mg/kg/day and 0.0025 mg/kg/day for females (13-50 years) and the general population, respectively. The female (13-50 year) aRfD is based on adverse developmental effects (increased post implantation loss and decreased viable fetuses) at 1.5 mg/kg/day in a rabbit developmental study, while the aRfD for the general population is based on increased salivation in maternal rats at 3 mg/kg/day in a rat developmental study.

The chronic RfD is 0.0016 mg/kg/day based on adverse developmental effects in the rabbit developmental study. An uncertainty factor of 300 (10X for interspecies extrapolation, 10X for intraspecies variability, and 3X for database uncertainties) was applied to the NOAEL to obtain the acute and chronic RfDs. A database uncertainty factor of 3X is applied to non-occupational risk assessments for zinc pyrithione, due to the lack of characterization of neurotoxic dose-response relationships for zinc pyrithione, and the need for additional neurotoxicity testing. A 3X factor for lack of neurotoxicity data (as opposed to a higher factor of 10X) is adequate because neurotoxicity observed in the available data occurs at similar effect levels as other adverse responses, the doses and endpoints selected for dietary and non-dietary assessments encompass the doses at which neurotoxicity is observed, there is no quantitative evidence of susceptibility to the toxic effects of zinc pyrithione, and traditional uncertainty factors afford a degree of protection that is considered conservative.

**Incidental oral endpoints**: The short-term, and intermediate-term incidental oral endpoint of 0.75 mg/kg/day is based on increased salivation in maternal rats at 3 mg/kg/day in a rat developmental study.

**Dermal endpoints**: The short-term, intermediate-term, and long-term dermal endpoint is based on body weight decrements observed at 1000 mg/kg/day in a subchronic dermal toxicity study. The dermal no-observed-adverse effect level (NOAEL) is 100 mg/kg/day.

**Inhalation endpoints**: The short-, intermediate and long-term inhalation endpoint of 0.13 mg/kg/day (0.0005 mg/L, the NOAEL) is based on labored breathing, rales, increased salivation, decreased activity, dry red-brown material around the nose, increased absolute and relative lung weights, and death of undetermined cause at 0.0025 mg/L (0.65 mg/kg/day) in a whole body subchronic rat inhalation study.

**Table 1. Toxicological Endpoints**

| Exposure Scenario | Dose Used in Risk Assessment, UF | FQPA SF and Endpoint for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| Acute Dietary (Females 13 - 50 years) | NOAEL = 0.5 mg/kg/day<br><br>UF = 100<br>DB=3x<br>**Acute RfD**=0.0016 mg/kg/day | FQPA SF = 1x<br>**aPAD=**acute RfD / FQPA SF<br>= 0.0016 mg/kg/day | Developmental Toxicity Study in Rabbits<br><br>LOAEL = 1.5 mg/kg/day, based on increased post-implantation loss and decreased viable fetuses |
| Acute Dietary (General population, including infants/children) | NOAEL = 0.75 mg/kg/day<br><br>UF = 100<br>DB=3x<br>**Acute RfD**=0.0025 mg/kg/day | FQPA SF = 1x<br>**aPAD=**acute RfD / FQPA SF<br>= 0.0025 mg/kg/day | Developmental Toxicity Study in Rats<br><br>LOAEL = 3.0 mg/kg/day based on increased salivation in maternal rats. |
| Chronic Dietary (all populations) | NOAEL = 0.5 mg/kg/day<br><br>UF = 100<br>DB=3x<br>**Chronic RfD**=0.0016 mg/kg/day | FQPA SF = 1x<br>**cPAD=**chronic RfD / FQPA SF<br>= 0.0016 mg/kg/day | Developmental Toxicity Study in Rabbits<br><br>LOAEL = 1.5 mg/kg/day, based on increased post-implantation loss and decreased viable fetuses |
| Incidental Oral, Short- and Intermediate-Term | Maternal NOAEL= 0.75 mg/kg/day | **Target MOE** = 300 (residential) | Developmental Toxicity Study in Rats<br>LOAEL = 3.0 mg/kg/day, Based on increased salivation in maternal rats. |
| Short-, Intermediate-, and Long-Term Dermal | Dermal NOAEL = 100 mg/kg/day | **Target MOE** = 300 (residential)<br>100 (occupational) | 90-Day Subchronic Dermal Toxicity in Rats<br><br>LOAEL = 1000 mg/kg/day, based on decreased body weight gain, food consumption, and food |

| | | | |
|---|---|---|---|
| | | | efficiency in female rats. |
| Short-, Intermediate-, and Long-Term Inhalation | Inhalation NOAEL = 0.0005 mg/L (0.13 mg/kg/day) | **Target MOE** = 300 (residential) 100 (occupational) | 90-Day Subchronic Inhalation Toxicity Study in Rats<br><br>LOAEL = 0.0025 mg/L (0.65 mg/kg/day) based on clinical signs of toxicity, decreased activity, and increased lung weights. |

**FQPA SAFETY FACTOR.**

In 2003, the ADTC committee concluded that the hazard based FQPA safety factor can be reduced to **1X** because the degree of concern is low (i.e. a complete developmental and reproductive database is available with clear NOAELs/LOAELs for parental and offspring toxicity) and there are no residual uncertainties for prenatal toxicity. The developmental toxicity database shows effects in offspring at similar dose levels as effects in adults, while a reproductive toxicity study for sodium pyrithione (a structurally related chemical) shows effects in offspring at doses above those occurring in parental animals. Effects observed in offspring from developmental toxicity studies have been selected for use in dietary risk assessments, thus being protective of infants and children.

Based on Agency policy, a RfD modified by a FQPA safety factor is a population adjusted dose (PAD). The Agency calculated an acute PAD (aPAD) and a chronic PAD (cPAD), and uses this value to estimate acute and chronic dietary risk. The acute PAD is the acute RfD divided by the FQPA safety factor. The cPAD is the chronic RfD divided by the FQPA safety factor.

