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

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JUL 27 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Carcinogenicity Peer Review of Cacodylic Acid

FROM: Steven Malish, Ph.D. *S. J. Malish 1/20/94*
Review Section IV, Toxicology Branch II
Health Effects Division (7509C)

and

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Manager, Carcinogenicity Peer Review Committee
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Health Effects Division (7509C)

TO: Cynthia Giles-Parker
Product Manager #22
Fungicide-Herbicide Branch
Registration Division (7505C)

and

Jay Ellenberger
Special Review and Reregistration Division (7508W)

THROUGH: Penelope *Penelope* Crisp, Ph.D.
Director, Health Effects Division (7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on December 8, 1993 to discuss and evaluate the weight-of-the-evidence on cacodylic acid [CA] with particular reference to its carcinogenic potential. The CPMC concluded that CA should be classified as a Group B2 - Probable Human Carcinogen, based on increases in urinary bladder tumors (rare tumor type) in both sexes of the Fischer rat and increases in fibrosarcomas (multiple organs) in female B6C3F1 mice. The CPMC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1), based on the total (papillomas and carcinomas) urinary tumors in the rat, both for females alone and for males and females combined.

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SUMMARY

In a two year dietary feeding study in Fischer F344 rats there was an increase in urinary transitional cell bladder tumors with hyperplasia in both sexes. In females, there were statistically significant increases for both carcinomas alone and combined papillomas/carcinomas, and there were also statistically significant trends for both. In males there was a numerical increase in carcinoma alone, which was considered to be biologically significant because of the rarity of this tumor type. It was also noted that both sexes of the rat could have tolerated a higher dose.

In a two year feeding study in B6C3F1 mice there was an increase in fibrosarcomas (multiple organs) in females at the HDT. The incidence of this tumor at the HDT exceeded that of historical controls at the testing facility, but was not statistically significant, although there was a statistically significant trend. There was also non-neoplastic pathology seen in the urinary bladders of male mice similar to that seen in both sexes in the rat study. The dosing in this mouse study was determined to be adequate in males, but not adequate for assessing the carcinogenic potential in females. [Details are provided in Section F. "The Weight of Evidence".]

There was no evidence for mutagenicity when cacodylic acid was tested in Salmonella assay, or mouse lymphoma or mouse micronucleus assays.

The CPRC agreed that the SAR data described in the technical document neither adds nor detracts from the evidence.

There were insufficient data on the presence of crystals or calculi in the bladder to attribute the carcinogenic response as being secondary to the toxicity of the chemical.

The decision to classify cacodylic acid as a Group B2 was based on evidence in two species: increases in urinary bladder tumors (rare tumor type) in both sexes of the Fischer rat and increases in fibrosarcomas (multiple organs) in female B6C3F1 mice.

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A. Individuals in Attendance at the meetings:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Penny Fenner-Crisp

Penny A. Fenner-Crisp

Reto Engler

Reto Engler

William Burnam

William Burnam

Karl Baetcke

Karl Baetcke

Marcia Van Gemert

Marcia Van Gemert

Kerry Dearfield

Kerry Dearfield

Elizabeth Doyle

Elizabeth A. Doyle

Hugh Pettigrew

Hugh Pettigrew

Esther Rinde

Esther Rinde

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Steven Malish¹

Steven J. Malish

Jess Rowland

Jess Rowland

Lori Brunsman

Lori Brunsman

Lucas Brennecke²
(PAI/Clement)

Lucas H. Brennecke

3. Other Attendees:

Karen Whitby (HED)

¹ Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

² Signature indicates concurrence with pathology report.

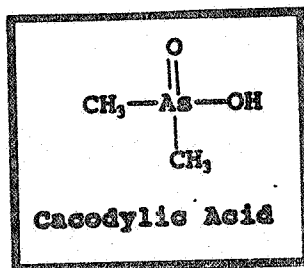
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B. Material Reviewed:

The material available for review consisted of Data Evaluation Records and other data summaries prepared by Dr. Steven Malish, and statistical analyses prepared by Lori Brunsman. The material reviewed is attached to the file copy of this report. A detailed presentation of the data follows.

C. Background Information:

Cacodylic acid (dimethylarsenic acid) is used as a herbicide in non-selective weed control and as a cotton defoliant. The P.C. Code is 012501 and the Caswell No. is 133. The structure of cacodylic acid is shown below:



The Registrant conducted a carcinogenicity study in mice and a combined chronic toxicity/carcinogenicity study in rats.

