108501

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: March 23, 1979

SUBJECT: Pesticide Petition 9F-2134 & Registration No. 241-243. Tolerance of 0.1 ppm of Prowl in/on potatoes. Caswell#454BB

FROM: John Doherty, Ph.D
Toxicology Branch (TS-769)

TO: R.J. Taylor
Product Manager#25 (TS-767)

Recommendation - PP#9F2134

1) PP#9F2134 cannot be favorably approved until the questions raised by Dr. R. Engler concerning the 2-year rat study are answered to the satisfaction of TOXICOLOGY BRANCH, (see the 8 pt review and Engler's memo dated Jan. 8, 1977 enclosed).

2) The relevance of the above questions concerning the pathology report is stressed since CHEMISTRY BRANCH has denied this tolerance because of the presence of nitrosamines in the product. Their recommendation (see Smith memo Jan. 22, 1979, PP#9F2134), stated that a residue of 0.018 ppm of nitrosamines would be maximum.

3) OPP policy on the nitrosamine question is not yet established. The dual problem of their being significant (?) residues of nitrosamines and unanswered questions concerning the pathology report make it improper to grant this tolerance at this time.

4) The 2-year rat study should be audited if no response is made to this inquiry.

Remarks: Reg. No. 241-243

1) The formulation designated as PROWL has been changed in composition several times since earlier reviews by TOXICOLOGY BRANCH. See the letter of R. Mountfort to A. Bliznick, Jan. 10, 1979. The signal word is WARNING and this was based upon skin irritation results.

2) The acute toxicity of technical PROWL is as follows.

A)	Acute Oral Rat LD50	1.25 gm/kg male/1.05 gm/kg female
B)	Dermal Rabbit LD50	> 5 gm/kg
C)	Skin Irritation	Not irritating
D)	Eye Irritation	Not irritating

(Referenced Petitions 4G1451 and 5F1556)

3) Eye and Skin irritation are frequently due, in part, to the inerts in the formulation. Therefore, TOXICOLOGY BRANCH requests the following:

1. Dermal Irritation - rabbits

2. Eye Irritation - rabbits

The tests must be conducted with the product as formulated.

Other Remarks:

1) In a review by R. Engler concerning PP#7G1923, dated April 7, 1977, it was requested that a cataractogenic study be submitted. This study is reviewed here and appears to demonstrate a lack of cataractogenic potential. However this study was conducted by IBT and is dated Jan. 5, 1977. It may require validating.

2) Several mutagenicity tests with PROWL are also reviewed here and no evidence of mutagenicity was demonstrated.

8 pt. Review of PROWL

1) TOXICOLOGICAL DATA considered in evaluating PP#9F2134 are as follows:

A) For technical PROWL subacute and long-term tests.

1)	21 day dermal (rabbit)	No effect at 1 g/kg/day
2)	90 day rat oral	NEL ≥ 500 ppm
3)	90 day dog oral	NEL ≥ 62.5 mg/day or 2500 ppm
4)	2-year rat feeding	NEL > 500 ppm, no oncogenic effect
5)	18-month mouse feeding	NEL > 500 ppm, no oncogenic effect
6)	3-generation rat reproduction	NEL > 500 ppm
7)	Teratology (rat)	No effect at 1 g/kg/day
8)	Dominant Lethal Study	No effect at 2500 ppm
9)	Effect on male mammary gland	No effect at 5000 ppm

The above are abstracted from a previous review by R. Engler, Feb. 18, 1977 concerning PP#7G1896.

2) Data considered desirable but currently lacking.

a) The teratology study was done by IBT and has not yet been validated.
b) A memo dated January 8, 1977 written by R. Engler to R. Taylor concerning a special follow up report on the rat 2-year study raised several serious questions concerning the validity of the NEL for this study. American Cyanamid Company has not yet replied to this letter in writing.

Therefore the NEL may be lower than the 500 ppm stated.

3) TOXICOLOGY BRANCH has no knowledge if the IBT study will be validated or if American Cyanamid will respond to the 2-year rat study pathology report questions.

4) Other tolerances are listed on the computer printout sheet.

5) If a NEL of 500 ppm based upon the rat study is used in conjunction with a 100 fold safety factor the ADI will be 0.2500 mg/kg/day and the MPI will be 15.000 mg/day/60 kg person.

Granting a tolerance of 0.100 ppm on potatoes will change the % ADI from 0.05% to 0.11%.

6) Answered in 5 above.

7) No pending regulatory actions against this chemical other than it is on the list of compounds containing nitrosamines. Pendimethalin is not on the list of RPAR chemicals.

8) The determination of the ADI was based upon a 2-year rat study that needs further verification that 500 ppm was indeed the NEL level.

17-Day Cataractogenic Study with Prowl Technical in White Leghorn Chicks.

Industrial Bio-Test, Jan. 5, 1977, IBT No. 8580-09771. (Wedge's Creek Research Farm)

4 groups of 15 chickens that were 14 days old were fed diets of either standard chick ration, 1,000 or 3,000 ppm of technical PROWL or 3,000 ppm of 2,4-dinitrophenol (positive control). The diets were administered for 17 consecutive days.

All animals dying during the study and the survivors (after sacrifice) were subjected to gross postmortem examination for lenticular opacity.

Results

No birds receiving the test chemical (PROWL) died during the experiment. Gross autopsy revealed no differences in the lens of the chicks receiving PROWL when compared to the untreated controls.

The positive control (2,4-dinitrophenol) animals developed bilateral cataract within hours after administration of the chemical. Twelve of the 15 chicks in this group died.

This test provides SUPPLEMENTARY DATA.

There are no guidelines for such a test at present within EPA. This test demonstrates that PROWL does not have serious potential to produce lenticular damage.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

Mutagenicity Tests of Typical PROWL Herbicide and of Minor Component CL 94,269.

R.H. Gustafson, Ph.D, American Cyanamid Company. (no report date or study number)

Three samples of PROWL (N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine), technical grade typifying commercial production batches were evalulated in the Ames Mutagenicity Assay. Also, two samples of a CL 94,269, a nitrosamine found in the technical product, was also tested.

A. The Salmonella strains were supplied by Dr. Bruce N. Ames and were histidine auxotrophs. A reverse mutation is required before these bacteria can grow in the absence of histidine. E. Coli was supplied by Dr. R. McCalla, this is tryptophan auxotroph. Both the "plate tests" and "disc tests" with and without activation of the test chemicals by rat liver S-9 microsomal supernatant.

All test compounds were evaluated at 1000, 100 or 10 µg per plate and assayed in triplicate for each organism with and without metabolic activation. At 1000 µg/plate there was usually a solubility problem, but at the lower levels, all chemicals were in solution.

PROWL or its nitroso contaminant were not found to cause mutations in any of the systems when the plate test was run with and without metabolic activation. In each of the tests the respective positive controls gave the expected results.

PROWL and its nitroso contaminant were also negative in the Ames disc test and the positive controls gave the expected results.

B. The "host mediated assay" was also run using crude process PROWL Cl 94,269 (99% purity) at dose levels of 6.4,10.0 and 16.6 mg/mouse. S. typhimurium test or strain was used for this assay and the standard mutagen, dimethylnitrosamine, was positive in this test. No evidence of mutation effect was noted for the test chemicals.

These tests are CORE MINIMUM and demonstrate a lack of mutagenicity at the levels tested.

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