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

OCT 18 1989

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. No. 100-524. Technical Diazinon (MG-8): Additional (Requested by Toxicology Branch) Information Submitted by Ciba-Geigy Corporation to Clarify or Upgrade Previously Evaluated Studies.

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Krystyna K. Locke 10/16/89

TO: George T. LaRocca, PM Team (15)
Insecticide-Rodenticide Branch
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THRU: Roger Gardner, Acting Section Head
Section I, Toxicology Branch I (IRS)
Health Effects Division (H7509C)
10-17-89

Record Nos.: 246561/249230/249245 Tox. Chem. No.: 342
T.B. Project Nos.: 9-1627/9-1908/9-1909

In February, 1989, Toxicology Branch I has completed an evaluation of several studies with Technical Diazinon. Studies listed below required additional information for the purpose of clarification or upgrading.

Study/Lab/Study No./ Date/MRID (Accession) No.	Classification of Study
Mutagenicity (L5178Y/TK+/- mouse lymphoma; Ciba-Geigy Limited, Basle, Switzerland; No. 840396; 7/31/86. 406608-02	Provisionally Acceptable
Subchronic oral (6 weeks)- rat; Ciba-Geigy Corporation; No. 88076 (MIN 872348); 7/20/88. 408150-03	Supplementary (Preliminary study)
Subchronic oral (90 days)- rat; Ciba-Geigy Corporation; No. 88083 (MIN 882011); 8/4/88. 408150-03	Guideline

Subchronic oral (90 days)-dog; Ciba-Geigy Corporation; No. 88072 (MIN 882012); 8/4/88. 408150-04 — Supplementary

The current submission contains the requested information. Based on these data, the mouse lymphoma mutagenicity study and the 90-day dog feeding study are being upgraded to Acceptable and Core-Guideline, respectively. Single errors, originally present in each of the rat studies, have also been corrected by Ciba-Geigy Corporation. (See Attachments A, B, C and D for details.)

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Attachment A

Mouse Lymphoma Mutagenicity Study with Diazinon (MG-8): Additional Data

Record No.: 246561

HED Project No.: 9-1627

Response to EPA Requests Concerning the Mouse Lymphoma Study with Diazinon (GS 24480 Tech); MRID No. 406608-02

MRID (Additional Data): 411197-01

1) It was not stated whether positive controls (DMN and EMS), both liquids, were used in the assay medium as purchased or were first diluted with DMSO. Since in the RESULTS section Diazinon-treated cell cultures were compared with solvent controls and those containing DMN and EMS with negative controls, the Agency assumes that positive controls were used as purchased. Please clarify this in writing.

The solvent (DMSO) control was used for all cultures treated with the test substance as the negative control. The absolute negative control was used for the cultures treated with positive reference substances as the negative control, due to the fact that the positive reference substances have been applied to the cultures without any solvent.

2) Purities of the positive control substances were not reported. Please submit this information.

DMN:	**Purchased from:**	**Merck-Schuchart**
	Batch:	**3198258**
	Purity:	**98%**
EMS:	**Purchased from:**	**Merck-Schuchart**
	Batch:	**3196073**
	Purity:	**98%**

3) Relative Suspension Growth (% of Control): Tables 1, 4, and 7. Using "Daily Counts", values reported for "Relative Susp. Growth" could not be obtained. A sample calculation must be submitted.

The relative suspension growth rates are defined as the ratio of the suspension growth factors of the treated and the negative control cultures. The suspension growth factors were determined by daily counting the cell number in the cultures for the three days following the treatment. After every cell counting, the cell number of the cultures was adjusted to the initial value ($3x10^5$ cells/ml). For every culture, the suspension growth factor was calculated by multiplication of the three cell-count values. The relative suspension growth rates were calculated using the suspension growth factors obtained from the treated cultures divided by the suspension growth factor of the negative control culture.

