(5-1-95) (1

ANTIMICROBIAL PROGRAM BRANCH TOXICOLOGY REVIEW FOR HAZARD EVALUATION AND LABEL.

SUBDIVISION F

Guideline	Study Title	
81-1	Acute Oral Toxicity in the Rat	X
81-2	Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig	X
81-3	Acute Inhalation Toxicity in the Rat	
81-4	Primary Eye Irritation in the Rabbit	X
81-5	Primary Dermal Irritation Study	X
81-6	Dermal Sensitization in the Guinea Pig	X
81-7	Acute Neurotoxicity in the Hen	

The review of the submitted toxicity data for product .: Proxel XL2 .....

Registration Number: ID # 10182 UNL

Toxcity category: 1 due to its Acute oral, dermal , eye , skin , inhalation, or dermal sensitization.

The product will be used as : Industrial Microbiocide

Review of the submitted data places the product in the following Toxicity Cat.:

Acute Oral III Acute Dermal N/R Acute Inhalation N/R

Eye Irritation 1 N/R. Skin Irritation 1 N/R N/R= Not required

Dermal Sensitization (Sensitizer, negative , other N/R)

Other studies required or recomended : No other studies required

CPR Status : This product requires / does not special packaging

Label : Revise the label as follows: No adverse comments

Signal Word to be used: DANGER

1/10

Statement of Practical Treatment :

No adverse Commnets

Other comments and recomendations : The only study required is the Acute Oral. Other studies are not required due to the pH of the product that is 13.5 . The acute dermal study is equivacal and is not accepted

Precautionary Statement : No adverse comments

The submmited data was reviewer by Alex Arce in May 1 95

All submitted studies were performed at the Zeneca Central Toxicology Laboratory; The study numbers are : A.O- AR 4314 , A D- AR 4312 , Skin EB 4326, Sensitization GG6269

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ANTIMICROBIAL PROGRAM BRANCH TOXICOLOGY REVIEW

Pesticide Assesment , Subdivision F,Hazard Evaluation, Human and Domestic Animals.

Date In 4-21-95.. Date Out .5-195.. Reviewed By A. Arce.. Date 5-1-95..

EPA Registration Number or File Symbol : 10182-UNL.....

Date Division Received 04-20-95 Type of Product Ind. Antimicrobial

Data Accession No(s) 535960-07-08-09-10 Product Manager No. 31 Johnoson/Sindell

Product Name : PROXEL XL2

Company Name : Zeneca AG. Products

Submission Purpose : Review of submitted Toxicology data and label review

Chemical Formulation : Liquid

Active Ingredient 1,2-Benzoisothiozoline % 9.0 %

Good Laboratory Practices and statement of data confidentiality claims Complied

Protocol; CFR Guidelines : Studies adhere to guidelines

Test Substance or Test material (Chemical Name) Benzoiso-thiazoline

Form: Technical .....Manufacturing Use Product..... Formulation... X

Source ..ICI Specialty Chemical... Lot No. BX 360,ADH 420280 Cas No.....Purity PURE

Other Pertaining Information : Not relevant

Conclusion The dermal Toxcity Ld50 study is unacceptable due to equivocal results. The use of rats for the Acute dermal toxcity gave results that were not comparable to the results obtained , in the Skin irritation study using rabbits. Thus the results of the Acute Dermal using rats is equivocal since no signs of irritation were observed , while in the skin irritation using rabbits severe skin irritation was observed . Thus I concluded that the absorption of the product tested using rats gives results that are unacceptable.

Coments

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Data Review

Test Laboratory and Identification number for this test Zeneca # Ar 4314

ACUTE ORAL LD 50 CFR 81-1

Report Date 11-30-94 MRID No.435960-01 Method of testing CFR 81-1

Material Tested (Solid . liquid,Percent AI,End Use Product , Technical)

Specie (At least 5 adult rats) sex M.& F. Age. A..group. 4 groups

Dosing ; Levels tested .250,1000,.2500 and 5000 mg/kg

Vehicle control: None used

Individual observations ....one..... Times /day

Observation period (for 14 days) Yes

Individual daily observations :.at.dosing.and.at.the.7.and.14th days (each day)

Individual body weights :.At. dosing.and.at.the.7.and.the.14 th day

Gross necropsy: In all animals

Procedure The rats were treated with the material in empty stomachs , by gavage and observed for signs of toxicity at schedulled intervals

Results : Signs of toxicity. Decreased activity. , piloerection , salivation

Mortality : Males , none , Females 2/5 at 2500 and 4/5 at the 5000 dose level

Body weights / Unremarkable

Gross necropsy. One female at the 2500 mg/kg dose level, blood in the atomach wall

Comments: The study is acceptable

Conclusion: Toxicity Category..111... From Acute Oral LD 50. 3536 mg/kg M
3068 mg/kg F

Core Classification (.Guide.Lines., Minimum, .Supplementary.data,.Unacceptable.

