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

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MAR 21 1991

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Consideration of Cyfluthrin for Special Review Based on Developmental Effects.

Tox. Chem. No. 266E

TO: George LaRocca (PM Team #15)
Registration Division (H7505C)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section I, Toxicology Branch I
Health Effects Division (H7509C)

John E. Whalan
3-6-91

THRU: Roger L. Gardner, Section Head
Section I, Toxicology Branch I
Health Effects Division (H7509C)

Roger L. Gardner
3-8-91 KB 3/11/91

Several months ago, Adam Heyward (RD) conveyed a query from you regarding the need for a special review of FCR 1272 (cyfluthrin) in light of positive findings in a recently reviewed inhalation developmental toxicity study performed at Bayer AG Toxicology Division (John Whalan memorandum; EPA No. 3125-356; November 28, 1989). Although this study had a number of serious deficiencies, it was classified Core Minimum because it was evident that FCR 1272 caused developmental toxicity when administered by inhalation. The true nature and extent of developmental effects could not be assessed because of poor study documentation.

The positive findings in the inhalation developmental study were in sharp contrast to the negative findings reported in past reviews of oral rat and rabbit studies performed at the same laboratory. The metabolism data were inadequate to explain a pharmacokinetic or pharmacodynamic rationale for this dichotomy. A reexamination of the old reproduction and developmental toxicity studies was performed to see whether any toxic endpoints had been overlooked. These studies, which had been classified Core Minimum, were found to be deficient.

The results of this investigation were presented to Bill Burnam, Karl Baetcke, Roger Gardner, and Steve Dapson (teratologist). The following recommendations received unanimous concurrence:

1. Cyfluthrin should not go to special review. The quality of the developmental toxicity data is too poor to allow meaningful dialogue at this time.

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2. The Registrant should be informed that the Oral Developmental Toxicity studies performed at Bayer (Reports Nos. 10562 and 11855) are not acceptable. They should be repeated, since it is unlikely sufficient data are available to make them fully evaluable.

3. Both of the Bayer Oral Developmental Toxicity studies were considered in establishing a reference dose (RfD) in 1986. The HED RfD Workgroup will be notified that neither of these studies are acceptable. The requirement for a rat developmental toxicity study can be satisfied by another study performed by Research & Consulting Company AG. The requirement for a rabbit developmental toxicity study, however, will remain a data gap. The impact of the Inhalation Developmental Toxicity study on the RfD cannot be assessed at this time. Currently, confidence in the principle study, the data base, and the RfD is "High." The quality of the data base, and the RfD, should be reconsidered.

4. Although the Inhalation Developmental Toxicology study performed at Bayer AG Toxicology Division (Report No. 97403) was classified "Core Minimum" according to HED practice, it was not adequate. The Registrant should submit additional data which address the study deficiencies.

5. The Oral Reproduction study will not be rereviewed at this time since the reproductive NOEL is greater than the RfD (0.025 mg/kg/day). The study will receive a thorough review at a later date, and a decision on its validity will be made at that time.

The following pages contain summaries of defined doses reported in the old DER's, followed by the results of my reexaminations of the studies and the DER's. Copies of the DER's referenced in this memorandum are attached.

cc George Ghali
(RfD Workgroup)

ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS — CORE MINIMUM

Bayer AG Institute fur Toxikologie; Report No. 10562, January 20, 1982; EPA Document No. 4285

Reviewed by John Doherty (February 15, 1985). The defined doses are as follows:

Maternal NOEL = 3 mg/kg/day
Maternal LEL = 10 mg/kg/day (behavioral changes in gait and coordination)
Developmental NOEL >30 mg/kg/day (HDT)

RESULTS OF REEXAMINATION: The study report was only 18 pages in length, and was poorly written. Insufficient data were provided for meaningful evaluation. The report was lacking individual daily observations, body weights, and food consumption data. There was no attempt to count corpora lutea, early and late resorptions, or viable fetuses/sex. There was no way of knowing whether all fetuses received external examinations. At the low dose, there did not appear to be any developmental toxicity (one monster was found); in the absence of data tables, there is no way of knowing whether the low-dose group was free of significant developmental toxicity. The test article was formulated in Lutrol (NOTE: The vehicle in the rabbit study was Cremophor EL).