The calculation is:
(Example: Table 4, Exp. without activation, EMS)
Daily cell counts ($x10^{-5}$/ml) of a treated culture (EMS):
4.8, 9.3, 4.1 Multiplication of the values: 183.02
Daily cell counts ($x10^{-5}$/ml) of the abs. neg. control culture:
9.4, 13.5, 12.1 Multiplication of the values: 1535.49
Relative suspension growth = 183.02/1535.49 = 0.119 = 11.9%

4) Mutant frequencies (Tables 4 and 7) were calculated using the following formula: "(Mutant clones x 800/viable clones)/3.2". No explanation is provided as to what the "800" and "3.2" in this formula are. This information must be submitted.

The mutant frequency is defined as the number of $TK^{-/-}$ mutants observed per 10^6 cells. In the study, this number was determined by counting the number of BUdR-resistant clones obtained after seeding 10^6 viable (=clonable) cells.

The calculation is:

(Example: Table 4, Exp. without activation, solvent control)

Number of BUdR-resistant (mutant) clones:

8 tubes counted, total 94 clones

Number of the cells (clonable and not clonable) tested:

8 tubes seeded, each 4×10^5 cells

= 3.2×10^6 cells

Percentage of clonable cells: Percentage of the number of clones developed after seeding a defined (low) number of cells.

clone counting: 4 tubes, total 430 clones

cells seeded: 4 tubes, each 200 cells = 800 cells

clonable cells (%): 100%*430/800 = 53.75%

Therefore the mutant frequency was calculated to be:

$94/(3.2 \times 10^6 * (430/800)) = 54.7 \times 10^{-6}$

Attachment B

Diazinon (MG-8): Six-Week Oral Toxicity Study with Rats: Additional Data

Record No.: 249230

HED Project No.: 9-1908

RESPONSE TO EPA ON THE SUBCHRONIC ORAL TOXICITY (RAT) 6-WEEK PRELIMINARY STUDY; MRID No. 408150-03

MRID No. (Additional Data): 411812-01

EPA Comment 1 - "There is an error on page 11 of the submitted report which should be corrected. The mean daily dose of Diazinon (MG-8) for Group 3 females was reported as 0.02 mg/kg, whereas 0.2 mg/kg is the correct value. Similarly, dose range for this group should be 0.2-0.2 mg/kg/day and not 0.02-0.02 mg/kg/day as reported."

CIBA-GEIGY Response

EPA has correctly pointed to a typographical error which has been corrected. The corrected page is in the attached report amendment 1. (Page 14 of 15)

EPA Comment 2 - "There is an ambiguity on page 10 of the submitted report which requires clarification. The following was reported regarding cholinesterase determination: 'Prior to initiation of treatment (test days -6, -5, and -4) and on test days 15, 16, 25 and 26, blood samples were obtained under ether anesthesia from the retro-orbital plexus for analysis of serum cholinesterase and RBC cholinesterase.' However, serum and RBC acetylcholinesterase activities were reported for the pretest day 5 and the treatment days 14 and 24."

CIBA-GEIGY Response

As EPA noted in the above statement (taken from the report), the laboratory took blood samples from the animals over several days, however, the enzyme data are reported as only on one of the days that the blood samples were taken.

It is respectfully stated that the laboratory has a "standardized method" of reporting the data under a single-day table heading for each given time period when actually the blood collection period may take longer than one day. Each animal is only bled once at each collection time interval although the time interval extended longer than a single day.

For the blood collection in this study, the collection period was day -6, -5 and -4 and reported on a table with the heading as Day -5; for collection period day 15 and 16, the table heading was day 14; for collection period day 25 and 26, the table heading was day 24.

Corrected Page

Attachment B, Comment 1

3. RESULTS AND DISCUSSION

Review of baseline data indicated that all animals assigned to the study were healthy and suitable for use. The dietary concentration of the high-dose group was increased from 1000 ppm to 2000 ppm on test day 15 and from 2000 to 4000 ppm on test day 36. No other known circumstances or errors occurred that were considered to have compromised the integrity of the study.

3.1. Chemical Analyses and Dosimetry

Review of the dietary analyses data indicated that Diazinon was uniformly distributed in feed at the target concentrations of 0.5, 2.0, 100 or 1000/2000/4000 ppm. These analyses are presented in Appendix 9.3 and 9.4. The mean and range of the daily dose on a mg/kg basis for Groups 2, 3, 4 and 5 are summarized below and presented in Table 8.6.

