008776

7-11-90

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 100-463
Diazinon 4E

FROM: Lucy D. Markarian 7/11/90
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)

TO: K. Samek (PM 74)
Registration Division (H75-05C)

APPLICANT: Ciba-Gigy Corporation
Agricultural Division
P.O. Box 18300
Greensboro, NC 27419

FORMULATION FROM LABEL:

| Active Ingredient(s): | % by wt. |
|---|---|
| Diazinon: [O,O-Diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl phosphorothioate] | 47.5 |
| | |
| | |
| | |
| Inert Ingredient(s): . . . . . | 52.5 |
| Total | 100.0% |

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BACKGROUND: Agricultural Division of Ciba-Geigy has submitted six studies in support of their product Diazinon 4E registered under EPA symbol 100-463:

Acute Oral Toxicity

Acute Dermal Toxicity

Acute Eye Irritation

Acute Dermal Irritation

Dermal Sensitization

Acute Inhalation toxicity

RECOMMENDATION: Three of the tests acute oral, Primary dermal irritation and acute inhalation are accepted as core guidline data.

1. The dermal toxicity Test is accepted but considered core minimum data because The Test material is introduced to the skin with a syringe after the animals are wrapped in gauze and surgical stockinette. The manner of application does not guarantee the even distribution of the test material as the wrappings are opaque and absorbant.

2. The acute eye irritation data is considered to be core minimum because of the improper scoring of the ocular lesions. When fluorescein stain is positive, however faintly, it is confirmation of opacity. It is a sign That says There is at least a minimum of opacity and must be recorded as such. There is no provision in the Draize scoring system That allows The area of the stain to be indicated without acknowledging

RECOMMENDATION: (Cont)

opacity. According to EPA regulations regardless of the grade of opacity the deciding factor for classification of the Toxicity is the reversibility of the lesion and the length of Time it takes to achieve this.
The area of stippling need not be specified, it is either present or absent.

The regulations do not call for testing washed eyes.

3. The sensitization data is conditionally called supplimentary

a. It is assumed that the method used is modified Beuhler. The guidelines require that the method be specified. Clarification must be presented

b. It is stated in the report that a preliminary Screenig for the determination of the induction and elicitation concentrations was made. However the procedure for, and the results of this screenig ARE missing from the report. This data must be presented

c. According to Beuhler*,** naive controls have to be used in the test. The significance of reactions in the Test animals is based on the incidence and intensity of the reactions as compared to the reactions in the control groups. No naive controls were used

The applican may upgrade the rating of supplimentary by presenting the missing data and explaining why naive controls were not used.

* Harry L. Ritz, Edwin V. Beuhler - Current Concepts in Cutaneous Toxicity - Academic Press Inc. pp 25-39

** Robinson, Nusair, Fletcher & Ritz - A review of the Buehler Guinea Pig Skin Sensitization Test and its use in a risk assessment process for human Skin Sensitization. Toxicology, 61 (1990) 91-107

LABELING:

The Signal word is "Caution". ~~Contains petroleum distillates~~.

The Precautionary Statement must Include:

Harmful if swallowed, inhaled or absorbed Through skin. Causes moderate eye injury. Avoid contact with eyes and skin or breathing vapor or spray mist. Remove contaminated clothing and wash before reuse. Wash with soap and water after handling.

The Statement of practical Treatment must include:

If swallowed - Call physician. Do not induce vomiting, may cause aspiration pneumonia

If inhaled - Remove victim to fresh air, if not breathing give artificial respiration, preferably mouth to mouth. Get medical attention.

If in eyes - Flush with plenty of water, call physician if irritation persists

If on skin - Wash with plenty of soap and water get medical attention.

# DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§81-1)

Product Manager: (74) Reviewer: Lucy D. Markarian
MRID No.: 413326-16 Report Date: 7/11/90
Testing Facility: Stillmeadow, Inc. Huston, Texas Report No. 6306-89
Author(s): Janice O. Kuhn
Species: Rat, Sprague Dawley
Age: Not specified Observation Days (Post Exposure): (14); other ( )
Weight: ♂ 185-217g ♀ 182-219g
Source: Harlan Sprague Dawley, Huston Texas
Test Material: Diazinon 4E FL 89164/ Batch code GP96200/ FL 89 1641 (ambarlique
Quality Assurance (40 CFR §160.12): included

Conclusion:

1. $LD_{50}$ (mg/kg): Males = 1723 mg/kg (1604 - 1852 mg/kg) Females = 1503 mg/kg (1360 - 1661 mg/kg; Combined = 1553 mg/kg (averaged
2. The estimated $LD_{50}$ is
3. Tox. Category: III. Classification: Core guideline

Procedure (Deviations From §81-1): Rats were intubated at four levels, were observed 3 times on the first day of test and once a day thereafter. Weights were recorded on days 1, 7, & 14. As well as at death. Necropsy was performed at death and at termination.

Results:

Reported Mortality

| DOSAGE ( mg/kg) | (NUMBER KILLED/NUMBER TESTED) Males | Females | Combined |
|---|---|---|---|
| 1200 | | 1/10 | 1/10 |
| 1500 | | 5/10 | 5/10 |
| 1600 | 3/10 | | 3/10 |
| 1700 | | 7/10 | 7/10 |
| 1900 | 7/10 | | 7/10 |
| 2000 | | 10/10 | 10/10 |
| 2100 | 10/10 | | 10/10 |
| 2400 | 10/10 | | 10/10 |
| | | | |

Symptomology & Gross Necropsy Findings:

Signs of systemic toxicity included piloerection, decreased activity, polyuria, salivation, diarrhea discharge from eyes & nose and tremors at all levels. All survivors recovered between Days 6 and 8. Gross necropsy findings included signs of salivation, nasal discharge, chromodacryorrhea, polyuria & diarrhea as well as distended gastro-intestinal tracts with gas & discoloration of the contents in the 30 animals that died. There was no observable gross pathology in the survivors.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: ( 74 )
Reviewer: Lucy D. Markarian
MRID No.: 413326-17
Report Date: 7/11/90
Testing Laboratory: Stillmeadow Inc. Huston Texas
Report No. 6383-89
Author(s): Janice O. Kuhn
Species: Rabbit, New Zealand white, Ray Nichols Rabbitry, Lumberton Texas
Sex: 5♂ 5♀
Wt.: ♂ 2.750 - 3.250 ♀ 2.450 - 3.250
Test Material: Diazinon 4E FL 891691 (amber liquid)
Quality Assurance (40 CFR §160.12): included

Summary:

1. $LD_{50}$ (mg/kg): Males = _____; Females = _____; Combined = _____;
2. The estimated $LD_{50}$ is Greater Than 2020 mg/kg
3. Tox. Category: III. Classification: Core minimum

Procedure (Deviations From §81-2): Undiluted Test material were applied to the shaved skin of animals by first wrapping the animal in gauze and orthopedic stockinette and then introducing it by syringe under the wrappings. At 24 hours the wrappings were removed, exposed areas washed with tap water & cleancloth. Observations were at 1/2, 3, & 6 hrs the first day and daily thereafter. Body weights were taken on day: 0, 7, & 14 and at death. Necropsy was performed at Termination and at death

Results:

Reported Mortality

| DOSAGE ( mg/kg) | (NUMBER KILLED/NUMBER TESTED) Males | Females | Combined |
|---|---|---|---|
| 2020 | 1/5 | 0/5 | 1/10 |
| | | | |
| | | | |
| | | | |
| | | | |

Symptomology & Gross Necropsy Findings:

Signs of systemic toxicity were diarrhea in four animals and decreased defecation in one female.

The Necropsy of the animal that succumbed to treatment included signs of diarrhea & nasal discharge and gastrointestinal tract distended with gas with stomach full of tan slurry and white mucoid material in the small intestines. The Necropsy of the survivors revealed no abnormalities.

