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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Cacodylic Acid-Carcinogenicity Study in Mice

TO: Betty Crompton
PM Team Reviewer (51)
Generic Chemical Support Branch, SRRD (H7508C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 12/2/91
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 12/10/91
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 12/11/91
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant:	Luxembourg-Pamol, Inc., Memphis, TN
Chemical:	Dimethylhydroxyarsine oxide; dimethylarsinic acid
Synonym:	Cacodylic acid
Project No.:	1-2071
Caswell No.:	133
Record No.:	none. Case: 801418; Submission: S400512
Identifying No.:	012501-042519
MRID No.:	419146-01
Action Requested:	Reregistration data for review.

Comment: The Registrant has submitted a final report of "Cacodylic Acid - Oncogenicity Study in the Mouse", conducted at Life Science Research Israel in response to the Data Call-In Notice for Chronic Toxicological and Ground Water Data for Cacodylic Acid.

The study has been reviewed, and the DER is appended. Treatment of mice with Cacodylic acid at dose levels in the diet of 8, 40, 200, and 500 ppm for 104 weeks did not affect survival, body weight/ body-weight gain, or food consumption in either sex. Water intake was increased in the high-dose males. There were no differences among the groups with respect to clinical observations, gross pathology, and organ weight, with the exception of a dose-related increase in relative liver weight in males at the two highest dose levels, which was not accompanied by any microscopic lesion. There

was an increase in the incidence of vacuolar degeneration of the transitional epithelium of the urinary bladder in both sexes at the 200 and 500 ppm dose levels and in females at 40 ppm. Progressive glomerulonephropathy was increased in both sexes at 500 ppm and in males at 200 ppm. Nephrocalcinosis was increased in males at the high-dose level. With the exception of fibrosarcoma (multiple systems), there was no increase in the incidence of neoplastic lesions in either sex. The incidence of fibrosarcoma in the high-dose females was increased compared to the concurrent control females, was slightly greater than the upper limit noted in the NTP historical control data, and was greater than the range observed at the testing facility.

Based on the lack of any significant effect on body weight/gain, food consumption, clinical signs, and no information on how the dose levels were chosen, TB II concludes that Cacodylic acid has not been tested at a dose level sufficiently high to address its carcinogenic potential. This study does not satisfy the guideline requirement (83-5) for a carcinogenicity study in mice, although it may be upgraded by the submission of (1) an adequate justification for the dose levels chosen, (2) the criteria for exclusion of organ weights from the group means, and (3) an explanation of why the clinical pathology data from all animals was not reported.

Reviewed by: Linda L. Taylor, Ph.D. Linda Taylor 12/2/91
Section II, Tox. Branch II (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 12/10/91
Section II Head, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Carcinogenicity-mouse TOX. CHEM NO: 133

MRID NO.: 419146-01

TEST MATERIAL: Cacodylic acid

SYNONYMS: dimethylhydroxyarsine oxide; dimethylarsinic acid

STUDY NUMBER: Project ID PAL/014/CAC

SPONSOR: Luxembourg Industries (Pamol) Ltd.

TESTING FACILITY: Life Sciences Research Israel Ltd.

TITLE OF REPORT: Cacodylic Acid Oncogenicity Study in the Mouse

AUTHOR(S): E. Gur, A. Nyska, M. Pirak, T. Waner, and S. Crown

REPORT ISSUED: December 24, 1990

Quality Assurance: A quality assurance statement was provided.

CONCLUSION: Based on the lack of any significant effect on body weight/gain, food consumption, clinical signs following treatment of mice with Cacodylic acid at dose levels of 8, 40, 200, and 500 ppm for 104 weeks, and no information on how the dose levels were chosen, TB II concludes that Cacodylic acid has not been tested at a dose level sufficiently high to address its carcinogenic potential. This study does not satisfy the guideline requirement (83-5) for a carcinogenicity study in mice.

Classification: core-Supplementary, pending submission of (1) an adequate justification for the dose levels chosen, (2) the criteria for exclusion of organ weights from the group means, and (3) an explanation of why the clinical pathology data from all animals were not reported.

