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Engler

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

009002

DATE: March 10, 1977

SUBJECT: Extension of temporary tolerance for Pydrin, 0.2 ppm on Cottonseed and 0.02 ppm in fat of milk.

FROM: Toxicology Branch (WH-567)

TO: Ms. Libby Zink
Special Registration Section (WH-567)

PP No.: 6G1755 and 201-EUP-50

Petitioner: Shell Chemical Co.

Recommendations:

1. Because of the unresolved questions relating to neuropathy, the temporary tolerance, and especailly the EUP should only be granted after the petitioner has reduced the total acreage to 5000 or less.

2. Several studies reviewed must be either repeated or additional information should be provided, see items 7, 14, 15, and 17 of review.

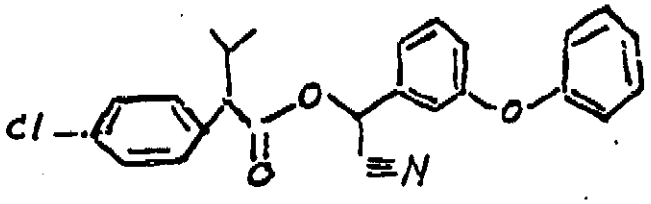
3. We suggest that the quantitative and qualitative aspect of neuropathy be further studied by (a) showing a NEL of Pydrin in the rat and also relating the clinical NEL with the histopathological NEL; acute and subacute (10-15 days) exposure should be used. (b) investigating the neuropathy in different animal species, such as the chicken, dog, and rabbit. In that these studies are of a qualitative nature it is important that doses at or near the LD-50 for the species are used. For the quantitative as well as the qualitative studies it will be important to compare the actions of Pydrin with the effects of Resmethrin and natural pyrethrins.

4. The NEL for neuropathy also should be conclusively demonstrated in subacute studies.

Substance Identification:

Benzeneacetic acid 4,-Chloro(α-1-methyl-ethyl)
Cyano (3-phenoxyphenyl)methyl ester.
SD 43775
S5602
FMC 44713 — ?
WL 43775

1. No Prior Petitions.



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Summary of Previous Toxicity Data

See memo of June 10, 1976

1. Oral LD_{50} (rat)	:	1-3 g/kg in water 450 mg/kg in DSMO
(hamster)		760 mg/kg
2. dermal LD_{50} rabbit	:	1-3 g/kg
3. Formulation:		
LD_{50} oral (rat)	:	1.25 g/kg
LD_{50} dermal (rabbit)		> 2 g/kg
LC_{50} inhal. (rat)		> 3.34 mg/l
eye irritation (rabbit)		corneal damage not reversed in 7 days in 3/6 animals.
skin irritation (rabbit)		mildly irritating
skin sensitization (g. pig)		not sensitizing
4. 90-day feeding study - rats	:	NEL equal or less than 125 ppm. Sciatic nerves analyzed, no effects noted at 2000 ppm (highest dose).
5. 2-year rat feeding study (3-month report)	:	See 1 year report below
6. 90-day feeding study - dogs	:	NEL 500 ppm, most peripheral nerves indicated as "missing".
7. Teratology - rabbits	:	No effect at 50 mg/kg/day (highest dose).
8. Mutagenicity tests	:	
bone marrow analysis - hamster		negative
dominant lethal - mice		negative
9. 3-generation reproduction - rat (interim report)	:	no adverse effects on first generation up to 250 ppm (highest level fed).

Review

1. Oral LD_{50} Mice (tech) - TIR 74-020-76

4 per sex per level. LD_{50} = 117 (67-186) mg/kg. Hypersensitivity, tremors, salivation and convulsions were observed. IP administration showed an LD_{50} of more than 1171 mg/kg, upon repetition of ip test LD_{50} was determined to be 154 mg/kg (TIR 74-021-76 toxicity).

2. Acute Inhalation (mice and rats)

Sumitomo Chemical Co. - August 1975

The LC_{50} was greater than 101 mg/m^3 for both rats and mice (both sexes). The concentration was analytically determined and the LC_{50} is expressed as active ingredient, actually an 8% emulsion was used to prepare the mist. The exposure period was 3 hours.