While the rat study was found acceptable and classified as Core Minimum, the mouse carcinogenicity study was classified as Core Supplementary, since no justification was provided for the doses used. In response to the Agency's classification as supplementary, the registrant submitted a 90-day study in the mouse [MRID 423625-01] that had been used to select the dose levels for the carcinogenicity study. This study demonstrated that the maximum tolerated dose (MTD) was >500 to <2,000 ppm. Following a review of the registrant's response to upgrade the mouse carcinogenicity study, the Agency requested that the mouse study be repeated at 0 and 1000 ppm for both sexes [Memo: S. Malish to B. Driscoe, Oct. 3, 1992].

In response, the registrant has requested the Agency to allow a split dose approach using a dose of approximately 750 ppm for males and 1,000 ppm for females, since at 1000 ppm in males, the MTD may be exceeded due to a delayed or cumulative toxicity. The CPRC was asked to evaluate the need for a repeat mouse study using the split dose approach.

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D. Evaluation of Carcinogenicity Evidence:

1. Carcinogenicity Study in Mouse

Reference: Cacodylic Acid Oncogenicity Study in the Mouse. Study No. PAL/014/CAC. Life Science Research, Israel, Report Issued: December 24, 1990. [MRID 419146-01; HED Doc. No. 008891].

a. Experimental Design

Cacodylic acid was incorporated into the diet of 5 groups of 56 B6C3F1 mice/sex at concentrations, respectively, of 0, 8, 40, 200 and 500 ppm for 104 weeks. These upper limit values correspond to 0, 2, 10, 50 and 126 mg/kg/day for males and 0, 3, 13, 62 and 151 mg/kg/day for females.

b. Discussion of Tumor Data²

The incidence of fibrosarcoma (multiple organs) in the high dose female was increased [6/56; 11%] vs. the control [2/56, 4%] and resulted in a statistically significant [$p < 0.01$] positive trend. This increased incidence was slightly greater than the upper limit noted in the NTP historical control [0 - 8%] and greater than the range observed at the testing facility [1.6 - 2%]. Fibrosarcoma combined with fibroma as two stages of the same disease showed a significant positive trend [$p < 0.01$] in females and in the data combined by sex. No significant neoplastic lesions were observed when only males were evaluated (Table 1).

Table 1. Incidence of Neoplastic Lesions in the B6C3F1 Mouse Fed Cacodylic Acid.

No. with Neoplasms	Male					Female				
	0	8	40	200	500	0	8	40	200	500
Dose Level (ppm)										
No. Examined	56	56	56	56	56	56	56	56	56	56
Abdominal Wall and Cavity Fibrosarcoma	0	0	0	0	0	1	0	0	0	0
Multiple Organs Fibrosarcoma	0	0	2	4	1	2**	0	1	1	6
Combined/Analyzed by Disease Condition Fibroma or Fibrosarcoma	0	0	2	4	2	3**	0	1	1	6

** $p < 0.01$ (trend)

²Note: Statistical analyses provided in the study report for the mouse study were not reanalyzed by HED.

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c. Non-neoplastic Lesions

(i) Urinary bladder

Treatment with cacodylic acid exacerbated the vacuolar degeneration of the superficial cells of the transitional epithelium of the urinary bladder. A pair-wise statistical significance ($p < 0.001$) and dose related increase occurred in the male (200 and 500 ppm) and female (40, 200 and 500 ppm) vs. the respective controls (Table 2). In the rat, cacodylic acid also caused an increase in vacuolar degeneration of the urinary bladder similar to that seen in the mouse. Females were affected at 40 ppm and 100 ppm while males were affected at only 100 ppm (see rat chronic/carcinogenicity study).

Table 2. Incidence of Urinary Bladder Lesions in the B6C3F1 Mouse Fed Cacodylic Acid.

Dose Level (ppm)	Male					Female				
	0	8	40	200	500	0	8	40	200	500
Urinary Bladder Examined (#)	54	53	53	53	53	51	53	48	53	53
Transitional epithelium: Vacuolar degeneration (#)										
-focal	0	1	0	41	11	1	1	20	4	1
-multifocal	0	0	0	8	27	0	0	0	10	12
-diffuse	0	0	0	1	5	0	0	0	38	40
Total (#)	0	1	0	50**	53**	1	1	20**	52**	53**

** $p < 0.01$

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(ii) Kidney

A progressive glomerulonephropathy and nephrocalcinosis showed a positive statistically significant trend ($p < 0.05$ and $p < 0.001$ respectively), among the males (Table 3).

