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CASWELL FILE

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

008217

DEC 28 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID No.: 100-524. Diazinon MG8 (Technical): Evaluation of Six Acute Toxicity Studies.

Record No.: 264917
HED Project No.: 0-1715
Tox. Chem. No.: 342

FROM: Krystyna K. Locke, Toxicologist Krystyna K. Locke 9/19/90
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

TO: Karen M Samek, PM/RM Team No. 74
Reregistration Branch
Special Review/Reregistration Division (H7508C)

THRU: Roger Gardner, Acting Section Head Roger Gardner
Section I, Toxicology Branch I (IRS) 12-19-90 KB 12/21/90
Health Effects Division (H7509C)

Toxicology Branch I/HED has completed an evaluation of 6 acute toxicity studies which were submitted by CIBA-GEIGY Corporation to support the reregistration of Diazinon MG8. All of these studies, listed below by title and with EPA Guideline numbers, were conducted at Stillmeadow, Inc., Houston, Texas, and each study was classified by TB/HED as Acceptable.

81-1. Acute Oral Toxicity Study in Rats; No.: 5942-89; March 28, 1989. MRID: 414072-18.

LD_{50} (mg/kg): 1350 (males); 1160 (females); 1250 (males and females)

Toxicity category: III

81-2. Acute Dermal Toxicity Study in Rabbits; No.: 5943-89; March 10, 1989. MRID: 414072-19.

LD_{50}: > 2020 mg/kg (Only dose tested; males and females; limit dose = 2000 mg/kg)

Toxicity category: III

1

81-3. Acute Inhalation Toxicity Study in Rats; No.: 5947-89; March 30, 1989. MRID: 414072-20.
LC_{50}: > 2.33 mg/L (Analytical concentration; only dose tested with males and females; 4-hour whole-body exposure; respirable particles.)

Toxicity category: III

81-4. Primary Eye Irritation Study in Rabbits; No.: 5944-89; February 20, 1989. MRID: 414072-21.

Maximum Average Score: 9.0 (Unwashed eyes; minimally irritating)
5.3 (Washed eyes; minimally irritating)

Toxicity category: III

81-5. Primary Dermal Irritation Study in Rabbits; No.: 5945-89; March 3, 1989. MRID: 414072-22.

Maximum Irritation Score: 2.8 (Slight irritant)

Toxicity category: III

81-6. Dermal Sensitization Study in Guinea Pigs; No.: 5946-89; March 29, 1989. MRID: 414072-23.

Diazinon MG8 was not a skin sensitizer in this study (test not identified, but description resembles a modified Buehler test). Positive control used: 2,4-Dinitrochlorobenzene.

Complete Data Evaluation Records (DERs) for the above studies are attached.

The registrant has also submitted a document entitled Investigations Regarding the Acute Toxicity of the CIBA-GEIGY Insecticide Diazinon MG-8, authored by Dr. W. Campbell and dated December 12, 1989; MRID: 414072-17. This document consists of summaries of studies listed above. TB/HED acknowledges receipt of this document.

2

008217

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Reviewed by: Krystyna K. Locke, Toxicologist
Section I, Tox. Branch I/IRS (H7509C)
Secondary reviewer: Roger Gardner, Acting Section Head Roger Gardner 12-19-90
Section I, Tox. Branch I/IRS (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 81-1. Acute Oral (Rat) TOX. CHEM. NO.: 342

MRID NO.: 414072-18

TEST MATERIAL: Diazinon MG8 (Technical); Lot No.: FL880045; amber liquid stable at room temperature; purity: not provided by sponsor but, in other studies, this material had purity (a.i. content) of about 87.7%.

STUDY NUMBER(S): 5942-89

SPONSOR: CIBA-GEIGY Corporation, Greensboro, N.C.

TESTING FACILITY: Stillmeadow, Inc., Houston, Texas

TITLE OF REPORT: Acute Oral Toxicity Study in Rats

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: March 28, 1989

CONCLUSIONS:

Classification: Acceptable

The acute oral LD_{50} values, slope function and 95% confidence limits were as follows:

	LD_{50} (mg/kg)	95% Confidence Limits (mg/kg)	Slope Function (S)	95% Confidence Limits
Males	1350	1140-1610	1.15	1.07-1.23
Females	1160	999-1350	1.13	1.07-1.19
Overall	1250	1080-1450	1.18	1.10-1.27

The above values were calculated by the procedure of Litchfield, J.T., Jr., and Wilcoxon, F.: A Simplified Method of Evaluating Dose-Effect Experiments, J. Pharm. & Exp. Ther., 96, 99-115, 1949.

