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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 26 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 201-URI. New Pydrin Formulation - SS
Pydrin® 1.9 EC. Accession Number 254112, 254117, 254118.

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THRU: Charles L. Trichilo, Chief
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and

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Shell wishes to register a new formulation of fenvalerate [Pydrin®, cyano(3-phenoxyphenyl)methyl-α-(1-methylethyl)-4-chlorobenzeneacetate]. Tolerance for residues of fenvalerate have been established on a variety of raw agricultural commodities including meat and milk at 0.1-50 ppm [40 CFR §180.379] and feeds [21 CFR § 561.97].

Currently, the technical active ingredient (SD43775) [redacted] The registered formulated product, Pydrin® 2.4 EC (EPA Reg. No. 201-401), contains 2.4 lbs ai per gallon. The new technical is SS Pydrin®.

The manufacturing process and formulation of SS Pydrin are discussed in the Confidential Appendix. [redacted] reactions should be described and its chemical composition and nature have to be furnished. The technical material produced in this manner contains [redacted] The levels of the impurities are not likely to pose any residue problems. Two of the alternate inerts have not been cleared under 40 CFR §180.1001. The registrant will need to seek clearance or submit chemical compositions on these materials.

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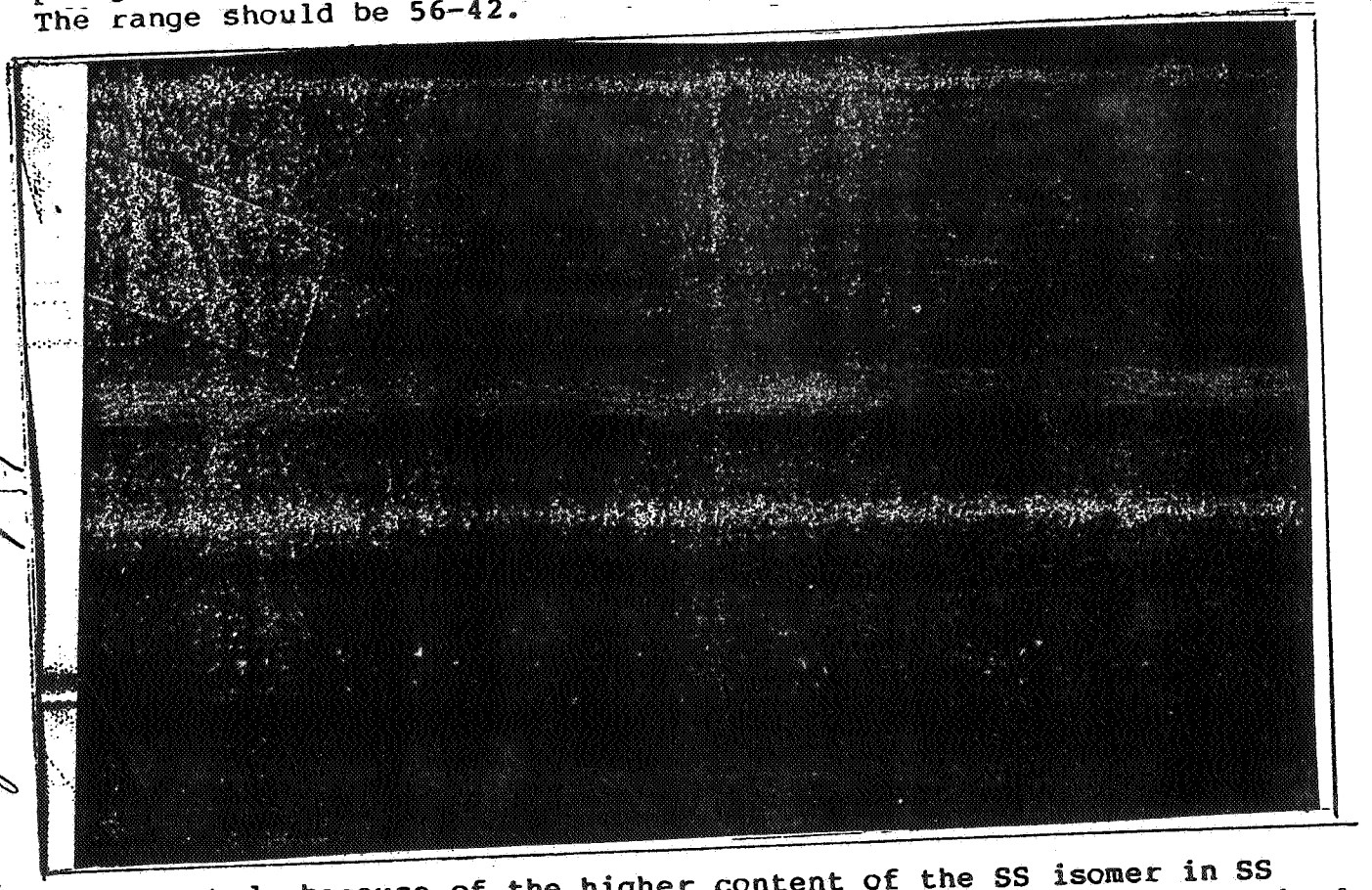
The proposed SS Pydrin® 1.9 EC product is intended to replace the currently registered Pydrin® 2.4 EC product on all crops and uses. A copy of the propsed label has been provided and judged to be acceptable. A minor error is found in the number of acres treated per gallon of 1.9 EC used on European corn borer under field-corn. The range should be 56-42.