Table 3. Incidence of Kidney Lesions in B6C3F1 Mouse Fed Cacodylic Acid.

No. With Lesions	Male					Female				
	0	8	40	200	500	0	8	40	200	500
Dose Level (ppm)										
Kidneys Examined (#)	54	56	56	53	53	51	53	49	53	53
Progressive glomerulonephropathy (#)	18	22	17	30	31	4	6	8	5	12
-slight, subchronic	0	0	1	0	0	0	0	2	0	0
-moderate, subchronic	1	0	0	1	0	0	0	0	0	0
-marked, subchronic	0	1	0	0	0	0	0	0	0	0
-slight, chronic	0	0	0	0	1	0	0	0	0	0
-marked, chronic										
Total (#)	17*	23	18	31	32	4	6	10	5	12
Nephrocalcinosis: slight, focal (#)	31**	25	28	30	48	2	1	1	1	2

* $p < 0.05$

** $p < 0.01$

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d. Toxicological Effects

Treatment had no adverse effect on survival, body weight and body weight gain in the female, food consumption, hematology, organ weights or gross pathology. Males showed a 16% decrease in body weight gain at the high dose (500 ppm).

e. Adequacy of Dosing for Assessment of Carcinogenic Potential

In the subchronic study, body weight gain was approximately 30% and 15% lower than the controls in males and females, respectively, at the highest dose tested, 2000 ppm. In addition, vacuolar degeneration of the superficial cells of the transitional epithelium of the urinary bladder were seen in both sexes at 500 and 2,000 ppm. In the subchronic study the maximum tolerated dose was between 500 and 2,000 ppm. Based on these findings, the dose levels selected for the carcinogenicity study were 0, 8, 40, 200 and 500 ppm.

In the carcinogenicity study, males at the high dose (500 ppm) exhibited a 16% decrease in the rate of body weight gain while the body weight gain of females was comparable to the controls. The vacuolar degeneration of the superficial transitional epithelium of the urinary bladder did not result in life-threatening toxicity [i.e. early mortality].

Based on these observations, the CPRC considered the dose levels used in the carcinogenicity study to be adequate in male mice for accessing the carcinogenicity potential for cacodylic acid. However, due to the lack of any effect on body weight or other parameters, the highest dose tested was not adequate to fully access carcinogenicity in female mice.

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2. Chronic Toxicity/Carcinogenicity Study in Rats.

Reference: Cacodylic Acid: Combined Chronic Feeding and Oncogenicity Study in the Rat. Study No. PAL/010/CAC. Report Issued: October 30, 1989, Life Science Research Israel, Ltd. [MRID 418621-01; HED Doc. No[s]. 009391, 010550].

a. Experimental Design

Cacodylic acid was incorporated into the diet of 5 groups of 60 Fischer F344 rats/sex at concentrations, respectively, of 0, 2, 10, 40 and 100 ppm for 104 weeks. These values correspond to 0, 0.14, 0.73, 2.8 and 7.3 mg/kg/day in males and 0, 0.16, 0.79, 3.2 and 8.0 mg/kg/day in females. All animals were sacrificed at 104 weeks.

b. Discussion of Tumor Data

Transitional cell neoplasms [papillomas and/or carcinomas] of the urinary bladder were observed in both sexes of rats. The tumor incidences and statistical analyses are presented in Table 4 and 5 for the males and females, respectively.

In males, papillomas were observed at 10 ppm [1/59, 2%] and at 40 ppm [1/57, 2%] while carcinomas were seen at 2 ppm [1/59, 2%] and 100 ppm [2/55, 4%]. None of these tumors showed statistical significance when compared to the controls either in the pair-wise comparisons or the trend test. Neither papillomas nor carcinomas were observed in the controls (Table 4).

In females, no papillomas were observed at any dose except at 100 ppm [4/58, 7%]. Although this increase did not show statistical significance in a pair-wise comparison test, there was a positive trend ($p < 0.01$) for this tumor type. Carcinomas were seen at 100 ppm [6/58; 10%] compared to none in the controls. This increase showed significance both in the pair-wise test ($p < 0.05$) and the trend test ($p < 0.01$) [Table 5].

