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000740

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BETASAN - A herbicide - Stauffer Chemical Co.
N-Beta O,O-Diisopropyl dithiophosphoryl ethyl benzene sufamonide.

We have reviewed the available data on Betasan - a nondiscriminatory herbicide.

The information, in general, shows a good safety factor as to acute toxicity, but longer trials show aberrations in organ weights, limited histopathological examination, or absence of histopathological data. Some trials appear to have had concurrent animal infections. We need:

1) Histopathological results of Report 370 - a four week rat study at levels of 150, 300, 525 ppm.

2) Metabolic data. None included in our data.

3) Kidney function test. Kidney damage and pyelonephritis was a factor in some trials together with organ weight observations.

4) A ninety day feeding study is needed to help clarify the organ weight, histopathologic changes, the spleen enlargement and lung congestion. Amongst the general gross and histopathological examination, particular attention should be directed to lungs, kidney, liver, spleen, brain, adrenal, thyroid, gonads. Enzyme determinations would be of assistance.

5) [redacted] We should have subacute information on this.

6) Chemical and physical properties, ultraviolet, etc.

7) Copy of original label.



Dr. Maurice R. Woulfe

cc: Betasan Folder

MRWoulfe:nlh

000740 ⑥

March 2, 1966

BETASAN

N-Beta 0,0-Diisopropyl dithiophosphoryl ethyl benzene sulfonamide

Acute Rat Oral

$LD_{50}$ with technical grade = ♂ 3750 - ♀ 2370 mg/kg

$LD_{50}$ with diluted at [redacted] ♂ 819 mg/kg - ♀ 704 mg/kg.

5 rats/level
Toxic signs included depression, tremors, lacrimation, salivation, excessive urination and defecation, prostration, and loss of coordination.

No gross autopsy observations were made.

Acute Eye Irritation (Rabbits)

0.1 ml (125 mg) in one eye of rabbit which was not washed out. Corneal opacity and iritis were minimal. All normal at 72 hours (irritation).

Acute Dermal (Rabbits) (24 hrs. exposure)

a) 2/level - 0.9, 2.7, and 8.1 ml/kg (1125, 3375, and 10,125 mg/kg) were used.
b) No deaths - No pharmacologic signs
c) Erythema and edema were proportional to dosage level and persisted three days.
d) Neurosis was present at 8th day in the high level
e) 10,125 mg/kg produced 80 - 90% CHE inhibition of red cell and 50 - 60% of plasma enzymes.
f) 3375 mg/kg produced 20 - 30% CHE inhibition of red cell enzymes
g) No gross abnormalities noted at autopsy.
h) Chemical is a moderate irritant
i) Chemical is absorbed through skin

Acute Inhalation (Rat)

10 ♂ = 10 ♀ /level x 2 levels of 2.0 and 8.0 mg/L x 1 hr.

a) No deaths in either level
b) @ 2.0 mg/L - mild signs of discomfort, excessive preening and rapid resp. negative at 24 hrs.
c) @ 8.0 mg/L - depressed - some lacrimation & ruffled fur - negative at 24 hrs.



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d) Autopsy - spleen enlargement in a # of animals
e) Brain cholinesterase - 8.0 mg/L had 30 -.40% inhibition @ 24 hrs.
- 2.0 mg/L had ~ 20% @ 24 hrs. - both are based on controls of 4 week feeding study - because this study had no control animals.

@ 14 days brain cholinesterase was normal.

f) Histopathological observations (lung, trachea, and some spleens in ♀) - varying degrees of interaveolar septal thickening in lung; some peribronchial and peribronchiolar round cell & macrophage infiltration and some congestion. Some evidence of ectopic hemopoiesis in spleens.

Stauffer Chemical Co.

Acute Oral $LD_{50}$ Rats
a) 5 rats/level all ♂'s
b) wt range 175 - 295 gm - (older rats)
c) Unfasted animals were tested
d)
e) Observed for seven days
f) $LD_{50}$ for this study = 708 µl/kg (862 mg/kg)
g) No systemic effect at 464 ul/kg (564 mg/kg)
h) The 828 mg/kg & 1217 mg/kg showed signs of poisoning at 2 - 4 hrs. (muscarinic & nicotinic acitivity induced by organophosphates

1.0 ml/kg = 1.218 mg/kg ?

A) Ave. $LD_{50}$ with undiluted = 770 mg/kg with range of 611 - 931 mg/kg.

Woodard Research Corporation

1. Acute Oral $LD_{50}$ of Betasan 4-E* (4 lbs/gal) or (479 mg/ml)

a) 5 ♂ and 5 ♀ /level - 4 levels (wt 150 - 360 gm)
b) fasted overnight
c) At autopsy some splenic enlargement was noted
d) $LD_{50}$ ♂ = 819 mg/kg ♀ = 704 mg/kg
e) Toxic signs - depression, tremors, lacrimation, salivation, excessive urination and defecation, protration and loss of coordination.



