3

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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

13783

SUBJECT: Baythroid™ 2 Induced Neurotoxicity in Rats, Mice, Hens, and Dogs; A Compilation of Available Data

Tox. Chem No. 266E

TO: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

John E Whalan
5-14-86

Baythroid™ 2 (cyfluthrin, FCR 1272) is a synthetic pyrethroid which induces neurotoxicity in rats, mice, hens, and dogs. This effect was first discovered by John Doherty and Ed Budd in the course of an EUP Request on Cotton (Budd and Doherty; 2-15-85; PP 4F3046/FAP 4H5427 and EPA Reg. No. 3125-GLR). Copies of the pertinent pages from this document are attached (Appendix A). There were six neurotoxicity studies submitted in support of this EUP. The findings in these studies were as follows:

Bayer, A.G., Institut fur Toxikologie; Report No. 9753; 1-27-81; Accession No. 072009 [p. 43]

Delayed Neurotoxicity in Hens (Oral Administration x 1) - Core Supplementary.

Hens were dosed at 1000, 2500, and 5000 mg/kg. There were no toxic signs at 1000 mg/kg. Six of 10 hens dosed at 2500 mg/kg had excitation for the first 3 days. One hen dosed at 5000 mg/kg developed unspecified neurotoxic signs on day 14 and died on day 19. Another hen developed neurologic symptoms on day 27, and had moderate fiber alterations in the sciatic nerve which included axon fragmentation, occasional swelling, and eosinophilia of the axon fragments and vacuolation of the myelin sheaths. The day of necropsy was not given.

Delayed Neurotoxicity in Hens (Oral Administration x 2) - Core Supplementary.

Hens were dosed at 5000 mg/kg/day on two occasions 21 days apart. Behavioral changes resembling delayed neurotoxicity [unspecified] in 4/36 hens. Nerve fiber degeneration was found histopathologically 21 days after the second dose in the majority of treated hens, including myelin sheaths that were distended, and optically void or granularly disintegrated. The axons were described as swollen or fragmented and in some areas activated, or proliferated Schwann's cells were noted. The nerves also contained macrophages in which cytoplasm contained granular material.

Delayed Neurotoxicity in Hens (Oral Administration x 5) - Core Supplementary.

Hens were dosed at 5000 mg/kg/day over 5 consecutive days. This was a lethal dose. Behavioral changes were observed in 3/6 surviving hens. Clinical signs included drowsiness and a cramped gait in 3/6 surviving hens. Nerve fiber degeneration also observed histopathologically 43 days after the fifth dose. Treatment-related fiber degeneration, i.e., distension or granular disintegration of the medullary sheath, swollen or fragmented axis cylinders, and proliferated Schwann's cell in the sciatic nerve were reported. One hen had similar lesions in the spinal marrow.

Mobay; Study No. 165; 3-9-81; Accession No. 0972009 [p. 45]

Delayed Neurotoxicity in Hens (Oral Administration x 1) - Core Supplementary.

Hens were dosed at 5000 mg/kg. There were no behavioral changes. No microscopy of nervous tissue was performed.

Delayed Neurotoxicity in Hens (Oral Administration x 2) - Core Minimum.

Hens were dosed at 5000 mg/kg/day on days 1 and 7. There were no behavioral and microscopic changes in the nervous tissue. Histopathology was performed 49 days after the second dose.

Bayer, A.G., Institute of Toxicology; Report No. 10768; 3-29-82; Accession No. 072009 [p. 46]

Delayed Neurotoxicity in Hens (Dermal Administration x 5 days/week, 3 weeks) - Core Minimum.

There was no microscopic or behavioral evidence of delayed neurotoxicity by the dermal route at 5000 mg/kg/day (occluded). The day of necropsy was not given. [NOTE: All hens were apathetic during the first week, and 2 hens continued to be apathetic through days 38 and 51, respectively.]

Bayer, A.G., Institute of Toxicology; Report No. 10705; 3-10-82; Accession No. 072009 [p. 35]

5-Month Neurotoxicity in Rats (Oral Administration) - Core Minimum.

Not neurotoxic (axonal degeneration or myelin effects) at 60-80 mg/kg/day orally by gavage for 5 months. [NOTE: Clinical signs included apathy, shaggy coat, troubled respiration, digging, grooming, tremors, gait abnormalities, and excessive salivation. The rats were probably necropsied on the last day of dosing, but this was not reported in the review.]

Based on these findings, the Doherty/Budd review requested the Registrant to resolve several questions. The following text is quoted from that review:

The registrant is also requested to provide an explanation and/or rationale for the different results observed in the acute delayed

neurotoxicity tests in chickens between the studies performed by Bayer AG Institute of Toxicology (in Germany) and those performed by Mobay Chemical Corporation (in the United States). Some points that should be addressed include:

- Possible differences in the test material

  ° Including a consideration of impurities, contaminants and/or manufacturing by-products in the test material.

  ° Including a consideration of possibly different ratios of active ingredient isomers in the test material.

- Possible differences in the test animals used

  ° Including a consideration of strain, source, etc.

  ° Including a consideration of normal background incidence of nervous system lesions in historical control animals of the same strain and source (if possible).

- Possible differences in investigational techniques employed

- Other

These questions remain unanswered.

The EUP on cotton was not delayed because of the inconclusive results of the acute delayed neurotoxicity tests in chickens (based on a 1-25-86 meeting attended by Dr. Farber, Bill Burnam, Ed Budd, and John Whalan). It was the opinion of the group present that the considerable toxicology data base in mammalian species did not suggest an unreasonable potential hazard to the nervous system of humans under conditions of use. Nevertheless, a neurotoxic esterase study was requested as an attempt to resolve the findings.

Mobay Chemical Corporation submitted a Neurotoxicity Study of the Effect of FCR 1272 on Neurotoxic Esterase (Neurotoxic Target Enzyme) in Hens. This study was reviewed by the Toxicology Branch (Whalan, 5-1-86; EPA No. 3125-GLR) and was classified Core Supplementary (Appendix B). The study was poorly reported and had many deficiencies. There were no indications of significant inhibition of neurotoxic esterase.

Two other unsolicited subacute rat neurotoxicity studies were submitted and reviewed by the Toxicology Branch (Whalan, 5-22-85; EPA No. 4F-3046) (Appendix C). Both studies were Core Supplementary, but have since been upgraded to Core Guideline after the Registrant resolved the study deficiencies (Whalan, 5-5-86; EPA No. 3125-GLR). The findings in these studies were as follows:

Bayer AG Institut Fur Toxikologie; Mobay No. 86305; 12-27-83; Accession No. [none]

Subacute Neurotoxicity of Orally Administered FCR 1272 in Rats - Core Guideline.

Rats were orally dosed with 60 mg/kg/day of FCR 1272 for 14 consecutive days. They were observed for an additional 14 days, then necropsied. Clinical signs included non-specific disturbed behavior, rolling, tremors, stretched gait, uncoordinated gait, excessive salivation, phonation, weight loss (males), and death. There were microscopic findings of slight brain hemorrhages (males), and necrosis of the skeletal muscle fibers (males).

Nihon Tokushu Noyaku Seizo K.K. Agricultural Chemicals Institute; Mobay No. 86427; 6-30-83; Accession No. [none]

Subacute Neurotoxicity of Orally Administered FCR 1272 in Rats - Core Guideline.

Rats were orally dosed over 14 consecutive days with 80 mg/kg/day of FCR 1272 (reduced to 40 mg/kg/day after 5 doses). Clinical signs included straddled gait, slow leg movement, titubation, excess salivation, red tears, and reduced weight gain. Ten rats were sacrificed and examined histopathologically on days 1 and 5, and at 1, 2, and 3 months, respectively. Light microscopic examination revealed minimal axonal degeneration (myelin swelling and desquamation) in a single fiber of the sciatic nerve at days 1 (6/8), and 5 (3/8), and months 1 (3/8), and 2 (2/9). Electron microscopic lesions included microtubular dilatation with proliferation of neurofilaments and mitochondria degeneration in the sciatic nerve at days 1 and 5, and at 1 month. These same lesions were also seen in the femoral nerve of a rat on day 5.

The above studies were designed to assess neurotoxicity. Other studies were performed for the purpose of acquiring an EUP in cotton which also had some mention of neurotoxicity (Budd and Doherty; 2-15-85; PP 4F3046/FAP 4H5427 and EPA Reg. No. 3125-GLR). These studies reported clinical signs or histopathology indicative of neurotoxicity:

FCR 1272 28-Day Subacute Oral Toxicity Study in Rats - Core Minimum. [p. 26]

Clinical signs in rats orally dosed at 80 mg/kg/day during the first and third weeks and at 40 mg/kg/day during the second and fourth weeks included apathy, ruffled coat, dyspnea, excessive salivation, hyperkinesis, ataxia, and athetosis (involuntary ceaseless occurrence of slow, sinuous writhing movements) and chorea (ceaseless occurrence of a wide variety of rapid, highly complex, jerky movements that appear to be well coordinated but are performed involuntarily). A single rat dosed at 20 mg/kg/day had these signs.

FCR 1272 Short-Term Toxicity Tests on Rats (4-Week Feeding and 4-Week Recovery Tests) - Core Supplementary. [p. 30]

Rats dosed at 1000 ppm (100 mg/kg/day) in the feed had straddled gaits, excessive salivation and/or nervousness that reversed in the latter part of the dosing period. Minimal degrees of single nerve fiber degeneration in the sciatic nerve were occasionally found. The number of incidences were not reported. These lesions were said to have disappeared after 4 weeks of recovery [reversal of clinical signs].

FCR 1272 Short-Term Toxicity Tests on Mice (4-Week Feeding and 4-Week Recovery Tests) - Core Supplementary. [p. 31]

Mice dosed at 1000 and 3000 ppm (150 and 450 mg/kg/day) had ataxia and/or emaciation. There were no histopathologic lesions reported in nervous tissue.

