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

AUG 0 2 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Methyl Parathion- 21-Day Dermal Toxicity Study in Rabbits

TO: Robert Richards/Larry Schnaubelt PM 72
SRRD (H7508W)

FROM: K. Clark Swentzel 7/29/92
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ID NO.	053501
CASE	818931
BARCODE:	177611
MRID	422637-01
SUBMISSION NO.	S-417043
PC NO.	053501
CASWELL NO.	372
REGISTRANT:	Cheminova Agro A/S

Requested Action

Review 21-day dermal toxicity study with methyl parathion on rabbits.

Conclusion

Methyl parathion was evaluated in a 21-day dermal toxicity study in rabbits at dosages of 0 (vehicle control, 1% carboxymethylcellulose), 1, 5, 10 and 100 mg/kg/day.

There were no mortalities or clinical signs of toxicity during the study. No adverse effects were apparent based on body weight, body weight gain, food consumption, clinical pathology parameters or organ weights. Histopathologic evaluations of the kidneys, liver and skin from high-dose rabbits did not reveal any treatment-related effects.

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No dermal effects were seen in treated males, however, slight erythema and edema was induced in 1, 5 and 10 mg/kg/day females; one 10 mg/kg/day female also had slight fissuring. The severity of these reactions did not increase with dosage. No dermal reactions were reported in 100 mg/kg/day females. Although no dermal effects were seen in treated males, the noted effects in females obviates the establishment of a NOEL for local dermal toxicity in this study.

Treatment-related RBC cholinesterase inhibition was seen in 10 and 100 mg/kg/day males and females.

The LOEL for systemic toxicity was 10 mg/kg/day based on RBC cholinesterase inhibition in both sexes and the NOEL was 5 mg/kg/day under the conditions of this study.

A definitive NOEL for local dermal toxicity could not be determined in this study.

Core classification: supplementary. This study does not satisfy guideline requirements for a 21-day dermal toxicity study (82-2). This study may be upgraded when the registrant provides the purity of test material.

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K. Clark Swentzel 7/29/92

Reviewed by: K. Clark Swentzel
Tox. Branch II, Section II (H7509C)
Secondary Reviewer
Marcia van Gemert, Ph.D.
Tox. Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 21-Day Dermal Toxicity in Rabbits Tox. Chem. No. 372

MRID NO. 422637-01

TEST MATERIAL: o-p-nitrophenyl phosphorothioate

SYNONYMS: Methyl parathion

STUDY NO. 67376

SPONSOR: Cheminova Agro A/S

TESTING FACILITY: Arthur D. Little Inc.

TITLE OF REPORT: 21-Day Subchronic Dermal Toxicity Study with Methyl Parathion in Rabbits

AUTHOR: M.E.P. Goad

REPORT ISSUED: January 28, 1992

COMPLIANCE STATEMENTS: Signed and dated Quality Assurance and GLP Compliance Statements were included on pages 6 and 3 of the report, respectively.

CONCLUSIONS

Methyl parathion was evaluated in a 21-day dermal toxicity study in rabbits at dosages of 0, 1, 5 10 and 100 mg/kg/day.

There were no mortalities or clinical signs of toxicity during the study. No adverse effects were apparent based on body weight, body weight gain, food consumption, clinical pathology parameters or organ weights. Histopathologic evaluations of the kidneys, liver and skin from high-dose rabbits did not reveal any treatment-related effects.

Although no dermal effects were seen in treated males, dermal irritation occurred in 1, 5 and 10 mg/kg/day females; no irritation was seen in control and high-dose females.

Treatment-related RBC cholinesterase inhibition was seen in 10 and 100 mg/kg/day males and females.

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The LOEL for systemic toxicity was 10 mg/kg/day based on RBC cholinesterase inhibition in both sexes and the NOEL was 5 mg/kg/day under the conditions of this study.

A definitive NOEL for local dermal toxicity could not be determined in this study.

TEST MATERIAL

Description:

The test material provided by the registrant was a yellow liquid (lot no. 95-IA-84). Purity was not provided in the report. A reference standard, provided as a solid, was reported to be 99.3 % pure (lot no. 40227-02).

The vehicle was carboxymethylcellulose (CMC: lot no. 03114KX, Aldrich Chem. Co.)

Stability:

Sonicated suspensions of the test material in 1% CMC were analyzed for stability on days 7, 10, 14 and 22.

It was shown that methyl parathion was stable at room temperature at concentrations of 0.9 and 109 mg/ml for 22 days.

Homogeneity of the test material in suspension:

The sonicated suspensions used for stability tests were also used to determine the homogeneity of the test material. Aliquots from the top, middle and bottom were analyzed in duplicate by gas chromatography (GC).

The analytical results showed that all measure concentrations were well within 10% of target concentrations in both suspensions.

Preparation for administration:

Dose suspensions of 1, 5, 10 and 100 mg/ml in 1% CMC were prepared once (except the 100 mg/ml which broke on day 14) during the test. The vehicle control was 1% CMC. These suspensions were analyzed via GC one day prior to the start of dosing and after the last day of dosing.

