5/7/86

005104

MEMORANDUM

SUBJECT: 10182-EUP-UR. Karate™. Application for Experimental Use Permit. No. 10182-EUP-UR

Tox. Chem. No. 725C

TO: George LaRocca (PM Team #15)
Registration Division (TS-767c)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division

Record No. 160568

Background:

ICI Americas is requesting an Experimental Use Permit for Karate 1EC for evaluation against destructive insects on alfalfa, field corn/popcorn, sweet corn, cotton, grain sorghum, lettuce, soybeans, sunflowers and winter wheat. They are planning to test 1732 pounds of active ingredient on 9200 acres in each of two successive years, 1986 and 1987. The total amount will be 3464 pounds a.i. for testing on 18,400 acres, distributed over eleven crops. No temporary tolerances are being proposed because the treated crops will be either destroyed or used for research purposes.

The experimental program will cover a large area of the United States, including many of the Northeastern, Southeastern, Mid-Western, Mid-Southern and Western areas. The method of application will be foliar spray and the application interval will be as needed. Acreage will range from 100-2000 acres per crop per year spread over the entire country (total of 9400 acres per year for all crops).

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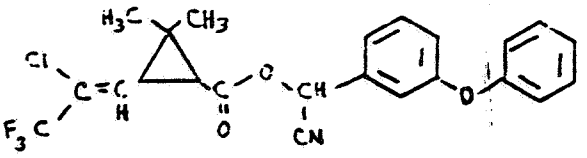
Substance identification:

Karate™ is an insecticide which contains the pyrethroid PP321, a constituent of the pyrethroid insecticide cyhalothrin, previously reviewed by the Agency.

1. Chemical name: (R+S)-alpha-cyano-3-phenoxy-phenyl-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2, dimethyl-cyclo-propane carboxylate, a mixture of the (Z)-(1R, 3R), S-ester and (Z)-(1S,3R), R-ester.

2. Synonyms: PP321, Substituent of Cyhalothrin

3. Structure:



Technical data - Technical Product

1. Molecular weight: 449.9
2. Purity of technical material: 96.5%
3. Physical state: solid, white (pure), beige (technical)
4. Melting point: 49.2°C (pure PP321)
   47.5-48.5°C (technical PP321)
5. Partition coefficient: log P_{ow}: 7.0 at 20°C
6. Vapor pressure: 2 x 10^{-7} Kpa at 60°C
   2 x 10^{-7} Kpa at 20°C (by extrapolation)
7. Dissociation constant: pKa - not measurable
8. Solubility: 4-5 x 10^{-3} ppm in water
9. Specific gravity: 1.33 at 25°C
10. Boiling point: decomposes at approx. 275°C before boiling at atmospheric pressure.
11. Flash point: 185°C

Technical data - Formulated Material

1. Color: Dark amber
2. Specific gravity: 0.909
3. Boiling point: 96-220°C
4. Vapor pressure: 20.6 mm Hg at 24°C
5. pH: 5.91 (5% by volume in dist. water at 25°C)
6. Flash point: 115 (Seta Flash, °F)
7. Oxidizing or reducing action: no known hazard
8. Explosiveness: no known hazard
9. Viscosity: 11.0 centistokes at 25°C
10. Corrosion characteristics: no known hazard
11. Storage stability: stable at 5°, 20°, 37°C for 6 months.

Comments:

1. The following toxicity studies are recommended to be submitted in support of the proposed EUP (ref. EPA Pesticide Assessment Guidelines Subdivision I - Experimental Use Permits, October, 1982). Those requirements that have been satisfied are indicated:

	Required	Satisfied
End Use Product		
Acute oral LD_{50}	Yes	Yes
Acute dermal LD_{50}	Yes	Yes
Primary dermal irritation	Yes	Yes
Primary eye irritation	Yes	Yes
Acute inhalation LC_{50}	Yes	Yes
Dermal sensitization	Yes	Yes

2. The dermal irritation study was conducted on both the technical product of cyhalothrin and PP321, using the same animals. The use of the same animals for testing two formulations is not normally done and is not good science. It is acceptable in this particular case because PP321 is a substituent of cyhalothrin and because neither was irritating to rabbit skin under the conditions of the study. However, this type of procedure should not be done in future studies.

3. Only one dose level was useful for evaluating the skin sensitization potential of the end use product for PP321 because of excessive irritation in controls at higher dose levels. In addition, fresh controls were used at the rechallenge for two other dose levels. These controls were not even the same sex as the treated animals. This invalidated this part of the study.

4. More information on the formulation is needed for the eye irritation study on the end-use product. No information on the purity was given. In addition, this study was not reported well. For several data points, only raw data was given and no summary tables were submitted.

5. The draft label (9/35) should be changed to fit with toxicity category I because the dermal irritation category is corrosive and because the inhalation study is classified as toxicity category I. The label should contain the signal word "DANGER" on the front panel, the word "Poison" should appear in red on a background of distinctly contrasting color and the skull and crossbones should appear in immediate proximity to the word "poison". In addition, the precautionary statement should state that the formulation could be corrosive to the skin.

The registrant should also include a statement that the formulation is a potential sensitizer. The statement of practical treatment should also be placed in a position on the label that reflects Toxicity Category I.

6. The inerts are cleared for use.

7. The Toxicology Branch recommends in favor of the issuance of an Experimental Use Permit for Karate 1EC insecticide, once the label has been modified.

LAMBDA - CYHALOTHRIN 128897

Page _____ is not included in this copy.

