6-6-88

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN -6 1988

006738

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: HOE 046360 (Penoxoprop ethyl) Review of 6 Acute Studies on the 7.4% Formulation

TO: E. Wilson, PM 23
Registration Division (TS-767)

FROM: Margaret L. Jones M. L. Jones 3 June 1988
Review Section III
Toxicology Branch
Hazard Evaluation Division (TS-769)

THROUGH: Marcia van Gemert, Ph.D., Head
Review Section III
Toxicology Branch M. van Gemert 6/3/88

and Theodore M. Farber, Ph.D., Chief
Toxicology Branch
Hazard Evaluation Division (TS-769) 6/6/88

Tox. Chem. 431C Record No.:221409
221410

Accession Nos: 406066-03 through 406066-09

Registrant: Hoechst Tox. Project No.: 8-0728

Action Requested: Review 6 acute toxicity studies on the 7.4% formulation for Super Whip™ and Super Acclaim™ herbicides.

Conclusions: The results of the battery of acute studies are found below.

Acute oral toxicity: LD_{50} male rat > 5000 mg/kg
LD_{50} female rat = 4410 mg/kg
Core grade minimum
Toxicity category III

Acute dermal toxicity: LD_{50} male and female rat > 5000 mg/kg
Core grade minimum
Toxicity category III

1

Acute inhalation toxicity:	Undetermined due to 40% mortality at the two highest doses tested. Core grade supplementary Toxicity category undetermined
Primary Eye Irritation:	The substance is a slight occular irritant in rabbits. Core grade minimum Toxicity category III
Skin Sensitization:	The substance is not a skin sensitizer in the guinea pig. Core grade minimum
Primary Dermal Irritation:	The substance is a slight dermal irritant in the rabbit. Core grade minimum Toxicity category IV

A screen of inert ingredients in the formulation of these products revealed that each ingredient is registered under 40 CFR 180.1001.

006738

Guideline Series 81-1: Acute Oral

Reviewed by: Margaret L. Jones M.L. Jones 27 May 1988
Section III, Toxicology Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D., Head
Review Section III, Toxicology Branch (TS-769C) M. van Gemert 6/3/88

DATA EVALUATION REPORT

Chemical: HOE -046360; (D+)-ethyl-2-(4-(6- chloro-2-benzoxazolyloxy) -phenoxy)-propanoate

Study Type: Acute Oral Toxicity in Male and Female Rats

Accession No.: 406066-04

Synonyms: Super Whip™ and Super Acclaim™

Testing Facility: Pharma Research Toxicology and Pathology
HOECHST AKTIENGESELLSCHAFT, Frankfurt, W.Germany

Title of Report: HOE-046360-Oil in Water Emulsion (75 g/l) (HOE-046360 OH EW07 A202) Testing for Acute Oral Toxicity in the Male and Female Wistar Rat

Authors: Diehl, K.H., Leist, K.H.

Study Number: 87.0513, Report No. A36865, 87.0754

Sponsor: Hoechst Celanese Corporation, Somerville, N.J.

Report issued: July 8, 1987

Conclusions: LD_{50} male rat $\geq$ 5000 mg/kg bodyweight
LD_{50} female rat = 4410 mg/kg bodyweight; the 95% confidence interval for the female LD_{50} is 0.00 to 1.0 E75.

Study: Core grade minimum

Toxicity Category III

A. Materials:

1. Test compound: Hoe 046360, oil in water emulsion 75 (g/l); code Hoe 046360 OH EW07 A202; white liquid; purity: 7.4% (w/w) active ingredient; certificate of analysis No. 3547, impurities not analyzed; Batch No.: Pfl. Hr. 2714

2. Test animals: Species: Wistar rat; Strain: Hoe: WISKf(SPF71); Age (at start of study): males, 7 weeks, females, 9 weeks; Weight: males, mean wt. = 193g (range 168-215g), females, mean wt. = 182g (167-194g); Source: HOECHST AG, Kastengrund, SPF breeding colony; Acclimation: 5 days

3. Diet: Altromin 1324 rat diet (Altromin GmbH, Lage/Lippe), ad libitum. Animals were fasted from 16 hr before study to 3-4 hr after treatment.

4. Statistical methods: The LD50 was calculated with mortality rates using probit analysis for females. Due to mortality rates in males, an LD50 could not be calculated.

