UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

900 AH

DATE: May 23, 1979

SUBJECT: LARVIN 500 Insecticide; PP#9G2152; Requested tolerances for ethanimidothioic acid and its metabolites at 0.1 ppm in or on soybean straw and 0.4 ppm in or on cotton. EPA Reg.#1016-EUP-LE

FROM: William Dykstra, Ph.D
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Toxicology Branch (TS-769

TO: Frank Sanders
Product Manager#21

WSW WHR 6/18/79

Registrant: Union Carbide Corporation
Agricultural Products Division

Recommnedations:

1. The EUP and proposed tolerances are not toxicologically supported. In order to evaluate the human hazards from exposure to the product, the following toxicology studies are required.

I: With techical UC51762

(a) teratology - 2 species
(b) delayed neurotoxicity - 1 species (hens)
(c) oral LD50 - female rats
(d) dermal LD50 - rabbits (both sexes)
(e) primary skin irritation - rabbits
(f) primary eye irritation - rabbits

II: With formulated product

(a) oral LD50 - rats (both sexes)
(b) dermal LD50 - rabbits (both sexes)
(c) inhalation LC50 - rats (both sexes)
(d) primary eye irritation - rabbits
(e) primary skin irritation - rabbits
(f) skin sensitization - guinea pigs

2. The inert ingredient [redacted] has not been cleared for agricultural use.

Review

Active ingredient: Dimethyl N,N[1]-[thiobis[(methylimino)carbonyloxy]]bis[ethanimidothioate], 44%; inerts - 56%

Contains 500g active/L

Spontaneously reversible AChE.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Larvin 500 is an aqueous flowable product diluted with H_2O for application by ground or air spraying. Only for commerical usage. Apply when insects first appear and repeat as needed at 5-7 day intervals. Air application: 3-5 gals./acre

Cotton - Don't apply less than 7 days before harvest. Forage not fed to livestock.

Soybeans - Don't apply less than 28 days before harvest.

Application rates: cotton - 11-29 (.33 - .9 lbs active) ozs./acre; soybeans-7.5 - 15 (.23 - .45 lbs active) ozs./acre

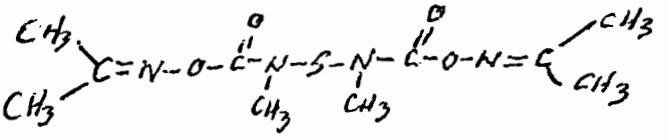
Chemistry

Common Name: not available

Chemical Name: Ethanimidothioic acid, N,N[1]-[thiobis[(methylimino)carbonyloxy]]bis-dimethyl ester

Synonyms: U 51762

Structure:



Mol. Weight: 354.5

Physical/Chemical Properties of Pesticide Chemical

Appearance - white, crystalline powder with slightly sulfurous odor

Melting Point: 173-174°C

Vapor pressure - 4.3 X 10^{-5} mm Hg at 20°C; 1.1, 3.2, 5.2 X 10^{-4} mm Hg at 35, 45, 55°C, respectively.

Solubility at 25°C:

Solvent	% Solubility
Acetone	0.8%
Acetonitrile	2.0%
Ethyl acetate	0.2%
Ethyl ether	0.1%
Methanol	0.3%
Methylene chloride	15%
Water	approx. 35 ppm
Xylene	0.3%

Stability: Stable in light & ambient conditions, unstable in alkaline conditions.

Hydrolytic stability - Hydrolysed in acid in or basic condition. Main degradation product is methomyl which

hydrolyzes further in basic medium to S-methyl thioacetohydroximate.

Density at 20°C - 1.4424 g/ml

pH: 1 g/100 ml H_2O produces a pH of 6.65 at 21.5°C

Composition of Technial - technical is a solid

Components	% by Weight
UC 51762	97% min.
[redacted]	

Composition of Formulation

Components	% by Weight
UC 51762 Tech.	44.0
[redacted]	

Chemical/Physical Properties of Formulation:

Solubility: Soluble in water, insoluble in kerosene, xylene, HAN

pH; 4.4

Specific gravity at 20°C & 7 weeks at 50°C

Analysis: [redacted]

Hazard Evaluation of Larvan 500 Insecticide (UC 51762) studies submitted by Union Carbide Corp., 11/16/78, Acc. No. 097646 bis-1-Methylthioacetaldehyde-O-(N-methylcarbamoyl)oximino-sulfide

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IMPURITY AND INERT INGREDIENT INFORMATION ARE NOT INCLUDED

I. Acute Toxicity Studies of UC 51762 in Rats & Rabbits (Carnegie-Mellon Institute of Research, 5/9/75, Report No. 38-55).

A. Oral LD50 Study in Rats. Report No. 38-55).

Test Material: technical

1. Procedure

Twelve Wistar male rats, 90-120g, were divided into 3 groups of 4 animals each which were administered 80.0, 160.0, or 320.0 mg/kg of test substance by gavage. Observations for mortality, toxic signs, and body weight changes were made during 14 days post-treatment. Necropsies were done.

2. Results

a) Mortality: LD50 = 160 (98.1 - 261) mg/kg
b) Toxic Signs: Tremors
c) Body Weight Changes: Unremarkable
d) Necropsy:

i) Survivors: Unremarkable
ii) Decedents: Slight petechiae hemorrhages in lungs, speckled and slightly congested kidneys, stomach filled with liquid, slightly yellow intestines.

3. Conclusions

a) Classification: Supplementary Data

i) The effect of the test material was not evaluated in female rats. Further testing in males is not necessary.

b) Tox. Cat.: II

B. Acute Dermal LD50 Study in Rats. Report No. 328-55, Document#1

Test Material: technical

1. Procedure

Six male albino rats, 176-199g, were divided into 2 groups of 4 and 2 animals each which received dermal appliations of 1600 and 400 mg/kg of test material, respectively, under occlusive dressing. Abraded test sites were not used. Dressing was removed at 4 hours following appliation. Animals were observed for mortality, toxic signs, and body weight changes during 14 days post-treatment. Necropsies were done.

2. Results

a) Mortality: LD50 $>$ 1600 mg/kg

b) Toxic Signs: Tremors
c) Body Weight Changes: Dose-related reduction in gain.
d) Necropsy: Mottled livers, pink pylorus, yellow and gas-filled intestine.

3. Conclusions

a) Classification: Supplementary Data

i) Only a 4-hour instead of a 24-hour exposure period was used.
ii) Only male rats were used.
iii) It is clear why only 2 animals were used in the 400 mg/kg dosage group. Neither of these died, but 1/4 animals in the 1600 mg/kg group died.
iv) Abraded test sites were not used.

b) Tox. Cat.: Cannot be determined at this time.

C. Acute Inhalation LC50 Study in Rats. Report No. 38-55, Document#1

Test Material: technical

1. Procedure

Six rats, weights, sex, and strain unspecified, were placed into a 60 L inhalation chamber and were exposed for 148 min. to 2000 mg/m^3 of test material generated as an aerosol, 13% w/w in dimethyl sulfoxide. Observations for mortality, body weight changes, and toxic signs were continued during 14 days post-exposure. Necropsies were done.

2. Results

a) Mortality: None. LC50 $>$ 2000 mg/m^3. 148 min.
b) Toxic Signs: Salivation, tremors, gasping, prostration during exposure.
c) Body Weight Gain: 27-58g
d) Necropsy: Unremarkable

3. Conclusions

a) Classification: Core-Minimum Data

i) Although only 6 animals of unspecified weight and sex were used, the high concentration of test material and duration of exposure use allows an adequate definition of the relative inhalation toxicity.

b) Tox. Cat.: III (2000 mg/m^3 or 2000 mg/L)

D. Primary Skin Irritation Study in Rabbits. Report No. 38-55, Document#1

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Test Material: technical

1. Procedure

Onto uncovered intact skin of each of 5 rabbits was applied 0.01 ml of test material in methyl phthalate. Skin irritation was evaluated during the 24 hours post-treatment.

2. Results

Skin Irritation: Unremarkable in 4 rabbits, moderate capillary injection on 1 from 1&2 w/v in DMP.

3. Conclusions

a) Classification: Invalid Data

i) It appears that the animals were exposed to a solution of test material. The skin irritation test should be done only with undiluted test material. Furthermore, the dilution is not clear.

b) At least 0.5g (solids) or 0.5 ml (liquid) of test material should be applied.

c) Test sites must be covered during the 24-hour exposure period.

d) Driaze scoring as apparently not used.

ii) Irritation should be evaluated at least 24 and 72 hours post-treatment.

b) Tox. Cat.: Cannot be determined at this time.