FCR 1272 Subacute Inhalational Toxicity Study on Rats - Core Minimum [p. 33]

Rats were dosed with an aerosol of 11.5 and 69.6 mg/m^3 of test article in a vehicle of PEG 400/ethanol (1:1) for 6 hours/day, 5 days/week, for 3 weeks. These rats had ungroomed coats, a stiff unsteady gait, and excessive salivation. There were no histopathologic lesions reported in nervous tissue.

FCR 1272 Chronic Toxicity Study in Dogs (Six-Month Feeding Experiment) - Core Minimum. [p. 37]

Beagles dosed at 600 ppm (15 mg/kg/day) in their feed had a stiff gait (hind limb abnormality), uncoordination, and arched backs (which developed late in the study). There were no anomalies noted in the several reflex tests conducted, or in body temperature or pulse rate. There were no histopathologic lesions reported in nervous tissue.

FCR 1272 Chronic Toxicity to Dogs on Oral Administration (12-Months Feeding Study) - Core Minimum. [Addendum]

Two Beagles dosed at 640 ppm (16 mg/kg/day) in their feed exhibited slow and unsure movements as a result of swaying, and a slightly clumsy gait primarily in the hind quarters. They were reluctant to move. These signs were seen during week 36 for one dog and during week 37 for the other.

In summary, signs of frank or possible neurotoxicity were seen in rats, mice, hens, and dogs. The following table presents the lowest doses at which neurotoxicity was observed in any study:

Rats (oral)	60 mg/kg/day x 14 (mean dose)
Rats (inhalation)	11.5 mg/m^3 x 15
Mice (oral)	150 mg/kg/day x 4 weeks
Hens (oral)	5000 mg/kg/day x 1
Hens (dermal)	5000 mg/kg/day x 15 (equivocal neurotoxicity)
Dogs (oral)	15 mg/kg/day x 6 months

Appendix A

Reviewer

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

004285

FEB 15 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP 4F3046/FAP 4H5427 and EPA Reg. No. 3125-GLR. Cyfluthrin (Baythroid). Request for Tolerances for Residues of Cyfluthrin in/on Cottonseed, Cottonseed Oil, Cottonseed Hulls, Meat and Milk. Request for Registration of Baythroid 2 Formulated Product.

Tox Chem No. 266E

TO: Timothy A. Gardner, Product Manager #17
Registration Division (TS-767)

FROM: J. D. Doherty, Ph.D.
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

and

Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

2/14/85

THRU: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Theodore M. Farber
2/14/85

Requested Action:

The Mobay Chemical Corporation (Kansas City, MO) requests registration of the formulated product Baythroid 2 (EPA #3125-GLR) for use on cotton together with the following tolerances (revised May 9, 1984).

Crop	Proposed Tolerances (ppm)
Cottonseed	1.0
Meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep	0.05
Milk	0.01
Cottonseed, refined, deodorized oil	2.00
Cottonseed, hulls	2.50

004285

2

Cyfluthrin is a new synthetic pyrethroid insecticide. This is the first request for permanent tolerances for this chemical.

Conclusions:

1. All toxicology studies required to support the proposed registration of Baythroid 2 for use on cotton (only) and the requested tolerances have been submitted to and have been reviewed by Toxicology Branch.

   NOTE: Toxicology Branch was informed by Chris Dively (PM Team #17) on 1/31/85 that she had spoken with G.E. Brussell (Mobay Chemical Corporation) on 1/31/85 and that he had assured her that the formulated product described in this review as Baythroid 240 EC and the formulated product for which registration is proposed for use on cotton (i.e. Baythroid 2, EPA #3125-GLR) are identical and that only the "name" had been changed. Toxicology Branch requests that Mobay be asked by Registration Division to verify this statement in writing prior to registration of Baythroid 2 for use on cotton.

2. Toxicology Branch has no objection to the proposed registration and tolerances provided that the following requirements are adequately addressed and responses submitted to Toxicology Branch within a reasonable period of time. It is not necessary that this be done prior to registration of Baythroid 2 for use on cotton or prior to establishment of the tolerances. In other words, the following are "conditional requirements."

   a. Many of the toxicology studies were not signed by the persons responsible for the work. Signed reports of these studies must be submitted to EPA. Failure to submit the signed reports will result in reclassification of the studies to INVALID status.

   b. Neurotoxicity studies in chickens. Cyfluthrin was tested in several studies for possible delayed type neurotoxicity. Evidence of nerve fiber degeneration was noted in some of these studies. The data generated thus far are not conclusive with respect to determining the potential for cyfluthrin to produce delayed type neurotoxicity in chickens.

004285

The registrant is requested to conduct an additional study to assist in determining the potential of cyfluthrin to affect the nervous system. This study should be a "hen brain neurotoxic esterase" study. It is strongly suggested that the registrant, prior to performing this study, submit the proposed protocol to Toxicology Branch for comment.

Note - Toxicology Branch does not consider the inconclusive results of the acute delayed neurotoxicity tests in chickens to be of sufficient concern at this time to warrant delaying the registration of this product and the associated tolerances. Considerable toxicology data in mammalian species is presently available which does not suggest an unreasonable potential hazard to the nervous system of humans under conditions of use. Toxicology Branch considers the latter evidence to be more relevant to its determination of potential hazards to humans. Nevertheless, in order to assist in the resolution of this outstanding issue, the "hen brain neurotoxic esterase study" is required to be performed and submitted.

It is suggested that the registrant consider information presented in the following reference when designing the "hen brain neurotoxic esterase study."

Johnson, M. K., Structure-activity relationships for substrates and inhibitors of hen brain neurotoxic esterase, Biochem. Pharmacol., 24: 797-805, 1975.

This study should include a negative control group and a positive control group of hens. Toxicology Branch is aware that relatively few toxicology laboratories are prepared to perform this type of study. Nevertheless, a few do. If requested by the registrant, Toxicology Branch will supply the names of some laboratories that have the capability of performing this study. Toxicology Branch is also willing to discuss with the registrant, if requested, problems that may arise during the design and/or performance of this study.

The registrant is also requested to provide an explanation and/or rationale for the different results observed in the acute delayed neurotoxicity tests in chickens between the studies performed by Bayer AG Institute of Toxicology (in Germany) and those performed by Mobay Chemical Corporation (in the United States). Some points that should be addressed include:

- Possible differences in the test material

  ° Including a consideration of impurities, contaminants and/or manufacturing by-products in the test material.

  ° Including a consideration of possibly different ratios of active ingredient isomers in the test material.

- Possible differences in the test animals used

  ° Including a consideration of strain, source, etc.

  ° Including a consideration of normal background incidence of nervous system lesions in historical control animals of the same strain and source (if possible).

- Possible differences in investigational techniques employed.

- Other

c. Mutagenicity Studies:

The following additional mutagenicity studies are required:

- gene mutation in mammalian cells in culture

- cytogenetics assay in mammalian cells in culture

- DNA repair assay in mammalian cells in culture.

3. The inerts in the formulated product BAYTHROID 2 are cleared for the proposed use.

4. The following changes in the precautionary statements are recommended.

Add "May be fatal if inhaled." [Note: the product is Tox. Cat. II by inhalation exposure.]

Delete "No specific symptoms. Acute poisoning accompanied by general depression and illness."

004285

8-Point Review

1. Toxicity data with technical grade cyfluthrin considered in support of this tolerance (selected studies).

Acute Oral LD50, rats	LD50 = 590 mg/kg, males LD50 = 1,189 mg/kg, females
Acute Oral LD50, mice	LD50 = 291 mg/kg, males LD50 = 609 mg/kg, females
Acute Dermal LD50, rats	LD50 > 5,000 mg/kg, males and females
Acute Inhalation LC50, rats	LC50 > 1.089 mg/L, males and females
Dermal Sensitization, guinea pigs	Not a sensitizer
90-Day Feeding, rats	NOEL = 300 ppm (HDT)
6-Month Feeding, dogs	NOEL = 200 ppm LOEL = 600 ppm
12-Month Feeding, dogs	NOEL = 160 ppm LOEL = 640 ppm
2-Year Feeding/Oncogenicity, rats	Not oncogenic at dosage levels up to and including 450 ppm (HDT) NOEL = 50 ppm (or 2.5 mg/kg/day) LOEL = 150 ppm
23-Month Oncogenicity, mice	Not oncogenic at dosage levels up to and including 800 ppm (HDT)
3-Generation Reproduction, rats	NOEL = 50 ppm LOEL = 150 ppm
Teratology, rats	Not teratogenic at dosage levels up to and including 30 mg/kg/day (HDT)
Teratology, rabbits	Not teratogenic at dosage levels up to and including 45 mg/kg/day (HDT)
Delayed Neurotoxicity, hens (oral administration)	Inconclusive results.
Delayed Neurotoxicity, hens (dermal administration)	Negative for delayed effects on the nervous system

004285

8-Point Review (contd.)

21-Day Inhalation, hens	Negative for delayed effects on the nervous system
5-Month Neurotoxicity, rats	Negative for delayed effects on the nervous system

Mutagenicity Studies:

Reverse Mutation Assays (with and without metabolic activation).

S. typhimurium	Negative
E. coli	Negative
S. cerevisiae	Negative

Recombination Assays

B. subtilis	Negative
S. cerevisiae	Negative

2. Additional toxicity data considered desirable ("conditional requirements" - see "Conclusions", above)

   a. "Hen brain neurotoxic esterase" study (see "Conclusions")
   b. Gene mutation in mammalian cells in culture
   c. Cytogenetic assay in mammalian cells in culture
   d. DNA repair assay in mammalian cells in culture

3. The above additional toxicity studies are requested in this review.

4. This is the first F petition for cyfluthrin.

5. Establishing these tolerances will result in 1.13% of the MPI being used up. (See computer printout, attached.)

6. The 2-year chronic feeding/oncogenicity study in rats with a NOEL of 50 ppm (equal to 2.5 mg/kg/day) and a safety factor of 100 were used to calculate the ADI (0.025 mg/kg/day). The MPI is 1.50 mg/day (60 kg).