A. MATERIALS

1. Test compound: cacodylic acid; Description - white crystalline solid; Batch # - 1007; Purity - 99.5%. NOTE: Page 19 indicates this as the %, as provided by the Sponsor; in Table 3, three shipments of Batch # 1007 each indicate the % as 99.8 a.i. on the label.

2. Test animals: Species: mouse; Strain: B6C3F1 hybrid (a cross between C57BL/6NCrlBRxC3H/HenCrlBR); Age: 3 weeks at receipt; Weight: males 4.8-13.9 g, females 6.0-14.3 g (ranges derived from a 10% sample of the incoming mice); Source: Charles River Wiga GmbH, Germany.

NOTE: The protocol indicates that the animals will be obtained from Charles River Breeding Laboratories, USA and that they are derived from C3H/H1 males and C57B1 females. Additionally, body weight is stated to be 10-15 grams on arrival and 15-20 grams at study initiation.

B. STUDY DESIGN

1. Animal assignment

Prior to study initiation, the animals were acclimated for 13 days and 10/sex were sacrificed and subjected to necropsy to assess the health status of the group. The animals were assigned to cages by tables of random numbers; body weights of all animals on test at study initiation were said to be within 20% of the mean number for its sex.

There were 55 mice/sex/group, which were fed diets containing 0, 8, 40, 200, or 500 ppm test material for two years. Terminal sacrifice occurred between Weeks 108 and 112. An additional 16 males/group were designated as protocol spares (treated as those in the main groups) and were incorporated into the study in cases where animals had to be replaced for reasons other than treatment. The unused spares were discarded after 8 weeks of treatment. NOTE: The final report did not state why there were no female protocol spares; the protocol indicated that excessively aggressive males and severely mutilated mice would be replaced. Twelve mice/sex were held as veterinary controls to be used in aiding diagnosis if any outbreak of disease occurred.

The animals had access to feed [Altromin diet 1321N (Altromin International Ltd., Lage, West Germany)] from open cup feeders placed on the cage floor and water (bottles) ad libitum. The mice were housed 4/cage (apparently sexes separately) in Type M2 cages (North Kent Plastics Ltd., UK), which consisted of a polypropylene body and stainless steel grid floor and top.

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2. Diet preparation

Diets were prepared weekly by adding the test material to the basal diet (powdered), mixing, and adding more basal diet to achieve the highest concentration (500 ppm). From this,the lower diet concentrations were prepared by adding additional basal diet to achieve the appropriate concentrations. Samples of treated food were analyzed for stability and homogeneity prior to study initiation (by analysis of 2 samples of each concentration after storage for 10 days in the animal holding room) and concentration at Weeks 1, 2, 4, and 8, and approximately bimonthly thereafter.

RESULTS

Analysis of the diets showed that mixing procedures were adequate, and the prepared diets were found to be stable. The concentrations attained were ±20% of the desired concentrations.

3. Statistics - The following procedures were utilized: body weight, food consumption, water intake, absolute organ weight, and hematology-homogeneity of variances (Bartlett's test); when homogeneous ($p>0.01$), a parametric analysis of variance (ANOVA) was applied; when the F values were significant, Dunnett's multiple range test was applied; when variances were non-homogeneous, analysis was by the Kruskal-Wallis non-parametric ANOVA. If significant difference detected between groups, Dunn's test was applied. Survival-SAS Lifetest Procedure censoring for accidental deaths and scheduled deaths. Organ weights-necropsy body weight used as covariant; multiple 't'-tests applied. Pathology data-methods are described on pages 1064-1066 of the report, copy appended.

C. METHODS AND RESULTS

1. Observations

Each mouse was routinely weighed for the first 13 weeks of treatment, at Week 15, monthly thereafter until Week 95, then weekly. Food consumption was measured weekly for the first 13 weeks of the study for males, for the first 12 weeks and Week 14 for females, and monthly from Week 16 on for both sexes. Water intake was measured weekly (1-13 weeks), then monthly thereafter. Animals were observed daily for signs of ill health and toxicity, and a careful examination (with palpation) was performed at least once a week. Palpable swellings were identified as to location and described as to appearance, consistency, and size.

RESULTS

1. Toxicity/Mortality (survival): There were no clinical signs that could be related to test material exposure. Survival was comparable among the groups for both sexes. The Survival Density Function (SDF) is shown below.

