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

AUG 2 8 1992

009707

EXPEDITE

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Group I generic quaternary ammonium compounds: Didecyldimethylammoniumchloride (EPA Pesticide Chemical Code 069149, Toxicology Chemical Code 331A) - rat teratology study and rat 90 day dermal toxicity study.
EPA DP Barcode: D180618, EPA Submission No. S383632, MRID No. 418867-01 and 413059-0.

TO: Cynthia Giles-Parker/Clarence Lewis, PM 22
Anti-Microbial Program Branch
Registration Division (H7505C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/27/92
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (H7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. J M Ioannou 8-27-92
Section Head, Review Section I
and
Marcia van Gemert, Ph.D.
Branch Chief, Toxicology Branch II
Health Effects Division (H7509C) Marcia van Gemert 8/27/92

Action Requested: Review of a rat teratology study and a rat 90 day dermal toxicity study for the Dialkyl Group on the Group I generic quat, didecyldimethylammoniumchloride.

Recommendations: TB II reviewed the rat teratology study and a rat 90 day dermal toxicity study for the Group I generic quats, didecyldimethylammoniumchloride. The following are the conclusions from the 2 studies:

1. "Developmental Toxicity Evaluation of Didecyldimethylammoniumchloride Administered by Gavage to CD® (Sprague-Dawley) Rats" (Laboratory Project ID 53-534, Bushy Run Research Center, May 17, 1991, MRID # 418867-01):

Didecyldimethylammoniumchloride (80.8 % a.i.) was administered by gavage on gestation days 6 through 15, inclusive to Sprague-Dawley (CD®)[Crl:CD®BR] female albino rats from Charles River Breeding Laboratories, Inc. at dose levels of 1, 10 and 20 mg/kg/day. Maternal toxicity was observed at the mid and high dose groups in the form of increased incidence of clinical signs, a decrease in body weight gain during the dosing period, the dosing period plus

1

240

post dosing period and for the corrected body weight gains for the high dose, also low food efficiency compared with controls. Developmental toxicity was noted at the high dose in the form of increased incidence of skeletal variations.

Maternal NOEL = 1 mg/kg/day
Maternal LOEL = 10 mg/kg/day
Developmental Toxicity NOEL = 10 mg/kg/day
Developmental Toxicity LOEL = 20 mg/kg/day

The study is classified as Core Minimum Data and satisfies the guideline requirement (§83-3 a) for a developmental toxicity (teratology) study in rats.

2. "Ninety-Day Subchronic Dermal Toxicity Study with Didecyldimethylammoniumchloride in Rats" (Laboratory Project ID 51-554, Bushy Run Research Center, October 7, 1988, MRID # 413059-01):

This study was reviewed previously by TB I in Memorandum dated April 15, 1992 (B. Dementi to J. Wilson). The Data Evaluation Record (document # 009429) prepared by Dynamac reached the following conclusions:

> "Based on the absence of overt systemic effects, the systemic LOEL and NOEL could not be determined; however the NOEL ≥ 12 mg/kg/day, the highest dose tested. On the basis of increased skin irritation at the mid- and high dose, the LOEL for dermal irritation in males is 6 mg/kg/day, and the NOEL is 2 mg/kg/day DDAC. The LOEL for dermal irritation in females is 2 mg/kg/day, the lowest dose tested, based on acanthosis of the treated skin; the NOEL is ≤ 2 mg/kg/day when applied to approximately 45 cm^2 for 6 hours each day.
>
> The study was classified as CORE Supplementary; the highest dose level was not adequate to achieve systemic toxicity. The study may be upgraded when additional histological data are submitted."

Subsequently, based on Dr. H. Spencer's recommendations (Memorandum, H. Spencer to J. Wilson, dated April 15, 1992) this study was deemed acceptable to satisfy the guideline requirement §82-3 for a 90-day dermal toxicity study in rats.

