FENVALERATE — TOX REVIEW dated 9/26/84 pp. 273-282

SEP 26 1984

MEMORANDUM

SUBJECT: PP 4F3021/4H5423 (Accession No. 072258). The Shell Oil Company Proposes that Tolerances be Established for the Pesticide Chemical Fenvalerate (Pydrin® 2.5 EC, EPA No. 201-401) in/on the Commodities Wheat and Barley.

Tox Chem No. 77A

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and

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ABK 9/5/84

WSB 9.25.84

THRU: Edwin R. Budd, Section Head
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THRU: William L. Burnam, Chief
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The Shell Chemical Company proposes that tolerances be established for the pesticide chemical fenvalerate (Pydrin® 2.5 EC, EPA No. 201-401) in/on the following commodities:

Commodity	Tolerance (ppm)
Barley grain	5.0
Barley forage, hay, straw	40.0
Wheat grain	1.0
Wheat milled products (except flour)	5.0
Wheat forage, hay, straw	25.0

The Toxicology Branch is not able to act favorably on this petition. The rationale for the Toxicology Branch position is presented as follows:

The Maximum Permissable Intake (MPI) is currently calculated using the rat no-observed-effect-level (NOEL) of 250 ppm. This value is equivalent to 12.5 mg/kg/day. The application of a safety factor of 100 results in a calculated Acceptable Daily Intake (ADI) value of 0.1250 mg/kg/day and an MPI of 7.50 mg/day (60 kg).

Published permanent tolerances (see attached) utilized 10.61% of the ADI and published and unpublished Toxicology Branch approved tolerances utilized 33.11% of the ADI when the rat study is used in calculating the percent of the ADI utilized.

The registrant has now submitted the results of a six-month dog study. The lowest dose tested (LDT) of 250 ppm produced effects. A NOEL was therefore not attained. The effects produced at the LDT were determined by the Toxicology Branch reviewer to be as follows:

- emesis
- headshaking
- biting of the extremities
- normocytic anemia
- increased serum cholesterol levels
- possible CNS and peripheral nerve dysfunction
- hepatic microgranulomatosis

The issues of normocytic anemia and increased serum cholesterol levels, however, have been resolved between the Agency and the registrant and are no longer considered effects at the LDT.

~~The observed effect of hepatic~~ microgranulomatosis should soon be resolved based on verbal information presented by the registrant at a previously held meeting. This leaves the effects of emesis, headshaking, biting of the extremities and possible CNS and peripheral nerve dysfunction still supporting the Toxicology Branch position of a no no-observable-effect-level at 250 ppm. The onset and severity of effects could however be considered mild and the result of a somewhat above threshold dose for these effects. In spite of these effects the ADI will be now be calculated using the dog study since it was classified as a core-guideline study and on a mg/kg basis provides a more conservative value in calculating the ADI than does the rat. This comparison is shown as follows:

Species	mg/kg	Dose (ppm)	SF	ADI (mg/kg/day)	MPI [(mg/day) 60 kg]
Rat	12.5	250 (NOEL)	100	0.1250	7.50
Dog	6.25	250 (LDT)	100	0.0625	3.75

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The ADI will be considered provisional pending the submission and review of a 1 year dog study which the registrant has agreed to conduct.

Using the dog study in calculating the percent of the ADI utilized (see attached) results in published permanent tolerances utilizing 21.43% of the ADI and published permanent and unpublished Toxicology Branch approved tolerances combined utilizing 66.21% of the ADI.

The Toxicology Branch is now left in the position of considering pending and future tolerance requests in the absence of a NOEL in the dog. Toxicology Branch, in order to deal with this situation, has taken a dual approach by:

- Calculating the PMPI and the percent of the PMPI utilized with and without the contributing TMRC for wheat and barley, for all permanent and unpublished Toxicology Branch approved tolerances using the experimentally determined LDT of 250 ppm in its calculations from the six (6) month dog study and,

- Calculating the PMPI and the percent of the PMPI utilized with and without the contributing TMRC for wheat and barley for all permanent and unpublished Toxicology Branch approved tolerances using a projected and conservative hypothetical NOEL of 100 ppm in the 1 year dog study.