Regarding the study review (DER), this study is not acceptable, and the Core Classification of MINIMUM is inappropriate. There was no mention of defined doses in the DER, but defined doses were listed in the "One-Liners." The Maternal LEL of 10 mg/kg/-day was based on "behavioral changes in gait and coordination." Six of 25 rats at this dose had "high stepping gait." Six of 25 rats at the highest dose (30 mg/kg/day) also had these signs, and occasional ataxia and decreased motility as well (the report did not give incidence). There does not seem to be a lot of difference between these two doses, possibly because these signs are not dose or compound-related. Considering the poor data presentation in the study report, it is not appropriate to assign defined doses.

It would not be reasonable to compare the dubious results of this Bayer study against those in an Oral Developmental Toxicity Study in Rats performed at Research & Consulting Company AG.

ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS CORE MINIMUM

Bayer AG Institute fur Toxikologie; Report No. 11855, June 1, 1983; EPA Document No. 4285

Reviewed by John Doherty (February 15, 1985). The defined doses are as follows:

Maternal NOEL = 15 mg/kg/day
Maternal LEL = 45 mg/kg/day (abortion and resorption)
Developmental NCEL >45 mg/kg/day (HDT)

RESULTS OF REEXAMINATION: The study report was only 21 pages in length, and was poorly written. Insufficient data were provided for meaningful evaluation. The report was lacking individual daily observations, body weights, and food consumption data. There was no attempt to count corpora lutea, early and late resorptions, or viable fetuses/sex. It is doubtful that significant maternal effects were found at the high-dose; two does aborted, and one had complete resorption. These findings are not unusual in rabbits, particularly if the rabbits are stressed, as they were in this study, by exposure to loud construction noise from the floor below. Necropries were apparently not performed on the adults. The test article was formulated in Cremophor EL which is too toxic to use orally as a vehicle when other, less toxic vehicles are available (NOTE: The vehicle in the rat study was Lutrol).

Regarding the study review (DER), this study is not acceptable, and the Core Classification of MINIMUM is inappropriate. There was no mention of defined doses in the DER, but defined doses were listed in the "One-Liners." The Maternal LEL of 45 mg/kg-/day was based on abortion and resorption. Since abortion and resorption are common in rabbits, and no other toxicity was reported at this dose, the LEL was overly conservative. Considering the poor data presentation in the study report, it is not appropriate to assign defined doses.

ORAL REPRODUCTION STUDY IN RATS — CORE MINIMUM

Bayer AG Institute fur Toxikologie; Report No. 11870; June 8, 1983; EPA Document No. 4285

Reviewed by John Doherty (February 15, 1985). The defined doses are as follows:

Systemic NOEL = 50 ppm (1.5 mg/kg/day)
Systemic LEL = 150 ppm (4.5 mg/kg/day; body weight decrease in pups)
Reproductive NOEL = 50 ppm (1.5 mg/kg/day)
Reproductive LEL = 150 ppm (4.5 mg/kg/day; decreased viability index)

RESULTS OF REEXAMINATION: This study was far better than the two developmental toxicity studies. It was 319 pages in length, and fairly comprehensive, but it still had a number of deficiencies. The test article was a 50% pre-mix concentrate with Wessalon S (not further specified). Five batches of pre-mix were used. Half the required number of males were used. There were no individual litter observations. The report failed to mention when the mating males and the breeding females were sacrificed. Only the F_{2b} and F_{3b} rats, and rats which died on study were necropsied. Histopathology was done only on one male and one female F_{3b} pup/dam for 10 control dams and 10 control high-dose dams, and their F_{2b} parents.

