5-17-89

Accession No. 407009-06

DATA EVALUATION RECORD

1. **CHEMICAL:** Ethyltrianol.
Shaughnessey No.

2. **TEST MATERIAL:** HWG 1608, batch #16001/83, 97.0% purity, a solid.

3. **STUDY TYPE:** Avian Single-Dose Oral LD50 Tests.
Species Tested: White Leghorn hens.
Quails (Coturnix coturnix japonicus).

4. **CITATION:** Pauluhn, J. 1984. HWG 1608: Study for Acute Oral Toxicity to Hens and Quails. Report No. 94405. Prepared by Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld. Submitted by Mobay Corporation, Stilwell, KS. EPA Accession No. 407009-06.

5. **REVIEWED BY:**
Prapimpan Kosalwat, Ph.D.
Staff Toxicologist
KBN Engineering and
Applied Sciences, Inc.

Signature: P. Kosalwat
Date: 11/8/88

6. **APPROVED BY:**

James R. Newman, Ph.D.
Project Manager/
Principal Scientist
KBN Engineering and
Applied Sciences, Inc.

Signature: James R Newman
Date: 11/14/88

Henry T. Craven, M.S.
Supervisor, EEB/HED
USEPA

Signature:
Date: 5/17/89
Henry T. Craven 5/17/89

7. **CONCLUSIONS:** This study does not fulfill the guideline requirements for avian single-dose oral LD50 tests due to numerous deviations from the SEP. With LD50 values of greater than 2000 mg/kg body weight, HWG 1608 would be considered practically non-toxic to both white Leghorn hen and quail (Coturnix coturnix japonicus). The NOEL was less than 600 mg/kg body weight, the lowest dose tested. A more precise NOEL could not be determined due to adverse effects found at all test levels.

8. **RECOMMENDATIONS:** N/A.

9. **BACKGROUND:**

10. **DISCUSSION OF INDIVIDUAL TESTS:** N/A.

11. **MATERIALS AND METHODS:**

A. **Test Animals:**

1) Conventionally kept adult white Leghorn hens (laying) from breeder BRINKSCHULTE, Tenden. They were about fifteen to twenty months old, with body weights of 1 to 2 kg.

2) Male and female quails (Coturnix coturnix japonicus) from breeder GRAF DEGENFELD'SCHES Rendamt, Eppingen. They weighed approximately 120 to 180 g.

The birds were kept in a controlled climate in individual cages, and had access to an open-air run with natural flooring. The hens were given PPUT-LVK Poultry Grain Food from SSNIFF Co., while the quails received 60 Chick Starter Food from HOEVELER Co. Water was available ad libitum. The birds were acclimatized for at least four weeks before test initiation.

B. **Test System:** The test system used in this study was assumed to be the same as that used to acclimate the birds.

C. **Dosage:** Single-dose oral LD50 tests. Nominal dosages selected for the studies are presented in Tables 1 and 2 (attached).

D. **Design:** The test designs are presented in Tables 1 and 2. Five to ten birds were used per treatment level. HWG 1608 was formulated in Cremophor EL/water (2 g Cremophor EL to 100 ml distilled water), and administered once orally by stomach tube. The volume administered was 5 to 20 ml/kg body weight for the hens and 10 to 20 mg/kg body weight for the quails.

The observation period was 28 to maximum of 35 days for the hens and 14 days for the quails. During the observation period, the signs were noted daily (except for the weekends) and the body weights recorded weekly. At the end of the observation period, the animals were sacrificed with Evipan and, like the animals which died during the study, dissected and grossly appraised.

E. Statistics: When possible, the median lethal dose (LD50), was calculated by Rosiello et al.'s method (J. Tox. and Environ. Health 3, 797-809, 1977). The procedure was based on Bliss' maximum likelihood method (Q.J. Pharmacol. 11, 192-216, 1938).