TLGR 0097-75 a spray was prepared from a solution containing 3 g/l active ingredient. The droplets had a median diameter of 77 µm. Rats were exposed for 4 hours. No untoward reactions were observed with the exception of an abnormal gait of females; this effect disappeared.

3. Eye and Skin Irritation - rabbit (tech.)- TIR 74-094-76

The chemical was not irritating to the eyes; maximum score of 4/110 after 24 hours.

Sumitomo Chemical Co. - August 1975

No irritation to skin and eyes, protocol and reporting not entirely satisfactory, test however is valid especially in conjunction with above TIR test and because effects were virtually zero.

4. Skin Sensitization-Guinea pigs

Sumitomo Chemical Co. - August 1975

Pydrin was not a sensitizing agent, the positive control (2.4 Dinitro chlorobenzene) produced signs of sensitization. Although reactions upon each sensitizing injection are not reported the study is acceptable. Two concentrations of the chemical were injected; 1% and 5%.

5. Subacute Inhalation Toxicity (rats and mice)

Sumitomo Chemical Co. - Nov. 8, 1976

10 animals per sex per level were exposed to 0, 2, 7, 20 mg/m^3 for 4 weeks, 3 hours per day. The only effect which was noted was hypersensitivity of rats and mice at the highest level. Hematology, blood chemistry, body and organ weights, and gross and histopathology were unremarkable; histopathology on brain and spinal cord recorded but not on sciatic nerve.

6. One-Year Feeding Study in Mice (3-month report)

Sumitomo Chemical Co. - Nov. 10, 1976

About 40 mice per sex per level were fed 0, 100, 300, 1000, and 3000 ppm Pydrin. After 3 months 10 mice from each dosage group were sacrificed.

Results:

At 1000 and 3000 ppm mice were hypersensitive, mortality at 3000 ppm shows an increasing trend, body weight gains at 1000, and 3000 was less. At 1000 and 3000 ppm there was liver pathology noted and at 3000 ppm some kidney pathology was present. Liver pathology was not indicative of cirrhotic or hyperplastic changes. Brain, spinal cord and sciatic nerve were normal.

7. One-Year Feeding Study - rats (6-month report)

Sumitomo Chemical Co. - Nov. 10, 1976

30 rats per sex per level were fed 0, 50, 150, 500, and 1500 ppm Pydrin. 12 rats per dosage group were sacrificed after 6 months. Hypersensitivity was observed in the highest dosage group but symptoms became less pronounced after 11th week. Mortalities were unremarkable for the 6 months. Body weight gain was slightly depressed in males at 150 ppm and above. Liver weights (males) and pituitary weights (females) were increased at the highest feeding level. Urinalysis, hematology and blood chemistry were unremarkable. Histopathological examination is in progress.

8. Lifetime Feeding Study - rats

LBI 2541, one year report - December 1976

93 rats per sex per dose were exposed to 1, 5, 25 and 250 ppm Pydrin, the control group consisted of 183 rats per sex. Two other groups were on test for 26 weeks, 22 animals per sex per dose at 0, and 500 ppm. After 3, 6, and 12 months 10 animals per sex per level were sacrificed (20 per sex for control group); this sacrifice schedule, however, was not strictly adhered to. Body weights, hematology blood chemistry, and urinalysis were unremarkable. No excessive mortality was observed. Gross and histopathology was unremarkable. No compound related effect thus was noted at any dosage level. Brain, spinal cord and sciatic nerve histopathology is reported in detail, no adverse effects were noted.

9. Lifetime Feeding Study - golden Syrian hamsters (1-year interim report)

LBI 2542 - Dec. 1976

92 animals per sex per level were fed 1, 5, 25, and 250 ppm Pydrin, the control group consisted of 250 animals per sex. There was an overall hign mortality rate; about 50% of the animals were dead after 1 year. The cause of death was "wet tail", a recognized condition of hamsters. Hematology, blood chemistry and urinalysis was unremarkable. There were pathological findings in the pituitary, spleen, liver, adrenals, kidneys and some in the pancreas, these findings however were equally seen (incidence as well as severity) in control animals. Histopathology of nervous tissues (including sciatic nerves) was negative. A decision whether or not this study will represent a valid feeding and/or oncogenic study must be reserved until a final report is received; the high mortality figures may interfere with the validation of this study.