E. Primary Eye Irritation Study in Rabbits. Report No. 38-55, Document#1

Test Material: technical

1. Procedure

Into rabbit eye was placed either 40 mg of solid test material or a H2W/V dilution in dimethyl phthalate (0.5 ml). Eyes were examined by fluorescein staining at 24 hours post-treatment.

2. Results

Eye Injuries: Minor corneal injury from solid material, trace injury from diluted material.

3. Conclusions

a) Classification: Invalid Data

i) Numbers of test animals/exposure group were not indicated.

ii) At least 50 mg of solid test material should have been instilled.
iii) Injuries should have been scored at least through 7 days post-treatment according to the method of Draize et al. (1944).

b) Tox. Cat.: Cannot be determined at this time.

F. Acute LD50 Study of UC 51762 in Mice (Carnegie-Mellon Institute, Report No. 40-6, 1/20/77). Document#1

Test Material: technical

1. Procedure

Twelve mice, unspecified strain and weight, were divided into 3 groups of 14 mice each which were given 80, 160, or 320 mg/kg of test material by gavage in corn oil. Observations for mortality, toxic signs, and body weight changes were made during 14 days post-treatment. Necropsies were performed.

2. Results

a) Mortality: LD50 = 226 (148 - 346) mg/kg
b) Toxic Signs: Salivation, tremors, sluggishness.
c) Body Weight Changes: No remarkable gain or loss; stayed constant.
d) Necropsy:

i) Decedents: Mottled livers and spleen, speckled and congested kidneys gas-or liquid-filled stomachs, distended intestines also liquid-filled and yellow, slightly congested adrenals.

ii) Survivors: Unremarkable

3. Conclusions

a) Classification: Supplementary Data

i) Sex and initial weights of the mice are not clear. The effect of test material on both male and female mice should have been evaluated.

b) Tox. Cat.: II (Provisional)

G. Acute Inhalation LC50 Study of UC 51762 in Rats (Carnegie-Mellon, Report No. 40-61, 5/17/77). Document#3

Test Material: technical

1. Procedure

Twelve rats, sex and weights unspecified, were divided into 2 groups of 6 animals each which were placed into a 120 L inhalation chamber and were exposed for 4 hours to either 190n or 340 mg/m^3 of test material generated as a dust. Dust concentration was estimated gravimetrically every half hour. Observations for mortality and toxic signs were made during 14 days post-exposure. Necropsies were done.

2. Results 2/6 at 190, 6/6 at 340

a) Mortaliry: LC50 = 220 (150 - 320) mg/m^3, 4 hours
b). Toxic Signs: Tremors, salivation, lacrimation, bulging eyes, gasping during exposure, poor coordination. Effects on body weights were not reported.
c) Necropsy:

i) Decedents: Congested to hemorrhaged lungs, froth in tracheae

ii) Survivors: Unremarkable

3. Conclusions

a) Classification: Supplementary Data

i) The sex and initial weights of the animals is not clear. Effects on both 5 male and 5 female rats should have been evaluated to more conclusively define the acute inhalation LC50. The 220 mg/m^3 is borderline between Tox. Cat. I and Tox. Cat. II.

b) Tox. Cat.: II (200 mg/m^3 220 ug/L) (Provisional)

H. Acute Oral LD50 Study in Guinea Pigs (Carnegie-Mellon, Report No. 40.142, 10/3/77). Document#4

Test Material: technical

1. Procedure

Fifteen albino male Hartley guinea pugs, 870-1316g, were separated into 3 groups of 5 animals each which were given 80, 160, or 320 mg/kg of test material in corn oil by gavage. The animals were previously used for a sensitization test with no sensitization resulting. Animals were observed for mortality, toxic signs, and bodyw eight changes for 2 weeks post-treatment. Necropsues were done.

2. Results

a) Mortality: LD50 = 160 (94.3 - 271 mg/kg)
b) Toxic Signs: Wet fur, no water consumption over 3 days.
c) Body Weight Changes: Loss of 20 to 77g in all survivors.
d) Necropsy:

i) Survivors: Injected and liquid-filled stomachs and intestines.

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ii) Decedents: Wet fur, petechiae to diffuse hemorrhages in lungs, mottled livers with prominent acini, pale, mottled, slightly congested kidneys, distended gas-and liquif-filled stomachs injected, pink, transparent stomach and intestines.

3. Conclusions

a) Classification: Supplementary Data

i) The results adequately show the acute oral toxicity of the test material in males; however, female animlas also should have been evaluated in the study.

b) Tox. Cat.: II (Provisional)

I. Acute Toxicity Studies with UC 51762 in Rats (Carnegie-Mellon, Report No. 41-25, 2/15/78). Document#5

Test Material: technical

1. Procedure

Thirty Wistar male rats, 90-120g, were divided into 6 groups of 5 animals each which were given either (a)80, 160, or 320 mg/kg of fresh test material or (b)80, 160, or 320 mg/kg of test material held 24 hours before dosing by gavage. Test material was delivered as a suspension in corn oil. Observations for mortality, toxic signs, and body weight changes were continued over 14 days post-treatment. Necropsies were done.

2. Results

Fresh test material

a) Mortality: 171(116 to 254) mg/kg
b) Toxic Signs: Tremors
c) Body Weight Changes: Unremarkable
d) Necropsy:

i) Decedents: Petechiae in lungs, slightly congested kidneys, distended, transparent, and liquid-filled stomachs, liquid-filled, slightly injected, and pink intestines.
ii) Survivors: Unremarkable

24-Hour Preparation

a) Mortality: LD50 = 180 (83.7-386) mg/kg
b) Toxic Signs: Tremors, convulsions
c) Body Weight Changes: Dose-related reduction in gain.
d) Necropsy:

i) Decedents: Petechiae in lungs, mottled livers, pale, slightly congested kidneys, slightly congested adrenals, transparent, liquid-filled stomachs, opaque, injected, liquid-filled, pink intestines.
ii) Survivors: Prominent liver acini

3. Conclusions

a) Classification: Supplementary Data

i) The acute oral toxicity of the test material in males is adequately shown in the present study. However, effects in female rats should also have been evaluated.

b) Preparation of the test maaterial suspension 24 hours pre-dosing did not change the acute oral toxicity in rats.

c) Tox. Cat.: II (Provisional)

J. Acute Ihalation LC50 Study if UC 51762 in Rats. Report No. 41-25, Document#5

Test Material: technical

1. Procedure

Six rats, strain and weights unspecified, were placed into a 120 L inhalation chamber and were exposed to 2400 mg/m^3 of test material generated as a dust for 1 hour. Analytical concentrations of test substance were gravimetrically measured every half hour. Animals were observed for mortality, toxic signs, and body weight changes for 2 weeks post-exposure. Necropsies were done.

2. Results

a) Mortality: 5 deaths. LC50 > 2400 mg/m^3,/hour
b) Toxic Signs: Immediate mastication, gasping, salivation, clear nasal discharge, coordination loss.
c) Body Weight Changes: Gain of 47g.
d) Necropsy:

i) Survivors: Unremarkable
ii) Decedents: Congested livers, reddened lungs, gas-filled stomachs.

3. Conclusions:

a) Classification: Supplementary Data

i) Only 1 concentration level was used. Other exposure level should be used to better define the acute inhalational toxicity in rats.
ii) The sex and weights of the animals were not stated. Male and female rats should be used.

b) Tox. Cat.: III (2400 ug/L 2400 mg/m^3) (Provisional)

K. Acute Dermal Toxicity UC 51762 in Rabbits (Carnegie-Mellon, Report No. 41-93, 6/12/78). Document#6

Test Material: technical

1. Procedure

Seven male albino rabbits, 3-5 months old, received dermal applications of 3200 mg/kg of test material suspended in corn oil under occlusive dressing. Dressing and residual test material were removed at 24 hours post-application. Observations for mortality, toxic signs, and body weight changes were continued for 2 weeks post-treatment. Necropsies were done. No animals with abraded test sites were used.

c) Tox. Cat.: technical

J. Acute Inhalation LC50 Study of UC 51762 in Rats. Report#41-5, Document#5

Test Material: technical

1. Procedure

Six rats, strain and weights unspecified, were placed into a 120 L inhalation chamber and were exposed to 2400 mg/m^3 of test material generatied as a dust for 1 hour. Analytical concentrations of test subtances were gravimetrically measured every half hour. Animals were observed for mortality, toxic signs, and body weight changes for 2 weeks post-exposure. Nercopsies were done.

2. Results

a) Mortality: 5 deaths. LC50 $\angle$ 2400 mg/m^3,/hour
b) Toxic Signs: Immediate mastication, gasping, salivation, clear nasal discharge, coordination loss.
c) Body Weight Changes: Gain of 47g.
d) Necropsy:

i) Survivors: Unremarkable
ii) Decedents: congested livers, reddened lungs, gas-filled stomachs.

