



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

JAN 10 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Additional response to comments regarding the RfD/Peer Review Committee meeting on Clethodim
HED Proj. No. 1-0211
Caswell No. 721F
D158557

From: James N. Rowe, Ph.D. *James N. Rowe*
Toxicology Branch II (H7509C) 1/8/91

To: George Ghali, Ph.D./Rick Whiting
RfD/Peer Review Committee
Health Effects Division (H7509C)

Thru: Marcia vanGemert, Ph.D., Chief *Marcia vanGemert*
Toxicology Branch II - H.F.A. 1/9/91
Health Effects Division (H7509C)

Additional responses to comments and questions regarding the developmental toxicity studies reviewed by the RfD Committee on September 21, 1990 are presented below. I am forwarding my responses for dissemination to the appropriate members of the Committee for their consideration (See attached historical control data).

o What are the historical control incidences of 1) split thoracic centra in CrL:CD@ (COBS) rats tested at Biodynamics Labs, Inc. and 2) hyoid, angulated ala(e) in New Zealand White, Hra:(NZW)SPF, rabbits tested at Argus Research Labs, Inc. in the respective developmental toxicity studies?

1) The incidence of split thoracic centra in CD rats at Biodynamics, Inc. was 0%, 0/805 litters/6689 fetuses, for the years 1976-1985.

The total mean fetal incidence of split thoracic centra in CD rats at Biodynamics, Inc. was 1.1% (47/4397) fetuses for the years 1984-1989. The fetal incidence range was 0.0% (0/143) to 3.4% (5/145) fetuses for individual studies. The total mean litter incidence was 6.8% (44/652) and the litter incidence range was 0.0% (0/20) to 21.7% (5/23) for individual studies.

2) The incidence of hyoid, angulated ala(e) in NZW rabbits at Argus Labs was 8.63% for litters (29/336) and 1.29% for fetuses (32/2482) for the years 1982-1985.

The total mean litter incidence of hyoid, angulated ala(e) in NZW rabbits at Argus Labs for the years 1985-1987 was 9.69% (40/413) with a range of 0.0% to 35.7% (0-5 litters: individual study incidences not given). The total mean fetal incidence was 1.73% (51/2952) with a range of 0.0% to 6.4% (0-7 fetuses).

The total mean litter incidence of hyoid, angulated ala(e) in NZW rabbits at Argus Labs for the years 1987-1989 was 17.29% (74/428) with a range of 0.0% to 46.2% (0-7 litters: individual study incidences not given). The total mean fetal incidence was 2.88% (89/3088) with a range of 0.0% to 8.7% (0-10 fetuses).

o Comparison of historical control incidences of split thoracic centra in CD rats and hyoid, angulated ala (e) in NZW rabbits with findings in Clethodim developmental studies of same species (MRID Nos 410301-16 and 410301-15, respectively).

RATS	(low)	(mid)		
Dose:	10 mg/kg	100 mg/kg	vs historical controls	
			(range/84-89)	
Split thoracic centra				
Fetuses	4/170(2.4)	0(0)*		0 to 3.4
Litters	3/25(12)	0(0)		0 to 21.7
RABBITS	(low)	(mid)	(high)	
Dose:	25 mg/kg	100 mg/kg	300 mg/kg	vs histor. controls
				(range/87-89)
Hyoid, angulated ala(e)				
Fetuses	6/115(5.2)	0(0)	7/111(6.3)	0 to 8.7
Litters	4/17(23.5)	0(0)	6/17(35.3)	0 to 46.2

[* number of fetuses or litters (percent)]

Based upon the similar incidences of findings between the historical controls and the test animals in both the rat and rabbit studies, it is concluded that these developmental changes were not biologically significant and do not impact the original conclusions of the study reviewer. There are presently no additional data gaps remaining for this chemical.

cc M. Erumusele-Matzer (PM 23)

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Attachment
HED Project No. 1-0211

Bio/dynamics Inc.
RUSH

October 25, 1990

J. Roger Rittenhouse
Toxicologist Specialist
Chevron Environmental Health Center, Inc.
15299 San Pablo Avenue
Richmond, California 94806

Dear Dr. Rittenhouse:

Enclosed is our historical control tabulation for the ossification variation "Thoracic Vertebrel Centrum Split". This is a tabulation of data for individual rat teratology/developmental toxicity studies completed within our facility over the 1984-1989 interval. The control data for the study of interest to the peer review panel (the CHEVRON RE-45601 Teratology Rat Study) is part of this tabulation and this study is coded "SS".

