(5-8-95)

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 B D 20.....

.....

Registration Number:..101 82601.....

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 ..111.... Acute Dermal IV..(rats.) Acute Inhalation..Not Required

Eye Irritation .1..... Skin Irritation .11.....

Dermal Sensitization (Sensitizer, ~~negative~~, other POSITIVE)

Other studies required or recomended : Revise AO and AD

CPR Status : This product requires / does not special packaging

Label : Revise the label as follows:.....

No adverse comments

Signal Word to be used:.....DANGER.....

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Statement of Practical Treatment :

Acceptable

Other comments and recomendations : The use of rats for the Acute Dermal Ld 50 study requires an explanation , since rabbits are the prefered specie for this test and the fact that while using a lower concentration of the product, 9.0% Benzoisothiazoline in rabbits the irritation reported was severe while a 19.3 % concentration used in rats for the Ld 50 , dermal study shows mild irritation response .

Precautionary Statement :

The product was diluted with dionized water for the Acute Oral Ld50 , it also requires an explanation since the use of a solvent could change the results of the study.

The submmited data was reviewer by Alex Arce on May 4 to 8 of May 1994

NOTE : The submitted data was performed at the Zeneca Laboratory and follows the CFR 40 Guidelines and the GLP

ANTIMICROBIAL PROGRAM BRANCH TOXICOLOGY REVIEW

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

Date In 4-27-94 Date Out 5-8-95 Reviewed By A. Arce Date 5- 95

EPA Registration Number or File Symbol 10182 GOI

Date Division Received 12-19-94 Type of Product Industrial Microbioci

Data Accession No(s).434895-06,07,08,and 09 Product Manager No. Johnson/Swindell

Product Name Proxel BD 20

Company Name : Zeneca Biocides

Submission Purpose : Review of Toxcity Data and label review

Chemical Formulation : Liquid

Active Ingredient % 1,2 Benziso thiazoline 19.3 %

Good Laboratory Practices and statement of data confidentiality claims

Yes . GLP Compliance

Protocol; CFR Guidelines were followed

Test Substance or Test material (Chemical Name) . Benzisothiazoline

Form: Technical Manufacturing Use Product X Formulation

Source CTL Lot No Yoo180/032 Cas No. No Purity : Pure

Other Pertaining Information : None required

Conclusion : Request to have a conference with the registrant to clear discrepancies as the use of rats for the AD and the use of water for the A O

Coments As previously stated .

Data Review

Test Laboratory and Identification number for this test : Zeneca AR 5822

ACUTE ORAL LD 50 CFR 81-1

Report Date ..11-22-94MRID No.434895-06 Method of testing .....CFR 81-1.....

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

Specie (At least 5 adult rats) sex M.and.F Age..A.group.5.....

Dosing ; Levels tested .in.mg/kg..:.500.m-f, .1000 m-f, 1500 m,2000 and 5000 f.

Vehicle control..:.dionized.water.....

Individual observations .daily..... Times /day

Observation period (for 14 days) .....Yes..... .....

Individual daily observations .:.for.systemic.toxicity.....

Individual body weights :.At.intervals.,.acceptable.....

Gross necropsy..:.All.animals.....

Procedure : The rats were treated with the material in empty stomachs , by gavage using 5 dose levels and observed for signs of toxicity

Results : Signs of toxicity..:. Pilo.erection.,.irrigular.breathing.,.curvature of the spine

Mortality :.1/5.at.1000.dose.,.f-3/5.at.500.m-4/5.m.and.2/5.f.at.2000and.5/5.at.50(

Body weights /..Survivors.have.a.temporary.loss.with.a.recovery.....

Gross necropsy:.Severe.G.I.tract.irritation.....

Comments..:.the.product.appears.to.induce.pain.....

Conclusion: Toxicity Category....III. From Acute Oral LD 50..1,500 mg/kg.....

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

Explanation..:.Requires.an.explanation.for.the.use.of.dionized.water.....

Signal word to be used .....DANGER (due to the eye irritation.....

Data Review

Test Laboratory and Identification number for this test : Zeneca CR 3180

ACUTE DERMAL LD-50 . CFR 81-2

Report Date 11-22-94 MRID No. 434895-07 Method of testing: 81-2

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

Animals (At least 5/group) Specie. Rats Sex. m-f Age. Adult

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

Dosing 2000mg/kg .... single dermal. Patch test...Yes.. Occluded ..... Yes

Time in contact with the skin .24.hours.....Method of removal.;.Manual./.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~~) ..Yes.

Individual observation(at least one day) Yes

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

Individual body weights ..at schedulled intervals ; acceptable

Gross necropsy ....All animals

Procedure : The rats were treated with the material in previously prepared places of the skin and observed for signs of systemeic toxicity and dermal irritatir

Results ; Signs of toxicity : None (brown stains are reported).....