Sex	Group	Dietary Concentration (ppm)	Mean Daily Dose (mg/kg/day)	Range (mg/kg/day)
M	1	0	--	--
	2	0.5	0.04	0.03 - 0.06
	3	2.0	0.2	0.1 - 0.2
	4	100	8.4	6.7 - 11.1
	5	1000	105.1	102.8 - 107.4
		2000	152.7	142.9 - 157.7
		4000	236.6	-- --
F	1	0	--	-- --
	2	0.5	0.05	0.04 - 0.06
	3	2.0	0.2	0.2 - 0.2
	4	100	9.4	8.0 - 11.4
	5	1000	114.9	113.6 - 116.1
		2000	194.2	184.7 - 207.2
		4000	284.9	-- --

Attachment C

Diazinon (MG-8): 90-Day Oral Toxicity Study with Rats: Additional Data

Record No.: 249230

HED Project No.: 9-1908

RESPONSE TO EPA ON THE SUBCHRONIC ORAL TOXICITY (RAT) 90-DAY STUDY ; MRID No. 408150-03

MRID No. (Additional Data): 411812-02

EPA Comment:

"This study is well planned and generally well reported. However, there is one error in the clinical biochemistry results. It was reported on page 25 of the submission that serum potassium was elevated in the 2500 ppm females. Yet, data on page 130 clearly indicate that inorganic phosphorous, and not potassium, was elevated in that group.

CIBA-GEIGY Response

EPA has correctly identified an error in the report. The corrected page is in the attached report amendment. (Page 12 of 13)

Corrected Page

Attachment C

a reduction in cholesterol and an increase in SGPT in males at 2500 ppm; a decrease in glucose in females at 0.5 ppm; decreases in SGPT in females at 0.5, 250 and 2500 ppm; decreases in sodium in males at 5 ppm and in females at 2500 ppm; a decrease in chloride and an increase in inorganic phosphorus in females at 2500 ppm. These effects were not considered to be treatment-related due to the magnitude of change, lack of a dose-response relationship and/or the majority of individual animal values being within the concurrent control range. Group mean biochemistry data are summarized in Table 8.9., and individual animal data are included in Appendix 9.1.6.

3.9. Urinalysis

There were no treatment-related changes observed in mean urinalysis values in either sex on dose day 81 at feeding levels up to 2500 ppm. A statistically significant increase in mean urine specific gravity was noted in both sexes at 2500 ppm; due to the proximity to the respective control values and lack of a dose-response relationship, this change was considered to be incidental. Group mean and individual animal urinalysis data are presented in Table 8.10. and Appendix 9.1.7., respectively.

3.10. Organ Weight

A statistically significant, treatment-related increase in the mean absolute and relative (to body weight) liver weight was observed on dose day 94 in females at 2500 ppm. This effect correlated with microscopic evidence of minimal centrolobular hepatocellular hypertrophy in the majority of females at this dose level. A statistically significant increase in the mean relative (to body weight) kidney (females) weights

Attachment D

Diazinon (MG-8): 90-Day Oral Toxicity Study with Dogs: Additional Data

Record No.: 249245

HED Project No.: 9-1909

RESPONSE TO EPA ON THE SUBCHRONIC ORAL TOXICITY (DOG) 90-DAY STUDY ; MRID No. 408150-04

MRID No. (Additional Data): 411812-03

EPA comment - 1. "Although the study number and the animal ID numbers are correct, and the findings reported in the individual pathology data agree with those discussed in other sections of the submission, individual histopathology data (pages 485-493) were reported for dose levels of 20, 100, 500 or 1500 ppm. Since the dose levels of Diazinon (MG-8) used in this study were 0.1, 0.5, 150 or 300 ppm, correctly identified pages 485-488 and 490-493 are required."

CIBA-GEIGY Response

EPA has correctly noted an error in the report. Corrected pages are in attached report amendment 1 (Pages 30-37 of 39).

EPA comment - 2. "In the mortality records (pages 324 and 325), an ... observation period of 14 days is reported for each dog. Since the acclimation period was about 6 weeks, the study was initiated on January 26, 1988, and the necropsies were performed on April 27, 28 and 29, this ambiguity (14-day observation period) requires an explanation."