SURVIVAL DENSITY FUNCTION

GROUP	MALES	FEMALES
1	80.0	82.1
2	89.3	87.5
3	89.3	80.0
4	83.7	87.5
5	91.0	78.6

2. Bodyweight

Body weight was decreased in the mid-high and high-dose males, although the magnitude of the change was small. There was no difference in body weight among the females. Body-weight gain was also decreased in males only, but this was of small magnitude also until the latter part of the study.

Body Weight (% of control)				
WEEK/dose	8 ppm	40ppm	200 ppm	500 ppm
MALES				
0	98	101	101	99
1	97	99	100	99
2	100	101	101	100
3	98	98	99	96**
4	98	98	99	97*
7	99	99	98	96**
13	98	99	98	97**
19	98	98	98*	95***
31	97	98	98	94***
51	96	98	98	95**
79	97	100	100	94*
91	97	99	99	93**
95	96	98	98	92***
98	97	100	99	93**
104	96	97	97	91***

Body Weight (% of control)				
WEEK/dose	8 ppm	40ppm	200 ppm	500 ppm
FEMALES				
0	100	100	101	102
1	102	101	102	104**
2	101	99	101	102
3	100	98	101	101
4	101	99	101	101
13	100	99	102	100
51	106*	100	101	99
79	104	99	101	102
91	102	99	101	101
104	104	101	101	98

* p<0.05; ** p<0.01; *** p<0.001

BODY-WEIGHT GAIN (grams)					
Interval Dose	0 ppm	8 ppm	40 ppm	200 ppm	500 ppm
MALES					
0-1	2.8	2.5	2.5	2.6	2.7
0-2	4.2	4.4	4.3	4.3	4.2
0-4	7.2	7.0	6.6	6.9	6.5
0-13	13.0	12.8	12.6	12.3	12.2
0-27	17.7	17.1	16.9	16.8	16.4
0-51	22.6	21.4	21.8	21.8	20.5
0-91	24.0	22.9	23.6	23.4	21.0
0-104	23.1	21.6	21.9	21.8	19.5
FEMALES					
0-1	0.7	1.0	0.8	1.0	1.0
0-2	1.8	1.9	1.6	1.9	1.8
0-4	3.9	4.0	3.7	3.9	3.8
0-13	8.1	8.2	7.8	8.4	7.7
0-27	11.9	12.3	11.5	12.2	11.5
0-51	16.1	18.0	16.0	16.3	15.5
0-91	22.4	23.2	21.9	22.7	22.5
0-104	21.9	23.3	22.3	22.2	20.9

3. Food consumption and compound intake

Consumption was determined and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

RESULTS

In general, there was a decrease in food intake in the treated animals at the start of the study, but there was no dose response observed in either sex. The food conversion ratio did not indicate any difference among the groups of either sex as to the efficiency of food utilization during the first 3 months of the study. The achieved dosages declined during the study due to the reduction in the ratio of food consumption to body weight. The maximum and minimum achieved dosages (mg/kg/day) for each group are shown below.

Dose/Group	8 ppm	40 ppm	200 ppm	500 ppm
MALES	2.1-0.8	9.8-4.2	49.7-20.8	125.7-58.2
FEMALES	2.5-0.9	12.7-4.6	61.9-24.4	151.4-42.6

4. Water intake

Water intake was measured weekly for the first 13 weeks and monthly thereafter (per cage).

RESULTS

There was an increase in water intake in the high-dose males from Week 32 until termination. The next highest dose group also displayed an increase periodically from Week 24 on in males. Females at the highest dose level displayed increased intake on several occasions.