The study review (DER) was lacking in detail. A cursory review of the report suggests that the defined doses are inappropriate. The doses used were 0, 50, 150, and 450 ppm. The viability indexes for the F_3b generation (the generation most affected) were 99%, 92.3%, 89.0% and 77.4%, respectively. The reviewer considered the 92.3% value to be, "reasonably close to and within control range values," and thus defined the low-dose as the Reproductive NOEL. Considering that viability was essentially the same at both the low (92.3%) and mid-dose (89.0%), but substantially reduced at the high-dose (77.4%), the Reproductive NOEL probably should have been defined as 150 ppm (4.5 mg/kg/day).

Reviewed by: John E. Whalan JW 7-21-89
Section II, Tox. Branch I (TS-769C)
Secondary reviewer: Edwin R. Budd 7/31/89
Section II, Tox. Branch I (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: Teratology Study in Rats by Inhalation

ACCESSION NUMBER: 407804-01

TOX. CHEM. NO.: 266E

TEST MATERIAL: FCR 1272 (93% pure)
Batch No. 233490583
Brownish viscous substance

MRID NO.: N/A

SYNONYMS: Cyfluthrin

STUDY NUMBER(S): Bayer No. T 0020125, T 3021686
Mobay No. 97403

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer AG Toxicology Division (Fed. Rep. of Germany)

TITLE OF REPORT: Study for Embryotoxic Effects on Rats After Inhalation

AUTHOR(S): M. Renhof and J. Pauluhn

REPORT ISSUED: February 1, 1988

CONCLUSIONS: Despite the deficiencies of this study, it is evident that FCR 1272 is teratogenic when administered by inhalation. Striking differences between this study and an oral teratology study performed at the same laboratory suggest that bypassing portal circulation may expose the rats to more parent compound and less metabolite. The defined doses are as follows:

Maternal NOEL = 0.0011 mg/l
Maternal LEL = 0.0047 mg/l (reduced motility, dyspnea, piloerection, ungroomed coats, and eye irritation)
Developmental NOEL = 0.00059 mg/l
Developmental LEL = 0.0011 mg/l (unspecified sternal anomalies, increased runt incidence)

STUDY CLASSIFICATION: This study is classified CORE MINIMUM. Despite its deficiencies, this study is acceptable because it demonstrated cyfluthrin's teratogenic potential. Skeletal anomaly incidence was presented by general structure only (e.g. sternum, skull, extremities, etc.); there was no way of telling where the anomalies were found, or what the anomalies actually were (e.g. fusions, delayed ossifications, etc.). There was also no presentation of visceral anomaly data, although some data were combined with the list of external malformations. The criteria used for defining a runt were not given. Historical control data would have been useful. This study received Quality Assurance review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: This study was performed in two parts, the first study and the second study. In the First Study, four groups of 30 female (187-250 g) Bor:WISW (SPF Cpb) rats were inseminated by being housed overnight with males (>300 g). The presence of sperm in the vaginal smears following mating established gestation day 0. The females were exposed head-only to the test article in a 20 liter PVC dynamic inhalation chamber for 6 hours/day on gestation days 6 through 15. The nominal FCR 1272 chamber concentrations were 0 (vehicle control), 0.001, 0.005, and 0.025 mg/l. In the Second study, additional groups of 30 inseminated females were similarly exposed to nominal chamber concentrations of 0 (vehicle control), 0.0001, 0.0003, 0.0006, and 0.005 mg/l. An oxygen enriched atmosphere (30%) was provided for the 0.005 mg/l group to see if the embryotoxic effects seen in the first study at this concentration could be lessened.

The test article was dissolved in a 1:1 mixture of Lutrol (polyethylene glycol E 400) and ethanol. The test article formulations were prepared daily, and aerosolized with binary spray nozzles. Samples of the chamber atmospheres were collected on cotton wool in glass tubes placed in the rats' breathing zone. Analytical measurements were made using gas chromatography and high pressure liquid chromatography. Particle size measurements were made with an APS 3300 aerodynamic particle sizer and a Berner cascade impactor. The integrity of the aerosol generator was assured during exposure with a Ratfisch RS 55 total hydrocarbon analyser. Food and water were available ad libitum.

