DATA EVALUATION RECORD

1. CHEMICAL: Methyl Parathion (MP)

2. FORMULATION: MP (94.32% A. I.)


4. REVIEWED BY: Gerald M. Marquardt, Ph.D. Pharmacologist, EPA
   Signature: [Signature]
   Date: 3/31/82

5. APPROVED BY: Christine F. Chaissen, Ph.D. Section Head, EPA
   Signature: [Signature]
   Date: 3/31/82
6. **TOPIC:** This study has information pertinent to Discipline Toxicology. 
   Topic: Subchronic Oral Toxicity.

This study relates to the Proposed Guidelines data requirement 163.82-1.

7. **CONCLUSION:** Beagle dogs (four animals/sex/treatment group) were fed 0.0, 0.3, 1.0 or 3.0 mg/kg/d X 90 days MP in this study. All dogs survived this experiment. The food consumption and the body weight of the treated animals were not significantly different from those of control. Fasting blood sugar (FBS), blood urea nitrogen (BUN), Serum Glutamic Oxaloecetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Gamma Glutamyl Transpeptidase (GGTP), and Serum Alkaline Phosphatase (SAP) had unremarkable activities at various times in the different treatment groups.

Plasma ChE levels were significantly lower than control for high-dose animals (at 13 weeks). Red blood cell (RBC) ChE activities were significantly reduced in high-dose animals (at 6 and 13 weeks) and in mid-dose animals (at 13 weeks). Brain ChE levels were significantly reduced in high-dose animals (at 13 weeks).
RBC counts, hemoglobin (HGB) levels, hematocrits (HMCT), white blood cell (WBC) counts, WBC differential counts, RBC and WBC morphologies, and platelet estimates were similar in all of the animals throughout this study.

The appearance, specific gravity, pH, protein content, sugar content, RBC/h.p.f., and WBC/h.p.f. were similar in the urines of control and treated animals at all times.

The weights of the thyroid glands, heart, spleen, liver, kidneys, brain, and the gonads were similar for all treated and control animals. The weight of pituitary glands was statistically higher in high-dose females; histopathologic examination of the pituitary glands of these animals revealed no abnormalities. The organ weights were similar in all control and treated animals.

Gross and microscopic examinations of all animals (at necropsy) revealed no compound-related abnormalities.

8. MATERIALS AND METHODS:

Test Substance: MP (94.32% A.I.) was mixed with Wayne Dog Food (meal form) for administration to test animals. Food consumption was measured daily and water was administered ad libitum.
Organism: Purebred beagle dogs (4 animals/sex/treatment group; 4.5-8.0 kg in weight; approximately four months of age) were used in this study. Four animals/sex were used in each treatment group; these animals received either 0.0, 0.3, 1.0 or 3.0 mg/kg/d x 90 days MP during this experiment.

Experimental Procedure: SGPT, BUN, FBS, SAP, and GGTP levels were analyzed on an Abbott Bichromatic Analyzer 100 for all blood samples (the volume and source of these samples were not described) before testing, at 6 weeks, and at the termination of this study. All animals were fasted 24-36 hours prior to the collection of blood samples.

Plasma, RBC and brain ChE activities were determined colorometrically by accepted procedures. ChE activities in plasma and in the RBC samples (the volume and the source of these samples were not described) were determined (after 24-36 hours of fasting) at 0, 6, and 13 weeks. Brain (the source and weight of these samples were not described) ChE activities were determined (after 24-36 hours of fasting) at the termination of this study.

The following hematological parameters were examined for all animals at weeks 0, 6 and 13: RBC and WBC counts (determined in a Coulter Counter), WBC Differential Counts (determined in a Coulter Counter), HMCt (determined in an International Micro-Hematocit Centrifuge), and HGB levels (determined spectrophotometrically). The volume and the source of these samples were not described.
Urine samples (volume not specified) were obtained in metabolism cages from all animals at 0, 6 and 13 weeks. Urine samples were examined for color, appearance, pH, specific gravity, protein content, sugar content, RBC/h.p.f. and the WBC/h.p.f. All analyses were done by accepted procedures.

The following organs were removed and weighed at necropsy: thyroid glands, heart, spleen, liver, kidneys, adrenal glands, gonads, pituitary gland, and the brain.

At the termination of this study all dogs were euthanized with Somlethol (i.v. administration) after 24-36 hours of fasting and subsequently necropsied. The skin, eyes, tongue, mammary glands, skeletal muscle (lumbar vertebrae), bone marrow, salivary glands, lymph nodes, thyroid glands, trachea, urinary bladder, esophagus, aorta, thymus, heart, liver, kidney, adrenal glands, spleen, pancreas, stomach, intestines, gall bladder, prostrate, uterus, gonads, pituitary gland, brain, spinal cord, and peripheral nerve (sciatic nerve). The tissues were then embedded in paraffin stained with hematoxylin and Eosin, and were examined microscopically.