If I can be of additional help to you, please call.

Sincerely,

Ray

Raymond E. Schroeder, M.S., DABT
Study Director
Manager of Reproduction/Teratology

CRTO
ENVIRONMENTAL GROUP

RES:spf

OCT 26 '90

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Historical Control Data - Bio/dynamics, Inc.
CD~~0~~ Rat - Day 20 Gestation Fetal Specimens
1984 - 1989

Ossification Variation Data - Amplified

Thoracic Vertebral Centrum - Split

Study No.(ID)	Year	Fetal Incidence		Litter Incidence	
		No. ^a	%	No. ^b	%
FF	1984	1/162	0.6	1/24	4.2
GG	1984	2/144	1.4	2/23	8.7
HH	1984	4/148	2.7	4/23	17.4
II	1984	5/161	3.1	4/24	16.7
JJ	1984	2/143	1.4	2/23	8.7
KK	1985	0/137	0.0	0/20	0.0
LL	1985	2/137	1.5	2/23	8.7
MM	1985	0/144	0.0	0/24	0.0
NN	1985	1/150	0.7	1/24	4.2
OO	1985	0/149	0.0	0/23	0.0
PP	1985	2/170	1.2	2/24	8.3
QQ	1985	1/210	0.5	1/21	4.8
RR	1986	0/163	0.0	0/24	0.0
SS	1986	1/168	0.6	1/25	4.0
TT	1987	1/153	0.7	1/22	4.5
UU	1987	3/173	1.7	3/24	12.5
VV	1987	1/147	0.7	1/23	4.3
WW	1987	5/145	3.4	5/23	21.7
XX	1987	0/143	0.0	0/22	0.0
YY	1988	1/159	0.6	1/24	4.2
ZZ	1988	1/187	0.5	1/24	4.2
AAA	1988	3/172	1.7	2/25	8.0
BBB	1988	1/165	0.6	1/22	4.5
CCC	1989	5/192	2.6	4/29	13.8
DDD	1989	2/190	1.1	2/30	6.7
EEE	1989	0/203	0.0	0/30	0.0
FFF	1989	3/182	1.6	3/29	10.3

Overall: 47/4397(1.1%)

44/652(6.8%)

Total: 28.9

180.4

Mean: 1.1%

6.7%

N: 27

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Range: 0.0-3.4%

0.0-21.7%

^aNo. of affected fetuses/No. of fetuses evaluated

^bNo. litters containing affected fetuses/No. of litters evaluated

SUMMARY
FETAL SKELETAL ALTERATIONS
NZW RABBITS

PERIOD 1987-1989
STUDIES 32
LITTERS EXAMINED 428
FETUSES EXAMINED 3088

ALTERATIONS	N	%	RANGE / STUDY N %	# OF STUDIES W/ ALTERATION
SKULL				
Summarization of all irregular L ossification of skull	388	90.65	2-18 (57.1-100)	32
	F 1061	34.36	13-63 (14.0-73.7)	
Anterior and/or Posterior Fontanelle				
: Enlarged (Slight)	L 1	.23	0-1 (0-5.6)	1
(Grade 1)	F 1	.03	0-1 (0-0.7)	
: Enlarged (Moderate)	L 5	1.17	0-3 (0-16.7)	3
(Grade 2)	F 5	.16	0-3 (0-2.2)	
: Enlarged (Marked)	L 2	.47	0-1 (0-6.2)	2
(Grade 3)	F 2	.06	0-1 (0-1.0)	
: Irregularly shaped	L 5	1.17	0-2 (0-11.8)	4
	F 5	.16	0-2 (0-2.0)	
Anterior Fontanelle				
: Enlarged (Marked)	L 2	.47	0-1 (0-16.7)	2
(Grade 3)	F 3	.10	0-2 (0-5.0)	
Posterior Fontanelle				
: Enlarged (Extreme)	L 1	.23	0-1 (0-16.7)	1
(Grade 4)	F 1	.03	0-1 (0-2.5)	
Frontals				
: Irregular sutures	L 252	58.88	1-13 (21.4-100)	32
	F 444	14.38	3-24 (3.2-34.5)	
: Interfrontals present	L 152	35.51	0-12 (0-100)	31
	F 224	7.25	0-18 (0-31.6)	
: Intrafrontals present	L 28	6.54	0-5 (0-33.3)	18
	F 34	1.10	0-6 (0-6.1)	
: Fused	L 3	.70	0-1 (0-6.2)	3
	F 3	.10	0-1 (0-1.0)	
: Contains holes	L 48	11.21	0-10 (0-55.6)	19
	F 77	2.49	0-28 (0-20.3)	
: Suture enlarged	L 1	.23	0-1 (0-7.1)	1
	F 1	.03	0-1 (0-1.0)	
Parietal(s)				
: Contain holes	L 11	2.57	0-3 (0-17.6)	8
	F 11	.36	0-3 (0-2.5)	
: Irregular suture	L 32	7.48	0-5 (0-30.8)	16
	F 35	1.13	0-6 (0-5.6)	
: Interparietals present	L 1	.23	0-1 (0-10.0)	1
	F 1	.03	0-1 (0-1.5)	
: Intraparietals present	L 25	5.84	0-4 (0-22.2)	15
	F 31	1.00	0-6 (0-6.8)	

