UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

454BB

SUBJECT: Prowl, N-(1-ethylpropyl)-3,4,-dimethyl-2,6-dinitro benzenamine, also CL 92553 and AC 92553. American Cyanamid, Herbicide.

DATE: 2/22/75

FROM: TB

CASWELL FILE

TO: Product Manager

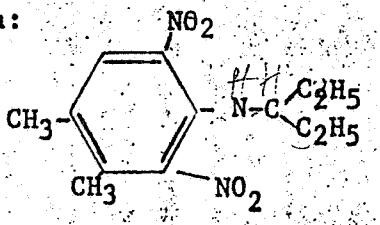
Pesticide Petition and requested tolerances:

5F1556	5G1567	5G1580
0.1 ppm in corn grain forage, and fodder, and cotton seed	0.1 ppm in cotton seed	0.1 ppm in soy beans forage and hay

Registration: Prowl 4E 241-EXP-X

Previous Petitions: 4G 1451 0.1 ppm in corn grain, forage and fodder

Chemical Formula:



Formulation:

PROWL 4E Herbicide

Active Ingredient:	%W/W
PROWL Technical	49.2
Inerts:	(44.3 real)
[redacted]	

* are cleared under 180.1001(d). We have no records of clearance of the [redacted] is permitted for use on growing crops.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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Comments and Conclusions:

Registration: The parent compound has a very low toxicity, but the formulation contains a high percentage of [redacted] and also is irritating to the skin. TB therefore requests that the signal word be changed to "Danger" and that the side panel warnings be extended to include "causes eye and skin irritation". The first aid statment also must be changed because [redacted] containing formulations vomiting should NOT be induced.

Tolerances: Prowl, N-(1-ethylpropyl)-2,3,-dimethyl-2,6,-dinitro-benzenamine has a very low toxicity. In long-term studies, reproduction studies and 90-day studies the Nel for rats, mice, and dogs was at least 500 ppm. At the next higher dose (5000 ppm) toxic effects were marginal, showing slight depressions of weight gains, increased liver weight, etc, but no severe toxic signs, Other considerations permitting, the requested tolerances of 0.1 ppm on corn, cotton seed, and soy beans can be toxicologically supported.

Toxicological Evaluation:

Some of these tests were previously reviewed, Dr. R. Schmidt, PP# 1451, but expecially long term studies had only interim reports at that time.

Acute tests:	Oral LD_{50} male rat	1250(560-2780) mg/kg	prostration and
	Oral LD_{50} female rats	1050(310-3610) mg/kg	lethargy
	Oral LD_{50} dog (f. and m.)	>500 mg/kg	
	Oral LD_{50} male mouse	1620(860-3070) mg/kg	lethargy
	Oral LD_{50} female mouse	1340(950-1880) mg/kg	
	Dermal LD_{50} male rabbit	>5000 mg/kg	

Skin irritation: (rabbit) no irritation (score 0), 0.5 g/application.

Eye irritation: (rabbit) no irritation (transient conjunctivitis in one rabbit at 24 h,, 0.1 g/eye)

30-day feeding studies with rats and mice: rats were fed 800, 1600 and 3200ppm and mice 500, 1000 and 2000 ppm (10 m and 10 f per level). Plasma glucose for male rats at 3200 ppm was slightly higher than controls. organ weights (livers and kidneys) were sometimes statistically different ($p<0.05$) but the effects were neither dose related nor consistent (liver-weights increased for rats, decreased for mice).

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2

30-day feeding with dogs: Beagles were exposed to 0.125, 0,25 and 1.0 g/kg/day. At the lower dose in the diet for two weeks then by gelatin capsule at the high doses by gelatin capsules only. Food consumtion was slightly affected by the treatment, and thus weight gains, but the changes were very minor. Other parameters such as organ weights, hematology, and clinical blood chemistry showed no deviations from the norm.

Acute studies with 4E formulation:

LD_{50} male rats 3380(2810-4070) mg/kg. The formulation was irritating to the skin (score 5 on a scale of 8; Draize score). The formulation was less irritating to eyes (Draize score of 17 at 24 h.; 6 at 72 h.)

Inhalation study: Rats were exposed to the technical compound at a nominal concentration of 320 mg/l for 4 hours. No death or adverse effects other than irritability and sluggishness were observed.

21-day dermal study: (technical and 4E formulation) Rabbits were treated daily for 6 hours, 5 days per week for 3 weeks. The technical product was applied at levels of 250, 500 and 1000 mg/kg and the formulation was applied at 0.5, 1.0, and 2.0 ml/kg. Controls received sham formulation (vehicle) without technical compound. No systemic toxicity was noted in the treated animals. The animals exposed to the technical product showed only slight or no signs of edema and erythema. The animals treated with formulation showed slight to moderate erythema and edema but less so than the vehicle treated controls which showed moderate to severe reactions.