The current total TMRC for all published and unpublished Toxicology Branch approved tolerances as of August 16, 1984 and reflected on the attached computer printout dated August 29, 1983 was 2.4828 mg/day.

The Toxicology Branch has calculated a range of hypothetical NOELs for the 1 year dog study. The percent of the PADI utilized at each NOEL using the current total TMRC of 2.4828 mg/day with and without the TMRC contribution from wheat and barley, is shown in the following table.

NOEL (ppm)	PMPI	% PMPI Utilized 8/16/84 1/ Pub./Un-pub. tolerances	% PMPI Utilized Less Wheat/Barley
250 2/	3.750	66.2	32.95
225	3.375	73.5	36.61
200	3.000	82.7	41.19
175	2.625	94.5	47.07
150	2.250	110.3	54.92
125	1.875	132.0	65.90
100*	1.500	165.5	82.38

1/ TMRC as of 8/16/84 was 2.4829 mg/day. The computer printout is however dated 8/29/83.

2/ LDT in 6 month dog study was not a NOEL.

As was stated earlier in this review Toxicology Branch is unable to determine a NOEL for the dog pending receipt and review of the 1 year dog study. Toxicology Branch has therefore projected a hypothetical and what appears to be a conservative NOEL of 100 ppm for the 1 year dog study. Using the value of 100 ppm and the total TMRC value of 2.4829 mg/kg (1.5 kg diet) it can be seen that 100% of the PMPI is exceeded by 65%. However, if the temporary tolerance (PP2G2636/ 3H538x) for wheat and barley are excluded from the current total TMRC [i.e. 2.4829-1.24714 = 1.23576 mg/kg (1.5 kg)], leaving only those petitions designated "F" (permanent) and "E" (minor use permanent tolerances) in the unpublished toxicology approved category the percent of the PMPI utilized would be 82.38%. Using the value of 250 ppm from the 6 month dog study and deleting the temporary tolerances for wheat and barley only 32.95% of the PMPI is utilized. These calculations resulting from the deletion of wheat and barley would allow for some pending and future tolerances to be issued and leave what would appear to be a confortable margin of safety pending receipt of the 1 year dog study.

* The selection of 100 ppm as the hypothetical NOEL in the calculations has been chosen using the following reasoning.

However, it should also be noted here that the dose value of 100 ppm is to be viewed from two aspects. In item #1 below, 100 ppm is viewed from the aspect of the technical [redacted] represents an expected NOEL based upon a re-doing of the dog study using this old technical formulation. In item #2, the 100 ppm value is to be viewed as a dose level based upon administration of [redacted] (1) year dog study [redacted] a further explanation).

(1) The NOEL of 100 ppm is a conservative value chosen by Toxicology Branch in the absence of a NOEL in the six month dog study.

(2) Chosing the 100 ppm level as the NOEL also involves the concept of equitoxic doses. The current technical [redacted] The Toxicology Branch would therefore be left in a position of calculating currently established tolerances on a formulation which is 2x as potent as the previous formulation tested. Toxicology Branch is not un-mindful of the fact that residues may also be decreased by 1/2 the application rate and residues may decrease by 50%. However, Toxicology Branch can not make this assumption and therefore suggests a meeting between Toxicology Branch, Residue Chemistry Branch and the registrant to discuss the overall issue with regard to the NOEL, new vs old dog study and residues.

Manufacturing process

There is also a strong and persuasive second argument for deleting the tolerance request for wheat and barley. This argument relates to the request for milk tolerances at 0.60 ppm in whole milk [refer also to PP 2F2657/FAP 2H5340, a petition proposing tolerances for Pydrin in/on grapes - supplemental submission of December 1983, Accession No. 072242. Toxicology Branch notes here that this supplemental petition was not submitted to Toxicology Branch for review and consideration to the best of this reviewer's knowledge]. The petitioner states in the petition for tolerances on wheat and barley that secondary residues in milk will not exceed those proposed in the petition for grapes. The petitioners statement was true when the ADI was calculated using the rat study. This statement is however no longer valid since the submission of the six (6) month dog study. This is shown by the following calculations and table.