Pages 4 through 9 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of product quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

X A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

_____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Studies Reviewed

.....Technical.....

Study	Results	Core Classification
Acute oral LD_{50} - rat	LD_{50}: 79 mg/kg (males) 56(40-78) mg/kg (females)	Minimum
Acute dermal LD_{50} - rat	LD_{50}: 632(300-900) mg/kg (males); 696(309-1169) mg/kg (females)	Minimum
Dermal Irritation - rabbit	Neither Cyhalothrin nor PP321 is irritating to rabbit skin	Minimum
Skin sensitization - guinea pig	Not sensitizing under conditions of bioassay	Guideline
Eye Irritation - rabbit	Mild irritant to rabbit eye	Guideline

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Studies Reviewed

.....13% Formulation.....

Study	Results	Core Classification
Acute oral LD_{50} - rat	LD_{50}:64 mg/kg formulation (males); 101 (75-213) mg/kg (females)	Minimum
Acute dermal LD_{50} - rat	LD_{50}: > 2ml formulation/kg	Guideline
Dermal irritation - rabbit	Extremely irritating to rabbit skin	Guideline
Skin sensitization - guinea pig	Mild sensitizer under conditions of study	Minimum
Eye irritation - rabbit	Moderately irritating to unwashed eyes & mildly irritating to washed eyes	Minimum
Acute inhalation LC_{50} - rat	LC_{50}:0.315 mg/l (males); 0.175 mg/l (females)	Guideline

eviewed by: Pamela Hurley
ection 2 , Tox. Branch (TS-769C)
econdary Reviewer: Edwin Budd
ection 2 , Tox. Branch (TS-769C)

005104

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Rat 81-1 TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 259805

TEST MATERIAL: ((RS)-alpha-cyano-3-phenoxybenzyl(1RS)-cis-3-(z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylate)

SYNONYMS: PP321, Karate, Cynalothrin

STUDY NUMBER(S): AR3279, AR3377

REPORT NUMBER: CTL/P/1102

SPONSOR: ICI, PLC. Plant Protection Div., Fernhurst Haslemere, Surrey, UK

TESTING FACILITY: ICI, PLC. Cntrl. Tox. Lab, Macclesfield Cheshire UK

TITLE OF REPORT: Acute Oral Toxicity Studies

AUTHOR(S): J. Southwood

REPORT ISSUED: 1/9/85

IDENTIFYING VOLUME: Volume II, Section C, Ref. 1C

CONCLUSION: The acute oral LD_{50}'s are 79 mg/kg for males & 56(40-78) mg/kg for females. No 95% Conf. Lim. could be calculated for males.

Toxicity Category: II

Classification: CORE MINIMUM

MATERIALS AND METHODS:

Chemical:

Two samples of PP321 were tested: CTL ref. # YO2537/001/003 (sample 1) and CTL ref. # YO2537/001/007 (sample 2). The purity of sample 1 was 92.6% and the purity of sample 2 was 96%.

Animals:

Alderly Park, SPF albino rats, age range of 5-7 weeks old, weighing between 151-235g for males and 122-178 for females were supplied by the ICI PLC Pharmaceuticals Animal Breeding Unit in Macclesfield, Cheshire, UK.

Protocol:

Five males and five females were tested at each dose level. Sample 1 was tested at five dose levels in corn oil: 29.7, 50.8, 62.5, 75.3 and 94.1 mg/kg; and sample 2 was tested at eight dose levels in corn oil : 11.3, 23, 24, 47, 102, 136, 137 and 216 mg/kg. A standard volume of 10 ml/kg was administered per animal. The animals were observed for signs of toxicity once between 30 and 100 minutes after dosing, between 3 and 6 hours after dosing, and once or twice per day for up to day 15. The animals were weighed on days -1, 1, 3, 6 (some), 8 and 15. All animals in extremis and those surviving to the end of the experiment were sacrificed using halothane and necropsied (except 1 animal). Mortality data from the two studies were combined for the calculation of the LD_{50} values.

esults:

For sample 1, dose level 62.5 mg/kg was only tested with five male rats and dose level 94.1 mg/kg was only tested with five female rats. Signs of toxicity were observed in all of the animals on day 2 and persisted in one animal to day 14. The most common effects seen were decreased activity, splayed gait, dehydration, upward curvature of the spine, urinary incontinence, piloerection, salivation and pinched-in sides. No macroscopic signs were detected at necropsy.

For sample 2, five dose levels were administered to groups of five male rats: 47, 102, 136, 137 and 216 mg/kg; and eight dose levels were administered to groups of five female rats: 11.3, 23, 24, 47, 102, 136, 137 and 216 mg/kg. None of the animals dosed with 11.3 mg/kg showed any signs of toxicity. The remainder of the animals showed signs of toxicity similar to those observed with sample 1. In three, the signs persisted until day 13. No macroscopic signs of toxicity were detected at necropsy.