Mortality : none.....

Body weights : Unremarkable.....

Necropsy : Unremarkable.....

Comments : The use of rats , instead of rabbits requires an explanation

Conclusion: Toxicity Category : Not stablished..... From Acute Dermal Ld 50 ...

Signal Word to be used ...DANGER (because the eye irritation),

Core Classification (Guidelines , Minimum, Supplementarydata Unacceptable

Explanation : The fact that the product induces dermal irritation in the rabbit and did not induced dermal inritation in the rat , plus the fact that the rsults of the test using a lower concentration are more severe

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Data Review

Test Laboratory and Identification number for this test

PRIMARY EYE IRRITATION TOXICITY CFR 81-4

Report Date 11-22-94 MRID No. 434895 Method of testing 81-4

Specie ..... Rabbit ..... Sex ..... Female ..... Age .. Adult .....

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~~) .... Yes .. , only one rabbit

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

Control eye. : Non. treated . dose in ml used (0.1 ml , other) or 100 mg if solid ..... . Material used to dilute the product ... None .....

Eyes were washed at Not washed ..... eyes were unwashed ..... Yes

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

Daily observations ... One day only .....

Procedure : Due to the severe pain , only one rabbit was used . The product was instilled into the conjunctival sac , Observations for irritation followed

Signs of eye irritation : Pain .....

Other toxic signs . : Severe .....

Corneal opacity ... Mild ..... Iritis ..... Yes ..... Conjuntivitis Severe

The eyes cleared at ... The rabbit was humanly sacrificed .....

Other pertinent observations : the product is a known severe irritant

Conclusion : Toxicity category ... 1 .....

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

Explanation : The use of one animal is acceptable due to the severe pain

Signal Word To be used .... DANGER .....

This test is not required

Data Review

Test Laboratory and Identification number for this test Zeneca EB 4324

PRIMARY DERMAL IRRITATION CFR 81-5

Report Date 11-22-94 MRID No. 434895-09 Method of testing 81-5

Specie ..Rabbit..... Sex..Female..... 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 .

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

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) in.the.flank.,.7X13.cm

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 4 hours after the application , washed with water

Examination and graded at intervals of (1,24,48,72 hours and.7xor days).....

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

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

Signs of irritation : desquamation anf thickness , stains

Erythema : well defined

Edema : Yes

The area treated , cleared at....14 th day.....

Conclusion : Toxicity Category ....11.....Signal word .DANGER (eye irri

Core Classification (Guidelines , Minimum , Supplementary , Unacceptable)

Explanation : Sufficient information was provided

Data Review

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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 use ..... 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% oxigen content....

Chamber temperature .....(2 cent+or --) relative humidity (40-60 %)...

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

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

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

Individual observation at interval (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 .....

NOT REQUIRED
PRODUCT USES
WILL NOT PRODUCE
AEROSOL

Data Review

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Test Laboratory and Identification number for this test Zeneca GG 6226

DERMAL SENSITIZATION CFR 81-6

Report Date .11-22-94 MRID No. 434895-10 Method of testing ..81-6.....

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

Material used for diluent : dionized 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

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..Magnusson and Kligman

Complete description of test...: It was provided.....

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

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

Control used:..Yes.....

Specie used :. 30. female. Guinea pigs... Number of applications perweek One

For how many weeks: one. week..... Days of rest between application 2 days..... Days of rest before challenge dose ..:.One week.....

Dose used for primary application .Inoculation.. other doses Topical.....

Challenge dose : In the scapular area, two weeks after induction

Areas of application :.Scapular .:. 30,10 and 3% induction in the left flank

Number of animals used : 30 feamles

Primary pilot study .:.Yes .. to establish dose levels....

Controls (positive .:.Mercaptobenzothiazole, negative ,.....

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

Induction Freunds adjuvant plus deinized water 1:1 top area
0.03 w/v test material in water Mid area
0.03 w/v test material in water 1:1 Low area

Procedure : 20 female guinea pigs were treated with the material in previously prepared areas of the skin for one week . After a rest period they were challenged with a lower dose

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Results

The test animals exhibit a mild redness at the challenge dose period

Erythema observed ....Mild.....

Test animals

Positive control severe

Negative control not used

Edema observed mnot reported

Positive control none

Negative control Not used

Test animals general observations : Unremarkable

Control animals , general observations...Unremarkable

Conclusion; the product is a dermal sensitizer .Yes..... irritant ....Yes....

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

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

Comments The study is acceptable for the purpuse of assigning a precautionary Statement in the label

Label signal words to be used /.....