CIBA-GEIGY Response

EPA has correctly noted an ambiguity in the report. The observation period refers to 14 without any units. As now corrected by the laboratory, the corrected page referring to the observation period is expressed in weeks and is in the attached report amendment 1 (Page 29 of 39).

EPA comment - 3. "According to the clinical biochemistry data, brain acetylcholinesterase activity for all dogs was determined on day 92 (pages 205 and 260). Yet, 50 or 75 percent of the dogs in each group were dosed for 93 or 94 days (pages 324 and 325). A clearer presentation of these data seems in order."

CIBA-GEIGY Response

It is respectfully stated that the laboratory has a "standardized reporting method" of presenting the data under a single day table heading for each given time period when the actual necropsy and blood collection intervals took longer than one day. The necropsy and final blood collection interval was over three days. The terminal brain cholinesterase data for all animals as well as most of the other data are expressed under one single table

heading day (day 92), however, the necropsy period lasted for three days (day 92-94).

EPA comment - 4. "A properly identified table is required on page 504. The currently available data (Table 6.3) is entitled Results of concentration analyses of Diazinon MG-8 in rodent feed. Yet, the study number and dose levels are those used for the 90-day oral feeding dog study."

CIBA-GEIGY Response

EPA has correctly noted an error in the report. A corrected page is in the attachment report amendment 1 (Page 38 of 39).

EPA comment - 5. "On page 21, the terms 'acetylcholinesterase levels' and 'acetylcholinesterase activity' are used interchangeably which is incorrect. Acetylcholinesterase activity was determined in this study."

CIBA-GEIGY Response

EPA is absolutely correct. Acetylcholinesterase activity was measured. A corrected page has been added to the report and is in the attached report amendment 1 (Page 27 of 39).

Corrected Page

Attachment D, Comment 2

DIAZINON (MG-8): 13-WEEK ORAL TOXICITY STUDY IN DOGS (MIN 882012)

9.1.1. Mortality record

(This appendix contains 3 pages)

Note: The mortality record is taken from the Beckman TOXSYS® report - Animal Removals by Sex and Treatment Group. The observation period is expressed in weeks.

Corrected Page

Attachment D, Comment 4

DIAZINON (MG-8): 13-WEEK ORAL TOXICITY STUDY IN DOGS (MIN 882012)
ANALYTICAL REPORT

TABLE 6.3.

Results of concentration analyses of Diazinon MG-8 in canine diet

Study Week	ACL No.	Target Concentration[a] (ppm)	Observed Concentration[a] (ppm)	Percent of Target Concentration
1	9607	0.100	0.129[b]	129
	9608	0.500	0.490	98
	9609	150	148	99
	9610	300	292	97
3	9677[c]	0.100	0.104	104
5	9737	0.100	0.0950	95
	9739	0.500	0.502	100
	9740	150	146	97
	9741	300	306	102
9	9919	0.100	0.0954	95
	9920	0.500	0.478	96
	9921	150	152	101
	9922	300	320	107
13	10054	0.100	0.101	101
	10055	0.500	0.525	105
	10056	150	143	95
	10057	300	282	94

[a]Concentrations are expressed in terms of pure Diazinon.

[b]The study director was notified of this result which was outside the limits specified in the protocol.

[c]Analysis requested by the study director.

007041

Reviewed by: Krystyna K. Locke, Toxicologist Krystyna K. Locke 12/6/88
Section I, Tox. Branch I/IRS (TS-769C)
Secondary reviewer: Edwin R. Budd, Section Head
Section I, Tox. Branch I/IRS (TS-769C)

ERB 12/6/88

DATA EVALUATION REPORT

STUDY TYPE: 82-1. Subchronic Oral Toxicity (Dog): 4-Week Preliminary Study

TOX. CHEM. NO.: 342

MRID NO.: 408150-04

TEST MATERIAL: Diazinon (MG-8);
Purity (content of a.i.): 87.7%
Lot No.: FL-872049

STUDY NUMBER(S): 88077 (MIN 872349)

SPONSOR: Ciba-Geigy Corporation, Agricultural Division, Greensboro, NC.