009707

Toxicology Branch II has reevaluated the data for this study and found that it **does not fulfill** the data requirement (§82-3) for a 90 day (subchronic) dermal toxicity study in rats and is thus downgraded to a supplementary data classification. The NOEL and LOEL for systemic toxicity were not established by this study, and the relevance of elevated lymph node aggregates to systemic toxicity has not been established. The study may be upgraded if the following information is supplied to the Agency and found to be acceptable:

1. **Since doses were based on a "preliminary skin irritation screen" (BRRC Project # 87-44-25009), this study and any further information/justification in support of the dose levels tested must be submitted.**

2. **Data on and information as to the relevance of the "lymph node aggregates" to systemic toxicity must be submitted.**

009707

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/26/92
Senior Pharmacologist, Review Section I, TB II/HED (H7509C)
Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. YMI 8-26-92
Section Head, Review Section I, TB II/HED (H7509C)

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rat Guideline: §83-3 a

EPA Identification No.s: EPA DP Barcode D180618
EPA Submission No. S383632
EPA MRID No. 418867-01
EPA Pesticide Chemical Code 069149
Toxicology Chemical Code 331A

Title of Report: Developmental Toxicity Evaluation of Didecyldimethylammoniumchloride Administered by Gavage to CD® (Sprague-Dawley) Rats

Test Material: Didecyldimethylammoniumchloride, as an 80% manufacturing use product (80.8 % w/w a.i.), Batch No. B-1889, a very viscous honey-colored liquid, CAS No. 7173-51-5

Sponsor: Lonza Inc, 17-17 Route 208, Fair Lawn NJ 07410

Study Number(s): Laboratory Project ID 53-534

Testing Facility: Bushy Run Research Center, 6702 Mellon Road, Export, PA 15632-8902

Author(s): T.L. Neeper-Bradley

Report Issued: May 17, 1991

Conclusions: Didecyldimethylammoniumchloride (80.8 % a.i.) was administered by gavage on gestation days 6 through 15, inclusive to Sprague-Dawley (CD®)[Crl:CD®BR] female albino rats from Charles River Breeding Laboratories, Inc. at dose levels of 1, 10 and 20 mg/kg/day. Maternal toxicity was observed at the mid and high dose groups in the form of increased incidence of clinical signs, a decrease in body weight gain during the dosing period, the dosing period plus post dosing period and for the corrected body weight gains for the high dose, also low food efficiency compared with controls. Developmental toxicity was noted at the high dose in the form of increased incidence of skeletal variations.

Maternal NOEL = 1 mg/kg/day
Maternal LOEL = 10 mg/kg/day
Developmental Toxicity NOEL = 10 mg/kg/day
Developmental Toxicity LOEL = 20 mg/kg/day

Core Classification: Core Minimum Data.
This study satisfies the guideline requirement (§83-3 a) for a developmental toxicity (teratology) study in rats.

4

A. Materials and Methods A copy of the "materials and methods" section from the investigators report is appended.

Test Compound: Purity: 80.8% w/w a.i.
Density: not provided
Description: a very viscous honey-colored liquid
Lot No.: Batch No. B-1889
Receipt date: November 24, 1987
other provided information: supplier: Lonza Inc., Fair Lawn, NJ
Contaminants: none provided

Vehicle(s): deionized Millipore® water (CAS No. 7732-18-5)

Test Animal(s): Species: albino rats
Strain: Sprague-Dawley (CD®)[Crl:CD®BR]
Source: Charles River Breeding Laboratories, Inc., Portage, MI
Age: 63 days old (males), 56 days (females)
BW: 250-300 gm (males), 175-200 gm (females)

B. Study Design

This study was designed to assess the developmental toxicity potential of didecyldimethylammoniumchloride when administered by gavage on gestation days 6 through 15, inclusive.

Mating Procedure

Rats were mated by a one male:one female ratio. Females were checked once daily (morning) for vaginal plugs (and the bending beneath the cage). The day of confirmation of mating was considered gestation day 0. The report states under treatment that "Timed-pregnant CD® (Sprague-Dawley) rat dams were dosed...", this contradicts the above mating protocol.

Animal Husbandry

Animals were kept under standard animals care conditions and received Purina Certified Ground Rodent Chow (Batch No. SEP 22 89 ID, Purina Mills, Inc., Waverly, NY) and tap water *ad libitum*. No indication if food or water were analyzed for contaminants.