10. Teratogenicity Study - mice

Sumitomo Chemical Co. - Nov. 5, 1976

Pregnant mice were dosed with 0, 5, 15, and 50 mg/kg Pydrin from day 6-15 of gestation. 20-21 animals were delivered by caesarean section on day 18. About 12 females in each group were allowed natural delivery, the pups were observed for growth development. Some of these pups were selected and mated after 11 weeks to determine their reproductive ability.

50 mg/kg was the highest tolerated dose, it caused irregular respiration, hypersensitivity, tremors and salivation after administration of compound. Numbers of corpus luteum, implantations, dead and living fetuses, and weights of fetuses were not affected by the compound. Gross anomalies

and skeletal anomalies are reported and no compound related effects were noted. The report is on individual pups and not on litters and soft tissue anomalies are not reported. The study is, nevertheless, valid to judge that Pydrin is not a teratogen. The part of the study which deals with naturally delivered fetuses is not reviewed in detail; generally no adverse effects were noted on the offsprings.

11. Host Mediated Mutagenicity

TLGR 0002.76 - January 1976

Mice were dosed with 25 and 50 mg/kg Pydrin. S. cerevisiae were placed in the peritoneum of animals. 400 mg/kg ethyl methan sulphonate was used as positive control. The frequency of revertants was measured. The positive control showed mutagenic effects. Pydrin showed a positive effect on the tryptophane locus in one of three experiemtns, this effect can be discounted as real, since it could not be repeated and the positive control furthermore consistently affected both loci.

12. Effect of Pydrin on the Liver Mono-Oxydase System in Rats

TLGR 0044.76 - July 1976

Hepatic microsomal enzymes was not induced by as much as 1000 ppm Pydrin administered via the diet.

13. Neuropathological Effects in Rats

TLGR 0078.76 - Nov. 1976

Rats were dosed with 1000, 500, 250, and 0 mg/kg. Clinical observations showed, the expected tremors, abnormal gaits and restlessness. All animals of the 1000 mg/kg group died. 4/12 males and 5/12 females

At the 250 mg/kg level 6/6 males and 5/6 females survived 8 days. Clinical signs regressed in surviving rats. The sciatic nerves posterior tibial nerves of all animals surviving 22 hours were analyzed. At 500 mg/kg all animals surviving 8 days (5/24) showed moderate to severe lesions which consisted of swelling, breaks, vacuolation in axons with vacuolation and phagocytosis of myelin. Those animals which survived only 48 hours showed less severe or no lesions and only swelling without breaks. At the 250 mg/kg level 3/6 males showed slight lesions consisting of swelling and breaks; 3/5 females showed slight to severe lesions of the same nature. The other animals at this level were without neuropathological signs.

(14) Acute Oral Toxicity for Rats

Biodynamics No. 4040-76 - Sept. 29, 1976

10 males and 10 females were dosed with 500 mg/kg. Animals were observed frequently during the first 24 hours and daily until termination on day 28. The clinical signs repeatedly mentioned in this review were observed. 8/10 females and 5/10 males survived for 28 days, the other animals died within 1-2 days. The spinal cord was sectioned in 3 places (cervical, lumbar, sacral) and one section of the sciatic nerve was prepared. Three stains were used, however only H&E and Luxol fast blue/cresylviolet were found acceptable. No nerve damage was observed by the histological technique. In order to consider this study valid, we request a further description of the analysis of the sciatic nerves, i.e., where was the section taken (distal, proximal). Furthermore we

would request that at least 3 more segments of the nerve of the surviving animals be sectioned by longitutinal section. Further analysis of the spinal cord is unnecessary.

15. Short-term Feeding Study in Rats

TLGR 0042.76 - June 1976

6 males and 6 females each were fed 0 and 2000 ppm Pydrin for 3 days. Clinical signs were as described previously. The sciatic nerves are reported to show no histopathological changes. In order to consider this study as valid we request further description on sectioning and staining of the nerve.