TESTING FACILITY: Division of Toxicology/Pathology, Ciba-Geigy Corporation, Summit, NJ.

TITLE OF REPORT: Diazinon (MG-8): Pilot 4-Week Oral Feeding Study in Dogs

AUTHOR(S): A. R. Singh, G. C. McCormick and A. T. Arthur

REPORT ISSUED: August 1, 1988

CONCLUSIONS:

NOEL: 0.5 ppm (0.02 mg/kg*; LTD); males

NOEL: < 0.5 ppm; females (Inhibition of serum AChE activity)

*Reported value based on analytical data

CLASSIFICATION: Core-Supplementary (Preliminary study)

The purpose of this study was to determine the preliminary subchronic toxicity profile of Diazinon (MG-8) in order to project dose levels for a subsequent 90-day oral toxicity study.

Groups of 4 male and 4 female beagle dogs received diets (400 g/day) containing Diazinon (MG-8) (0, 0.5, 2, 20 or 500 ppm) for four consecutive weeks. Emesis, weight loss and decreased food consumption were observed in the 500 ppm male and female groups. Dose-related significant inhibition of serum

acetylcholinesterase (AChE) activity occurred in all female groups and in all but the 0.5 ppm male groups. Erythrocyte and brain AChE activities were inhibited significantly only in the 500 ppm male and female groups. Neurological symptoms, generally associated with brain AChE inhibition, were not observed. Nothing remarkable was noted at necropsy. Histopathology was not performed.

EXPERIMENTAL PROCEDURES

Dosing was initiated on October 5, 1987, and terminated on November 3, 1987.

Beagle dogs (4/sex/group) received Diazinon (MG-8) in Certified Powdered Laboratory Purina Canine Diet #5007 at target concentrations of 0, 0.5, 2, 20 or 500 ppm for 4 consecutive weeks. Each animal received approximately 400 g of feed for about 3 hours each morning. Water was provided ad libitum through an automatic watering system. Diets were prepared weekly, stored at room temperature and analyzed for homogeneity and Diazinon (MG-8) concentration. Dietary levels of Diazinon (MG-8) were adjusted for purity. Diazinon (MG-8) was stored at 2-8° C.

The dogs were: 1) obtained from Marshall Farms, North Rose, NY; 2) acclimated for 2 weeks; 3) approximately 6 months old and weighing 6.7-8.1 kg (males) and 6.4-7.9 kg (females) at the initiation of dosing; 4) housed individually; and 5) identified by numbers tattooed on the ears. Nothing was said about assignment of animals to groups.

The following parameters were examined for all dogs on the study:

1. Observations for toxic signs: twice daily and once on weekends.
2. Body weight: on day 8 before dosing, just prior to dosing on day 1, weekly thereafter, and at the termination of the study (test days 30 or 31).
3. Food consumption: determined weekly.
4. Acetylcholinesterase activity: in serum and RBC, two weeks before dosing and on dosing days 14 and 25; in brain, at the termination of the study.
5. Necropsy
6. Absolute and relative (percent of terminal body weight) brain weight.

Parameters 2, 3, 4 and 6 were analyzed statistically by two-tailed Dunnett t test and Bartlett test for variability.

Histopathology was not performed.

RESULTS

Homogeneity, Concentration and Stability of Diazinon (MG-8) in Diets

Diets were checked for homogeneity during the first test week by determining the concentration of Diazinon (MG-8) in the top, middle and bottom of the batches of feed. Analyses of multiple samples of test formulations indicated that homogeneity ranged from 90.6 to 98.6%, which was regarded as acceptable.

The mean analytical concentrations of Diazinon (MG-8) in diets administered to Groups 2 (0.5 ppm), 3 (2 ppm), 4 (20 ppm), and 5 (500 ppm) were 90, 97, 95 and 99%, respectively, of the target concentrations.

Diazinon (MG-8) was stable in diets for 27 days at room temperature.

Compound Intake

The mean daily intake of Diazinon (MG-8), calculated each week, was as follows:

	Diazinon (MG-8) (mg/kg b.w./day)*	
Diazinon (MG-8) in Diets (ppm)**	Males	Females
0.5	0.020	0.023
2.0	0.073	0.082
20	0.80	0.875
500	14.68	15.99

According to these data, males and females in each group ingested similar amounts of the test material.