7. There are no pending regulatory actions against the registration of cyfluthrin.

8. None.

Necropsy of the dead and sacrificed animals was said to have "conformed to the norm."

This study is CORE MINIMUM. Based on the data with Cremophor EL, the technical FCR 1272 should be classified as Tox. Cat. I.

Comparative study of rats on absorption of FCR 1272 after single oral administration in polyethylene glycol 400 or Cremophor EL/water as formulation vehicle.

Bayer AG Institute of Toxicology. Report No. 10715
March 10, 1982, EPA Acc. No. 072008, Tab 3.1.10b

In this study, two groups of 14 rats were dosed by stomach tube with FCR 1272 dissolved in either lutrol (polyethylene glycol 400) or Cremophor EL/distilled water at the dose level of 10 mg/kg. The rats were sacrificed at 0.5, 1, 2, 4, 6, 16 or 24 hours later (2 rats at each time interval) and the content of FCR 1272 in the blood and stomach was determined. The purpose of this study was an attempt to determine why FCR 1272 dissolved in Cremophor-distilled water emulsion was more toxic than that dissolved in polyethylene glycol 400.

The FCR-1272 used for this study was from batch B16170019 and had an isomer ratio of I 26.6%, II 19.1%, III 33.7%, IV 20.6%. When the blood and stomach contents were analyzed, the ratio of the different isomers was also determined in order to assess selective absorption of the isomers.

Analyses of the blood indicated that the concentration of FCR 1272 peaked after 1 hour and the rats showed signs of intoxication when FCR 1272 was administered with Cremophor. In contrast, when FCR 1272 was administered with polyethylene glycol the blood level peaked at 6 hours after dosing and the maximum blood level was about 1/5 of the level when the test substance was administered with Cremophor.

Consistent with the above, there was more FCR-1272 in the stomachs of the rats treated with polyethylene glycol than those treated with Cremophor.

Some differences were noted in the absorption of the cis and trans isomers but TR considers that there were an insufficient number of animals dosed to make meaningful comparisons at this time.

These data are CORE MINIMUM. The data provide an explanation as to why FCR 1272 dissolved in Cremophor and distilled water is more toxic than that dissolved in Lutrol (polyethylene glycol-400). The pyrethroid is absorbed from the GI tract quicker in the presence of Cremophor.

A. FCR 1272 28-Day Subacute Oral Toxicity Study in Rats

Bayer Ag Institut fur Toxikologie, Report No. 9039, March 28, 1980,
EPA Acc. No. 072008, Tab 3.3.2a

B. The test material for this study was FCR 1272 from batch 16001/79 and lot No. 2151. It was stated as being of 85% purity.

C. The test animals used were SPF-Wistar albino rats provided by the German supplier, F. Winkelmann. At the start of dosing they were reported to be between 120-140 grams.

Four dose groups of 20 males and 20 females were dosed with either the control, 5, 20 or 80 (40) mg/kg/day. The high dose group received 80 mg/kg day the 1st and 3rd weeks of treatment and 40 mg/kg/day the 2nd and 4th weeks of treatment. This change in dose level was deemed necessary because of the toxic reactions noted in response to 80 mg/kg/day. The test material was administered by gavage as a mixture with Lutrol (polyethylene glycol 400). The control group was dosed with Lutrol only. The rats were dosed for 28 days (4 weeks) and after this period 10 rats of each sex/group or one half of the survivors/sex/ group were sacrificed and examined histologically. The remaining rats were allowed 6 weeks for recovery before they were sacrificed.

D. Survival. No rats died in the control or groups receiving 5 or 20 mg/kg/day. 6 males and 1 female in the high-dose test group died.

E. Clinical Signs. The symptoms that were consistently noted in the high-dose group were "apathy, ruffled coat, dyspnea, salivation, hyperkinesis, ataxia, and athetotic and choreiform movements." Only a single rat in in the mid dose group was reported as having any of these symptoms.

F. Body Weight. The only effect noted was retarded (decreased) body weight gain among the males in the high dose group (12-13%). The females were unaffected. The survivors in the male high dose group recovered from their body weight decreases during the recovery phase.

For sections G, H and I below, blood and urine samples were taken after day 28 of treatment and for the survivors after the 6-week observation period. Five rats of each sex per group were analyzed.

G. Hematology. There were no chemically related changes in erythrocyte counts, leukocyte counts, hemoglobin, hematocrit, mean hemoglobin content of erythrocytes, mean corpusculor volume, thrombocyte count, reticulocyte count, differential blood count.

H. Clinical Chemistry. Some slight differences were noted in phosphorous, K^+ and Ca^{++} levels in the male groups only. The laboratory report stated that these differences lacked a true dose response relationship and that the values obtained were within normal limits. Alanine amino transferase was elevated in high-dose group males, there were no differences noted with regard to aspartate transaminase, alkaline phosphatase, urea, blood sugar, creatinine, Mg^{++}, Na^+ or Cl^-.

I. Urinalyses. No differences were noted as a result of a comprehensive examination.

J. Organ Weights. The thyroid, heart, lungs, liver, spleen, kidney, adrenal, testes and ovary were weighted. The liver weights of high-dose females (increase + 24%), kidney weights of the high-dose males (decrease 12%), and adrenal weights of high-dose males (increase 15%) and females

(increase 19%) were affected after dosing for 28 days. The liver weights of the females were reduced (mid-dose group 32% and the high-dose group also 32%) after six weeks of recovery.

A NOEL for changes in organ weight is set at 20 mg/kg/day. At 40 (80) mg/kg/day there is a definite change in liver weight and a change in adrenal weight. [Note: it is of interest that the laboratory suggests that the change in adrenal weight is due to stress on the rat.]

K. No unusual or dose-related gross necropsy findings were noted.

L. No unusual or dose-related histopathological findings were noted. In particular, there were no lesions in the liver or adrenals which were found to be related to administration of the test material.

M. N/A.

N. 1.) This study is CORE MINIMUM. The 28-day dosing schedule does not qualify this study as a 90-day dosing study for regulatory purposes.

2.) The study provides useful information in that a NOEL of 20 mg/kg/day for 28 days is established. At 40/80 mg/kg/day toxic signs (nerve symptoms, body weight loss and liver and adrenal weight changes) were noted. The apparent biphasic liver weight changes noted at termination (an increase) and after recovery (a decrease) should be looked for in subchronic and chronic feeding studies with this chemical.

3.) N/A.

A. FCR 1272 Subchronic toxicity study on rats (three-month feeding experiment)

Bayer Ag Institut fur Toxikologie, Report No. 9386, June 4, 1980, EPA Acc. No. 072008, Tab 3.3.2b

B. The test material used for this study was technical grade FCR 1272 from batch 16003/79 and was stated to be of 84.2% purity.

C. The test animals used were SPF Wistar (TNO W.74 strain) bred and supplied by Winkelmann, Borchem. The rats weighed 72-73 (females) and 76-77 (males) grams and were 30-35 days old at the start of feeding. The rats were dosed for 3 months as either controls, 30, 100, or 300 ppm and each group consisted of 30 males and 30 females per dose group.

D. Survival. Only two rats died and their cause of death was said to result from an overdose of ether used in taking the blood sample.

E. Clinical reactions. No behavioral or physical reactions were reported. All rats were reported as being not different from the controls.

F. No consistent dose dependent effects on body weight gain were noted. All of the groups consumed about 19 (males) or 14-15 (females) gms/day of feed.

FCR 1272 Short-term toxicity tests on rats (4-week feeding and 4-week recovery tests).

Nihon Tokushu Noyaku Seizo K.K. (Japan), Report No. 215, March 15, 1982. EPA Acc. No. 072008, Tab. 3.2.2.c.

This study is assigned a CORE SUPPLEMENTARY classification for the following reasons.

- no protocol was presented
- the test material lot number and percentage purity were not provided
- the feeding phase of the study was for 4 weeks - an insufficient time interval for a 90 day feeding study for regulatory purposes.

The study consisted of dosing 4 groups of 18 male and female rats (strain and supplier were not identified) with FCR 1272 for 4 weeks. After 4 weeks 12 rats of each sex per dose were sacrificed and examined. The remaining were allowed 4 weeks to recover from any effect. The dose levels used were 0, 100, 300 and 1000 ppm. Based on the study report, the following effects were noted at 1000 ppm only unless otherwise indicated.

- behavioral reactions (straddle gait, salivation and/or nervousness) which disappeared in the later part of the dosing period.
- body weight, food consumption and water consumption decreases.
- urinalysis - urobilinogen and ketone bodies
- hematology - decrease in RBC count, hematocrit, and hemoglobin contents
- decreases in total protein and glucose in the blood. Glucose level was also decreased (-12%) in the mid-dose level.
- increased weight of the submaxillary glands, increased relative liver and kidney weight. These weight changes regressed after recovery.
- histologically there was noted cytoplasmic swelling of the glandular epithelium in the submaxillary glands.
- minimal degrees of single nerve fiber degeneration in the sciatic nerve were occasionally found. The number of incidences were not reported. This was said to have disappeared after 4 weeks of recovery.

The NOEL for this study is 100 ppm. The LEL is 300 ppm (minimal decrease in blood glucose).

FCR 1272 Short-term toxicity tests on mice (4-week feeding and 4-week recovery tests).

Nihon Tokushu Noyaku Seizo K.K., Report No. 221, April 14, 1982, EPA Acc. No. 072008, Tab. 3.2.2.d.