Comments

The study is classed core minimum, because the weight of some of the test animals exceeds the 3.0kg limit the guidelines suggests for the test model. Also the test material was applied after the animal was wrapped with no guarantee that it was evenly spread over the designated area. The guidelines specify that the test material be applied to the skin and then wrapped.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: ( 74 )
MRID No.: 413326-18
Testing Laboratory: Stillmeadow Inc. Huston Texas
Author(s): Mark S. Halbert
Species: Rat, Sprague Dawley
Sex: ♂ & ♀ young adult
Source: Harlan Sprague Dawley, Inc. Huston Texas
Test Material: Diazinon 4E FL 89 1641 (amber liquid)
Quality Assurance (40 CFR §160.12): Included

Reviewer: Lucy D. Markarian
Report Date: 7/11/90
Report No. 6397-89

Weight: ♂ 246-259 g ♀ 193-210 g

Summary:

1. $LC_{50}$ (mg/kg): Males = _____; Females = _____; Combined = _____
2. The estimated $LC_{50}$ is Greater Than 1.34 mg/L
3. Mean Concentration: _____
4. Tox. Category: III. Classification: Core Guideline

Procedure (Deviations From §81-2): Exposure was for 4 hrs in a 300 L N.Y. university design stainless steel dynamic flow inhalation chamber. The aerosol was generated by pumping the test material through a pressure operated air nozzle with an attached nebulizer ball. The aerosol was diluted with filtered dry air. Air flow was maintained using a calibrated critical orifice and recorded at 30 minute intervals as well as temperature and humidity. The concentration of test material was determined hourly by gas chromatography and nominally at the end of the exposure. The analytical determination was made using Tracor Model 560 gas chromatographs

Results:

Reported Mortality

| Exposure Concentration (mg/L) | (NUMBER KILLED/NUMBER TESTED) Males | Females | Combined |
|---|---|---|---|
| 1.34 | 0/5 | 0/5 | 0/10 |
| | | | |
| | | | |
| | | | |
| | | | |

Symptomology & Gross Necropsy Findings:

Particle size determination was made using an Anderson cascade Impactor. Due to the volatility of the test material gravimetric determinations were not performed.

Observations were frequent during the study and once daily thereafter. Body weights were taken at initiation and on days 7 & 14. Necropsy was performed on all animals at termination.

## Results

Mean chamber Temperature 75° F Range 74-76° F

Mean chamber humidity 65% Range 59-74%

Mean Chamber Concentration 1.39 mg/L Range 1.1395 - 1.5818 mg/L (Gas Chromatograph

Nominal Concentration 18.7 mg/L

Particle Size Distribution

| Time Interval | % 1.1-2.1 μm | % 0.7-1.1 μm | % Less Than 0.7 μm | Mass Median Aerodynamic Diameter | Geometric S.D |
|---|---|---|---|---|---|
| 1 1/2 hrs | 34.97 | 20.29 | 15.0 | 1.508 | 2.053 |
| 3 1/2 hrs | 43.87 | 16.0 | 7.0 | 1.642 | 1.719 |

There was no mortality. During exposure all animals exhibited piloerection. Other signs of toxicity included decreased activity, lacrimation, ptosis, polyuria salivation, nasal discharge and respiratory gurds. Post exposure observation were piloerection. That cleared by day 5 in all animals.

Necropsy revealed slightly mottled red lung in 5/10 animals There were no other gross observation

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager: (74)
MRID No.: 413326-19
Testing Laboratory: Stillmeadow Inc. Huston, Texas
Author(s): Janice O. Kuhn
Species: Rabbit, New Zealand White
Sex: 3♂ 6♀ Weight: Not specified
Source: Ray Nichols Rabbitry, Lumberton, Texas
Dosage: 0.1 ml
Test Material: Diatinon 4E FL 891691 amber liquid
Quality Assurance (40 CFR §160.12): included

Reviewer: Lucy D. Markowitz
Report Date: 7/11/90
Report No. 6389-89

Summary:

Tox. Category: III Classification: Core minimum

Procedure (Deviation From §81-4): Test material instilled in pre-examined eyes. 6 animals were observed unwashed & 3 animals after washing following instillation. Presence or absence of ocular lesions confirmed with fluorescein stain at 24 hrs and at later intervals. Although opacity is indicated by fluorescein stain the scores has declined to accept this as opacity in the majority of instances. Therefore the Total scores for eyes at any given interval is less than what it should have been.