When papillomas and carcinomas were combined in females, the increase at the high dose [10/58; 17%] was significantly ($p < 0.01$) higher in the pair-wise and trend test analyses (Table 5).

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**Table 4. Male Urinary Bladder Transitional Cell Rates⁺
and Exact Trend Test and Fisher's Exact Test Results
(p values)**

Tumor Type	Dose (ppm)				
	0	2	10	40	100
Papillomas	0/60	0/59	1 ^a /59	1/57	0/55
(%)	(0)	(0)	(2)	(2)	(0)
p =	0.618	1.000	0.496	0.487	1.000
Carcinomas	0/60	1 ^b /59	0/59	0/57	2/55
(%)	(0)	(2)	(0)	(0)	(4)
p =	0.071	0.496	1.000	1.000	0.227
Combined	0/60	1/59	1/59	1/57	2/55
(%)	(0)	(2)	(2)	(2)	(4)
p =	0.105	0.496	0.496	0.487	0.227

⁺Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53

^aFirst papilloma observed at week 106, dose 10 ppm.

^bFirst carcinoma observed at week 54, dose 2 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 5. Female Urinary Bladder Transitional Cell Rates and Exact Trend Test and Fisher's Exact Test Results (p values)

Tumor Type	Dose (ppm)				
	0	2	10	40	100
Papillomas	0/59	0/59	0/57	0/56	4 ^a /58
(%)	(0)	(0)	(0)	(0)	(7)
p =	0.001**	1.000	1.000	1.000	0.057
Carcinomas	0/59	0/59	0/57	0/56	6 ^b /58
(%)	(0)	(0)	(0)	(0)	(10)
p =	0.000**	1.000	1.000	1.000	0.013*
Combined	0/59	0/59	0/57	0/56	10/58
(%)	(0)	(0)	(0)	(0)	(17)
p =	0.000**	1.000	1.000	1.000	0.001**

*Number of Tumor bearing animals/number of animals examined, excluding those that died or were sacrificed before week 53.

^a First papilloma observed at week 107, dose 100 ppm.

^b First carcinoma observed at week 87, dose 100 ppm.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

When compared to the historical control data, the papillomas, carcinomas or the combined tumors in males and females exceed the historical control incidences/range of both the testing laboratory and the NTP [Table 6].

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Table 6. LSRI and NTP Historical Control Data for P344 Rats with Transitional Cell Papilloma and Carcinomas.

	Laboratory's Historical Control Data		NTP Historical Control Data	
	M	F	M	F
No. Examined	306	306	2320	2320
Transitional Cell Tumor Type (#)				
Papilloma	0	0 (0%)	4 (0.2%)	4 (0.2%)
Carcinoma	0	10 (0.17%)	2 (0.1%)	1 (<0.1%)
Total	0	10 (0.17%)	3 (0.3%)	5 (0.2%)

c. Non-neoplastic Lesions

As shown in Table 7, treatment-related non-neoplastic changes seen in the urinary bladder included hyperplasia and vacuolar degeneration of the transitional epithelium and submucosal lymphocytic infiltration. Kidney lesions included pyelonephritis, medullary nephro-calcinosis, medullary tubular cystic dilation, hyperplasia of the epithelium lining of the renal papilla and glomerulonephropathy. Pelvic transitional cell hyperplasia was noted at the high dose in both sexes. A change in the thyroid cell epithelium from a normal flattened to cuboidal epithelium to an abnormal cuboidal to columnar epithelium occurred.

d. Toxicological Effects

Cacodylic Acid did not cause adverse effects on survival, body weight, body weight gain, food consumption, hematology, or clinical chemistry. Treatment did cause an increase in water consumption in both sexes at 40 and 100 ppm and a corresponding increase in the volume of urine excreted at the high dose.