16. Neurotoxic Effects of Some Synthetic Pyrethroids

Sumitomo Chemical Co. - Nov. 10, 1976

Pydrin was administered at 3000 ppm in the diet for 8 days to 10 rats (m&f). Clinical signs as reported before. Slight to moderate swelling of axons, and veryslight (5/10) disintegration of nerve fibers was observed. 143 (permethrin) showed very slight swelling at 6000 ppm, 149 slight to moderate swelling at 3000 ppm.

17. Examination of Rabbit Sciatic Nerves

From a 21 day/study (IBT 601-07889) TLG R 0082.76 dermal

Blocks of the sciatic nerve of the IBT study were analyzed. The original study consisted of 3 doses (300 mg/kg = highest dose) of technical and 3 doses (1000 mg/kg = maximal) of 2.4 EC Formulation. The nerves of the control group (19 animals) and the 300 mg/kg technical (20 animals) group were reanalyzed. It is stated that no abnormalities were noted.

This study cannot be considered valid without the following addition:

1. detailed information on the sectioning of the sciatic nerves.

2. the original study shows no clinical signs among the animals receiving 300 mg/kg/day of technical, whereas the 1000 mg/kg/day animals treated with formulation developed tremors (1000 mg/kg/day vehicle controls did not). The nerves of the animals showing the clinical signs should be reexamined as well.

18. Neurotoxic Effects Following Dermal Application

Sumitomo Chemical Co. - Nov. 11, 1976

5000 mg/kg was applied dermally to male rats in one dose and 2500 and 5000 mg/kg in five consecutive doses. After the single dose the rats survived showing customary clinical signs. On the 5th day rats were sacrificed. All 8 rats showed slight to moderate swelling of the axon, but no disintegration or demyelination. Upon repeated application 2/10 rats died at the 2500 mg/kg level and 3/10 at the 5000 mg/kg level. After a total of 7 days rats were sacrificed. All rats showed slight swelling of the axon and 2/8 showed very slight to slight disintegration but no demyelination.

19. Neurotoxic Effects of Some Synthetic Pyrethrins and Natural Pyrethrins by Dermal Application in Rats

Sumitomo Chemical Co. - Ref. No. 0054 - Dec. 17, 1976

Pydrin (S5602), NRDC149, and Permethrin (143), were given to rats by single application (500-5000 mg/kg) and by 5 day repeated application at levels of 250 to 5000 mg/kg. Resmethrin and natural Pyretnrins were

applied 5 consecutive times at a level of 5000 mg/kg. Pydrin, 149 and resmethrin showed the typical clinical signs, some animals at the high repetitive dose died. 143 (Permethrin) and natural pyrethrin showed only hypersensitivity by repeated application. Animals in single treatment groups were sacrificed on day 5 the others on day 7.

Results:

By single application Pydrin started showing some very slight effects at 1000 mg/kg, with slight effects at top level of 5000 mg/kg; 500 mg/kg was a NEL. 149 followed the same pattern except that at the highest level some fiber disintegration started to show; 500 mg/kg was a NEL. 143 (Permethrin) showed slight effects of swelling at 5000 mg/kg (only level tested). Upon repeated application the lowest effect level for Pydrin was 500 mg/kg with no effects at 250 mg/kg. For 149, 2500 mg/kg showed effects; no NEL was determined; 143 (Permethrin) showed effects at 2500 mg/kg, no NEL was determined. Resmethrin at 5000 mg/kg showed no effects in 3/9 rats, very slight effects in 4/9 and slight effects in 2/9. Natural pyrethrins showed slight effects at 5000 mg/kg, no NEL was determined.

Although a NEL was not determined for all compounds a preliminary ranking of the compounds can be done taking dose level and severity of effects into account. In order of increasing severity they can be ranked as follows: 1. Resmethrin 2. about equal: Pyrethrin and Permethrin (143) 3. about equal: Pydrin (S5602) and 149.

