RDCoberly:hjc
August 28, 1968

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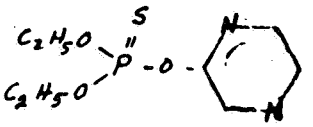
Chemical Name	:	O,O-Diethyl, O-2-pyrazinyl phosphorothioate
Trade Name	:	Cynem and Zinophos
Chemical Structure	:	
Empirical Formula	:	$C_8H_{13}N_2O_3PS$
Molecular Weight	:	248
Physical State	:	Liquid
Melting Point	:	-1.69°C
Solubility	:	Soluble in water and miscible with alcohols, ketones, and aromatic hydrocarbons.
Vapor Pressure	:	0.003 mm at 30°C
Purity	:	95% Technical grade
Use	:	Nematocide and soil insecticide
Company	:	American Cyanamid Co.

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COMMENTS

These data indicate this chemical to be extremely toxic by the various routes of administration. Accordingly the technical material and formulations containing approximately 10% of the technical material or greater should bear category 1 warnings. This product should not be used in or around the home.

The data reviewed did not include an antidote study, an eye study, an inhalation study, nor a demyelination study.

Acute Rat Oral (Tech)	:	LD_{50} = 12 mg/KG
Acute Cavy Dermal (Tech)	:	LD_{50} = 10 mg/KG
(5% Granular)	:	LD_{50} = 80 mg/KG as forumulation or 4 mg/KG of active ingredient.
(10% Granular)	:	LD_{50} = 45 mg/KG as formulation or 5 mg/KG of active ingredient.
Acute Rat Dermal (Tech)	:	LD_{50} = 11 mg/KG
Thirty-one Day Rat Feeding (Tech)	:	Levels tested were 0.2, 1.0, and 5.0 ppm (equivalent to 0.01, 0.09 and 0.46 mg/KG/day). No deaths were noted. Slight Ch.I. noted at 5.0 ppm. No effect level is 1.0 ppm.
90 Day Rat Feeding	:	Levels tested were 0.5, 2.0, 8.0, and 50 ppm. Weight inhibition Ch.I. noted at 50 ppm. Ch.I. also noted at 8.0 ppm. No effect level is approx. 2.0 ppm.
90 Day Dog Feeding	:	Levels tested were 0.5, 2.0, 8.0 and 25 ppm. Body weight loss at 25 ppm. Slight body weight loss at 8.0 ppm. Ch.I. at 2.0, 8.0 and 25 ppm. All animals at 25 ppm were anemic. No effect level is approx. 0.5 ppm.
14 Day Rat Dermal (Tech)	:	Levels tested were 2.5 and 5.0 mg/KG/day. Body weight gain inhibition noted at 5.0 mg/KG/day. Organ weights also affected at 5.0 mg/KG.

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Acute Rat Oral (Tech)

10 animals were tested per dosage level of 5, 10, 20, and 40 mg/KG.

Results

The acute oral LD_{50} = 12 mg/KG with a range of from 9-16 mg/KG.

Acute Cavy Dermal

This study was conducted with the technical material and 2 formulations 5% and 10% granular. The technical was applied as a solution in [redacted] The solid formulations were wetted with just sufficient water to form a paste. Length of contact was 24 hours. The area between the shoulder blades of each animal was closely clipped.

Results

The technical material had an LD_{50} equal to 10 mg/KG. The 5% granular formulation had an LD_{50} equal to 80 mg/KG (equal to 4 mg/KG of active ingredient). The 10% granular formulation had an LD_{50} equal to 45 mg/KG (equal to 5 mg/KG of active ingredient).

Acute Rat Dermal (Tech)

5 animals were tested per dosage level of 5, 10, 20, and 40 mg/KG. The test material was applied to the clipped area on each side of the dorsal mid line of each rat.

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Results

LD_{50} = 11 mg/KG with a range of from 8-15 mg/KG.

Thirty-one Day Rat Feeding (Tech)

10 rats were tested per dosage level of 0.2, 1.0, and 5.0 ppm (equivalent to 0.01, 0.09, and 0.46 mg/KG/day).

Results

No deaths occurred during this period and the appearance and behavior of all animals were normal. At autopsy no significant pathology was observed.

From blood which was drawn by heart puncture when the animals were sacrificed it was determined that no depression of mean cholinesterase activity was noted at the 0.2 and the 1.0 ppm level. A slight depression of plasma and erythrocyte cholinesterase activity was noted at the 5 ppm level. On this basis the no effect level is approx. 1.0 ppm.

90 Day Rat Feeding

30 males and 30 females were tested per dosage level of 0.5, 2.0, and 8.0 ppm. The high dosage level employed only 10 males and 10 females at 25 ppm for the first 4 weeks then it was raised to 50 ppm for the remainder of the study.