The rats were observed several times on the exposure days except during the exposures (because of restraint for head-only exposure). They were weighed on gestation days 0, 6, 9, 12, and 20.

The dams were sacrificed on day 20 and their pups removed by caesarean section. Their ovaries and uteri were examined for implantations, live young, embryonic and fetal deaths, fetal sex and weights, and external fetal abnormalities. Approximately a third of the fetuses were examined by the method of Wilson (1965) for visceral malformations, and the remaining fetuses were eviscerated, clarified, stained with alizarin red S, and examined for skeletal defects by the method of Dawson.

RESULTS: The results from the first and second studies will be presented together. Dose concentration analyses measured analytical concentrations to be within 13% and 17% of nominal in the first and second studies, respectively. The majority of aerosol particles in all concentrations were in the respirable range (<1 um). The nominal and analytical concentrations, mass median aerodynamic diameter (MMAD) values with geometric standard deviations, and mortality were as follows:

Concentration (mg/l/day) Nominal	Analytical	MMAD (Gsd)	Mortality
FIRST STUDY:			
0	0	1.40 (1.41) um	0/30
0.001	0.0011	1.23 (1.33) um	0/30
0.005	0.0047	1.45 (1.42) um	0/30
0.025	0.0237	1.23 (1.34) um	1/30*

SECOND STUDY:

0	0	1.43 (1.92) um	0/30
0.0001	0.00009	1.53 (1.69) um	0/30
0.0003	0.00025	1.29 (1.69) um	0/30
0.0006	0.00059	1.49 (1.75) um	0/30
0.0050†	0.00416†	1.46 (1.96) um	0/33

* One rat had its neck broken while being placed in an exposure tube.
† This exposure group was provided with an oxygen rich atmosphere (30%).

There were no compound-related maternal deaths. Dose-related clinical signs included reduced motility, dyspnea, piloerection, ungroomed coats, and eye irritation, and were only seen in the 0.00416, 0.0047, and 0.0237 mg/l groups. The 0.00416 mg/l group had an oxygen-rich atmosphere (30%) during exposure, and had significantly fewer and milder clinical signs than the nearly equivalent 0.0047 mg/l group. The supplemental oxygen allowed these rats to reduce their exposures by reducing their minute volumes. Body weight gain was comparable in all groups, and there were no compound-related gross lesions. The following tables present the status of their dams and offspring:

Dose (mg/l/day)	Gravid/ Mated	Implants Per Dam	Live Young Per Dam	Embryonic Deaths Early	Embryonic Deaths Late	Post-Implant. Loss %
FIRST STUDY:						
0	25/30	11.5	10.8	2	15	6.1
0.0011	29/30	12.2	11.3	5	20	7.4
0.0047	27/30	11.7	10.1	28	19	13.7
0.0237	29/30	11.6	9.3	6	57	19.8
SECOND STUDY :						
0	23/30	10.7	9.0	3	37	15.9
0.00009	29/30	11.4	9.6	10	42	15.8
0.00025	25/30	11.2	8.8	8	51	21.4
0.00059	29/30	11.0	9.2	6	46	16.4
0.00416†	22/30	11.2	9.5	5	32	15.2

Dose (mg/l/day)	Mean Fetal Weight (g)	% Male	Total Malformations	— Anomalies — Visceral	Skeletal	Runts (%)
FIRST STUDY:						
0	3.40	54	1	N/R	45/188 (24%)	1.9
0.0011	3.16	50	2	N/R	76/228 (33%)	17.7
0.0047	2.89	54	4	N/R	105/204 (51%)	48.4
0.0237	2.43	46	10	N/R	149/184 (81%)	81.4

SECOND STUDY:

0	3.48	49	1	N/R	58/143 (41%)	3.9
0.00009	3.51	54	3	N/R	71/195 (36%)	4.0
0.00025	3.53	50	5	N/R	41/156 (26%)	3.6
0.00059	3.47	53	1	N/R	54/186 (29%)	2.3
0.00416†	3.29	55	1	N/R	42/146 (29%)	12.0

† This exposure group was provided with an oxygen rich atmosphere (30%).