Toxicity Category: III

3

EXPERIMENTAL PROCEDURES

Rat, HSD:(SD) BR strain, 5 males and 5 females/group, received single doses of Diazinon MG8 (800, 1200 and 2020 mg/kg) and then were observed daily for 14 days. The animals were fasted for at least 16 hours and weighed 233-319 g (males) and 176-201 g (females) prior to treatment. Diazinon MG8 was administered by gavage as received (undiluted). The rats were:

1. Obtained from Harlan Sprague Dawley, Inc., Houston, Texas.

2. Acclimated for at least one week.

3. Housed, by sex, 1-3/cage.

4. Fed unrestricted Purina Formulab Chow #5008 and water (automatic system).

5. Identified by ear tags.

6. Weighed on days 7 and 14 (just before sacrifice) or at the time of discovery after death.

7. Examined grossly (all).

It was not stated how dose levels were selected or how animals were assigned to groups.

RESULTS

Mortality

There were no deaths in the low-dose group, but all of the animals died within 2 days after treatment in the high-dose group. In the mid-dose group, 1 male and 2 females died on day 2 and another female on day 4 after treatment.

Toxic Signs

Toxic signs observed at all dose levels in males and females included activity decrease, ataxia, body tremors, chromodacryorrhea, constricted pupils, corneal opacity, diarrhea, dilated pupils, epistaxis, exophthalmos, gasping, green urine, lacrimation, melanuria, muscle tremors, nasal discharge, piloerection, polyuria, salivation, stiffly extended hind limbs, and writhing. In the low-dose females, most signs appeared and disappeared on day 1 after dosing. In the remaining groups, most signs appeared within 3 hours after dosing and, in the survivors, disappeared within the next 3-4 days. Irrespective of dose levels, the severity of the reactions ranged from slight to extreme.

Body Weights

In the low-dose group, males and females gained 50-69 g and 27-37 g. respectively, during the 14-day observation period. The corresponding weight gains for the survivors in the mid-dose group were 69-72 g and 28-33 g, respectively. All of the nonsurvivors lost weight, those dying within 1 day after treatment, 6-19 g and those dying within 2 days after treatment, 15-29 g. The only mid-dose female that died on the observation day 4, lost 37 g.

Gross Necropsy Findings

No abnormalities were observed in the survivors. In the nonsurvivors, both mid-dose and high-dose, findings described as signs of chromodacryorrhea, diarrhea, green urine, lacrimation, nasal discharge, polyuria, and salivation; discoloration of the contents of the gastrointestinal tract, large intestine empty or nearly empty, testes drawn into abdominal cavity, and variations thereof were considered by the testing laboratory as unusual and possibly treatment-related.

COMMENTS

This study is well-planned, well-reported, meets the November 7, 1989 Acceptance Criteria and is, therefore, Acceptable. GLP Compliance Statement and Quality Assurance Statement are included.

5

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Reviewed by: Krystyna K. Locke, Toxicologist
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Secondary reviewer: Roger Gardner, Acting Section Head Roger Gardner 12-19-90
Section I, Tox. Branch I/IRS (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 81-2. Acute Dermal (Rabbit)

TOX. CHEM. NO.: 342
MRID NO.: 414072-19

TEST MATERIAL: Diazinon MG8 (Technical); Lot No.: FL880045; amber liquid stable at room temperature; purity: not provided by sponsor but, in other studies, this material had purity (a.i. content) of about 87.7%. Expiration date: January, 1991.

STUDY NUMBER(S): 5943-89

SPONSOR: CIBA-GEIGY Corporation, Greensboro, N.C.

TESTING FACILITY: Stillmeadow, Inc., Houston, Texas

TITLE OF REPORT: Acute Dermal Toxicity Study in Rabbits

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: March 10, 1989

CONCLUSIONS:

Classification: Acceptable

The acute dermal LD_{50} for males and females was > 2020 mg/kg (only dose tested; limit dose = 2000 mg/kg)

Toxicity Category: III

EXPERIMENTAL PROCEDURES

New Zealand white rabbits weighing 2.9-3.7 kg (males) and 2.8-3.2 kg (females), 5 males and 5 females, received single doses of Diazinon MG8 (2020 mg/kg, 1.82 ml/kg; limit dose = 2000 mg/kg) and then, after a 24-hour exposure, were observed daily for 14 days. Undiluted Diazinon MG8 was applied on clipped, free of hair, dorsal surface of the trunk (at least 10% of the total body surface area), occluded and then, at the termination of the exposure, the application site was washed with tap water and a clean wet cloth to remove as much remaining test material as possible. The rabbits were:

1. Obtained from Ray Nichols Rabbitry, Lumberton, Texas.

6

2. Acclimated for at least one week.

3. Housed singly.

4. Fed unrestricted Purina Rabbit Chow and water (automatic system).

5. Identified by ear tags.

6. Weighed on days 7 and 14 (just before sacrifice) or at the time of discovery after death.

7. Examined grossly (all).

RESULTS

Mortality

Two females died on day 3 after treatment.