This study is assigned a CORE SUPPLEMENTARY classification for the following reasons.

- no protocol was presented
- the test material lot number and batch number and percentage purity were not provided
- the study used mice and this species is not usually acceptable for the subchronic feeding study for regulatory purposes.

[Note: The information generated may be useful in selecting the dose levels for the mouse oncogenicity study.]

The study consisted of dosing 4 groups of 18 male and female mice. (The strain and supplier were not identified), with FCR 1272 for 4 weeks. After 4 weeks, 12 males and 12 females from each group were sacrificed. The remaining mice were sacrificed after allowing 4 weeks for recovery. The dose levels used were 0, 300, 1000 and 3,000 ppm.

Based on the study report, the following effects were noted.

- behavioral signs (at both 1000 and 3000 ppm) included ataxia and/or emaciation. One high dose female died as a result of intoxication.
- depression in growth rate for males (3000 ppm group) and females (1000 and 3000 ppm groups).
- possible decrease in white blood cells (3000 ppm group).
- increased blood levels of "AIP" and BUN (males 3000 ppm). [Note "AIP" was not definitely defined.]
- dark red livers in some 3000 ppm dose group males and females
- increased weight for the submaxillary glands and kidneys (3000 ppm, males and females). Increased liver weight (1000 ppm and above), decreased spleen (males), adrenals and ovaries (females) in the 3000 ppm groups.
- histopathology revealed chromatic nuclei in males (1000 ppm and above) and in females (3000 ppm). Cytoplasmic swelling of the submaxillary glands was found in mice receiving 1000 ppm and above.
- Most of these findings disappeared after the four week recovery period.

M. Special studies or aspects: Local reactions (dermal): Only reactions due to the abrasions caused by the sandpaper were noted. The test material did not appear to cause a local reaction at the site of application.

N. Conclusions

1) This study is CORE MINIMUM.

2) The NOEL is 250 mg/kg/day, the highest dose level tested.

A. FCR 1272 Subacute inhalational toxicity study on rats.

Bayer AG Institute fur Toxikologie, Report No. 9373, August 20, 1980. EPA Acc. No. 072009, Tab. 3.3.4

B. The test material used for this study was FCR 1272. It was from lot 16001/79 and was said to be of 85.3% purity.

The test material was generated into the atmosphere as a mixture with ethanol and lutrol (polyethylene glycol 400). The ethanol/lutrol mixture was 1:1. The aerosol was generated using a "dynamic flow inhalation apparatus" (i.e. see Kimmerle and Eben, Arch. Toxicol 30; 115, 1973).

For the first run of this experiment the apparatus was adjusted to generate aerosols with air concentrations of 10, 50 and 250 mg/m^3. Actual analysis of the atmosphere indicated that the concentrations were 2.3, 11.5 and 69.6 mg/m^3. Analysis for the particle size revealed that >90% were considered to be respireable (<3 u in diameter).

The control group received only the solvent at the rate of 20,000 ul solvent/m^3.

C. The test animals used for this study were male and female Wistar TNO/W 74 albino rats supplied by the Winkelmann, Borchen. At the start of the study they were nearly adult (180-220 gmes in weight). Each group consisted of 10 males and 10 females. They were exposed to the atmosphere containing CFR 1272 for 6 hours at a time, for 5 days per week for 3 weeks (15 exposures of 6 hours duration).

D. Survival. A single rat (male) receiving the high dose level died and its death was thought to be related to exposure.

E. Behavior reactions. The mid- and high-dose groups were reported as being effected and displayed ungroomed coat, a stiff, unsteady gait and eventually increased salivation.

A NOEL of 2.3 mg/m^3 is assigned for behavioral reactions.

F. Body weight. Weight gain was affected in all dosed groups. The low-dose groups did not gain weight. The mid- and high-dose groups had body weights lower after exposure than before. For example, the high-dose male group lost 4% of their body weight.

A NOEL for effects on body weight is <2.3 mg/m^3, the lowest dose level tested.

[Note for sections G, H, and I below blood and urine samples were performed on 5 male and 5 female rats from each group after the final exposure].

G. Hematology. No effects were noted on the blood elements (8 different parameters and the differential white blood cell counts were investigated).

H. Clinical chemistries. No effects were noted on aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, plasma urea, sugar or bilirubin. Serum electrolytes were not measured.

I. Urinalysis. There were no changes reported in the urine composition.

J. Organ weights. The thyroid, heart, lung, liver, spleen, kidneys, adrenals, testes, or ovaries were weighed. Of these, the following were indicated by the testing laboratory as being different from the control.

- heart - lower for all treated male groups, but higher for females
- liver - lower for male groups
- kidney - lower for male groups
- lung - lower for the high-dose males
- spleen - lower for the high-dose males
- thyroid - higher for the females
- adrenal - higher for females
- testes - higher for all male groups

Toxicology Branch notes the differences as above but considers that the magnitude and consistency of the effects do not require the conclusion that the differences noted were the result of the test material.

K. Gross pathology - The study report states that gross pathology performed on the rats sacrificed at the end of the experiment did not reveal any test compound-related tissue alterations.

L. Histopathology - Some 21 tissue types (including bone marrow smears) were reportedly evaluated for each of 5 rats of each sex per group. The only findings which the laboratory reported as related to the test material were inflammation of the trachea and emphysema of the lung.

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M. Special Studies

1) Body temperature - The body temperature was measured rectally after the 1st, 5th, 10th and 15th exposure. The pre-exposure recordings were shown to be remarkably constant. However, there were several indications of the high-dose group (males and females) and sometimes the mid-dose group.

The testing laboratory dismissed the apparent differences as not being of sufficient consistency or magnitude to be of toxicological concern.

2) Liver enzyme levels - No effects were noted on N-demethylase, O-demethylase or cytochrone P-450.

Special Insert

Because the first experiment did not show a definite NOEL for "untoward effects" a second study was initiated. The second study utilized 4 groups exposed to either the solvent only (20,000 ul/m^3 of air), 2 mg/m^3, 10 mg/m^3 or 50 mg/m^3 of FCR 1272. By analytical concentration these levels were 0, 0.4, 1.4 and 10.5 mg/m^3 of FCR 1272. The mean particle size was determined and it was found that >96% were respirable for this study.

In the second study the rats dosed with 10.5 mg/m^3 only showed the behavioral reactions and their weight gain was said to be slightly less than the controls.

In the second study differences in the weights of the liver (high-dose group males) and spleen (high-dose group males) were lower. Other differences were noted for the relative weights of the adrenals (males and females) and heart (females).

There were no gross or histopathological changes noted.

N. Conclusions.

1) CORE classification of this study is MINIMUM. The pathology was done on only 5 rats of each sex per dose group.

2) The NOEL is 1.4 mg/m^3. At higher dose levels there are noted behavioral, body weight and organ weight changes.

A. FCR 1272 study for nerve damage effect on the rat after 5 months oral application.

Bayer, A.G., Institute of Toxicology, Report No. 10705, March 10, 1982. EPA Acc. No. 072009, Tab. 3.3.5

B. The test material used for this study was FCR 1272 and was from batch 16001/79 and was stated as being of 83.3% purity.

C. The test animals used were Wistar TNO/W74 albino rats bred by Winkelmann Borchem. They were young at the initiation of the study (140-150 gm). 15 male and 15 female rats were dosed orally with the test material in Lutrol. They were dosed 7 days a week for 5 months by stomach tube. The dose level used was 60-80 mg/kg bw. This dose range was chosen so that the rats always showed symptoms. A solvent control group of 15 rats of each sex was also run.

D. Survival. 4 control rats died. 10 treated rats died. This indicates that deaths were likely due to the test material.

E. Behavioral reactions. The treated rats reportedly showed "non-specific behavior disturbances" (apathy, out-of-condition coat, troubled respiration). Digging and grooming, tremors, gait abonormalities and salivation were also noted. No indications of paralysis were noted.

F. Body weights. The males showed signs of lower weight gain. The females were apparently not affected.

G. No hematology was conducted.

H. Liver tissue was assessed for N-demethylase, O-demethylase and cytochrome P-450 activity. Increases in these enzymes were not observed following 5 months of treatment with FCR 1272.

I. Urinalysis was not performed.

J. Organ weights. (Only the liver, kidney and brains were evaluated for weight changes.) The liver (-11%) and kidney (-19%) were depressed for the males. The liver (+16%) was increased for the females.

K. Gross necropsy. No gross necropsy lesions were noted which were definitely related to the test material.

L. Histopathology. The liver, kidneys, adrenals, brain, spinal marrow and nn ischiadici (sciatic nerve) of 5 females and 5 males were prepared for histopathology. The brain and spinal marrow were stained with Nissel's method and Luxol Fast Blue respectively.

No test chemical lesions were noted by histological examination. There were no lesions reported in either the brain or sciatic nerve.

N. Conclusions.

1. This study is CORE MINIMUM.

2. No effects on the structure of the nervous system were noted.

A. FCR 1272 chronic toxicity study in dogs (six-month feeding experiment)

Bayer, A.G., Institut fur Toxikologie, Report No. 9991, June 2, 1981. EPA Acc. No. 072009, Tab. 3.5.2a.

B. The test material for this study was FCR 1272 from batch 16003/79 which was stated to have a purity of 84.8%.

C. The test animals were beagle dogs. They were 24 and 31 weeks old at the start of the experiment. There were 4 test groups each with 6 male and 6 female dogs. The dose levels were 0, 65, 200 and 600 ppm of FCR 1272 and the dogs were fed their diets for 26 weeks (185-186 total dosing days).

D. Survival. One dog died as a result of fighting. This dog was in group II (600 ppm) and was replaced by another dog (which received the test diet for 165 days). There was no effect of the test material.