*Based on analytical data
**Target concentrations

Clinical Signs

Treatment-related signs were observed only in the 500 ppm groups and included emesis (in 3 males and 4 females) and cachexia/emaciation in one female. There was no mortality.

Body Weight

Weight losses were observed at 500 ppm in both sexes throughout the study. On treatment days 21 and 28, males in this group weighed 4.0 and 6.2%, respectively, less than they did at the initiation of treatment. The corresponding weight losses for the females were 6.6 and 8.4%, respectively. All of these weight

losses, except 6.6%, were statistically significant ($0.01 < p \leq 0.05$).

Food Consumption

Decreased food consumption was observed at 500 ppm in both sexes throughout the study. During treatment weeks 2, 3, and 4, males consumed 17.7, 33.8** and 36.4**% less food, respectively, than did the controls. The corresponding decreases in food consumption for the females were 26.4*, 41.1** and 39.2**%, respectively. (* $0.01 < p \leq 0.05$; ** $p \leq 0.01$)

Acetylcholinesterase Activity

Compared with the controls, serum acetylcholinesterase (AChE) activity was significantly inhibited in the males in Groups 3, 4 and 5, and in all female groups. Erythrocyte and brain AChE activities were significantly inhibited only in Group 5. These data are summarized below.

Inhibition of AChE Activity

Group	Diazinon (MG-8) (ppm)	Dosing Day	RBC Percent Inhibition	Serum Percent Inhibition	Brain Percent Inhibition
					in Male Dogs
2	0.5	14	0	8.8	
		25	0.8	8.4	0
3	2	14	10.6	40.9**	
		25	11.3*	38.5**	2.7
4	20	14	9.7	69.5**	
		25	6.5	64.6**	1.3
5	500	14	38.8**	80.8**	
		25	29.8**	80.5**	44.4**
					in Female Dogs
2	0.5	14	5.3	29.6**	
		25	7.6	28.3**	4.1
3	2	14	1.8	47.7**	
		25	8.4	48.7**	3.8
4	20	14	0	69.8**	
		25	10.9	67.3**	9.9
5	500	14	25.7**	80.0**	
		25	37.8**	81.5**	50.4**

* $0.01 < p \leq 0.05$ ** $p \leq 0.01$

It was not reported what procedure was used for the determination of AChE activity and AChE activity was reported only as mu/mL. Although reported for dosing day 25, brain AChE activity was determined only at the termination of the study.

Necropsy

There were no treatment-related findings.

Brain Weight

There were no statistically significant differences in the mean absolute or relative (percent of terminal body weight) weights of the brain when the Diazinon (MG-8)-treated dogs were compared with the controls.

Comments

Although brain AChE activity was inhibited 44% in the high-dose (500 ppm) males and 50% in the high-dose females, the animals had no neurological symptoms.

Based on the results of this study, the maximum tolerated dose (MTD) was considered by the testing laboratory to be between 20 and 500 ppm. Toxicology Branch I/IRS agrees with this conclusion.

Based on the results of this study, "the essential no-observable-effect level (NOEL)," according to the testing laboratory, was 0.5 ppm. The term "essential NOEL" was somewhat clarified in the attachment entitled TOXICOLOGICAL ASSESSMENT OF DIAZINON; C. Breckenridge; Ciba-Geigy Corporation; August 29, 1988. (MRID 408150-01). The following statement was made on page 10 of the attachment: "The no observable effect level was less than 0.5 ppm although the changes noted at 0.5 ppm, were not considered biologically significant, adverse effects of treatment."

Toxicology Branch I/IRS concluded that a NOEL for the male dogs was 0.5 ppm, but it was < 0.5 ppm for the female dogs (because of significant inhibition of serum AChE activity at this level).