As expected, because of the higher content of the SS isomer in SS Pydrin® than Pydrin®, lesser amount of active ingredient is required for the new product. Application rates of the proposed product on all crops and uses relative to the registered product are reduced by a factor of 4.5 (3.6 for use on southern pine seed orchards).

Residue studies in order to compare residue levels resulting from applications of currently registered product (Pydrin® 2.4 EC) and proposed product (SS Pydrin® 1.9 EC) were conducted on alfalfa, soybeans and field corn. The analysis procedure involved blending sample with hexane/isopropanol or hexane/acetone, filtering and final dissolution in hexane. The sample was further cleaned up on a column before GC analysis for parent according to method MMS-R-478-1, "Determination of SD 43775 Residues in Crops, Animal Tissues, Soil and Water-Electron Capture Gas Chromatographic Method" and for photodegradate SD 54597 (see Attachment) according to method MMS-R-527-2, "Determination of SD 54597 Residues in Crops, Animal Tissues, Eggs and Milk-HPLC Method". Limit of detection is 0.01

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ppm for parent and 0.02 ppm for the photodegradate SD 54597. Controls for SD 43775 and MO 20616 were <0.01-0.02 ppm; <0.02 ppm for SD 54597. Chromatograms are acceptable.

All trials were conducted in California by ground application using Pydrin® 2.4 EC and SS Pydrin® 0.64 EC. Following a single application of 0.2 lb ai/A Pydrin or 0.067 lb ai/A SS Pydrin on alfalfa and a PHI of 14 days, residues on green alfalfa were 3.6 ppm parent and 0.26 ppm photodegradate for the registered product and 0.92 ppm parent and 0.05 ppm photodegradate for SS Pydrin.

Four applications were applied to soybeans at two 7-day and one 11-day intervals using rates of 0.2 lb ai/A Pydrin and 0.052 lb ai/A SS Pydrin. Residues determined 28 days after last treatment were 0.07 ppm parent and <0.02 ppm photodegradate for Pydrin, and 0.04 ppm parent and <0.02 ppm photodegradate for SS Pydrin. On soybean fodder, residues due to Pydrin were 3.6 ppm parent, 0.38 ppm photodegradate and due to SS Pydrin were 2.2 ppm parent, 0.15 ppm photodegradate.