3. Conclusions

a) Classification: Supplementary Data

i) Only 1 concentrations level was used. Other exposure levels should be used to better define the acute inhalational toxicity in rats.
ii) The sex and weights of the animals were not stated. Male and female rats should be used.

b) Tox. Cat.: II (2400 ug/L 2400 mg/m^3) (Provisional)

K. Acute Dermal Toxicity UC 51762 in Rabbits (Carnegie-Mellon, Report No. 41-93, 6/12/78). Document#6

Test Material: technical

1. Procedure

Seven male albino rabbits, 3-5 months old, received dermal applications of 3200 mg/kg of test material suspended in corn oil under occlusive dressings. Dressing and residual test material were removed at 24 hours post-application. Observations for mortality, toxic signs, and body weight changes were continued for 2 weeks post-treatment. Neropsies were done. No animals with abraded test sites were used.

2. Results

a) Mortality: One death . LD50 = 3200 mg/kg
b) Body Weight Changes: Unremarkable
c) Toxic Signs: Unremarkable
d) Necropsy:

i) Decedents: Reddened lung and kidney sections, with mottled acini, injected intestines.
ii) Survivors: Mottled kidneys.

3. Conclusions

a) Classification: Supplementary Data
i) Only males were used. Corn oil as a diluent instead of saline.
ii) Animals with abraded test sites were not used.
iii) Body weights in conjunction with food intake were not determined daily.

b) Tox. Cat.: III

L. Seven-Day Feeding Study of UC 51762 in Rats (Carnegie-Mellon, Report No. 38-136, 11/7/75). Document#7

Test Material: technical

1. Procedure

Forty albino Harlan Wistar rats, 80-140g, divided into 4 groups of 10 animals each (5 males and 5 females) were given 0, 5, 25, or 100 mg/kg/day of test material in the diet for 1 week. Actual feeding levels were 5, 22, and 93 mg/kg/day. The animals were gang-caged (2-3/cages). Observations for mortality, toxic signs, and body weight changes were made during the feeding period. Livers and kidneys were weighed.

2. Results

a) Mortality: 1 female in the 100 mg/kg/day group died.
b) Food Consumption: Slightly lower in high-dose males.
c) Body Weight Changes: Significant reduction of gain in high-dose males.
d) Liver & Kidney Weights/Organ/Body: Unremarkable; however kidney/body weights were increased to the same degree in all treatment group males. Decreased liver weights in high-dose males.

3. Conclusions

a) Classification: Supplementary Data

i) The feeding period was only 7 days, and, thereafter, does not meet guidelines standards for feeding studies. Apparently a range finding study.
ii) Necropsies were not done.
iii) Only livers and kidneys were weighed.

b) The apparent NEL is 22 mg/kg/day (actual feeding levels).

M. Seven-Day Feeding Study of UC51762 in Rats (carnegie-Mellon Institute, Report No. 41-100, 6/19/78). Document#8

Test Material: technical

Fifty albino Wistar rats, 167-358g, divided into 5 groups of 10 animals each (5 males and 5 females) were given 0 (controls given stock diet only, 0 (controls given 1 ml acetone)/2.33g diet), 18.0, 55.0, or 165.0 mg/kg/dfay of test material in the diet for 7 days. Observations for mortality, toxic signs and body weight changes were made during the 7-day feeding period. Kidneys and livers were weighed at sacrifice. Animals were gang-caged (2-3 males & 5 females/cage).

2. Results

a) Mortality: No deaths
b) Toxic Signs: Unremarkable
c) Body Weight Changes: Dose-related reduction or loss weight in all dosage groups, males and females.
d) Food Consumption Data: Slight dose-related decreased in all treatment groups male and female.
e) Liver & Kidney, Organ/Body Weights: Decreased kidney & kidney/body. Decreased liver & kidney to body weights of similar magnitude in intermediate and high-dose males & females.

3. Conclusions

a) Classification: Supplementary Data

i) Feeding was only 7 days.
ii) Necropsies were not done.

b) Based on body weight changes, the NEL is 18.0 mg/kg/day.

N. Seven-Day Feeding Study of UC51762 in Mice (Carnegie-Mellon, Report No. 40-7, 1/24/77). Document#9

Test Material: technical

1. Procedure

Fifty CD-1 Charles River mice, 19-25g, divided into 5 groups of 10 animals each (5 males and 5 females) which were given 0 (2 control groups), 15, 45, or 90 mg/kg/day of test material in the diet for 7 days. Animals were observed for mortality, toxic signs and body weight changes during the feeding period. Livers and kidneys were weighed at sacrifice.

2. Results

a). Mortality: One high-dose female died due to technical error.
b) Toxic Signs: Unremarkable
c) Body Weight Changes: Unremarkable
d) Liver and kidney, Organ/Body Weights: Slightly increased kidney weights of similar magnitude in high - and intermediate - dose males vs. one of the two control groups.

3. Conclusions

a) Classification: Supplementary Data

i) Feeding was for 7 days.
ii) Necropsies were not done.

b) The NEL in this study appears to be 15 mg/kg/day. The kidney effects in males were not dose-related, and the difference was only against 1 of the 2 control groups.

O. Thirteen-Week Study of UC51762 in Rats (Carnegie-Mellon Institute, 4/6/78, Report No. 41-63). Document#10

Test Material: technical

1. Procedure

One hundred twenty Fischer 344 (COBS CD F/CrL BR) rats, 97.4-118.5g, were divided into 6 groups of 20 animals each (10 males and 10 females) which received 0 (controls), 0 (second control group), 1, 3, 10, or 30 mg/kg/day of test material in the diet for 13 weeks. The rats were housed (2/cage). Observations for mortality and toxic signs were made daily. Food consumption and body weights were determined weekly. Weekly water consumption was estimated monthly. Hematologic, clinical chemistry, and urine analyses and cholinesterase assays were done at the termination of the 13-week study in rats in the control, 10, and 30 mg/kg/day groups. The following parameters were measured:

1) Hematology: Red cell count, packed cell volume, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white cell count.

2) Clinical Chemistry: Urea nitrogen, glucose, alkaline phosphatase, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, albumin, creatinine, calcium.

3) Cholinesterase: Plasma, erythrocyte, brain

4) Urine: Volume, specific garvity, pH, protein, glucose, ketone, bilirubin, occult blood, nitrite, urobilinogen, color, turbidity, microscopic elements.

Necropsies were done on all animals. The following organs were weighed: liver, kidneys, spleen, heart, adrenals, testes. Histopathologic examination of the following tissues and organs from control and high-dsoe rats was done:

kidneys	Adrenals	Thymus
Urinary Bladder	Trachea	Mesenteric Lymph Nodes
Pituitary	Lung	Esophagus
Thyroid	Heart	Stomach
Parathyroid	Spleen	Duodenum
Jejunum	Salivary glands	Oviduct
Ileum	Testes	Uterus
Colon	Accessory Sex Glands	Brain
Pancreas	Ovaries	Spinal Cord
Liver	Adipose tissue	Skeletal Muscle
Bone Marrow	Bone	Eye

Furthermore, gross lesions from all animals were examined microscopically.

2. Results

a) Mortality: Unremarkable; 2 deaths/sex in each dosage group.

b) Toxic Signs: (Including Cholinesterase): Unremarkable.

c) Food and Water Consumption: Unremarkable except for slight dose-related decrease in water consumption in females.

d) Body Weight Changes: Unremarkable in males, decrease of similar magnitude in 10 and 30 mg/kg females.

e) Organ, Organ/Body Weights: Slightly increased spleen weight in high-dose males, slightly increased kidney/body weights in females.

f) Clinical Chemistry: Slightly high calcium levels in high-dose males.

g) Hematology: Slightly decreased hemoglobin in high-dose males. Slightly increased wbc in high-dose males & dose-relationship in intermediate & high-dose females.

h) Cholinesterase:

30	10	3	1	Con A	Con B
12.3	11.1	-	-	10.5	10.2

Brain chol. slightly lower in high-dose males.

i) Urine Anal is: Increased urine volume in ... h-dose males, decreased urine volume and s ightly increased specific gravity in high-dose females.

j) Neropsy: Unremarkable

l) Histopathology:

	Male					
	30	10	3	1	Con A	Con B
Kidney: (Foral tubular hyperplasia)	3/9	0/9	0/10	0/10	0/9	0/8

	Female					
	30	10	3	1	Con A	Con B
Kidney: (Foral tubular hyperplasia	0	0	0	0	0	0

3. Conclusions

a) Classification: Core-Guidelines

b) NOEL concluded to be 30 mg/kg/day on basis of weight loss, reduced hemoglobin, reduced rbc chol. Decreased weight in females given 10 mg/kg/day appears to be due to less food * water consumption, especially since other remarkable effects were not found in this group.