The embryonic death data are skewed. Specifically, each study had one group with anomalous values, and the second study had late embryonic deaths 2-3 times that expected based on the first study. Late embryonic death was significantly increased (4-fold) in the 0.0237 mg/l group in the first study compared to the controls. There was a significant increase in post implantation loss in females dosed at 0.0047 and 0.0237 mg/l in the first study.

Pup weights were reduced 15% and 29% respectively in the 0.0047 and 0.0237 mg/l groups in the first study. There were surprisingly high incidences of runts during this study - as many as 81.4% in one group. There were dose-related incidences in all dosed group in the first study (0.0011, 0.0047, and 0.023 mg/l), and in the high-dose (0.00416 mg/l) in the second study. Unfortunately, the criteria for defining a runt was not given.

There were dose-related increases in skeletal anomalies in the sternum (0.0011, 0.0047, and 0.0237 mg/l), spinal column (0.0047 and 0.0237 mg/l), and the extremities, pelvis, and skull (0.0237 mg/l). The report failed to mention specifics about the locations and nature of these anomalies.

The report also failed to distinguish between external malformations and visceral anomalies. The list of total malformations on the previous page is actually a combination of the two. Although there were sporadic incidences of individual pups with severe defects, the only dose-related malformation was microphthalmia in the 0.0237 mg/l group.

The report considered impairment in fetal development at concentrations of 0.0011 mg/l or greater to be a secondary effect due to the impairment of ventilation. It did not specify whether this maternal hypoxia was due to suppression (e.g. anesthetic effect) or mechanical effect (blocked airways). The 0.00416 mg/l group was used as evidence that the administration of supplemental oxygen lessened fetal trauma. While skeletal anomalies and the runt incidence were lower in this group, the other data do not support the laboratory's conclusions. Discrepancies between studies one and two, and the use of supplemental oxygen for only one group make any such comparisons invalid.

There is no evidence that FCR 1272 suppressed respiration, and it is unlikely the low concentrations could have caused airway blockage. FCR 1272 probably reduced maternal energy, and the administration of supplemental oxygen only complicated study interpretation. Any apparent decrease in maternal and fetal toxicity probably resulted from reduced test article exposure as a consequence of oxygen-induced reductions in maternal minute volumes. The 0.00416 mg/l group has been eliminated from consideration for the defined doses.

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.

2. The test animals used were SPF rats of the BOR:WISW strain and were bred by a German supplier. At the start of the study, the rats were 5-6 weeks old. There were 4 groups of 10 males and 20 females in each test group and they were dosed as either 0, 50, 150 or 450 ppm. Six sets of litters were bred. F_1a and F_1b from the F_0 parental groups; F_2a and F_2b from the F_1b parental groups and F_3a and F_3b from the F_2b parental groups. For each mating one male rat was mated with 2 female rats.

3. Survival, general appearance and behavioral reactions in adult rats. No test chemical related deaths were reported. Body weight gain for the adults was definitely depressed at 450 ppm for all groups.

4. Reproductive performance

   a. Fertility index (number of pregnant females/number of mated females.) No consistent change in the fertility index was noted. Usually 90-100% pregnancies resulted. The F_1b parents had occasions of 65-85% pregnancies and the F_2b generation high dose group resulted in the lowest rate (65%). This trend was not evident in the F_3a or b generations.

   b. Gestation index (number of females with live litters/number of pregnant females). No effects were noted and the gestation index was usually 90-100%.

   c. Viability index (number of live pups after 5 days/number of pups born). Indication of decreased viability was evident for the F_1a, F_2a, F_2a and F_3b generations. The F_3a and F_3b generations were most noticeably affected. For example, the F_3b generation had viability indexes of 99.0, 92.3, 89.0, and 77.4 for the control, low, mid and high dose groups.

