Caswell 284A

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

$$CH_2 = CHCH_2 \diagdown \overset{O}{\overset{\|}{N}}CCH\,Cl_2$$
$$CH_2 = CHCH_2 \diagup$$

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.

A. Toxicity data

1. New Data

a. Acute toxicity (technical R-25788)

Species	Sex	Route	LC/LD_{50}
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

Potentiation Studies (oral administration of LD_{25} of R-25788 plus LD_{25} 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

Species	Sex	Route	LD_{50} or LC_{50}	Symptoms
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*

prostate*	uterus*
pituitary gland	duodenum
muscle	bladder
pancreas	lymph node
mammary gland	bone marrow
stomach	brain
eyes	

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 pellage and alteration of locomotor activity. Blood pressures and ECG's were obtained at 0, 5, 8 and 13 weeks; a thorough opthalmalogical 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.

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.

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 R-25788		
	Control	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 resorpton sites	14	16	15
Per cent resorption	5.8	7.4	6.41
Corpora lutea of pregnancy	243	235	245

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 ommisions 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.

David L. Ritter

David L. Ritter, Pharmacologist
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 8/9/72