B. Study Design:

1. Test groups:

Twenty (20) males and fifteen (15) females were distributed to the following dose groups (copied from page 11 of test report 87.0754):

Dose mg/kg bw	Concentration % (w/v)	Volume applied ml/kg bw	Number of males/females	
3150	31.5	10	5	-
4000	40.0	10	5	5
4500	45.0	10	5	5
5000	50.0	10	5	5

2. Test procedure:

Fasted animals were treated by gavage. Following treatment, observations continued for 14 days, recording signs and time of appearance of toxicity, times of death, and weekly weights. Deceased animals were examined in autopsy. Surviving animals were killed via carbon dioxide asphyxiation and examined.

C. Observations and Results

1. Clinical observations:

Clinical signs of toxicity were similar in males and females and signs appeared starting at 10 minutes post exposure and continuing through day 7 post exposure in several groups. Signs included

squatting position, reduced spontaneous activity, contracted flanks, uncoordinated gait and staggering gait which appeared in all dose groups, the majority of signs starting at 10 minutes post exposure. Other signs which appeared in all dose groups, the majority of which started at 30 minutes to 6 hours post exposure, included narrowed palpebral fissures, high legged gait, reduced respiratory rate, irregular breathing, piloerection and blood-crusted snout. Signs disappeared in survivors by day 3-4 in low and high dose males and by day 8 in low-mid and mid-high dose males. In females, signs disappeared by day 8-9 at the low and mid doses and by day 5 in high dose females.

2. Bodyweight measurements:

Animals were weighed after death and survivors were weighed on days 0, 7 and 14.

Bodyweights in surviving males on day 14 were 28-53% greater than weights on day 0 (individual weights). Bodyweights in (6) males dying between treatment and day 1 were essentially similar to starting weights. A slight bodyweight loss was observed in one male dying on day 2.

Bodyweights in surviving females on day 14 were 14-24% greater than weights on day 0 (individual weights). Bodyweights in (5) females dying between treatment and day 1 showed some weight loss (3-7%). In (3) females dying on day 2, the weight loss was more severe (8-10%).

Bodyweights in surviving animals were apparently not affected by test substance.

3. Autopsy findings:

In males and females found dead (2 males per dose; 1-low dose, 4-mid dose, and 3-high dose females) the following abnormalities were noted:

white fluid in stomach
yellow-orange, red-orange, or red-brown mass in small intestine
reddened small intestine
light colored spots in liver
beginnings of autolysis

In males found dead, yellow-white structures (0.4 mm in diameter) in the urinary bladder were noted at all doses. No such structures were ntoed in females.

At the final sacrifice (survivors to 14 days), no abnormalities were noted.

D. Discussion and conclusions:

1. Author's conclusions: The LD50 for females was 4410 mg/kg bw with 95% c.i. of 0.000 to 1.0E 75. The LD50 for males was $\geq$ 5000 mg/kg/day.

2. Toxicology Branch discussion and conclusions: Mortality was noted at all doses and it appears lower doses could have been administered in order to better approximate a dose-response curve for this chemical.

Guideline Series 81-2: Acute Dermal

006738

Reviewed by: Margaret L. Jones M.L. Jones 27 May 1988
Section III, Toxicology Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D., Head
Review Section III, Toxicology Branch (TS-769C) M. van Gemert 6/3/88

DATA EVALUATION REPORT

Chemical: HOE -046360; (D+)-ethyl-2-(4-(6- chloro-2-benzoxazolyloxy) -phenoxy)-propanoate

Study Type: Acute Dermal Toxicity in Male and Female Rats

Accession No.: 406066-05

Synonyms: Super Whip™ and Super Acclaim™

Testing Facility: Pharma Research Toxicology and Pathology
HOECHST AKTIENGESELLSCHAFT, Frankfurt, W.Germany

Title of Report: HOE-046360-Oil in Water Emulsion (75 g/l) (HOE-046360 OH EW07 A202) Testing for Acute Dermal Toxicity in the Male and Female Wistar Rat

Authors: Diehl, K.H., Leist, K.H.

Study Number: 87.0516, Report No. A36860, 87.0688

Sponsor: Hoechst Celanese Corporation, Somerville, N.J.

