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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: DCPA - LIST A CHEMICAL
90-DAY FEEDING STUDY - RAT

TO: ERIC FERIS
PRODUCT MANAGER (50)
REGISTRATION DIVISION (H7505C)

FROM: LINDA L. TAYLOR, PH.D. Linda Lee Taylor 5/6/91
TOXICOLOGY BRANCH II, SECTION II
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THRU: K. CLARK SWENTZEL K. Clark Swentzel 5/6/91
SECTION II HEAD, TOXICOLOGY BRANCH II
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AND

MARCIA VAN GEMERT, PH.D. Marcia Gemert 5/9/91
CHIEF, TOXICOLOGY BRANCH/HFAS/HED (H7509C)

REGISTRANT: ISK BIOTECH CORPORATION
CHEMICAL: DIMETHYL TETRACHLOROTEREPHTHATATE
SYNONYMS: DCPA, DACTHAL
PROJECT NO.: 1-0735
CASWELL NO.: 382
RECORD NO.: NOT PROVIDED; CASE: 819191; SUBMISSION: S391334
IDENTIFYING NO.: 078701
MRID NO.: 417679-01
ACTION REQUESTED: THIS STUDY IS FLAGGED FOR IMMEDIATE REVIEW.

COMMENT: DCPA IS A LIST A CHEMICAL AND THIS 90-DAY FEEDING STUDY WAS SUBMITTED TO FULFILL A DATA REQUIREMENT. THE STUDY HAS BEEN REVIEWED, AND THE DER IS APPENDED.

THERE WERE NO TREATMENT-RELATED EFFECTS ON SURVIVAL OR CLINICAL SIGNS IN EITHER SEX FOLLOWING EXPOSURE TO DCPA AT DOSE LEVELS OF 10, 50, 100, 150, AND 1000 MG/KG/DAY IN THE DIET FOR 90 DAYS. THE HIGH-DOSE FEMALES DISPLAYED SLIGHTLY LOWER BODY WEIGHT/GAIN/FOOD CONSUMPTION. THERE WERE TREATMENT-RELATED EFFECTS ON THE LUNGS, LIVER, AND THYROID OF BOTH SEXES, AND A SLIGHT EFFECT ON THE KIDNEYS OF THE MALES. DCPA APPEARS TO BE TOLERATED WELL BY THE RAT. THE NOEL CAN BE SET AT 10 MG/KG, THE LEL AT 50 MG/KG, BASED ON INCREASED LIVER WEIGHT. THE LEL FOR MICROSCOPIC FINDINGS WAS 50 MG/KG.

THIS 90-DAY SUBCHRONIC FEEDING STUDY IS CLASSIFIED CORE MINIMUM, AND IT SATISFIES THE GUIDELINE REQUIREMENTS (82-1) FOR A SUBCHRONIC FEEDING STUDY.

REVIEWED BY: LINDA L. TAYLOR, PH.D. Linda Lee Taylor 5/6/91
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SECONDARY REVIEWER: K. CLARK SWENTZEL K. Clark Swentzel 5/6/91
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DATA EVALUATION REPORT

STUDY TYPE: 90-DAY FEEDING - RATS TOX. CHEM. NO.: 382

MRID NO.: 417679-01

TEST MATERIAL: TECHNICAL DCPA

SYNONYMS: DACTHAL; DIMETHYL-2,3,5,6-TETRACHLOROTEREPHTHALATE; DS-893; SDS-893

STUDY NUMBER: 3338-89-0208-TX-002

SPONSOR: ISK BIOTECH CORPORATION

TESTING FACILITY: RICERCA, INC. DEPARTMENT OF TOXICOLOGY & ANIMAL METABOLISM
EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

TITLE OF REPORT: A 90-DAY FEEDING STUDY IN RATS WITH TECHNICAL DCPA

AUTHORS: F. LUCAS AND G. BENZ

REPORT ISSUED: JANUARY 22, 1991

QUALITY ASSURANCE: A QUALITY ASSURANCE STATEMENT WAS PROVIDED.