E. Clinical observations. There were no differences in the general appearance of the dogs. Behavioral reactions were noted only in the dogs receiving 600 ppm. These included hind limb abnormalities such as stiff gait, uncoordination, arching backs (these developed in the later weeks of the experiment). Other signs in the group receiving 600 ppm included vomiting and diarrhea. There were no differences noted in the several reflex tests conducted or in body temperature or pulse rate.

F. Body weight and food consumption. Apparent decreases in body weight were evident at the dose levels of 200 and 600 ppm, but statistical significance was not attained for the high dose group. TR considers that not enough dogs were available per group to conclude that small differences noted were related to the test material. There were no differences noted with regard to food or water consumption.

Note: For sections G, H, and I, blood and urine samples were obtained at weeks 0, 4, 7, 13 and 26. All dogs in each test group were used.

G. Hematology. The following parameters were measured: hematocrit, hemoglobin, erythrocyte count, thrombocyte count, reticulocyte count, MCV, MCHC, MCH, sedimentation rate and thromboplastin time, leucocyte count and differential blood cell count. There were no test chemical effects on these parameters.

H. Clinical chemistry. The following parameters were measured: glucose, urea, creatinine, total protein, glutamate-oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase (GPT), alkaline phosphatase (AP), bilirubin, cholesterol, glutamate dehydrogenase (GLDH), Na^+, K^+ and Cl^-. Serum protein electrophoresis.

There was no test chemical effect on any of these parameters.

I. Urinalysis - No test chemical effects were noted on the various parameters investigated. The urinalyses were considered by this reviewer to be comprehensive.

J. Organ weights. The heart, lung, liver, kidneys, spleen, testes, ovaries, thyroid, adrenals, thymus, prostate, brain and pancreas were weighed.

Of these organs, only the thymus showed signs of depressed weight. For example, the male groups mid (-35%) and high (-34%) and female high dose group (-28%) were decreased in weight. The relative weights of these groups for the thymus were also similarly lower.

The liver weights were not affected.

K. Gross Pathology. There were no test chemical related lesions noted at gross necropsy. A possible exception may be that the female higher dose test group had 2 incidences of atrophied thymus.

L. Histopathology. Some 28 organs/tissues were examined for the control and high dose group dogs, but there were no test chemical related lesions noted.

M. Special studies.

1. Opthalmoscopic examination - (at weeks 0, 4, 7, 13 and 26). The examination included inspection of the outer parts, the transparent media and the ocular fundus. Opthalmoscopic examinations did not reveal test chemical effects.

2. Liver enzyme. No effects were noted on the activity of N-demethylase or cytochrome P-450 assayed in liver homogenates.

Conclusions

1. This study is CORE MINIMUM. Only the control and high dose group dogs were examined histologically.

2. A NOEL of 200 ppm is assigned. At 600 ppm there is evidence of neurological effects (hind limb effects) and gastrointestinal disturbance.

FCR 1272 (Proposed Common Name: Cyfluthrin) Multigeneration Study in Rats.

Bayer, A.G., Institute fur Toxikologie, Report No. 11870 (also Mobil No. 85881), June 8, 1983. EPA Acc. No. 072009, Tab. 3.6.2.

1. The test material used for this study was FCR 1272 and was from five batches designated as 2/80, 3/80, 5/80, 6/80 and 7/80. The purity of the material was not stated because the batches were as "pre-mix concentrates" at 50% with Wessalon S. The report stated that stability and homogeneity in the feed were checked before the start of the study but supporting data were not provided in the report.

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A consideration of the results in this FCR 1272 study (with respect to "arthrogryposis") in relation to the historical control data presented above for the same lesion, has led Toxicology Branch to conclude that "arthrogyposis" observed in this study is most likely not related to the administration of test material.

F. Conclusion

This study is classified as CORE MINIMUM. The report is not signed.

FCR 1272 Neurotoxicity study in hens

Bayer, A.G., Institut fur Toxikologie, Report No. 9753. January 27, 1981, EPA Acc. No. 072009, Tab. 3.6.6a.

[Note: This study consists of four parts: acute single dose oral LD_{50} in hens determination; single dose oral neurotoxicity study; two oral doses at a three week interval study; and five oral doses within one week study.]

The test material used for these studies was technical grade FCR 1272. Three individual batches were used: batch 16001/79 of 85.3% purity; batch 16003/79 of 84.8% purity; and batch 16003/80 of 94.3% purity.

The test animals used for these studies were White Leghorn hens (layers) bred and supplied by Mechow, Wappertal and Brinkschulte, Semlen. Apparently they were obtained from separate and independent suppliers. They were said to be between 15 to 20 months old and weighed between 1 and 2 kg.

Part 1 and Part 2. Acute oral LD_{50} and single oral dosing.

3 groups of 10 hens were dosed with either 1000, 2500 or 5000 mg/kg of tes material that was suspended in polyethylene glycol 400 and observed for up to 42 days after treatment.

5 of the 10 hens dosed with 5000 mg/kg died. Thus, the LD_{50} in hens was considered to be 5000 mg/kg.

6 of the 10 hens receiving 2500 mg/kg were said to show signs of intoxicat ("excitation") during the first 3 days following treatment. The hens dosed with 1000 mg/kg were said to be symptom free.

Two of the hens dosed with 5000 mg/kg showed signs of neurotoxic response. One of these developed symptoms (after first apparently recovering) on the 14th day and eventually died on day 19. The other developed symptoms on days 27 and 28. Histology of the brain, spinal marrow and left and right Nervi ischiadici (sciatic nerve) revealed "moderate" fiber alterations in the sciati nerve. These alterations included axon fragmentation, occasional swelling and eosinophilia of the axon fragments and vacuolation of the myelin sheaths.

Part 3: Two oral applications at 3 week intervals.

30 hens were dosed with 5000 mg/kg (the maximum practical dose) by gavage on two occasions 21 days apart. After a second 21 days, any hens showing symptoms were perfused with 10% Formalin to fix the nerve tissue. In addition, several birds not showing symptoms were fixed in situ. The brain, spinal marrow and Nervi ischiadici were excised, processed and histologically examined. A separate group of 5 hens were dosed with 375 mg/kg of the positive control TOCP. These birds were fixed and excised after 21 days following treatment.

The hens dosed with TOCP showed both behavioral (within 7-8 days) and histological evidence of a positive response.

The birds dosed with FCR 1272 were said to show initial signs of intoxication (first 3 days) but were said to be normal thereafter until the second dose was administered. Following the second treatment, 4 hens died. There was a series of symptoms which most hens showed which regressed in a few days post-treatment and a second set of symptoms which developed in 4 birds. The latter symptoms resembled delayed type neurotoxicity. Histopathology of these birds indicated that nerve fiber degeneration was present in the majority of the birds dosed with FCR 1272. The myelin sheath was distended and the myelin sheath was described as being optically void or granularly disintegrated. The axons were described as swollen or fragmented and in some areas activated or proliferated Schwann's cells were noted. The nerves also contained macrophages in which cytoplasm contained granular material.

Part 3 confirms a positive response that was noted in Part 2. It should be noted that there was no negative control group (solvent only) for either Parts 1, 2 or 3.

Part 4. Five oral applications within one week. In this part of the study, 10 hens were dosed with 5000 mg/kg of FCR 1272 from batch 16003/80 for five consecutive days and observed for 43 days.

6 of these hens were eventually perfused and the nervous system removed for histological examination. 4 of the hens died due to the initial effects of the toxicant. All hens showed initial toxic responses that disappeared eventually. Behavioral disorders accompanied by drowsiness and a cramped gait developed in 3 of the six survivors. The 3 hens which showed symptoms were perfused when found in a moribund state. The other 3 hens were perfused on day 43 of the study.

Necropsy and histology of the heart, liver, lungs, spleen, kidneys, ovaries, crop, esophagus, stomach, intestine, leg and pectoral muscle were also done.

Mottled kidneys and brittle livers were noted at necropsy. No treatment related lesions were noted in non-nervous system tissue by histopathological analysis.

Treatment-related fiber degeneration, i.e., distension or granular disintegration of the medullary sheath, swollen or fragmented axis cylinders and proliferated Schwann's cell in the sciatic nerve were reported. One hen had similar lesions in the spinal marrow.

This positive result confirms the results of the previous studies.

These studies show that under the conditions of these assays FCR 1272 induces a delayed type neuropathy.

These studies are SUPPLEMENTARY. They do not utilize a proper negative control group (solvent only) or properly attempt to study a dose response.

Investigative Neurotoxicity Studies in Hens

Mobay, Study No. 165, March 9, 1981, EPA Acc. No. 0972009, Tab. 3.6.6b.

In this study three synthetic pyrethroids were tested for their potential to cause neurotoxicity in hens. The three chemicals were FCR 1272 (cyfluthrin), NAK 1472 ((+)-trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylic acid-pentafluorobenzyl ester and NAK 1654 (the (-) pure form of NAK 1472).

Groups of 10 hens (17 months of age) were dosed with either FCR 1272 (5000 mg/kg), NAK 1472 (1000 mg/kg), NAK 1654 (2500 mg/kg) or TOCP (500 mg/kg) and were observed for 56 days before being sacrificed. The test materials were dissolved in Carbowax prior to dosing.

In a second experiment, FCR 1272 was administered (in carbowax) at 5000 mg/kg to a group of 20 hens on two occasions 7 days apart. A positive control group of 5 hens were dosed with 500 mg/kg of TOCP. An untreated control group of 4 hens were also included. The hens were observed for 49 days.

The results of the single dosing experiment indicated that no hens dosed with the three pyrethroids showed signs of neurotoxicity (behavioral, no microscopy). The hens dosed with FCR 1272 showed initial weight loss but recovered. The positive control group (TOCP treated) developed the delayed type neurotoxicity.