18-month carcinogenicity studies in mice: (Bio-dynamics, East Milestone, N.J.) Mice (Charles River CD-1) were exposed to 100, 500, and 2500 ppm tech, product. After 8 weeks the 2500 ppm group was exposed to 5000 ppm. There were 150 mice per group. The mean body weights of high-dose females were significantly lower througout the experiment; this effect was not related to lessened food intake. Adrenal weights (males) and adrenal/body weights (males and females) were higher at the high-dose level, so were thyroids and thyroid/body weights. No histopathology in these tissues was apparent. Hematology was normal in all groups. Clinical chemistry, including ChE was normal with the exception of an elevated blood glucose level in one female exposed to 100 ppm (no dose response). Histopathological examination showed no remarkable pathology and carcinomas.

3

90-day and 2-year studies in rats: Rats (Long-Evans) were exposed to 100, 500, and 2500 (5000 after 6 weeks) ppm via diet. 120 rats were used per group, 20 were sacrificed for the 90-day study. The mean body weights were lower for both sexes in the high-dose group starting with the 5th week. Hematology was unremarkable. At 90 days the alk. phosphatase levels for high and medium males and all females were slightly depressed. This effect was not noted at 24 months. Fluctuations in ChE levels were noted but were not dose related nor were the differences extreme. The liver weights for males and females were significantly higher ($p<0.01$) at the high-dose level at 90 days. At the lower level the significance of any effect was less ($p<0.05$) and not consistent. After 24 months the effect on liver weights persisted at the high level but at the lower levels no effects were noted. There was also a hepatocyte hypertrophy and hyperplasia noted at the high level after 2 years. No increase in tumor or cancer incidence was note at any feeding level.

Effects on male mammary glands after 90-feeding; 20 weanling rats (Sprague-Dawley) were fed 2500 ppm for 6 weeks and 5000 ppm thereafter. The mammary glands were examined histologically. The appearance of the glands was unremarkable, without any signs of hyperplasia (Pharmacopathics Res.)

3-generation reproduction study in rats (Long-Evans): 10 males and 20 females per generation. The animals were exposed via diet to 500 and 5000 ppm of techn. material. The parents F_0 were mated three times. The second generation was selected from the F_{1c} group; they were mated twice to produce the F_{2a} and F_{2b} litters. Each of these litter groups were mated once to produce the F_{3a} and $F_{3a'}$ litters. The most flagrant evidence of toxicity at the high-dose was the decreased mean weight of pups at 21 days and a slight possibility of lessened survival rate of pups to 21 days. The investigator, therefore, removed the high-dose diet from lactating females until pups were weaned to avoid these minor effects. Considering the minimally toxic effects, this would really not have been necessary. The two F_3 generations were investigated for abnormalities. No significant abnormalities were found in treated groups (small or missing testicles were observed in 4 of 243 offsprings; about 120 males).

90-day feeding tests with dogs: The feeding levels were 62.5 mg/kg/day (2500 ppm) 250, and 1000 mg/kg/day. The two higher doses were administered with gelatin capsules. 8 dogs were used per level. The effects noted were weight losses in two of the middle-dose group and in 6 of the dogs in the high-dose group. Hematology was normal. Clinical chemistry values were also normal with one elevated BUN value at the high-dose level. Tissues examined grossly and microscopically did not show any pathological changes.

Dominant lethal test (rat): Each group consisted of 15 weanling male rats. They were exposed for 60 days to 500 and 5000 ppm via diet and then mated once a week for 8 weeks to virgin females. The females were sacrificed on the 13th day of pregnancy. The number of pregnancies, corpora lutea, implantation sites, live fetuses and resoprtion sites were determined. There were no remarkable differences between controls and treated animals.

Teratology Study (rats, Charles River): 20 animals per group were dosed with 500 and 1000 mg/kg/day orally (intubation) on day 6 to 15 of gestation. No teratogenic effect was noted. At the high dose 2 females died and fetal body weights were slightly reduced.

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Toxicology Branch
Registration Division

cc: Branch Reading File
REngler:ir: 2/22/75
Initial G.E. Whitmore

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draft 2/21/75 G. E. W.

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SUBJECT: Prowl 4E, Registration 241-EXP-X, Amendment to memo dated 2/22/75

DATE: MAR 19 1975

FROM: TB

TO: Product Manager

Related Petitions: 5F1556, 5G1567, 5G1580

On page 2, under comments and conclusions TB asked that the signal word be changed to "Danger" and that the irritation to the skin (rather than eyes) must be stressed. This was based on a skin irritation score of 5 (Draize), all other toxicity studies would not indicate the category I warning. Reconsidering this situation, it was concluded that the signal word should be left as is, namely "Warning" but that the hazard from dermal exposure still must be stresse on the side panel. All other conclusions about Prowl and the 4E formulation remain the same.

NOTE: There are no strict guidelines as to which signal word should be used when skin irritation is the determining factor. The Draize score is not related to such terms as corrosive or irritating. It would be helpful to arrive at a consensus in order to avoid inconsistencies in labeling. It could, for example, be proposed that the following relation of Draize score and cautionary statement should be used:

Draize score	Signal word
0-2	None
2-4	Caution
4-6	Warning
6-8	Danger

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cc: Branch Reading File

REngler:gac 3/13/75

Initial: G.E. Whitmore

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6