Classification of study: Core-Supplementary (It was a preliminary study)

Reviewed by: Krystyna K. Locke, Toxicologist Krystyna K. Locke 2/7/89
Section I, Tox. Branch I/IRS (TS-769C)
Secondary reviewer: Edwin R. Budd, Section Head
Section I, Tox. Branch I/IRS (TS-769C) Budd 2/15/89

DATA EVALUATION REPORT

STUDY TYPE: 82-1. Subchronic Oral Toxicity (Dog): 90-Day Study

TOX. CHEM. NO.: 342

MRID NO.: 408150-04

TEST MATERIAL: Diazinon (MG-8); Purity (content of a.i.): 87.7%; Lot No.: FL:872049

STUDY NUMBER(S): 88072 (MIN 882012)

SPONSOR: Ciba-Geigy Corporation, Agricultural Division, Greensboro, NC

TESTING FACILITY: Division of Toxicology/Pathology, Ciba-Geigy Corporation, Summit, NJ

TITLE OF REPORT: Diazinon (MG-8): 90-Day Oral Toxicity Study in Dogs

AUTHOR(S): T. B. Barnes

REPORT ISSUED: August 4, 1988

CONCLUSIONS:

NOEL: 0.1 ppm (0.0034 mg/kg* for males and 0.0037 mg/kg*for females), based on the inhibition of acetyl-cholinesterase (AChE) activity in serum.

LEL: 0.5 ppm (0.020 mg/kg* for males and 0.021 mg/kg* for females); inhibition of serum AChE activity in both sexes.

*Reported values based on analytical data

CLASSIFICATION: Core-Supplementary, because of errors and ambiguities detailed in the review under COMMENTS. This classification will be upgraded to Core-Guideline upon receipt and acceptance by Toxicology Branch of the requested data.

Groups of 4 male and 4 female beagle dogs received diets (400 g/day) containing Diazinon (MG-8) (0, 0.1, 0.5, 150 or 300 ppm)

for 13 consecutive weeks (92-94 days). According to the testing laboratory, these dose levels were equivalent to 0, 0.0034, 0.02, 5.9 and 10.9 mg/kg of body weight for males in Groups 1, 2, 3, 4 and 5, respectively. The corresponding values for the females were 0, 0.0037, 0.021, 5.6 and 11.6 mg/kg, respectively.

Treatment-related effects included inhibition of serum AChE activities in Groups 3, 4, and 5, and of erythrocyte (RBC) and brain AChE activities in Groups 4 and 5; emesis/diarrhea, decreased weight gain, mean total protein and calcium levels in Groups 4 and 5; and pancreatic acinar atrophy in one Group 5 male. There were no deaths during the study. Neurological symptoms, generally associated with brain AChE inhibition, were not observed.

EXPERIMENTAL PROCEDURES

Dosing was initiated on January 26, 1988, and the study terminated on April 29, 1988. Necropsies were performed on April 27, 28 and 29, 1988.

Beagle dogs (4/sex/group) received Diazinon (MG-8) in Certified Powdered Laboratory Purina Canine Diet #5007 at target concentrations of 0, 0.1, 0.5, 150 or 300 ppm for 13 consecutive weeks. Each animal received approximately 400 g of feed for about 3 hours each morning. Water was provided ad libitum through an automatic watering system. Diets were prepared weekly, stored at room temperature and analyzed for homogeneity and Diazinon (MG-8) concentration. The dose levels used were based on the results of a preliminary study (No. 88077/MIN 872349; see separate review) and the dietary levels were adjusted for purity. Diazinon (MG-8) was stored a 2-8° C.

The dogs were: 1) obtained from Laboratory Research Enterprises, Inc., Kalamazoo, MI; 2) acclimated for 6 weeks; 3) approximately 6 months old and weighing 6.5-9.9 kg (males) and 6.1-9.3 kg (females); 4) assigned randomly to groups through a computerized system based on body weight; 5) housed individually at 69±5° F, relative humidity of 50±20%, and 12-hour light/dark cycle; and 6) identified by ear tattoos.

The following parameters were examined for all dogs on the study:

1. Daily observations for toxic signs and mortality.
2. Body weight: at predose week 2, prior to dosing during week 1, and weekly thereafter.
3. Food consumption: determined weekly.
4. Physical/auditory examinations: at predose week 3 and at the termination of the study.
5. Ophthalmoscopic examinations: at predose week 3 and at