9-30-85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D C. 20460

004702

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 1. Zinc Oxide for Incorporation Into Nylon Fiber as an Antimicrobial Agent in the Manufacture of Carpets.
2. Manufacturing-Use Only Product [99.7% ai]
EPA File Symbol 524-GLU

Tox. Chem. #920

Accession No. 256240

FROM: Yiannakis M. Ioannou, Ph.D.
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Y.M. Ioannou 9-17-1985

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THRU: Albin B. Kocialski, Ph.D.
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ABK 9/19/85

and

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for TMF 9/30/85

The Monsanto Company, a producer of nylon carpet yarns, has applied for the registration of zinc oxide which would be incorporated into carpet nylon as a textile biocide. The registrant in support of their application has submitted four (4) acute studies (classified as core-guideline) and has indirectly, but not formally, requested a waiver for additional toxicological

testing. The indirect request for a data waiver is shown by Monsanto's reference of the following:

A. Zinc oxide has been exempted from residue tolerances as an inert ingredient in pesticide formulations applied to growing crops or raw agricultural products after harvest (40 CFR:181.001 Subpart C, 1982).

B. Zinc is regulated in the secondary drinking water regulations on the basis of taste considerations. In the proposed National Revised Primary Drinking Water Regulations, the EPA states that zinc is relatively nontoxic and recommends an SMCL of 5 ug/l based on aesthetic reasons (40 CFR, Part 141; FR 48 Part 194, P. 45517).

C. The FDA has proposed to recognize zinc oxide as generally recognized as safe (GRAS) as an indirect food ingredient (20 CFR 182, 184, 186; FR 47 Part 207 P. 47441, October 26, 1932).

The FDA has proposed, on the recommendations of the Advisory Review Panel, to regard zinc oxide as safe and effective as an over-the-counter (OTC) skin protectant drug product (21 CFR 347; FR 43; 151 PP. 34628, August 4, 1978).

D. Proposed rules in the FEDERAL REGISTER (40 CFR Part 162; FR Vol. 47:240 P. 55967, December 14, 1982).

E. Pharmaceutical preparations with a long use history.

Monsanto has also submitted summary data showing that the zinc oxide present in the carpet is tightly bound and incorporated in the nylon fiber matrix and that during the dyeing process of the nylon virtually all extractable zinc oxide would be removed.

Furthermore, Monsanto has estimated human exposure for an infant to be eight (8) times greater from an ointment (Desityn® 40% zinc oxide) used in the control of diaper rash than the possible exposure from the amount of zinc oxide contained in a 50-square yard carpet (6.4 oz vs. 0.8 oz) for a 1-month period.

Toxicology Branch has no objection to the registration of this product for this use provided that:

1. Monsanto submit a formal data waiver request.

2. The label carry the following wording:

CAUTION

Avoid skin and eye contact.
Wash after handling.

Subject: Acute Oral Toxicity (LD_{50}) Study in Rats with Zinc Oxide

Test Material: Zinc Oxide (IR-84-401)

Accession Number: 256240

Sponsor: Monsanto Company

Testing Facility: International Research and Development Corporation

Study Number: IRDC Study Number 401-345

Testing Period: October 24 to November 6, 1984

Report Submitted to Sponsor: December 1984

Materials and Methods:

Male and female young adult Sprague-Dawley rats (Charles River CD® - obtained from Charles River Canada, Inc., St. Constant, Quebec) weighing 200 to 216 g were used in this study. All animals were housed individually in hanging wire-mesh cages and quarantined for 7 days prior to study initiation with food and water available ad libitum. The animals were kept in a room with controlled temperature, humidity, and light. Diet was withheld from all animals for 18 hours prior to dosing and 3 to 4 hours after dosing.

The test article, zinc oxide, was prepared as a weight to volume suspension in cottonseed oil at 5,000 mg/10 ml. The suspension was administered orally (via gavage) to a group of 10 rats (5 male and 5 female) at a single dose of 5,000 mg/kg body weight.

