

Caswell 284A

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

PC 041401
PC 041405
PC 041404

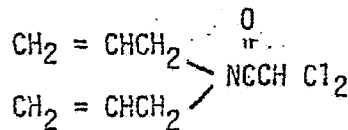
Date: August 7, 1972
Reply to
Attn of:

Subject: R-25788; N,N-diallyl dichloroacetamide, proposal for an exemption from tolerances (inert).^{1/}
To:

Mr. Drew M. Baker, Chief
Petitions Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 2F1273

Stauffer Chemical Co.
1200 South 47th Street
Richmond, California 94804



TOXICOLOGICAL EVALUATION

A. Formulations

1. Technical Product (R-25788)

N,N diallyl dichloroacetamide ----- 98.0%
N,N diallyl trichloroacetamide ----- 0.1-0.6%

2. Up to 8-1/3% in terms of active herbicide content:

Eptam[®] - S-ethyl dipropylthiocarbamate: 12:1 ratio
Sutan[®] - S-ethyl diisobutylthiocarbamate: 24:1 ratio
Vernam[®] - S-propyl dipropylthiocarbamate: 12:1 ratio

^{1/} R-25788 is to be used as a crop injury protectant in order to permit the use of higher concentrations of herbicide in crops.

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A. Toxicity data

1. New Data

a. Acute toxicity (technical R-25788)

| <u>Species</u> | <u>Sex</u> | <u>Route</u> | <u>LC/LD₅₀</u> |
|----------------|------------|--------------|---------------------------|
| Rat | M | PO | 4450 mg/kg |
| Rat | F | PO | 2540 |
| Mouse | M | PO | 2200 |
| Mouse | F | PO | 2200 |
| Guinea Pig | M | PO | 3450 |
| Guinea Pig | F | PO | 2250 |
| Rat | M | IP | 960 |
| Rat | F | IP | 950 |
| Mouse | M | IP | 1320 |
| Mouse | F | IP | 880 |
| Guinea Pig | M&F | IP | 1070 |

Potential Studies (oral administration of LD₂₅ of R-25788 plus LD₂₅ herbicide)

| | |
|--|----------------|
| Eptam LD ₂₅ + R-25788 LD ₂₅ | 5/10 mortality |
| Vernam LD ₂₅ + R-25788 LD ₂₅ | 5/10 mortality |
| Sutan LD ₂₅ + R-25788 LD ₂₅ | 5/10 mortality |

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Miscellaneous Acute Studies

| <u>Species</u> | <u>Sex</u> | <u>Route</u> | <u>LD₅₀ or LC₅₀</u> | <u>Symptoms</u> |
|----------------|------------|--------------|---|----------------------|
| Rat | F | PO | 2000 mg/kg | depression |
| Rabbit | - | Dermal Acute | no mortality up to 4640 mg/kg | |
| Rabbit | - | Acute Eye | no local effects noted | |
| Rat | F | PO | 2710 mg/kg | depression |
| Mongrel Dogs | M&F | PO | Ca. 320 mg/kg | tremors, prostration |

b. Subacute Toxicity

Rat 13 week feeding study (Woodard Research Corp*5/7/72)

Methods

Charles River rats were divided into four groups of 15 males and 15 females each and fed diets containing technical R-25788 at levels of 0, 10, 40 or 160 mg/kg/day for 13 weeks.

They were observed daily for habitus, behavior and survival; food intake and body weights were recorded weekly and each was thoroughly examined at weighing.

Hematology consisting of Hb, Hct, coagulation time, thrombocyte and total and differential counts were made from five males and five females each from the control and from the high-dose groups at 4, 8 and 13 weeks.

Blood glucose, prothrombin times and SGPT were also determined in these animals.

The following tissues from all animals were prepared for histopathological examination; (*) denotes organs weighed.

heart*
liver*
spleen*
adrenals*

lungs*
kidneys*
gonads*
thyroid*

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prostate*
pituitary gland
muscle
pancreas
mammary gland
stomach
eyes

uterus*
duodenum
bladder
lymph node
bone marrow
brain

Results

Appearance was unaffected and behavior was not impaired. Some body weight-rate-gain loss was noted in the 160 and 40 mg/kg groups as compared to controls. This appeared more prevalent in the later weeks of the experiment. Food intake was somewhat reduced at the 40 and 160 mg/kg levels; this could have been due to reduced weight gain rate in these animals.

Hematological and clinical findings were unremarkable for effect of R-25788. Organ weight ratios were not significantly affected.

Slight to moderate increase in cell size, vacuolization and degranulation of hepatic cell cytoplasm was evident in the 160 and 40 mg/kg males, and in the 160 mg/kg females but not the controls.

Conclusions

The no-effect level for this study is 10 mg/kg/day or 200 ppm in the diet, based on systemic effects.

13 week feeding study in dogs (Woodard Research Corp., 5/17/72).