Toxic Signs

Diarrhea, decreased defecation, no defecation and nasal discharge were noted in 1-3 males on day 2 after treatment. These same signs, plus salivation and muscle tremors, were observed in 1-3 females, also on day 2 after treatment. With the exception of decreased defecation in one male, toxic signs were not observed on day 6 after treatment. In most instances, the severity of the toxic signs ranged from slight to moderate.

Body Weights

All of the surviving rabbits gained weight during the observation period: males, 0.2-0.4 kg and females, 0.1-0.5 kg. The two nonsurviving females lost weight: one, 0.27 kg and another, 0.55 kg.

Necropsy Findings

No abnormalities were observed in the survivors. In the nonsurvivors, findings described as signs of diarrhea, lacrimation, nasal discharge, and salivation; gastrointestinal tract distended with gas, and discoloration of the contents of the stomach, and variations thereof were considered by the testing laboratory as unusual and possibly treatment-related.

COMMENTS

This study is well-planned, well-reported, meets the November 7, 1989 Acceptance Criteria and is, therefore, Acceptable. GLP Compliance Statement and Quality Assurance Statement are included.

7

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Reviewed by: Krystyna K. Locke, Toxicologist K. K. Locke 9/19/90
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Secondary reviewer: Roger Gardner, Acting Section Head Roger Gardner 12-18-90
Section I, Tox. Branch I/IRS (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 81-3. Acute Inhalation (Rat)

TOX. CHEM. NO.: 342
MRID NO.: 414072-20

TEST MATERIAL: Diazinon MG8 (Technical); Lot No.: FL880045; amber liquid stable at room temperature; purity: not provided by sponsor but, in other studies, this material had purity (a.i. content) of about 87.7%. Expiration date: January, 1991.

STUDY NUMBER(S): 5947-89

SPONSOR: CIBA-GEIGY Corporation, Greensboro, N.C.

TESTING FACILITY: Stillmeadow, Inc., Houston, Texas

TITLE OF REPORT: Acute Inhalation Toxicity Study in Rats

AUTHOR(S): Mark S. Holbert

REPORT ISSUED: March 30, 1989

CONCLUSIONS:

Classification: Acceptable

LC_{50}: > 2.33 mg/L (Analytical concentration; highest mean dose obtained from undiluted test material; males and females; respirable particles; 4-hour whole-body exposure)

Toxicity category: III

EXPERIMENTAL PROCEDURES

Rats, HSD:(SD) BR strain, 5 males and 5 females, were exposed (whole body) for 4 hours to a respirable aerosol generated from undiluted Diazinon MG8 and then were observed for 14 days. During the exposure period, the rats were individually housed in stainless steel cages within a 200-liter stainless steel inhalation chamber. Due to chamber design, only 4 rats (2 males and 2 females) could be observed during the exposure period; observations after 4 hours included all animals. The concentration of Diazinon MG8 in the exposure atmosphere, determined every hour, ranged from 2.067 to 2.533 mg/L (mean: 2.327 mg/L). Other inhalation chamber operating parameters,

8

recorded at 30-minute intervals, were as follows: relative humidity, 48-63% (mean: 53.6%); temperature, 68-70° F (mean: 68.9° F) and air flow rate, 77.2 Lpm. The rats were:

1. Obtained from Harlan Sprague Dawley, Inc., Houston, Texas.

2. Acclimated for at least one week.

3. Housed, by sex, 1-3/cage.

4. Fed unrestricted Purina Formulab Chow #5008 and water (automatic system).

5. Identified by ear punch.

6. Weighed on days 7 and 14 (just before sacrifice); prior to treatment, the rats weighed 249-272 g (males) and 187-198 g (females).

7. Examined grossly (all).

Particle size determinations were made using an Andersen cascade impactor. Due to the volatility of the test material, gravimetric determinations were not performed.

RESULTS

Mortality and Toxic Signs

There was no mortality. Toxic signs (piloerection, activity decrease, ptosis and nasal discharge) were observed in males and females within 0.5 an hour after exposure but, with the exception of piloerection, disappeared within 0.5 an hour after the termination of the exposure. Piloerection persisted through the observation day 2 in males and day 3 in females. Salivation, observed in males and females at 2.5 hours after exposure, disappeared shortly after the termination of the exposure. Polyuria was observed in 3 females on the observation day 1, in 2 on day 2, and in none on day 3.

Body Weights

All rats gained weight during the observation period: males, 44-57 g and females, 18-25 g.

Necropsy Findings

No abnormalities were observed in any rat.