Report issued: June 4, 1987

Conclusions: LD_{50} male and female rat > 5000 mg/kg bodyweight

Study: Core grade minimum

Toxicity Category III

A. Materials:

1. Test compound: Hoe 046360, oil in water emulsion 75 (g/l); code Hoe 046360 OH EW07 A202; white liquid; purity: 7.4% (w/w) active ingredient; certificate of analysis No. 3547 (27 April, 1987); impurities not analyzed; Batch No.: Pfl. Hr. 2714; Density (used to calculate volume for application): 1.02 kg/l.

2. Test animals: Species: Wistar rat; Strain: Hoe: WISKf(SPF71); Age (at start of study): males: 7 weeks, females: 9 weeks; Weight: males, mean wt: 194g (range 187-200g); females, mean wt: 190 (range 186-193); Source: HOECHST AG, Kastengrund, SPF breeding colony

3. Diet: Altromin 1324 rat diet (Altromn GmbH, Lage/Lippe) ad libitum. Tap water was allowed in plastic bottles, ad libitum.

B. Study Design:

1. Test groups:

Five (5) male and five (5) female Wistar rats were administered 5000 mg/kg level of the test substance to determine the need for a full acute dermal toxicity study. The dose given was 5000 mg/kg bodyweight in a volume of 4.902 ml/kg in a 100% (w/v) concentration. The test substance was administered undiluted.

2. Treatment of animals:

Hair was removed mechanically from the dorsal skin of the animals to create an area approximately 30cm^2, leaving skin intact. Test substance was applied undiluted to the exposed skin in one single application. The test patch was covered with aluminum foil 6 x 8 cm. The foil was held in place with an elastic plaster bandage.

Following 24 hr. dermal exposure the bandage was removed and treated skin washed with warm water to remove unabsorbed test substance.

Animals were observed following application and for 14 days thereafter with weekly weighings. After the observation period, animals were killed with CO_2 asphyxiation, dissected and examined macroscopically.

C. Observations and Results:

1. Mortality:

There were no deaths during the study. The lethal dose is therefore above 5000 mg/kg based on these results.

4. Signs of toxicity and bodyweight observations:

No clinical signs of toxicity were noted during the study other than scaling of skin, and peeling of scales. Bodyweights increased in males an average of 17% on day 7 and 40% on day 14. Bodyweights increased in females an average of 5% on day 7 and 12% on day 14.

5. Observations at autopsy:

No macroscopic abnormalities were noted at final sacrifice.

D. Discussion and Conclusions:

1. Limit test:

The limit test for acute dermal testing has been fufilled by this study. A dose greater than the limit dose of 2000 mg/kg has been used without producing any mortality or observed signs of severe reaction to the test substance.

2. Toxicology Branch comments and conclusions:

The LD_{50} in male and female Wistar rats is greater than 5000 mg/kg bodyweight as demonstrated in this study. It appears that the limit test has been satisfied and no further acute dermal toxicity study will be required at this time.

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Guideline Series 81-3: Acute Inhalation

Reviewed by: Margaret L. Jones M L Jones 3 June 1988
Section III, Toxicology Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D., Head
Review Section III, Toxicology Branch (TS-769C) M. van Gemert 6/3/88

DATA EVALUATION REPORT

Chemical: HOE -046360; (D+)-ethyl-2-(4-(6- chloro-2-benzoxazolyloxy) -phenoxy)-propanoate

Study Type: Acute Inhalation Toxicity in Male and Female Rats

Accession No.: 406066-06

Synonyms: Super Whip™ and Super Acclaim™; 7.4% formulation of a.i.

Testing Facility: Pharma Research Toxicology and Pathology
HOECHST AKTIENGESELLSCHAFT, Frankfurt, W.Germany

Title of Report: HOE-046360-Oil in Water Emulsion (75 g/l) (HOE-046360 OH EW07 A202) Testing for Acute Aerosol Inhalation Toxicity in the Male and Female SPF Wistar Rat- Four-Hour LC_{50}

Authors: Hofmann, T., Jung, R.

Study Number: 87.0518, Report No. A37205, 87.1480

Sponsor: Hoechst Celanese Corporation, Somerville, N.J.

