6-21-90

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

008000

JUN 21 1990

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Super Whip™ Herbicide and Super Acclaim™ Herbicide

TO: Miller/Mountfort, Product Manager 23
Registration Division (H7505C)

FROM: Byron T. Backus, Ph.D., Toxicologist Byron T. Backus 6/14/90
Herbicide/Fungicide/Antimicrobial Support Branch
HED (H7509C)

THROUGH: K. Clark Swentzel K. Clark Swentzel 6/14/90
Section Head, Review Section II
Herbicide/Fungicide/Antimicrobial Support Branch
HED (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 6/20/90
Herbicide/Fungicide/Antimicrobial Toxicology Branch
HED (H7509C)

EPA Record No. 252003 and 251410 MRID No. 412301-01

Project No. 9-2171

EPA Reg. No. 8340-GU, 8340-GL

Tox. Chem. 431C

Action Requested:

Review the registrant's response to a previous toxicology review of an inhalation LC_{50} study.

Background:

This study was previously reviewed by M. Jones (see the attached copy of a DER dated June 3, 1988). At that time the study was classified as supplementary, and it was stated that the toxicity category could not be determined from the study findings. Also, questions were asked regarding where samples were taken, what attempts were made to produce an aerosol with smaller particle sizes, whether or not the animals may have been breathing extraneous air, the statistical methods used, and what the nominal concentrations of test material were.

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Comments and Recommendations:

1. According to the information supplied by the registrant, air samples were taken from openings which, under other circumstances, would be fitted with a plastic tube containing an animal. The air flow through the tubes containing the animals is reported as minimal and not leading to a significant dilution of the aerosol; it is also indicated that, for purposes of obtaining concentration measurements, "the samples are taken from the edge of the chamber, i.e. the same region otherwise occupied by the animal's noses."

2. The "nominal input-concentrations" are reported as:

Measured value (mg/l)	Nominal value (mg/l)
3.31	150
8.72	281
7.56	375

3. The statistical formulas given are appropriate for calculations of mean particle sizes, particle distributions, mean values and standard deviations.

4. According to the registrant, the test material, because of its very high viscosity, could not be dispersed into smaller particles. From the original review of June 3, 1988, 20% of the mass was represented by particles $\leq$ 2.00 μm at a measured concentration of 3.31 mg/l; at 8.72 mg/l it was 29%; and at 7.56 mg/l it was 24%. Using these percentages then the following exposures occured to particles $\leq$ 2 μm:

3.31 mg/l x 0.20 = 0.662 mg/l
8.72 mg/l x 0.29 = 2.53 mg/l
7.56 mg/l x 0.24 = 1.81 mg/l

At the lowest concentration 1/10 animals died. The combined probability that only 1/10 or 0/10 animals would die if the LC50 value was 0.662 mg/l (4-hr exposure) is 11/1024, or 0.011. It can therefore be stated that, within 95% confidence limits, the LC50 $\geq$ 0.662 mg/l, and this is given additional support by the incidence of mortality at the higher concentrations (4/10 in each case). On this basis, the test material can be assigned to toxicity category III (0.5 mg/l $\leq$ LC_{50} $\leq$ 5.0 mg/l for 4-hr exposure).

5. With the additional information and clarifications supplied by the registrant, the classification of this study is upgraded to core minimum. The test material is in toxicity category III in terms of potential inhalation exposure hazard, and the LC_{50} $\geq$ 0.662 mg/l (4-hr exposure).

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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.

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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.

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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

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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)

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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.