Corn plants were treated six times beginning at the 2-leaf stage until ears formed. Residues on grain due to both formulations (0.2 lb ai/A Pydrin and 0.052 lb ai/A SS Pydrin) 21 days after last application were all non-detectable: <0.01 ppm for parent and <0.02 ppm for the photodegradate. For corn stover, residues due to Pydrin were 6.3 ppm parent and 0.38 ppm for photodegradate. The new formulation resulted in 2.4 ppm parent and 0.11 ppm photodegradate.

Residues on alfalfa, soybeans and corn as a result of the requested uses of SS Pydrin® are all lower when compared with the approved uses of the current product. Based on this and the fact that application rates of SS Pydrin® on all the other crops are reduced by a factor of 4.5, the various established tolerances are adequate to cover residues from proposed SS Pydrin uses. It should be noted that photodegradate SD 54597 is not of toxicological importance and thus not a residue of concern (TOX memo of A. Kocialski, 7/19/84, PP# 3F3002).

Five metabolism studies on rats and one on rats and mice were also submitted. The purpose of these studies is to compare the nature, qualitatively and quantitatively, of metabolism between the two technical materials containing different levels of the active isomer SD 47443. Four (Tabs 1-4) of these studies conducted by Shell are considered to be truly comparative and thus will be discussed as a whole.

^{14}C-Fenvalerate labeled at the chlorophenyl (acid portion) or phenoxyphenyl (alcohol portion) position in racemic SD 43775 or SS [redacted] A single oral dose of 8.4 mg/Kg formulated in corn oil was introduced to five male and five female rats by stomach intubation. Since majority of

the activity was accounted for in the urine and feces 48 hours after dosing, urine and fecal excreta from Day 1 and Day 2 were pooled and analyzed qualitatively and quantitatively by liquid scintillation counting, two-dimensional TLC, preparative TLC and gas chromatography.

Confirmation of chemical structures is by MS. Animal tissues were similarly analyzed when the rats were sacrificed on Day 5. ^{14}C-Carbon dioxide was collected in a separate experiment and since little if any $^{14}CO_2$ was detected 24 hours after dosing (same dose rate on one male and one female rat), this was not pursued.

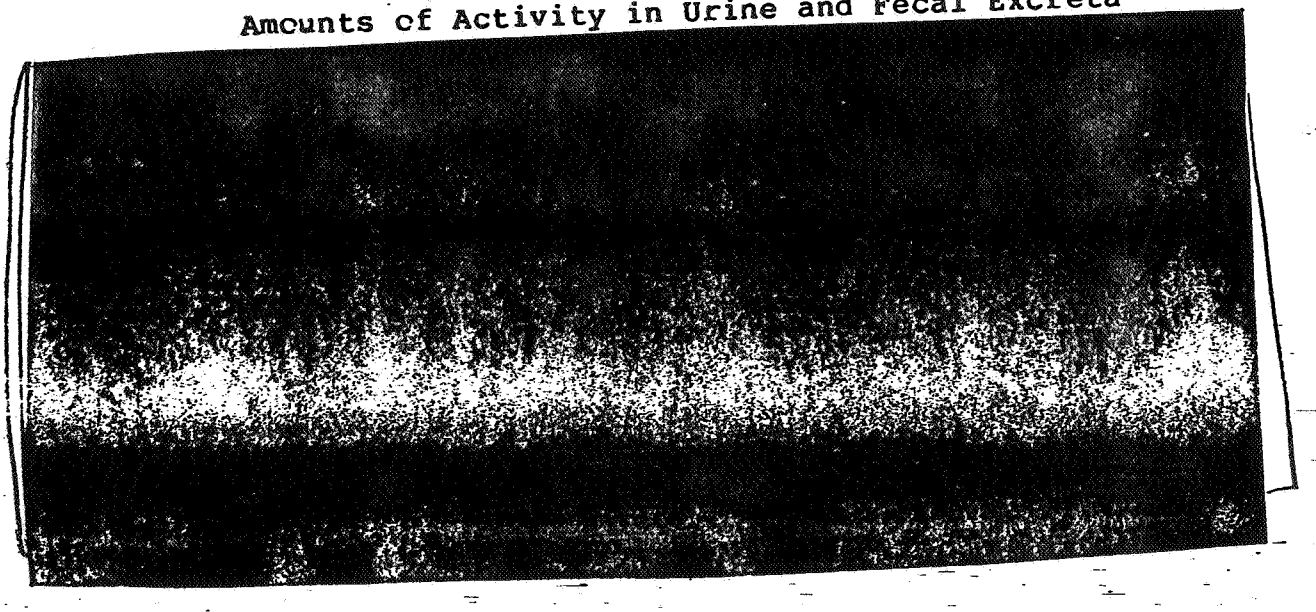
In the preparation of urine samples for analysis, aliquots of pooled Day 1 and Day 2 urine samples were adjusted to pH 3 with 6 N HCl, ethyl acetate extracted, dried and analyzed. The remaining aqueous phase was hydrolyzed by β-glucuronidase and sulfatase enzymes, again extracted with ethyl acetate, dried and analyzed. If more than 5% of the initial activity still remained in the aqueous phase, an acid hydrolysis was conducted for further analysis.