The data showed that all concentrations were within 10% of the theoretical concentrations throughout the dosing period.

TEST ANIMALS

Housing and acclimation:

Male and female New Zealand white rabbits were obtained from Hazleton Research Products, Denver, PA. Animals were placed in

quarantine for a minimum of 7 days and were observed during this period; body weights were obtained prior to randomization. Each animal was identified with numbered ear tag and a corresponding cage card. Body weights were 2.2-2.4 kg (average 2.2 kg) for males and 2.0-2.3 kg for females (average 2.2 kg) at the initiation of the study. The age range of the animals was not reported. The animals were housed individually in stainless steel cages with wire mesh bottoms.

Diet and drinking water:

Purina Certified High Fiber Rabbit Chow #5325 and municipal tap water were provided to each animal ad libitum.

Environmental conditions:

The rabbits were housed in a room with a 12-hour light cycle, a temperature of 19-29°C and a relative humidity of 42-58%.

STATISTICS

Statistical analyses of food consumption, body weight, cholinesterase, hematology and clinical chemistry data were analyzed. In all cases, males and females were considered separately. Differences among the groups in body weight, food consumption, cholinesterase, hematology and clinical chemistry values and organ weights were determined by a one-way analysis of variance. If there were statistically significant differences among the groups at $p \leq 0.05$, a Duncan's multiple comparisons test was performed.

EXPERIMENTAL PROCEDURES

Randomization and group assignment:

Animals were assigned to Groups 1-5 on the basis of body weight using a computer randomization program. Five animals per sex were assigned to each of the following groups:

Group	Dosage (mg/kg/day)
1	vehicle control
2	1
3	5
4	10
5	100

Treatment:

The fur was clipped from the dorsal trunk area ("10% of the total body surface area") of each rabbit prior to the first dose and approximately weekly thereafter.

Treatment groups were administered one of four dose levels: 1, 5, 10 or 100 mg/kg of active ingredient. Control groups were administered a volume of vehicle control (1% CMC) equal to the test volume administered to the high dose group. The dosing volumes were adjusted once a week according to the body weight of the animals taken that same day.

The animals received 21 consecutive daily doses (5 days/week for 3 weeks) for 6 hours/day. Test material was placed either directly on the skin or to gauze which was applied to the skin site. The test article was held in contact with the skin using porous eight-ply gauze dressing secured by non-occlusive adhesive surgical or bandage tape, or equivalent non-occlusive tape. After the exposure period, the wraps were removed and the residual test article was washed from the site using liquid hand soap, warm water and gauze sponges.

Clinical observations and mortality:

The rabbits were observed once daily for systemic and dermal toxicity as well as mortality. Clinical observations included changes in mucous membranes, respiratory, gastrointestinal and neuromuscular systems as well as general behavior.

Results:

The only clinical sign noted by the investigator was increased activity in 1 Group 3 female and 1 Group 4 female. No animal died or was sacrificed during the study.

Dermal observations:

The application site on each animal was examined daily for erythema, edema, desquamation, atonia, fissuring and eschar. The scale used to evaluate the severity of skin reactions was provided in Appendix C of the report (Appended page 1).

Results:

Dermal reactions are summarized in Table 7 from the report (Appended page 2). One Group 1 male had erythema and partial eschar on day 21; no dermal effects were observed in any other male.

One Group 2 female had slight erythema and edema, 2 Group 3 females had slight erythema and edema, 4 Group 4 females had slight erythema, 3 had slight edema and 1 had slight fissuring. No dermal reactions were seen in Group 1 and Group 5 females.

Body weight and food consumption:

Individual body weights were measured on days 1, 8, 15 and 22 (day of necropsy) and food consumption was measured weekly. Food was available ad libitum throughout the study, but was withheld prior to necropsy and blood collection for pre-study cholinesterase assays.

Results:

Body weights and food consumption were comparable between groups for both sexes throughout the study.

Cholinesterase assays:

Pre-test blood samples were obtained from an ear artery or vein for baseline serum/plasma and erythrocyte (RBC) cholinesterase analyses. Plasma, RBC and brain samples were collected at the termination of the study for analyses.

Results:

Decreases in plasma cholinesterase in 5 and 100 mg/kg/day males (29 and 27% below controls, respectively) were statistically significant (Appended pages 3, 4, 5 and 6; Table 8 from the report). The decrease at 5 mg/kg/day does not appear to be toxicologically significant since it was not part of a dose-response trend, one value (animal # 2915) was a low outlier and the mean pre-test value for this group was 11% below the corresponding control. Treatment-related RBC cholinesterase inhibition was seen in 10 mg/kg/day males (-35%) and females (-30%) and 100 mg/kg/day males (-37%) and females (-38%).