CONCLUSIONS: UNDER THE CONDITIONS OF THE STUDY, EXPOSURE TO DCPA AT DOSE LEVELS OF 10, 50, 100, 150, AND 1000 MG/KG/DAY IN THE DIET FOR 90 DAYS RESULTED IN ONLY SLIGHT DECREASES IN BODY WEIGHT AND FOOD CONSUMPTION IN THE HIGH-DOSE FEMALES ONLY. THERE WERE TREATMENT-RELATED EFFECTS ON THE LIVER (INCREASED WEIGHT AND CENTRILOBULAR HYPERTROPHY), LUNG (INCREASED ACCUMULATION OF FOAMY MACROPHAGES), KIDNEY (INCREASED WEIGHT, EPITHELIAL HYPERPLASIA, TUBULAR HYPERTROPHY, REGENERATIVE EPITHELIUM IN MALES), AND THYROID (FOLLICULAR HYPERTROPHY). THE NOEL CAN BE SET AT 10 MG/KG, THE LEL AT 50 MG/KG, BASED ON INCREASED LIVER WEIGHT. THE LEL FOR MICROSCOPIC EFFECTS WAS 50 MG/KG.

CLASSIFICATION: CORE MINIMUM. THIS STUDY SATISFIES THE GUIDELINE REQUIREMENTS (82-1) FOR A SUBCHRONIC FEEDING STUDY IN RODENTS.

A. MATERIALS:

1. TEST COMPOUND: TECHNICAL DCPA; DESCRIPTION: CREAMY WHITE POWDER; BATCH #: LOT # 10148, T-170-2; PURITY: 98.0%.

2. TEST ANIMALS: SPECIES: RAT; STRAIN: CD VAF/PLUS SPRAGUE-DAWLEY; AGE: 5-6 WEEKS OLD; WEIGHT: MALES 149-201 G, FEMALES 126-165 G; SOURCE: CHARLES RIVER LABORATORIES, PORTAGE, MICHIGAN.

3. STATISTICS: BODY WEIGHT, FOOD CONSUMPTION, TERMINAL BODY WEIGHT, ORGAN WEIGHT, AND CLINICAL PATHOLOGY - TREATED COMPARED TO CONTROL USING BARTLETT'S TEST (1) TO TEST FOR NORMALITY/HOMOGENEITY OF VARIANCE. WHEN THE TEST SHOWED NO SIGNIFICANCE, BONFERRONI'S T-TEST (2) FOR DIFFERENCE BETWEEN GROUPS AND A TEST FOR TREND WERE PERFORMED. WHEN BARTLETT'S TEST SHOWED A LACK OF NORMALITY/VARIANCE HOMOGENEITY, DUNN'S TEST (3) FOR DIFFERENCE BETWEEN GROUPS AND JONCKHEERE'S TEST (3) FOR TREND WERE PERFORMED. SURVIVAL AND INCIDENCE OF ACCUMULATION OF FOAMY MACROPHAGES - TREATED COMPARED TO THE CONTROL USING FISHER'S EXACT TEST (4) AT THE EXPERIMENTAL-WISE 5% AND 1% LEVELS OF SIGNIFICANCE.

B. STUDY DESIGN:

1. METHODOLOGY: ONE-HUNDRED AND TWENTY MALES AND 120 FEMALES WERE RANDOMLY ASSIGNED (RANDOMIZATION UNRESTRICTED EXCEPT THAT THE BODY WEIGHT MEANS OF THE TREATMENT GROUPS AT ASSIGNMENT WERE REQUIRED TO BE WITHIN 5% OF THE BODY WEIGHT MEAN OF THE CONTROLS)TO THIS STUDY AS FOLLOWS:

GROUP	# RATS/SEX	DOSE LEVEL (MG/KG/DAY)	DAYS ON TEST
1	15	0	90
2	15	10	90
3	15	50	90
4	15	100	90
5	15	150	90
6	15	1000	90
7°	10	0	60
8°	10	1000	60