In the second experiment, only a single hen showed some signs of neurotoxic response but this was evident by the behavioral response only and on day 30. Necropsy and histopathology failed to confirm the presence of lesions in the nervous system. The condition of this hen was determined (by the laboratory) to be due to "egg-yolk peritonitis."

[Note: The data table indicates that 2 hens died (or were sacrificed) but the text refers to only one hen which was sacrificed.]

The positive control (TOCP treated hens) and the untreated hens responded as expected.

The first experiment is is CORE SUPPLEMENTARY (no microscopy). The second experiment is CORE MINIMUM. Under the conditions of this assay, no evidence that FCR 1272 induced neurotoxicity in hens developed.

FCR 1272 (cyfluthrin, baythroid active ingredient) neurotoxicity study on chickens after cutaneous administration (cumulation tests).

Bayer, A.G., Institute of Toxicology, Report No. 10768, March 29, 1982, EPA Acc. No. 072009, Tab. 3.6.6c.

The test material used for this study was FCR 1272 and was from two lots (batch 16003/80, 91.4% pure and from batch 816170019, 95.0% pure).

It should be noted that the dermal route is not the usual method of application for a hen neurotoxicity study. Hens were treated dermally (cutaneously) with the test material (made into a paste with cellulose powder) at a dose level of 5000 mg/kg. In the first study (called the pilot study), ten hens were exposed for 5 days for 23 hours each day. For the second study, 10 adult hens were treated for 3 weeks each workday for 6 hours at 5000 mg/kg. The hens were dosed at the axillae following preparation by removing any feathers. The test material was kept in place by a dressing wrap. Prior to sacrifice, the nervous tissue was fixed in situ by formalin infusion. The brain, segments of the cervical, thoracic and lumbar regions of the spinal cord and proximal and distal areas of the right and left ischiadici (sciatic nerve) were examined.

Exposure to 5000 mg/kg/day for 23 hours (5 times) resulted in 2 deaths that occurred on the 3rd and 10th day after cessation of treatment. All of the other hens were said to have recovered from the major symptoms (apathy and disturbed behavior). Other signs included local irritation and weight loss. Histopatholoy of the hens revealed that 2 had a "minimal segment-like nerve fiber degeneration" (sciatic nerve) but this type is often found in untreated hens.

Exposure to 5000 mg/kg/day for six hours for 15 exposures resulted in hens that appeared "apathetic." For most of the hens this symptom was reversed after the first week but for 2 hens, this symptom persisted until the 38th and 51st day after the start of treatment. Other signs included local irritation and body weight loss. There were no signs, either behavioral or microscopic, that indicated a neurotoxic (delayed type) response to treatment with FCR 1272.

This study is CORE MINIMUM. No evidence of delayed type neurotoxicity was evident under the conditions of this study. It should be noted that the dermal route is not the usual method of application for studying delayed type neurotoxicity.

Acute Oral Toxicity of Baythroid 240 EC in Rats

Mobay, Study No. 83-011-03, August 11, 1983, EPA Acc. No. 072008, Tab. 3.2A.2.

8 groups of male and female fasted Sprague-Dawley rats were dosed with either 46 (females only), 74, 118, 188, 300, 480, 768, 1229, or 1966 (males only) mg/kg of Baythroid 240 EC (25.2% cyfluthrin) and observed for 14 days. The test material was dissolved in Carbowax and administered by gavage.

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ADDENDUM

The following study was reviewed by Edwin R. Budd/Toxicology Branch.

FCR 1272 Chronic Toxicity to Dogs on Oral Administration (12-Months Feeding Study)

Bayer AG Institute of Toxicology: Report No. 11983; (Mobay Repot No. 86031): August 3, 1983. EPA Acc. No. 073256.

Study Design

The test material for this study was technical grade FCR 1272 (from several batches). As a 50% premix with Wessalon S, it was mixed in pulverized dog feed and presented to singly caged pure-bred male and female beagle dogs for 12 months. Analyses of the feed for content of active ingredient were performed at 1, 13, 26, 39 and 52 weeks. Six male and six female dogs per dosage level were treated at dosage levels of 0 (control), 40, 160 and 640 ppm.

The dogs were observed several times daily for appearance and behavior. Feed consumption was recorded daily. Body weights were determined weekly. Detailed general examinations (including reflex tests, body temperatures and pulse rates) were performed prior to administration of test material and at 6, 13, 26, 39 and 52 weeks. Ophthalmoscopic examinations were performed prior to administration of test material and at 5, 13, 29, 39 and 52 weeks.

The following laboratory examinations (hematology, clinical chemistries and urinalyses) were conducted on all dogs prior to administration of the test material and at 6, 13, 26, 39 and 52 weeks.

Hematology:	hematocrit, hemoglobin, erythrocyte count, MCV, MCH, MCHC, thrombocyte count, reticulocyte count, thromboplastin time, blood sedimentation rate, leucocyte count and differential blood count.
Clinical Chemistries:	blood sugar, urea, creatinine, total protein, GOT, GPT, AP, bilirubin, cholesterol, GLDH, sodium, potassium, calcium and chloride.
Urinalyses:	volume, specific gravity, protein, glucose, blood, bilirubin, ketone bodies and pH. The urine sediment was also examined microscopically.

Gross necropsies were performed on all dogs at termination of the study. Organ weights were determined for heart, lung, liver, kidneys, spleen, thyroid, adrenals, prostate, brain, pancreas, testicles or ovaries. The following tissues/organs were microscopically examined for the control and high dosage level animals (only): heart, liver, lung, spleen, kidneys, brain, adrenals, thyroid, pituitary, testicles, epididymis, prostate, ovaries, uterus, parotid, esophagus, stomach, intestines, pancreas, gall bladder, skeletal muscle, urinary bladder, aorta, lymph nodes, thymus, mammary glands, eye, optic nerve, sciatic nerve, bone and bone marrow.

Results:

All dogs survived the 12-month treatment period. No biologically meaningful differences in appearance and/or behavior were observed between control and test dogs during the entire study except for the following:

1. Two high dosage level dogs, on a single occasion for each dog (at 36 weeks for one dog and at 37 weeks for the other dog), exhibited "slow and unsure movements" consisting more specifically of a "swaying, slightly clumsy gait primarily in the hind quarters." The animals were "reluctant to move, and walked or ran ---- generally stiffly."

2. At the highest dosage level, vomiting and pasty to liquid feces were observed considerably more frequently than in the control, low or mid dosage level dogs.

Both 1. and 2. (above) are considered by Toxicology Branch to be related to the administration of test material.

General examinations (including reflex tests, body temperatures and pulse rates) and ophthalmoscopic examinations were negative for effects due to the test material.

Mean feed consumption was reduced in the high dosage level male group, but this was due mostly to the poor eating habits of one single animal in this group. The decreased mean food consumption in this group was probably not related to the test material. Water consumption was unaffected by the test material.

Mean body weights of the high dosage level male group were consistently depressed below those of the control group throughout the entire 12-month study. This was interpreted by Toxicology Branch as an effect due to the test material. Mean body weights of females were unaffected. Increases in mean body weights from initiation of the study to termination of the study are presented below.

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MEAN INCREASE IN BODY WEIGHT DURING STUDY

DOSAGE LEVEL	MALES	FEMALES
0 (control)	+ 3.7 kg	+ 3.4 kg
40 ppm	+ 4.2 kg	+ 3.4 kg
160 ppm	+ 4.8 kg	+ 3.6 kg
640 ppm	+ 2.6 kg	+ 3.8 kg

Results of hematological, clinical chemistry and urinalyses were all negative with respect to any biologically meaningful differences between control and test animals. Gross necropsies were similarly negative. Organ weights and organ/body weight ratios were also negative except for an increased spleen weight and spleen/body weight ratio for high dosage level females. Due to the high variability in spleen weights and the lack of any indicaton of effect on the spleen during gross necropsy and histopathology, it is likely that this observation was a random finding and not related to the administration of the test material.

The results of histopathological examination of tissues/organs from the control and high dosage level animals did not suggest any lesions attributable to treatment with the test material.

Conclusion:

This study is classified as CORE MINIMUM. The NOEL is 160 ppm. The LOEL is 640 ppm. At 640 ppm, slight "ataxia" was observed in two dogs on one occasion each. Increased vomiting, increased pasty to liquid feces, and decreased mean body weights in males were also observed at 640 ppm.

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Appendix B

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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of a Neurotoxicity Study of Baythroid™ in Hens

EPA No. 3125-GLR
Record No. 167963

Project No. 1414
Tox. Chem. No. 266E

TO: Christine Dively (PM Team #15)
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

Mobay Chemical Corporation submitted a Neurotoxicity Study of the Effect of FCR 1272 on Neurotoxic Esterase (Neurotoxic Target Enzyme) in Hens. This study was requested by John Doherty and Edwin Budd (ref. PP 4F3046/FAP 4H5427 and EPA Reg. No. 3125-GLR; 2-15-85)

This study was reviewed by the Toxicology Branch and was classified Core Supplementary. The study was poorly reported and had many deficiencies. There were no indications of significant inhibition of neurotoxic esterase.

Since the report was not signed by either the contributing scientists or the Quality Assurance officer, the validity of the report is in doubt. In the Doherty/Budd review, the failure of the Registrant to submit signed reports was mentioned along with the warning that studies would be classified Invalid unless signed reports were submitted. This warning has gone unheeded, but will be enforced on all future studies.

The Doherty/Budd review requested the Registrant to resolve several questions. The following text is quoted from that review:

> The registrant is also requested to provide an explanation and/or rationale for the different results observed in the acute delayed neurotoxicity tests in chickens between the studies performed by Bayer AG Institute of Toxicology (in Germany) and those performed by Mobay Chemical Corporation (in the United States). Some points that should be addressed include:
>
> - Possible differences in the test material
>
> ° Including a consideration of impurities, contaminants and/or manufacturing by-products in the test material.