For analysis of fecal samples, the Day 1 and Day 2 combined excreta were extracted with 10% aqueous CH_3OH, separated, and the solvent phase was further diluted with water before extraction with ethyl acetate. The organic layer was dried and analyzed. If the remaining aqueous phase retained greater than 5% of the initial activity, additional acid hydrolysis before analysis was carried out.

As can be seen from Table I, total urinary and fecal excreta on Day 5 accounted for 78.5 - 112.4% of the applied dose, and 89.5-98.3% of the urinary and fecal activity was eliminated by Day 2.

Table I

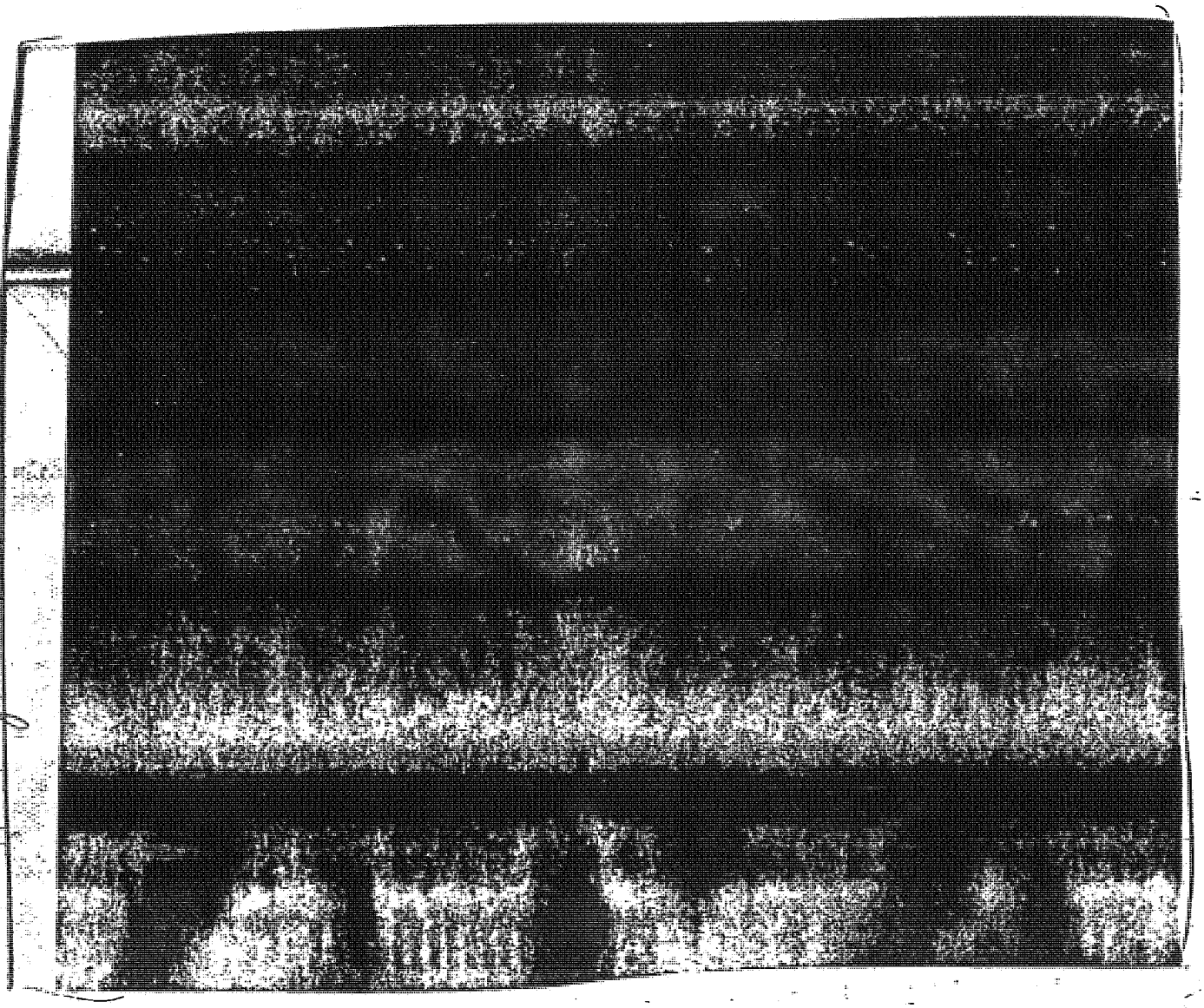
Amounts of Activity in Urine and Fecal Excreta*