Results

Both male and female rats receiving the 50 ppm diet exhibited a moderate growth depression during the study. This effect became apparent after the 4th week of testing when the dietary

dosage level was increased from 25 to 50 ppm. Food consumption data was comparable. No mortalities or abnormal behavior were noted among the test animals. The hematologic studies and urine analysis were within normal limits.

Significant depressions in plasma and erythrocyte cholinesterase activity were observed in the rats receiving 8.0 ppm. The animals receiving the dietary level of 50 ppm showed significant cholinesterase depression of the plasma, e-ythrocyte and brain cholinesterase activity.

The microscopic examination of the adrenal gland, urinary bladder, brain, heart, small and large intestine, kidney, lung, liver, lymph node, ovary, pancreas, pituitary, prostate, seminal fesicle, skeletal muscle, spleen, stomach, testes, thyroid gland, trachea and uterus showed no adverse findings which were attributable to the ingestion of the test material.

90 Dat Dog Feeding

2 males and 2 females were tested per dosage level of 0.5, 2.0, 8.0, and 25 ppm (the 50 ppm was reduced to 25 ppm at 4 weeks).

Results

All dogs receiving the high dosage level exhibited a considerable weight loss during the test period. The majority of this weight was lost during the first 4 weeks of the study when the high dosage level was 50 ppm. When this was reduced from 50 to 25 ppm at 4 weeks the animals showed an increase in food

consumption but not in body weight. The dogs in the 8.0 ppm level showed a very slight body weight loss during the first several weeks of the study.

1 death occurred at the high level at 28 days. Death was due to inanition.

Hematologic studies and urine analysis did not indicate any abnormalities. The results of blood glucose, blood urea nitrogen and serum alkaline phosphatase determinations did not indicate any abnormalities. Liver function tests did not indicate any organ dysfunction.

A marked depression in plasma and erythrocyte activity was noted among the animals in the 2 highest dietary levels. The animals receiving 2.0 ppm exhibited border line effects. No depression in either plasma or erythrocyte cholinesterase activity was noted in the animals receiving the dietary level of 0.5 ppm.

At this point the study contradicts itself and states that all surviving dogs in the 25 ppm level and 1 female controlled dog were anemic. This begins to appear more logical as other evidence of anemic animals was noted throughout other studies with this chemical.'

Brain cholinesterase activity was depressed among the dogs receiving the dosage level of 25 ppm.

The results of the microscopic examination conducted on the 7

tissues and organs from the surviving animals receiving the dietary level of 25 ppm did not reveal any histopathologic changes which could be correlated with ingestion of the test material.

14 Day Rat Dermal (Tech)

10 males and 10 females were tested per dosage level of 2.5 and 5.0 mg/KG/day. The skin on the back of 1/2 of the animals was abraded prior to dosing and every other day there on out.

Results

Compared to their controls the 5 mg/KG abraded skin and the 2.5 mg/KG intact skin males had significant decreases in mean weight gain. At this point the report states that since the 5 mg/KG intact skin males do not differ significantly from their controls it is concluded that the decrease at 1/2 that level is coincidental and unrelated to treatment. I disagree with this because while the inhibition of body weight gain of the 5 mg/KG males was not significant it was sufficiently high enough to indicate a compound effect. In actual terms of value these animals showed a 16.5% reduction in body weight gain as compared to the abraded animals which showed a 22.5% reduction in body weight gain. In further support of this it should be noted that the females of the 5 mg/KG level both showed significant reduction in body weight gain.

All the animals receiving the 2.5 mg/KG level showed an inhibition in body weight gain. As indicated above only the 2.5 mg/KG intact males showed a significant decrease. The abraded

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males at this level showed a 7.5%reduction and the intact skin females showed a 13.8% reduction and the abraded females showed a 11.4% reduction in body weight gain.

With the exception of the 2.5 mg/KG intact female and the 2.5 mg/KG abraded male the animals showed a reduction also in food consumption. A reduction in food utilization was also noted for each test group.

Comment - It appears that the inhibition of body weight gain for the majority of the animals is due at least in part to a corresponding reduction in food consumption.

Significant increases in mean kidney weight, expressed as % of body weight, occurred among intact and abraded skin females receiving 5 mg/KG. A significant decrease in mean liver weight was found for abraded skin males receiving 2.5 mg/KG. Since no difference was noted between control and 5 mg/KG males, the apparent increase at the lower dosage level was judged to be unrelated to treatment.

Both groups of females at the 5.0 mg/KG level had significant increases in mean kidney weight. No significant difference in mean kidney weight occurred between the 2.5 mg/KG females and the control females. No significant differences in mean kidney weight was observed between any of the male animals.

Under microscopic examination no significant lesions were noted at the high level.