Water Intake (% of Control Value)				
Week/dose	8 ppm	40 ppm	200 ppm	500 ppm
MALES				
1	93	96	96	95
2	97	97	104	96
4	99	93	97	90
13	99	100	95	91
16	101	104	101	100
20	104	104	105	105
24	106	111	112	113
40	102	107	117*	113*
49	112	108	116	119
52	118**	108	115*	117*
56	104	101	111	106
60	102	105	116	122**
64	101	99	111	114**
68	104	102	109	119*
76	99	104	114	119*
80	101	102	106	121***
84	99	102	104	115*
88	98	106	107	114*
92	102	102	109	118***
96	101	106	113	115*
100	101	104	106	111
104	96	97	97	110
FEMALES				
1	105	103	104	102
2	100	106	104	100
4	100	99	102	95
13	98	93*	100	112
16	101	96	106	102
20	103	98	107	101
24	97	102	111	118**
40	91	96	102	98
49	91	98	104	111
52	89*	97	97	106
56	103	102	108	114
60	97	97	106	110
64	95	97	100	104
68	99	101	109	116**
76	93	94	102	104
80	101	102	107	112
84	99	103	105	112**
88	96	103	108	107
92	99	99	105	101
96	97	97	99	101
100	99	102	111	109
104	96	100	103	106

* p<0.05; ** p<0.01; *** p<0.001

5. Ophthalmological examination

None were performed.

6. Clinical Pathology

Blood was collected from the tail of each mouse at 12, 18, and 24 months, and blood smears for differential white blood cell counts were prepared and stained by the modified Romanowsky stain. Only the control and high-dose groups were examined. The following cell types were scored: Neutrophils (N),

Lymphocytes (L), Eosinophils (E), Monocytes (M), Normocytes (NORM).

RESULTS

At 51 and 106 weeks, the high-dose males displayed decreases in the relative number of neutrophils (78 and 83% of control value, respectively). At 79 weeks, control and high-dose males displayed comparable values. Additionally, the high-dose males displayed decreased values for eosinophils and monocytes at weeks 79 and 106 compared to control values, but statistical significance was not attained. High-dose females displayed decreased lymphocytes at week 106 (89% of control value); increased monocytes at all time points, although statistical significance was attained at week 106 only. Increased eosinophils were observed in the high-dose females at weeks 79 and 106, but statistical significance was not attained. NOTE: The data presented show values for 9-10 animals per sex, although the methods section indicated that blood was collected from all mice at each time point.

Clinical Pathology■

	N	L	E	M
MALES/51				
C	26.7	68.9	3.70	0.70
H	20.7* (78%)	74.3 (108)	3.60 (97)	1.40 (200)
MALES 79				
C	30.9	65.4	2.11	1.56
H	30.1 (97)	67.1 (103)	1.56 (78)	1.22 (78)
MALES 106				
C	27.7	65.6	5.10	1.60
H	23.0 (83%)	73.3 (112)	2.50 (49)	1.20 (75)
FEMALES 51				
C	22.7	74.2	2.33	0.78
H	21.3 (94)	76.0 (102)	1.70 (73)	1.00 (128)
FEMALES 79				
C	31.3	65.8	1.80	1.10
H	30.3 (97)	64.9 (99)	3.30 (183)	1.50 (136)
FEMALES 106				
C	18.3	79.4	1.70	0.60
H	24.3 (133)	70.3* (89)	3.00 (176)	2.40** (400)
MH	22.3 (122)	75.1 (95)	1.60 (94)	0.90 (150)

■ #'s are % WBC; (% of control); * p<0.05; ** p<0.01

7. Clinical Chemistry

None was performed.

8. Urinalysis

Urine was not collected.

9. Sacrifice and Pathology

All animals that died or were sacrificed on schedule were subject to gross pathological examination, which included the examination of the external surfaces including all natural orifices, the cranial, thoracic, abdominal, and pelvic cavities, and an examination of the carcass. The brain, kidneys (left and right), liver, and testes (males) were weighed. The CHECKED (X) tissues were collected for histological examination. The kidneys, liver, lungs, parathyroid, thyroid, and urinary bladder were examined microscopically in all animals of both sexes. All other organs/tissues were examined in all control and high-dose animals of both sexes and in all animals dying on test.