Calculation of Milk Tolerance in Children *

$$\frac{770 \text{ grams (total dietary intake)}}{4000 \text{ grams (infant body wt.)}} \quad \frac{0.30 \text{ mg (current tol.)}}{1.0 \text{ kg (conversion value)}} = 0.05775 \text{ mg/kg/day}$$

0.05775 mg/kg/day = total dietary intake = ADI for infant

$$\frac{0.05775 \text{ mg/kg/day}}{\text{(PADI from dog study) } 0.0625 \text{ mg/kg/day}} = 92.4\% \text{ ADI utilized}$$

* Calculations based upon the value of 250 ppm, which was the LOT in the dog study.

Tabulating the percent of the PADI utilized in calculating milk tolerances for children and using the hypothetical dog NOELs presented earlier in this review the following table is presented which demonstrates the percent PADI utilized at the respective tolerance levels.

NOEL (ppm)	PADI	% PADI Utilized Based on 0.3 ppm Milk Tolerance[1/]	% PADI Utilized Based on 0.6 ppm Milk Tolerance
250[2/]	0.0625	92.4	184.8
225[3/]	0.0562	102.7	205.4
200[3/]	0.0500	115.5	231.0
175[3/]	0.0437	132.15	264.3
150[3/]	0.0375	154.0	308.0
125[3/]	0.0312	185.0	370.0
100[3/]	0.0250	231.0	462.0

1/ 100% of ADI in children = 0.05775 mg/kg/day

2/ Based on the experimental value in 6 month dog study which showed No-NOEL. LDT value = 250 ppm.

3/ Based on a hypothetical NOEL in 1 year dog study.

The examination of the above table reveals that at the current permanent tolerance of 0.3 ppm for milk 92.4 percent of the PADI is already utilized when the calculation employs a value of 250 ppm. A request for a milk tolerance of 0.60 ppm would exceed 100% of the PADI by 84% using the value of 250 ppm. Calculating the percent of the PADI utilized using 100 ppm as a NOEL and the current milk tolerance of 0.3 ppm reveals an even more striking value. Here 100% of the PADI is exceeded by 131.0%. A petition for a milk tolerance at 0.6 ppm at the same NOEL would exceed 100% of the PADI by 362%.

Summary:

Toxicology Branch is unable to recommend favorably on this petition due to the fact that and MPI can not be calculated in the absence of a NOEL in the dog. The LDT (250 ppm) was not a NOEL. The NOEL therefore lies below this value. Hypothetical NOELs and the LDT were therefore used in calculating a PADI. These calculations revealed that:

- when the LDT (250 ppm) from the dog study was used in calculating the PADI, 66.2% of the PMPI was utilized when all permanent and unpublished Toxicology Branch approved tolerances were used in the calculations. When the conservative and hypothetical value of 100 ppm was used in the same calculations the percent of the PADI utilized was 165.5%. However, when the TMRC contributed by both wheat and barley are deleted from the calculations only 32.95% of the PADI is utilized when using the value of 250 ppm in the calculations, and 82.38% of the PADI is utilized when deleting wheat and barley from the calculations and using 100 ppm as the hypothetical NOEL.

- secondly with respect to the milk tolerance calculations for children it was shown that at 250 ppm and a milk tolerance level of 0.3 ppm 92.4% of the PADI is utilized and at a tolerance level of 0.6 ppm 184.8% of the PADI is utilized. Using a hypothetical and conservative value of 100 ppm, and the current permanent tolerance of 0.30 ppm for milk the PADI is exceeded by 131.0% and at a tolerance level of 0.60 the PADI is exceeded by 362.0%.