Particle Size Distribution*

Particle size distribution in the inhalation chamber was as follows:

2-Hour Distribution:

Size Range (µm)	% in Size Range
≥ 10.0	2.71
9.0 - 10.0	1.35
5.8 - 9.0	6.96
4.7 - 5.8	3.99
3.3 - 4.7	20.13
2.1 - 3.3	23.19
1.1 - 2.1	31.69
0.7 - 1.1	6.20
0.4 - 0.7	3.48
0.0 - 0.4	0.25

Mass Median Aerodynamic Diameter = 2.490 µm
Geometric Standard Deviation = 1.981

3¼- Hour Distribution:

Size Range (µm)	% in Size Range
≥ 10.0	2.97
9.0 - 10.0	0.40
5.8 - 9.0	3.51
4.7 - 5.8	1.75
3.3 - 4.7	15.15
2.1 - 3.3	22.32
1.1 - 2.1	38.15
0.7 - 1.1	8.93
0.4 - 0.7	6.35
0.0 - 0.4	0.40

Mass Median Aerodynamic Diameter = 2.046 µm
Geometric Standard Deviation = 1.988

COMMENTS

This study is well-planned, well-reported, meets the November 7, 1989 Acceptance Criteria and is, therefore, Acceptable. GLP Compliance Statement and Quality Assurance Statement are included.

*Finney, D.J.: PROBIT ANALYSIS. 3rd ed., Chapters 3 and 4, 1971, Cambridge University Press.

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Secondary reviewer: Roger Gardner, Acting Section Head Roger Gardner 12-18-90
Section I, Tox. Branch I/IRS (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 81-4. Primary Eye Irritation (Rabbit)

TOX. CHEM. NO.: 342
MRID NO.: 414072-21

TEST MATERIAL: Diazinon MG8 (Technical); Lot No.: FL880045; amber liquid stable at room temperature; purity: not provided by sponsor but, in other studies, this material had purity (a.i. content) of about 87.7%. Expiration date: January, 1991.

STUDY NUMBER(S): 5944-89

SPONSOR: CIBA-GEIGY Corporation, Greensboro, N.C.

TEST FACILITY: Stillmeadow, Inc., Houston, Texas

TITLE OF REPORT: Primary Eye Irritation Study in Rabbits

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: February 20, 1989

CONCLUSIONS:

Classification: Acceptable

This study was conducted with 9 rabbits; the eyes of 3 rabbits were washed after treatment and the eyes of 6 rabbits were left unwashed. The maximum average irritation scores, obtained at 1 hour after treatment, were as follows:

Nonwash Maximum Average Score = 9.0 (Minimally Irritating)
Wash Maximum Average Score = 5.3 (Minimally Irritating)

All irritation had cleared by 72 hours.

Toxicity category: III

EXPERIMENTAL PROCEDURES

Undiluted Diazinon MG8, 0.1 ml, was placed into the conjunctival sac of the right eye of 9 New Zealand young adult white rabbits, 3 males and 6 females. Following a 30-second exposure, the eyes of 3 females were washed with room temperature deionized water for one minute, whereas the eyes of the 6 remaining rabbits were left unwashed. Both eyes of each rabbit

11

were examined at 24 hours prior to treatment, just before treatment and at 1, 24, 48 and 72 hours after treatment. The examinations were performed with and without 0.2% fluorescein sodium ophthalmic solution (used to detect corneal involvement). Ocular reactions were evaluated according to the scoring scale detailed in Attachment I. The rabbits were:

1. Obtained from Ray Nichols Rabbitry, Lumberton, Texas.

2. Acclimated for at least one week.

3. Housed singly.

4. Fed unrestricted Purina Rabbit Chow and water (automatic system).

5. Identified by ear tags.

RESULTS

Corneal opacity and iritis were not observed in any eyes, washed and unwashed. Conjunctivae were affected as follows:

Redness (mostly Grade 1) appeared in the treated eyes of all 9 rabbits within the first hour after exposure and disappeared within the same hour (1 female), 24 hours later (4 females and 1 male) or 48 hours later (2 males and 1 female).

Chemosis (Grades 1 or 2) was observed in the treated eyes of all 9 rabbits only within the first hour after exposure.

Discharge in the treated unwashed eyes (Grades 3 at 1 hour, 1 at 24 hours, and 0 at 48 hours after treatment) was observed in 2 males and 2 females. There was no discharge in the treated unwashed eyes of the remaining male and female.

Discharge in the treated washed eyes (Grade 1) was observed in 2 rabbits at 1 hour and in 1 rabbit at 24 hours after exposure. There was no discharge in the treated washed eye of the third rabbit.

Necrosis or Ulceration were not observed in this study.

The average irritation score for each time interval was as follows:

Time After Treatment (Hours)	Nonwash Average Score	Wash Average Score
1	9.0	5.3
24	3.0	2.0
48	1.0	0.0
72	0.0	0.0

COMMENTS

This study is well-planned, well-reported, meets the November 7, 1989 Acceptance Criteria and is, therefore, Acceptable. GLP Compliance Statement and Quality Assurance Statement are included.

Attachment I

RABBIT EYE IRRITATION
Grading Scale

I. Cornea

A. Opacity - degree (area most dense taken for reading)

No opacity.....
Slight dulling of normal luster.....
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible.....
Easily discernible translucent areas, details of iris slightly obscured.....
Nacreous areas, no details of iris visible, size of pupil barely discernible.....
Complete corneal opacity, iris not discernible.....