Report issued: November 4, 1987

Conclusions: Five/sex/dose Wistar rats were tested with 3.31, 7.56, or 8.52 mg/l of the test substance. LC_{50} not determined due to 40% mortality in the two highest dose groups for males and females. Disturbances of motility, respiration, and reflexes were noted. Corneal opacity was also observed at the mid and high doses.

Study: Core grade -Supplementary

Toxicity Category - Undetermined. A full description of how and where samples were taken will be necessary; attempts to produce smaller particle sizes should be described. See Toxicolgy Branch evaluation for discussion of deficiencies.

A. Materials:

1. Test compound: Hoe 046360, oil in water emulsion 75 (g/l); code Hoe 046360 OH EW07 A202; white liquid; purity: 7.4% (w/w) active ingredient; certificate of analysis No. 3547, impurities not analyzed; Batch No.: Pfl. Hr. 2714

2. Test animals: Species: Wistar rat; Strain: Hoe: WISKf(SPF71); Age (at start of study): 8 - 10 weeks; Weight (at start of study): males, 208g (range 197-229g); females, 196g (range 190-206g); Source: HOECHST AG, Kastengrund, SPF breeding colony; period of acclimation: 5 days

3. Diet: Altromin 1324 rat diet (Altromin GmbH, Lage Lippe), ad libitum. Tap water was administered in plastic bottles, ad libitum.

4. Quality Assurance was reported in conformity with OECD Principles of GLP (4 Feb 1983).

5. The statistical analysis programs used were not described.

B. Methods and Results:

1. Animal assignment:

Group	Volume(ml/hr)	Actual conc. in exposure chamber (mg/l air)	Number of animals Males	Females
1	120	3.31	5	5
2	225	8.52	5	5
3	300	7.56	5	5

2. Generation of Test Atmosphere, Exposure Apparatus, and Measurements:

Air was pumped into the top of a glass (800 l/hr) and stainless steel "Dynamik" inhalation cylinder (vol 60 l.)after passing through an oil separaton filter, an absolute filter at a pressure of 4 bar, and into a special nozzle with welded-in supply tube for injection of the test substance into the nozzle. Test substance was injected into the nozzle at constant speed using a continuous infusions apparatus. At the bottom of the chamber, a suction device drew off aerosol at 1100 l/hr to maintain negative pressure in the chamber. Extraneous air was drawn in through animal tubes where animals were placed individually with only noses projecting into the inhalation chamber.

Air monitoring equipment (Hartmann & Braun) monitored CO, CO_2, O_2, humidity, and temperature. Groups 1 and 3 lack humidity information due to defective monitor for this measurement.

Values for gases, humidity and temperature were within acceptable guideline limits.

Total concentration in the test chamber was measured by drawing 31 l. in 60 min. from each chamber, passing the "respiratory air" through three gas-washing flasks linked in series, filled with methanol (analytical grade, Riedel de Haen) resting in a cold bath. The amount of active ingredient was isolated by HPLC and converted values were then recorded in the results, as follows:

Concentration of Test Substance in Aerosol

Group	Volume (ml/hr)	Analytical Concentration Technical Chem. (mg/l)	Test Substance (mg/l)
1	120	0.245	3.31
2	225	0.645	8.72
3	300	0.56	7.56

To convert from technical chemical concentration to test substance concentration, a ratio was used (e.g.: 1/0.074 = 13.5, 13.5x0.56 = 7.56). "Respiratory air" was not defined. Since no information was found in the test report describing where samples were taken (ie. from the breathing zone of the animals) and whether appropriate time was allowed for equilibration of the test chamber, no conclusions can be made from the reported data.

Particle size distribution (APS 33 Aerodynamic Particle Sizer, TSI, Inc, St. Paul). Measurements were made every 30 min. and recorded hourly.

Particle Size Measurements

Group	Volume (ml/hr)	Particle Size (u)	Respirable Particles < 2 u Percent
1	120	1.98	90
2	225	1.98	91
3	300	1.98	93

The particle sizes are those which occured with greatest frequency for four measurements per dose level. At this size, however, the majority of the weight of compound introduced was not respirable, as reported in the printout attached to the study. At 120 ml/hr, 20% of the mass is represented by particles $\leq$ 2.00 U, at 225 ml/hr, only 29% of the mass is represented and at 300 ml/hr, only 24% of the mass is represented by the above particle size.

