



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

005166

MAY 30 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

TO: N. Bhushan Mandava, PM # 45
RSERB
Registration Division TS-767C

FROM: D. Ritter, Acting Section Head
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

Caswell #: 284A.

Potomac #: P1126.

Subject: PP # 6F3344:

N, N-diallyl dichloroacetamide; R-25788; proposal to amend 40 CFR 180.1026 to permit use as an inert ingredient when used in formulations containing S-ethyl cyclohexylethylthiocarbamate (cycloate) applied to cornfields before the corn plant emerges.

Recommendation:

Amend 40 CFR 180.1026 as requested.

Basis for the Recommendation:

The toxicological data base supports the action.

Detailed Considerations:

The following studies were reviewed under PP # 2F1273 by D. Ritter, 8/7/72, and served as the basis for granting the initial exemption:

- ° 13 Week Rat Feeding Study NOEL = 10 mg/kg/day or 200 ppm in the diet.
- ° 13 Week Dog Feeding Study NOEL = 24 mg/kg/day or 960 ppm in the diet (HLT).
- ° Rat Teratology Study NOEL = 40 mg/kg/day (HLT) for maternal and fetal toxicity and for teratogenicity on days 6 thru 15 of gestation.

9/2 5-12-86
just 5/30/86
Alfa W/B
5/30/86

)

These studies are acceptable for CORE purposes; hence they will also support the present proposal.

New studies submitted under this petition have been evaluated and are appended:

- Rat Oral LD₅₀ = 2080 mg/kg (males) and 2030 (females).
- Rat Acute Inhalation LC₅₀ > 5.6 mg/L air.
- Rabbit Eye Irritation - PIS = 0/110; not an eye irritant.
- Rabbit Primary Dermal Irritation - PIS = 0.81/8.0; mild irritant.
- 14 Week Rat Inhalation Study NOEL = 2 mg/M³.

DATA EVALUATION REPORTN, N-diallyl dichloroacetamide; R-25788

PP # 6F3344

STUDY: 14 Week Inhalation Study, Rat.LABORATORY: Environmental Health Center, Farmington, Conn.STUDY DIRECTOR: H. S. Knapp.DATE: 3/9/83.STUDY NUMBER: T-10773.ACCESSION NUMBER: 260824MATERIAL TESTED: R-25788, 97.6% pure; Lot # EHC-139-19.ANIMALS: Sprague-Dawley Albino male and female rats, 18 per sex per group.METHODS:Exposure Schedule

Animals were exposed to nominal aerial concentrations of 0, 2, 20 or 200 mg/M³, six hours a day, 5 days a week for 14 weeks.

Husbandry

Standard GLP.

Food and Water

Food ad lib except during exposure. Water ad lib at all times.

Aerosol Exposure

The low and middle doses were generated by a nebulizer while the high dose was generated using a Collison compressed air nebulizer. The aerosol was electrically neutralized prior to introduction into the exposure chamber. The controls received untreated air. The air used to generate the aerosol was dry and oil-free.

Aerosol Sampling

The chamber concentration was determined by sampling chamber atmosphere using resin adsorption tubes, extracting with acetone and analyzing by GLC. The particle size was determined using high-volume cascade impactor. The chamber concentrations were determined to be 100 % expected for the low and middle dose, and 96 % for the high dose. The mean particle size was 3.0 um at 200 mg/M³, but the material was present only as a vapor at the 20 and 2 mg/M³ levels.

Animal Observations

Body weights - initially and weekly thereafter.

Food consumption - initially and weekly thereafter.

mortality and toxic signs - twice daily.

Ophthalmic exams - initially and at termination

Clinical Determinations

Hematogram

HCT
Platelets

Hb
Total & Diff. leukos

RBC

Serum Chemistry

Alk.Ph.
LDH
Tot. Prot.
Tot. & Dir. Bilirubin
Na*

SGPT
BUN
Tot. Glob.
Tot. Cholesterol
Cl*

SGOT
Glucose
Album.
Ca*
K*

* At termination only.

4

Autopsy

The following organs were preserved in 10 % buffered neutral formalin:

Skeletal M.	Nerve	Tibia/femur
Sternum	Lungs	Trachea
Nasal passages	Nasal Sinus	Heart
Spleen	Thymus	Lymph nodes
Salvary Gl.	Complete GI tract	Pancreas
Liver	Kidneys	Bladder
Prostate	Seminal vesicles	Uterus

RESULTS:

Mortality - All animals but one survived the exposure. One male in the 20 mg exposure group died during the 3rd week of causes related to malocclusion.

Body weights - High dose males and females gained only 72 and 71% of the weight gained by the other groups.

Food Consumption - High dose males and females consumed statistically significantly less feed than did animals in the other groups.

Clinical Signs of Toxicity - Animals in the high and middle groups exhibited chromorhinorrhea, salivation and seminal plugs (males only).

The NOEL for Toxic Signs is 2 mg/M³.

Clinical determinations

Hematology - no statistically significant differences were reported for any test group.