X		X		X	
Digestive system		Cardiovasc./Hemat.		Neurologic	
X	Tongue	X	Aorta	X	Brain (3 levels)
X	Salivary glands	X	Heart	X	Periph. nerve (sciatic)
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes*	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes (optic n.)
X	Jejunum	X	Thymus	Glandular	
X	Ileum	Urogenital		X	Adrenal gland
X	Cecum	X	Kidneys		Lacrimal gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	X	Testes	X	Parathyroids
X	Liver	X	Epididymides	X	Thyroids
X	Gall bladder	X	Prostate	Other	
X	Pancreas	X	Seminal vesicle	X	Bone
Respiratory		X	Ovaries	X	Skeletal muscle
X	Trachea	X	Uterus	X	Skin
X	Lung		(corpus/ cervix)	X	All gross lesions and masses
X	Nasal Passages			X	Harderian glands
	Pharynx				
	Larynx				

* cervical, mesenteric, abnormal

RESULTS

a. Organ weight - The absolute and relative liver weight of the low-dose males was significantly decreased compared to the control value, as was the necropsy body weight of this group. The relative liver weight was significantly increased in males at the two highest dose levels, and females of the lowest dose level displayed a significant decrease in both the relative brain and relative liver weight. NOTE: In the tables of individual organ weights, some values are marked as excluded from the group mean values, but there is no information provided as to the criteria applied to determine which values

to exclude.

b. Gross pathology - The findings were said to be comparable among the groups of both sexes and commonly observed in aged B6C3F1 mice. No treatment-related changes were noted.

c. Microscopic pathology - 1) Non-neoplastic: URINARY BLADDER - Vascular degeneration of the superficial cells of the transitional epithelium of the urinary bladder was increased ($p<0.001$) in both sexes, and the increase was dose-related in both sexes (see below). Additionally, a slightly increased incidence of submucosal lymphocytic infiltration was observed in both sexes, but statistical significance was not attained, and there was no clear dose response. It was noted that the lesion is commonly observed in untreated mice.

	MALES					FEMALES				
Dose level (ppm)	0	8	40	200	500	0	8	40	200	500
# urinary bladders examined	54	56	56	53	53	51	53	49	53	53
Transitional epithelium:										
vacuolar degeneration-focal	0	1	0	41	11	1	1	20	4	1
-multifocal	0	0	0	8	37	0	0	0	10	12
-diffuse	0	0	0	1	5	0	0	0	38	40
Submucosa:lymphocytic infiltration	29	37	41	41	35	39	42	39	45	44

KIDNEY - Progressive glomerulonephropathy and nephrocalcinosis showed a positive significant trend ($p<0.05$ and 0.001, respectively) among the males; when combined by sex, the trend persisted ($p<0.01$ and 0.001, respectively). The authors considered these to be treatment-related, and noted that these lesions are consistent with the normal spectrum of spontaneous renal lesions observed in aged B6C3F1 mice. TB II agrees that the test material appears to exacerbate these spontaneous renal lesions of B6C3F1 mice.

	MALES					FEMALES				
Dose level (ppm)	0	8	40	200	500	0	8	40	200	500
# kidneys examined	56	56	56	56	56	56	55	56	56	56
Progressive glomerulonephropathy:										
-slight, subchronic	16	22	17	30	31	4	6	8	5	12
-moderate, subchronic	0	0	1	0	0	0	0	2	0	0
-marked, subchronic	1	0	0	1	0	0	0	0	0	0
-slight, chronic	0	1	0	0	0	0	0	0	0	0
-marked, chronic	0	0	0	0	1	0	0	0	0	0
Nephrocalcinosis: slight, focal	31	25	28	30	46	2	1	1	1	2

DIGESTIVE SYSTEM - There was a dose-related increase ($p<0.05$) in pancreatitis (acute or subchronic) in males, and a significant ($p<0.05$) negative trend in females (see below).

BODY CAVITIES - Mononuclear cell infiltration (focal) of the fat pads was found associated with dose in females and when the data were combined by sex (see below).

Incidence of Non-neoplastic Lesions in Pancreas and Abdominal Wall

	MALES					FEMALES				
Dose level (ppm)	0	8	40	200	500	0	8	40	200	500
# pancreas examined	55	8	9	12	56	54	11	11	9	55
Pancreatitis-acute or subchronic	0	0	1	2	4	6	3	0	0	4
# abdominal walls	18	9	6	12	19	25	14	9	5	29
Fat pads-mononuclear cell infiltration	11	2	4	2	11	16	3	2	0	20

2) Neoplastic - There was a statistically significant increase ($p<0.01$) in fibrosarcoma in the high-dose females (10.7%) observed in the abdominal wall and cavity, which was slightly greater than the NTP's upper limit [NTP: (neuro) fibrosarcoma 0-8%], and greater than the testing facility's range [1.6-2.0]. There was a non-significant positive trend in males. The trend in the data combined by sex was significant also [$p<0.01$]. Fibrosarcoma combined with fibroma as two stages of the same disease was found significant [$p<0.05$] in each sex (NOTE: This statement is not supported by the data with respect to the male). When these two lesion were combined as two forms of the same disease, a significant result [$p<0.01$] was observed in females and in the data combined by sex. No significant result was observed in males.