B. Area of cornea involved

One quarter (or less), but not zero.....
Greater than one quarter, but less than half.....
Greater than half, but less than three quarters.....
Greater than three quarters, up to whole area.....

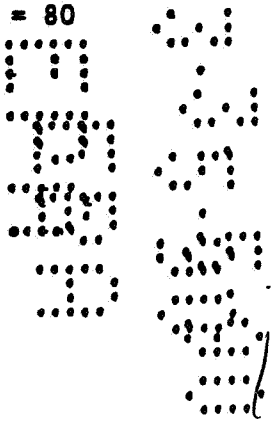
C. Fluorescein Staining - appearance of yellow-green staining of cornea

Cornea not examined with fluorescein.....
No fluorescein staining.....
Positive fluorescein staining.....
Area of cornea involved
One quarter (or less), but not zero.....
Greater than one quarter, but less than half.....
Greater than half, but less than three quarters.....
Greater than three quarters, up to whole area.....

D. Stippling - appearance of pinpoint roughening

No stippling.....
Presence of stippling.....
Area of cornea involved
One quarter (or less), but not zero.....
Greater than one quarter, but less than half.....
Greater than half, but less than three quarters.....
Greater than three quarters, up to whole area.....

A X B X 5 Total Maximum = 80



RABBIT EYE IRRITATION
Grading Scale

II. Iris

A. Grades

Normal.....0
Markedly deepened folds, congestion, swelling, moderate circumcorneal injection (any of these or combination thereof), iris still reacting to light (sluggish reaction is positive).....1
No reaction to light, hemorrhage, gross destruction (any or all of these).....2

A X 5 Total Maximum = 10

III. Conjunctivae

A. Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal.....0
Some vessels definitely injected.....1
Diffuse, crimson red, individual vessels not easily discernible.....2
Diffuse beefy red.....3

B. Chemosis

No swelling.....0
Any swelling above normal (includes nictitating membrane).....1
Obvious swelling with partial eversion of lids.....2
Swelling with lids about half closed.....3
Swelling with lids more than half closed.....4

C. Discharge

No discharge.....0
Any amount different from normal (does not include small amounts observed in inner canthus of normal rabbits.).....1
Discharge with moistening of the lids and hairs adjacent to lids.....2
Discharge with moistening of the lids and hairs, and considerable area around the eye.....3

D. Necrosis or Ulceration of the palpebral and bulbar conjunctivae or nictitating membrane

No necrosis or ulceration.....0
Presence of necrosis or ulceration.....N

(A + B + C) X 2 Total Maximum = 20

The total score for the eye is the sum of all scores obtained for the cornea, iris, and conjunctivae with the possible maximum total score for the eye being equal to 110.

16

RABBIT EYE IRRITATION
Rating of Test Material Based on Eye Irritation

Rating	Maximum Average Score	Definition
Non-Irritating	0.0 - 0.5	To maintain this category, all scores at the 24-hour reading must be zero; otherwise, increase category one level.
Practically Non-Irritating	Greater than 0.5 - 2.5	To maintain this category, all scores at the 24-hour reading must be zero; otherwise, increase category one level.
Minimally Irritating	Greater than 2.5 - 15.0	To maintain this category, all scores at the 72-hour reading must be zero; otherwise, increase category one level.
Mildly Irritating	Greater than 15.0 - 25.0	To maintain this category, scores at the 7-day reading must be zero; otherwise, increase category one level.
Moderately Irritating	Greater than 25.0 - 50.0	To maintain this category, scores at the 7-day reading must be less than or equal to 10 for 60% or more of the animals. Also, the 7-day mean score must be less than or equal to 20. If the 7-day mean score is less than or equal to 20, but less than 60% of the animals show scores less than 10, then no animal among those showing scores greater than 10 can exceed a score of 30 if category is to be maintained; otherwise, increase category one level.
Severely Irritating	Greater than 50.0 - 80.0	To maintain this category, scores at the 7-day reading must be less than or equal to 30 for 60% or more of the animals. Also, the 7-day mean score must be less than or equal to 40. If the 7-day mean score is less than or equal to 40, but less than 60% of the animals show scores less than or equal to 30, then no animal among those showing scores greater than 30 can exceed a score of 60 if category is to be maintained; otherwise, increase category one level.
Extremely Irritating	Greater than 80.0 - 110.0	

NOTE: The category of the test material is not to be increased more than one level above its maximum average score.

17

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Section I, Tox. Branch I/IRS (H7509C)
Secondary reviewer: Roger Gardner, Acting Section Head Roger Gardner 12-18-90
Section I. Tox. Branch I/IRS (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 81-5. Primary Dermal Irritation (Rabbit)

TOX. CHEM. NO.: 342

MRID NO.: 414072-22

TEST MATERIAL: Diazinon MG8 (Technical): Lot No.: FL880045; amber liquid stable at room temperature; purity: not provided by sponsor but, in other studies, this material had purity (a.i. content) of about 87.7%. Expiration date: January, 1991.