Results:

Observations (number "positive"/number tested)

| | Hour | | Days | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | UW 1 | W | UW 1 | W | UW 2 | W | UW 3 | W | UW 4 | W | UW 7 | W | 14 | 21 | |
| Cornea Opacity | 0/6 | 0/3 | 6/6 | 0/3 | 6/6 | 0/3 | 6/6 | 0/3 | 3/6 | 0/3 | 0/6 | 0/3 | | | UW = unwashed |
| Iris | 0/6 | 0/3 | 0/6 | 0/3 | 0/6 | 0/3 | 0/6 | 0/3 | 0/6 | 0/3 | 0/6 | 0/3 | | | W = washed |
| Conjunctivae Redness | 6/6 | 3/3 | 6/6 | 3/3 | 6/6 | 3/3 | 6/6 | 3/3 | 6/6 | 3/3 | 0/6 | 0/3 | | | |
| Chemosis | 6/6 | 3/3 | 6/6 | 3/3 | 6/6 | 3/3 | 6/6 | 0/3 | 3/6 | 2/3 | 0/6 | 0/3 | | | |
| Discharge | 6/0 | 3/3 | 5/6 | 3/3 | 4/6 | 3/3 | 2/6 | 2/3 | 0/6 | 2/3 | 0/6 | 0/3 | | | |
| Stippling | 0/6 | 0/3 | 3/6 | 0/3 | 2/6 | 0/3 | 2/6 | 0/3 | 0/6 | 0/3 | 0/6 | 0/3 | | | |
| | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | |

Comments: If opacity is indicated by fluorescein stain it must be recorded as such and the intensity must be given. A minimum of (1) opacity is indicated whenever positive fluorescein stain is present. The Toxicity category is determined by the presence or absence of opacity as well as other parameters. The low total scores do not make a test material less toxic in the presence of opacity.
Washed eyes are not required by the regulations

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: ( 74 )
MRID No.: 413326-20
Testing Laboratory: Stillmeadow, Inc. Huston, Texas
Author(s): Janice O. Kuhn
Species: Rabbit, New Zealand white, Ray Nichols Rabbitry, Lumberton, Texas
Age: Young Adult
Sex : 3♂ + 3♀
Weight: not indicated
Dosage: 0.5 ml
Test Material: Diazinon 4E FL-891641 amber liquid
Quality Assurance (40 CFR §160.12): included

Reviewer: Lucy D. Markarian
Report Date: 7/11/90
Report No. 6385-89

Summary:

The Primary Irritation Index = 3.25

Toxicity Category: III

Classification: Core guideline

Procedure (Deviations From §81-5): Test material was applied to the shaved intact skin of rabbits for 4 hrs under gauze patches and wrapped in orthopedic stekinette. At 4 hrs wrappings were removed and test sites wiped with clean wet cloth. Sites were evaluated at 1, 24, 48, & 72 hrs and days 7, 10, 14, & 17.

Results:

Well defined erythema and slight to mild edema was observed at all sites at 1 and 24 hrs after the removal of the patches. Well defined erythema (3/6) and diffuse patchy erythema (3/6) persisted at 7 days accompanied by slight edema at all sites. Between Days 7-14 Two sites showed desquamation. On Day 14 2/6 still showed diffuse patchy erythema. All reactions cleared by day 17.

Special Comments:

The symbol "S" was used where desquamation was observed. This was clarified by Dr. Kuhn at a telephone conversation on 7/9/90. Written clarification ~~with follow~~ IS ATTACHED.

**STILLMEADOW, Inc.**
Biological Testing Laboratory
9525 Town Park Drive, Houston, Texas 77036
Telephone (713) 776-8828

July 9, 1990

Dr. Thomas Ellwanger
Environmental Protection Agency
Office of Pesticides and Toxic Substances
Registration Division (H7505C)
Washington, DC 20460

Dear Dr. Ellwanger:

I understand from a telephone call from Lucy Markarian that there is a question regarding our Study No. 6385-89, a primary skin irritation study, on CIBA-GEIGY's formulation Diazinon 4E FL 891641. Thank you for the opportunity to clarify the situation.

