DATE: March 21, 1980

CASWELL FILE

SUBJECT: PP 9F2134 and EPA Reg. No. 241-243. Proposed Tolerance of 0.1 ppm Pendimethalin in/on Potatoes. Caswell #454BB

FROM: John Doherty 3/25/80
Toxicology Branch/HED (TS-769)

TO: R. J. Taylor, PM #25
Registration Division (TS-767)

THRU: M. Adrian Gross, Chief
Toxicology Branch/HED (TS-769) 3/26/80

Conclusion:

This memo is intended to address all outstanding toxicological concerns related to this subject tolerance other than the "nitrosamine problem," which has been separately dealt with in a series of recent memos by M. Adrian Gross, Chief, Toxicology Branch.

With regard to the other outstanding toxicological concerns, the presently available toxicological data has been judged adequate to support the proposed tolerance of 0.1 ppm for residues of Pendimethalin in or on potatoes and the associated label change. It is suggested, however, that the applicant be requested to agree to initiate within a reasonable period of time the following two additional studies:

A. 6 month or longer subchronic feeding study in a non-rodent species (dogs)

B. Teratology study in a second species.

Remarks:

A. Re: PROWL Herbicide, EPA Reg. No. 241-243

i. The inerts in this product are "cleared" under 40 CFR 180.1001 (d). See RCB memo by A. Smith dated January 22, 1979 on PP 9F2134.

ii. This product may be improperly labeled. A previous memo (J. Doherty; March 23, 1979) requested additional acute studies on this formulated product to clarify this issue. Results of these acute studies should be submitted as soon as possible.

B. Re: RCB Review and "Nitrosamine Problem"

i. The RCB review of this action (A. Smith; January 22, 1979) expressed reservations concerned with the nitrosamine content of PROWL. This issue has been addressed elsewhere by M. Adrian Gross (see above).

C. Re: Outstanding toxicological concerns other than the "nitrosamine problem" related to this subject tolerance (Answers to questions raised in the memo of J. Doherty; March 23, 1979; PP 9F2134).

i. In the original Toxicology Branch review of the 2-year rat chronic feeding/oncogenicity study referenced in support of this action (R. Engler; 1/8/77 and 2/18/77), questions were raised concerning the histopathologic results that were reported in this study. In a subsequent submisssion by the applicant (EPA accession #096138), the requested answers and additional information on the histopathologic results were supplied to EPA. On the basis of this additional information, the original NOEL set for this study (500 ppm) is now being changed to 100 ppm. Louis Kasza, DVM, Toxicology Branch pathologist, concurs with this reassignment of the NOEL (personal communication, 3/19/80).

The rationale for this reassignment is as follows:

An increase in secretory globules was observed in the follicular epithelial cells of the thyroid in both the high dose (5000 ppm) and intermediate dose (500 ppm) males and females when compared to controls. This increase appears to be dose dependent and to have resulted from administration of the test material.

This reassignment of the NOEL for this study to 100 ppm supersedes an earlier interpretation of the same additional pathologic data given in a memo by R. Gessert, 1/16/79. Although the observed thyroid effect is not considered to be a degenerative morphologic lesion, it nevertheless is considered to be a significant effect due to administration of the test material.

This issue (answers to Engler's questions and the assignment of a NOEL for this study) is now resolved.

ii. The IBT study concerned with determining the cataractogenic potential of Pendimethalin has recently been audited and validated. Results of this study were negative for cataracts. According to G. Burin, (personal communication 3/19/80) of Toxicology Branch, this study is valid and acceptable. Validation of this IBT cataractogenic study is now resolved.

iii. In response to EPA's request, the registrant contracted to audit a rat teratology study conducted by IBT and submitted in support of PP 5F1556 (EPA Accession No. 112850). The results of this audit are summarized in L. Anderson's memo dated February 4, 1980. According to this memo, the study audited is Invalid. The particular study that was audited, however, is not the same teratology study with Pendimethalin that was submitted to EPA (IBT apparently has 2 rat teratology studies with Pendimethalin).

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Thus, EPA's request to audit the study in question has not yet been fulfilled. Until an adequate audit of this study has been received by Toxicology Branch, the IBT rat teratology study cannot be used in support of registrations and tolerances.