P. Thirteen Week Oral Toxicity Study of UC 51762 in Dogs (Carnegie-Mellon, Report No. 41-98, 5/31/78). Document#11

Test Material: technical

1. Procedure

Thirty-two beagle dogs, 7.2-10.0 kg, divided into 4 groups of 8 animals each (4 males and 4 females) were given 0 (controls), 15, 40, or 90* mg/kg/day of test material in the diet for 13 weeks. Fresh diets were prepared weekly. Food consumption, water consumption, and body weights were recorded daily, three times weekly, and weekly, respectively, the animals were observed for mortality and toxic signs weekly. Hematologic, clinical chemistry, and cholinesterase and urine analyses were done 3 times during the study weeks and were based on the following parameters:

*Due to early deaths of 2 dogs, the high-dose females were given 76 mg/kg/day of test material after day 36.

Hematology: Red blood cell counts, packed cell volume, hemoglobin, mean cell volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte count, sedimentation rate, platelet count, white blood cell count, differential count.

Blood Chemistry: Urea nitrogen, glucose, alkaline phosphatase, serum glutamic - pyruvic transaminase, serum glutamic-oxalacetic transaminase, albumin, creatinine, calcium.

Cholinesterase: Plasma and erythrocyte

Urine Analysis: Volume, specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood, nitrite, color, turbidity, microscopic elements.

Necropies were done on all animals. Livers, kidneys, spleens, hearts, adrenals, brains, and testes were weighed. Samples of brain were retained for cholinesterase assays. The following organs and tissues were examined microscopically:

Pituitary	Aorta	Kidneys
Thyroid	Thymus	Urinary Bladder
Parathyroid	Lymph Nodes	Testes
Adrenals	Spleen	Epididymus
Heart	Lungs	Prostate
Ovary	Skeletal Muscle	Duodenum
Ovidect	Skin	Small Intestines
Uterus	Stomach	Colon
Liver	Pancreas	Femur
Gall Bladder	Brain	Femoral Marrow
Eye		

2. Results

a) Mortality: Two high-dose females died on days 26 and 36.

b) Toxic Signs: Episodic anorexia, vomiting, loose stools, increased water consumption, increased urine volume - severity of signs was dose-related. Incidental findings include lymphoid hyperplasia of the nictitating membrane in a 15 mg/kg females, a sialocyst on the neck of a control female, inflammation of the skin of another control female, and gain infection in a high-dose male which was treated with penicillin, streptomycin. Prior to death, decedents exhibited anorexia, hypoactivity, pallor of the oral mucosa, gummy blood-tinged stools, and muscular rigidity.

c) Diet and Food Consumption: Slight dose-related decrease in food intake in females. Dose-related increase in water consumption in males and females.

d) Body Weight Changes:

	Dosage			
	90	45	15	0
Male	1.10	1.20	1.60	1.10
Female	0	0.1	1.00	1.25

e) Organ, Organ/Body Weights: Slight dose-related increase in male liver weights, increased high-dose weight, slightly increased high-dose female spleen weight, slight dose-related increased spleen/body weight, slight dose-related female decreased adrenal weights, slightly dose-related decreased female heart rates.

f) Clinical Chemistry:

	90	45	15	0
Male alkaline phosphate	25	30	35	47
Male SGPT	80*	23	17	20
Female alkaline phosphate	29	31	40	48
Female SGPT	153*	18	17	18

g) Hematology:

Male RBC	4.74*	5.41*	6.38	6.41
Male PCV	34.6*	39.5*	44.8	45.2
Male Reticulocyte count	3.6*	1.6	1.0	1.0
Male Hgb	11.1*	12.9*	14.9	15.2
Male Platelets	400,167	281,372	283,630	211.127
Female RBC	4.87*	5.95*	6.63	6.77
Female PCV	35.5*	43.0	46.2	46.8
Female Hgb	11.6*	14.7	15.5	15.6
Female Reticulocyte count	3.2*	1.3	0.6	0.7

h) Cholinesterase Assays:

	90	45	15	0
Plasma	138.9	88.6	92.1	94.3

i) Urine Analysis:

Urinary vol.	584*	501	310	299

j) Necropsy:

i) Decedents: 2 females that died; hemorrhagic lesions in gi tract, lymph nodes, and adrenals, markedly reduced adrenal sizes, uterus, renal infarcts, myocardial hemorrhages.

Survivors: Unremarkable

Femoral bone marrow — Male

	90	45	15	0
Dark Red	4/4	4/4	0/4	0/4

(continued from last page)

Female

90	45	15	0
2/2	2/4	1/4	0/4

k) Histopathology:

	90	45	15	0
Lymph node erythrophagocytosis	3/4	4/11	1/4	2/4
Spleen, hemosiderosis	4/4	4/4	3/4	3/4
Extramedullary hema topoesis spleen	2/4	4/4	0/4	0/4
Vaculated tubular epithelium kidneys	1/4	3/4	0/4	0/4
Liver inflammation focal & diffuse	2/4	2/4	2/2	0/4
Liver, pigmented Kupffer cells	3/4	0/4	0/4	0/4

Female

Lymph node erythrophagocytosis	2/2	4/4	2/4	4/4
Spleen, hemosiderosis	1/2	4/4	4/4	3/4
Extramedullary hema topoesis spleen	2/2	3/4	2/4	1/4
Vaculated tubular epithelium kidneys	2/2	4/4	4/4	2/4
Liver inflammation focal & diffuse	2/2	2/4	2/4	0/4
Liver, pigmented Kupffer cells	1/2	0/4	0/4	0/4

Femoral marrow	90	45	15	0
4^+ cellularity	2/2	0/4	0/4	1/4
3^+ "	2/4	2/4	1/4	0/4
2^+ "	0/4	2/4	3/4	2/4
1^+ "	0/4	0/4	0/4	1/4

Female

Femoral marrow				
4^+ cellularity	0/2	0/4	0/4	0/4
3^+ "	2/2	1/4	1/4	0/4
2^+ "	0/2	3/4	3/4	2/4
1^+ "	0/2	0/4	0/4	0/4

3. Conclusions

a) Classification: Core-Minimum Data

i) Only 4 dogs/sex/dosage level were used.

b) Based on body weight changes, anemic signs, and clinical chemistry results the 90-day subacute NOEL is concluded to be 15 mg/kg/day [redacted].

(Published Data Included by reference)

Q. Toxicity Studies with Methyl-N- (Methylamino)carbonyl oxy-ethanimidothioate (E.I. du Pont de Nemours and Company, Inc., 9/11/75). Document#12

1. Procedure

1. Methods

Acute Oral Toxicity Document#12

Ten Charles River (ChR-CD) male and female rats/dosage level were given dosage ranging from 12 to 26 mg/kg of unformulated methomyl as a 0.1 or 0.5% suspension in peanut oil by gavage, and were observed for 14 days post-treatment. Methomyl was administered by gavage as a solution in acetone: peanut oil (1:10) to male rabbits and guinea pigs in dosages ranging from 5 to 60 mg/kg, and the animals were observed for 14 days following treatment. Additionally, male beagle dogs were given single doses of 102-20 mg/kg in gelation capsules, and young adult rhesus monkeys of both sexes in single doses ranging from 5 to 40 mg/kg. Ten 1-year old hens were given single oral dosages of methomyl as a 5% suspension in acetone: water (1:10) and were observed over 14 days after treatment.

Subacute Oral Toxicity Document#12

Six male ChR-CD rats were given 5.1 mg/kg/day of methomyl as a 0.1% suspension in peanut oil for 5 days/weeks. Half the survivors were sacrificed at 4 hours following the final dosing, and the remainder were killed after a 14-day recovery period. Cholinesterase activity was determined.

Acute Dermal Toxicity Document#12

Six adult male albino rabbits received dermal application of (intact skin) 5000 mg/kg of unformulated methomyl in an aqueous suspension under occlusive dressing. Dressing and test material were removed at 24 hours post-application, and the animals were observed for 14 days.

Subacute Dermal Toxicity Document#12

Dosages of 200 mg/kg as a 5% solution were applied once daily 5 days/week, 3 weeks onto intact or abraded test sites on 5 male and 5 female rabbits. Dressing was placed over the test sites for 6 hours after treatment a which time dressing and test material were removed.