° Including a consideration of possibly different ratios of active ingredient isomers in the test material.

- Possible differences in the test animals used

° Including a consideration of strain, source, etc.

° Including a consideration of normal background incidence of nervous system lesions in historical control animals of the same strain and source (if possible).

- Possible differences in investigational techniques employed

- Other

These questions remain unanswered.

NEUROTOXICITY STUDY OF THE EFFECT OF FCR 1272 ON NEUROTOXIC ESTERASE (NEUROTOXIC TARGET ENZYME) IN HENS

Bayer AG Institute of Toxicology; Report No. 13821; September 16, 1985; Accession No. 261433

PROTOCOL: Neurotoxic esterase (NTE) activity was assessed by the method of M.K. Johnson (Arch. Toxicol. 37, 1977, 113-115). Adult White Leghorn chickens (1.25-1.70 kg; 7-10 months old) were randomly assigned to three groups of 15 hens/group. One group was dosed by stomach tube with 20 ml/kg of a 25% (w/v) solution of FCR 1272 (92.9% purity) in polyethylene glycol 400 (PEG 400) at a dose of 5000 mg/kg/day for 3 days. This dose, which was a maximum attainable dose, was based on previous studies in which "clear signs and possibly mortalities" [sic] were observed after a single dose. The intent of this study was not to observe delayed neurotoxicity, but rather to detect NTE inhibition (an early indicator of delayed neurotoxicity) 24 hours after administration of one or two potentially lethal doses. A positive control group was dosed with TOCP (triorthocresylphosphate) in PEG 400 at a dose of 100 mg/kg/day. A third group constituted a vehicle control group and was dosed with PEG 400. Food and water were available ad libitum.

All hens were observed several times each day for clinical signs. They were weighed on day 1 only. They were all examined for gross lesions at the time of death or sacrifice. There were no histopathologic examinations performed. Three hens from each group were sacrificed by decapitation 24 hours after the first and second dosings. Their brains, spinal cords, and sciatic nerves were removed and evaluated for NTE activity.

RESULTS: The study was to last for 14 days, but all surviving hens were sacrificed on day 3 since all the hens dosed with FCR 1272 had died by then. The cumulative mortality (%) was as follows:

	Day 1	Day 2	Day 3
FCR 1272	0	25	100
TOCP	8	9	9
PEG 400	0	11	11

The vehicle and positive control compounds caused some lethality, but the test article was totally lethal. Clinical signs included fluffed plumage, lassitude, shrunken comb, spasms, salivation, dyspnea, and vocalization in hens treated with FCR 1272; slightly fluffed plumage and shrunken comb in the positive controls (TOCP); and slightly fluffed plumage, lassitude, apathy, and shrunken comb in the vehicle controls (PEG 400). There was no mention of the number of dead, moribund, or viable hens in any group. Gross lesions were seen only in the hens that died. Gross lesions seen in hens dosed with the test article included crops distended and filled with fluid, lungs distended and filled with fluid, and patchy livers. Gross lesions in the positive controls included crops distended and filled with fluid, and well-filled gall bladders. Gross lesions in the vehicle controls included crops distended and filled with fluid, patchy livers, and yellowish discoloration of the mucosa of the glandular stomach.

NTE activity in the brain, spinal cord and sciatic nerve in the test article group and vehicle control group were typically low 24 hours after the first and second doses. One hen, which was sacrificed 24 hours after the first dose of FCR 1272, had 53.3% NTE inhibition in the sciatic nerve. This value was approaching the 80% inhibition criteria that indicates the onset of delayed neurotoxicity. NTE activity in the positive control group (TOCP) was inhibited 80.4 to 94.6% 24 hours after the first and second doses, demonstrating the efficacy of the protocol. Thus, the test article did not significantly inhibit NTE.

This study is CORE SUPPLEMENTARY. All assays should have been performed in duplicate, but there was no evidence that this was done. The reference date for the method used in performing this study was incorrectly reported as 1972. The appendix, which contained the FCR 1272 and TOCP stability data, was missing from the report. Dose concentration analyses were apparently not performed. There was no way to determine the number of dead, moribund, or viable hens in each group. Room humidity was poorly regulated, and ranged from 50-90%. The report was signed by the translator, but not by the contributing scientists. A Quality Assurance statement was included in the report, but it too was unsigned. Considering the overall poor quality of the report presentation, it was obvious that the report was never reviewed for Quality Assurance, and is therefore of questionable validity. The Core classification of this study can be upgraded when the above deficiencies are resolved (including an explanation for the wide fluctuations in room humidity).

Tox Chem No. 266E File Last Updated 5-05-86 Current Date

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Neurotoxicity - hens Bayer AG Institute of Toxicology; #13821; 09-16-85	FCR 1272 (92.9% pure)	261433	The test article did not significantly inhibit neurotoxic esterase (neurotoxic target enzyme). Clinical signs: Fluffed plumage, lassitude, shrunken comb, spasms, salivation, dyspnea, and vocalization. All hens died within 3 days. Gross pathology: Crops distended and filled with fluid, lungs distended and filled with fluid, and patchy livers. Histopathology: Not needed. Level tested: 5000 mg/kg/day X 3 days (gavage) in White Leghorn strain. There were also positive controls (TOCP) and vehicle controls (PEG 400).		Supplementary

Appendix C

REVIEWER

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

004461

MAY 22 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA No. 4F-3046; Subacute Neurotoxicity Studies of Orally Administered Baythroid™ 2 on Rats

Tox. Chem No. 266E

TO: Christine Dively, PM Team # 17
Registration Division (TS-767c)

FROM: John E. Whalan, Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

Budd 5/21/85

The Toxicology Branch has reviewed two subacute neurotoxicity studies of orally administered Baythroid™ 2 (FCR 1272) on rats. The registrant, Mobay Chemical Corporation, supplied these reports in an effort to resolve the questions that the Toxicology Branch has on the neurotoxicity of Baythroid™ 2. Of major concern was the finding of nerve fiber degeneration at a dose of 1000 ppm (100 mg/kg/day) in a previously submitted 4-week rat feeding study (ref. PP#4G-2976 and FAP#4H-5416, J. Doherty).

Both studies are Core Supplementary and contain numerous inadequacies and inconsistencies. One of these studies confirmed the findings of nerve damage at a dose which was slightly lower than that used in the aforementioned study.

The submission of these studies does not alter the previously made request to conduct a hen brain neurotoxic esterase study to better define any potential neurotoxic hazard (ref. PP# 4F-3046, J. Doherty, dated 2-15-85).

004461

SUBACUTE NEUROTOXICITY of Orally Administered FCR 1272 in Rats

Bayer AG Institut Fur Toxikologie; Mobay Report No. 86305; December 27, 1983

Protocol: Groups of five male and five female Wistar Bor:WISW (SPF-Cpb) rats (130-150 g) were orally dosed by stomach tube with toxic doses of FCR 1272 (96.5% pure) formulated in polyethylene glycol 400. They were dosed once daily for 14 days at 0 (PEG 400 vehicle control), 50 (males only), and 60 mg/kg/day. They were observed for 14 days for clinical signs and body weight changes.

At the end of the study, they were sacrificed by heart puncture exsanguination while under anesthesia, and perfused with 100 ml of 10% formalin. The brain, spinal column (with spinal cord), sciatic nerve, and rear femoral musculature were dissected out and further fixed in formalin. Other unspecified organs were removed and preserved, but were not examined. Half of each brain was sectioned sagittally, and the other half was sectioned frontally. Multiple longitudinal and transverse sections of the cervical, thoracic, and lumbar spinal column and cord were decalcified in EDTA and embedded. The tissue sections werre stained with hematoxylin and eosin and Luxol blue (myelin sheath specific), and the axis cylinders were coated with silver using Glee's method (modified by Novotny).

Results: Clinical signs of toxicity commenced on day 2 in all compound treated groups, and included non-specific disturbed behavior, rolling, tremors, stretched gait, uncoordinated gait, and salivation. The 60 mg/kg/day males occasionally phonated. Four male rats dosed at 60 mg/kg/day died between treatment days 5 and 8. No gross lesions were found in these animals. Body weight gains were normal in the dosed and control females and in the male controls. The males dosed at 50 and 60 mg/kg/day initially lost weight between days 1 and 6, then gained weight at a reduced rate; at the end of the study they weighed significantly less than the control males.

No gross lesions were reported. Slight brain hemorrhages were observed in the males which died during the study. These lesions were attributed to a terminal cardiovascular disorder with necrosis of the vascular walls. One of these males also had necroses of the skeletal muscle fibers.

This study is CORE SUPPLEMENTARY. It was lacking the signatures of the scientists and pathologist. The histopathology tables were lacking all data that pertained to "normal variability specific to the species and the animals' ages, and the conventional conditions under which they were kept." Also lacking was a presentation of the gross lesions.

004461

SUBACUTE NEUROTOXICITY of Orally Administered FCR 1272 in Rats

Nihon Tokushu Noyaku Seizo K. K. Agricultural Chemicals Institute; Mobay Report No. 86427; June 30, 1983

Protocol: Male SD rats (6 weeks old) were orally dosed with FCR 1272 (95% pure) in polyethylene glycol 400 for 14 days at doses of 0 (PEG 400 vehicle control) and 80 mg/kg/day. After 5 doses at 80 mg/kg/day, the dosage was reduced to 40 mg/kg/day due to the severity of toxic response. The rats were observed at unspecified intervals for clinical signs throughout the study, and weighed at 1 and 5 days, and at 1, 2, and 3 months.