**DIETARY (FOOD) RISK ASSESSMENTS**

EPA considered potential dietary exposure to zinc pyrithione residues in food (see Table 2 below) and water. When assessing acute and chronic (non-cancer) dietary risk, EPA considered potential dietary exposure to the U.S. population including infants and children as well as to females 13-50 years, based on the developmental toxicity potential of this active ingredient. EPA expresses dietary risk estimates as a percentage of the aPAD or cPAD. Dietary exposures that are less than 100% of the aPAD or cPAD are below the Agency's level of concern. Estimates of dietary risk are based upon the detailed analysis in the residue chemistry chapter (memo from N. Shamim to J. Fairfax, D251938).

**Acute Dietary Risk**. Acute dietary risks were calculated from use of zinc pyrithione as an antimicrobial pesticide in food packaging materials and repeat use of polymeric food contact materials. Dietary exposure to zinc pyrithione can result from migration of the active ingredient from the treated article. EPA has determined that, based on the assumptions and models used, the acute dietary risk from exposure to zinc pyrithione **does not exceed** the Agency's level of concern for all subpopulations examined. The highest dietary risk estimate is **2.7% of the acute PAD**, for infants and children.

**Chronic Dietary Risk**. The acute dietary risk analysis are used to assess potential chronic dietary exposure. The risk analysis assumes daily exposure from contact with polymeric treated articles that come into contact with food. The chronic non-cancer dietary analysis indicates all risk estimates are **below** the Agency's level of concern for all population subgroups. The highest dietary risk estimate is **4.2% of the chronic PAD**, for infants and children.

**Table 2. Summary of Dietary Exposure and Risk for Zinc Pyrithione**

| Population Subgroup** | Acute Dietary | | Chronic Dietary | |
|---|---|---|---|---|
| | Dietary Exposure (mg/kg/day) [a] | % aPAD [b] | Dietary Exposure (mg/kg/day) [a] | % cPAD [b] |
| adult male | $2.8x10^{-5}$ | 1.1 | $2.8x10^{-5}$ | 1.8 |
| females (13-50 years) | $3.3x10^{-5}$ | 2.1 | $3.3x10^{-5}$ | 2.1 |
| infants/children | $6.7x10^{-5}$ | 2.7 | $6.7x10^{-5}$ | 4.2 |

a-- acute and chronic exposure analysis based on daily consumption of 0.002 mg/person/day for adults and body weights of 70 kg and 60 kg for males and females, respectively. For infants/children, exposure based on daily consumption of 0.00067 mg/person/day; and a 10 kg body weight.

b-- %PAD = dietary exposure (mg/kg/day) / aPAD or cPAD, where aPAD= 0.0025 mg/kg/day for general population; aPAD=0.0016 for females of child bearing age; and cPAD=0.0016 mg/kg/day

**Drinking Water Dietary Risk.** Certain surface waters destined for drinking water can be exposed to zinc pyrithione from the leaching from antifoulant boat paints. To assess drinking water impact, the Agency estimated predicted environmental concentrations (PEC's) that range from 0.0144 to 0.101 ppb zinc pyrithione, using conservative assumptions and the Marine Antifoulant Model-Predicted Environmental Concentration (MAM-PEC) model. Because there is a lack of data for zinc pyrithione concentrations in fresh waters, the PECs estimated by MAM-PEC were used to assess potential drinking water exposures the could result from antifoulant paint on boats in fresh water such as lakes and rivers. The PECs were used to assess both acute and chronic drinking water exposures. Based on current Agency policy, drinking water level of comparison (DWLOCs) are compared to the PEC. When the PEC is greater than the DWLOC, EPA considers the estimate of aggregate risk to exceed the Agency's level of concern and would be unacceptable. (See Aggregate Discussion below for results of aggregate dietary, drinking water and residential risk).

Details of the water exposure estimates are present in the memorandum (memo from S. Mostaghimi to D. Smegal, D301373, April 2004), while details on chemical-specific inputs into the models are presented in the Environmental Fate Chapter (memo from N. Shamim to D. Smegal, D301372, April 2004).

## *Exposure Risk Assessment*

**Residential (Non-Occupational) Exposure and Risk**

Zinc pyrithione is incorporated into many substrates that can result in **non-dietary** exposure, such as footwear, shower curtains, plastic toys, rubber gloves, carpet fibers, synthetic floor coverings, plastic furniture, mattress liners/ticking/covers, paints, sealants and caulks, etc. The Agency evaluated potential post-application exposures to these consumer products that contain zinc pyrithione. Scenarios evaluated, which were considered to be representative of all possible exposure scenarios, included: dermal and inhalation exposure to residential handlers during painting activities, dermal contact with treated shoe sole liners, incidental ingestion of residues on treated toys (i.e., object-to-mouth), and incidental ingestion of residues on hands (i.e., hand-to-mouth) from contact with treated toys/objects.

The Agency also evaluated exposures to residential handlers that could use zinc pyrithione-containing antifoulant paints on recreational boats, or other paints or consumer products that contain zinc pyrithione as a material preservative. Details of the residential exposure assessment can be found within the companion memorandum (memorandum from D. Aviado/D. Smegal, D301370, April 2004), and in Tables 3 and 4, below.

Duration of exposure is short-term (1-30 days) for residential handler dermal and inhalation exposure, and short-, and intermediate-term (1 -6 months) for incidental oral postapplication exposures to children. Dermal exposures from postapplication contact were considered to represent a long-term scenario (> 6 months). The scenarios were evaluated based on the Residential Exposure Assessment Standard Operating Procedures (SOPs), product label maximum application rates, related use information, Agency standard assumptions, and Pesticide Handlers Exposure Database (PHED) unit exposure data (for residential handlers).

Residential postapplication exposures show that short-, intermediate-, and long-term dermal risks are **not of concern** (i.e. MOEs $\geq$ 300) for adult/child contact with zinc pyrithione-treated rubber/plastic articles, and short- and intermediate-term incidental oral exposure scenarios for infants/children that could contact zinc pyrithione-treated toys via toy-to-mouth, and hand-to-mouth exposures.

Residential handler exposure scenarios with risk estimates that **exceed** the Agency's level of concern (i.e., MOEs < 300) are related to the use of zinc pyrithione in paints:

- Residential handlers that paint using an airless sprayer:
  (antifoulant paint use: dermal MOE=100 for large boats, inhalation MOEs=6-33;
  material preservative use in paints: dermal MOE=118, and inhalation MOE=15;

- Residential handlers that paint using a brush (antifoulant paint use for all boat sizes: dermal MOE=22-120; inhalation MOE=18-97 using PHED and inhalation

MOE= 5-140 using Health and Safety Executive (HSE) data (Garrod et al. 2000).