° SATELLITE GROUPS USED TO EXAMINE LUNGS ONLY

THE ANIMALS WERE FED PURINA CERTIFIED RODENT CHOW® %5002 (MEAL) AND WATER AD LIBITUM. DIETS WERE PREPARED WEEKLY AND STORED IN THE DARK AT ROOM TEMPERATURE. THE TEST MATERIAL WAS MILLED TWICE TO PRODUCE A MATERIAL WITH A PARTICLE SIZE SIMILAR TO THE PARTICLE SIZE OF THE FORMULATED PRODUCTS (AVERAGE PARTICLE SIZE 5.5 μ) PRIOR TO MIXTURE IN THE BASAL DIET. THE DIETARY CONCENTRATIONS OF TECHNICAL DCPA WERE ADJUSTED WEEKLY (BASED ON THE PRECEDING WEEK'S BODY WEIGHT AND FOOD CONSUMPTION DATA) TO ASSURE CONSTANT DOSAGES. THE ACHIEVED DOSAGES OF TEST MATERIAL WERE CALCULATED AT THE END OF EACH WEEK FROM THE BODY WEIGHT, FOOD CONSUMPTION, AND NOMINAL DIETARY CONCENTRATION FOR THAT WEEK. HOMOGENEITY OF THE TEST MATERIAL IN THE DIETS AT VARIOUS CONCENTRATIONS WAS ASSESSED PRIOR TO STUDY INITIATION AND PRIOR TO A CHANGE IN THE METHOD OF DIET PREPARATION FOR THE GROUP 6

DIET. THE STABILITY OF DCPA IN THE DIET AT A LOW AND HIGH CONCENTRATION WAS DETERMINED AT 7, 14, AND 21 DAYS. SAMPLES OF EACH BATCH OF CONTROL AND TREATED DIET WERE COLLECTED AND ANALYZED WEEKLY. ADDITIONALLY, HOMOGENEITY OF MIXING WAS DETERMINED, AND THE DIETARY LEVELS ATTAINED WERE VERIFIED.

RESULTS

THE DIETS WERE FOUND TO BE HOMOGENEOUSLY MIXED IN THE FEED. THE PRETEST STABILITY STUDIES INDICATED THAT THE TEST MATERIAL WAS STABLE IN THE DIET FOR UP TO 21 DAYS AT ROOM TEMPERATURE. ANALYSES OF THE TEST DIETS FOR CONCENTRATIONS ATTAINED INDICATED THAT, WITH ONE EXCEPTION, THE DIETS WERE WITHIN 9% OF THE TARGET CONCENTRATION. THE DIET PREPARED FOR WEEK 8 FOR THE 1000 MG/KG/DAY GROUPS (FEMALES IN GROUPS 6 AND 8) WAS 50% OF THE INTENDED CONCENTRATION. THIS DIET WAS FED FOR ONE WEEK IN THE MIDDLE OF THE STUDY, BUT THIS WOULD NOT APPEAR TO AFFECT THE OVERALL STUDY RESULTS. THE COMPOUND CONSUMPTION WAS DETERMINED TO BE WITHIN 2% OF THE INTENDED TARGET CONSUMPTION FOR BOTH MALES AND FEMALES.

2. CLINICAL OBSERVATIONS: THE ANIMALS WERE OBSERVED TWICE DAILY, AND THE TYPE OF CLINICAL SIGNS, TIME OF ONSET, AND DURATION OF SIGNS WAS RECORDED. A COMPLETE PHYSICAL EXAMINATION WAS CONDUCTED AND INDIVIDUAL BODY WEIGHTS AND FOOD CONSUMPTION WERE RECORDED WEEKLY, FROM ONE WEEK PRIOR TO STUDY INITIATION UNTIL STUDY TERMINATION.

RESULTS

SURVIVAL AND CLINICAL OBSERVATIONS

ALL ANIMALS SURVIVED UNTIL STUDY TERMINATION. ONE FEMALE FROM GROUPS 1, 5, AND 6 DIED IMMEDIATELY AFTER TERMINAL ORBITAL SINUS BLEEDING, WHICH COUPLED TO INSUFFICIENT WATER INTAKE, WAS SAID TO BE THE PROBABLE CAUSE OF THESE DEATHS. THERE WERE NO TREATMENT-RELATED CLINICAL FINDINGS SEEN DURING THE STUDY.