Dermal Irritation and Sensitization Document#12

To evalute irritancy to the skin, methomyl was applied to the intact and abraded skin of ten albino male guinea pigs as a 60% paste in propylene glycol (formulated) and as a 26% solution in cellocolve (unformulated), and the 24-hour reaction as a paste onto abraded skin of 5 albino guinea pigs. 3 X weekly for 3 weeks, and other guinea pigs received 4 intradermal injectionsq of 0.1 ml of a 1% solution. The animals were challenged after a 2-week rest period.

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Eye Irritation Document#12

Into both eyes of 4 adult male rabbits was applied 10 mg of solid unformulated test material (2 rabbits) or 0.1 ml of a 10% solution in propylene glycol. One eye of each pair was not washed, but the other eye was washed for 1 minute with water at 20 seconds post-instillation. Eyes were examined at 1, 2, 3, 4, and 6 hours after treatment. Eyes were examined at 1, 2, 3, and 6 days.

Acute Inhalation Toxicity Document#12

Male ChR-CD rats were exposed to 14.6 to 143.4 ppm (analytical concentrations) of the test material as an aqueous mist for 4 hours. Animals were in 16L inhalation chamber. Six rats/group were used and were observed for 14-days post-exposure.

Teratology Study Document#12

New Zealand White rabbits were fed 0, 50, and 100 ppm of methomyl on days 8-16 of gestation. Some animals were sacrificed on days 29 or 30 to allow delivery of young by Cesarian section, and others were permitted normal delivery of young. Resorptions were estimated. Fetuses were weighed and externally examined. One third of the fetuses/litter were used for skeletal examinations with Alizian Red S.

Demyelination Study Document#12

Ten 1-year old hens were given single oral doses of 28 mg/kg of test material as a 5% suspension in acetone: water (1:10). Survivors were observed for 22 days post-treatment when sacrifice and necropsies were performed. The sciatic nerve was examined microscopically. A positive control group dosed with 500 mg/kg of TOCP was also studied.

90-Day Feeding Studies Document#12

Rats: 10 male and 10 female ChR-CD rats/group received 0, 10, 50, 125 or 250 ppm of methomyl in the diet. At 6 weeks, the 125 ppm level was raised to 500 ppm. Body weights, food consumption, and toxic signs were recorded weekly. Hematologic and urine analyses were done on 5 rats/sex/dose initially and at 1, 2, and 3 months. Cholinesterase assays of red blood cells and plasma were done; 5 males and 5 females of the 500 ppm group at 2 months and the control, 250, and 500 ppm groups at the end of the study. All animals were sacrificed at 3 months, and tissues and organs were examined grossly and histologically. Organs were weighed.

Dogs: Thirty-two beagle dogs, 11-13 months old, were divided into 4 groups of 8 animals each (4 males and 4 females) which were given 0, 50, 100, or 400 ppm of mnethomyl in the diet. Fresh diets were prepared weekly. Toxic signs were recorded daily. Food consumtion and body weights were determined weekly. Hematologic, clinical chemistry, and urine analyses were done initially and at 1, 2, and 3 months. The dogs were sarificed at 3 months. Necropsies were performed, and tissues and organs were examined histopathologically. Organs were weighed.

Two-Year Feeding Studies Document#12

Rats: Four hundred twenty weanling ChR-CD ats separated into 6 groups of 70 animals each (35 males and 35 females) received 0 (control), 0 (second controls), 50, 100, 200 and 400 ppm of methomyl in the diet for 22 months. Fresh diets were made weekly. Body weights and food consumption were determined weekly during the first 6 months, biweekly during the following 6 months, and monthly thereafter. Toxic signs were evaluated "regularly". Hematologic (at 3, 6, 12, 18, and 22 months), clinical chemistry (at 6 and 12 months) andurine (at 6, 21, and 22 months) analyses were done based on tyhe following parameters:

Hematology: Erythrocyte counts, total and differential leukocyte counts, hemoglobin, hematocrit.

Clinical Chemistry: Urea nitrogen, serum glutamic-pyruvic transaminase, alkaline phosphatase, fasting blood sugar.

Urine: Color, pH, specific gravity, sugar, protein, bilirubin, occult blood, microscopic elements. Pooled samples based on sex and group.

Five rats/sex/dosage group were sacrificed for gross and histopathologic evaluation. Surviving animals sacrificed at 22 months were similarly evaluated. Organ weights were recorded. The study was ended at 22 months because of high incidence of repiratory disease in control and test animals.

Dogs: Forty young adult pure-bred beagles divided into 5 groups of 8 dogs each (4 males and 4 females) received 0, 50, 100, 400, or 1000 ppm of methomyl in the diet for 22 months. Fresh diets were prepared weekly. Body weights and food consumption were recorded weekly. Hematologic, biochemical, and urine analyses were done initially and at 3, 6, 12, 18 and 24 months and included the following parameters:

Hematology: Erythrocyte counts, total and differential leukocyte counts, hemoglobin, hematocrit.

Biochemical: Urea nitrogen, blood sugar, alkaline phosphate, serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase prothrombin time, serum electrolytes, total protein, albumin.

Plasma and erythrocyte cholinesterase activities were determined initially in all dogs, during week 9 in control and high-dose dogs, and during weeks 13 in high-dose dogs. At 1 year dog/sex/group was sacrificed for histopathological examination. Survivors sacrificed at 2 years were examined grossly and histopathologically. Organs were weighed.

Reproduction Study in Rats. Document#12

Male and female weanling ChR-CD rats were given 0, 50, or 100 ppm of methomyl in the diet for 3 months. At 3 months 10 males and 20 females/dosage group were bred to produce F1a and F1b litters. Ten male and 20 female rats/dosage group from F1b litter were fed appropriate diet for 3 months until bred to yield F1a and F1b litters. Records were made of all matings, number of pregnancies, number of young in each litter born and born alive, and body weights of the young at weaning. Reproduction and lactation indices were calculated. Ten females and 10 males from F3b litters/dosage were examined histopathologically.

2. Results

Acute Oral Toxicity Document#12

Oral LD50 (unformulated chemical) = male rats, 17 (14.3-20.2) mg/kg, female rats 23.5 (21.8-25.4) mg/kg. Toxic Signs - Pallid eyes, chewing motions, profuse salivation, lacrimation, bulging eyes, fasciculations tremors. Unremarkable necropsy. Minimal lethal dose = 15 mg/kg in guinea pigs, 30 mg/kg in dogs, 40 mg/kg in monkeys.

Oral LD50 in hems - 28 mg/kg. Toxic Signs - Lacrimation, salivation, convulsions, respiratory disorders. Unremarkable necropsy.

Dermal LD50 in rabbits 5000 mg/kg. Unremarkable toxicity.

Inhalation LC50 in rats = 76.8 ppm. Toxic Signs - Tremors, irregular breathing, grooming action, salivation, lacrimation, bulging eyes during exposure. Recovery post-exposure.

Mild skin irritant and not a sensitizer on guniea pig skin.

Eye - Mild conjunctivitis, no corneal opacity.

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Subacute Toxicity Document#12

All rats survived 10 daily doses of 5.1 mg/kg/day of methomyl. Toxic signs were similar to those observed in the acute oral study. Cholinesterase activity was normal and histopathology was unremarkable.

All rats survived in the 90-day feeding study. No toxic signs. Weight gain and food consumption was slightly reduced in 250 and 500 ppm animals. Hematology, clinical chemistry, urinalysis unremarkable. Histology unremarkable. At 3 months, 250 ppm females had decreased red blood count and increase in bone marrow erythyroid components. NEL = 50 ppm

No remarkable toxicity was found in the 90-day dog study. NEL = 400 ppm

Subacute dermal toxicity in rabbits:

Intact skin - No deaths. Toxic Signs - Nasal discharges, wheezing, diarrhea, bloating.

Abraded skin - 2 d eaths, Toxic Signs - Depression, labored respiration, nasal discharge, salivation, mastication, tremors, poor coordination, hypersensitivity, abdominal hypertonia.

Unremarkable histopathology - NEL 200 mg/kg/day

Teratology Document#12

No toxic signs in mothers or young. NEL = 100 ppm

Demyelination Document#12

No neurotoxic signs or histological abnormalities of sciatic nerve in test hens. TOCP induced leg paralysis & sciatic nerve degeneration. NEL = 28 mg/kg

Chronic Toxicity Document#12

Rats. No remarkable mortality. Body weights of 400 ppm values (wks 1-52) and food consumption of 200 and 400 ppm males (wks 1-26) were significantly lower than control values. Body weights (wk 1-52) of 200 ppm male + 400 ppm female were lower though not significantly, than control values.

Hematology - Female, g/100 ml hemoglobin

Group	12	18	22 months
0	14.6	15.4	14.7
0	15.3	14.8	15.3
50	15.0	13.7	14.4
100	14.9	13.4	14.6
200	14.6	13.0	13.8
400	13.5	12.9	12.7

Except at 18 months, leucocyte counts were lower in high-dose females at each measurement.