- Residential handlers that paint using an aerosol spray can (inhalation MOE=271).

These risk estimates are based on a number of conservative assumptions. For example, the inhalation endpoint is based on a whole body rat 90-day inhalation study, while there is a full 10-fold factor between the dermal NOAEL (100 mg/kg/day) and the lowest observed adverse effect level (LOAEL) (1000 mg/kg/day).

The Agency also assessed residential dermal exposure from use of zinc pyrithione-containing shampoo. Although not a registered use under the EPA's authority, non-dietary *non-pesticidal use* of zinc pyrithione in anti-dandruff shampoo was considered in the aggregate risk assessment. The Agency evaluated a conservative screening-level scenario involving once-daily use of zinc pyrithione-containing shampoo. The estimated dermal MOE is 3,300, based on conservative assumptions, and the results of a study that measured radioactivity associated with metabolized zinc pyrithione (zinc pyrithione) in the urine for 5 days following a single shampoo application containing radiolabeled zinc pyrithione.

**Table 3. Summary of Short-, and Intermediate- Term Residential Post-application Exposure and Risks (c)**

| Scenario | Receptor | Use | Potential Dose[a] (mg/kg/day) | Dermal MOE[b] Target MOE ≥ 300 | Oral MOE[b] Target MOE ≥ 300 |
|---|---|---|---|---|---|
| Dermal Contact to Rubber/Plastic Incorporated with Preservative | Adult | Rubber/Plastic (Shoe Liner) | 1.3E-2 | 7,700 | NA |
| | Toddlers | | 2.2E-2 | 4,500 | NA |
| Non-Dietary Ingestion Toy-to-Mouth | Infants | Rubber/Plastic | 0.0004 | NA | 2,000 |
| Non-Dietary Ingestion Hand-to-Mouth | Infants | Rubber/Plastic | 0.0003 | NA | 2,500 |
| Total Exposure and Risk | Infant | Rubber/Plastic | 0.0007 (total oral) | NA | 1,100 |
| | Toddler | | 2.2E-2 (dermal) | 4,500 | NA |
| | Adult | | 1.3E-2 (dermal) | 7,700 | NA |

**Table 3 footnotes:**

NA = Not applicable.

[a] PDR calculations for each scenario above are outlined in the attached Occupational/Residential Assessment (memo from D. Aviado/D. Smegal, April 2004

[b] MOE= NOAEL (mg/kg/day) / PDR (mg/kg/day).Dermal NOAEL is 100 mg/kg/day; oral NOAEL general population and children is 0.75 mg/kg/day.

c Dermal risks are also for long-term exposures.

**Table 4**
**Estimates of Exposures and Risks to Residential Handlers of Zinc Pyrithione**

| Scenario[a] | Dermal Dose (mg/kg/day) [b] | Inhalation Dose (mg/kg/day)[c] | Dermal MOE [d] Acceptable MOE ≥ 300 | Inhalation [e] MOE Acceptable MOE ≥ 300 |
|---|---|---|---|---|
| **Residential Handlers: Do-it-Yourself Boat Hull Painters (Antifoulant Use) [EPA Reg Nos. 64684-4 (4.8% ai) and 2693-194 (47% ai)] All Estimates Based on 3 Coats of Paint in One Day** | | | | |
| (1a) Brush [f] (PHED) | 4.5-0.86 | 0.0071-0.0013 | 22-120 | 18-97 |
| (1b) Brush [f] (Garrod et al. 2000) | Not evaluated (exposure data of insufficient quality) | 2-6 hours of painting | Not evaluated | 5-140 |
| (2) Airless Sprayer [f] | 0.96-0.18 | 0.021-0.004 | 100-550 | 6-33 |
| **Residential Handlers: Paints Containing Zinc Pyrithione (Materials Preservative Use)** | | | | |
| (3) Handling zinc pyrithione-containing paint end products using a paint brush application method | 0.328 | 4.0E-4 | 304 | 325 |
| (4) Handling zinc pyrithione-containing paint end products using an airless sprayer application method | 0.846 | 8.89E-3 | 118 | 15 |
| (5) Handling zinc pyrithione-containing paint end products using an aerosol spray can application method | 0.044 | 4.80E-4 | 2,273 | 271 |

Table 4 Footnotes:

[a] Scenarios based on use patterns described on labels and LUIS report. Secondary residential handlers include homeowners who apply products containing zinc pyrithione incorporated as a general preservative for paint.

[b] Dermal Dose (mg/kg/day) = [Unit Dermal Exposure (mg/lb ai) * Use Rate (lb ai/lb product or lb ai/gal product) * Amount Handled per Day (lb product/day)] / Body Weight (kg).
* Use of gloves as PPE assumes a 90% protection factor.

[c] Inhalation Dose (mg/kg/day) = [Unit Inhalation Exposure (mg/lb ai) * Use Rate (lb ai/lb product or lb ai/gal product) * Amount Handled per Day (lb product/day)] / Body Weight (kg).** Use of organic vapor respirator as PPE assumes a 90% protection factor.

[d] Dermal MOE = Dermal NOAEL (mg/kg/day) / Dermal Dose (mg/kg/day). Where the dermal NOAEL is 100 mg/kg/day.

[e] Inhalation MOE = Inhalation NOAEL (mg/kg/day) / Inhalation Dose (mg/kg/day). Where the inhalation NOAEL of 0.0005 mg/L/day is converted to 0.13 mg/kg/day, or the route-specific inhalation MOE = (0.5 $mg/m^3$ x 6 hrs/day animal) / [(paint air conc mg/3/%ai x % ai in paint x hrs painting) x (1 $m^3$ work breathing rate / 0.4 $m^3$ resting breathing rate)]. Note: The route-specific inhalation MOEs do not coincide with the route-extrapolation inhalation MOEs because of the differences in methodologies (e.g., UE, dose vs air conc, estimates of hours painting versus amount of ai handled].

[f] Dermal and Inhalation doses and MOEs vary depending on boat size. Boat sizes assessed are 14ftx5ft, 20 ftx8 ft, and 30ftx10ft.