The acute oral LD_{50} value for male rats was calculated to be 79 mg/kg and the acute oral LD_{50} value for female rats was calculated to be 56 (40-78) mg/kg.

iscussion:

The pattern of mortality in the male rat data set was such that no 95% confidence limits could be calculated. An approximate lower confidence limit was set by the highest dose giving zero mortality (>51 mg/kg). There appeared to be some variation in the mortality pattern between the two samples which may have altered the LD_{50} value for males to a slight degree. For sample 1, 4/5 animals dosed at 62.5 mg/kg and 5/5 animals dosed at 75.3 mg/kg died before termination of the experiment. For sample 2, 1/5 animals dosed at 102 mg/kg, 3/5 animals at 136 mg/kg and 5/5 animals at 137 mg/kg died prior to termination of the experiment. The same discrepancy occurred with the female mortality data as well. Five of five animals died at a dose level of 94.1 mg/kg with sample 1 whereas 3/5 animals died at a dose level of 136 mg/kg with sample 2. As a result of these discrepancies and since it was necessary to combine two experiments to obtain the best results, this study is classified as CORE MINIMUM.

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by: Pamela Hurley
, Tox. Branch (TS-769C)
Reviewer: Edwin Budd
, Tox. Branch (TS-769C)

005104

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal (rat) 81-2 TOX. CHEM. NO.: 725C

SESSION NUMBER: 259805

TEST MATERIAL: [(RS)-alpha-cyano-3-phenoxybenzyl(1RS)-cis-3-(z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylate]

SYNONYMS: PP321, Karate, Cyhalothrin

STUDY NUMBER(S): CR1690

REPORT NUMBER: CTL/P/1149

SPONSOR: ICI, PLC, Plant Protection Division, Fernhurst, Haslemere, Surrey, UK

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab., Alderly Park, Macclesfield, UK

TITLE OF REPORT: PP321: Acute Dermal Toxicity

AUTHOR(S): JE Barber

REPORT ISSUED: 1/11/85

IDENTIFYING VOLUME: Vol. II, Section C, Ref. 2C

CONCLUSION: The acute dermal LD_{50}'s are 632 (approx. 300-900) mg/kg for males & 696 (309-1169) mg/kg for females.

Toxicity Category: II

Classification: Core Minimum

MATERIALS AND METHODS:

Chemical:

The sample of PP321 was obtained from ICI PLC, Plant Protection Division and had a purity of 92.6%. The CTL reference number was YO2537/001/003.

Animals:

Alderly Park SPF albino rats were supplied by the Animal Breeding Unit of ICI PLC, Pharmaceuticals Division. Their ages ranged from 5 to 10 weeks and their weights ranged from 162-247g for males and 126-235g for females.

Protocol:

Five male and five female animals were used per dose level (300, 600, 750, 900 and 1200 mg/kg were tested). The hair from the dorso-lumbar region of each animal was removed 16-32 hours prior to treatment.

The test material was made into a paste with propylene glycol (0.05 ml) and applied to a patch which was in turn applied to each shorn back for 24 hours with adhesive impermeable polyethylene tape. At the end of the 24 hours, the material was removed and the skin cleansed with water. The animals were observed for signs of systemic toxicity 2-4 hours after application and once or twice daily up to day 15. The animals were weighed on days 1, 3, 6, 8 and 15. Upon termination, all animals were killed with halothane BP and necropsied for macroscopic abnormalities.

Results:

The dose level of 750 mg/kg was administered to five male rats only and the dose level of 1200 mg/kg was administered to five female rats only. Signs of systemic toxicity were observed in all animals. These included decreased activity, tiptoe gait, splayed gait, loss of stability, dehydration, signs of urinary incontinence and upward curvature of the spine. Animals generally did not recover until after day 10. No macroscopic signs of toxicity were detected in any of the animals which were examined by necropsy. The acute dermal LD_{50} values were calculated to be 632 (300-900 approx.) mg/kg for males and 696 (309-1169) mg/kg for females. The 95% confidence limits were represented by the highest dose with zero mortality and the lowest dose with 100% mortality.

Discussion:

The clinical signs are consistent with pyrethroid toxicity. There were two deviations from the EPA Guidelines: the age and weight range of the animals was quite wide and was slightly lower than the recommended value and several dose levels contained only one sex (probably chosen because of sex differences in toxicity). In addition, the 95% confidence limits had to be approximated using the highest dose levels with 0% mortalities and the lowest dose levels with 100% mortalities. The study is classified as Core Minimum.

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Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

005104

DATA EVALUATION REPORT

STUDY TYPE: Dermal Irritation 81-5 (rabbit) TOX. CHEM. NO.: 271F
725C

ACCESSION NUMBER: 259805

TEST MATERIALS: [(RS)-a-cyano-3-phenoxybenzyl(1RS)-cis-3-(z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylate]

SYNONYMS: Cynalothrin and PP321 (Karate, an enantiomeric pair of Cyhalothrin)

STUDY NUMBER(S): EB2430

REPORT NUMBER: CTL/P/1139

SPONSOR: ICI PLC, Plant Protection Division, Surrey, UK

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab. Macclesfield, Cheshire UK

TITLE OF REPORT: PP321 and Cyhalothrin: Skin Irritation Study

AUTHOR(S): Victoria Pritchard

REPORT ISSUED: 1/11/85

IDENTIFYING VOLUME: Vol. II, Section C, Tab 3C

CONCLUSION: Neither Cyhalothrin nor PP321 is irritating to the rabbit skin after 4 hours exposure.

Toxicity Category: IV

Classification: Core Minimum due to the application of the two compounds on the same animals.

MATERIALS AND METHODS:

Chemical:

The sample of PP321 (ref. P13) had a purity of 96.5% (w/w) and the sample of cynalothrin (ref. BX8) had a purity of 92.9%. The samples were supplied by ICI PLC, Plant Protection Division, Berkshire, UK. The CTL references numbers were YC2537/001/009 and YC0102/010/022 for PP321 and Cynalothrin respectively.