Methods

Young pure-bred beagles were divided into groups containing 4 males and 4 females each. They received 0, 80, 240 or 940 ppm of technical R-25788 for thirteen weeks in the diet. Observations were made for clinical effects, weight, behavior, stool or urinary changes and emesis. Weekly body weights, TPR's and physical examination results were recorded including condition of the peltage and alteration of locomotor activity. Blood pressures and ECG's were obtained at 0, 5, 8 and 13 weeks; a thorough ophthalmological examination was performed at these times also.

Hematology was done initially and at 4, 8 and 13 weeks and included Hct., Hb., Sed. rate, total and differential leukocyte and thrombocyte counts and coagulation time.

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Clinical chemistry determinations including BUN, alkaline phosphatase, glucose, prothrombin times, SGOT and SGPT were performed at the same intervals.

Urinalyses initially and at 4, 8 and 13 weeks included examination for appearance, pH, Sp. Gr., albumin, glucose and formed elements.

Following death by exsanguination the following organs from the control and 960 ppm dogs were prepared and examined histopathologically: (*) = organs also weighed.

| | |
|-----------------|------------------|
| heart* | lungs* |
| liver* | kidneys* |
| spleen* | thyroid* |
| adrenal | prostate* |
| uterus* | gonads* |
| pituitary* | brain |
| peripheral N. | esophagus |
| intestine | stomach |
| pancreas | salivary Gl. |
| thymus | trachea |
| gall bladder | muscle |
| urinary bladder | lymph node |
| bone marrow | spinal cord |
| mammary Gl. | skin (abdominal) |

Results

Careful examination of the data failed to reveal any effect that could be attributed to administration of R-25788 to dogs for 13 weeks.

Conclusions

A no-effect level for toxic action of R-25788 is greater than 960 ppm in the diet of dogs for thirteen weeks.

Rat Teratology Study (Woodard Research Corp., 1/28/72).

Methods

Twenty impregnated female Charles River rats per group were exposed to 0, 10 or 40 mg/kg/day of R-25788 in the diet from day 6 through day 15 of gestation. Body weight and feed consumption were measured initially and at days 6, 15 and 20 of gestation.

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Fetuses were obtained by Caesarian section on day twenty and the number of viable and dead fetuses, total body weight of viable fetuses and external signs of fetal abnormality were recorded.

Uterine implantation and resorption sites were counted. Numbers of corpora lutea was also determined.

One third of the fetuses were preserved in Bouin's fixative and the heads were sectioned for gross examination. The visceral cavities were opened and their contents were examined for abnormalities. The remaining fetuses were cleared and stained for skeletal examination.

Results

The data showed that there were no differences between the three groups; no gross abnormalities could be detected that might have resulted from R-25788 treatment, and the groups were comparable for visceral and skeletal effects.

Maternal Effects

| | Dose Level - mg/kg/day | | |
|--------------------------------|------------------------|---------|-------|
| | Control | R-25788 | |
| | | 40 | 10 |
| Females pregnant per group | 20/20 | 18/20 | 18/20 |
| Total live fetuses | 277 | 200 | 219 |
| Total dead fetuses | 0 | 0 | 0 |
| Live fetuses per litter | 11.4 | 11.1 | 12.2 |
| Total fetal body wt. (g) | 846 | 707 | 804 |
| Mean fetal body wt. (g) | 3.73 | 3.54 | 3.84 |
| Total male fetuses | 113 | 95 | 112 |
| Total female fetuses | 114 | 105 | 107 |
| Total implantation sites | 241 | 216 | 234 |
| Implantation sites, left horn | 106 | 107 | 108 |
| Implantation sites, right horn | 135 | 109 | 126 |
| Total resorption sites | 14 | 16 | 15 |
| Per cent resorption | 5.8 | 7.4 | 6.41 |
| Corpora lutea of pregnancy | 243 | 235 | 245 |

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Conclusions

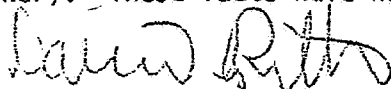
R-25788 is not teratogenic in rats at levels up to 40 mg/kg when administered orally from day 6 through 15 of gestation.

C. Recommendations

The most sensitive test animal appears to be the rat, with a 13 week feeding no-effect level of 200 ppm R-25788 in the diet. Those symptoms noted at higher levels were not in my opinion severe. In summary, this material has a very low level of toxicity in the tested animals and an exemption from tolerances would seem to be appropriate.

We note that the purpose in adding this chemical to certain herbicides is to protect crop plants against injury by higher than normal concentration of the herbicide. We defer to CB as to the effect such increase in tank concentration of herbicide might have on residue levels of those herbicides in RAC's.

Petitioner has added certain omissions to the data in section "D" (letter of 7/5/72), and has requested filing under 408.(e) of FFD&CA as an inert (letter of 5/25/72). It will be filed under 408.(d) instead (letter of 8/2/72, D.M. Baker). These facts have no bearing on the above conclusions and recommendations.



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Toxicology Branch
Pesticides Tolerances Division

cc: JGCummings
PRD/EPA
Atlanta Branch (CLewis)
Perrine Branch
Division Reading File
Branch Reading File
PP# 2F1273

R/D Init:GEWhitmore 8/4/72
DLRitter:dtb 8/9/72
Init:CHWilliams

CHW
5/9/72

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