After each weighing interval, 5 control rats and 10 treated rats were sacrificed by injection of sodium pentobarbital and sodium heparin. The rats were lumbotonized, and 10% buffered formalin perfused through the left ventricle. The brain, spinal cord (cervical, thoracic, and lumbar sections), sciatic nerve, femoral nerve, femoral muscle, and gastrocnemial muscle were excised and stained with hematoxylin and eosin, and Kluver-Barrera and Bodian stains for nervous tissues. Presumably, no additional fixation was attempted beyond the initial perfusion. These tissues were examined with a light microscope.

Tissues of one control and two treated rats at each sacrifice interval (except the 2 month interval) were examined with an electron microscope. These rats were fixed by perfusion with 2% glutaraldehyde (4°C). The above tissues were excised and further fixed with osmium acid. These tissues were doubly stained with uranil acetate and lead nitrate. The following tissues were then examined:

cortex of the cerebrum
vermis cerebelli
ventral and lateral funiculus of the spinal cord (cervical)
ventral funiculus of the spinal cord (thoracic and lumbar)
sciatic nerve
femoral nerve
femoral muscle
gastrocnemial muscle

Results: All of the treated rats had slight to moderate straddled gait, slow leg movement, and titubation which were most severe several hours after dosing. Some rats also salivated and had red tears. Reducing the dose after day 5 from 80 to 40 mg/kg/day caused a reversal in these toxic signs in all rats by the end of the second week. The clinical signs for the control group were not reported. Body weights for the treated groups lagged behind the control group for an undetermined time, but both groups had similar weights by the end of the study.

Light microscopic examination revealed minimal axonal degeneration (myelin swelling and desquamation) in a single fiber of the sciatic nerve at days 1 (6/8), and 5 (3/8), and months 1 (3/8), and 2 (2/9). No other lesions were seen in the dosed and control groups.

Electron microscopy revealed microtubular dilatation with proliferation of neurofilaments and mitochondria degeneration in the sciatic nerve at days 1 and 5, and at 1 month in the dosed rats. These same lesions were also seen in the femoral nerve of a day 5 rat. No other lesions were reported in any other dosed or control rats.

004461

This study is CORE SUPPLEMENTARY. It was lacking the signatures of the scientists and pathologist. The method of orally dosing the rats was not described, and the schedule for observing clinical signs was not given. No clinical signs were reported for any control animals. The study protocol, results section, and body weight graph were not consistent in regards to the times of measurement and periods of divergent weights. The histopathology tables were lacking all data that were judged to be not caused by the test article. There were contradictions between the results section and the pathology tables in regard to the number of animals affected. Also lacking was a presentation of the gross lesions.

Tox Chem No. 266E Baythroid | File Last Updated _____ | Current Date 5-20-85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subacute Oral Neurotoxicity - Rat; Bayer AG Institut Fur Toxikologie; Mobay #86305; 12-27-83	FCR 1272 (96.5% pure)	None	Clinical signs: Non-specific disturbed behavior, rolling, tremors, stretched gait, uncoordinated gait, salivation, phonation, weight loss (males), and death. Gross pathology: None Microscopic pathology: Slight brain hemorrhages (males), necrosis of the skeletal muscle fibers (male). Levels tested: 0 (PEG 400 vehicle control), 50 (males only), and 60 mg/kg/day X 14 days, by stomach tube in Wistar Bor:WISW (SPF-Cpb) strain.		Supplementary
Subacute Oral Neurotoxicity - Rat; Nihon Tokushu Noyaku Seizo K. K. Agricultural Chemicals Institute; Mobay #86427; 6-30-83	FCR 1272 (95% pure)	None	Clinical signs: Straddled gait, slow leg movement, titubation, salivation, red tears, reduced weight gain. Gross pathology: Not reported Microscopic pathology: Light - Axonal degeneration of sciatic nerve. EM - Microtubular dilatation with proliferation of neurofilaments and mitochondria degeneration in the sciatic and femoral nerves. Levels tested: 0 (PEG 400 vehicle control) and 80 mg/kg/day (reduced to 40 mg/kg/day after 5 doses) X14 days, by unspecified oral route in male SD strain.		Supplementary

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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Company Response - Submission of Additional Data to Supplement Two Baythroid" Neurotoxicity Studies in Rats

EPA No. 3125-GLR
Record No. 169470

Project No. 1436
Tox. Chem. No. 266E

TO: Christine Dively (PM Team #15)
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

John E Whalan
5-5-86

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

Toxicology Branch reviewed two neurotoxicity studies in rats (J. Whalan; EPA No. 4F-3046; May 22, 1985) submitted by Mobay Chemical Corporation. There were a number of deficiencies in both study reports to which the Registrant has now responded. The following are itemizations of the deficiencies and the data submitted. The revised Core status of these studies follows each presentation.

1. Subacute Neurotoxicity of Orally Administered FCR 1272 in Rats, Bayer AG Institut Fur Toxikologie; Bayer Report No. 12338, Mobay Report No. 86305; December 27, 1983.
The response was in the form of an addendum to the report.

   A. This report was lacking the signatures of the participating scientists and pathologist - The Registrant submitted a copy of the signed discussion page (page 24) from the German report. Although this page had no report number to identify it, it did appear to come from this report.

   B. The histopathology tables were lacking all data that pertained to what was described by the authors as "normal variability specific to the species and the animals' ages, and the conventional conditions under which they were kept." - The pathologist, Dr. G. Kaliner, gave a description of what was reported in the histopathology tables as "histopathologically unremarkable. These lesions included such findings as "degenerated, short segments of individual fibers (digestion chambers), and the occurrence of individual round cells and mast cells."

C. The report was lacking a presentation of the gross lesions - The gross pathology data were presented. These data demonstrate that most rats dosed at 50 or 60 mg/kg/day had distended lungs; this was not mentioned in the report, and it is not regarded as a compound-related effect. Further, the four males which died in the 60 mg/kg/day group died on days 6-9, not days 5-8 as reported.

On the basis of these clarifications, the Core classification for this study can now be upgraded to CORE GUIDELINE.

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2. Subacute Neurotoxicity of Orally Administered FCR 1272 in Rats, Nihon Tokushu Noyaku Seizo K. K. Agricultural Chemicals Institute; Mobay Report No. 86427; June 30, 1983. A complete revised report was submitted.

A. This report was lacking the signatures of the participating scientists and pathologist - Dr. Iyatomi did not want to sign the English translation of the report because he believes that only the original (in Japanese) should be signed. This line of logic is flawed, because the purpose of the signatures is not to verify the accuracy of the translation, but rather to verify that the study was actually performed, and the data are correct. More specifically, these signatures assign responsibility for the study to the participating scientists and pathologists, not the translator (who may not know anything about the study). Dr. Iyatomi was the Supervisor of this study. He signed page 12, assuming responsibility for the translation. He also said that he sent a signed Japanese report, but a copy was not received in the Toxicology Branch. This objection will be waived since the report was signed by Dr. Iyatomi, the Study Supervisor.

B. The method of orally dosing the rats was not described - The rats were "forcedly" dosed p.o. Presumably, this means that they were dosed by stomach tube.

C. The schedule for observing clinical signs was not given - "All of rats [sic] were daily inspected on their appearance and behavior through the 14-day administration period and 3-month observation period."

D. No clinical signs were reported for any control animals - There were no clinical signs observed in any control animals.

E. The study protocol, results section, and body weight graph were not consistent in regards to the times of measurement and periods of divergent weights - All of the rats, "were weighed daily on the administration period, and at 1st and 5th day, 2nd week, 1st, 2nd and 3rd month of observation period." The body weight data presented in tables and a graph were reported weekly during the administration period, and as specified during the observation period. This procedure is appropriate.

F. The histopathology tables were lacking all data for lesions that were judged to be not caused by the test article - A complete presentation of histopathology revealed no lesions other than sciatic nerve axonal degeneration (previously reported).

G. There were contradictions between the results section and the pathology tables in regard to the number of animals affected - The results section in the revised report agrees with the pathology tables.

H. The report was lacking a presentation of the gross lesions - There were few gross examinations performed because, "Autopsy was not inspected in all of animals, because the macro-changes in color and/or size occurred by the perfusion fixation." This is a reasonable procedure.

On the basis of these clarifications, the Core classification for this study can now be upgraded to CORE GUIDELINE.

Tox Chem No. 266E Baythroid | File Last Updated _____ | Current Date 5-05-86

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subacute Oral Neurotoxicity - Rat; Bayer AG Institut Fur Toxikologie; Mobay #86305; 12-27-83	FCR 1272 (96.5% pure)	None	Clinical signs: Non-specific disturbed behavior, rolling, tremors, stretched gait, uncoordinated gait, salivation, phonation, weight loss (males), and death. Gross pathology: None Microscopic pathology: Slight brain hemorrhages (males), necrosis of the skeletal muscle fibers (male). Levels tested: 0 (PEG 400 vehicle control), 50 (males only), and 60 mg/kg/day X 14 days, by stomach tube in Wistar Bor:WISW (SPF-Cpb) strain.		Guideline
Subacute Oral Neurotoxicity - Rat; Nihon Tokushu Noyaku Seizo K. K. Agricultural Chemicals Institute; Mobay #86427; 6-30-83	FCR 1272 (95% pure)	None	Clinical signs: Straddled gait, slow leg movement, titubation, salivation, red tears, reduced weight gain. Gross pathology: Not needed. Microscopic pathology: Light - Axonal degeneration of sciatic nerve. EM - Microtubular dilatation with proliferation of neurofilaments and mitochondria degeneration in the sciatic and femoral nerves. Levels tested: 0 (PEG 400 vehicle control) and 80 mg/kg/day (reduced to 40 mg/kg/day after 5 doses) X14 days, by unspecified oral route in male SD strain.		Guideline

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Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**05/14/86**
File ID:	**00000000**
Accession Number:	**412-04-0236**

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08/19/2004