Group Arrangement:

Test Group	Dose Level (mg/kg)	Number Assigned
Control	Vehicle	25
Low Dose	1.0	25
Mid Dose	10.0	25
High Dose	20.0	25

5

244

Dose Administration:

All doses were administered in a volume of 5.0 ml/kg of body weight/day prepared twice during the dosing period. The dosing solutions were analyzed for concentration and stability. Dosing was based on the most recent body weight. Dose levels were based on pilot study (BRRC Report Number 53-533); no data were provided on this study.

Observations

The animals were checked twice daily for mortality or abnormal condition and daily (twice daily during the dosing period) for clinical signs. Dams were sacrificed on day 21 of gestation. Examinations at sacrifice consisted of: opening and examination of the maternal body cavity by a mid-sagittal thoracolaparotomy. The investigators examined the gravid uterus, ovaries (counting the corpora lutea), cervix, vagina, and abdominal and thoracic organs macroscopically. They further examined the lumen and lining of the esophagus, stomach and trachea for evidence of irritation by dosing solutions or gavage errors. The uterus was examined for signs of hemorrhage, weighed and dissected longitudinally. The live and dead fetuses, early and late resorption sites were recorded. Apparently nongravid uteri were stained using the method of Salewski to detect early resorptions. The investigators also recorded maternal liver weights.

The fetuses were examined in the following manner: they were weighed, sexed, examined for external "malformations" including cleft palate, and "variations". One-half of the fetuses of each litter were examined for visceral ("thoracic and abdominal") abnormalities by a modification of the Staple's technique. The heads were fixed in Bouin's solution for examination of the craniofacial structures by a modified Wilson's technique. The remaining half of each litter were eviscerated and processed for skeletal staining by a method using alizarin red S described by Crary; following this they were examined for "malformations and variations".

Historical control data were not provided to allow comparison with concurrent controls.

Statistical analysis

The following statistical analysis methods were employed:

The unit of comparison was the pregnant female or the litter (Weil, 1970). Results of the quantitative continuous variables (e.g., maternal body weights, organ weights, fetal weights, etc.) were intercompared for the three treatment groups and vehicle control group by use of Levene's test for equal variances (Levene, 1960), analysis of variance (ANOVA), and t-tests with Bonferroni probabilities for pairwise comparisons. When Levene's test indicated homogeneous variances, and the ANOVA was significant, the pooled t-test was used. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances (Brown and Forsythe, 1974) followed, when necessary, by the separate variance t-test.

Nonparametric data were statistically treated using the Kruskal-Wallis test (Sokal and Rohlf, 1969) followed by the Mann-Whitney U test (Sokal and Rohlf, 1969) when appropriate. Incidence data were compared using Fisher's Exact Test (Sokal and Rohlf, 1969). For all statistical tests, the probability value of $p < 0.05$ (two-tailed) was used as the critical level of significance.

Compliance

A signed "Statement of Confidentiality Claims" was provided, no confidentiality was claimed.

A signed statement of "Compliance with FIFRA Good Laboratory Practices" was provided.

A signed "FIFRA Flagging Statement" was provided, study neither meets nor exceeds the applicable criteria.

A signed "Quality Assurance Unit Study Inspection Summary" statement was provided.

C. Results

Analysis of Dosing Solutions

The investigators stated that "The dosing solutions were homogeneous, stable for at least 12 days when stored at room temperature, and within 97.0 to 103.8 % of nominal." Data provided support this statement.

Maternal Toxicity:

Mortality

No animals were reported to have died, there were no abortions and no animals delivered early.

Clinical Observations

At sacrifice, 1 animal in the low and mid dose groups and 2 animals in the high dose groups were not pregnant, apparently shown by staining of the uterus. The investigators provided group summary and individual animal data. The following table presents a summary of the clinical observations.

Table I: Clinical Observations (#days/#animals[a])

Dose (mg/kg) Observation	Control	1.0	10.0	20.0
Urine Stains	0	0	0	2/2[a]
Unkempt	0	0	0	2/2
Urogenital discharge	1/1	0	0	0
Audible respiration	0	0	29/6	80/17
Gasping	0	0	0	4/2
Perinasal encrustation	0	0	0	7/3
Perioral encrustion	0	0	0	2/1
Loose stool	0	0	0	3/2

[a] = number of observation days/number of animals presenting with the observation

As can be seen from the above data the mid and high dose group presented with cardio-pulmonary observations in the form of audible respiration with the high dose presented with other observations as well.