3. Exposure to test substance and Observations:

Exposure duration was 4 hours throughout which observations were made. Observations began 5 minutes after treatment and continued at approximately 200, 240, and 420 minutes. Recorded observations continued daily thereafter for 14 days (males and females exposed to 3.31 mg/l, and 7.56 mg/l) or 35 days for males exposed to 8.72 mg/l and 63 days for females exposed to 8.72 mg/l.

Since no information was found in the test report describing where samples were taken, no statements can be made about the

concentrations of test substance producing a particular toxic effect.

Observations

During Exposure (5 min - 420 min)

3.31 mg/l	Males	Females
irregular breathing	x	x
reddened eye	x	x
ataxia	x	x
squatting	x	x
uncoordinated gait	x	x
piloerection	x	x
jerky breathing	x	x
7.56 mg/l		
irregular breathing	x	x
uncoordinated gait	x	x
ataxia	x	x
squatting	x	x
reddened eye	x	x
8.72 mg/l		
irregular breathing	x	x
uncoordinated gait	x	x
drowsiness	x	x
corneal, placing and paw pinch reflexes weak	x	x
reddened eye	x	x
ataxia	x	x
jerky breathing	x	x
piloerection	x	x

Following Exposure (days 1-14, and beyond, where indicated

3.31 mg/l	Males	Females
squatting	x	x
jerky breathing	x	x
uncoordinated gait		x
piloerection		x
wheezing	x	
contracted flanks	x	x
sneezing	x	
narr. palp. fissures	x	x (d1-5)
high legged gait	x (d8-10)	x
7.56 mg/l	x	
irregular breathing		x (d2-5)
uncoordinated gait	x (d1-4)	
squatting	x (d1-7)	x (d1-8)
corneal opacity	x (d1-6)	x (d1-12)
jerky breathing	x (d1-6)	
red crusted eye	x (d1-4)	
wheezing	x (d1-6)	
contracted flanks	x (d1-8)	x (d1-6)
narr. palp. fissures	x (d1-4)	
high legged gait		x (d1-10)
sneezing		x (d3-8)

8.72 mg/l		
irregular breathing	x	x
uncoordinated gait	x	
reddened eye	x (d1-6)	x (d1-6)
piloerection	x (d1-11)	x (d1-14)
squatting	x (d1-11, d16-24)	x (d1-22
narr. palp. fissures	x (d1-9)	x (d1-8)
high-legged gait	x (d1-10;	x (d1-26)
sneezing	x (d1-9, d13-26)	x (d1-22)
aggressiveness	x (d3-7)	
corneal opacity		x (d2-7)
hairloss due to $KMnO_4$		x (d1-63)

4. Mortality:

One low dose male died on day 2. Three mid dose males died on days 3-5. One high dose male died on day 6 and one on day 19. No females in the low dose group died. One mid dose female doed on day 3. One high dose females died on day 4 and one on dya 58.

Group	Actual conc. (mg/l)	Males	Females	Total
1	3.31	1/5 (20%)	0/5 (0)	1/10 (10%)
2	7.56	3/5 (60%)	1/5 (20%)	4/10 (40%)
3	8.72	2/5 (40%)	2/5 (40%)	4/10 (40%)

5. Results at Autopsy

Males found dead during study, one each at low dose had liver with light colored patches or reddened, two at high dose had inflated G.I., and three at mid dose had dark red lungs and one at high dose had light-beige lungs.

Females found dead during study, one mid dose animal had reddened lungs.

In males and females killed at termination there were no macroscopically visible findings.

5. Bodyweights

Animals surviving to day 14

In males surviving to day 14 there was an apparent initial slowing of bodyweight gain from day 0-7 (-17-+17%) with a greater spurt in bodyweight gain from day 8-14 (-2-37%). [The animal losing 17% by day 7 had gained 31 g by day 14 to reduce the loss to -2%.] High dose males were observed to day 35 when measured bodyweight gains were 53-66%.

In females surviving to day 14 there was likewise an apparent initial slowing of bodyweight gain from day 0-7 (-9-+8) with a greater spurt in bodyweight gain from day 8-14 (-1-+20). One animal showed a 28% loss in weight for this period, however, thereafter recovered slowly and by day 63 had gained 17% bodyweight compared with initial weight.