Animals:

Female New Zealand white albino rabbits were supplied by Mellor Rabbits, Chadderton Heights, Chaccerton, Nr Oldham, Greater Manchester, UK. They were aged between 11 and 17 weeks and weighed 2.22-3.46 kg.

Protocol:

Twenty-four hours prior to test, 6 animals were shaved with veterinary clippers. PP321 (approx. 500 mg) was moistened to a paste with distilled water and applied to the test site (25mm x 25mm) on the left flank. Undiluted cyhalothrin was weighed onto a piece of surgical gauze (approx. 500 mg liquid) and applied to a similar area on the right flank of each rabbit. Both sides were covered with surgical gauze, surgical tape and a piece of impermeable rubber sheeting wrapped with adhesive impermeable polyethylene tape. The sites were exposed to the test materials for four hours, after which the dressings were removed and the sites were cleansed with methylated spirits and water and dried. Twenty hours after removal of the dressings, plastic collars were fitted to all of the animals. Edema and erythema were assessed using the Draize method at 1, 20, 44 and 68 hours, and 5, 7, 9 and 14 days after removal of the dressings. The scores were calculated separately for each flank of each animal.

RESULTS:

No erythema was observed for either PP321 or Cyhalothrin. For PP321, slight edema was seen in 4/6 animals the first hour after application. It disappeared by 20 hours. For Cyhalothrin, slight edema was observed in 5/6 animals the first hour after application. Very slight edema remained by 20 hours and had disappeared by 44 hours in 2/6 animals. The mean erythema scores for both compounds was zero, the mean edema score for PP321 was zero and the mean edema score for cyhalothrin was 0.1. Both compounds were classified as non-irritating.

DISCUSSION:

Applying two compounds at the same time to the same animal is not usually acceptable. However, in this case it is accepted because Karate is a more purified form of Cyhalothrin and because neither is irritating. As a result of this unusual procedure, control areas were not available for observation, but since neither was irritating, they served as their own controls. In addition, this study is verified by the results of an earlier study conducted on Cyhalothrin by the same company.

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Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

005104

DATA EVALUATION REPORT

STUDY TYPE: Skin Sensitization 81-6 (guinea pig) TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 259805

TEST MATERIAL: (R+S)-a-cyano-3-(phenoxyphenyl) methyl (1S+1R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

SYNONYMS: Karate, PP321

STUDY NUMBER(S): GG2940

REPORT NUMBER: CTL/P/1054

SPONSOR: ICI PLC, Plant Protection Division, Haslemere, Surrey, UK

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab., Alderly Park, Macclesfield, UK

TITLE OF REPORT: PP321: Skin Sensitization Study

AUTHOR(S): Victoria K. Pritchard

REPORT ISSUED: 7/17/84

IDENTIFYING VOLUME: Vol. II, Section C, Tab 4C

CONCLUSION: PP321 does not appear to be a sensitizer under the conditions of this bioassay.

Classification: Core Guideline

MATERIALS AND METHODS:

Chemical:

PP321 was supplied by ICI PLC, Plant Protection Division, Berkshire, UK. It contained 96.5% pure substance (w/w), had a sample ref. # D3239/11 and a CTL reference # Y02537/001/013.

Animals:

Male Dunkin Hartley albino guinea pigs were supplied by the Animal Breeding Unit at ICI PLC, Pharmaceuticals Division, Alderly Park, Cheshire, UK. They weighed between 315-455 g and were aged between 4-7 weeks.

Protocol:

PP321 was tested as a 5% (w/v) solution in corn oil, and as a 5% (w/v) solution in corn oil: Freund's complete adjuvant (1:1) in the intradermal induction phase; as a 1% (w/v) solution in corn oil in the topical induction phase, and as a 1% (w/v) solution in corn oil in the challenge. The dose levels for each phase of the main study were determined by a 'sighting' study. Thirty guinea pigs were used for the main study, 20 test and 10 control. For the induction phase, hair was removed from each animal and a row of 3 injections (0.1 ml each) was made on each side of the mid-line. The injections were:

1) Freund's complete adjuvant plus corn oil in the ratio 1:1
2) a 5% (w/v) solution of the test substance in corn oil
3) a 5% (w/v) solution of the test substance in a 1:1 preparation of Freund's complete adjuvant plus corn oil

One week later, the scapular area was clipped again and treated with a topical application of the test substance as a 1% (w/v) solution in corn oil. The solution (0.25 ml) was applied on filter paper and held in place with surgical tape. The tape was covered by a strip of adhesive bandage and self-adhesive PVC tape and kept in place for 48 hours. The controls were treated in the same manner except that they were induced by:

1) Freund's complete adjuvant plus corn oil in the ratio 1:1
2) corn oil
3) Freund's complete adjuvant plus corn oil in the ratio 1:1

The topical applications followed the same procedure as for the test animals except that corn oil only was applied to the filter paper.

For the challenge phase, 2 weeks after topical induction, an area on one flank of each animal was clipped with veterinary clippers and a 1% (w/v) solution of the test substance (0.05 ml) was applied to filter paper which was subsequently placed on the animals for 24 hours with an occlusive dressing. Erythemous reactions were evaluated 24 and 48 hours post removal of the dressings. The sensitization response was evaluated by subtracting the percentage of control animals that responded from the percentage of test animals that responded and compared with the classification scheme of Magnusson and Kligman (maximization method).