Treated animals were observed for signs of toxicity and mortality at 1, 2.5, 4, and 8 hours after dosing and twice daily for the remainder of the 14-day observation period. Individual body weights were recorded just prior to dosing and on days 8 and 15 after dosing. Gross necropsies were performed on all animals at the termination of the study.

Results:

All male and female rats survived until termination of the study and they all appeared normal for the entire observation period. All animals gained weight during the study (as seen on days 8 and 15) although it cannot be determined, due to the lack of vehicle controls, whether the increase in body weight was as expected. Upon necropsy, nine out of 10 rats did not exhibit any visible abnormalities and only one male rat was noted for hydronephrosis of both kidneys.

Conclusions:

The AOLD50 for zinc oxide in male and female Sprague-Dawley rats was determined to be greater then 5,000 mg/kg.

Classification: Core - Guideline

Category of Toxicity: IV

Subject: Acute Dermal Toxicity (LD_{50}) Study in Rabbits with Zinc Oxide

Test Material: Zinc Oxide (IR-84-401)

Accession Number: 256240

Sponsor: Monsanto Company

Testing Facility: International Research and Development Corporation

Study Number: IRDC Study Number 401-346

Testing Period: October 24 to November 7, 1984

Report Submitted to Sponsor: December 1984

Materials and Methods:

Five male and five female young adult New Zealand white rabbits (obtained from Langshaw Farms, Inc., Augusta, Michigan) weighing 2122 to 2622 g each were acclimated to laboratory conditions for a period of 19 days prior to treatment. Animals were housed in individual hanging wire-mesh cages and placed in an animal room with controlled temperature, humidity, and light. Food and water were available ad libitum.

Twenty-four hours prior to treatment, the hair was removed from the back of each rabbit (approximately 25 to 30% of the body surface). The test article was moistened with 12 ml of deionized water (immediately prior to application) and applied to the intact skin of each rabbit (covering the entire shaved area) at a dose level of 5,000 mg/kg body weight. Following application, the treated area was wrapped with gauze and held in place with Dermiform® tape. Collars (E-Jay Saf-T Shields) were attached and remained on the rabbits for the duration of the study. The gauze dressing and tape were removed 24 hours after application and the test sites were washed with tap water and dried with disposable paper towels.

Treated animals were observed for signs of toxicity and mortality at 1, 2.5, and 4 hours following treatment and twice daily for the remainder of the 14-day observation period. Individual body weights were recorded immediately prior to treatment and on days 8 and 15 after treatment. Gross necropsies were performed on all animals at the termination of the study.

Results:

None of the treated animals died during the study. Toxicity signs were seen only in three female rabbits and consisted mainly of inappetence and abnormal defecation. Body weight data indicated that there exists sex specificity in zinc oxide toxicity in rabbits. Male rabbits (4 out of 5) gained weight, ranging from 4 to 15 percent, by day 15 of the study while female rabbits (4 out of 5) lost weight, ranging from 5 to 10 percent, during the same period.

Gross necropsy did not reveal any abnormalities either internally or at the test article application site.

Conclusions:

The ADLD50 for zinc oxide in male and female New Zealand white rabbits was determined to be greater than 5,000 mg/kg body weight.

Classification: Core - Guideline

Category of Toxicity: III

Subje t: Primary Dermal Irritation Study (4- and 24-Hour Exposure) in Rabbit with Zinc Oxide

Test Material: Zinc Oxide (IR-84-401)

Accession Number: 256240

Sponsor: Monsanto Company

Testing Facility: International Research and Development Corporation

Study Number: IRDC Study Number 401-347

Testing Period: October 25 to October 28, 1984

Report Submitted to Sponsor: October 31, 1984

Materials and Methods:

Three male and three female young adult New Zealand white rabbits (Langshaw Farms, Inc., Augusta, Michigan) weighing 2080 to 2713 g each were acclimated to laboratory conditions for a period of 20 days prior to treatment. All animals were individually housed in hanging wire-mesh cages placed in an animal room with controlled temperature, humidity, and light. Food and water were available ad libitum.