Explanation.:.Sufficient.information.was.submitted

Signal word to be used ..DANGER due to it irritation properties

Data Review

Test Laboratory and Identification number for this test : Zeneca # CR3182

ACUTE DERMAL LD 50 . CFR 81-2

Report Date .11-22-95 MRID No.435960.. Method of testing:...81-2.....

Material tested (Technical , percent of AI, Solid , liquid , End use)...Liquid

Animals (At least 5/group) Specie..RAT..... Sex.M&F... Age...A..

Weight (Rat,200-300 g., rabbit, 2-3 kg.,gyinia pig,350-400 g.).....

Dosing .One dose..... single dermal. Patch test.....Occluded.....

Time in contact with the skin ...24.Hours.....Method of removal:using water...

Vehicle control used.:.None.....

Dose level tested (Limit 2000mg/kg) Yes

Application site preparation (Clipped , Shaved , time as 24 hours prior).....

Percent of body area material applied to(at least 10%)...Yes.....

Protective cover used (porous non irritatiing , wrap with tape , other)....

Individual observation(at least one day) Yes

Lenght of observation period (14 days) other ...Yes.....

Individual body weights ...At intervals during the study.....

Gross necropsy ...All animals.

Procedure : Previuosly prepared areas of the skin of the rats were treated with the material and observed for signs of toxicity and dermal irritation

Results ; Signs of toxicity ..None.....

Mortality ..None.....

Body weights .Acceptable.....

Necropsy .Unremarkable.....To note.....

Comments : Application of the product failed to induce dermal irritation. While using rabbits, irritation of severe nature was observed.

Conclusion: Toxicity Category. Not established.... From Acute Dermal Ld 50 2000 m

Signal Word to be used .....DANGER due to eye irritation observed.....,

Core Classification (Guidelines , Minimum, Supplementarydat, Unacceptable

Explanation .: Requires explanation for the use of rats instead of the use of rabbits, Since, while tested for skin irritation using rabbits the results werepatentaband severe

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Data Review

Test Laboratory and Identification number for this test

PRIMARY EYE IRRITATION TOXICITY CFR 81-4

Report Date .... MRID No .... Method of testing ....

Specie .... Sex .... Age.............

Identity of the material (Technical, dilution % , End use product, solid liquid , other .)..

Note , study is not required if product is corrosive , has a pH of less than 2 or greater than 11, causes severe dermal irritation

Number of rabbits or other specie used (6 minimum) ....

Method of instillation (conjunctival sac .... other.......)

Control eye............. Dose in ml used (0.1 ml , other) or 100 mg if solid .... Material used to dilute the product.........................

Eyes were washed at.................. eyes were unwashed ....

Eyes examination at .... intervals (1, 24, 48, 72 hours and at....

Daily observations ....

Procedure

Signs of eye irritation ....

Other toxic signs ....

Corneal opacity .... Iritis .... Conjuntivitis

The eyes cleared at..

Other pertinent observations

Conclusion : Toxicity category..

Core classification .... (Guidelines, Minimum, Supplementary , Unacceptabl

Explanation

Signal Word To be used ....

NOT REQUIRED

NOT SUBMITTED

DUE TO 13/5 PH OF

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Data Review

Test Laboratory and Identification number for this test Zeneca Eb 4326

PRIMARY DERMAL IRRITATION CFR 81-5

Report Date 11-2294 MRID No. 435960. Method of testing ...81-5.....

Specie Rabbit ..... Sex. F..... Age adult.....

Identity of the material .... (Technical , dilution , End_use_product , solid , liquid , other).....Diluent.solution.used.none.....

NOTE This study is not require if the product is corrosive , has a pH of 2 to 11.5 or if it has been prove to induce known severe irritation . pH=13.5

Number of animals used (6 adult males or females) ..6 females

Methods of testing . (Single dose , dermal application) .....Yes.....

Duration of exposure (4 hours) .....Yes.....

Application site (shaved , clipped , other) ..... Time (24 hours before)

Area of a pplication , (site , area in cm. other) ...Acceptable.....

Application site ; material under protective wrap, gauze . patch, non irritating tape . Yes

Time of material in contact and time when it was removed and the area washed

After 4 hours the patch was removed and the areas cleaned

Examination and graded at intervals of (1,24,48,72 hours . 28. . OR days).....