RESULTS:

None of the test animals responded following challenge with PP321 as a 1% (w/v) solution in corn oil. It was not considered to be a sensitizer in this case.

DISCUSSION:

PP321 does not appear to be a sensitizer under the conditions of this bioassay.

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Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

005104

DATA EVALUATION REPORT

STUDY TYPE: Eye Irritation 81-4 (rabbit) TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 259805

TEST MATERIAL: (R+S)-a-cyano-3-(phenoxyphenyl) methyl (1S+1R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

SYNONYMS: Karate, Cyhalothrin, PP321

STUDY NUMBER(S): FB3152

REPORT NUMBER: CTL/P/1207

SPONSOR: ICI PLC, Plant Protection Division, Surrey, UK

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab., Alderly Park, Macclesfield, UK

TITLE OF REPORT: PP321: Eye Irritation Study

AUTHOR(S): Victoria Pritchard

REPORT ISSUED: 1/29/85

IDENTIFYING VOLUME: Volume II, Section C, Tab 5

CONCLUSION: PP321 is classified as a mild irritant to the rabbit eye.

Toxicity Category: II

Classification: Core Guideline

MATERIALS AND METHODS:

Chemical:

The sample was supplied by ICI PLC, Jealott's Hill, Bracknell, Berksnire, UK and had a purity of 96.5% (w/w). The ref. # was P13, D3239/11 and the CTL reference # was Y02537/001/014.

Animals:

Male New Zealand albino rabbits were supplied by Hacking and Churchill, Wyton, Cambridgesnire, UK. They were aged between 11 and 17 weeks and weighed between 2.59-3.65 g.

Protocol:

Six rabbits were used for the test. Approximately 100 mg of the test substance was applied into the conjunctival sac of the left eye of each animal. The right eyes were used as controls. The initial pain reaction was assessed using a 6-point scale. Two hours after treatment, a local anaesthetic was given to 2 rabbits. The eyes of all animals were examined according to the Draize scale at 1-2 hours, 1, 2, 3, 4, 7, 10 or 11 days (2 animals), 13 (1 animal) and 17 (1 animal) days after treatment. A modified form of the Kay and Calandra system was used to interpret and classify the scores. Fluorescein staining was used on days 1, 2, 3, 4, 7, 13 and 17 as an aid in the assessment of corneal damage.

RESULTS:

Practically no or slight initial pain was observed immediately after application of the test substance. Approximately 1/4 of the substance was displaced from the conjunctival sac of all the rabbits after application. One hour post application, conjunctival effects were noted in all animals which consisted of slight or moderate redness, slight or mild chemosis, and slight or severe discharge. Two days following treatment, slight or moderate redness, slight chemosis and slight discharge were present in all animals. By day 4, 4 animals had recovered and the remaining two animals had slight redness which disappeared by day 10. Possible paraesthesia effects were noted in all animals during the first 24 hours of the study. A local anaesthetic was administered to 2 animals in order to alleviate their discomfort, however, little change was observed. Additional effects indicative of irritation were observed during the study and included: erythema on the upper and/or lower eyelids, convoluted eyelids, thickening of the eyelids and scabbing of the periorbital skin probably due to rubbing of the eyes. PP321 was classified as a mild irritant to the rabbit eye (class 4 on a 1-8 point scale).

DISCUSSION:

No effects were observed with either the cornea or iris. The maximum mean total score for the conjunctiva was 11.3 at 1-2 hours. The score decreased to 0.3 by day 7. On the Kay and Calandra scale, this compound is classified as a mild irritant. The toxicity category is II.

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ction 2 , Tox. Branch (TS-769C)
condary Reviewer: Edwin Budd
ction 2 , Tox. Branch (TS-769C)

005104

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral + Dermal 81-1 + 81-2 (rat) TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 259805

TEST MATERIAL: (R+S)-cyano-3-(phenoxyphenyl) methyl (1S+1R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

SYNONYMS: Karate, Cyhalothrin, PP321

STUDY NUMBER(S): AR3617 and CR1933

REPORT NUMBER: CTL/P/1270

SPONSOR: ICI PLC, Plant Protection Division, Surrey, UK

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab., Alderly Park, Macclesfield, UK

TITLE OF REPORT: PP321: Acute Oral and Dermal Toxicity of An Oil-Based Formulation to the Rat

AUTHOR(S): Victoria Pritchard

REPORT ISSUED: 4/24/85

IDENTIFYING VOLUME: Vol. II, Section C, Tab 6C

CONCLUSION: Acute oral LD_{50} 64 mg formulation/kg (males), 101 (75-213) mg formulation/kg (females); acute dermal LD_{50} > 2ml formulation/kg

Toxicity Category: II for oral and III for dermal

Classification: Core Minimum for the acute oral study and Core Guideline for the acute dermal study.

MATERIALS AND METHODS:

Chemical:

The test sample was obtained from ICI PLC, ICI Americas Inc, Goldsboro, NC. The reference #'s are: 193/17B, formulation ref. GFU383C, CTL ref. YO4443/001/001. The purity was reported to be 13.1% (w/w) PP321.

Animals:

Alderly Park SPF albino rats were supplied by the Animal Breeding Unit, ICI PLC, Pharmaceuticals Div., Macclesfield, UK. The rats were between 7-11 weeks old and weighed between 231-293g for males and between 184-221g for females.

