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CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

JUL 23 1992

MEMORANDUM

Subject: HWG 1608 (Tebuconazole) technical. Historical data teratogenicity.
Tox Chem No. 463
HED Project No. 2-0434
MRID Nos. 419620-01 (mice) and 419620-02 (rats)
Barcode Nos. D170461, D170469, D170478, D170487
Submission Nos. S405934, S405949, S405952, S405979
Pesticide Petition Nos. 9F3724, 9F3818, 9G3817, 9H5575

From: Alberto Protzel, Ph.D. 7/8/92
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To: Ms. Susan Lewis/Mr. Benjamin Chambliss
PM-21
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Thru: James N. Rowe, Ph.D., Head 7/14/92
Review Section III
Toxicology Branch II
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and

Marcia van Gemert, Ph.D., Chief 7/16/92
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ACTION:
Summary of historical control data for developmental toxicity studies in mice and rats.

In correspondence dated march 25 1991, the EPA/HED requested additional mouse and rat historical control data, which were deemed necessary to conduct a Peer Review of the Developmental Toxicity of Folicur.

In response to this request, the Registrant (Miles Inc.) submitted the following two studies:

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1. HWG 1608. Study of Embryotoxic Effects on Mice After Oral Administration. Supplemental Submission to EPA MRID 40821501. [MRID 419620-01]

2. Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Rat. Supplemental Submission to EPA MRID 407009-43. [MRID 419620-02].

Data from these studies are summarized below.

CONCLUSIONS:

1. HWG 1608. Study of Embryotoxic Effects on Mice After Oral Administration. Supplemental Submission to EPA MRID 408215-01. Report No. 97411-3. M. Renhof (author). 7/12/1991. [MRID 419620-01] .

A. Introduction

The mouse oral developmental study for which the historical control data were requested (MRID 408215-01) was performed at the Bayer Institute of Toxicology, Wuppertal (FRG) from 1/86-4/86 using NMRI/ORIG Kisslegg mice, bred by IVANOVAS.

The present submission contains historical data obtained from mouse studies performed at the testing laboratory (Bayer Institute of Toxicology) for the years 1983-1989. Other than specifying that the mouse NMRI strain was used, no other details on the strains were given. As shown in Table 1, data from the following six studies were included:

Table 1. Source of historical control data on NMRI mice[a]

Year	Study No.	Number of inseminated mice	Remarks
1983	T1007545	25	-
1983	T9007624	25	-
1985	T2021144	25	-
1986	T5021859	25	Concurrent control for MRID 408215-01, the study for which historical data were requested.
1986	No Number	30	Only examined for external malformations.[b]
1989	T9033893	23	-

[a] No details on the strain were given.
[b] Only examined for external malformations.

The submitted mouse historical data are summarized below in Tables 2-3 in the form of ranges, with the respective values from the oral teratology mouse study (MRID No. 408215-01) for comparison.

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Table 2. Cesarean section observations[a].

Parameter	Historical Range	Concurrent Control[b]	Mouse Oral Study (MRID 408215-01) LDT	MDT	HDT
No. mated/inseminated	23-30	25	25	25	25
Pregnancy rate (%)	84-92	96	92	92	80
Number/dam					
Implantations	10.2-12.2	10.6	11.1	10.7	11.4
Fetuses	9.6-11.4	9.8	10.2	10.2	10.1
Resorptions	0.7-1.6	0.8	1.0	0.5	1.3
Mean weights					
Fetal weight[c]	1.12-1.35	1.36(.08)	1.37(.07)	1.37(.13)	1.30(.12)
Placental weight	0.09-0.10	0.10	0.10	0.10	0.11*

[a] From pp. 6-7 of the Study Report.
[b] Study T5021859 from Table 1 (Concurrent control to MRID 408215-01)
[c] Standard deviation (s.d.) in parentheses. The larger s.d. at the MDT and HDT are consistent with the significant ($p \leq 0.05$) incidence of runts/dam at the MDT (0.91) and HDT (1.20) vs concurrent controls (0.21). Runting rate at the LDT was 0.18.
* $p \leq 0.05$ vs. concurrent controls.