12. REPORTED RESULTS:

1) Hens: Mortality data are presented in Table 1 (attached). The signs of toxicity for hens included staggering gait with prostration on stomach and apathy, muscular lassitude (drooping wings), coma, vocalization, fluffed plumage and accelerated respiration. Four out of five surviving hens in the 4000-mg/kg group were temporarily free of signs in the second observation week, then the signs reappeared. Staggering gaits were observed on the day of administration in the 1000-mg/kg only. During the observation period, the weekly recorded weight gains were reduced from 4000 mg/kg body weight onwards (for individual and mean body weights).

Necropsy of the animals dying during observation period revealed emaciation, hyperaemia of lung and intestine, liver patchy and clay-colored, crop distended, and gall bladder very full. Animals sacrificed at the end of observation were found to have liver brittle, cyst containing water in abdominal cavity. However, the author did not think the abnormalities found in the sacrificed animals were induced by HWG 1608.

2) Quails: Mortality data are presented in Table 2 (attached). The signs of toxicity included staggering gait and prostration on stomach, apathy, fluffed plumage, muscular lassitude (drooping wings), and accelerated respiration. Only accelerated respiration was observed in the 600-mg/kg group on the day of administration. An effect on the weekly recorded weight gains was noted from 1000 mg/kg body weight onwards (for individual and mean weights).

Necropsy of the animals dying during observation period revealed crop distended and filled with fluid, liver mottled, and gall bladder very full. There was no indication of grossly apparent organ damage.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES: HWG 1608 had slight acute oral toxicity to hens and quails. The oral LD50 value for hen was 4488 (95% C.L. = 4158-4846) mg/kg body weight, while the values for male quail and female quail were approximately 4438 mg/kg body weight and 2912 (95% C.L. = 1787-4746) mg/kg body weight, respectively.

The type of sign and causes of death were attributed particularly to a non-specific central nervous effect. There were no indications of specific organotoxic effects.

"The study conformed generally to the OECD principles of Good Laboratory Practice (GLP, Bundesanzeiger 35, 3-16, March 2, 1983)."

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Test Procedure: The test procedures and the report, in general, did not follow the SEP guidelines. Deviations were found as follows:

o The hens used in this study were not identified by species name.

o Both hens and quails used in the study were not recommended species. No justification was given in this regards.

o The age of the quail was not reported.

o Cremophor EL is not a recommended vehicle for the test.

o Control and vehicle control groups are required by the guidelines but were not included in these tests.

o Ten birds per treatment level are strongly recommended by the SEP. Some treatment levels in this study used only five birds.

o On page 6 of the report, the volume of test material administered was reported as ml/kg for the hens and mg/kg for the quails. The reviewer assumed that the latter unit was actually ml/kg.

o Data on the amount of test material given to each bird were not included in the report. Therefore, the dosages given to each bird could not be verified.

o The range of concentrations tested did not include a no-observed-effect level.

o The description of the test system (i.e., size and construction material of the cages, lighting conditions and photoperiod, temperature, and relative humidity) was not provided in the report.

o The diet compositions were not reported.

o The observation period for the hen test ranged from 28 to 35 days. All birds within the same test should be observed for the same period of time.

B. Statistical Analysis: The LD50 values for each species were calculated using EPA's TOXANAL computer program (the printouts are attached).

C. Discussion/Results: This study does not fulfill the guideline requirements for avian oral LD50 tests due to numerous deviations from the SEP. The LD50 value for the hens tested was 4486 (95% C.L. = 3948-5783) mg/kg body weight, while the LD50 value for combined data from male and female quails was 3512 (95% C.L. = 2386-6485) mg/kg body weight. When the data from male and female quails were analyzed separately, the LD50 value for female (2918 mg/kg) was much lower than that for the male (4438 mg/kg).