**Aggregate Exposure and Risk**:

The aggregate risk assessment includes combined exposures from indirect food contact, drinking water, and non-dietary (residential) uses. It is inappropriate to aggregate oral, dermal and inhalation exposures because of different toxicological endpoints for the oral (salivation and developmental effects), dermal (decreased body weight and food consumption) and inhalation (clinical signs of toxicity, and lung effects) exposure routes.

**Acute.** The acute aggregate food (from indirect food contact) and drinking water exposure (from antifoulant paint use) **do not exceed** the Agency's level of concern for adults or children as indicated in Table 5 below. Percentages of the acute PAD occupied from food sources were highest for infants and children (2.7%), and were less for adult males and females 13-50 years. All of the acute DWLOCs (24-86 ppb) are greater than the PECs of 0.0144 to 0.101 ppb, indicating that aggregate exposures are not of concern.

**Table 5. DWLOCs for Acute Aggregate Dietary Exposure**

| Population Subgroup | Acute Scenario | | | | | |
|---|---|---|---|---|---|---|
| | aPAD mg/kg/day | Acute Food Exp mg/kg/day | Max Acute Water Exp mg/kg/day[1] | Surface Water PEC ($\mu$g/L)[2] | Acute DWLOC ($\mu$g/L)[3] | Potential Risk Concern [4] |
| Males | 0.0025 | 0.000028 | 0.00247 | 0.0144-0.101 | 86 | No |
| Females 13-50 years | 0.0016 | 0.000033 | 0.001567 | | 47 | No |
| Infants/Children | 0.0025 | 0.000067 | 0.00243 | | 24 | No |

Table 5 footnotes;

[1] Maximum acute water exposure (mg/kg/day) = [(acute PAD (mg/kg/day) - acute food exposure (mg/kg/day)]

[2] Based on sea water for antifoulant use on recreational boats.

[3] Acute DWLOC($\mu$g/L) = [maximum acute water exposure (mg/kg/day) x body weight (kg)]

[water consumption (L/day) x $10^{-3}$ mg/$\mu$g]

where body weight is 70 kg, 60 kg and 10 kg for adult males, females and children, respectively and drinking water intake rates are 2 L/day and 1L/day for adults and children, respectively.

[4] Does the surface water PEC exceed the acute DWLOC?

**Short and Intermediate Term**. Short- and intermediate-term aggregate risk assessments includes average dietary exposures from food and water, in addition to residential exposures (if applicable). However, because the toxicological endpoints are different for oral (salivation and developmental effects), dermal (decreased body weight and food consumption), and inhalation (clinical signs of toxicity and lung effects) exposures, potential dietary (oral) exposures were not aggregated with potential dermal or inhalation exposure from residential use. However, all oral exposures were aggregated in Table 6 below (i.e., food, drinking water, hand-to-mouth, and toy-to-mouth), while a separate dermal aggregate assessment was conducted to assess dermal residential exposures (i.e., shoe liners, painting, and anti-dandruff shampoo).

***ORAL***. The short- and intermediate-term oral aggregate risks for dietary, residential (incidental oral) and drinking water exposure **do not exceed** the Agency's level of concern for adult males and females and infants/children. It should be noted that several conservative assumptions were used in this assessment.

***DERMAL.*** Two separate dermal aggregate MOEs are presented because it was assumed that a resident would apply paint using either a paintbrush or an aerosol can. Dermal short- and intermediate-term aggregate MOEs for an adult resident that could simultaneously contact shoe liners, paint containing zinc pyrithione (as a material preservative) via an aerosol can and anti-dandruff shampoo are greater than the target MOE of 300, and thus **do not exceed** the Agency's level of concern.

However, if an adult resident applies paint using a paintbrush the dermal aggregate MOEs are slightly less than the target MOE of 300 (270) and **are of concern**. In addition, it should be noted that dermal risks are already of concern for residents that could apply antifoulant paint to their boats (dermal MOEs range from 22-120 for a paintbrush, and 100 for an airless sprayer for larger boats), or use an airless sprayer to apply products when zinc pyrithione is used as a material preservative. Thus, these scenarios were not considered in the aggregate risk assessment. A number of conservative assumptions were used in calculating the dermal aggregate risk estimates.

***INHALATION***. The only uses which pose inhalation exposure are from the residential handler uses of paint, which have MOEs that **exceed the Agency's level of concern** (inhalation MOEs range from 5-140 for antifoulant paint use and 15-271 for paint containing zinc pyrithione as a materials preservative). However, these risk estimates are conservative because they are based on a whole-body rat 90-day inhalation study.

| Table 6. Summary of Oral Short- and Intermediate-Term (ST/IT) Aggregate Exposure and DWLOC Calculations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Population Subgroup** | **ST/IT NOAEL (mg/kg/day)/ Target MOE** | **Chronic Food Exp mg/kg/day/ (MOE)** | **ST/IT Oral Residential Exposure (mg/kg/day)/ (MOE)** | **MOE Water Exp[1]** | **Allowable ST/IT Water Exp (mg/kg/day) [6]** | **Surface Water PEC ($\mu$g/L)[2]** | **ST/IT DWLOC ($\mu$g/L)[3]** | **Potential Risk Concern[4]** |
| Males | 0.75/300 | 0.000028/ (26785) | NA | 306 | 0.0024 | 0.0144-0.101 | 86 | No |
| Females 13-50 years | | 0.000033/ (22727) | NA | 307 | 0.0024 | | 73 | No |
| Infants/ Children | | 0.000067/ (11195) | 0.0007/ (1100)[5] | 434 | 0.0017 | | 17 | No |

Table 6 footnotes:
ST= short-term; IT=intermediate term
NA= Not applicable, no residential incidental oral exposure expected.

1 $MOE_{water} = 1 / [1/ MOE_{aggregate} - (1/MOE_{food} + 1/MOE_{oral\ res})]$

2 Based on sea water for antifoulant use on recreational boats.

3 ST/IT DWLOC($\mu$g/L) = [maximum ST/IT water exposure (mg/kg/day) x body weight (kg)] / [water consumption (L/day) x $10^{-3}$ mg/$\mu$g]
where body weight is 70 kg, 60 kg and 10 kg for adult males, females and children, respectively and drinking water intake rates are 2 L/day and 1L/day for adults and children, respectively.