STUDY NUMBER(S): 5945-89

SPONSOR: CIBA-GEIGY Corporation, Greensboro, N.C.

TESTING FACILITY: Stillmeadow, Inc., Houston, Texas

TITLE OF REPORT: Primary Dermal Irritation Study in Rabbits

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: March 3, 1989

CONCLUSIONS:

Classification: Acceptable

This study was conducted with 6 rabbits, 3 males and 3 females. The maximum average irritation score, obtained at 1 hour after termination of the exposure (wiping of the application sites) was as follows:

Maximum Irritation Score = 2.8
Descriptive Rating: Slight Irritant

All irritation had cleared by day 14.

Toxicity category: III

EXPERIMENTAL PROCEDURES

Young adult New Zealand white rabbits (3 males and 3 females) and undiluted Diazinon MG8 were used in this study. Diazinon MG8, 0.5 ml, was applied on clipped, free of hair dorsal areas (8 cm^2) of the trunk, occluded and then, after a 4-hour exposure, the wrappings and patches were removed and the

18

application sites wiped with a clean wet cloth to remove as much residual test material as possible. There was one test site per animal. The test sites were observed for erythema, edema, eschar formation and other dermal effects at 1, 24, 48 and 72 hours, and on days 7, 10 and 14 after the termination of the exposure. Dermal reactions were evaluated according to the scoring scale detailed in Attachment I. The rabbits were:

1. Obtained from Ray Nichols Rabbitry, Lumberton, Texas.

2. Acclimated for at least one week.

3. Housed singly.

4. Fed unrestricted Purina Chow and water (automatic system).

5. Identified by ear tags.

RESULTS

Erythema (Score 1 or 2) was observed in all rabbits during the first 48 hours after the termination of the exposure, in 5 rabbits at 72 hours, in 3 on day 7, in 2 on day 10 and in none on day 14. Both sexes responded similarly to the test material.

Edema (Score 1) was observed in 5 rabbits during the first 48 hours after the termination of the exposure, in 3 rabbits at 72 hours, and in none on day 7.

Other dermal effects were not observed.

The average irritation score for each observation time was as follows:

Observation Time	IRRITATION SCORE
1 Hour	2.8
24 Hour	2.5
48 Hour	2.3
72 Hour	1.7
Day 7	0.5
Day 10	0.3
Day 14	0.0

COMMENTS

This study is well-planned, well-reported, meets the November 7, 1989 Acceptance Criteria and is, therefore, Acceptable. GLP Compliance Statement and Quality Assurance Statement are included.

19

Attachment I

RABBIT SKIN IRRITATION
Evaluation of Skin Reactions

Erythema and Eschar Formation	Value
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Maximum Possible	4

Edema Formation	Value
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond the area of exposure)	4
Maximum Possible	4

RABBIT SKIN IRRITATION
Classification of Test Material Based on the Maximum Irritation Score

Descriptive Rating	Maximum Irritation Score	Remarks
Practically Not an Irritant	0.0 - 0.4	
Slight Irritant	0.5 - 3.0	
Moderate Irritant	3.1 - 5.0	
Severe Irritant	5.1 - 7.0	Severe erythema or edema without tissue destruction.
Corrosive	7.1 - 8.0	Tissue destruction into the dermis and/or scarring.

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Reviewed by: Krystyna K. Locke, Toxicologist K.K. Locke 9/19/90
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Section I. Tox. Branch I/IRS (H7509C) 12-18-90

DATA EVALUATION REPORT

STUDY TYPE: 81-6. Dermal Sensitization (Guinea Pig)

TOX. CHEM. NO.: 342
MRID NO.: 414072-23

TEST MATERIAL: Diazinon MG8 (Technical); Lot No.: FL880045; amber liquid stable at room temperature; purity: not provided by sponsor but, in other studies, this material had purity (a.i. content) of about 87.7%. Expiration date: January, 1991.

STUDY NUMBER(S): 5946-89

SPONSOR: CIBA-GEIGY Corporation, Greensboro, N.C.

TEST FACILITY: Stillmeadow, Inc., Houston, Texas

TITLE OF REPORT: Dermal Sensitization Study in Guinea Pigs

AUTHOR(S): Janice O. Kuhn

REPORT ISSUED: March 29, 1989

CONCLUSIONS:

Classification: Acceptable

Diazinon MG8 was not a skin sensitizer in this study. The test, apparently a modified Buehler test, involved 10 induction treatments and, 14 days later, 2 challenge treatments, both made on the same day. One challange dose was applied on the same site as the induction treatments and another on a new site. Undiluted Diazinon MG8 was used in 3 induction applications and a 10% v/v ethanolic solution of Diazinon MG8 in the remaining induction applications and in the challenge treatments; the ose was reduced because of the death of one animal on study day 7. 1-Chloro-2,4-dinitrobenzene, 0.06% w/v solution in ethanol, was used as a positive control. There were 10 male Hartley albino guinea pigs per group and 0.5 ml of a test material was used in each treatment.