The concern expressed was the meaning of the symbol "S" in Table 1. If you will refer to Page 11 of the report, the Legend to Table 1, you will see the symbol "S" defined under "Other Observations" as "sloughing of skin of various thicknesses". In this laboratory, we have used the phrase to indicate a superficial loss of the uppermost layers of skin, a process which is not uncommon in our experience when an irritation process is subsiding or clearing.

I hope I have been able to clarify the results of the subject study. Please feel free to call me if there are further questions.

Sincerely,

Janice O. Kuhn

Janice O. Kuhn, Ph.D.
Toxicologist

JOK/jcc

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: ( 74 ) Reviewer: Lucy D. Markarian
MRID NO.: 413326-21 Report Date: 7/11/90
Testing Laboratory: Stillmeadow, Inc. Huston Texas Report No. 6386-89
Author(s): Janice O. Kuhn
Species: Guinea Pig, Hartley
Sex: Male Weight: 285 - 335 g
Source: Harlan Sprague Dawley, Huston Texas
Test Material: Diazinon 4E FL-891641
Positive Control Material: DNCB
Quality Assurance (40 CFR §160.12): included

Method: unspecified

Summary:
1. This product is / is not a dermal sensitizer.
2. Classification: Supplementary

Procedure (Deviation From §81-6): Two groups of 10 animals used: Group I - Positive control, Treated with 0.6% DNCB in ETOH Group II - Test, Treated with undiluted Diazinon 4E, as received, and determined to be a non irritating concentration. There were 10 induction Treatments on days 1, 3, 6, 8, 10, 13, 15, 17, 20, and 22. Each material was applied in 0.5ml aliquots under 2.8cm gauze pad secured to a 3.8 x 5cm piece of adhesive tape. The Trunks of the animals were wrapped in polyethylene film and they were restrained for the 6hour exposure. The Results: Same sites were used for all induction applications, and scored 24 hrs after the exposures. Additionally applications 1 and 10 were scored at 48 hours. Challenge was on day 36 at two naive sites per animal using same concentrations as the induction. The results were scored at 24 and 48 hrs after the challenge. There were no naive controls. Two animals died, one on day 15, and the other on day 19 during induction.

Results

The positive control animals showed mild to severe erythema and edema starting after the 3rd induction application. All sites had eschar at the end of the induction period. At challenge The ones applied at the left front were all positive, the ones applied at the right rear were 4/10 positive at 24 hrs and 3/10 positive at 48 hrs.

In the Test group the induction applications resulted in slight non confluent erythema between the 3rd & 10th applications as well as slight edema in 6/8 after the fourth application. At challenge There were no positive reactions either at 24 or 48 hrs. at any of the Test Sites.

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Tox Chem No. 11 89 File Last Updated _____ Current Date 7/11/90

| udy/Lab/Study #/Date | Material | EPA Accession No. | Results: $LD_{50}$, $LC_{50}$, PIS, NOEL, LEL | TOX. Cat. | CORE Grade/ Doc. No. |
|---|---|---|---|---|---|
| Stillmeadow Inc.<br>Biological Testing Laboratory<br>9525 Town Park Drive<br>Huston, Texas 77036 | Diazinon 4E<br>FL 891641<br>Batch Code GP96001 | | | | |
| Acute Oral Toxicity<br># 6306-89 8/8/89 | " | 413326-16 | $LD_{50}$ ♂ 1723 (1604-1852) mg/kg<br>♀ 1503 (1360-1661) mg/kg | III | core guideline |
| Acute Dermal Toxicity<br># 6383-89 8/16/89 | " | 413326-17 | $LD_{50}$ greater than 2020 mg/kg | III | core minimum |
| Acute Eye Irritation<br># 6384-89 8/8/89 | " | 413326-19 | Moderate eye irritant lesions clearing in 7 days | III | core minimum |
| Acute Primary Dermal Irritation<br># 6385-89 8/14/89 | " | 413326-20 | PII - 3.25<br>Moderate skin irritant clearing by day 21 | III | core guideline |
| Dermal Sensitization<br># 6386-89 9/28/89 | " | 413326-21 | | - | conditional supplementary |
| Acute Inhalation Toxicity<br># 6387-89 11/6/89 | " | 413326-18 | $LC_{50}$ greater than 1.34 mg/L | III | core guideline |