8

247

Body Weight

The investigators supplied group mean data and individual animal data. The following table presents body weight gain data:

Table II: Body Weight Gains (grams)[a]

Days:	0-6	6-15	15-21	6-21[1]	0-21	Corrected 6-21[1]	Corrected 0-21
Control	27.7	35.9	86.5	122.3	150.0	24.1	51.8
LDT	29.5	39.9	89.8	129.7	159.2	27.1	56.6
MDT	29.1	34.1	86.9	121.1	150.1	24.1	53.1
HDT	29.3	24.6	86.7	111.4	140.7	16.3	45.6

[1] = calculated by reviewer (corrected = 6-21 (or 0-21) minus gravid uterus weight)
[a] = Data extracted from Report 53-534, Tables 3 and 6.

As can be seen above there appears to be a treatment related decrease in body weight gain during the dosing period (gestation days 6-15), the dosing period plus post dosing period (gestation days 6-21) and for the corrected body weight gains for the high dose.

Food Consumption

The investigators supplied group mean data and individual animal data. The following table presents food consumption data for periods similar to the body weight gain data:

Table III: Food Consumption Data (gm/animal/day)[a]

Days:	0-6	6-15	15-21	6-21[1]	0-21[1]
Control	21.0	22.2	25.4	23.5	22.8
LDT	22.2	23.2	26.1	24.4	23.7
MDT	21.8	22.6	25.7	23.9	23.3
HDT	21.9	20.7	24.9	22.4	22.3

[1] = calculated by reviewer
[a] = Data extracted from Report 53-534, Table 4.

Table IV: Food Efficiency Data (%)

Days:	0-6	6-15	15-21	6-21[1]	0-21[1]
Control	22.0	18.0	56.8	34.7	31.3
LDT	22.2	19.1	57.3	35.4	32.0
MDT	22.3	16.8	56.4	33.8	30.7
HDT	22.3	13.2	58.0	33.2	30.0

[1] = calculated by reviewer, from above data Tables II and III.

The low efficiency compared with controls during the dosing period for the mid and high dose groups indicates possible toxicity in the consuming animals.

Gross Pathological Observations

The investigators supplied group mean and individual animal data. The following tables from the investigators report presents the summary of the necropsy observations and the liver weight measurements.

TABLE 5
DEVELOPMENTAL TOXICITY STUDY OF DIDECYLDIMETHYLAMMONIUMCHLORIDE
ADMINISTERED BY GAVAGE TO CD® (SPRAGUE-DAWLEY) RATS
SUMMARY OF NECROPSY OBSERVATIONS
ALL PREGNANT FEMALES SACRIFICED AT SCHEDULED LAPAROTOMY

GROUP: MG/KG/DAY	0.0	1.0	10.0	20.0
NUMBER OF ANIMALS IN DOSE GROUP	25	25	25	25
NUMBER OF ANIMALS SACRIFICED	25	24	24	23
STOMACH NON-GL				
ULCERATION(S)	0	0	0	2
INTESTINES				
GAS-FILLED	0	0	0	2
UTERUS				
CONTAINS BLOOD (BY HEMASTIX)	1	0	0	0
LUNGS				
COLOR CHANGE	0	0	1	2
FOCUS OR FOCI	0	0	0	1
CONSOLIDATED	0	0	0	1
KIDNEYS				
HYDRONEPHROSIS	1	0	0	1

None significantly different from control group

Table 6
DEVELOPMENTAL TOXICITY STUDY OF DIDECYLDIMETHYLAMMONIUMCHLORIDE
ADMINISTERED BY GAVAGE TO CD® (SPRAGUE-DAWLEY) RATS
SUMMARY OF MATERNAL ORGAN WEIGHTS (GRAMS)