However, the registrant has recently submitted an additional teratology study in rats performed by Hazelton Laboratories (Project No. 362-155, August 17, 1979). This study was classified as Core-Guidelines (see W. Dykstra memo dated January 24, 1980). Teratogenic or fetotoxic effects were not observed at doses up to 500 mg/kg/day. Therefore, for the purposes of registrations/tolerances, there is at least one valid teratogenic study. The issue of auditing the IBT study, therefore, need not hinder this current action with Pendimethalin.

8-Point "Free Standing" Summary

1. Data considered in 'setting" the tolerance (selected studies).

	Study	Results
i.	Acute Oral LD50, rats	1.25 gm/kg, males 1.05 gm/kg, females
ii.	Acute Dermal LD50, rabbits	>5.0 gm/kg
iii.	Skin and Eye Irritation, rabbits	Not irritating
iv.	21-day Dermal, rabbits	NOEL = 1 gm/kg/day
v.	90-day feeding study, rats	NOEL = 500 ppm
vi.	90-day feeding study, dogs	NOEL = 62.5 mg/kg/day (or 2500 ppm)
vii.	18-month oncogenesis, mice	NOEL = 500 ppm, no oncogenic effects
viii.	2-year chronic feeding/ oncogenesis, rats	NOEL = 100 ppm, no oncogenic effects

(The NOEL for this study has been reassigned to 100 ppm. See "Remarks" above.)

ix.	3-generation reproduction, rats	NOEL = 500 ppm
x.	Dominant Lethal Study	No effect at 2500 ppm (highest dose)
xi.	Effect on male mammary glands	No effect at 5000 ppm (highest dose)

(The above is extracted from a previous review by R. Engler; Feb. 18, 1977, concerning PP 7G1896.)

xii. Teratology, rats (Hazelton study)	Not teratogenic or fetotoxic at doses up to 500 mg/kg/day.
(See W. Dysktra memo, dated January 24, 1980)	
xiii. Cataractogenic study (IBT Study)	Negative at 3000 ppm
xiv. Ames Mutagenicity Assay	Negative at levels up to 1000 µg/plate
xv. Host Mediated Assay, mice	Negative at doses up to 16.6 mg/mouse

(See J. Doherty memo, dated March 23, 1979)

2. Data considered desirable but currently lacking.

   i. 6-month or longer subchronic feeding study in a non-rodent species (dogs)

   ii. Teratology study in a second species

3. Toxicology Branch has suggested that the applicant be requested to initiate these two studies. See "Conclusion" in this memo.

4. See attached computer printout for summary of other tolerances granted for this pesticide.

5. The % ADI used up will be increased to 0.53% if this tolerance (potatoes) is established.

6. The MPI is 3.00 mg/day/60 kg person. The 2-year rat chronic feeding/oncogenicity study with a NOEL of 100 ppm was used to calculate the ADI. The ADI is 0.05 mg/kg/day. A safety factor of 100 was used.

7. None known at this time.

8. Establishment of this tolerance should be contingent upon a favorable resolution of the "nitrosamine problem". See conclusion.

OPP:HED:TOX: J.DOHERTY:sb 3/21/80 X73710 TS-769 Rm. 816 CM 2 #5

File last updated 3/24/80

ACCEPTABLE DAILY INTAKE DATA

RAT, Older NOEL		S.F.	ADI	MPI
mg/kg	ppm		mg/kg/day	mg/day/60kg
5.000	100.00	100	0.0500	3.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day/1.5kg
Corn,grain(68)	0.100	1.00	0.00150
Cottonseed(41)	0.100	0.15	0.00022
Soybeans(148)	0.100	0.92	0.00138

MPI	TMRC	% ADI
3.0000 mg/day/60kg	0.0031 mg/day/1.5kg	0.10

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Unpublished, Tox Approved PP6F1741,6G1740,6G1739,7G1896,7G1923

CROP	Tolerance	Food Factor	mg/day/1.5kg
Peanuts(115)	0.100	0.36	0.00054
Beans(9)	0.100	2.04	0.00306
Sunflower(156)	0.100	0.03	0.00005
Peas(117)	0.100	0.69	0.00104

MPI	TMRC	% ADI
3.0000 mg/day/60kg	0.0078 mg/day/1.5kg	0.26

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Current Action 9F2134

CROP	Tolerance	Food Factor	mg/day/1.5kg
Potatoes(127)	0.100	5.43	0.00814

MPI	TMRC	% ADI
3.0000 mg/day/60kg	0.0159 mg/day/1.5kg	0.53

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2? JAN 1979

PP# 9F2134: Pendimethalin in Potatoes. Evaluation of analytical method and residue data

Alfred Smith, Chemist, Residue Chemistry Branch, HED (TS-769)

R. J. Taylor (PM #25), FHB, RD (TS-767) and Toxicology Branch, HED (TS-769)

Thru: Chief, RCB

The American Cyanamid Company proposes a tolerance for combined residues of the herbicide pendimethalin, N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamine, and its metabolite (4-(1-ethylpropyl) amino)-2-methyl-3,5-dinitro benzyl alcohol in or on potatoes at 0.1 ppm.