With all LD50 values obtained in this study, HWG 1608 would be considered practically non-toxic to both bird species tested, when administered as oral single dose. The NOEL was considered to be less than 600 mg/kg, the lowest dose tested. A more precise NOEL could not be determined due to adverse effects found at all test levels.

D. Adequacy of the Study:

(1) Classification: Invalid.

(2) Rationale: The test procedures did not follow the SEP as described in Section 14.A.

(3) Repairability: No.

15. COMPLETION OF ONE-LINER: Yes, November 2, 1988.

Page_____ is not included in this copy.

Pages 6 through 7 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

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____ Sales or other commercial/financial information.

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X FIFRA registration data.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

KOSALWAT HWG 1608 HEN 11-01-88

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CONC.	NUMBER EXPOSED	NUMBER DEAD	PERCENT DEAD	BINOMIAL PROB.(PERCENT)
5000	5	4	80	18.75
4500	10	5	50	62.30469
4000	5	1	20	18.75
3000	5	0	0	3.125
1000	5	0	0	3.125

THE BINOMIAL TEST SHOWS THAT 0 AND +INFINITY CAN BE
USED AS STATISTICALLY SOUND CONSERVATIVE 95 PERCENT
CONFIDENCE LIMITS, BECAUSE THE ACTUAL CONFIDENCE LEVEL
ASSOCIATED WITH THESE LIMITS IS GREATER THAN 95 PERCENT.

AN APPROXIMATE LC50 FOR THIS SET OF DATA IS 4500.002

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS	
3	.4977138	4485.719	3947.632	5783.219

NO CONVERGENCE IN 25 ITERATIONS. THE PROBIT METHOD
PROBABLY CANNOT BE USED WITH THIS SET OF DATA.

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KOSALWAT HWG 1608 MALE QUAIL 11-01-88

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CONC.	NUMBER EXPOSED	NUMBER DEAD	PERCENT DEAD	BINOMIAL PROB.(PERCENT)
5000	5	3	60.00001	50
3000	5	1	20	18.75
1000	5	0	0	3.125

THE BINOMIAL TEST SHOWS THAT 0 AND +INFINITY CAN BE USED AS STATISTICALLY SOUND CONSERVATIVE 95 PERCENT CONFIDENCE LIMITS, BECAUSE THE ACTUAL CONFIDENCE LEVEL ASSOCIATED WITH THESE LIMITS IS GREATER THAN 95 PERCENT.

AN APPROXIMATE LC50 FOR THIS SET OF DATA IS 4420.562

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS	
1	2.813005	4420.562	0	+INFINITY

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
6	1.905438	1	.9532822

SLOPE = 5.025573

95 PERCENT CONFIDENCE LIMITS =-1.911607 AND 11.96275

LC50 = 4437.854

95 PERCENT CONFIDENCE LIMITS = 0 AND +INFINITY

LC10 = 2480.08

95 PERCENT CONFIDENCE LIMITS = 0 AND 3677.771

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KOSALWAT HWG 1608 FEMALE QUAIL 11-01-88

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CONC.	NUMBER EXPOSED	NUMBER DEAD	PERCENT DEAD	BINOMIAL PROB.(PERCENT)
5000	10	7	70	17.1875
3000	5	3	60.00001	50
1700	5	1	20	18.75
1000	5	1	20	18.75
600	5	0	0	3.125

THE BINOMIAL TEST SHOWS THAT 0 AND +INFINITY CAN BE USED AS STATISTICALLY SOUND CONSERVATIVE 95 PERCENT CONFIDENCE LIMITS, BECAUSE THE ACTUAL CONFIDENCE LEVEL ASSOCIATED WITH THESE LIMITS IS GREATER THAN 95 PERCENT.