BODY WEIGHT AND FOOD CONSUMPTION

BODY WEIGHT WAS COMPARABLE AMONG THE GROUPS THROUGHOUT THE STUDY FOR BOTH SEXES, ALTHOUGH THERE WAS A SIGNIFICANT TREND TOWARD LOWER BODY WEIGHT WITH INCREASING DOSE IN FEMALES. AT STUDY TERMINATION, BODY-WEIGHT GAIN FOR THE HIGH-DOSE MALES WAS 8% LOWER THAN CONTROL VALUE AND FOR THE HIGH-DOSE FEMALES, IT WAS 14% LOWER THAN CONTROL.

FOOD CONSUMPTION ON A MEAN ABSOLUTE BASIS WAS CONSISTENTLY LOWER IN THE HIGH-DOSE FEMALES THROUGHOUT THE STUDY COMPARED TO CONTROL VALUE; FOOD CONSUMPTION ON A RELATIVE TO BODY WEIGHT BASIS DID NOT SHOW ANY CONSISTENT DIFFERENCE FOR EITHER SEX.

3. BLOOD ANALYSES

HEMATOLOGY: BLOOD SAMPLES WERE OBTAINED FROM ALL ANIMALS (EXCEPT THOSE IN GROUPS 7 AND 8) AFTER 45 AND 90 DAYS OF EXPOSURE. FOOD WAS WITHHELD FOR 16 TO 20 HOURS PRIOR TO SAMPLE COLLECTION. THE CHECKED (X) PARAMETERS WERE EXAMINED.

X	HEMATOCRIT (HCT)
X	HEMOGLOBIN (HGB)
X	LEUKOCYTE COUNT (WBC)
X	ERYTHROCYTE COUNT (RBC)
	PLATELET COUNT
	THROMOBCYTE COUNT
X	PROTHROMBIN TIME
X	ACTIVATED PARTIAL THROMBOPLASTIN TIME
X	LEUKOCYTE DIFFERENTIAL COUNT†
X	MEAN CORPUSCULAR HGB (MCH)
X	MEAN CORPUSCULAR HGB CONC (MCHC)
X	MEAN CORPUSCULAR VOLUME (MCV)
	RETICULOCYTE COUNT
	METHEMOGLOBIN
	HEINZ BODIES
	HOWELL-JOLLY BODIES

† CONTROL AND HIGH DOSE ONLY

RESULTS

THERE WERE NO TREATMENT-RELATED EFFECTS OBSERVED ON ANY OF THE MEASURED PARAMETERS IN EITHER SEX, ALTHOUGH WBC WAS DECREASED IN BOTH SEXES AT BOTH INTERVALS [7/8 WEEKS (83-87% OF CONTROL VALUE); AT 14 WEEKS (75-78% OF CONTROL VALUE)]. THE MEAN DIFFERENTIAL LEUKOCYTE COUNT DID NOT SHOW ANY SIGNIFICANT DIFFERENCES IN DISTRIBUTION OF CELLS (EXCEPT A STATISTICALLY SIGNIFICANT DECREASE IN EOSINOPHILS IN HIGH-DOSE FEMALES) OR A TREATMENT-RELATED INCREASE IN ABNORMAL ERYTHROCYTE TYPE CELLS.

CLINICAL CHEMISTRY: BLOOD SAMPLES WERE OBTAINED AS STATED ABOVE. THE CHECKED (X) PARAMETERS WERE EXAMINED.

	ELECTROLYTES:
X	CALCIUM*
X	CHLORIDE*
	MAGNESIUM*
X	PHOSPHOROUS*
X	POTASSIUM*
X	SODIUM*
	ENZYMES
X	ALKALINE PHOSPHATASE
	CHOLINESTERASE
	CREATININE PHOSPHOKINASE*
	LACTIC ACID DEHYDROGENASE
X	ALANINE TRANSAMINASE (ALT)*
X	ASPARTATE TRANSAMINASE (AST)*
	GAMMA GLUTAMYL TRANSFERASE
	GLUTAMATE DEHYDROGENASE