Significantly higher testes/body weights in high-dose males were found; however, numerical values were not provided.

Compound-related histopathological changes included kidney (protein imbibition, vacuolated epithelial cells in proximal convoluted tubules, tubular dilatation and hypertrophy, protein in tubules in 400 ppm males and females and spleens (increased incidence and severity of extramedullary hematoporesis) in 200 and 400 ppm females. Incidence of neoplastic lesions in high-dose rats generally comparable to those found in controls.

NEL = 100 ppm. Clarify generally.

Dogs. One high-dose & a replacement female died. Two males showed tremors, salivation, incoordination, circling movements. Anemia was found in high level dogs. No tremors were found. Kidneys - pigment deposition in 400 & 1000 ppm males & 1000 females & epithelial swelling in 1000 ppm males and females; spleen - increased extramedullary hematoporesis is 1000 ppm animals increased pigment deposition in 400 and 1000 ppm animals; liver - increased bile duct proliferation; bone marow - increased activity in 1000 ppm animals NEL = 100 ppm. Supplementary Data. Rsults summarized in sentence or as means in tables.

R. Reproduction Study in Rats. Do cument#12

No remarkable parameter or fetal toxicity - NEL = 100 ppm.

Acute Oral LD50 Study of UC45650 (S-methyl O-(methylcarbamoyl) acetothiohydroximate) in Rats (Cargegie-Mellon, Report#39-40, 3-1-76) Document#13

1. Procedure

Twelve male Wistar rats, 90-120g, separated into 3 groups of 4 animals each were dosed with 20, 40, or 80 mg/kg of test substance by gavage. Observations for mortality, toxic signs, and body weight changes were done for 2 weeks post-treatment. Necropsies were done.

2. Results

a) Mortality: LD50 = 47.6 (36.1-72.7) mg/kg
b) Toxic Signs: Tremors, salivation, lacrimation
c) Body Weight Changes: Unremarkable
d) Necropsy:

i) Decedents: Mottled livers, speckled & slightly congested kidneys, liquid-filled * injected intestines.

ii) Survivors: Unremarkable

3. Conclusions

a) Classification: Core-Minimum Data

i) Although only 4 animals of 1 sex were used in each dosage group, the severity of the acute oral toxicity in rats is adequately defined.

ii) Body weights in conjunction with food intake were not determined daily.

b) Tox. Cat.: I

Seven-Day Feeding Study of UC45650 in Rats (Carnegie-Mellon, Project#41-102, 6/19/78). Document#14

1. Procedure

Fifty Wistar albino rats, 162-261g, were divided in 5 groups of 10 animals each (5 males and 5 females) which received 0 (controls fed stock diet), 0 (solvent controls), 5, 16, or 48 mg/kg/day of test material for 7 days. The animals were group housed (2-3 males/cage, 5 females/cage). Fresh diets were made weekly. Observations for mortality and toxic signs were made daily.

Body weights were determined 3 X during the study, and food consumption for the week was estimated. Livers and kidneys were weighed on sacrifice at the end of the study.

2. Results

a) Mortality: No deaths.
b) Food Consumption: Decrease in 16.0 females (15.9 g/rat/day) 48.0 males (19.5) and females (12.9).
c) Body Weight Changes:

	48.0		16.0		5.0		0		0 (acetone)	
	M	F	M	F	M	F	M	F	M	F
Day 1	-9.8	-9.8	1.8	-2.4	5.6	0	7.4	1.8	7.0	0.8
Day 3	7.6	-2.8	39.4	8.0	38.4	13	39.8	14.0	39.4	16.8
Day 7	22.8	5.8	47.0	17.4	52.6	21	58.8	29.0	58.8	29.4

d) Organ, Organ/Body Weights: Decreased liver & liver/body weights in high-dose males, dose-related decreased liver weights in females; decreased kidney weights in high-dose males & intermediate & high-dose females.

3. Conclusions

a) Classification: Supplementary Data

i) Test material was administered in the diet for 7 days.

b) NEL 5.0 mg/kg/day based on body weights.

Thirteen-Week Feeding Study of Methomyl in Rats (Carnegie-Mellon, Report#41-64, 4/6/78). Document#15

1. Procedure

One hundred twenty Fischer 344 (CDBS CD FlCrl BR) rats, 97.5-118.5g were divided into 6 groups of 20 animals each (10 males and 10 females) which received o (control group), 0 (second control group), 1, 3, 10, or 30 mg/kg/day of methomyl in the diet for 13 weeks. Housing was 2 rats/cage. Fresh diet was prepared weekly. Observations for toxic signs and mortality were made daily. Body weights and food consumption were determined weekly. Water consumption was estimated monthly. Spun-packed red blood cell volumes were determined at 2, 5, and 9 weeks. Hematologic, clinical chemistry, cholinesterase, and urine analyses done at 13 weeks based on following:

Hematology: Red cell count, packed cell volume, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white cell count.

Clinical Chemistry: Urea nitrogen, glucose, alkaline phosphate, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, albumin creatinine, calcium.

Cholinesterase: Plasma, erythrocyte, brain

Urine: Volume, specific gravity, pH, glucose, ketone, bilirubin, occult blood, nitrite, urobilinogen, color, turbidity, microscopic elements.

Necropsies were done on all decedents and all survivors at the end of the study. The following organs were weighed: Liver, kidneys, spleen, heart, adr enals, testes. Histopathological examination included the following organs and tissues:

Kidneys	Adrenals	Thymus
Urinary Bladder	Trachea	Mesenteric lymph node
Pituitary	Lung	Esophagus
Thyroid	Heart	Stomach
Parathyroid	Salivary glands	Oviduct
Jejunum	Testes	Uterus
Ileum	Epididymes	Brain
Colon	Prostate	Spinal cord
Pancreas	Ovaries	Skeletal muscle
Liver	Bone	Adipose tissue
Bone marrow		
All gross lesions		

2. Results

a) Mortality: Unremarkable
b) Toxic Signs: Unremarkable
c) Food Consumption: Unremarkable
d) Body Weight Changes:

	Gain(g)					
	30	10	3	1	0	0
Males	180.1	193.6	182.5	180.2	187.7	182.0
Females	76.6[-]a	76.3[-]a	73.4[b]	72.1	84.7	87.4

a) p .05 b) p 0.1

ml/rat/day

	30	10	3	1	0	0
Males	19.2	20.0[a]	18.8	18.8	18.8	19.5
Females	13.5[a,b]	13.8[-a]	13.3[a,b]	13.2[a,b]	15.2	15.8

a) p 0.05 b) p 0.01

f) Organ, Organ/Body Weights:

a) Males: Unremarkable
b) Females: Unremarkable

Statistically significant differences were sporadic and not dose-related.

g) Clinical Chemistry: Slight reddened alkaline phosphate in high-dose females, slightly reduced creatinine in high-dose males.

h) Hematology:

		RBC	Hgb	WBC
Males:	30	7.23	15.6[a,b]	10,042
	10	7.36	15.7[-,b]	9,398
	0-A	7.55	16.2	8,391
	0-B	7.67	16.4	8,859
Females:	30	6.68	14.8	8,755
	10	7.29	15.8	7,891
	0-A	7.30	15.6	7,536
	0-B	7.24	15.8	7,581

a) p .05 b) p .01

i) Cholinesterase:

	30	10	0-A	0-B
Erythrocyte RBC: Males	12.3[b,c]	11.4	10.5	10.2
Females	1.4[a,-]	10.2	9.8	10.2

a) p .05 b) p .001

j) Urine Analyses: Unremarkable

k) Necropsy: Unremarkable

l) Histopathology:

	30	10	3	1	0-A	0-B
Male, kidneys intra-nullum inclusions	4/9	0/9	1/10	1/10	1/9	1/8
Female, adrenals: mild congestion	3/10				0/10	0/1(

3. Conclusions

a) Classification: Core-Guidelines

b) NEL is 3 mg/kg/day based on hemoglobin, white blood cells, hematocrit, cholinesterase in males. Body weight loss in females considered to be result of reduced water intake and in the absence of a dose-relationship, the significance of this finding is not clear.

Acute Oral LD50 Study of 1-Methylsulfonyl-N-(methylcarbamoyloxy)-acetimidate (UC54172) in Rats (Carnegie-Mellon, Report#41-25, 2/15/78). Document#16

1. Procedure

Twelve Wistar male rats, 90-120g, divided into 3 groups of 4 animals each were administered 160, 320, or 640 mg/kg of test material in corn oil by gavage. Observations for mortality, body weight changes and toxic signs were continued during 14 days following treatment. Necropsies were done.