20. Neurotoxic Effects of Natural Pyrethrins and Resmethrin by Oral Application

Sumitomo Chemical Co. - Ref. No. 0052 - Dec. 17, 1976

Natural Pyrethrin was given to rats at levels of 675 - 5000 mg/kg, resmethrin at levels of 5000 to 2000 mg/kg. Both substances caused typical clinical signs, including hind leg ataxia at higher levels. Rats were sacrificed within 24 hours for histopathological examination. Both compounds showed swelling of neural axons at higher levels (5000 mg/kg for Pyrethrin - 1000 mg/kg for resmethrin). This study shows that by oral administration as well neuropathology can be induced with resmethrin and natural pyrethrins. Quantitative comparison with the studies done on the "pyrethroids" is not possible, since other protocols were used, in repeated doses, longer time interval to sacrifice.

21. Mutagenicity Tests with Pydrin in Bacterial Systems

Sumitomo Chemical Co. - Ref. No. 0055 - Dec. 29, 1976

Pydrin was assayed in several microbial mutagenicity screen tests. Positive controls were N-methyl N'-nitroso-N-nitrosoguanidine (MNNG), 2-acetylaminofluorene (AAF) and dimethyl nitrosoamine (DMNA).

Results:

Rec-assay with H17 and M45 strains of B. subtilis showed no growth inhibition with Pydrin (10,000 µg), these strains were susceptible to MNNG.

An Ames test with and without rat liver enzyme activation showed negative results in 4 S. typhimurium strains. MNNG showed revertants without activation, AAF after enzyme activation.

A mutation frequency test with the same Salmonella strains showed the same effects as described for the Ames test.

A host medicated (mice) assay showed no increased mutation frequency as a result of Pydrin, the positive control DMNA showed a positive result. (test organism S. typhimurium)

Summary of data reviewed on Technical Pydrin

1.	Oral LD_{50} in mice	: 117 mg/kg
2.	Inhalation LC_{50} rats & mice	: > 101 mg/m^3/3 hours
3.	Eye and skin irritation (rabbit)	: not irritating
4.	Skin sensitization (guinea pig)	: not a sensitizer
5.	Subacute inhalation (rats & mice)	: NEL > 20 mg/m^3, histopathology on sciatic nerve not reported.
6.	1-year feeding study in mice (3 month report)	: provisional NEL 300 ppm peripheral nerve showed no changes at highest feeding level (3000 ppm)
7.	1-year feeding study in rats (6 month report)	: provisional NEL 50 ppm, sl. depressed weight gain in males at 150 ppm. Histopathology in progress.
8.	2-year feeding study in rats (1 year report)	: provisional NEL 250 ppm (highest dose). Histopathology on peripheral nerve showed no effect.
9.	Lifetime feeding study in hamsters (1 year report)	: provisional NEL 250 ppm (highest dose). Peripheral nerve negative. high mortality due to wet tail.
10.	Teratology in mice	: no effect at 50 mg/kg (highest tolerated dose).
11.	Host mediated mutagenicity	: no effect (S. cereviciae)
12.	Liver mono-oxydase	: no effect (1000 ppm)
13.	Neuropathology rats (single dose)	: about 50% of rats at 250 mg/kg showed slight neuropathy, severe lesions at higher levels.
14.	Acute toxicity rats	: no neuropathy was observed at 500 mg/kg. Study not valid without detail reporting of peripheral nerve histopathology.

15. Short term feeding (rats)	:	No neuropathy of peripheral nerve after feeding 2000 ppm for 8 days. Study not valid without detail reporting of histopathology procedure and grading.
16. Neurotoxic effects (rats)	:	neuropathy reported after feeding 3000 ppm for 8 days.
17. Examination of rabbit sciatic nerve	:	no neuropathy reported in rabbits exposed to 300 mg/kg/day for 21 days. Study not valid without further detail on histopathology.
18. Neurotoxicity by dermal route (rat)	:	neuropathy after single dose of 5000 mg/kg or repeated dose of 2500 mg/kg.
19. Neurotoxicity by dermal route (rat)	:	NEL 500 mg by single dose NEL 250 mg/kg by 5 repeated doses information on other compounds.
20. Neurotoxicity of natural Pyrethrin and resmethrin (oral route, rat)	:	neuropathy at 3000 mg/kg for Pyrethrin, 10,000 mg/kg for resmethrin.
21. Mutagenicity tests	:	Negative - Ames test Negative - Rec-assay Negative - host mediated (S typhimurium)

Reto Engler, Ph.D.

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