4 Does the surface water PEC exceed the DWLOC?

5 Based on total oral exposure for infants/children on Table 3 for zinc pyrithione treated toys.

6 Short-term oral NOAEL (0.75 mg/kg/day) / $MOE_{aggregate}$.

**Chronic**. Chronic aggregate risk determines the combined risk from average daily exposure in the diet (food + water) with those exposures arising as a result of residential uses (if applicable). This assessment includes chronic food and drinking water exposures because the long-term residential exposures are through the dermal route of exposure (i.e., anti-dandruff shampoo use, or shoe liner exposure), which should not be aggregated with oral exposures due to different toxicological endpoints.

As noted previously, chronic dietary exposures **do not exceed** the Agency's level of concern (highest exposure represents 4.2% of the cPAD for infants and children). The chronic DWLOCs are greater than the PEC for adults and infants/children (see Table 7 below), indicating that aggregate food and drinking water exposure do not exceed the Agency's level of concern. These results are based upon a number of conservative assumptions regarding dietary and water exposure and do not necessarily represent the most refined drinking water assessment.

| Table 7. DWLOCs for Chronic Aggregate Exposure | | | | | | |
|---|---|---|---|---|---|---|
| **Population Subgroup** | **Chronic Scenario** | | | | | |
| | **cPAD mg/kg/day** | **Chronic Food Exp mg/kg/day** | **Max Chronic Water Exp mg/kg/day[1]** | **Surface Water PEC (ppb)[2]** | **Chronic DWLOC ($\mu$g/L)[3]** | **Potential Risk Concern[4]** |
| Males | 0.0016 | 0.000028 | 0.00157 | 0.0144-0.101 | 55 | No |
| Females 13-50 years | | 0.000033 | 0.00156 | | 47 | No |
| Infants/Children | | 0.000067 | 0.00153 | | 15 | No |

Table 7 footnotes:

[1] Maximum chronic water exposure (mg/kg/day) = [(chronic PAD (mg/kg/day) - chronic food exposure (mg/kg/day)]

[2] Based on sea water for antifoulant use on recreational boats.

[3] Chronic DWLOC($\mu$g/L) = [maximum chronic water exposure (mg/kg/day) x body weight (kg)] / [water consumption (L/day) x $10^{-3}$ mg/$\mu$g]
where body weight is 70 kg, 60 kg and 10 kg for adult males, females and children, respectively and drinking water intake rates are 2 L/day and 1L/day for adults and children, respectively.

[4] Does the surface water PEC exceed the chronic DWLOC?

## OCCUPATIONAL EXPOSURE AND RISK.

The Agency has determined that there is potential for worker exposure to zinc pyrithione through mixing, loading, application, and handling activities associated with zinc pyrithione pesticide products. There are potential exposures from use in commercial, and industrial settings via the dermal and inhalation routes. Based on the EPA-registered use patterns, appropriate primary and secondary handler exposure scenarios were identified for zinc pyrithione. An exposure/risk assessment for occupational antifoulant boat paint use, which is subject to a time-limited registration, was not included in this assessment but will be evaluated later, following the submission of relevant worker exposure data for this use.

In general terms, EPA defines "primary" handler exposure as direct exposure to the pesticide formulation during mixing/loading/applying operations. "Secondary" handler exposure is defined as exposure to a pesticide active ingredient as a direct result of its incorporation into an end product. Examples of secondary handler exposure include the application of treated paints and coatings, and building materials such as caulks, adhesives, spackling, groutings, sealants, stucco and joint cements. 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 while applying building materials. Therefore, occupational handler exposures were assessed for the application of paint, as this scenario represents maximum possible exposure to the chemical. Under this scenario, dermal and inhalation exposures were assessed for brush, airless sprayer, and aerosol application methods.

The exposure and risk assessment for primary and secondary occupational handlers (see Table 8 below) was conducted using product label maximum application rates, related use information from the technical registrant (Arch Chemicals, Inc), Agency standard values for industrial practices, unit exposure data from the Chemical Manufacturers Association (CMA) and the Pesticide Handlers Exposure Database (PHED), and relevant scientific literature.

For mixing/loading liquids and powders in closed systems (i.e., using a metered pump, or automatic-dispensing techniques), the margin of exposure (MOE) calculations indicate risks do not exceed the Agency's level of concern (i.e., target MOEs $\geq$100) for the dermal and inhalation exposure scenarios assessed. The "dermal" exposure risks are not of concern (i.e., MOE $\geq$100) for potential short-term, intermediate-term, and long-term exposures during open mixing/loading of powders and liquids for all the scenarios assessed. Also, the dermal and inhalation MOEs for the laundered fabrics scenarios were **not of concern**.

However, the following short-, intermediate-, and long-term exposure scenarios have MOEs which **are of concern** (i.e., MOEs < 100):

- Mixing/loading/applying powders and liquids for general preservative use patterns using **open pour** methods (inhalation MOE = 50 for liquid formulations; inhalation MOE = 15 for powder formulation);

- Mixing/loading/applying powders and liquids for paint preservation using **open pour** methods (inhalation MOE = 50 for liquid formulations; inhalation MOE = 15 for powder formulation), and

- Handling zinc pyrithione-containing paint products (as a material preservative) using an **airless sprayer** application method (inhalation MOEs = 44 and 4.4 with and without the use of an organic vapor respirator as PPE, respectively, and dermal MOE = 74 without the use of gloves as PPE).

It is assumed that in real-use situations for airless sprayer applications, the occupational handlers will have adequate respiratory protection by wearing either a dust/mist or organic vapor respirator and PPE recommended by the paint manufacturers for spray equipment applications. The Agency may consider requiring risk mitigation steps, such as closed delivery systems and/or use of a respirator and additional PPE during open pouring. Although the dermal MOE for airless spray painting operations is of concern (MOE=74) without gloves, the MOE is not of concern (MOE = 200) when gloves are worn as protective equipment. It is assumed that in real-use situations for airless sprayer applications, the occupational handlers will have adequate dermal protection by wearing gloves as may be recommended by paint manufacturers during spray equipment applications. Dermal and inhalation MOEs obtained for the painting scenarios involving use of paint brush and aerosol spray can application methods were found to be of no risk concern.