      For the purpose of this study, the NOEL is set at 50 ppm because the decrease at 50 ppm is not consistent through the 6 litter sets and it is considered by this reviewer to be reasonably close to and within control range values.

   d. Lactation index (number of live pups after 4 weeks/no. of live pups at day 5, after reduction to 10): decreases in the lactation index were evident for the F_1a, F_1b, F_2a, F_2b and F_3b litter sets. The maximum difference was found for the F_2a and F_2b groups which were 75.8 and 72.4% for the mid and high dose levels versus 93.1% for the control group.

5. Condition of the pups

   a. Sex ratio - was not affected, there were approximately equal numbers of males and females.

b. Number of pups - For the F_1b and the F_3a groups there appeared to be few pups in the high dose group, but this trend was not evident in the other 4 litter sets.

c. Stillbirths - The F_1b group had 6 stillbirths in the high dose test group but the other litter sets did not show evidence of dose related stillbirths.

d. Body weight at birth - Body weight of the pups at birth was small for some occasions but this was not consistent for the high dose test group for all 6 of the litter sets.

e. Body weight gain of the pups - A NOEL for decrease or retarded weight gain is set at 50 ppm. At 150 and 450 ppm there was noted consistent effects and slower weight gain.

6. Gross necropsy and histopathology. The 4-week-old pups from the F_3b generation and their parents (the F_2b generation) were necropsied and subjected to histopathology. A single male and female from each of 10 dams from the control and high dose groups were examined histologically.

No dose related changes were noted by either gross necropsy or histopathology of the parents or pups examined.

The livers, kidneys and testes or ovaries of the parental rats were weighed but no test chemical effects were noted.

Conclusion: This study is Core Minimum. The NOEL for a decrease in the viability index is set at 50 ppm. There were noted occasions of pup deaths at 150 and 450 ppm. A NOEL for systemic effects is set at 50 ppm. Body weight decreases in the pups are noted at 150 and 450 ppm.

A. FCR 1272 [Study 007] Evaluation for embryotoxic and teratogenic effects on orally dosed rats.

Bayer, A.G., Institute fur Toxikologie, Report No. 10562, January 20, 1982. EPA Acc. No. 072009, Tab. 3.6.3a

B. The test material for this study was FCR 1272 and was from batch 16001/79 and was stated as being of 85% purity.

C. The test animals used for this study were male and female BAY: FB30 rats which were bred by the Bayer AG Institute. At the start of the study the females were between 181-247 gms (2-1/2 - 3-1/2 months of age), the males were between 350-500 gms (3-6 months of age). The males were allowed to inseminate the females such that ideally there would be about 25 pregnant females per dose group. Mating was allowed to take place overnight and the presence of a vaginal smear confirmed mating and the female was assumed to be pregnant. The pregnant females were dosed with either 0, 3, 10 or 30 mg/kg of test material (in lutrol or lutrol alone) on days 6 to 15 of gestation. On the 20th day of gestation the rats were sacrificed by CO_2 gas and the pups delivered by caesarean section.

D. Effects on the dams. None of the dams died. The dams in the mid and high dose group were described as exhibiting a "high stepping gait." Some of the dams in the high dose group were said to be ataxic and exhibited decreased motility. There was no adverse effect on weight gain throughout gestation.

There were 25, 23, 25 and 27 pregnant rats for the control, low, mid and high dose test groups.

There were no effects noted related to the in utero investigations made (number of implantations, litter size, number of resorptions, average placenta or weight).

E. Effects on the pups. There were 277, 261, 257 and 251 total number of fetuses for the control, low, mid and high dose test groups. Approximately 1/3 of these from each group were assessed for visceral deformities by a modified Wilsons technique. The remaining 2/3 were assessed for bone development.

No test chemical effects on either soft tissue or bone development were reported as resulting. There was a total of 14 deformed fetuses reported. 10 of these were in the control group.

F. Conclusion

1. Core classification of this study is MINIMUM.

   a. The report is unsigned.