AN APPROXIMATE LC50 FOR THIS SET OF DATA IS 2616.034

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS	
2	1.476713	2848.844	0	+INFINITY

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
4	.4641772	1	.8352881

SLOPE = 2.552984

95 PERCENT CONFIDENCE LIMITS = .8136221 AND 4.292347

LC50 = 2918.27

95 PERCENT CONFIDENCE LIMITS = 1696.55 AND 6340.864

LC10 = 928.2575

95 PERCENT CONFIDENCE LIMITS = 92.19 AND 1622.685

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Combined data from males and females.

KOSALWAT HWG 1608 QUAIL 11-01-88

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CONC.	NUMBER EXPOSED	NUMBER DEAD	PERCENT DEAD	BINOMIAL PROB.(PERCENT)
5000	15	10	66.66667	15.08789
3000	10	4	40	37.69531
1700	5	1	20	18.75
1000	10	1	10	1.074219
600	5	0	0	3.125

THE BINOMIAL TEST SHOWS THAT 0 AND +INFINITY CAN BE USED AS STATISTICALLY SOUND CONSERVATIVE 95 PERCENT CONFIDENCE LIMITS, BECAUSE THE ACTUAL CONFIDENCE LEVEL ASSOCIATED WITH THESE LIMITS IS GREATER THAN 95 PERCENT.

AN APPROXIMATE LC50 FOR THIS SET OF DATA IS 3616.144

RESULTS CALCULATED USING THE MOVING AVERAGE METHOD

SPAN	G	LC50	95 PERCENT CONFIDENCE LIMITS	
2	1.09895	3544.669	0	+INFINITY

RESULTS CALCULATED USING THE PROBIT METHOD

ITERATIONS	G	H	GOODNESS OF FIT PROBABILITY
4	.3564489	1	.9711759

SLOPE = 2.63708

95 PERCENT CONFIDENCE LIMITS = 1.062655 AND 4.211504

LC50 = 3512.402

95 PERCENT CONFIDENCE LIMITS = 2386.028 AND 6484.638

LC10 = 1158.806

95 PERCENT CONFIDENCE LIMITS = 269.3597 AND 1830.433

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No. _____ Chemical Name Ethyltrianol Chemical Class _____ Page 1 of 2

(HWG 1608)

Study/Species/Lab/ Accession	Chemical % a.i.	Results	Reviewer/ Date	Validati Status
14-Day Single Dose Oral LD_{50}		LD50 = mg/kg (95% C.L.) Contr. Mort.(%)=		
Species		Slope= # Animals/Level= Age(Days)= Sex =		
Lab		14-Day Dose Level mg/kg/(% Mortality) ( ), ( ), ( ), ( ), ( )		
Acc.		Comments:		
14-Day Single Dose Oral LD_{50} 88-35		LD50 = 4486 mg/kg. (95% C.L. 3948-5783) moving average method Contr. Mort.(%)= N/A		
Species White Leghorn hens	97	Slope= N/A # Animals/Level= 5-10 Age(Days)= 112-147 Sex = Female	PK/11-2-88	Invalid
Lab Bayer AG		14-Day Dose Level mg/kg/(% Mortality) 1000(0), 3000(0), 4000(20), 4500(50), 5000(80)		
Acc. 407009-06		Comments:		
8-Day Dietary LC_{50}		LC50 = ppm (95% C.L.) Contr. Mort.(%)=		
Species		Slope= # Animals/Level= Age(Days)= Sex =		
Lab		8-Day Dose Level ppm/(%Mortality) ( ), ( ), ( ), ( ), ( )		
Acc.		Comments:		
8-Day Dietary LC_{50}		LC50 = ppm (95% C.L.) Contr. Mort.(%)=		
Species		Slope= # Animals/Level= Age(Days)= Sex =		
Lab		8-Day Dose Level ppm/(%Mortality) ( ), ( ), ( ), ( ), ( )		
Acc.		Comments:		
48-Hour LC_{50}		LC50 = pp__ (95% C.L.) Contr. Mort.(%)= Sol. Contr. Mort.(%)=		
Species		Slope= # Animals/Level= Temperature =		
Lab		48-Hour Dose Level pp /(%Mortality) ( ), ( ), ( ), ( ), ( )		
Acc.		Comments:		
96-Hour LC_{50}		LC50 = pp__ (95% C.L.) Con. Mor.(%)= Sol. Con. Mor.(%)=		
Species		Slope= # Animals/Level= Temp.=		
Lab		96-Hour Dose Level pp /(%Mortality) ( ), ( ), ( ), ( ), ( )		
Acc.		Comments:		
96-Hour LC_{50}		LC50 = pp__ (95% C.L.) Con. Mort.(%)= Sol. Con. Mort.(%)=		
Species		Slope= # Animals/Level= Temp.=		
Lab		96-Hour Dose Level pp /(%Mortality) ( ), ( ), ( ), ( ), ( )		
Acc.		Comments:		