Primary occupational post-application dermal and inhalation exposures are limited to mists, steams, or vapors resulting from manufacturing process operations. These exposures are likely to be minimal because of the dilution of the pesticide during processing and the low vapor pressure of the active ingredient, and thus were not quantitatively evaluated in this report.

**Table 8. Estimates of Exposures and Risks to Occupational Handlers of Zinc Pyrithione**

| Application Scenario(a) | Use Rate (lb ai/1000 lb, or lb ai/100 gal)(b) | Amount Handled (lb/day or gal/day)(c) | Dermal MOE(d) Target MOE ≥100 | Inhalation MOE(e) Target MOE ≥100 |
|---|---|---|---|---|
| **Primary Occupational Handler: General Preservatives Uses: Dry Film, In Can, and Material Preservation** | | | | |
| (1a) Mixing/loading/applying liquid pesticide concentrates using open pour methods | 5 lb ai/1,000 lb | 10,000 lb/day | 1037 | 50 |
| (1b) Mixing/loading/applying liquid pesticide concentrates using metering equipment (pump liquid) | 5 lb ai/1,000 lb | 10,000 lb/day | 2.23E+4 | 452 |
| (1c) Mixing/loading/applying powder pesticide concentrates using open pour methods | 5 lb ai/1,000 lb | 10,000 lb/day | 300 | 15 |
| (1d) Mixing/loading/applying powder pesticide concentrates using metering equipment (automatic-dispensing techniques) | 5 lb ai/1,000 lb | 10,000 lb/day | 2.23E+4 | 452 |
| **Primary Occupational Handler: Paints: Dry Film Preservation** | | | | |
| (2a) Mixing/loading/applying liquid pesticide concentrates using open pour methods | 5 lb ai/100 gal | 1,000 gal | 1037 | 50 |
| (2b) Mixing/loading/applying liquid pesticide concentrates using metering equipment (pump liquid) | 5 lb ai/100 gal | 1,000 gal | 2.23E+4 | 452 |
| (2c) Mixing/loading/applying powder pesticide concentrates using open pour methods | 5 lb ai/100 gal | 1,000 gal | 300 | 15 |
| (2d) Mixing/loading/applying powder pesticide concentrates using metering equipment (automatic-dispensing techniques) | 5 lb ai/100 gal | 1,000 gal | 2.23E+4 | 452 |
| **Primary Occupational Handler: Fabrics/Textiles: Laundering Treatment for Material Preservation** | | | | |
| (3a) Mixing/loading/applying liquid pesticide concentrates using open pour methods | 0.25 lb ai/1,000 gal | 1,000 gal | 2.07E+5 | 1.01E+4 |
| (3b) Mixing/loading/applying liquid pesticide concentrates using metering equipment (pump liquid) | 0.25 lb ai/1,000 gal | 1,000 gal | 4.45E+6 | 9.03E+4 |

| Table 8. Estimates of Exposures and Risks to Occupational Handlers of Zinc Pyrithione | | | | |
|---|---|---|---|---|
| **Application Scenario(a)** | **Use Rate (lb ai/1000 lb, or lb ai/100 gal)(b)** | **Amount Handled (lb/day or gal/day)(c)** | **Dermal MOE(d) Target MOE ≥100** | **Inhalation MOE(e) Target MOE ≥100** |
| (3c) Mixing/loading/applying powder pesticide concentrates using open pour methods | 1 lb ai/1,000 gal | 1,000 gal | 1.5E+4 | 728 |
| (3d) Mixing/loading/applying powder pesticide concentrates using metering equipment (automatic-dispensing techniques) | 1 lb ai/1,000 gal | 1,000 gal | 1.11E+6 | 2.26E+4 |
| **Secondary Occupational Handler: Paints Containing Zinc Pyrithione (Materials Preservative)** | | | | |
| (4a) Handling zinc pyrithione-containing paint end products using a paint brush application method | 5 lb ai/100 gal | 5 gal/day | 156 | 130 |
| (4b) Handling zinc pyrithione-containing paint end products using an airless sprayer application method | 5 lb ai/100 gal | 50 gal/day | 74 | 4.4 |
| | | | 200 (PPE) (f) | 44 (PPE)(f) |
| (4c) Handling zinc pyrithione-containing paint end products using an aerosol spray can application method | 5 lb ai/100 gal | 0.28 gal/day (3 12-oz cans) | 2,632 | 500 |

Table 8 Footnotes:

(a) Scenarios based on use patterns described on labels and LUIS report. Primary occupational handlers include people who add zinc pyrithione as a general preservative to products such as food/non-food contact adhesives; floor tile adhesives; caulks and sealants; grout and patching compounds; food/non-food contact polymeric materials; rubber and thermoplastic resins; preservatives in latex paint; architectural coatings; dry film preservative in products such as dry wall and building materials; and laundered fabrics.

(b) Represents the maximum use rates on the registered zinc pyrithione product labels; EPA Registration Nos.: 1258-840 and 1258-841.

(C) Standard EPA default assumptions: 10,000 for caulk; 1,000 for paint; and 1,000 for laundered fabric.

(d) Dermal MOE = Dermal NOAEL (mg/kg/day) / Dermal Dose (mg/kg/day). Where the dermal NOAEL is 100 mg/kg/day.

(e) Inhalation MOE = Inhalation NOAEL (mg/kg/day) / Inhalation Dose (mg/kg/day). Where the inhalation NOAEL of 0.0005 mg/L/day is converted to 0.13 mg/kg/day.

(f) PPE for inhalation is organic vapor respirator, which provides approximately 90% protection.

## CUMULATIVE RISKS

Section 408 of the FFDCA stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to 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

mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe. EPA does not have, at this time, available data to determine whether zinc pyrithione has a common mechanism of toxicity with other substances including sodium pyrithione.

**Endocrine Disruption**

The reproductive and growth impacts to aquatic organisms (see Ecological Risk section below) indicate that zinc pyrithione is a potential endocrine disruptor. The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect.....".