2. Note - In a more recent submission from Mobay Chemical Corporation (January 14, 1985; EPA Accession No. 073255), historical control data for this strain of rat (FB30-Long Evans derived) was submitted. The data was for rats from the same breeding source and from the same laboratory (Bayer AG Institute of Toxicology, Germany) that performed this study on FCR 1272. The data covered 108 rat teratology studies conducted from 1971 to 1980 on 2,189 dams and 24,193 fetuses. The data is in Mobay report number 80211, dated August 20, 1980.

A. FCR 1272 [The active ingredient of Baythroid™] Study of embryotoxic (and teratogenic) effects on rabbits after oral administration.

Bayer, A.G., Institute fur Toxikologie, Report No. 11855, (also Mobay No. 85879), June 1, 1983. EPA Acc. No. 072009, Tab. 3.6.3b.

B. The test material used for this study was FCR 1272, from Batch No. 816170017 and was said to be of 95.0% purity.

C. The test animals used for this study were Himalayan rabbits (CHBB:HM strain, bred in Germany). Female rabbits were mated with males and copulation was verified by observation. Four groups of 15 inseminated rabbits were eventually dosed at either 0, 5, 15 or 45 mg/kg of the test material on days

6 through 18 (13 administrations). Of the 15 per group, there were 15, 15, 13 and 14 rabbits which proved to be actually pregnant for the control, low, mid and high dose groups. The rabbits were sacrificed on day 29 of gestation and the pups delivered by caesarean section.

D. Effects on the dams. There were no mortalities, body weight changes or behavioral reactions noted. Intrauterine effects were probably evident in the high dose group because two of the dams in this group aborted and a third had a complete resorption. Because of the abortions and resorption, there were 15, 15, 13 and 11 litters available after 28 days of gestation.

E. Effects on the pups. There were 100, 84, 92 and 70 pups available for the control, low, mid and high dose test groups. The low number in the high dose group is consistent with the two abortions and resorption. The pups from the dosed groups were stated as being equivalent to the controls with respect to size, weight, appearance, necropsy observations, bone and visceral development. The test laboratory asserted that there were no effects at all due to the test material.

"Arthrogryposis" (persistent flexure or contracture of a joint) was observed in FCR 1272 treated groups at a fetal incidence rate of 0, 2.4%, 2.2% and 4.3% and at a litter incidence rate of 0, 6.7%, 15.4% and 9.1% for the control, low, mid and high dosage levels respectively. See below for an assessment of this observation.

The only other noteworthy malformation reported was "asymmetrically positioned and deformed tailbone." There were 4 pups (from a single dam in the group receiving 15 mg/kg/day) with this lesion.

Note - In a more recent submission from Mobay Chemical Corporation (January 14, 1985; EPA Accession No. 073255), historical control data for this strain of rabbit (Himalayan) was submitted. The data was for rabbits from the same breeding sources and from the same laboratory (Bayer AG Institute of Toxicology, Germany) that performed this study on FCR 1272. One set of data (Mobay report No. 80210; dated January, 1981) covered 51 rabbit teratology studies conducted from 1971 until 1980 on 625 dams and 4,077 fetuses. A second set of data (Mobay report No. 88768, dated December 13, 1984) covered 27 studies conducted from 1980 until 1983 on 379 dams and 2,329 fetuses.

With respect to "arthrogryposis", the first set of data presented an overall incidence of 37/4077 (0.91%) for fetuses and 32/625 (5.1%) for litters. 25/51 of the studies had some incidence of "arthrogryposis" in the control fetuses. In 8 studies, the incidence in fetuses was > 2.0%; in 3 of these studies, it was >3.0%; and in 2 of these, it was $\geq$ 5.0%. The highest incidence for fetuses in a single study was 5.4% and for litters was 20-33%. In terms of litter incidence, 5 studies had a litter incidence of $\geq$ 14%. The second set of data presented an overall incidence of 33/2329 (1.4%) for fetuses and a maximum of 33/379 (8.7%) for litters.

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, Senden. 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 test 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 intoxication ("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 sciatic nerve. These alterations included axon fragmentation, occasional swelling and eosinophilia of the axon fragments and vacuolation of the myelin sheaths.