No. _____ Chemical Name Ethyltrianol (HWG 1608) Chemical Class ____ Page 2 of 2

Study/Species/Lab/ Accession	Chemical % a.i.	Results	Reviewer/ Date	Validati Status
14-Day Single Dose Oral LD_{50}		LD50 = 4438 mg/kg (95% C.L. 0 - ∞) Contr. Mort.(%) = N/A		
Species Coturnix coturnix japonicus	97	Slope = 5.03 # Animals/Level = 5 Age(Days) = Unknown Sex = male	PK/11-2-88	Invalio
Lab Bayer AG		14-Day Dose Level mg/kg/(% Mortality): 1000 (0), 3000 (20), 5000 (60), ( ), ( )		
Acc. 407009-06		Comments:		
14-Day Single Dose Oral LD_{50}		LD50 = 2918 mg/kg. (95% C.L. 1697 - 6341) Contr. Mort.(%) = N/A		
Species Coturnix coturnix japonicus	97	Slope = 2.55 # Animals/Level = 5-10 Age(Days) = unknown Sex = female	PK/11-2-88	Invali
Lab Bayer AG		14-Day Dose Level mg/kg/(% Mortality): 600 (0), 1000 (20), 1700 (20), 3000 (60), 5000 (70)		
Acc. 407009-06		Comments:		
8-Day Dietary LC_{50}		LC50 = ppm (95% C.L.) Contr. Mort.(%) =		
Species		Slope = # Animals/Level = Age(Days) = Sex =		
Lab	____	8-Day Dose Level ppm/(%Mortality): ( ), ( ), ( ), ( ), ( )	_____	___
Acc.		Comments:		
8-Day Dietary LC_{50}		LC50 = ppm (95% C.L.) Contr. Mort.(%) =		
Species		Slope = # Animals/Level = Age(Days) = Sex =		
Lab	____	8-Day Dose Level ppm/(%Mortality): ( ), ( ), ( ), ( ), ( )	_____	___
Acc.		Comments:		
48-Hour LC_{50}		LC50 = pp__ (95% C.L.) Contr. Mort.(%) = Sol. Contr. Mort.(%) =		
Species		Slope = # Animals/Level = Temperature =		
Lab	____	48-Hour Dose Level pp /(%Mortality): ( ), ( ), ( ), ( ), ( )	_____	___
Acc.		Comments:		
96-Hour LC_{50}		LC50 = pp__ (95% C.L.) Con. Mor.(%) = Sol. Con. Mor.(%) =		
Species		Slope = # Animals/Level = Temp.=		
Lab	____	96-Hour Dose Level pp /(%Mortality): ( ), ( ), ( ), ( ), ( )	_____	___
Acc.		Comments:		
96-Hour LC_{50}		LC50 = pp__ (95% C.L.) Con. Mort.(%) = Sol. Con. Mort.(%) =		
Species		Slope = # Animals/Level = Temp.=		
Lab	____	96-Hour Dose Level pp /(%Mortality): ( ), ( ), ( ), ( ), ( )	_____	___
Acc.		Comments:		