Table 3. Incidence of malformations[a]

Parameter	Historical Range[b]	Concurrent Control[c]	Mouse Oral Study (MRID 408215-01) LDT	MDT	HDT
Fetuses per dam with :					
Malformations	0.00-0.17	0.04	0.18	0.0	0.65*
Skeletal retardations/deviations	0.13-0.43	0.08	0.05	0.17	0.40
External/visceral Malformations					
Litters					
Number	0/23-2/18	1/24	2/23	0/23	8/20
Percent	0.0-11.1	4.2	8.7	0.00	40.0
Fetuses					
Number	0/220-3/207	1/236	4/234	0/234	13/202
Percent	0.0-1.4	0.4	1.7	0.00	6.4

[a] Data from pp. 7 and 9 of the Study Report.
[b] Data from the 1986 study marked "No number" were omitted because only skeletal external observations were made: 1/286 fetuses, 0.3%; and 1/25 litters, 4.0%.
[c] Study T5021859 from Table 1 (Concurrent control to MRID 408215-01).
* $p \leq 0.05$

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Table 4. Summary of malformation, skeletal findings incidence*

Parameter	Litters affected Number (%)	Fetuses affected Number (%)
External malformations		
Number Examined	133	1421
Exencephaly	2 (1.5)	2 (0.14)
Open eye	1 (0.8)	1 (0.07)
Prosopo-gnathoschisis	1 (0.8)	1 (0.07)
Cleft palate	4 (3.0)	5(0.35)
Visceral Malformations		
Number Examined	108	378
Slight dilation of brain ventricles (1-3)	1 (0.9)	1 (0.26)
Skeletal Malformations		
Number examined	108	757
Dysplasia of extremities	1 (0.9)	1 (0.13)
Deformed vertebrae	1 (0.9)	1 (0.13)
Deformed ribs	1 (0.9)	1 (0.13)
Shortened tail	1 (0.9)	1 (0.13)
Skeletal Retardations		
Number examined	108	757
Hyoid Non-ossified	3 (2.8)	4 (0.5)
Cranium incompletely ossified	2 (1.9)	3 (0.4)
Anterior fontanelle enlarged	6 (5.6)	13 (1.7)
Vetebrae incompletely ossified	4 (3.7)	4 (0.5)
Sternebrae bipartite	1 (0.9	1 (0.1)

* From pp. 10-11 of the Study Report.

2. Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Rat. Supplemental Submission to EPA MRID 407009-43. Report No. 96756. H. Becker, W. Vogel, and Ch. Terrier. 4/28/1988. [MRID 419620-02].

The rat oral developmental toxicity study for which the historical control data were requested (MRID 407009-43) was performed by RCC, Research & Consulting Company AG and RCC Umweltchemie AG, Itingen/Switzerland during the period of 11/15/1986-12/23/1986 using Wistar/HAN (Kfm WIST, Outbred, SPF Quality) obtained from KFM, Kleintierfarm Madoerin AG.

The present submission contains historical data obtained from rat studies performed at the testing laboratory (RCC, Research & Consulting Company AG, Itingen/Switzerland) for the 1985-1988 period using also Wistar/HAN (Kfm WIST, Outbred, SPF Quality) rats.

Table 5 summarizes cesarean section historical observations with data presented as ranges. Attachment 1 summarizes external, visceral, and skeletal

examinations for the years 1985-1988. The data in Attachment 1 summarizes historical results observed (in controls) in 31 studies comprising 763 litters and 8822 fetuses. Low frequency observations include:

- Agenesis of tail: observed once in each of two studies [one study in 1987 and another in 1985] with an overall litter frequency of 2/763 (0.26%).
- Anopthalmia and decreased or absent jaw development: observed once in each of two studies [one study in 1986 and another in 1985] with an overall litter frequency of 2/763 (0.26%).