	FEMALES			
GROUP: MG/KG/DAY	0.0	1.0	10.0	20.0
INITIAL BODY WEIGHT (g)				
MEAN	223.22	223.85	223.96	223.04
S.D.	9.569	9.623	9.218	9.618
N	25	24	24	23
BODY WEIGHT AT SACRIFICE (g)				
MEAN	373.26	383.09	374.09	363.69
S.D.	25.731	20.605	28.512	37.060
N	25	24	24	23
GRAVID UTERINE WEIGHT (g)				
MEAN	98.243	102.606	97.036	95.093
S.D.	9.7008	11.0864	14.4243	11.2199
N	25	24	24	23
CORRECTED BODY WEIGHT (g)[a]				
MEAN	275.02	280.48	277.06	268.60
S.D.	20.249	17.545	22.476	30.164
N	25	24	24	23
CORRECTED WEIGHT CHANGE (g)[b]				
MEAN	51.80	56.63	53.10	45.56
S.D.	13.503	13.419	16.709	25.521
N	25	24	24	23
LIVER WEIGHT (g)				
MEAN	12.935	13.340	12.962	13.176
S.D.	1.6385	1.2930	1.6845	1.9833
N	25	24	24	23
RELATIVE LIVER WEIGHT (%)[c]				
MEAN	4.696	4.754	4.668	4.902
S.D.	0.4017	0.3680	0.3784	0.4919
N	25	24	24	23

None significantly different from control group
[a] Corrected body weight = body weight at sacrifice minus gravid uterine weight.
[b] Corrected weight change = corrected body weight minus initial body weight.
[c] Value is a percentage of corrected body weight

Cesarean Section Observations

Table V: Cesarean Section Observations[a]

Dose:	Control	LDT	MDT	HDT
#Animals Assigned	25	25	25	25
#Animals Mated/Inseminated	25	25	25	25
#Animals Pregnant	25	24	24	23
Pregnancy Rate (%)	100	96	96	92
Maternal Wastage				
#Died	0	0	0	0
#Died/pregnant	0	0	0	0
#Non pregnant	0	1	1	2
#Aborted	0	0	0	0
#Premature Delivery	0	0	0	0
Total Corpora Lutea	354	353	346	332
Corpora Lutea/dam	14.2	14.7	14.4	14.4
Total Implantations	342	344	339	322
Implantations/Dam	13.7	14.3	14.1	14.0
Total Live Fetuses	337	337	319	311
Live Fetuses/Dam	13.5	14.0	13.3	13.5
Total Resorptions	5	7	19	11
Early	5	6	18	10
Late	0	1	1	1
Resorptions/Dam	0.2	0.3	0.8	0.5
Total Dead Fetuses	0	0	0	0
Dead Fetuses/Dam	0	0	0	0
Mean Fetal Weight (gm)	5.2	5.2	5.2	5.0
Preimplantation Loss(%)[1]	3.4	2.6	2.0	3.0
Postimplantation Loss(%)[2]	1.5	2.0	5.9	3.4
Sex Ratio (% Male)	51.8	52.2	47.8	47.2

[1] = total corpora lutea - total implantations / total corpora lutea X 100
[2] = total implantations - total live fetuses /total implantations X 100
[a] = Data extracted from Report 53-534 Tables 1 and 7.

No treatment related effects were noted in the above data.

11

250

Developmental Toxicity

External Observations

The following tables from the investigators report present the external examination data, divided into their descriptive "malformations" and variations". No treatment related findings were noted.

TABLE 8
DEVELOPMENTAL TOXICITY TUDY OF DIDECYLDIMETHYLAMMONIUMCHLORIDE
ADMINISTERED BY GAVAGE TO CD® (SPRAGUE-DAWLEY) RATS
SUMMARY OF MALFORMATIONS IN FETUSES AND LITTERS[a]

	FETUSES				LITTERS			
GROUP: MG/KG/DAY	0	1	10	20	0	1	10	20
NUMBER EXAMINED EXTERNALLY[b]	337	337	319	311	25	24	24	23
THREAD-LIKE TAIL	1	0	0	0	1	0	0	0
	0.3	0.0	0.0	0.0	4.0	0.0	0.0	0.0
IMPERFORATE ANUS	1	0	0	0	1	0	0	0
	0.3	0.0	0.0	0.0	4.0	0.0	0.0	0.0
UMBILICAL HERNIA	0	0	0	1	0	0	0	1
	0.0	0.0	0.0	0.3	0.0	0.0	0.0	4.3
MICROGNATHIA	0	0	0	1	0	0	0	1
	0.0	0.0	0.0	0.3	0.0	0.0	0.0	4.3
EYE BULGE MISSING	0	0	0	1	0	0	0	1
	0.0	0.0	0.0	0.3	0.0	0.0	0.0	4.3
FETUS EDEMATOUS	0	0	1	0	0	0	1	0
	0.0	0.0	0.3	0.0	0.0	0.0	4.2	0.0
FOOT SHORTENED	1	0	0	0	1	0	0	0
	0.3	0.0	0.0	0.0	4.0	0.0	0.0	0.0

None significantly different from control (0.0 MG/KG/DAY)
See footnotes on last page of table.