	OTHER:
X	ALBUMIN*
X	BLOOD CREATININE*
X	BLOOD UREA NITROGEN*
	CHOLESTEROL*
X	ALBUMIN/GLOBULIN RATIO
X	GLUCOSE*
X	TOTAL BILIRUBIN*
X	TOTAL PROTEIN*
	TRIGLYCERIDES
	SERUM PROTEIN ELECTROPHORESIS
X	GLOBULIN
X	SORBITOL DEHYDROGENASE

RESULTS

THERE WERE NO DIFFERENCES OBSERVED IN ANY OF THE PARAMETERS MEASURED THAT

ARE CONSIDERED BIOLOGICALLY SIGNIFICANT. FOR EXAMPLE, TOTAL BILIRUBIN WAS DECREASED IN THE FEMALES AT BOTH TIME POINTS AND THE HIGH-DOSE VALUE WAS 78% OF THE CONTROL VALUE AT BOTH TIME POINTS. ADDITIONALLY, ASPARTATE TRANSAMINASE AND ALKALINE PHOSPHATASE VALUES WERE SIGNIFICANTLY LOWER AT VARIOUS TIMES COMPARED TO CONTROL VALUES, BUT THESE PARAMETERS ARE NORMALLY CONSIDERED INDICATIVE OF AN EFFECT IF ELEVATED.

4. URINALYSIS - OVERNIGHT URINE SAMPLES WERE COLLECTED AFTER 45 AND 90 DAYS FROM 5 RATS/SEX FROM THE CONTROL AND HIGH-DOSE GROUPS (FOOD WITHELD FOR 16-20 HOURS DURING COLLECTION). THE CHECKED (X) PARAMETERS WERE EXAMINED.

X	APPEARANCE	X	GLUCOSE
X	VOLUME	X	KETONES
X	SPECIFIC GRAVITY	X	BILIRUBIN
X	PH	X	BLOOD
	SEDIMENT (MICROSCOPIC)		NITRATE
X	PROTEIN	X	UROBILINOGEN
	USMOLALITY	X	NITRITES
X	COLOR		

RESULTS

THERE WERE NO DIFFERENCES OBSERVED AMONG THE GROUPS OF EITHER SEX IN ANY OF THE MEASURED PARAMETERS.

6. GROSS PATHOLOGY: ALL ANIMALS WERE SUBJECTED TO A FULL MACROSCOPIC EXAMINATION AT SACRIFICE (NO INFORMATION ON WHETHER ANIMALS WERE FASTED OVERNIGHT WAS PROVIDED). THE FOLLOWING ORGANS FROM THE MAIN GROUP WERE WEIGHED: KIDNEYS, LIVER, TESTES/OVARIES, BRAIN, AND THYMUS. ONLY THE LUNG AND EAR TAG WERE TAKEN FROM THE SATELLITE ANIMALS.

RESULTS

THERE WERE TREATMENT-RELATED EFFECTS NOTED AT NECROPSY ON THE LUNGS, KIDNEYS, AND LIVER. WHITE FOCI WERE OBSERVED IN THE LUNGS OF THE TREATED ANIMALS AS FOLLOWS:

	MALES						FEMALES					
	C	10	50	100	150	1000	C	10	50	100	150	1000
WHITE FOCI												
60 DAYS N=10	0					0	0					1
90 DAYS N=15	0	0	2	2	1	8	0	0	0	2	0	6

TWO HIGH-DOSE MALES DISPLAYED KIDNEYS THAT HAD A GRANULAR APPEARANCE, AND ONE OF THESE WAS ALSO NOTED TO BE ENLARGED.

THERE WAS A TREATMENT-RELATED INCREASE IN LIVER AND KIDNEY WEIGHT (ABSOLUTE, RELATIVE TO BODY AND BRAIN WEIGHT).