Toxicology Branch Evaluation:

The study is supplementary due to several deficiencies. If the deficiencies are in the reporting, the study may be upgraded with additional information.

1. Particle size: The description of the test chamber and apparatus used to create the aerosol does not indicate any efforts to produce smaller particle sizes. The nozzle used may not be adequate and a nebulizer may be required to create a fine mist. From the reported information, it appears the majority of test substance did not reach the test animals.

2. Samples from breathing zone: There is no information about where or how samples were taken. The reported values may not be from readings taken at the breathing zone of the animals and may not be useful in the assessment of the inhalation toxicity of the test substance.

3. Air entered around tubes containing the animals: With a volume of 800 l/hr pumped into the chamber and 1100 l/hr drawn out, it is clear a sizable amount of air may have entered through animal tubes, as described in the report. It is possible the animals were breathing the extraneous air from outside rather than the aerosol.

4. Statistical methods should be described.

5. Nominal concentration should be reported. The only concentration reported appears to be analytical, calculated from a 30 l sample from each dose level. This value would possible explain why a larger volume (300 ml/hr) produced a lower concentration in the test chamber (7.56 mg/l), as compared to 225 ml/hr which apparently produced a concentration of 8.52 mg/l.

Guideline Series 81-5: Primary Dermal Irrit.

Reviewed by: Margaret L. Jones M L Jones 3 June 1988
Section III, Toxicology Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D., Head
Review Section III, Toxicology Branch (TS-769C) M. van Gemert 6/3/88

DATA EVALUATION REPORT

Chemical: HOE -046360; (D+)-ethyl-2-(4-(6- chloro-2-benzoxazolyloxy) -phenoxy)-propanoate

Study Type: Primary Dermal Irritation in Rabbits

Accession No.: 406066-08

Synonyms: Super Whip™ and Super Acclaim™; 7.4% formulation of a.i.

Testing Facility: Pharma Research Toxicology and Pathology
HOECHST AKTIENGESELLSCHAFT, Frankfurt, W.Germany

Title of Report: HOE-046360-Oil in Water Emulsion (75 g/l) (HOE-046360 OH EW07 A202) Testing for Primary Dermal Irritation in the Rabbit

Authors: Diehl, K.H., Leist, K.H.

Study Number: 87.0514, Report No. A36862, 87.0734

Sponsor: Hoechst Celanese Corporation, Somerville, N.J.

Report issued: June 29, 1987

Conclusions: The test substance as tested in 6 New Zealand albino rabbits was slightly irritating based on scoring by Draize which considered the skin reaction from 30-60 min. through 72 hours.

Study: Core grade minimum

Toxicity Category IV

A. Materials:

1. Test compound: Hoe 046360, oil in water emulsion 75 (g/l); code Hoe 046360 OH EW07 A202; white liquid; purity: 7.4% (w/w) active ingredient; certificate of analysis No. 3547, impurities not analyzed; Batch No.: Pfl. Hr. 2714

2. Test animals: Species: New Zealand albino rabbit; Age (at start of study): 3 - 5 months; Weight (at start of study): 2.9 - 3.9 kg; Source: HOECHST AG, Kastengrund, conventional breed

3. Diet: Altromin 2123 maintenance diet - rabbits (Altromin GmbH, Lage/Lippe), ad libitum and hay (approx. 15 g./day).

4. Water: deionised, chlorinated water from automatic water dispensers, ad libitum.

B. Study Design and Results:

1. Procedure: Hair in the dorsal region of 6 rabbits was removed with an electric clipper 24 hours before the test procedure creating a patch 25 cm^2. A 2.5 cm square patch of surgical plaster with cellulose was fixed on the shaved skin and 0.5 ml of undiluted test substance was applied to the under side of the patch. The patch was then covered with a semi-occlusive bandage. Examinations of the skin took place at 30 and 60 minutes, and at 24, 48, and 72 hours after removal of the patch. Additional examinations of skin took place after 7, 14, and 21 days since skin effects were noted at 72 hours.

Skin irritation was evaluated for erythema, eschar formation and edema according to the scale of Draize. Other dermal changes were also recorded. The scoring method appears on appended page 1.