TABLE 9
DEVELOPMENTAL TOXICITY STUDY OF DIDECYLDIMETHYLAMMONIUMCHLORIDE
ADMINISTERED BY GAVAGE TO CD® (SPRAGUE-DAWLEY) RATS
SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

	FETUSES				LITTERS			
GROUP: MG/KG/DAY	0	1	10	20	0	1	10	20
NUMBER EXAMINED EXTERNALLY[b]	337	337	319	311	25	24	24	23
ECCHYMOSIS - TRUNK	1	2	1	2	1	2	1	2
	0.3	0.6	0.3	0.6	4.0	8.3	4.2	8.7
ECCHYMOSIS - EXTREMITIES	1	0	0	0	1	0	0	0
	0.3	0.0	0.0	0.0	4.0	0.0	0.0	0.0
ECCHYMOSIS - HEAD	0	0	1	0	0	0	1	0
	0.0	0.0	0.3	0.0	0.0	0.0	4.2	0.0
ASYMETRIC MANDIBLE	0	0	1	0	0	0	1	0
	0.0	0.0	0.3	0.0	0.0	0.0	4.2	0.0

None significantly different from control (0.0 MG/KG/DAY)
See footnotes on last page of table.

12

Visceral Observations

The following tables from the investigators report present the visceral examination data, divided into their descriptive "malformations" and variations". No treatment related findings were noted.

TABLE 8
DEVELOPMENTAL TOXICITY STUDY OF DIDECYLDIMETHYLAMMONIUMCHLORIDE
ADMINISTERED BY GAVAGE TO CD® (SPRAGUE-DAWLEY) RATS
SUMMARY OF MALFORMATIONS IN FETUSES AND LITTERS[a]

GROUP: MG/KG/DAY	FETUSES 0	1	10	20	LITTERS 0	1	10	20
NUMBER EXAMINED VISCERALLY[c]	176	175	164	162	25	24	24	23
HYDRONEPHROSIS - BILATERAL	1 0.6	0 0.0	1 0.6	0 0.0	1 4.0	0 0.0	1 4.2	0 0.0
HYDRONEPHROSIS - UNILATERAL	0 0.0	0 0.0	1 0.6	0 0.0	0 0.0	0 0.0	1 4.2	0 0.0
HYDROURETER - BILATERAL	2 1.1	3 1.7	12 7.3	4 2.5	2 8.0	2 8.3	5 20.8	3 13.0
HYDROURETER - UNILATERAL	1 0.6	3 1.7	2 1.2	2 1.2	1 4.0	3 12.5	2 8.3	2 8.7
UMBILICAL HERNIA	0 0.0	0 0.0	0 0.0	1 0.6	0 0.0	0 0.0	0 0.0	1 4.3

None significantly different from control (0.0 MG/KG/DAY)
See footnotes on last page of table.