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Protocol:

Acute Oral Toxicity:

Five males and 5 females per dose level were used for the test. The dose levels were 52, 75, 110 and 213 mg formulation/kg. The formulation was given as a dilution in deionized water. The animals were observed for signs of toxicity once between 30 and 90 minutes, between 3-5 hours and once daily post dosing, up to day 15. They were weighed on days -1, 1, 3, 6, 8 and 15. Animals dieing in extremis and those killed at termination were all examined by necropsy for any macroscopic abnormalities.

Acute Dermal Toxicity:

Five male and 5 female rats were used for this study. Sixteen to 32 hours prior to application of the test substance, hair was removed from the dorso-lumbar region of each animal. The maximum dose of 2 ml formulation/kg was used for this study. The formulation was kept in contact with the skin for 24 hours by means of occlusive dressings (aluminum foil patch and adhesive impermeable polyethylene tape). At the end of the exposure period, the site was cleansed with warm water and dried. The animals were observed for signs of toxicity once between 1 and 2 hours after application and then once daily up to day 15. They were weighed immediately before application and days 3, 8 and 15. All animals were examined by necropsy for any macroscopic abnormalities.

RESULTS:

Acute Oral Toxicity:

Deaths occurred within 2 days of dosing. All the females died at the top dose and none died at the 2 lowest doses. The acute oral LD_{50} values were calculated to be 64 mg formulation/kg for males (no confidence limits estimable due to the pattern of mortalities) and 101 (75-213 approx.) mg formulation/kg for females. Signs of toxicity became apparent between 3-5 hours post dosing and all surviving animals except one 75mg/kg female had recovered by day 8. The following signs of toxicity were noted: ataxia, reduced stability, chromodacryorrhea, lacrimation, piloerection, salivation, urinary incontinence/signs of incontinence and upward curvature of the spine. No macroscopic abnormalities were detected at necropsy.

Acute Dermal Toxicity:

One female was killed in extremis on day 4. The acute dermal LD_{50} for both males and females was calculated to be in excess of 2 ml formulation/kg. Signs of toxicity appeared within 24 hours and persisted up to day 8. The signs were similar to those noted in the acute oral study. The females were slightly most sensitive than the males. Signs of moderate skin irritation were also noted: erythema, desquamation, edema, thickening, wrinkling, necrosis and scabbing. No macroscopic abnormalities were detected at necropsy.

DISCUSSION:

The mortality data for the acute oral study prevented accurate calculations of the 95% confidence limits for the LD_{50}'s.

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005104

DATA EVALUATION REPORT

STUDY TYPE: Dermal Irritation 81-5 (rabbit) TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 259805

TEST MATERIAL: (R+S)-a-cyano-3-(phenoxyphenyl) methyl (1S+1R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

SYNONYMS: PP321, Karate, Cyhalothrin

STUDY NUMBER(S): EB2657

REPORT NUMBER: CTL/P/1265

SPONSOR: ICI PLC, Plant Protection Division, Surrey, UK

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab., Alderly Park, Macclesfield, UK

TITLE OF REPORT: PP321: Skin Irritation of an Oil-Based Formulation to the Rabbit

AUTHOR(S): Jeanette E. Barber

REPORT ISSUED: 6/4/85

IDENTIFYING VOLUME: Vol. II, Section C, Tab. 7C

CONCLUSION: The PP321 formulation is extremely irritating to rabbit skin under the conditions of this study.

Toxicity Category: I

Classification: Core Guideline

MATERIALS AND METHODS:

Chemical:

The sample was obtained from ICI PLC, ICI Americas Inc, Goldsboro, NC. The stated purity was 13.1% (w/w) and the reference #'s were as follows: batch ref. 193/17B, formulation ref. GFU 383C, CTL ref. YO4443/001/001. It was an amber colored liquid.

Animals:

Female New Zealand albino rabbits were supplied by Hacking and Churchill, Abbots Ripton Road, Wyton, Cambridgeshire, UK. The animals were aged between 11 and 17 weeks and weighed between 2736-3877 g.

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Protocol:

Six animals were used for the test. Twenty-four hours prior to the test, the animals were clipped of hair on the left flank. 0.5 ml of the undiluted formulation was applied to the test site, covered with surgical gauze, surgical tape, impermeable rubber sheeting and impermeable polyethylene tape. After 5 hours the dressing was removed and the test site was cleansed with warm water and dried. The degree of erythema and edema was assessed using the Draize scale at approximately 1, 25, 49 and 73 hours, and 6, 10, 13 and 17 days after removal of the dressings.

RESULTS:

One hour after removal of the dressings all of the animals had moderate to severe erythema which intensified to severe erythema by day seven (six days after removal of the dressing). Five of the six animals recovered by day 11 and the remaining animal recovered by day 14. One hour following removal of the dressings, all of the animals had slight or moderate edema. At the 49-hour reading this had intensified to severe edema in 5/6 animals and to moderate edema in 1 animal. By day 7 no edema persisted in any of the animals. All of the animals had either slight, moderate or severe desquamation. 5 had slight or moderate thickening (this obscured the scoring of the edema at the 72-hour reading in 2 animals), 5 had slight or moderate cracking, 3 had pale scabs and one had bite/scratch marks at the edge of the site. Two animals had recovered by the end of the observation period (17 days after removal of the dressings), but slight desquamation remained in the rest of the animals. The mean erythema and edema scores were calculated to be 3.3 and 3.4 respectively. Signs of severe irritation were seen during the study.