Results: No clinical signs of intoxication were noted in any of the animals at 30 and 60 minutes or at 24, 48, or 72 hours, at 7, 14, or 21 days. The skin surface of animals was dry and chapped throughout the study and coarse scales and cracked skin were observed from day 7-21.

The irritance index for 30-60 min. through 72 hours as calculated by the study authors is 2.2. Scores for erythema were 1-3 for all animals during this period. The substance was slightly irritating based on the results.

Toxicology Branch Evaluation: The substance appears to be a slight dermal irritant, as concluded by the study authors. There appears to be a calculating error at 72 hours (the score should be 18 rather than 15), however this does not alter the final conclusion. Erythema continued to day 7 then tapered off and by 21 days no irritation was noted.

Guideline Series 81-6: Skin Sensitization

Reviewed by: Margaret L. Jones M. L. Jones 3 June 1988
Section III, Toxicology Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D., Head
Review Section III, Toxicology Branch (TS-769C) M. van Gemert 6/3/88

DATA EVALUATION REPORT

Chemical: HOE -046360; (D+)-ethyl-2-(4-(6- chloro-2-benzoxazolyloxy) -phenoxy)-propanoate

Study Type: Skin Sensitization in Guinea Pig

Accession No.: 406066-09

Synonyms: Super Whip™ and Super Acclaim™; 7.4% formulation of a.i.

Testing Facility: Pharma Research Toxicology and Pathology
HOECHST AKTIENGESELLSCHAFT, Frankfurt, W.Germany

Title of Report: HOE-046360-Oil in Water Emulsion (75 g/l) (HOE-046360 OH EW07 A202) Testing for Sensitizing Properties in the Pirbright-White Guinea Pig According to the Technique of Buehler

Authors: Diehl, K.H., Leist, K.H.

Study Number: 87.0519, Report No. A37366, 87.0011

Sponsor: Hoechst Celanese Corporation, Somerville, N.J.

Report issued: January 15, 1987

Conclusions: Twenty (20) male Pirbright-White guinea pigs were tested with a 20% dose in 0.5 ml applied to the left flank after removal of hair. The test substance was negative for dermal sensitization in guinea pigs.

Study: Core grade minimum

A. Materials:

1. Test compound: Hoe 046360, oil in water emulsion 75 (g/l); code Hoe 046360 OH EW07 A202; white liquid; purity: 7.4% (w/w) active ingredient; certificate of analysis No. 3547 (24 April 1987), impurities nc analyzed; Batch No.: Pfl. Hr. 2714

2. Test animals: Species: Pirbright-White guinea pig; Age (at start of study): 10 weeks; Weight (at start of study): 441g (300-567g); Source: HOECHST AG, Kastengrund, conventional breed

3. Diet: ERKA 8300 mixed diet for guinea-pigs and rabbits, ad libitum.

4. Water: tap water in plastic bottles, ad libitum

B. Study Design:

1. Determination of Primary non-irritancy concentration:

Two guinea pigs were used to test each potential dose level for the full sensitizing test. Doses of 5%, 20% and 50% in 0.5 ml were applied to the left flank of two animals after mechanical removal of hair. The dose was applied on a 2X2 cm cellulose patch which was attached and covered occlusively (polyethylene film and a bandage, 'Fixomull') for 6 hours. Examinations were made 24 hours after each application for erythema and oedema and scored according to Draize.

Results: After the second treatment with 50% suspension of the test substance, the skin of one animal was dry and chapped. After the third treatment, the skin was dry and chapped with fine scales in all treatment animals. Based on these observations, the 20% dose was selected as the appropriate dose to use for the full sensitizing test.

2. Main test for sensitizing properties:

Twenty male guinea pigs were used for the test group. Ten control animals were treated similarly with 0.5 ml isotonic saline. Procedure was similar to that for treating animals tested for non-irritancy concentration. The schedule for the test procedures is found in appended page 1 (pate 12 of test report 88.0011).

Results: There were no effects on bodyweight or clinical signs of intoxication during the study. Observations of dry and chapped skin began after the third treatment and continued through the ninth treatment. After the fourth treatment, fine scales were also observed in 5/20 animals. As the study proceeded, the above observations increased in numbers (more animals involved each time) and coarse scales appeared on one animal.

Reaction to challange treatment was negative. Twentyfour hours after challenge and 48 hours after challenge, there were no observations of erythema or edema.