	MALES			FEMALES		
	Organ wt. (g)	Rel. BW° g/100 g	Rel. BrW° g/100 g	Organ wt.	Rel. BW° g/100 g	Rel. BrW° g/100 g
Dose (mg/kg)	LIVER					
Cont.	23.1	3.7	10.4	9.7	3.2	5.0
10	23.7	3.9	10.7	10.5	3.5	5.4
50	24.2	3.9	11.1	11.4**	3.7**	5.9**
100	24.9	3.98	11.5	11.0*	3.7**	5.7*
150	24.9	4.2**	11.6	10.9*	3.7**	5.8**
1000	28.2**	4.8**	13.2**	11.7**	4.3**	6.2**

	MALES			FEMALES		
	Organ wt. (g)	Rel. BW° g/100 g	Rel. BrW° g/100 g	Organ wt.	Rel. BW° g/100 g	Rel. BrW° g/100 g
Dose (mg/kg)	KIDNEYS					
Cont.	4.1	0.63	1.8	1.9	0.65	1.0
10	4.3	0.66	1.9	2.2	0.72	1.1
50	4.2	0.61	1.9	2.1	0.71	1.1
100	4.4	0.64	2.0*	2.2**	0.74**	1.2**
150	4.6*	0.66	2.1**	2.1	0.71	1.1
1000	5.1**	0.66	2.4**	2.1	0.77**	1.1

* $P<0.05$; ** $P<0.01$; ° relative weights g/100 g body weight

7. Histopathology: The following organs/tissues (checked (X)) were preserved from all animals at terminal sacrifice, except the satellite animals; only the lungs and ear with tag were taken.

	Digestive system		**Cardiovasc./Hemat.**		**Neurologic**
	Tongue	X	Aorta	X	Brain
X	Salivary glands	X	Heart	X	Periph. nerve
X	Esophagus	X	Bone marrow	X	Spinal cord
X	Stomach	X	Lymph nodes*	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes with optic nerve
X	Jejunum	X	Thymus		**Glandular**
X	Ileum		**Urogenital**	X	Adrenals
X	Cecum	X	Kidneys		Lacrimal gland (Harderian)
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	X	Testes	X	Parathyroids
X	Liver	X	Epididymides	X	Thyroids
	Gall bladder	X	Prostate		**Other**
X	Pancreas	X	Seminal vesicle	X	Bone (femur & sternum)
	Respiratory	X	Ovaries	X	Skeletal muscle
	Trachea	X	Uterus	X	Skin
X	Lung	X	Cervix	X	All gross lesions and masses
	Nose	X	Vagina		Head
	Pharynx		Oviduct		Coagulating gland
	Larynx			X	Ear and ear tag

* mesenteric & cervical

RESULTS

LUNG: THERE WAS A DOSE-RELATED INCREASE IN THE INCIDENCE AND SEVERITY OF ACCUMULATION OF FOAMY MACROPHAGES IN THE LUNG, WHICH CORRELATED WITH INCREASE IN WHITE FOCI OBSERVED AT NECROPSY. THE INCIDENCE WAS STATISTICALLY SIGNIFICANT AT THE HIGH-DOSE LEVEL IN BOTH SEXES, AND THERE WAS A STATISTICALLY SIGNIFICANT TREND AT THE 0.01 LEVEL.

INCIDENCE AND SEVERITY OF ACCUMULATION OF FOAMY MACROPHAGES

MAIN GROUPS	DOSE (MG/KG/DAY)					
N=15	0	10	50	100	150	1000
MALES						
INCIDENCE	5	9	9	9	11	15**
SEVERITY						
MINIMAL	5	8	8	5	7	8
SLIGHT/MILD	0	1	0	4	4	5
MODERATE	0	0	1	0	0	2
FEMALES						
INCIDENCE	4	6	11	8	9	14**
SEVERITY						
MINIMAL	4	6	11	6	8	5
SLIGHT/MILD	0	0	0	2	1	8
MODERATE	0	0	0	0	0	1

SATELLITE GROUPS	DOSE (MG/KG/DAY)			
	MALES		FEMALES	
N=10	0	1000	0	1000
INCIDENCE	5	8	1	6
SEVERITY				
MINIMAL	5	6	1	5
SLIGHT/MILD	0	2	0	1

** $p<0.01$

LIVER: THERE WAS A DOSE-RELATED INCREASE IN THE INCIDENCE AND SEVERITY OF CENTRILOBULAR HYPERTROPHY IN BOTH SEXES, WHICH CORRELATED WITH THE INCREASED LIVER WEIGHT FOUND AT NECROPSY.