Tolerances are established for pendimethalin at 0.1 ppm in corn grain, fodder and forage, cottonseed, soybeans, soybean forage, and soybean hay (§180.361).

Conclusions

1. Technical pendimethalin and the pendimethalin formulation contain a nitrosoamine component at levels [redacted].

2. The nature of the residue in plants and animals is adequately understood.

3. Adequate analytical methods are available for enforcement of the proposed tolerance.

4. Residues, if any, in potatoes would be less than the proposed tolerance. The proposed toleranee level represents the analytical sensitivity of the residue method.

5. Residues of metribuzin or Eptam in or on potatoes are not likely to exceed their established tolerances.

6. Residues of the nitrosoamine component, if any, in potatoes would be a maximum of approximately [redacted]. We defer to Toxicology Branch as to the toxicological significance of nitrosoamines at such levels.

7. No residues are likely to occur in eggs, milk, meat, fat, or meat byproducts of livestock (§180.6(a)(3)).

Recommendation

We recommend against the proposed tolerance. A favorable recommendation is contingent upon the following:

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

1. We have estimated that nitrosoamine residues, if any, in potatoes would be a maximum of [redacted] If Toxicology should consider this level as toxicologically significant, then residue data on potatoes obtained with a validated analytical method will be necessary.

Detailed Considerations

Proposed Uses

Pendimethalin is formulated as PROWL(R), an emulsifiable concentrate containing 44% active ingredient (4 lb a.i./gal.), for preemergence incorporated application to soils planted to potatoes. Pendimethalin alone: apply at 0.75-1.5 lb act/A depending upon the soil composition.

Tank-Mix:

Apply pendimethalin + metribuzin as a preemergence treatment after planting up to ground cracking but before potatoes and weeds emerge. Where drag-off is practiced, apply before, at or after drag-off but before potatoes and weeds emerge completely. Apply at rates of 0.5-1.5 lb pendimethalin/A + 0.25-0.5 lb metribuzin/A depending on the soil type. Apply 0.5-1.5 lb Prowl/A + 2.6-6.1 lb Eptam/A as above.

Metribuzin, (4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5 (4H)-one), is registered for use on potatoes at rates of 0.5-1.0 lb act/A and has an established tolerance of 0.6 ppm in potatoes (§180.332).

Eptam, (S-ethyl dipropylthiocarbamate), is registered for use on potatoes as above at a maximum rate of 6.1 lb act/A and has an established tolerance of, 0.1 ppm (§180.117).

The formulations inert ingredinets are cleared for use under §180.1001.

The manufacturing process for technical pendimethalin is included in PP# 5F1556. Technical pendimethalin contains 91-94% pendimethalin. Technical pendimethalin also contains [redacted] of a nitrosoamine component, [redacted] as determined by high pressure liquid chromatography (see PP# 5F1556). The Prowl formulation will contain approximately [redacted] of the nitrosoamine component. When pendimethalin is applied to soils at the maximum rate of 1.5 pounds per acre, the nitrosoamine component will be applied to soils at a rate of about [redacted] If all the nitrosoamine were taken up and absorbed by the potatoes, then the potatoes would contain a maximum level [redacted] ppm of the nitrosoamine component. (One acre of potatoes yields approximately 25,700 pounds of potatoes. Agricultural Statistics, 1977).

Nature of the Residue

We have considered the plant and animal metabolism of pendimethalin in previous reviews (PP6G1739, PP51556, and PP6G1740). Pendimethalin is absorbed, metabolized, and translocated by bean, potato, corn, cotton, and peanut plants. The significant components of plant residues are the parent compound pendimethalin and its benzyl alcohol metabolite.

Feeding studies with animals show ingested pendimethalin is extensively metabolized and excreted by cows, goats, and rats. Some deposition of residues occurs in tissues, but no tendency toward storage or concentration is noted.