TABLE 9
DEVELOPMENTAL TOXICITY STUDY OF DIDECYLDIMETHYLAMMONIUMCHLORIDE
ADMINISTERED BY GAVAGE TO CD® (SPRAGUE-DAWLEY) RATS
SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP: MG/KG/DAY	FETUSES 0	1	10	20	LITTERS 0	1	10	20
NUMBER EXAMINED VISCERALLY[c]	176	175	164	162	25	24	24	23
NASAL PASSAGES CONSTRICTED	1 0.6	0 0.0	0 0.0	1 0.6	1 4.0	0 0.0	0 0.0	1 4.3
LATERAL VENTRICLE DILATED - NO DEPRESSION	1 0.6	4 2.3	3 1.8	4 2.5	1 4.0	4 16.7	2 8.3	4 17.4
SHORT INNOMINATE ARTERY	0 0.0	0 0.0	1 0.6	1 0.6	0 0.0	0 0.0	1 4.2	1 4.3
FETAL ATELECTASIS	31 17.6	19 10.9	16 9.8	20 12.3	15 60.0	9 37.5	11 45.8	13 56.5
PARTIAL FETAL ATELECTASIS	30 17.0	32 18.3	28 17.1	41 25.3	13 52.0	18 75.0	14 58.3	15 65.2
TAN TISSUE TAG - MEDIAN LOBE	0 0.0	0 0.0	0 0.0	4 2.5	0 0.0	0 0.0	0 0.0	3 13.0
STOMACH EMPTY	2 1.1	1 0.6	1 0.6	1 0.6	1 4.0	1 4.2	1 4.2	1 4.3
DILATED RENAL PELVIS - BILATERAL	17 9.7	30 17.1	27 16.5	13 8.0	8 32.0	13 54.2	12 50.0	7 30.4
DILATED RENAL PELVIS - UNILATERAL	4 2.3	16 9.1	9 5.5	11 6.8	4 16.0	10 41.7	5 20.8	8 34.8
KIDNEYS - PALE	0 0.0	0 0.0	2 1.2	1 0.6	0 0.0	0 0.0	2 8.3	1 4.3
DILATED URETERS - BILATERAL	18 10.2	33 18.9	30 18.3	19 11.7	14 56.0	16 66.7	16 66.7	8 34.8
DILATED URETER - UNILATERAL	10 5.7	14 8.0	5 3.0	7 4.3	10 40.0	9 37.5	3 12.5	5 21.7
URINARY BLADDER DISTENDED	0 0.0	0 0.0	3 1.8	0 0.0	0 0.0	0 0.0	2 8.3	0 0.0
THORACIC CAVITY FLUID FILLED	0 0.0	0 0.0	1 0.6	0 0.0	0 0.0	0 0.0	1 4.2	0 0.0
ALL VISCERA - PALE	0 0.0	0 0.0	1 0.6	0 0.0	0 0.0	0 0.0	1 4.2	0 0.0

None significantly different from control (0.0 MG/KG/DAY)
See footnotes on last page of table.

Skeletal Observations

The following tables from the investigators report present the skeletal examination data, divided into their descriptive "malformations". The "variations" are on the following attached tables.

TABLE 8
DEVELOPMENTAL TOXICITY STUDY OF DIDECYLDIMETHYLAMMONIUMCHLORIDE
ADMINISTERED BY GAVAGE TO CD® (SPRAGUE-DAWLEY) RATS
SUMMARY OF MALFORMATIONS IN FETUSES AND LITTERS[a]

GROUP: MG/KG/DAY	FETUSES 0	FETUSES 1	FETUSES 10	FETUSES 20	LITTERS 0	LITTERS 1	LITTERS 10	LITTERS 20
NUMBER EXAMINED SKELETALLY[d]	161	162	155	149	25	24	24	23
CERVICAL CENTRA MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
CERVICAL ARCH(ES) MISSING	2 1.2	0 0.0	0 0.0	0 0.0	2 8.0	0 0.0	0 0.0	0 0.0
ALL THORACIC CENTRA MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
ALL THORACIC ARCHES MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
ALL LUMBAR CENTRA MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
ALL LUMBAR ARCHES MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
LUMBAR CENTRUM #6 - MISSING	0 0.0	0 0.0	0 0.0	1 0.7	0 0.0	0 0.0	0 0.0	1 4.3
LUMBAR ARCH(ES) #6 - MISSING	0 0.0	0 0.0	0 0.0	1 0.7	0 0.0	0 0.0	0 0.0	1 4.3
ALL SACRAL CENTRA MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
ALL SACRAL ARCHES MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
ALL CAUDAL CENTRA MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
ALL CAUDAL ARCHES MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
MISSING RIB #13 - ON THORACIC ARCH #13 - UNILATERAL	0 0.0	0 0.0	2 1.3	0 0.0	0 0.0	0 0.0	2 8.3	0 0.0
ALL RIBS MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
NASAL - FUSED	0 0.0	0 0.0	0 0.0	1 0.7	0 0.0	0 0.0	0 0.0	1 4.3
NASAL - MISSHAPEN	0 0.0	0 0.0	0 0.0	1 0.7	0 0.0	0 0.0	0 0.0	1 4.3
PREMAXILLARY - FUSED	0 0.0	0 0.0	0 0.0	1 0.7	0 0.0	0 0.0	0 0.0	1 4.3
PREMAXILLARY - MISSHAPEN	0 0.0	0 0.0	0 0.0	1 0.7	0 0.0	0 0.0	0 0.0	1 4.3
MANDIBLE - FUSED	0 0.0	0 0.0	0 0.0	1 0.7	0 0.0	0 0.0	0 0.0	1 4.3
SOME PROXIMAL PHALANGES (HINDLIMB) MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0
SOME DISTAL PHALANGES (HINDLIMB) MISSING	1 0.6	0 0.0	0 0.0	0 0.0	1 4.0	0 0.0	0 0.0	0 0.0