Twenty-four hours prior to the initiation of the study the hair was removed from the back of each rabbit and two test sites (1 square inch each) were marked with indelible ink. Undiluted 0.5 g of zinc oxide, moistened with 0.5 ml of deionized water, was applied on one of the test sites covered with a gauze patch and secured with Dermiform® tape. This was the semi-occluded site. After 4 hours of exposure, the patch was removed and the test site washed with tap water. Zinc oxide was then applied to the other test site of each rabbit and wrapped with gauze bandaging, Saran Wrap®, and Dermiform® tape. This was the occluded site. After 24 hours of exposure the bandaging materials were removed and the test site washed with tap water as above.

The test sites (occluded and semi-occluded) were evaluated for dermal irritation, erythema, and edema (by the method of Draize) at approximately 30 minutes, 24, and 48 hours following patch removal. For the semi-occluded sites a 72-hour evaluation was also conducted.

Results:

No signs of toxicity were seen in any of the treated rabbits. Furthermore, none of the treated sites (either occluded or semi-occluded) showed any signs of irritation (either erythema or edema).

Conclusion:

The primary irritation index for zinc oxide in male and female rabbits was found to be 0. Thus, zinc oxide is not a skin irritant.

Classification: Core - Guideline

Category of Toxicity: IV

Subject: Primary Eye Irritation Study in Rabbits with Zinc Oxide

Test Material: Zinc Oxide (IR-84-401)

Accession Number: 256240

Sponsor: Monsanto Company

Testing Facility: International Research and Development Corporation

Study Number: IRDC Study Number 401-348

Testing Period: October 25 to October 28, 1984

Report Submitted to Sponsor: October 31, 1984

Materials and Methods:

Three male and three female young adult New Zealand white rabbits (Langshaw Farms, Inc., Augusta, Michigan) weighing 2149 to 3096 g each, were acclimated to laboratory conditions for a period of 20 days prior to treatment. All animals were housed in individual hanging wire-mesh cages placed in an animal room with controlled temperature, humidity, and light. Food and water with available ad libitum.

All animals were treated with 60 mg of undiluted zinc oxide. The test article was placed into the conjunctival sac of the right eye of each rabbit, and the eyelid was gently held together for 1 second. The treated eyes were washed with 100 ml of lukewarm water (over a 1-minute period) 24 hours after instillation of the test article into the eye. The left eye of each animal served as control.

Treated (right) and untreated (left) eyes were examined at 1, 24, 48, and 72 hours following initiation of the study and the results recorded according to the scoring method of Draize. Sodium fluorescein examination was conducted in all animals following the 72-hour grading of the eye reaction.

Results:

Maximum ocular irritation was observed at the 1-hour observations interval in all rabbits. The irritation was entirely present in the conjunctival of treated eyes and consisted, for the most part, of grade 2 redness and swelling and grade 1 discharge.

The irritation (grade 1 redness) persisted for 24 hours in 2 of the animals. The eyes of all rabbits were clear within 48 hours post-treatment. The sodium fluorescein examination conducted on day 3 of the observation period was negative. No other toxic signs were seen in any of the animals.

Conclusions:

Zinc oxide appears to be a mild irritant causing reversible eye irritation in male and female rabbits.

Classification: Core - Guideline

Category of Toxicity: III

Results:

Maximum ocular irritation was observed at the 1-hour observations interval in all rabbits. The irritation was entirely present in the conjunctival of treated eyes and consisted, for the most part, of grade 2 redness and swelling and grade 1 discharge.

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Conclusions:

Zinc oxide appears to be a mild irritant causing reversible eye irritation in male and female rabbits.

Classification: Core - Guideline

Category of Toxicity: III