2. Acute Dermal (Rabbits)

a) Four rabbits/level (1.0, 2.15, 4.64, & 10.0 ml/kg)
b) Undiluted material was used.
c) 24 hr. exposure observed for 14 days.
d) $LD_{50}$ = 3.16 ml/kg (3950 mg/kg as 100% or 3752 as 95% pure)
e) Animals @ 1.0 and 2.15 ml/kg levels showed no toxic effects - had only 1 death @ 2.15 ml/kg.
f) @ 24 to 48 hrs the 4.64 ml/kg level appeared weak and depressed and exhibited tremors, ataxia and labored respiration. Surviving animal (1/4) remained normal throughout study.

g) @ 24 hrs. the 10.0 ml/kg showed depression, weakness and labored respiration. No survivors.
h) Incomplete absorption was indicated.
i) Gross autopsies on animals that died showed erythemic to hemorrhagic lungs.
j) Surviving animals at autopsy appeared OK.

3.. Acute Eye Irritation - (Rabbits) (Material placed in conjunctival sac for 30 seconds)

a) Total of three animals used
b) 50 µl of test material put in left eye
c) Produced a mild degree of eye irritation
d) @ 48 hrs. eyes appeared normal.

Biochemical Research

1. Four-Week Rat Feeding Study (95% pure)

a) 5 ♂ & 5 ♀ /level x 4 levels of 35, 70, 140, 280 mg/kg/day
b) No deaths
c) ♂ & ♀ @ 280 mg/kg/day wt change was T/C = 69% ♂ & T/C = 86% ♀
d) Low levels loss no wt.
e) ♂ & ♀ @ 280 mg/kg ate less food than control.
f) Hematological data - within normal limits.
g) CHE of 280 mg/kg - plasma 66% & RBC 82% inhibition ♂ & ♀ at 2 weeks.
h) @ 4 weeks RBC inhibition was 100% ♂ & ♀ & plasma ~ 80%. Brain CHE inhibited ~ 69% ♂ & 50% ♀. Other feeding levels showed roughly graded responses.
i) Autopsy - no gross abnormalities.
j) Mean wts of liver, pancreas, adrenal, & thyroid in males @ the 280 mg/kg/day were elevated, may be due to decreased body wts except for adrenal & thyroid.
k) Liver & pancreas relative wts were also somewhat elevated in ♀ @ 280 mg/kg/day. Also a reduction in ovarian & uterine wt, both actual and relative.
l) Histological changes noted in liver @ the 280, 140, & 70 mg/kg/day levels - renals, thyroid & pancreatic changes in 280 mg/kg/day.

2. Subacute Four Week Feeding Study Rats
(or 4, 8, 13 mg/25 gram feed/rat/day)

a) Tested @ 150, 300, 525 ppm - 6 rats ♂/level.
b) No deaths
c) Wt. gain OK.
d) Some depression of food consumption.
e) Plasma cholinesterase data shows slight depression @ all levels including controls. No significant difference.
f) Thyroid wts appeared slightly increased. Wts. of adrenal, heart, liver, kidney, spleen & gonads were OK.
g) Gross autopsies proved negative.

h) Histological findings will be reported later. When?

Dermal Toxicity - Twenty day (Rabbit) (4 E Formulation)

a) 4/levels of 0.5, 0.25, 0.1 ml/kg/day or 240, 120, 48 mg/kg/day
b) Treated qd x 5/wk for 3 weeks.
c) No deaths.
d) Mild to moderate skin erythema & edema were noted in all test animals - returned normal at 10 days.
e) 25 - 60% inhibition in red cell CHE was noted in 3/4 @ the 240 mg/kg/day level.
f) Autopsy showed pitting of kidneys in 3/4 @ high level 2/3 in middle level & 1/4 in low level.
g) Test animals had more liver glycogen depletion than controls.
h) Pyelonephritis - more in test than control. Concentrated in the 0.1 mg/kg.

Subacute Dermal Tox (Rabbits) (10 G Formulation) - 3 weeks.

a) 2 ♂ + ♀ /level of 5.0, 2.5, 1.0 g/kg @ qd x 5/wk x 3 wks.
b) Some wt. loss in the 5.0 g/kg level for only 2 wks.
c) Plasma & BBC CHE were normal.
d) Hematological data - OK
e) Autopsy - no gross abnormalities
f) Pathologist finding - liver congestion and chronic pyelonephritis not correlated with Betasan-liver, kidney, skin, adrenal, gonads, and thyroid were examined.
h) No dermal irritation.