DISCUSSION:

When the scores are averaged for the 24 hour and 72 hour readings (Draize method), the mean scores are 3.1 each for edema and erythema. The scores quoted in the Results Section are averages for all the readings. The Primary Irritation Index based on the Draize method is rated as severely irritating. The Primary Irritation Index based on the scores given in the submission is rated as extremely irritating. The latter index is chosen because the erythema was still intensifying after 72 hours. The Toxicity Category is I (corrosive .

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005104

DATA EVALUATION REPORT

STUDY TYPE: Skin Sensitization 81-6 (G. Pig) TOX. CHEM. NO.: 723C

ACCESSION NUMBER: 259805

TEST MATERIAL: (R+S)-a-cyano-3-(phenoxyphenyl) methyl (1S+1R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

SYNONYMS: Karate, PP321, Cyhalothrin

STUDY NUMBER(S): GG3112

REPORT NUMBER: CTL/P/1255

SPONSOR: ICI PLC, Plant Protection Division, Surrey, UK

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab., Alderly Park, Cheshire, UK

TITLE OF REPORT: PP321: Skin Sensitization to the Guinea Pig of an Oil-Based Formulation

AUTHOR(S): Victoria Pritchard

REPORT ISSUED: 4/18/85

IDENTIFYING VOLUME: Vol. II, Section C, Tab 8C

CONCLUSION: The PP321 formulation is a mild sensitizer under the conditions of the study.

Classification: Core Minimum

MATERIALS AND METHODS:

Chemical:

The test sample, an amber-colored liquid, was supplied by ICI PLC, ICI Americas Inc., Goldsboro, NC. The purity was 13.1% (w/w) and the reference #'s were: 193/17B, formulation ref. GFU383C and CTL ref. Y04443/001/001.

Animals:

Male and female Dunkin Hartly albino guinea pigs were supplied by the Animal Breeding Unit, ICI PLC, Pharmaceuticals Div., Alderly Park, Macclesfield, Chesnire, UK. They were aged between 5-11 weeks and weighed between 384-422 g.

Protocol:

The formulation was tested for sensitizing capabilities by the method of Buehler. The dose levels for the challenge and induction phases of the study were determined by a 'sighting' study. A group of thirty male guinea pigs were selected for the main study, 20 test and 10 control animals. For the induction phase of the study, an area on the scapular region of each animal was clipped free of hair and treated with a topical application of 0.4 ml of the undiluted formulation. The formulation had been applied to a lint pad and covered with adhesive tape, adhesive bandage and PVC tape. Control animals were treated identically but without application of test material. The induction period was repeated at the same site during a two-week period for a total of 3 six-hour exposures. The interval between exposure periods was 7+/- 1 day. The irritation response was noted 24 hours after removal of each patch and before application of each subsequent patch. The animals were then left untreated for 2 weeks prior to the challenge phase. For the challenge phase, areas on both flanks of each animal were clipped free of hair. On the left flank, 0.2 ml of a 10% (w/v) dilution of the formulation in deionized water was applied and on the right flank, 0.2 ml of a 1% (w/v) dilution of the formulation in deionized water was applied. The application was onto a lint pad which was attached to a piece of rubber sheeting. Both were secured by adhesive impermeable polyethylene tape for six hours. Erythamatous reactions were quantified using a preset scale 24 and 48 hours after the removal of the dressings. The percentage of the control animals that responded was subtracted from the percentage of the treated animals that responded. Five days after the initial challenge, the animals were rechallenged using 5% (w/v) and 1% (w/v) concentrations. The formulation was applied to different sites than those used for the initial challenge. A fresh group of ten female control animals was used for the rechallenge.

RESULTS:

Scattered mild or moderate diffuse redness was seen in 15/20 test animals and scattered mild to intense redness was seen in 7/10 control animals after challenge with 10% (w/v) dilution. Scattered mild redness was seen in 7/20 test and 1/10 control animals after challenge with 1% dilution. The net % response for the 1% dilution was 25% (a mild sensitization response). With the 5% (w/v) dilution, scattered mild or intense redness was seen in 9/10 animals and in 2/10 control animals. In this case as well, the authors calculated the response to be 25% (a mild sensitization response). Following rechallenge with a 1% dilution (w/v), 1/10 animals responded with scattered mild redness and no controls responded. The authors calculated the response to be 5% (weak sensitization response).

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ISCUSSION:

The background irritation in control animals hinders the characterization of sensitization. The response that appears to be the most useful is the one observed with the 1% dilution on the first challenge. The excessive irritation in the control animals with the 10% dilution confounded the results. Also, since the rechallenge with 5% and 1% dilutions used fresh controls (female animals which did not match the male animals), this part of the study is not useful either. Therefore, the formulation is considered to be a mild sensitizer under the conditions of this study (results obtained from the 1% challenge).

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005104

DATA EVALUATION REPORT

STUDY TYPE: Eye Irritation 81-4 (rabbit) TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 259805

TEST MATERIAL: (R+S)-a-cyano-3-(phenoxyphenyl) methyl (1S+1R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

SYNONYMS: PP321, Karate, Cyhalothrin

STUDY NUMBER(S): 8333B

REPORT NUMBER: Not given

SPONSOR: ICI Americas, Inc., Wilmington, Delaware

TESTING FACILITY: Food + Drug Research Labs Inc., Waverly, N.Y.

TITLE OF REPORT: Primary Eye Irritation Study of PP321 EC in New Zealand White Rabbits

AUTHOR(S): E. Reagan, P. Becci

REPORT ISSUED: 12/18/84

IDENTIFYING VOLUME: Volume II, Section C, Tab Ref. 9C

CONCLUSION: Moderately irritating to unwashed eyes and mildly irritating to washed eyes.