EXPERIMENTAL PROCEDURES

This study was conducted in 1989. The first treatment occurred on February 8, the last on March 15 and the study was

23

terminated on March 17. It was not stated which of the methods regarded by EPA as acceptable was used, but the description of the test resembled a modified Buehler test.

Short-haired male Hartley albino guinea pigs, weighing 295-340 g when tested, were treated with 1-chloro-2,4-dinitrobenzene (Group I, positive control, 10 animals) of Diazinon MG8 (Group II; 10 animals). Undiluted Diazinon MG8, 0.5 ml per treatment, was used on days 1, 3 and 6, and diluted Diazinon MG8 (10% v/v solution in ethanol), also 0.5 ml per treatment, was used on days 8, 10, 13, 15, 17, 20, 22 and 36. The undiluted dose was initially selected from previous screening as the highest nonirritating level of the test material. However, because of the death of one animal on day 7, which was attributed to Diazinon MG8, the dose was thereafter reduced. Positive control, 0.5 ml per treatment, was used throughout the study as a 0.06% w/v solution in ethanol.

The test materials were applied on clipped, free of hair skin, occluded and then, after a 6-hour exposure, the wrappings and patches were removed, and the animals were returned to their cages. The first 10 treatments were an induction phase and the last one, 14 days later (on day 36), a challenge treatment. The induction and challenge applications were made on the left side of the back of the trunk (referred to by the testing laboratory as the Left Front Test Site or Original Test Site, or LF). On day 36, a challenge application was also made on the right side of the back of the trunk (referred to as Right Rear Test Site or Virgin Test Site, or RR).

Observations for skin reactions were made approximately 24 hours after each treatment. In addition, observations for skin reactions were made approximately 48 hours after treatments 1 and 10 (day 22) and the challenge treatment on day 36. Skin reactions (erythema and edema) were scored as detailed in Attachment I. The guinea pigs were:

1. Obtained from Harlan Sprague Dawley, Inc., Houston, Texas.

2. Acclimated for 6 days.

3. Housed 5/cage.

4. Fed unrestricted Purina Guinea Pig Chow and water (automatic system).

5. Identified by ear punch.

6. Weighed on days 0 and 35.

7. Examined grossly (only nonsurvivors).

RESULTS

Mortality

One animal died on study day 7, after 3 treatments with undiluted Diazinon MG8, and this death was attributed by the testing laboratory to Diazinon MG8. Gross necropsy revealed only an empty gastrointestinal tract; histopathology was not performed. No comment was made if any toxic signs were observed prior to death.

Body Weights

All animals in the positive control group gained weight, from 225 g to 335 g per animal during 35 days of study. In the Diazinon MG8-treated group, 8 animals gained 220-315 g per animal, but one guinea pig gained only 175 g during 35 days of study. The nonsurviving animal lost 105 g during 7 study days.

Skin Reactions

Following a challenge treatment with Diazinon MG8, neither erythema nor edema were observed on both application sites, that is, the original (LF) and the new (RR) sites. Very slight erythema and edema, each Grade 1, were observed in the Diazinon MG8-treated group during the induction period; erythema was observed infrequently and edema very infrequently. Eschar was observed only in 2 animals and only on the last day of the induction period. (For details, see Attachment II, pages 16 and 17).

Following a challenge treatment with positive control, erythema (Grade 1-4) was observed in all of the animals and edema (Grade 1-3) in 9 out of 10 animals. Erythema and edema, each Grade 1-4, were also observed in each animal during most of the induction period. Eschar was also observed in each animal during the induction period. (For details, see Attachment II, pages 15 and 17).

COMMENTS

In general, this study is well-planned, well-reported, meets the November 7, 1989 Acceptance Criteria and is, therefore, Acceptable. However, the test used (it looks like a modified Buehler test) was not referenced. Also, there is an ambiguity which requires clarification. The following is stated on page 6 of the submission, under Protocol Deviations:

"The protocol stated that the positive control animals would be treated with a 0.5% w/v solution of 2,4-dinitrochlorobenzene in ethanol. The dose was raised to 0.6% w/v in ethanol to ensure an adequate irritation response."

Yet, it is stated on all of the remaining pages of the submission that a 0.06% w/v solution of 2,4-dinitrochlorobenzene in ethanol was used in the positive control group.

GLP Compliance Statement and Quality Assurance Statement are included.