006738

Guideline Series 81-4: Primary Eye Irrit.

Reviewed by: Margaret L. Jones M. L. Jones 3 June 1988
Section III, Toxicology Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D., Head
Review Section III, Toxicology Branch (TS-769C) M. van Gemert 6/3/88

DATA EVALUATION REPORT

Chemical: HOE -046360; (D+)-ethyl-2-(4-(6- chloro-2-benzoxazolyloxy) -phenoxy)-propanoate

Study Type: Primary Eye Irritation in Rabbits

Accession No.: 406066-07

Synonyms: Super Whip™ and Super Acclaim™; 7.4% formulation of a.i.

Testing Facility: Pharma Research Toxicology and Pathology
HOECHST AKTIENGESELLSCHAFT, Frankfurt, W.Germany

Title of Report: HOE-046360-Oil in Water Emulsion (75 g/l) (HOE-046360 OH EW07 A202) Testing for Primary Eye Irritation in the Rabbit

Authors: Diehl, K.H., Leist, K.H.

Study Number: 87.0515, Report No. A36859, 87.0735

Sponsor: Hoechst Celanese Corporation, Somerville, N.J.

Report issued: July, 7, 1987

Conclusions: Nine New Zealand albino rabbits were tested with 0.1 ml. of test substance, 3 with eyes washed after one minute and 6 with eyes unwashed for 24 hours. The test substance was a slight occular irritant based on the results.

Study: Core grade minimum

Toxicity Category III

A. Materials:

1. Test compound: Hoe 046360, oil in water emulsion 75 (g/l); code Hoe 046360 OH EW07 A202; white liquid; purity: 7.4% (w/w) active ingredient; certificate of analysis No. 3547, impurities not analyzed; Batch No.: Pfl. Hr. 2714

2. Test animals: Species: New Zealand albino rabbit; Age (at start of study): 3 - 5 months; Weight (at start of study): 3.0 - 4.0 kg; Source: HOECHST AG, Kastengrund, conventional breed

3. Diet: Altromin 2123 maintenance diet - rabbits (Altromin GmbH, Lage/Lippe), ad libitum and hay (approx. 15 g./day).

4. Water: deionised, chlorinated water from automatic water dispensers, ad libitum.

B. Study Design:

1. Procedure:

Prior to testing, the eyes of all animals were examined for corneal lesions under UV light using 0.01% fluorescein-sodium solution. Only animals without abnormalities were used in the study.

A volume of 0.1 ml of test substance was applied once to one eye of each rabbit in the conjunctival sac of nine rabbits. After one minute the treated eyes of three animals were washed for one minute with physiological saline. The eyes of the remaining six animals were left unwashed for 24 hours. Each time examinations were made, the eyes were washed out with physiological saline, or at times when discharge was observed.

Examinations were made at 1, 24, 48, and 72 hours after application of test substance. At 24 and 72 hours, eyes were examined for corneal lesions under UV light, as described previously. Lesions in cornea, iris, or conjunctivae were graded numerically. Accompanying toxic effects and changes were recorded. Examinations were made on days 7 and 14 in animals still showing effects at 72 hours. The scoring method is described on appended page 1.

Results:

Reaction in (3) animals with eyes washed after one minute:
Conjunctivae were primarily involved, with scores of 1-2 for the first 24 hours for chemosis and scores of 1-3 for the first 72 hours for redness and slight discharge (clear and colorless) in one animal after one hour.

Reaction in (6) animals with eyes left unwashed for 24 hours:
Conjunctivae were involved with scores of 1-4 over the first 24 hours. Scores tapered to 1-3 by 72 hours. Considerable clear discharge was observed at one hour and white mucous discharge

persisted in one animal from 24 hours to 72 hours. Irritated iris was noted in 1-2 animals. Cornea was opaque in one animal by one hour with a large area of involvement. Cornea was also involved in 4 additional animals by 24 hours. The opacity in the first animal continued to 72 hours. By 7 days the irritation had disappeared except for slight chemosis and redness of the conjunctivae in one animal. This disappeared by 14 days.

Clinical signs of toxicity were not found in the test animals.

The study authors concluded the test substance was a slight irritant based on a maximum score of 22.

Toxicology Branch Conclusions: The test substance appears to be a slight dermal irritant based on the study results.