2. Results

a) Mortality: LD50 = 4.536 (296-692) mg/kg
b) Toxic Signs: Tremors
c) Body Weight Changes: Unremarkable
d) Necropsy:

i) Decedents: Petechia of lungs, prominent liver acini, distended stomach and intestines transparent and liquid-filled.

ii) Survivors: Liver mottled and acini prominent, kidneys with red foci, congested adrenals.

3. Conclusions

a) Classification: Supplementary Data

i) The acute oral toxicity of the test material is adeqa tely defined in males; however, the effect in females was not evaluated.

b) Tox. Cat.: II (Provisional)

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Seven-Day Feeding Study of UC54172 in Rats (Carnegie-Mellon, Report#41-106, 6/22/79). Document#17

1. Procedure

Fifty Wistar albino rats, 165-256g, separated into 5 groups of 10 animals each (5 males and 5 females) which were given 0 (control), 0 (acetone vehicle control), 50, 150, or 193.2 males; 247.0, females) mg/kg/day of test material in the diet for 7 days days. The rats gang-housed (2 or 3 males/cage; 5 females/cage). Observations for mortality and toxic signs were made daily. Body weights and food consumption were determined during the week. Necropsies were done, and livers and kidneys were weighed.

2. Results

a) Mortality: None
b) Diet Consumption:

Males	8.7	22.1	27.9	26.9	26.3
Females	8.3	15.8	20.5	20.9	20.2

c) Body Weight Changes:

Males	$-36.8^{c,c}$	$39.0^{b,a}$	57.4	58.8	58.8
Females	$-21.6^{c,c}$	$17.4^{a,a}$	21.4	29.0	29.4

a) p 0.5 b) p .01 c) p .001

d) Organs, Organ/Body Weights:

Male Liver	7.55	12.93	14.23	14.99	14.05
Male Kidney	1.82	2.36	2.54	2.70	2.51
Female Liver	6.79	8.70	9.76	10.04	10.58
Female Liver/Body	4.25	4.47	4.94	4.63	4.96
Female Kidney	1.41	1.68	1.77	1.63	1.81

a) p .05 b) p .01 c) p .001

e) Toxic Signs: Unremarkable

3) Conclusions

a) Classification: Supplementary Data

b) The NEL is concluded to be 50 mg/kg/day according to body and organ weight data obtained for females.

Acute Oral LD50 Study of 1-methylthioacetaldehyde O-(hydroxymethyl carbamoyl) oxine (UC58614) in Rats (Carnegie-Mellon, Reprot#41-133, 9/25/78). Document#18

1. Procedure

Twelve male Wistar rats, 90-120g, divided into 3 groups of 4 animals each were given 100, 200 or 400 mg/kg of test material in corn oil. Observations for mortality and toxic signs and body weight changes were made for 2 weeks after treatment. Necropsies were done.

2. Results

a) Mortality: LD50 = 200 (123-326) mg/kg
b) Toxic Signs: Tremors
c) Body Weight Changes: Unremarkable
d) Necropsy:

i) Decedents: Lungs reddened, stomach transparent, gas-filled, distended; kidney sections congested; intestine sections opaque or transparent, injected, distended, fluid-filled; adrenals congested.

ii) Survivors: Unremarkable

3. Conclusions

a) Classification: Supplementary Data

i) The test material was evaluated only in males.

b) Tox. Cat.: II (Provisional)

Seven-Day Feeding Study of UC58614 in Rats (Carnegie-Mellon, Report#41-107, 6/23/78). Document#19

1. Procedure

Fifty Wistar albino rats, 169-253g, were divided into 5 groups of 10 animals each (5 males and 5 females) which were given 0 (control), 0 (acetone solvent control), 17, 50 or 150 mg/kg/day of test chemical in the diet for 7 days. Animals were gang-caged (2-3 males or 5 females/cages). The animals were observed for mortality and toxic signs daily. Body weights and food consumption were determined during the week.

2. Results

a) Mortality: None
b) Food Consumption:

Males	22.6	24.1	25.9	26.9	26.3
Females	15.5	16.4	18.4	20.9	20.2

c) Body Weight Gain:

Males	32.6	49.8	54.6	58.8	58.8
Females	15.2	24.6	20.2	29.0	29.4

d) Organs, Organ/Body Weights:

Male Liver	12.99	13.40	13.55	14.99	14.05
Male Kidney	2.44	2.41	2.48	2.70	2.51
Female Liver	9.15	9.70	9.42	10.04	10.58

a) p .05 b) p .01

3. Conclusions

a) Classification: Supplementary Data

i) The test material was provided in the diet to the rats for only 7 days.

b) The NEL is concluded to be 17.0 mg/kg/day.

Acute Toxicity Studies of S-Methylacetothiohydroximate UC52702 in Rats and Rabbits (Carnegie-Mellon, Report#39-25, 2/16/76). Document#20

1. Procedure

Acute Oral LD50 - Eight Wistar male rats, 90-129g, were divided into 2 groups of 4 animals each which were given 500 or 1000 mg/kg of test material by gavage in corn oil.

Acute Dermal LD50 - Four male albino rats, 177-212g, were exposed to a dermal application of 1000 mg/kg in corn oil of test compound under occlusive dressing onto intact skin. Dressing was removed at 4 hours post-treatment.

Acute Inhalation LC50 - Six rats, sex and weights unspecificed, were placed into a 60L inhalation chamber and were exposed to 820 u/L of test material as an aqueous aerosol for 4 hours.

In the above 3 studies the animals were observed for mortality, toxic signs, and body weight changes during 14 days following treatment. Necropsies were done.

Skin Irritation - The test chemical was applied to uncovered intact skin of 2 groups of 5 rabbits either as a 25% suspension in acetone or from a suspension of 1 gram + 2 ml dimethyl phthalate. Injuries were graded during 24 hours after treatment.

Eye Irritation - Into the conjunctival sac of 3 groups of 5 rabbits was placed 40 mg of solid test material, 0.5 ml of a 1g + 2 ml DMP suspension, or 0.5 ml of a 15% suspension in DMP. Injuries were evaluated using sodium fluorescein at 24 hours post-instillation.

2. Results

a) Acute Oral LD50 - Mortality - LD50 = 794 (486-1300) mg/kg. Toxic Signs - Sluggishness, deep breathing, unsteady gait, tremor-like muscle spasms, deep-pink extremities. Body Weight Changes - Unremarkable. Necropsy - Decedents: Slight petechial hemorrhages in lungs, kidneys and livers mottled, kidneys slightly congested, stomachs and intestines distended and liquid-filled, intestines yellow; Survivors - Unremarkable.

b) Acute Dermal LD50 - Mortality - No deaths. LD50 1000 mg/kg Toxic Signs - Unremarkable. Body Weight Changes - Unremarkable. Necropsy - Unremarkable.

c) Acute Inhalation LC50 - Mortality - No deaths. LC50 820 ug/L, 4 hours. Toxic Signs - Increased breathing rate during exposure. Body Weight Changes - Unremarkable. Necropsy - Unremarkable.

d) Skin Irritation - No irritation under test conditions.

e) Eye Irritation - Severe corneal irritation with powder or 1g + 2 ml DMP. Slight corneal injury with 15% in DMP.

3. Conclusions

a) Classification:

i) Acute Oral LD50

Supplementary Data - The effect of the test chemical was evaluated only in males.

Tox. Cat.: II (Provisional)

ii) Acute Dermal LD50

Supplementary Data - Exposure to test material was for 4 instead of 24 hours. Only males were used. Animals with abraded test sites were not used. Dosage too low to adequately define toxicity.

Tox. Cat.: Cannot be determined

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iii) Acute Inhalation LC50

Supplementary Data - Only 6 animals of unstated sex were used. The exposure level was too low to allow a definitive evaluation of the inhalational toxicity.

Tox. Cat.: Cannot be determined.

iv) Skin Irritation

Invalid Data - Undiluted test material was not used. Test sites were uncovered, and restraint of animals was not indicated. Irritation should have been graded according to Draize et al (1944) for at least 72 hours post-treatment.

Tox. Cat.: Cannot be determined

(v) Eye Irritation

Supplementary Data - Injuries using undiluted test material should have been evaluated according to the method of Draize et al (1944) during at least 7 days following treatment.

The possible benefit of washing eyes post-treatment should have been determined.

Tox. Cat.: Cannot be determined.