	MALES					FEMALES					m+f
Dose level (ppm)	0	8	40	200	500	0	8	40	200	500	
# animals examined	56	56	56	56	56	56	55	56	56	56	
ABDOMINAL WALL AND CAVITY fibrosarcoma	0	0	0	0	0	1	0	0	0	0	NS
MULTIPLE ORGANS fibrosarcoma	0	0	2	4	1	2	0	1	1	6**	**
Analyzed by Disease Severity											
Fibroma (auricular)	0	0	0	0	1	0	0	0	0	0	NS
Fibrosarcoma (single/multiple organ)	0	0	2	4	1*	3	0	1	1	6*	**
Combined/Analyzed by Disease Condition Fibroma or Fibrosarcoma	0	0	2	4	2	3	0	1	1	6**	**

* $p<0.05$; ** $p<0.01$; NS=not significant

D. DISCUSSION

The authors concluded that the increase in fibrosarcoma observed in the high-dose females was not related to treatment for the following reasons: (1) only the incidence in the high-dose females deviated (slightly) from the NTP's historical control data; (2) the incidence noted among the treated males was within the NTP range; (3) the overall incidence is relatively low; (4) there was no dose response in the males; and (5) there was no dose response in the intermediate groups. TB II agrees with this assessment of the data.

Treatment of mice with Cacodylic acid at dose levels in the diet of 8, 40, 200, and 500 ppm for 104 weeks did not affect survival, body weight/body-weight gain, or food consumption in either sex. Water intake was increased in the high-dose males at several time points during the study. There was a small decrease in neutrophil counts at Week 51 in the high-dose males. At Week 106, the high-dose females displayed a decrease in lymphocyte count and an increase in monocyte count. There were no differences among the groups with respect to clinical observations, gross pathology, and organ weight, with the exception of a dose-related increase in relative liver weight in males at the two highest dose levels (106-107% of control value), which was not accompanied by any microscopic lesion. There was an increase in the incidence of vacuolar degeneration of the transitional epithelium of the urinary bladder in both sexes at the 200 and 500 ppm dose levels and in females at 40 ppm. Progressive glomerulonephropathy was increased in both sexes at 500 ppm and in males at 200 ppm. Nephrocalcinosis was increased in males at the high-dose level. With the exception of fibrosarcoma (multiple systems), there was no increase in the incidence of neoplastic lesions in either sex. The incidence of fibrosarcoma in the high-dose females was increased compared to the concurrent control females, was slightly greater than the upper limit noted in the NTP historical control data, and was greater than the range observed at the testing facility.

E. CONCLUSION

Based on the lack of any significant effect on body weight/gain, food consumption, clinical signs, and no information on how the dose levels were chosen (other than the statement that they "were selected in consultation with the Sponsor in consideration of the intended human therapeutic dose and known toxicity and pharmacokinetic data, including the results of a preliminary subchronic study, LSRI Schedule No. PAL/013/CAC", TB II concludes that Cacodylic acid has not been tested at a dose level sufficiently high to address its carcinogenic potential. This study does not satisfy the guideline requirement (83-5) for a carcinogenicity study in

mice, although it may be upgraded by the submission of (1) an adequate justification for the dose levels chosen, (2) the criteria for exclusion of organ weights from the group means, (3) an explanation of why the clinical pathology data from all animals was not reported, and (4) clarification of the statement regarding the significance of the incidence of fibrosarcoma combined with fibroma as two stages of the same disease in the male.

RIN # 1921-98

DERs (Reviews)

Page_____ is not included in this copy.

Pages 16 through 19 are not included.

The material not included contains the following type of information:

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