Signs of irritation or toxicity observed : For erythema , edema, corrosion . Yes

Procedure Previously prepared areas of the skin of the rabbits were treated with the material and observed for signs of irritation

Signs of irritation : severe response

Erythema : severe

Edema : severe

The area treated , cleared at.....10 + days

Conclusion : Toxicity Category .....1.....Signal word ..DANGER..

Core Classification (Guidelines , Minimum , Supplementary , Unacceptable)

Explanation Sufficient information was submitted to asign a Toxicity Category

Data Review

Test Laboratory and Identification number for this test

Acute Inhalation Toxicity LC 50 CFR 81-3

Report Date ..... MRID No..... Method of testing .....

Material Tested (Solid , liquid , % AI, end use product , technical)....

The product is a (gas, a solid , liquid , aerosol, other)....

Particle size..... Vapor hazard, toxicity known .....

Number of animals used ..... sex ..... age ..... specie.....

At least 5 young adults of each sex per group .....

Dosing time and method (At least 4 hours)

Chamber description ..... air flow dynamics .....

(at least 10 air changes/hour) ..... At least 19% oxygen content....

Chamber temperature .....(22cent+or --) relative humidity (40-60 %)...

Monitor rate of air flow ..... Monitor actual conc. of test mat. -

in breathing zone..... Aerodynamic particle size for eaerosol.....

Dose levels tested (sufficient to determine Tox Cat or Limit dose 5mg/l)

Individual observation at intervals (once a day)..... .....

Observation period (14 days minimum)

Individual body weights .....

Observations , toxicological signs .....

Signs of toxicity .....

Mortality.....

Necropsy on all animals

Changes in body weight .....

Comments .....

Data Review

Test Laboratory and Identification number for this test Zeneca GG 6260

DERMAL SENSITIZATION CFR 81-6

Report Date 11-30-94 MRID No. 435960. Method of testing ..81-6.....

Matr.. Tested (Technical , dilution % , End use product , solid , liquid)

Material used for diluent : Freunds Adjuvant or water

NOTE: This study is not required if the product is corrosive has a pH of 2 to 11.5 or if it is known sentizer or irritant to the skin pH 13.5

Method utilized Freund's complement adjuvant, Guinea pig maximization, split adjuvant ,Buehler..test or modified Buehler, Open epicutaneous , Mauer optimization , Footpad technique in Guinea pigs; Magnuson and Kligman

Complete description of test.. Yes the test was completely describded

Reference (CFR 81-6 , other .....)

Test followed essentials as described in reference document...Yes.....

Control used:..positive usin 2 mercaptobenzothiazole.....

Specie used ..../..Guinea pigs..... Number of applications perweek 3 injectio

For how many weeks...one week..... Days of rest between application ...One week..... Days of rest before challenge dose .One week.....

Dose used for primary application Intradermal induction ..... other doses .. topical applic.

Challenge dose : Dilutions of 30%, 10%, 3% and 1% were essayed

Areas of application : Scapular region in a previously clipped area

Number of animals used : 30 , female Guinea Pigs ; 20 for the test and 10 as Con

Primary pilot study .:.Yes a primary pilot study was conducted

Controls (positive ...Yes, separate study, negative , No.....

naive .....) Solvent controls .....

Positive control study: previously induced animals were challenged with a 30% w/v of 2 -mercaptobenzothiazole .

Procedure : After an induction application by inoculatio, a period of rest was allowed and then a challenge dose was administered. 3 areas were used for the test : a- in the top area , Freunds adjuvant and water , in the meddle area -the test material and water and in the botton area -test material in freunds adjuvant and water . The ratios were 0.1 % w/v

Results

The challenge dosing using the test material in four dilutions was negative (30, 30 , 3 and 1%) while the same animals showed a positive response while challenged with the positive material 2- mercaptobenzothiazole

Erythema observed negative for test animals.....

Test animals : negative for erythema and edema

Positive control : positive for erythema and edema

Negative control ; No used

Edema observed : negative for test animals , positive for positive controls

Positive control: positive

Negative control : not used

Test animals general observations : Unremarkable

Control animals , general observations.... Positive controls have a severe respor

Conclusion; the product is a dermal sensitizer .....No, negative..... irritant yes.....

doubtfull..... inconcluive .....

Core classification .....Guidelines , minimum, supplementary , unacceptable

Comments

This test is not required due to the pH of the material that is 13.5

Label signal words to be used /...Non.for.sensitization.....

DANGER , due to EYE/skin irritattion