INCIDENCE AND SEVERITY OF HYPERTROPHY

MAIN GROUPS	DOSE (MG/KG/DAY)					
N=15	0	10	50	100	150	1000
MALES						
INCIDENCE	0	0	0	7	13	14
SEVERITY						
MINIMAL	0	0	0	6	9	2
SLIGHT/MILD	0	0	0	1	4	9
MODERATE	0	0	0	0	0	3

INCIDENCE AND SEVERITY OF HYPERTROPHY (CONT'D)

MAIN GROUPS	DOSE (MG/KG/DAY)					
N=15	0	10	50	100	150	1000
FEMALES						
INCIDENCE	0	0	0	3	12	15
SEVERITY						
MINIMAL	0	0	0	3	12	6
SLIGHT/MILD	0	0	0	0	0	7
MODERATE	0	0	0	0	0	2

KIDNEYS: THERE WAS A TREATMENT-RELATED INCREASE IN THE INCIDENCE OF EPITHELIAL HYPERPLASIA IN MALES. TWO OF THE ANIMALS AT THE HIGH-DOSE LEVEL HAD KIDNEYS WITH A GRANULAR SURFACE AT NECROPSY. ADDITIONALLY, THE SEVERITY OF THE REGENERATIVE EPITHELIUM OBSERVED IN MALE KIDNEYS INCREASED WITH DOSE.

INCIDENCE AND SEVERITY OF KIDNEY LESIONS

	DOSE (MG/KG/DAY)					
N=15	0	10	50	100	150	1000
MALES						
REGENERATIVE EPITHELIUM						
INCIDENCE	11	12	13	13	12	15
SEVERITY						
MINIMAL	8	3	6	8	4	4
SLIGHT/MILD	2	6	4	4	2	5
MODERATE	1	3	3	1	5	4
MODERATELY SEVERE	0	0	0	0	1	1
SEVERE/HIGH	0	0	0	0	0	1
EPITHELIAL HYPERPLASIA						
INCIDENCE	1	0	1	1	3	5
SEVERITY						
SLIGHT/MILD	1	0	1	1	2	3
MODERATE	0	0	0	0	1	2

THYROID: FOLLICULAR CELL HYPERTROPHY WAS OBSERVED ONLY AT THE HIGH-DOSE LEVEL IN BOTH SEXES. ADDITIONALLY, FOCI OF CLUMPED COLLOID AND CYSTIC FOLLICLES WERE OBSERVED IN THE HIGH-DOSE MALES.

INCIDENCE AND SEVERITY OF THYROID LESIONS

	DOSE (MG/KG/DAY)					
N=15	0	10	50	100	150	1000
MALES						
FOLLICULAR CELL HYPERTROPHY						
INCIDENCE	0	0	0	0	0	13
SEVERITY						
MINIMAL						4
SLIGHT/MILD						9
FEMALES						
FOLLICULAR CELL HYPERTROPHY						
INCIDENCE	0	0	0	0	0	11
SEVERITY						
MINIMAL						7
SLIGHT/MILD						4

INCIDENCE AND SEVERITY OF THYROID LESIONS (CONT'D)

	Dose (mg/kg/day)					
N=15	0	10	50	100	150	1000
CLUMPED COLLOID						
MALES	0	0	0	0	0	13
FEMALES	0	0	0	0	0	1
CYSTIC FOLLICLES						
MALES	0	0	0	0	0	6
FEMALES	0	0	0	0	0	0