Clinical pathology:

Blood was collected from each rabbit on the day of scheduled sacrifice (day 22) for evaluation of selected hematology and clinical chemistry parameters. The animals were fasted overnight prior to blood sample collection. Blood samples were obtained via cardiac puncture. The following parameters were evaluated:

Hematology

Erythrocyte count
Hemoglobin concentration
Mean corpuscular hemoglobin (MCH)
Hematocrit
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin concentration (MCHC)

Platelet count
Total and differential leukocyte counts

Clinical chemistry

Albumin
Calcium
Glucose
Potassium

Sodium

Bilirubin (total & direct)
Urea nitrogen

Blood creatinine
Chloride
Phosphorous
Serumglutamic-oxaloacetic transaminase (aspartate aminotransferase) (AST)
Serum glutamic-pyruvic transaminase (alanine aminotransferase) (ALT)
Total serum protein

Results:

Hematology

Sporadic statistically significant changes in hematologic parameters noted in the report do not appear to be treatment-related. Decreases in segmented neutrophils in Group 2, 4 and 5 females were not dose-related and the p-value was probably influenced by two high individual control values. Increased eosinophils in Group 3 and 5 males appeared to be due to 2 high values in Group 5, 1 in Group 3 and 4 relatively low control values. The small number of animals per group must also be considered in these pairwise comparisons. Also, the investigator did not analyze pre-test blood samples to generate baseline data which could have been used for an additional comparison.

Clinical chemistry

The reported statistically significant changes in the investigated parameters do not appear to be treatment-related. Decreased chloride in Group 4 males, increased chloride and sodium in Group 4 males and increased phosphorous in Group 4 & 5 females were not dose-related changes. Increased AST and ALT in Group 5 females (not statistically significant) were due to increased values in one animal (# 2949); this animal did not have any noteworthy histopathologic changes reported for the liver.

Necropsy:

A gross necropsy on day 22 included the following: all orifices, carcass, cranial cavity, external and cut surfaces of the brain, external surfaces and all viscera and glands.

Organ weights were obtained for the brain, kidneys, liver, testes without epididymides and ovaries of all animals; paired organs were weighed together.

The following organs and tissues from each animal were preserved in 10% neutral buffered formalin: gross lesions, kidneys, liver, gonads, treated skin and untreated skin.

Results:

Gross necropsy

The gross observations reported do not appear to be treatment-related (Appended page 7; Table 11 from the report): kidney foci in 1 Group 1 male, 1 Group 2 female and 2 Group 4 females. A mottled red and tan caudate lobe of the liver was reported in 1 Group 5 female; the report author indicated that this liver appeared to have undergone torsion.

Organ weights

Neither the absolute nor relative organ weight data showed a treatment-related effect.

Histopathology:

The liver, kidneys, treated skin and untreated skin from control and high-dose animals and the gross lesions from rabbits in all groups were examined microscopically.

Results:

The reported histologic changes did not appear to be associated with treatment (Appended pages 8 & 9, Table 14 from the report). Foci of chronic inflammation of the kidneys were reported in 2 Group 1 males, 1 Group 5 male, 1 Group 2 female and 2 Group 4 females. One Group 5 female had local renal inflammation. The investigator indicated that the foci of chronic interstitial renal inflammation, typical of Encephalitozoon cuniculi infection, were characterized by focal interstitial infiltrates of macrophages, lymphocytes, some plasma cells and fibrocytes, and occasional heterophils. These foci were primarily seen in the renal cortex, but some were also seen in the medulla.

Minimal to mild hepatic extramedullary hematopoiesis was reported in 5 Group 1 males, 4 Group 5 males and 3 females each in Groups 1 and 5. The report indicated that this observation was typified by primarily periportal or centrilobular accumulations of hematopoietic cells of all series, but primarily heterophils.

The 1 Group 5 female, in which a mottled red and tan caudate lobe of the liver was noted above under gross necropsy, had mild to moderate centrilobular necrosis and chronic inflammation, which was associated with torsion of that liver lobe by the investigator.

DISCUSSION AND CONCLUSION

Methyl parathion was evaluated in a 21-day dermal toxicity study in rabbits at dosages of 0, 1, 5, 10 and 100 mg/kg/day.

There were no mortalities or clinical signs of toxicity during the study. No adverse effects were apparent based on body weight, body weight gain, food consumption, clinical pathology parameters or organ weights. Histopathologic evaluations of the kidneys, liver and skin from high-dose rabbits did not reveal any treatment-related effects.

No dermal effects were seen in treated males, however, slight erythema and edema was induced in Group 2, 3 and 4 females; 1 Group 4 females also had slight fissuring. The severity of these reactions did not increase with dosage. No dermal reactions were reported in Group 5 females. Although no dermal effects were seen in treated males, the noted effects in females obviates the establishment of a NOEL for local dermal toxicity in this study.

Treatment-related RBC cholinesterase inhibition was seen in Group 4 and 5 males and females.

The LOEL for systemic toxicity was 10 mg/kg/day based on RBC cholinesterase inhibition in both sexes and the NOEL was 5 mg/kg/day under the conditions of this study.

A definitive NOEL for local dermal toxicity could not be determined in this study.

Core classification: supplemental. This study does not satisfy guideline requirements for a 21-day dermal toxicity study (82-2). This study may be upgraded when the registrant provides the purity of the test material.

Page _____ is not included in this copy.

Pages 11 through 19 are not included in this copy.

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