Seven-Day Feeding Study of UC52702 in Rats (Carnegie-Mellon, Report#41-104, 6/2/78). Document#21

1. Procedure

Fifty male and female Wistar rats, 166-265g, were divided into 5 groups of 10 animals each (5 males and 5 females) which were given 0 (controls, 0 (acetone vehicle controls), 79, 120.8-14.5, or 199.4(m) - 243.2(f) mg/kg/day of test chemical in the diet for 7 days. The rats were gang-caged (2-3 males or 5 females/cage). Observations for mortality and toxic signs were made daily. Body weights and food consumption were determined during the week. Liver and kidney weights were recorded after sacrifice of the animals at the end of the study.

2. Results

a) Mortality: None
b) Food Consumption:

Males	5.0	11.7	23.1	26.9	26.3
Females	4.4	7.0	14.7	20.9	20.2

c) Body Weight Changes:

	High	Intermediate	Low	00	0 (acetone
Males	$-69.4^{c,c}$	$-29.4^{c,c}$	$37.8^{b,b}$	58.8	58.8
Females	$-52.6^{c,c}$	$-27.4^{c,c}$	$-21.6^{c,c}$	29.0	59.4

d) Organ, Organ/Body Weights:

	High	Intermediate	Low	0	0 (aceton
Male:					
Liver	$5.84^{c,c}$	$8.82^{c,c}$	$13.01^{b,-}$	14.99	14.05
Liver/Body	$3.48^{c,c}$	$4.22^{c,b}$	4.60	4.93	4.73
Kidney	$1.72^{c,c}$	$1.98^{c,c}$	$2.40^{a,-}$	2.70	2.51
Kidney/Body	$1.02^{-,c}$	$0.94^{-,a}$	0.85	0.89	0.84
Females:					
Liver	$4.39^{c,c}$	$6.09^{c,c}$	$8.40^{a,c}$	10.04	10.58
Liver/Body	$3.54^{c,c}$	$4.02^{b,c}$	4.53	4.63	4.96
Kidney	$1.20^{c,c}$	$1.44^{c,c}$	$1.61^{c,a}$	1.93	1.81
Kidney/Body	$0.98^{a,b}$		0.87	0.89	0.86

a) p .05 b) p .01 c) p .001

3. Conclusions

a) Classification: Supplementary Data

i) The test material was given to rats in the diet for only 7 da

b) A NEL cannot be determined because of weight loss in all treatment groups. Comparison of weight gain and diet consumption in the low dose groups suggests a test material effect, but the reduced diet consumption probably was influenced by the acid odor associated with UC 52702.

Acute Toxicity Data on Acetonitrile (Registry of Toxic Effects of Chemical Substances, Vol. II, National Institute for Occupational Safety and Health, 1977). Document#12

TXDS:	orl-rat	LD50	3800 mg/kg
	ihl-rat	LD50	8000 ppm/4H
	ipr-mus	LD50	500 mg/kg
	scu-mus	LDLo	700 mg/kg
	skn-rbt	LD50	1250 mg/kg
	scu-rbt	LD50	130 mg/kg
	scu-frg	LDL0	9100 mg/kg

Conclusions

a) Classification: Invalid Data

i) The data is merely summarized from various literature source: A complete description of the methodology and results should be available for review.

Acute Toxicity Data on Acetonitrile (Union Caebide Corp. Data Sheet). Document#23

1. Acute Oral LD50 = 2.46 g/kg
2. Acute Dermal LD50 = 1.25 ml/kg
3. Acute Inhalation LD50: 8000 ppm LC50 32000 ppm
4. Skin Irritation: Faint redness of short duration.
5. Eye Irritation: One drop caused severe eye injury.

2. Conclusions:

a) Classification: Invalid Data

i) The data are presented only in summary form. A complete description of the methodology and results for each study should be submitted.

Mutagenic Evaluation of CHF 41-43 (VC 5.7162) by the Ames Salmonella/Microsome Plate Test (Litton Bionetics Inc., Project No. 20838, 4/78). Document#24

1. Procedure

Five strains of Salmonella Typhimurium (TA-1535, TA-3537, TA-1538, TA-98, TA-100) and the D4 strain of Saccharomyces cerevisiae were evaluated. The activation medium used this study included the following:

Ingredient	Concentration/ml
TPN (sodium salt)	4 umol
Glucose-6-phosphate	5 umol
Sodium phosphate (dibasic)	100 umol
$MgCl_2$	8 umol
KCL	33 umol
Homogenate 59 fraction*	0.1 $\pm$ 0.5 ml

*Excluded for nonactivation medium.

The 59 Homogenate was prepared as a 9000 xg supernatant obtained from the liver of adult male rats treated with Arochlor 1254 for 5 days before sacrifice. The 59 samples were assayed for mg of protein/ml and p.448/p.450 activity.

All test chemicals used in this study were prepared in either distilled water or dimethylsulfoxide (DMSO).

Approximately 1 X 10^8 cells from an overnight culture of each strain were added to appropriate test tubes containing molten agar, biotin, and histidine.

Five dose levels of test material were used in the activation and nonactivation tests; and 0.5 ml of the reaction mixture was added to each suspension for activated cells. Activated and nonactivated cultures were poured onto minimal

agar plates which were incubated at 37°C for 48 hours. Yeast cultures were incubated at either 30°C (nonactivation) or 37°C (activation) for 3-5 days. Positive and solvent controls were concurrently maintained. The number of colonies on each plate was counted:

Dose levels of test chemcial were 1, 10, 100, 500, or 1000 ug. Solvent control plates contained 50 ul of DMSO. Positive control cultures included the following chemicals in 10g or 10 ul amounts as appropriate:

Strain	Non-Activation	Activation
TA-1535	EMS	Auth
TA-1537	QM	Auth
TA-1538	NF	Auth
TA-98	NF	Auth
TA-100	EMS	Auth
D4	EMS	Auth

2. Results

The results were negative (comparbale to solvent control values) in all treatment cultures. Cytotoxicity in the form of reduced colony counts was evident in some strains exposed to 1000 ug of test chemical to all positive control chemicals.

3. Conclusions

a) Classification: Supplementary Data (Provisional)

i) The results of the present study show the nonmutagenic potential of the test chemical in Salmonella and Saccharomyce cultures. However, the applicability of this study towards satisfying regulatory requirements must be deferred until guidelines for mutagenicity testing are finalized.

ii) It should be noted that the results of the present study, although showing a lack of mutagenic effect in prokaryotic and eukaryotic cells, may not in themselves be indicative of possible mutagenic effects in vivo.

iii) The positive control chemicals should be identified by the full chemical name instead of an abbreviation.

b) The mutagenic NEL indicated in the present study is 1000 ug.

Antidote Study of VC 51662 in Rats (Carnegie-Mellon, Report No. 41-59, 3/30/78). Document#25

1. Procedure

To determine the LD50, three groups of 5 male Wistar albino rats, 90-120g, each were given 80, 160, or 320 mg/kg of test material in corn oil by gavage. The animals were observed for mortality, toxic signs, and body weight changes for 2 weeks post-treatment. Necropsies were done. The evaluation of the antidotal potential of atropine sulfate was done according to the protocol below:

No. of Rats VC 51762 (mg/kg)		Dosage Atropine (mg/kg)	Antidote Schedule, Time after VC 51762 Dosage
5	298	-	-
5	372	-	-
5	298	10	5 min.
5	298	10	5 min.,.1 hr., 28 hr.
10	298	10	5 min. subsequently as needed with kinger's lactate
3	372	10	4 min., 1 hr., 6 hr.
10	-	10	Single dose

VC 51762 and atropine were given in corn oil and 0.99. saline, resepctively.

2. Results

LD50 Determination

a) Mortlaity: 149 (101-221) mg/kg
b) Body Weight Changes: Unremarkable
c) Toxic Signs: Tremors
d) Necropsy:

i) Victims: Slight petechiae of lungs; livers mottled; kidneys mottled and sections slightly congested; adrenals slightly congested; stomachs transparent, distended, and liquid-filled; intestines opaque and slightly pink.

ii) Survivors: Livers mottled with acini prominent; kidneys with red foci.

Antidotal Evaluations of Atropine

Dosage Atropine		No. Dead No. Dosed	Time to Death, Range	Toxic Signs
298		4/5	12-43 min.	Tremors, salivation lacrimation
372		5/5	10-28 min.	"
298	10	2/5	2 hrs. 1 day	Tremors
298	10	1/5	1 day	"
298	10	5/10	1-5 hrs. -2 day	"
372	10	4/5	45 min. - 2 days	"
-	10	0/10	-	"

3. Conclusions

a) Classification of LD50 Determination: Supplementary Data

i) Only males were used.

Tox. Cat.: II (Provisional)

Antidotal Study

a) Classification: Supplementary Data

i) The intent of this study was to evaluate the antidotal properties of atropine after oral administration of VC 51762.

b) The results show that atropine reduced the number of deaths and prolonged survivability in rats given 2 or 2.5 X the LD50 dose.

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