- Toxicology Branch suggests a meeting between Toxicology Branch, Residue Chemistry Branch and the registrant to discuss the overall issue(s) reflected in this review.

OPP:HED:TOX:A.KOCIALSKI:sb 8/22/84 TS-769 #3-D1

current as of 8/16/84

File last updated 5/6/83

ACCEPTABLE DAILY INTAKE DATA

RAT, Older Rats		S.F.	ADI	IPI
mg/kg	ppm		mg/kg/day	mg/day(60kg)
12.500	250.00	100	0.1250	7.5000

Publisned Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cottonseed (oil)(41)	0.200	0.15	0.00045
Peanuts(115)	0.020	0.36	0.00011
Potatoes(127)	0.020	5.43	0.00163
Soybeans (oil)(148)	0.050	0.92	0.00069
Cabbage,sauerkraut(22)	10.000	0.74	0.11037
Pecans(116)	0.200	0.03	0.00009
Cantaloupe(23)	1.000	0.52	0.00782
Honeydewmelons(71)	1.000	0.03	0.00045
Pumpkin,inc squash(131)	1.000	0.11	0.00169
Watermelon(169)	1.000	1.43	0.02146
Muskmelons(98)	1.000	0.03	0.00045
Pears(116)	2.000	0.26	0.00766
Apples(2)	2.000	2.53	0.07590
Cucumbers,inc pickl(46)	0.500	0.73	0.00544
Tomatoes(163)	1.000	2.87	0.04312
Summer Squash(155)	0.500	0.03	0.00023
Milk&Dairy Products(95)	0.300	26.62	0.12877
Cattle(26)	1.500	7.15	0.16165
Goats(62)	1.500	0.03	0.00068
Hogs(69)	1.500	3.43	0.07726
Horses(206)	1.500	0.03	0.00066
Sheep(145)	1.500	0.19	0.00437
Cauliflower(27)	0.500	0.07	0.00054
Broccoli(19)	2.000	0.10	0.00307
Beans,dry edible(10)	0.250	0.31	0.00116
Corn,grain(56)	0.20	1.00	0.00030
Peaches(114)	10.000	0.90	0.13490
Peas(117)	0.250	0.69	0.00261
Artichokes(4)	0.200	0.03	0.00009
Eggplant(53)	1.000	0.03	0.00045
Peppers(120)	1.000	0.12	0.00184

IPI	TMC	% ADI
7.5000 mg/day(60kg)	0.7959 mg/day(1.5kg)	10.61

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Unpublished,Tox Approved F1725,2143,2489,2593,2[illegible],1D2493,2566,2636,3H

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Poultry(128)	0.400	2.94	0.01766
Eggs(54)	0.200	2.77	0.00831
Celery(26)	3.000	0.29	0.01283
Lettuce(84)	10.000	1.31	0.19622
Filberts(58)	0.200	0.03	0.00009
Lettuce(84)	0.000	1.31	0.00000
Sorghum(147)	5.000	0.03	0.00225

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Sunflower (6)	1.000	0.03	0.00107
Corn, sweet(40)	0.150	1.43	0.02533
Cherries(30)	10.000	1.10	0.03300
Barley(6)	0.000	0.13	0.00000
Wheat(170)	0.000	10.38	1.04354
Oranges(106)	2.000	2.17	0.06500
Grapefruit(65)	2.000	0.99	0.02574
Lemons(62)	2.000	0.17	0.00521
Almonds(1)	0.200	0.03	0.00009
All foods(197)	0.750	100.00	0.07500
pulse peas(117)	0.750	0.69	0.00782

MPI	TMRC	% ADI
7.5000 mg/day(60kg)	2.4829 mg/day(1.5kg)	33.11

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Current Action Section 18

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Sunflower(156)	0.000	0.03	0.00000

MPI	TMRC	% ADI
7.5000 mg/day(60kg)	2.4829 mg/day(1.5kg)	33.11

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DRAFT