Toxicity Category: II

Classification: Core Minimum

MATERIALS AND METHODS:

Chemical:

PP321 EC was tested. No information was given on the formulation. The reference #'s were: FDRL Test Article ID: 84-0829, Sponsor ID: PP321 EC, GFU383C, 193/17B. The same reference numbers were given for a dermal irritation study conducted six months later in a different laboratory. Therefore, it is assumed that the concentration of the active ingredient in the formulation is approximately 13.1%.

Animals:

Nine young adult New Zealand White rabbits were obtained from LaCrosse Industries, Inc., Schenectady, New York. Their weights ranged from 2.24 - 3.25 kg. There were 3 males and 6 females.

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Protocol:

A volume of 0.1 ml of the test article was instilled in one conjunctival sac of each rabbit. Three eyes were irrigated with physiological saline 30 seconds after instillation of the test article. The eyes were examined and the grade of ocular reaction for each animal was recorded according to the method of Draize at 1, 24, 48 and 72 hours post treatment and on days 4, 7, 10, 13, 16, 19 and 21. Classification was based on the one animal from each group with the most severe ocular response.

RESULTS:

The highest mean irritation scores were 20.7 for unwashed eyes and 16.3 for washed eyes. The unwashed eyes were classified as moderately irritating and the washed eyes were classified as mildly irritating. The toxicity category for unwashed eyes is II.

DISCUSSION:

This was a poorly reported study. The purity and other information on the test article was not reported. The weight range of the animals was not reported up front. All the individual weights were in the appendix. The mean irritation scores were reported for each time point, but there were no summaries given for each of the parameters evaluated. Only raw data was given. More information on the test substance needs to be submitted.

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005104

DATA EVALUATION REPORT

STUDY TYPE: Acute Innalation 81-3 (rat) TOX. CHEM. NO.: 723C

ACCESSION NUMBER: 259805

TEST MATERIAL: (R+S)-a-cyano-3-(phenoxyphenyl) methyl (1S+1R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

SYNONYMS: Karate, PP321, Cyhalothrin

STUDY NUMBER(S): HRO563

REPORT NUMBER: CTL/P/1358

SPONSOR: Not given

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab., Alderly Park, Macclesfield, UK

TITLE OF REPORT: PP321: 4 Hour Acute Inhalation Toxicity Study in the Rat of a 13% EC Formulation

AUTHOR(S): AM Curry and IP Bennett

REPORT ISSUED: 8/9/85

IDENTIFYING VOLUME: Volume II, Section C, Tab 10C

CONCLUSION: The LC_{50}'s are as follows: males - 0.315 mg/l; females - 0.275 mg l

Toxicity Category: I

Classification: Core Guideline

MATERIALS AND METHODS:

Chemical:

The test substance was supplied by ICI Americas, Golcsboro, NC. It was a dark straw-colored liquid and contained 13.1% w/w PP321. The reference #'s are as follows: Formulation # GFU 383C, Div. Ref. # SA 31/85, CTL Ref. # YO4443/001/504-6.

Animals:

Twenty-five male and 25 female SPF Alpk/AP (Wistar-derived) rats were supplied by Alderly Park, Cheshire, UK. They were approximately 7 weeks old and had the following body weight ranges: males - 200-221; females - 189-218.

Protocol:

Five animals of each sex were tested per dose level. The target concentrations of PP321 were set at 0, 5, 25 and 100 mg/m^3. Animals were exposed to the test material for 4 hours. Aerosols of the formulation were generated by passing clean, dry air through a Wrights Nebuliser containing the formulation. The nominal atmospheric concentrations were calculated from measurments of the weight loss of the formulation used. Particulate concentrations were measured gravimetrically, close to the animals' breathing zone at various intervals during the exposure. The aerodynamic particle sizes were measured once during exposure with an Anderson mini sampler. Animals were exposed nose-only in restraining tubes. Bodyweights were taken on days -1, 1, 28 and 15. All animals were subjected to a macroscopic post-mortem examination.

RESULTS:

Nominal concentrations were as follows: 15, 89 and 241 mg/m^3 for 5, 25 and 100 mg/m^3 respectively. The analyzed PP321 concentrations were 3.6 +/-0.8, 25 +/-13 and 68 +/-26 mg/m^3 for the 3 target concentrations respectively. The LC_{50} values were calculated to be 41 (25-68) mg/m^3 for males and 23 (3.6-68) mg/m^3 for females, corresponding to 0.315 mg/l for males and 0.175 mg/l for females. At the top dose animals showed respiratory abnormalities (gasping), central nervous system activity (reduced reflexes) and convulsions. Six of ten animals at the highest dose level died during exposure to the test substance. The rest in that dose group and 2 females at the next level down were killed in extremis shortly after the exposure period. These also showed a pronounced effect on the nervous system. At the lowest dose level, respiratory irritation, piloerection and hunched posture were noted. None of these animals died during either the exposure or the observation period. The lungs of the animals that either died during exposure or were sacrificed shortly thereafter were heavier than normal for this age group. No treatment related effects were seen in animals which survived to day 15.

All the test atmospheres had inspirable (<15um AED) content >90% and the active ingredient accounted for approximately 18% of the total particulate concentration. There was little residual effect.

DISCUSSION:

This appears to be a well-run study. The mortality pattern in the males made it difficult to predict the 95% confidence intervals. Animals died only at the top dose.