[a] ... significantly different from control (0.0 MG/KG/DAY)

15

Several variations were increased (both fetal and litter incidence) in the high dose group: split anterior arch of the atlas; poorly ossified thoracic centrum #1, 10, and 12; bilobed thoracic centrum #11; unilateral short rib #13; poorly ossified parietal; poorly ossified sternebrae #4. This is considered evidence of developmental toxicity.

TABLE 9

DEVELOPMENTAL TOXICITY STUDY OF DIDECYLDIMETHYLAMMONIUMCHLORIDE
ADMINISTERED BY GAVAGE TO CD® (SPRAGUE-DAWLEY) RATS

SUMMARY OF VARIATIONS IN FETUSES AND LITTERS[a]

GROUP; MG/KG/DAY	FETUSES 0	FETUSES 1	FETUSES 10	FETUSES 20	LITTERS 0	LITTERS 1	LITTERS 10	LITTERS 20
NUMBER EXAMINED SKELETALLY[d]	161	162	155	149	25	24	24	23
CERVICAL CENTRA #1,#2,#3 AND/OR #4 POORLY OSSIFIED	70 43.5	70 43.2	74 47.7	59 39.6	25 100.0	23 95.8	23 95.8	22 95.7
CERVICAL CENTRA #1,#2,#3 AND/OR #4 UNOSSIFIED	112 69.6	123 75.9	132 85.2	118 79.2	24 96.0	23 95.8	24 100.0	22 95.7
CERVICAL CENTRA #1,#2,#3 AND/OR #4 BILOBED	13 8.1	10 6.2	7 4.5	15 10.1	9 36.0	9 37.5	7 29.2	9 39.1
CERVICAL CENTRUM #5 POORLY OSSIFIED	34 21.1	38 23.5	47 30.3	34 22.8	17 68.0	18 75.0	19 79.2	16 69.6
CERVICAL CENTRUM #5 UNOSSIFIED	47 29.2	36 22.2	38 24.5	47 31.5	18 72.0	14 58.3	19 79.2	12 52.2
CERVICAL CENTRUM #5 BILOBED	0 0.0	1 0.6	1 0.6	0 0.0	0 0.0	1 4.2	1 4.2	0 0.0
CERVICAL CENTRUM #6 POORLY OSSIFIED	41 25.5	42 25.9	44 28.4	28 18.8	21 84.0	19 79.2	21 87.5	18 78.3
CERVICAL CENTRUM #6 UNOSSIFIED	37 23.0	33 20.4	38 24.5	44 29.5	15 60.0	15 62.5	18 75.0	12 52.2
CERVICAL CENTRUM #6 BILOBED	0 0.0	3 1.9	0 0.0	0 0.0	0 0.0	1 4.2	0 0.0	0 0.0
CERVICAL CENTRUM #7 POORLY OSSIFIED	20 12.4	15 9.3	9 5.8	18 12.1	13 52.0	10 41.7	5* 20.8	11 47.8
CERVICAL CENTRUM #7 UNOSSIFIED	3 1.9	3 1.9	6 3.9	10 6.7	3 12.0	3 12.5	5 20.8	5 21.7
CERVICAL CENTRUM #7 BILOBED	0 0.0	3 1.9	1 0.6	4 2.7	0 0.0	3 12.5	1 4.2	3 13.0

[a] Significantly different from control (0.0 MG/KG/DAY) at .05 level using two-tailed Fisher's exact test.
See footnotes on last page of table.

16

28

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