Attachment 2 summarizes litter and fetal incidences of various specific skeletal observations for the years 1985-1988. The skeletal observations in Attachment 2 were selected for tabulation because the original rat oral study (MRID 407009-43) showed statistically significant elevations in:

- Fetal incidences of supernumerary ribs and of thoracic vertebra centrum dumbell shaped.
- Litter and fetal incidences of non-ossification of cervical vert. No.2, sacral vertebral arch 6R and digit 4R proximal phalanx.

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Table 5. Cesarean section observations[a]

Parameter	Range of values for parameter			
	1985	1986	1987	1988
No. of studies	8	8	8	7
No. of females mated	25-35	25	25	25
% pregnant	92-100	88-100	92-100	92-100
Corpora lutea				
No./dam	12.3-13.2	13.0-14.9	13.2-14.5	12.7-14.8
Pre-implantation loss				
% of corpora lutea	2.3-11.8	7.4-15.4	6.1-13.3	7.2-17.2
No./dam	0.3-1.5	0.9-2.3	0.9-1.8	0.9-2.5
Implantation sites				
No./dam	11.0-12.9	11.7-12.8	11.6-13.6	11.8-13.4
Post-implantation loss				
% of impl. sites	4.6-9.2	3.0-7.4	3.3-8.4	3.2-6.4
No./dam	0.5-1.0	0.3-0.9	0.4-1.0	0.6-1.1
Embryonic resorptions				
% of impl. sites	4.6-8.0	3.0-7.4	3.3-8.4	2.8-6.4
No./dam	0.5-1.0	0.3-0.9	0.4-1.0	0.4-0.8
Fetal resorptions				
% of impl. sites	0.0-0.4	0.0-0.7	0.0-1.3	0.0-1.0
No./dam	0.0	0.0-0.1	0.0-0.2	0.0
Total fetuses				
% of impl. sites	90.8-95.4	92.6-97.0	91.6-96.7	93.6-96.8
No./dam	10.3-12.0	11.3-12.0	10.8-12.9	11.0-12.7
% live fetuses	100	100	100	100
% males	46.5-51.4	45.0-51.9	46.4-54.6	46.9-52.6
% females	48.6-53.5	48.1-55.0	45.4-53.6	47.4-53.1
Weights of live fetuses				
mean	4.8-4.9	4.5-4.8	4.6-4.8	4.6-4.8

[a] From the Study Report: pp.8-9 (for 1985), pp. 38-39 (for 1986), pp. 55-56 (for 1987), and pp. 76-77 (for 1988).

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Attachments

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TEBUCONAZOLE

Page _____ is not included in this copy.

Pages 8 through 15 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

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_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

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_____ The document is not responsive to the request.

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.

Attachment 2
(Compiled from data in MRID 419620-02)

Fetal and litter incidences of skeletal observations in rats [From MRID 419620-02].