Serum Chemistry - no statistically significant differences were reported for any test group.

The NOEL for blood parameters is > 200 mg/M³.

Gross Necropsy

Statistically significant relative organ weight ratios were increased in the high dose males and females for the brain and heart; in the high and middle dose males and females for the kidney, and in the high dose males for the lungs and adrenal glands.

The NOEL for organ weight effects is 2 mg/M³.

5

Histopathology

The sponsor reported that lesions induced by inhalation exposure to the test material were confined to the nasal tract and included degeneration, attenuation and intraepithelial cyst formation in the olfactory epithelium of the dorsal nasal meatus. Preservation and multifocal hyperplasia of the olfactory basal cell layer was also reported. The frequency of these observations was statistically significant only in the high and middle dose males and females.

No histopathologic lesions were reported for the other organs.

The NOEL for histopathologic lesions of the upper respiratory tree is 2 mg/M³.

CONCLUSIONS:

The overall NOEL for this study is 2 mg/M³.

CORE RATING: Guideline.

DATA EVALUATION REPORT

005166

N, N-diallyl dichloroacetamide; R-25788

PP # 6F3344

STUDY: Acute Oral LD₅₀, Rat

LABORATORY: Richmond Toxicology Laboratory, Richmond, CA.

STUDY DIRECTOR: T. R. Castles

DATE: 6/6/78

STUDY NUMBER: T-6317

ACCESSION NUMBER: 260824

MATERIAL TESTED: R-25788, 97.7% pure; Lot # 4921-35-2.

ANIMALS: Sprague-Dawley Albino male rats, 10 per sex per dose level, except that those receiving 2000 and 4000 mg/kg contained 15 animals.

Sprague-Dawley Albino female rats, same as the males except that the 5000 mg/kg group contained only 5 animals.

METHODS:

Males:

Test Material was dissolved in 5 % EtOH in corn oil and administered by gavage as a single dose at levels of 500, 1000, 2000, 2500, 3000, 4000, or 5000 mg/kg BW.

Females:

Test material was dissolved in 5 % EtOH in corn oil and administered by gavage as a single dose at levels of 4000, 3000, 2500, 2000, 1500 or 1000 mg/kg BW.

Animals were observed for signs of toxicity and for mortality for 14 days thereafter. All animals dying during the study and all animals surviving the observation period were subjected gross post-mortem examination.

7

RESULTS:

Signs of toxicity included tremors, depression, salivation and convulsions.

Mortality - Males:

<u>Dose, mg/kg</u>	<u>5000</u>	<u>4000</u>	<u>3000</u>	<u>2500</u>	<u>3000</u>	<u>1000</u>	<u>500</u>
<u>Dead/Alive</u>	<u>10/10</u>	<u>13/15</u>	<u>9/10</u>	<u>5/10</u>	<u>3/15</u>	<u>1/10</u>	<u>0/10</u>

Mortality - Females:

<u>Dose, mg/kg</u>	<u>4000</u>	<u>3000</u>	<u>2500</u>	<u>2000</u>	<u>1500</u>	<u>1000</u>
<u>Dead/Alive</u>	<u>5/5</u>	<u>15/15</u>	<u>8/10</u>	<u>7/15</u>	<u>1/10</u>	<u>0/10</u>

CONCLUSIONS:

LD₅₀ Males = 2080 mg/kg

LD₅₀ Females = 2030 mg/kg

TOXICITY CATEGORY:

III.

CORE RATING:

Guideline.

8

DATA EVALUATION REPORT

005166

N, N-diallyl dichloroacetamide; R-25788

PP # 6F3344

STUDY: Acute Inhalation LD₅₀, Rat.

LABORATORY: Richmond Toxicology Laboratory Inhalation Facility, Richmond, CA.

STUDY DIRECTOR: J. L. Miller

DATE: 12/20/78

STUDY NUMBER: T-6590

ACCESSION NUMBER: 260824

MATERIAL TESTED: R-25788, 97.7% pure; Lot # GGJ-1301.

ANIMALS: Sprague-Dawley Albino male and female rats, 10 per sex.

METHODS:

The test material was passed through a nebulizer-discharger that removed static charges on the aerosol particles, then through a stainless steel tube into the exposure chamber using purified compressed air. The airflow was controlled at 110 L/minute. The exposure period was 4 hours. Chamber concentration of the aerosol was measured at 60 minute intervals. Nominal aerosol concentration was 5.6 mg/L. Particle size was measured twice during the exposure period using low volume cascade impactor and was reported in mass mean aerodynamic resistance diameters. Particle size was 2.9 - 3.0 um.

Animals were observed for mortality and signs of toxicity twice daily on days 0, 7 and 14. Body weights were recorded on days 0, 7 and 14. The following tissues and any abnormally-appearing tissues were removed at autopsy and placed in 10% neutral buffered formalin: trachea, larynx, nasal passages, lung, liver, kidney and heart.

Following exposure animals were housed under Standard GLP for the remainder of the observation period.