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SUMMARY
FETAL SKELETAL ALTERATIONS
NZW RABBITS

ALTERATIONS		N	%	RANGE / STUDY N	%	STUDIES W/ ALTERATION
SKULL (CONT.)						
Interparietals						
: Irregularly shaped	L	2	.47	0-1	(0-6.7)	2
	F	2	.06	0-1	(0-0.8)	
: Incompletely or not ossified	L	2	.47	0-1	(0-6.7)	2
	F	2	.06	0-1	(0-0.8)	
Nasals						
: Irregular suture	L	89	20.79	0-11	(0-64.7)	27
	F	120	3.89	0-17	(0-17.8)	
: Internasals	L	17	3.97	0-2	(0-14.3)	13
	F	18	.58	0-2	(0-2.3)	
: Intranasals	L	13	3.04	0-2	(0-16.7)	11
	F	13	.42	0-2	(0-2.5)	
: Displaced suture	L	154	35.98	0-15	(0-100)	24
	F	249	8.06	0-33	(0-23.9)	
: Fused	L	2	.47	0-1	(0-7.7)	2
	F	2	.06	0-1	(0-1.5)	
Nasal/Frontal sutures:	L	105	24.53	0-9	(0-100)	26
irregular and/or misaligned	F	161	5.21	0-15	(0-27.6)	
Palate, incompletely or not ossified	L	2	.47	0-1	(0-16.7)	2
	F	2	.06	0-1	(0-2.5)	
Eye Sockets, small	L	1	.23	0-1	(0-6.2)	1
	F	1	.03	0-1	(0-0.9)	
Premaxillae, incompletely ossified	L	1	.23	0-1	(0-7.1)	1
	F	1	.03	0-1	(0-1.0)	
HYOID						
Ala(e), angulated	L	74	17.29	0-7	(0-46.2)	24
	F	89	2.88	0-10	(0-8.7)	
VERTEBRAE						
Cervical						
: Atlas fused to Exoccipital	L	1	.23	0-1	(0-5.9)	1
	F	1	.03	0-1	(0-0.8)	
Thoracic						
: Hemivertebra	L	7	1.64	0-2	(0-11.8)	6
	F	9	.29	0-4	(0-3.1)	
: Fused arches and/or centra	L	10	2.34	0-2	(0-16.7)	8
	F	10	.32	0-2	(0-2.5)	
: One or more centra, unilateral ossification	L	9	2.10	0-2	(0-11.1)	8
	F	9	.29	0-2	(0-1.5)	
: Centrum, bifid	L	2	.47	0-1	(0-7.7)	2
	F	2	.06	0-1	(0-1.1)	
: Centra, one or more asymmetric	L	5	1.17	0-1	(0-10.0)	5
	F	6	.19	0-2	(0-1.6)	
: Arch, small	L	4	.93	0-1	(0-16.7)	4
	F	4	.13	0-1	(0-2.5)	