Statistical Analysis: Data were analyzed using the Student's t-test.
Results: All dogs survived this study. Some dogs (from all treatment groups) displayed loose stools and some dogs vomited at one time or another. The pulse rate and the pupillary diameter (both determined at the start and end of testing) were similar for all dogs. The pulse rate of high-dose female dogs (at 13 weeks) was, however, significantly ($p \leq 0.05$) reduced; the mean pulse rate of these animals was 121 compared to 161 for control animals. The authors of this study consider this to be of no biological significance; no explanation of this belief is provided.

Food consumption and the body weight of all treated animals were similar to the food consumption and the body weight of control animals at all times.

The FBS levels of high-dose animals (at week 0) and of high-dose males (at 13 weeks) were significantly lower than control. The authors attribute this to the fact that some dogs were fasted for longer than 24 hours prior to sacrifice; their explanation seems reasonable. The BUN of mid-dose females (at 6 weeks) was significantly higher than control. One of these animals had an extremely elevated BUN (31.5 mg%); histological examination of the urinary system of this animal, however, yielded normal results. SGOT values in the low-dose and the mid-dose males (at week 0) and the low-dose and the high-dose females (at weeks 0 and 6) were significantly lower than control.
Several dogs (in all treatment groups) had low SGOT values at 13 weeks; histological examinations revealed no hepatic damage. SGPT values of mid- and high-dose males (at 13 weeks) and the high-dose females (at 13 weeks) were significantly lower than control. GGTP values were similar for all treated and control animals at all times. SAP values were significantly reduced in mid-dose males (at 6 weeks) and in the high-dose females (at 13 weeks).

Plasma ChE activities were significantly lower in mid-dose males (at 13 weeks) and in the high-dose animals (at 6 and 13 weeks) [see table below]. RBC ChE activities were significantly depressed in high-dose animals (at 6 weeks) and in the mid-dose animals (at 13 weeks) [see table below]. Brain ChE activities were significantly reduced in high-dose animals (at 13 weeks) [see table below].

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a. MP was administered in the diet at 0.0, 0.3, 1.0, or 3.0 mg/kg/d for 13 weeks; ChE activities were determined in plasma, RBC, and brain samples (see the appropriate section of the Materials and Methods section of this DER for details).

b. These values indicate length of time (weeks) during which the animals were fed diets containing the appropriate amount of MP.

c. These values represent the mean (N=4) ChE activities for the appropriate samples [see the appropriate section of this DER for further details]. Results are expressed in terms of IU/ml for plasma and RBC ChE activities or IU/g for brain samples.

d. Significantly different from control (p ≤ 0.05).

RBC counts were normal for all animals; two male dogs [one control animal and one mid-dose animal (at 13 weeks)] had RBC counts of 4.6-4.9 million cells/mm³ (control RBC counts were 5.0-8.5 X 10⁶ cells/mm³) were histologically normal, however. HGB concentrations were normal for dogs at 0, 6, and 13 weeks; a couple of high-dose male dogs, 1 low-dose female dog (at 0 weeks) and 1 mid-dose female dog (at 13 weeks) had abnormal HGB concentrations, but this did not appear to be related to the administration of MP. HMCT values were similar for all dogs at 0, 6, 13 weeks. Low-dose males (at 6 weeks), and high-dose females (at 0 weeks) had significantly (p ≤ 0.05) reduced WBC counts.

Histological examinations revealed no abnormalities. All dogs displayed normal polymorphonuclear leukocyte-lymphocyte (WBC Differential Count greater than 1 at all times).
RBC morphologies were normal for all dogs; one control dog, one low-
dose dog, two mid-dose dogs, and 1 high-dose dog displayed mild
hypochronia and anisocytosis at week 0 and the high-dose dogs also
displayed these findings at 6 weeks. Platelet examinations revealed no
abnormalities for any dogs at any time.

The color, appearance, pH, and specific gravity of urine samples were
normal for all dogs at all times. No dogs displayed proteinuria,
hematuria, or glucosuria during this study. One high-dose female
displayed trace glucosuria and one mid-dose animal (at 0 weeks) and 1
high-dose animal (at 6 weeks) had significantly elevated WBC/h.p.f.
values. Histological examinations revealed no abnormalities in any of
the treated or control animals.

Organ weights and organ/body weight ratios were similar for all
animals; the pituitary gland of high-dose females weighed more than
control but histological examination revealed no abnormalities.

Gross and microscopic examinations of all animals were unremarkable.

10. DISCUSSION: MP administration to beagle dogs (0.3, 1.0, or 3.0
mg/kg/d x 90 days) produced significant decreases in plasma, RBC, and
brain ChE activities. Plasma ChE activities were significantly reduced
in high-dose animals (at 6 and 13 weeks) and mid-dose males (at 13
weeks). RBC ChE activities were significantly depressed in high-dose
animals (at 6 and 13 weeks) and mid-dose animals (at 13 weeks). Brain
ChE activities were significantly lower than control in high-dose
animals (at 13 weeks).
11. Discussion:
   This study demonstrates the following NOEL's:
   ....for plasma ChE at 13 weeks - 0.3 mg/kg/d
   ....for RBC ChE at 13 weeks - 0.3 mg/kg/d
   ....for brain ChE at 13 weeks - 1.0 mg/kg/d

12. CORE score - Core Guideline