Metabolites in urine were identified to be (see Attachment) SD 52667, 44064, 53065, 53919, 52666 and 90930 regardless of the level of S,S isomer SD 47443. Racemic SD 43775 seems to result in lower levels of SD 90930 but the major urinary metabolite for both technical materials is the same-SD 44064. The major fecal metabolite in both technical materials is the respective undegraded parent. Other common metabolites include SD 44064 and 48838. Complete distribution of metabolites is tabulated in Table II.

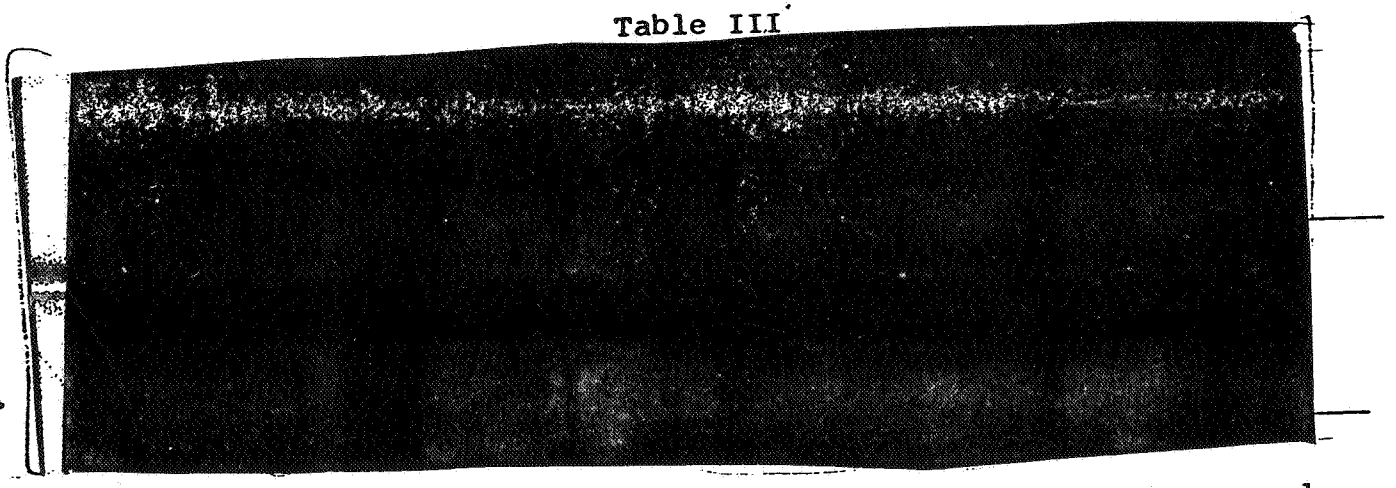
The fate of the alcohol portion of the molecule is elucidated from phenoxy-^{14}C-phenyl compounds. The primary metabolite in the urine is the hydroxylated phenoxybenzoic acid SD 46114 with minor amounts of non-hydroxylated compound SD 44607. The primary fecal metabolite remains to be the undegraded parent along with minor amounts of SD 48838, 44607 and 46114. See Table II for complete breakdown of metabolites.