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SUMMARY
FETAL SKELETAL ALTERATIONS
NZW RABBITS
1985-1987

STUDIES

26

LITTERS EXAMINED

413

FETUSES EXAMINED

2952

ALTERATIONS

SKULL

		N	X	RANGE N	STUDY X
Irregular Ossification	L	15	3.63	0-8	(0-50.0)
	F	30	1.02	0-18	(0-14.1)
Fontanelle: Enlarged	L	12	2.91	0-3	(0-16.7)
	F	15	0.51	0-4	(0-3.1)
: Irregularly shaped	L	9	2.18	0-5	(0-35.7)
	F	35	1.19	0-31	(0-30.7)
: Irregular ossification	L	4	0.97	0-3	(0-18.8)
	F	4	0.14	0-3	(0-2.3)
Frontals: Irregular suture	L	112	27.12	0-13	(0-76.5)
	F	197	6.67	0-21	(0-27.3)
: Interfrontals present	L	79	19.13	0-10	(0-62.5)
	F	117	3.96	0-20	(0-15.5)
: Intrafrontals present	L	22	5.33	0-10	(0-62.5)
	F	27	0.91	0-13	(0-13.5)
: Fused	L	2	0.48	0-1	(0-7.1)
	F	2	0.07	0-1	(0-0.9)
: Irregularly ossified	L	2	0.48	0-1	(0-7.1)
	F	8	0.27	0-7	(0-6.9)
: Contains holes	L	35	8.47	0-10	(0-55.6)
	F	64	2.17	0-28	(0-20.3)
Parietal(s): Incompletely ossified or not ossified	L	1	0.24	0-1	(0-7.1)
	F	1	0.03	0-1	(0-1.0)
: Contain holes	L	14	3.39	0-3	(0-21.9)
	F	24	0.81	0-10	(0-9.2)
: Irregular suture	L	30	7.26	0-6	(0-42.8)
	F	39	1.32	0-10	(0-9.2)
: Fused	L	1	0.24	0-1	(0-7.1)
	F	1	0.03	0-1	(0-0.9)
: Interparietals present	L	11	2.66	0-3	(0-16.7)
	F	12	0.41	0-3	(0-2.6)
: Intraparietals present	L	31	7.51	0-5	(0-31.2)
	F	38	1.29	0-7	(0-6.1)
Interparietals: Irregularly shaped	L	1	0.24	0-1	(0-5.6)
	F	1	0.03	0-1	(0-0.7)
: Incompletely ossified	L	2	0.48	0-1	(0-6.2)
	F	2	0.07	0-1	(0-0.8)

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SUMMARY
FETAL SKELETAL ALTERATIONS
NZW RABBITS

ALTERATIONS		N	$\bar{x}$	RANGE N	STUDY $\bar{x}$
SKULL (CONT.)					
Nasals: Irregular suture	L	62	15.01	0-10	(0-62.5)
	F	90	3.05	0-16	(0-17.8)
: Internasals	L	17	4.12	0-2	(0-12.5)
	F	18	0.61	0-2	(0-1.8)
: Intranasals	L	10	2.18	0-2	(0-11.8)
	F	11	0.37	0-3	(0-2.4)
: Displaced suture	L	21	5.08	0-15	(0-83.3)
	F	45	1.52	0-33	(0-23.9)
: Fused	L	1	0.24	0-1	(0-7.7)
	F	1	0.03	0-1	(0-0.8)
Nasal/Frontal, sutures	L	27	6.54	0-9	(0-50.0)
irregular and/or misaligned	F	36	1.22	0-13	(0-9.4)
Supraoccipitals, incompletely ossified	L	1	0.24	0-1	(0-6.2)
	F	1	0.03	0-1	(0-0.8)
Palate: Incompletely ossified	L	1	0.24	0-1	(0-7.1)
	F	2	0.07	0-2	(0-2.0)
HYOID					
Body, not ossified	L	3	0.73	0-2	(0-10.0)
	F	4	0.14	0-3	(0-2.2)
Ala(e), angulated	L	40	9.69	0-5	(0-35.7)
	F	51	1.76	0-7	(0-6.4)
VERTEBRAE					
Cervical: Hemivertebra	L	1	0.24	0-1	(0-6.2)
	F	1	0.03	0-1	(0-0.9)
Cervical: Unilateral ossification	L	1	0.24	0-1	(0-7.4)
	F	1	0.03	0-1	(0-1.0)
: Centrum, asymmetric	L	1	0.24	0-1	(0-5.3)
	F	1	0.03	0-1	(0-0.7)
: Arches, fused	L	1	0.24	0-2	(0-5.3)
	F	1	0.03	0-1	(0-0.7)

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