DISCUSSION

THERE WERE NO TREATMENT-RELATED EFFECTS ON SURVIVAL OR CLINICAL SIGNS IN EITHER SEX FOLLOWING EXPOSURE TO DCPA FOR 90 DAYS VIA THE DIET. THE HIGH-DOSE FEMALES DISPLAYED SLIGHTLY LOWER BODY WEIGHT/GAIN/FOOD CONSUMPTION. THERE WERE TREATMENT-RELATED EFFECTS ON THE LUNGS, LIVER, AND THYROID OF BOTH SEXES, AND A SLIGHT EFFECT ON THE KIDNEYS OF THE MALES. THE MICROSCOPIC FINDINGS OBSERVED IN THIS STUDY ARE SIMILAR TO THOSE OBSERVED IN THE 2 GENERATION REPRODUCTION STUDY (DER DATED APRIL 1, 1991) AND A 28-DAY FEEDING STUDY ON DCPA (UNDER REVIEW); I.E., FOAMY MACROPHAGES IN THE LUNG, LIVER HYPERTROPHY, KIDNEY AND THYROID EFFECTS. THE DATA SUGGEST THAT INCREASED LENGTH OF EXPOSURE CORRELATES WITH THE INCIDENCE OF THESE EFFECTS, ALTHOUGH NONE OF THE OBSERVATIONS SUGGESTS A PROGRESSION TOWARDS LIFE-THREATENING LESIONS.

CONCLUSION

RATS APPEAR TO TOLERATE DCPA WELL, SINCE AT DOSE LEVELS UP TO 1000 MG/KG, MINIMAL TOXIC EFFECTS ARE OBSERVED. THERE ARE DOSE-RELATED EFFECTS ON THE LIVER (INCREASED WEIGHT AND CENTRILOBULAR HYPERTROPHY), LUNG (INCREASED ACCUMULATION OF FOAMY MACROPHAGES), KIDNEY (INCREASED WEIGHT, EPITHELIAL HYPERPLASIA, TUBULAR HYPERTROPHY, REGENERATIVE EPITHELIUM IN MALES), AND THYROID (FOLLICULAR HYPERTROPHY) FOLLOWING EXPOSURE TO DCPA IN THE DIET AT DOSE LEVELS OF 10, 50, 100, 150, AND 1000 MG/KG/DAY FOR 90 DAYS. THE NOEL CAN BE SET AT 10 MG/KG, THE LEL AT 50 MG/KG, BASED ON INCREASED LIVER WEIGHT. THE LEL FOR MICROSCOPIC FINDINGS WAS 50 MG/KG. NOTE: THERE IS AN ONGOING 2-YEAR CHRONIC TOXICITY/CARCINOGENICITY STUDY IN RATS (INITIATED IN MARCH, 1990), WHICH SHOULD PROVIDE A MORE DEFINITIVE ASSESSMENT OF THE NOEL FOR SYSTEMIC TOXICITY OF DCPA.

THIS 90-DAY SUBCHRONIC FEEDING STUDY IS CLASSIFIED CORE MINIMUM, AND IT SATISFIES THE GUIDELINE REQUIREMENTS (82-1) FOR A SUBCHRONIC FEEDING STUDY IN RODENTS.

Tox Chem No. 382 Dacthal/DCPA | File Last Updated _____ | Current Date May 3, 1991

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	Tox Category	CORE Grade/ Doc. No.
90-DAY ORAL-RAT DEPART. TOX. & ANIMAL METABOLISM/EPL, INC. 3338-89-0208-TX-002 1/22/91	TECHNICAL DCPA (98.0%)	MRID # 417679-01	UNDER THE CONDITIONS OF THE STUDY, THERE WERE NO TREATMENT-RELATED EFFECTS ON SURVIVAL/CLINICAL SIGNS; HIGH-DOSE FEMALES DISPLAYED SLIGHTLY LOWER BODY WEIGHT/FOOD CONSUMPTION COMPARED TO CONTROL; THERE WERE TREATMENT-RELATED EFFECTS ON THE LUNGS, LIVER, & THYROID IN BOTH SEXES, AND EFFECTS IN THE KIDNEYS OF DOSED MALES; THE NOEL CAN BE SET AT 10 MG/KG, THE LEL AT 50 MG/KG, BASED ON INCREASED LIVER WEIGHT; THE LEL FOR MICROSCOPIC EFFECTS WAS 50 MG/KG. THIS STUDY SATISFIES THE GUIDELINE REQUIREMENTS (82-1) FOR A SUBCHRONIC FEEDING STUDY IN RODENTS.		MINIMUM