Table II
Amounts of Metabolites Expressed in % of Administered Dose



The level of residues in heart, liver, kidney, fat and muscle is tabulated in Table III. As can be seen, highest residues were found in liver and fat. Liver samples from two or three male and two or three female rats were further fractionated. GC analysis determined the absence of undegraded parent and no additional attempts were made to identify bound residues in liver tissues. Inguinal fat samples from the same rats were homogenized and hexane extracted. The amount of parent found in fat residues varied considerably between the racemic dose (34-80%, 54.6% ave) and SS isomer-enriched dose (6-30%, 14.6% ave). Previous metabolism studies identified undegraded parent as the major metabolite in the fat residues of rats and cattle (>90%, see memo of E. L. Gunderson, 4/21/78, PP7F2013) as well as poultry (82-85%, see memo of K. Arne, 2/21/84, PP2F2657/2H5340). The present rat metabolism study gives a significantly different result in fat residues and it appears that dosing with SS isomer-enriched material led to residues other than the undegraded parent as the primary metabolite in fat. Since as little as 6% of the fat residue in the present study has been positively identified, additional identification is deemed necessary.

Table III

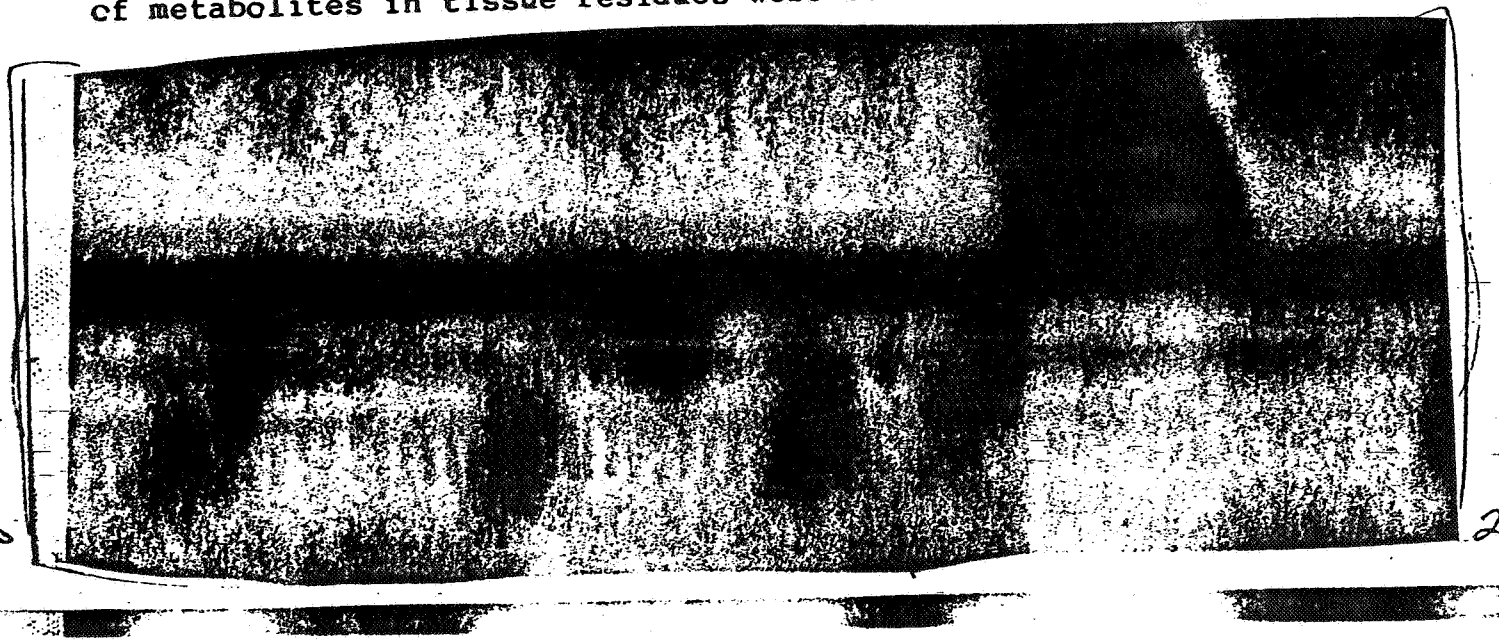


The remaining two studies were conducted by Sumitomo of Japan and later published in the Journal of Pesticide Science, 4 143 (1979) and 6, 317 (1981). In these studies, pooled urine from 0-2 days was lyophilized to dryness, methanol extracted before analysis and identification. Feces (0-2 day) were vacuum dried and ground or extracted with 10% aqueous methanol before analysis. Thiocyanate was precipitated as silver salt before analysis. Analytical techniques used were similar to those by Shell.