9

RESULTS:

There were no deaths reported in this study. Males were reported to have "... slight to moderate depression and bloodlike flecks around the face". These and the other rats were normal by day 2. There was no significant effects on body weight. At autopsy the lungs of several rats appeared "reddened". Females showed similar effects of exposure to the test material.

CONCLUSIONS:

The Inhalation LD₅₀ is greater than 5.6 mg/L

TOXICITY CATEGORY:

III

CORE RATING:

Guideline.

10

DATA EVALUATION REPORT

005166

N, N-diallyl dichloroacetamide; R-25788

PP # 6F3344

STUDY: Eye Irritation, Rabbit.

LABORATORY: Richmond Toxicology Laboratory, Richmond, CA.

STUDY DIRECTOR: T. R. Castles.

DATE: 6/6/78.

STUDY NUMBER: T-6317.

ACCESSION NUMBER: 260824.

MATERIAL TESTED: R-25788, 97.7% pure.

ANIMALS: New Zealand Albino rabbits, three unwashed eyes; three washed eyes for 2 seconds; three washed eyes for 4 seconds.

METHODS: 0.1 ml test materials was placed in one eye of each animal. Three animals' treated eye was washed with water/0.9 % saline for 20 seconds beginning 2 seconds after exposure to the test material. Three other animals were washed for 20 seconds beginning 4 seconds after exposure. the remaining animals did not have their eyes washed.* The untreated eyes served as controls. They treated eyes were scored for ocular lesions after the method of Draize (1965) at 24, 48 and 72 hours, and on post-exposure day 8.

RESULTS: The investigators reported no signs of corneal, irideal or conjunctival irritation in any animal.

CONCLUSIONS: The marterial failed elicit a measurable ocular response; hence the PII is 0/110.

* It was unclear whether tap water or 0.9 % saline was used; both are mentioned as being used as the washing medium.

11

005166

TOXICITY CATEGORY: Non-irritating in the rabbit eye.

CORE RATING: Mimimum Data.

REPAIRABLITY: Provide identity of rinsing medium.

REFERENCE

Draize, J.H., "Dermal Toxicity" in Appraisal of the Safety of chemicals in Food
Drugs and Cosmetics., Ed. Ass. Fd & Drg Officials of the U.S.
Topeka, 1965. pp. 46-59.

12

DATA EVALUATION REPORT

005166

N, N-diallyl dichloroacetamide; R-25788

PP # 6F3344

STUDY: Acute Dermal LD₅₀, Rabbit.

LABORATORY: Richmond Toxicology Laboratory, Richmond, CA.

STUDY DIRECTOR: T. R. Castles.

DATE: 6/6/78.

STUDY NUMBER: T-6317.

ACCESSION NUMBER: 260824.

MATERIAL TESTED: R-25788, 97.7% pure; Lot # 4921-35-2.

ANIMALS: New Zealand Albino rabbits, three males and three females

METHODS:

Skin of trunk was clipped free of hair; half the animals were abraded. The test material was introduced under an occlusive sleeve for 24 hours at a dose level of 5000 mg/kg BW. Following the exposure period the sites were cleansed and the animals observed for signs of toxicity and mortality for 14 days thereafter. All animals dying during the study and those surviving the 14 day observation period were subjected gross autopsy.

RESULTS:

One animal expired during the study. This animals' large intestine contained blood. One rabbit had a hard, pale liver while another had lungs and a liver that were brown.

No detailed analytical data accompany this study.

CONCLUSIONS:

The Dermal LD₅₀ in this study is greater than 5000 mg/kg.

TOXICITY CATEGORY:

III.

CORE RATING:

Supplemental.

REPAIRABILITY:

Submit detailed analytical data, e.g., body weights, animal identities and what animals had what toxic findings.

DATA EVALUATION REPORTN, N-diallyl dichloroacetamide; R-25788STUDY: Primary Dermal Irritation, Rabbit.

PP # 6F3344

LABORATORY: Richmond Toxicology Laboratory, Richmond, CA.STUDY DIRECTOR: T. R. Castles.DATE: 6/6/78.STUDY NUMBER: T-6317.ACCESSION NUMBER: 260824.MATERIAL TESTED: R-25788, 97.7% pure; Lot # 4921-35-2.ANIMALS: New Zealand Albino rabbits, numbers per sex not given.METHODS:

0.5 gm test material was introduced under one inch square occlusive patches on intact and abraded areas of the skin for 24 hours. The dressings were then removed and the sites were scored after the method of Draize (1965) and cleansed. Scores were taken again 48 and 72 hours.

RESULTS:

Erythema was reported following the 24 hour exposure period; this decreased in intensity by 48 hours and was gone by 72 hours. No edema was reported.

CONCLUSIONS:

Evaluation of the dermal lesions produced by 24 hours occlusive exposure to the test material reveals a PII of .81/8.

R-25788 is a mild dermal irritant.

TOXICITY CATEGORY:

III.

CORE RATING:

Guideline.