Attachment I

Legend to Table 1
GUINEA PIG SKIN SENSITIZATION
Evaluation of Skin Reactions

Erythema and Eschar Formation	Value
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Maximum Possible	4

Edema Formation	Value
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond the area of exposure)	4
Maximum Possible	4

Attachment II

Table 1
GUINEA PIG SKIN SENSITIZATION
Skin Reactions
Diazinon MG8 FL880045
Group I - Positive Control

Animal Number	Hours After Day of Treatment: LF Day 1 24	1 48	3 24	6 24	8 24	10 24	13 24	15 24	17 24	20 24	22 24	22 48	Challenge: LF 36 24	LF 36 48	RR 36 24	RR 36 48
Erythema																
1-M	0	0	0	1	1	2	3	3	3	3	3	3	2	2	1	0
2-M	0	0	0	0	1	2	3	3	3	3	3	3	2	2	0	0
3-M	0	0	0	1	2	2	2	2	3	3	3	3	2	1	0	0
4-M	0	0	0	1	2	3	3	4	4	4	4	4	2	2	1	0
5-M	0	0	0	0	1	3	3	4	4	4	4	4	2	2	0	0
6-M	0	0	0	0	1	1	2	2	2	2	2	2	1	1	0	0
7-M	0	0	0	1	2	2	2	2	3	3	3	3	2	2	1	0
8-M	0	0	0	0	1	2	2	2	2	3	3	3	1	1	0	0
9-M	0	0	0	1	1	2	2	3	4	4	4	4	4	3	1	0
10-M	0	0	0	0	1	2	2	2	3	3	3	3	2	1	0	0
Edema																
1-M	0	0	0	0	1	2e	3e	3e	3e	3e	3e	3e	2	1	0	0
2-M	0	0	0	0	0	1e	2e	2e	2e	3e	3e	3e	2	2	0	0
3-M	0	0	0	1	1	1	2	2e	2e	2e	3e	3e	1	1	0	0
4-M	0	0	0	0	0	2e	3e	3e	3e	4e	4e	4e	2	2	0	0
5-M	0	0	0	0	0	2e	3e	3e	4e	4e	4e	4e	1	1	0	0
6-M	0	0	0	0	0	1	1	1	2e	2e	2e	2e	1	1	0	0
7-M	0	0	0	0	1e	2e	2e	2e	2e	2e	3e	3e	2	2	0	0
8-M	0	0	0	0	0	1	1	1	2	2e	2e	2e	0	0	0	0
9-M	0	0	0	0	0	1	2e	3e	3e	4e	4e	4e	3	3	0	0
10-M	0	0	0	0	0	1	2	2e	2e	3e	3e	3e	1	1	0	0

LF - Left Front Test Site
RR - Right Rear Test Site
M - Male
e - Eschar formation

Table 1 (cont.)
GUINEA PIG SKIN SENSITIZATION
Skin Reactions
Diazinon MG8 FL880045
Group II - Test

Animal Number	Hours After Day of Treatment: LF Day 1 24	Day 1 48	3 24	6 24	8 24	10 24	13 24	15 24	17 24	20 24	22 24	22 48	Challenge: LF 36 24	LF 36 48	RR 36 24	RR 36 48
Erythema																
11-M	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0
12-M	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0
13-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14-M	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0
15-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16-M	0	0	0	0	1	0	1	1	1	0	0	0	0	0	0	0
17-M*	0	0	0													
18-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19-M	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0
20-M	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0
Edema																
11-M	0	0	0	0	0	0	0	0	0	1	1[e]	1[e]	0	0	0	0
12-M	0	0	0	0	0	0	0	1	1	1	1	1[e]	0	0	0	0
13-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17-M*	0	0	0													
18-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20-M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

LF - Left Front Test Site
RR - Right Rear Test Site
M - Male
e - Eschar formation
* - Animal found dead on Day 7 of the study.

Table 2
GUINEA PIG SKIN SENSITIZATION
Average Skin Reaction Scores
Diazinon MG8 FL880045

	Hours After Day of Treatment												Challenge			
	LF												LF		RR	
	Day 1		3	6	8	10	13	15	17	20	22		36		36	
Group	24	48	24	24	24	24	24	24	24	24	24	48	24	48	24	48
I (Positive Control)	0.0	0.0 (0.0)	0.0	0.6	1.6	3.5	4.5	4.9	5.6	6.1	6.3	6.3 (6.3)	3.5	3.1 (3.3)	0.4	0.0 (0.2)
II (Test)	0.0	0.0 (0.0)	0.0	0.1	0.1	0.0	0.2	0.6	0.6	0.7	0.6	0.6 (0.6)	0.0	0.0 (0.0)	0.0	0.0 (0.0)

LF - Left Front Test Site
RR - Right Rear Test Site

"An average score for each time period was obtained by adding all of the scores for each time period and dividing by the number of test sites scored for that time period. A marked increase in positive skin reactions for the virgin test site after the Day 36 treatment (challenge treatment) above those observed after the Day 1 treatment (initial treatment) is indicative of a sensitizing reaction."