Year of Study	% Fetuses / % litters in study number[a]							
	1	2	3	4	5	6	7	8
Thoracic vertebra centrum dumbell shaped								
1988	0.6/4.0	0.6/4.1	0/0	0/0	0/0	0/0	0/0	-
1987[c]	2.2/12.5	0.7/4.0	2.2/6.0	2.6/16.7	0/0	0.6/4.0	0.8/4.4	2.7/12.5
1986	0/0	0/0	0/0	0/0	0/0	1.4/8.3	2.3/13.6	0/0
1985	0/0	0/0	0/0	0/0	0/0	0.7/4.2	0/0	0/0
Cervical vertebra No. 2 (Non-ossification)								
1988	14.6/56.0	12.8/54.2	18.7/58.3	16.2/50.0	8.7/56.1	5.6/52.0	8.8/36.0	-
1987	24.5/54.2	29.1/80.0	22.1/76.0	12.8/60.0	15.5/64.0	13.3/60.0	14.7/47.8	23.8/58.3
1986	29.6/-	22.6/-	34.1/-	25.0/-	21.4/64.0	20.1/62.5	31.5/77.3	43.8/73.9
1985	23.6/-	18.1/-	35.4/-	24.1/-	28.7/-	30.7/-	17.3/-	28.4/-
Sacral vertebral arch 6 (R, Non-ossification)]								
1988	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
1987	0/0	0/0	2.2/4	0/0	0/0	0/0	0/0	0/0
1986	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
1985	0/-	0/-	0/-	0/-	0/-	0/-	0/-	0/-
Digit 4 proximal phalanx (R, Non-ossification)								
1988	2.4/12.0	5.4/29.2	0.7/4.2	2.1/12.5	2.9/13	6.8/28	3.8/16	-
1987	8.6/29.2	2.1/12.0	4.4/20.0	0.6/16.0	5.6/20.0	3.8/16.0	5.4/21.7	6.1/29.2
1986	3.5/-	4.8/-	9.1/-	3.8/-	6.2/12.0	0.7/16.7	5.4/6.4	21.9/47.8
1985	6.0/-	3.0/-	8.7/-	3.1/-	6.2/-	8.0/-	3.9/-	6.6/-
Supernumerary ribs (R):								
1988	8.5/32.0	3.4/16.7	5.8/20.8	24.6/70.8	8.7/34.8	19.3/64.0	8.8/28.0	-
1987	10.8/37.5	7.8/28.0	12.5/36.0	14.7/40.0	11.3/44.0	14.6/40.0	3.9/17.4	12.2/54.2
Supernumerary ribs (L):								
1988	7.3/24.0	2.7/16.7	6.5/20.8	21.1/66.7	9.4/34.8	16.1/56.0	8.2/20.0	-
1987	12.9/41.7	8.5/32.0	13.2/32.0	12.8/32.0	10.6/44.0	12.7/32.0	3.1/17.4	9.5/50.0

[a] The historical data covers: 1988: 7 studies, 1052 skeletons, & 170 litters; 1987: 8 studies, 1148 skeletons, & 195 litters; 1986: 8 studies, 1108 skeletons, & 189 litters; 1985: 8 studies, 1323 skeletons, & 763 litters; for a total of 31 studies, 4631 skeletons and 763 litters [From MRID 419620-02]

- No data.

[c] The data for 1987 covers thoracic/lumbar vertebral centrum(a) dumbell shaped/bipartite/abnormally ossified, thus it represents an upper limit for thoracic dumbell shaped incidence and is not truly comparable with the data for the other three years.

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

JUN 23 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: HWG 1608 Technical (Tebuconazole). Dog Chronic Study.
Tox Chem No. 463P
HED Project No. 2-0465.

From: Alberto Protzel, Ph.D. Alberto Protzel 6/17/92
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To: Ms. Susan Lewis/Mr. Benjamin Chambliss.
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Fungicide-Herbicide Branch
Registration Division (H7509C)

Thru: James N. Rowe, Ph.D., Head James N. Rowe 6/17/92
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Chief M van Gemert 6/18/92
Toxicology Branch II
Health Effects Division (7509C)

The following study is being reviewed:

Safety Evaluation of HWG 1608: Chronic (1 year) feeding study in dogs. M.C. Porter et al. June 28, 1989. Toxicology Dept. Miles Inc. Lab. Project ID. No. 99673. EPA MRID 420306-01.

Examination of the data for clinical pathology in p. 12 and Appendix E (pp. 77-132) of the Study Report indicates that only individual animal data have been submitted. There are no treatment group means (e.g. male controls, female controls, male 100 ppm, female 100 ppm, etc.) with standard deviations (as was done for liver microsomal enzymes and triglycerides in p. 83 of the Study Report).

Thus, to continue reviewing the subject study efficiently it will. necessary for the Registrant to submit:

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1. Group means with their standard deviations (and statistical significance, if any) for the clinical pathology data shown for individual dogs in Appendix E, pages 85-132.

2. Because the data for individual dogs contains values for pretest and weeks 15, 26, and 52, group means with standard deviations should be obtained for pretest, 15, 26, and 52 weeks.

3. Except for semiquantitative and non-quantitative parameters, means and standard deviations should be obtained for all parameters from WBCU through SPGR.