Following the 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 the Program include evaluations of potential effects in wildlife. For pesticide chemicals, 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 Agency's EDSP have been developed, zinc pyrithione may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

## Ecological Risk

A detailed ecological hazard and environmental risk assessment for zinc pyrithione is presented in the review of K. Montague (D301371, April 2004), while the detailed information on environmental fate is presented in the review of N. Shamim (D301372, April 2004). A brief summary is presented below. Because the antifoulant boat paint use is a conditional and time-limited approval, based on submission of acceptable data listed in the section below titled "Summary of Pending Confirmatory Data", this use will be fully assessed after the confirmatory data is received.

**ENVIRONMENTAL FATE/TRANSPORT**

Zinc-pyrithione is a complex (coordination) compound formed through a chemical reaction between the inorganic zinc ion and organic moiety pyrithione. Hydrolytically, the chemical is stable in water under abiotic and buffered conditions (pH 5, 7 and 9), as well as in simulated sea water. The extrapolated hydrolyic half-lives were 99, 120 and 123 days at a pH of 5, 7, and 9, respectively. In simulated sea water, the extrapolated half life was 96 days.

Photolytic measurements showed that zinc pyrithione rapidly degrades rapidly with a half life of 13 minutes in buffered medium, and in about 17 minutes in simulated sea water.

In a study on aerobic aquatic systems, zinc pyrithione degradation follows a biphasic (two phase) process. In the first phase it degrades rapidly with a half life of about 4 minutes in salt water, and in about 1.3 hours in fresh water samples. In a second phase, the half-lives of zinc pyrithione were 12.3 and 15 days for fresh water, and sea water respectively.

In a study on anaerobic aquatic systems, zinc pyrithione degradation also follows a biphasic process. In the first phase it degrades rapidly with a half life of about 2 hours in both salt and fresh water. In the second phase, the half-lives were 25 hours for fresh water and sea water. In anaerobic sediment, the half life was about 13 hours.

There are multiple degradation pathways which determine the concentration of zinc pyrithione in the environment. Under aerobic conditions, the zinc pyrithione degradation half life is about 36 minutes in aqueous systems, and is about 21.3 hours in sediment. Similarly, zinc pyrithione shows a tendency of degrading anaerobically in water within 30 minutes, and in about 19 hours in sediments.

Arch Chemicals submitted an outdoor microcosm study (MRID 45876501), which is not required by environmental fate requirements. This study was reviewed and found deficient in many ways. However, the Agency considers this data to be supplemental. The study indicates that zinc pyrithione degrades under simulated seawater conditions, under dark or in the presence of light. The half-lives under all conditions were less than 24 hours. The study also indicates that zinc pyrithione shows little tendency to accumulate in sediment, particularly if light is present. These results provide additional support to the findings of laboratory studies conducted to evaluate the various degradation pathways for zinc pyrithione.

Zinc pyrithione shows a moderately strong tendency to bind with soils and sediments: With salt water soil and sediment, its $K_d$s are 50 and 99, respectively. Tendency to bind with freshwater soils and sediments are less strong and observed $K_d$s are 11 and 48, respectively.

The reported Octanol/Water Partition coefficient $K_{OW}$ is < 1000 (Log Kow is 0.97). Zinc pyrithione is therefore not expected to bioaccumulate in aquatic organisms (fish etc.).

**ECOLOGICAL HAZARD AND RISK**

The ecological effects database for zinc pyrithione is adequate to support the indoor uses

considered in this RED. The antifoulant paint use expires 6/30/05 and will be evaluated upon submission of the required confirmatory ecotoxicity and worker exposure studies listed in the section below titled "Summary of Pending Confirmatory Data".

Zinc pyrithione is moderately toxic to birds via acute oral exposure, and slightly toxic to practically non-toxic to birds via dietary exposure. It is also acutely toxic to mammals via oral ingestion (Toxicity Category II). Exposure to terrestrial and aquatic organisms and plants is expected to be minimal from the registered indoor uses of zinc pyrithione. Risk to birds, mammals, fish, aquatic invertebrates, and plants, including endangered species, is not anticipated from the indoor uses of zinc pyrithione.

However, zinc pyrithione is very highly toxic on an acute basis at low ppb concentrations to freshwater and marine fish and invertebrates, as well as to aquatic plant species (see tables 9-15 below). It has been shown to cause adverse chronic impacts on freshwater and marine invertebrate reproduction and growth at very low concentrations. These adverse growth and reproductive effects indicate that zinc pyrithione may be a potential human endocrine disrupter.

**Table 9. Freshwater Fish Acute Toxicity of Zinc Pyrithione**

| Species | % ai | LC50 (ppb ai) (95 % c.i.) | NOAEC (ppb ai) | Toxicity Category | MRID No. Author/Year | Study Classification |
|---|---|---|---|---|---|---|
| Rainbow trout *(Oncorhynchus mykiss)* | 97.8 | 3.6 (3.07 - 4.33) | 1.6 | very highly toxic | 43864613 Boeri/1994 | core |
| Fathead minnow *(Pimephales promelas*) | 97.8 | 2.68 (2.10 - 3.27) | 1.1 | very highly toxic | 43864606 Boeri/1994 | core |

**Table 10. Freshwater Fish Early Life-Stage Toxicity of Zinc Omadine®** (parent)

| Species | % ai | NOAEC/ LOAEC (ppb) | Endpoints Affected | MRID No. Author/Year | Study Classification |
|---|---|---|---|---|---|
| Fathead minnow *(Pimephales promelas)* | 98.2 | 1.22/2.82 | Survival, sublethal effects (bent spinal columns), and length | 45204102 Boeri/1999 | core |

**Table 11. Freshwater Invertebrate Acute Toxicity of Zinc Pyrithione (parent)**

| Species | % ai | LC50 or EC50 (ppb ai) (95% c.i.) | NOAEC (ppb ai) | Toxicity Category | MRID No. Author/Year | Study Classification |
|---|---|---|---|---|---|---|
| Waterflea *(Daphnia magna)* | 97.8 | 8.25 (5.24 - 25.82) | < 1.1 | very highly toxic | 43864604 Boeri/1994 | core |
| Freshwater amphipod, *Hyalella azteca* | 98.2 | 136 ppb | | highly toxic | 449218-01 | Supplemental |