In the 1979 paper, experiments were performed on male rats using ^{14}C-fenvalerate or its parent acid SD44064 labeled at the carbonyl, benzylic or cyano position. A single oral dose of 8.4 mg/Kg or five consecutive daily doses of 1.7 mg/Kg was administered as a suspension in 10% Tween 80 (cleared under 180.1001). The animals were under observation for 6 or 14 days before they were sacrificed for tissue analysis. Experiments with ^{14}CO and $^{14}CH_2C_6H_5$ compounds showed 82-97.7% elimination of dose with no detectable $^{14}CO_2$ at the

end of six days. Radioactive CO_2 (ca 10% of the administered dose) was detected in the expired air of animals which were fed ^{14}CN-fenvalerate and the fecal and urine excreta could only account for 65-75% of the radioactivity six days after dosing. This is not surprising since the cyano group is the most labile one in the molecule. Results from ^{14}CO and $^{14}CH_2C_6H_5$ compounds showed fenvalerate, as such or hydroxylated, was the major (15-20%) fecal metabolite. Major urine metabolites were determined to be SD44064 (40.5%) and its hydroxylated derivatives SD53065 and 52666. No identification and quantitation of tissue metabolites were done (except for a few fat samples with CN label -see below). Comparative results between (S,S + S,R) isomer pair and the racemic mixture of ^{14}CN-fenvalerate showed fenvalerate, as such or hydroxylated, to be the major (18.9-19.5%) metabolite in feces, while thiocyanate was the major (7.6-9.8%) urine metabolite. Fat residues were determined to consist of 85-90% parent (apparently only CN labeled samples analyzed). Also, higher residues were detected in blood, hair and skin from ^{14}CN-labeled compounds than the others, but these results may be due to different metabolic uptake rates. In general, this study does not lend significant support to the purpose of this metabolism submission. The use of radioactive SD44064 rather than fenvalerate as dose further distorts the metabolism picture.