The nature of the residue in plants and animals is adequately delineated.

Analytical Methods

Two general procedures are provided for residue determinations. The parent compound pendimethalin is determined as such following extraction and cleanup steps. The benzyl alcohol metabolite is determined as the acetyl derivative following extraction and cleanup steps. Both compounds are determined using gas chromatography with an electron capture detection system (ECGC). A confirmatory procedure is also available (PP5F1556).

Untreated (control) samples of potatoes and potato vines had <0.012 ppm pendimethalin-equivalent residues. Control samples were fortified with pendimethalin and its metabolite at levels of 0.05-1.0 ppm. Recoveries were 68-137%.

The methods have been successfully tested with pendimethalin and its benzyl alcohol metabolite on cottonseed at levels of 0.05 ppm and 0.10 ppm (PP5F1556).

We believe that the results of the method trials can be extended to include potatoes.

Adequate analytical methods are available for enforcement.

The methods for metribuzin and Eptam have been approved by enforcement and are included in PAM, Volume II.

Residue Data

Samples were obtained from plots in states of the major potato growing regions. The soils had been treated with pendimethalin alone or in tank-mix combinations with metribuzin or Eptam according to the proposed uses.

Pendimethalin alone: treatments at rates of 1.0-4.0 lb act/A (approximately 2.7X maximum proposed rate) yielded no detectable residues (<0.05 ppm, method sensitivity) in vines or potatoes at intervals of 59-162 days after treatment (PHI).

Tank-Mix uses: treatments at rates of 0.75-2.0 lb pendimethalin/A + 0.25-0.75 lb metribuzin/A yielded no detectable residues of pendimethalin (<0.05 ppm) or metribuzin (<0.05 ppm) in potatoes.

Treatments at rates of 0.75-1.5 lb pendimethalin/A + 0.25-3 lb Eptam/A yielded no detectable residues of pendimethalin (<0.05 ppm) or Eptam (<0.02 ppm) in potatoes.

Residues of pendimethalin and its metabolite, either alone or in tank-mix combinations with metribuzin or Eptam, are not likely to exceed the proposed tolerance due to the proposed uses.

Residues of metribuzin or Eptam are not likely to exceed their established tolerances from the tank-mix uses.

Meat, Milk, and Eggs

Livestock feeding studies are submitted in PP5F1556. Lactating cows and lactating goats were fed pendimethalin daily at total diet levels of 0.5, 1.5, and 20 ppm (goats) and dry weight feed level of 1 ppm (cow) for periods of 10-21 days. No residues were noted in the milk of cows or goats due to feeding levels of 0.5-1.5 ppm.

Tissue analyses were performed only on the goats. Low levels of total radioactivity were noted. The liver had activity equivalent to 0.03, 0.04, and 0.25 ppm corresponding to the 0.5, 1.5, and 20 ppm feeding levels. The kidney had respective residue levels of 0.01, 0.04, and 0.09 ppm. The fat had residue levels of 0.01, 0.01, and 0.03 ppm from respective feeding levels of 0.5, 1.5, and 20 ppm. All other tissues had no detectable radioactivity (<0.01 ppm, method detection limit) from all feeding levels. Characterization of the urine and feces showed pendimethalin to be extensively metabolized and rapidly excreted. It is therefore probable that pendimethalin and its metabolite represent only a small portion of the total radioactivity noted in some tissues.

Potatoes are occasionally fed to livestock and constitute up to 50% of the diet.

Assuming a total diet of these items, all of which contain residues at 0.1 ppm, then the feeding study ingestion levels of 0.5, 1.0, and 1.5 ppm represent exaggeration factors of 5X-15X. The exaggeration factors are likely to be greater since pendimethalin residues, if present at all, represent only a fraction of the residues present in the feeding studies.

In view of the foregoing, it is unlikely that residues of pendimethalin will occur in the meat and milk of ruminants (cows, goats, sheep) from the proposed uses. Further, we believe that the results of the studies can be extended to include non-ruminants (horses, swine, poultry). Therefore, we conclude that no residues of pendimethalin are likely to occur in eggs, milk, meat, fat, and meat byproducts of livestock from the proposed uses (§180.6(a)(3)).

Alfred Smith

TS-769:RCB:ASMITH:sdb:X62610:RM108:WSME:1/19/79