**Table 12. Freshwater Aquatic Invertebrate Life-Cycle Toxicity of Zinc Pyrithione**

| Species | % ai | NOAEC/ LOAEC (ppb) | Endpoints Affected | MRID No. Author/Year | Study Classification |
|---|---|---|---|---|---|
| Waterflea *(Daphnia magna)* | 98.2 | 2.7/5.8 | reproduction length | 44535401 Boeri/1998 | core |

**Table 13 . Acute Toxicity of Zinc Pyrithione (parent) to Estuarine/Marine Fish**

| Species | % ai | LC50 (ppb ai) (95% c.i.) | NOAEC (ppb ai) | Toxicity Category | MRID No. Author/Year | Study Classification |
|---|---|---|---|---|---|---|
| Sheepshead minnow *(Cyprinodon variegatus)* | 97.8 | 400 (200-590) | 200 | highly toxic | 43864605 Boeri/1994 | core |

**Table 14: Acute Toxicity of Zinc Pyrithione (parent) to Estuarine/Marine Invertebrates**

| Species | % ai. | 96-hour LC50/EC50 (ppb) (95% c.i.) | NOAEC (ppb) | Toxicity Category | MRID No. Author/Year | Study Classification |
|---|---|---|---|---|---|---|
| Eastern oyster *(Crassostrea virginica)* shell deposition | 97.8 | 22.0 (18.9 - 27.3) | 7.1 | very highly toxic | 43864608 Boeri et al/1994 | core |
| Mysid (*Mysidopsis bahia*) | 97.8 | 4.7 (4.04-5.53) | 1.6 | very highly toxic | 43864607 Boeri et al/1994 | core |

| Table 15: Acute Toxicity of Zinc Pyrithione (parent) to Alga and Aquatic Plants | | | | | |
|---|---|---|---|---|---|
| Species | % ai. | 96-hour LC50/EC50 (ppb) (95% c.i.) | NOEC (ppb) | MRID No. Author/Year | Study Classification |
| Freshwater green alga *(Selenastrum capricornutum)* | 97.8 | 28.0 (24.3- 33.0) | 7.8 | 43864609 Ward et al/1994 | core |
| Blue-green alga (*Anabaena flos-aquae*) | 98.3 | 7.1 | 3.8 | 45564901 | core |
| Freshwater diatom *(Navicula pelliculosa*) | 98.3 | 2.6 | 2.4 | 45565001 | core |
| Aquatic vascular plant, duckweed (*Lemna gibba*) | 98.2 | 8.87 | 4.0 | 45204104 | core |

There may be short-lived water/sediment partitioning that could produce adverse acute toxicity exposures to the chemical for benthic, sediment-dwelling aquatic organisms. However, because zinc pyrithione degrades fairly quickly in both freshwater and saltwater soils and sediments, and the predicted environmental concentrations are low, any acute exposures are expected to be short-lived. It is not expected to persist for long periods in water and microbial soils and sediments.

Due to the high toxicity of the parent compound to aquatic organisms, coupled with the parent compound's tendency to break down fairly rapidly into more persistent degradates in aquatic systems, aquatic organism acute toxicity tests using two major degradates of zinc pyrithione were submitted. These data indicate that both pyridine sulfonic acid and pyrithione sulfonic acid are only slightly toxic to practically non-toxic to freshwater and marine/estuarine fish and invertebrates and aquatic plants.

**RISK TO ENDANGERED SPECIES**

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.

The Agency is currently engaged in a Proactive Conservation Review with USFWS and the National Marine Fisheries Service under section 7(a)(1) of the Endangered Species Act. The objective of this review is to clarify and develop consistent processes for endangered species risk assessments and consultations. Subsequent to the completion of this process, the Agency will reassess the potential effects of zinc pyrithione use to federally listed threatened and endangered species. Until such time as this analysis is completed, any overall environmental effects mitigation strategy developed by the Agency and/or any County Specific Pamphlets which address zinc pyrithione, or other boat antifoulant compounds, will serve as interim protection measures to reduce the likelihood that endangered and threatened species may be exposed to zinc pyrithione at levels of concern.

## Summary of Pending Confirmatory Data

There is concern for the neurotoxic effects of zinc pyrithione that have not been completely characterized in the available toxicology data. Acute and subchronic neurotoxicity studies (870.6200) are thus being required as confirmatory data for this chemical in order to characterize more fully this type of toxicity. Developmental neurotoxicity data is held in "reserve", pending the results of the required acute and subchronic neurotoxicity studies.

In addition, the following five confirmatory ecotoxicity studies were submitted too late to be part of this RED. The cut-off date for incorporating data into this risk assessment was 4/1/04.

73-1 Whole sediment acute freshwater invertebrate
73-2 Whole sediment acute marine invertebrate
850.5400 Marine diatom Skeletonema costatum
850.4225 Seedling emergence in rice
850.4250 Vegetative vigor dose response in rice

A confirmatory worker exposure study is currently under final design and scheduling to support the conditional registration of the antifoulant paint use. This study is an assessment of the potential inhalation and dermal exposure to zinc pyrithione antifoulant paints during outdoor painting of large ship hulls. It is required to be submitted by 1/1/05 and must satisfy the following guideline studies:

875.1200 Dermal exposure - indoor
875.1400 Inhalation exposure - indoor
875.1100 Dermal exposure - outdoor
875.1300 Inhalation exposure - outdoor

The following antifoulant use related data are considered "reserved" at this time. They must be submitted within twelve months of the date of the Agency's written request for these data. The need for these reserved data will be based upon the results of one or more of the above confirmatory or base studies, as determined by the Agency.

| | |
|---|---|
| GLN 72-5 | Fish Life Cycle |
| GLN 72-7 | Simulated or actual field testing for aquatic organisms |
| GLN 71-4 | Avian Reproduction |
| GLN 73-3 | Acute Pore Water Studies (fish and invertebrates) |
| GLN 74-1 | Whole Sediment Chronic Study (invertebrates) |
| Special Study: | Monitoring of Representative U.S. Waters |
| GLN 162-1 | Aerobic Soil Metabolism |
| GLN 162-2 | Anaerobic Soil Metabolism |
| GLN 164-2 | Aquatic Field Study |
| GLN 165-5 | Accumulation Study (Nontarget organism) |
| GLN (N/A) | Monitoring of Representative US Waters |