The 1981 paper contains the only study in which mouse metabolism was also examined. Experiments were conducted very similar to what has just been described in the earlier paper. A single oral dose at 4.2, 7 or 30 mg/Kg of radioactive fenvalerate labeled at chlorophenyl, phenoxyphenyl, carbonyl, benzylic or cyano position was administered to male and female rats and mice; the animals were observed for 6 or 7 days thereafter. No differences were noted regarding ester hydrolysis of fenvalerate as a primary metabolic step in rats and mice, but there is a greater extent of hydroxylation, by a factor of two, of the cleaved alcohol moiety in rats. From this study, the nature of metabolites in rats between SD47443 (S,S isomer) and the racemic mixture is the same. Metabolites include parent, SD44064 and 44607 and their hydroxylated derivatives SD48838, 52666 and 46114. This study agrees with the others in that SD46114 as such or conjugated is a significant portion of the total residues in feces and urine (see Table IV). No identification and quantitation of metabolites in tissue residues were conducted, however.



To summarize, a considerable (69-112%) amount of the administered dose is eliminated in the urine and fecal excreta at the end of 5 or 6 days. Significant residues were found in fat but not in kidney, liver or muscle. There is no significant difference between racemic and SS isomer-enriched fenvalerate with regard to kinds and amounts of metabolites observed in rats, except in fat. While undegraded parent made up the majority of fat residue in rats dosed with racemic SD47443 in the previous metabolism study (PP 7F2013), this is not the case with the current study. Nevertheless, metabolic processes generally include hydroxylation of the phenoxy ring, ester cleavage of the parent, and hydroxylation of chlorophenylisovaleric acid SD44064 and phenoxybenzoic acid SD44607.

As mentioned earlier, photodegradate SD54597 is not of toxicological importance and thus not a residue of concern (TOX memo of A. Kocialski, 7/19/84 PP3F3002). RCB is currently in the process of conducting a comparative study on the metabolism of different pyrethroids. The results of this study will be forwarded to TOX for their determination as to which metabolites are toxicologically significant.

Conclusions

1. [redacted] manufacturing processes has not been provided (see Confidential Appendix for details).

2. The chemical compositions of the [redacted] have not been furnished. Thus, we can not determine whether they have been cleared under 40 CFR §180.1001 (see Confidential Appendix for details).

3a. Residues on alfalfa, soybeans and corn resulting from the requested uses of SS Pydrin® are lower when compared with approved use of the current product.

3b. The various established tolerances are adequate to cover residues from proposed SS Pydrin uses based upon the residue data presented for alfalfa, corn and soybeans and the fact that the application rate reduced by a factor of 4.5 on all crops with tolerances.

4. The analytical methods employed in the determination of technical [redacted] are adequate. The technical material contains an average [redacted] with a minimum purity of 75%.

5a. In the present rat metabolism study, undegraded parent accounted for only ca 55% of fat residues when dosed with racemic fenvalerate, in sharp contrast to a previously reported study in which 90 or more percent of the fat residues was the parent (PP7F2013). Furthermore, when dosed with SS isomer-enriched fenvalerate, only ca 15% of the fat residues was determined to be the parent. No additional identification of residues or explanation of discrepancies has been furnished. This will be required.

5b. Except as noted in 5a, there is no significant difference in the types and amounts of metabolites observed in rats between racemic and SS isomer-enriched fenvalerate. The major metabolites observed in excreta are: parent, SD44064, SD46114 and SD48838.

6. RCB is currently conducting a comparative study on the metabolism of different synthetic pyrethroids. It should also be noted that photodegradate SD54597 has been determined to be toxicologically insignificant and thus is not a residue of concern. The registrant will be informed of the tolerance expression for residues in plants and animals after TOX has determined which metabolites are significant.

Recommendation

We recommend against registration of SS Pydrin® 1.9 EC for the deficiencies cited in Conclusions 1, 2, and 5a. Information to redress these deficiencies must be furnished before a favorable recommendation can be made. The petitioner should also be informed of Conclusion 6.

cc: Circu, R.F., S.F.
cc: with Confidential Appendix: PM-17, TOX, Cheng, Amened Use File.
RDI: ARR:10/29/84: RDS:10/30/84
TS-769:RCB:LC:bj:RM-810:CM#2: 11/18/84