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Table 7. Non-neoplastic Changes in Rats Fed Cacodylic Acid^a

Animals with Lesions [#]	Dose Level (ppm)									
	Males					Females				
	0	2	10	40	100	0	2	10	40	100
Urinary Bladder [# Examined]	60	59	60	58	59	60	59	60	59	60
Hyperplasia	0	0	0	6	40	0	1	0	29	48
Vacuolar Degeneration	0	0	0	1	23	0	0	0	21	26
Submucosal Lymphocytic Infiltration	1	1	0	1	15	2	1	2	5	12
Kidney [# Examined]	60	60	60	59	60	59	60	59	60	60
Pelvic Transitional Cell Hyperplasia	0	0	2	2	12	2	2	0	0	4
Pyelonephritis	0	0	0	0	4	0	0	0	0	0
Medullary Nephrocalcinosis	8	4	3	14	18	7	5	7	7	12
Medullary Tubular Cystic Dilation	0	0	0	3	13	0	0	0	0	5
Epithelial Lining Renal Papilla - Hyperplastic	4	2	8	6	30	8	6	4	0	14
Progressive Glomerulonephropathy	47	46	50	54	52	45	42	42	46	51
Thyroid ^b [# Examined]	59	60	60	60	60	60	60	60	60	59
Cuboidal/Columnar Epithelium	0	1	4	5	37	0	0	0	3	50

^a All degrees

^b Normal epithelium = flattened to cuboidal cells

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e. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dose levels for this study were selected based on the results of a 90 day study in which the LOEL (50 ppm) resulted in alterations in hematology, thyroid weight changes in the female and histopathological alterations in the thyroid.

In this rat chronic/carcinogenicity study, although the highest dose tested [100 ppm] did not elicit the typical systemic toxicity [i.e. mortality, $\geq 10\%$ decrease in body weight gains or clinical signs], this dose did induce non-neoplastic and neoplastic lesions in the urinary bladder in both sexes. In addition, non-neoplastic lesions were also seen in the kidneys and thyroid gland of both sexes. Therefore, the CPRC concluded that the high dose tested in this study was adequate to assess the carcinogenic potential of cacodylic acid in both sexes.

E. Additional Toxicology Data on Cacodylic Acid

1. Metabolism

Reference: Absorption, Distribution and Elimination of ^{14}C -Cacodylic Acid in the Rat. MRID No.423413-01; HED Doc. No.010353

[^{14}C -methyl]Cacodylic acid was administered to Sprague-Dawley CD rats as a single oral dose at 0, 5.0 or 50.0 mg/kg, a 14 day repeated dose regime at 5.0 mg/kg (unlabelled) followed by a single radiolabelled dose and a 5.0 mg/kg i.v. dose. The test material was rapidly and extensively absorbed. Whole blood of the oral dose groups contained approximately 19 to 29% of the administered dose. The radioactivity appeared concentrated mostly in the erythrocytes as cacodylic acid.

Three (3) metabolites were identified: monosodium methanearsonic acid, cacodylic acid and 2 unknowns (C & D). Cacodylic acid was the major urinary metabolite (17 to 20%) in the oral low and high dose groups. Metabolite C (7 to 13%) and Metabolite D (<2%); monosodium methanearsonic Acid ($\leq 1\%$) was present only in the urine of the high dose groups. The repeated dosed groups showed a different urinary profile, Metabolite C (28 to 36%) was the major metabolite followed by cacodylic acid (12%) and Metabolite D (6 to 8%). Fecal excretion of cacodylic acid in the oral dose groups ranged from 9% to 32%. Fecal Metabolite C ranged from 0.3% to 6% while fecal Metabolite D ranged from 0 to 0.3% [MRID 423413-01; HED Doc. No. 010353].

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2. Mutagenicity

Reference: Mutagenicity Studies with Cacodylic Acid

Salmonella Assay [MRID #41892706]; Mouse Lymphoma Assay [MRID #41892707]; Mouse Micronucleus Assay [MRID #41892708] HED Doc. No. 009562

In studies submitted to OPP, cacodylic acid was negative in the Salmonella, the mouse lymphoma gene mutation assay at the TK locus, and the mouse micronucleus assay. These three tests satisfy the current mutagenicity initial battery. The NTP also reported cacodylic acid to be negative in the Salmonella assay.

While there is little concern for the genotoxic potential for cacodylic acid based on this evidence, it is noted that other arsenic containing compounds [e.g. arsenic acid, arsenic pentoxide, potassium arsenite, sodium arsenate, sodium arsenite] all have been found to produce chromosomal aberrations in cultured mammalian cells.

3. Subchronic and Chronic Toxicity

Reference: Cacodylic Acid: Toxicity in Dietary Administration to Mice for 13-Weeks. MRID No. 423625-01; HED Doc.No.009775

Six groups of 12 mice/sex of the B6C3F1 strain were administered cacodylic acid at concentrations admixed in the feed at 0, 5, 50, 500, 2000 or 5000 ppm for 13 weeks. [MRID 423625-01, HED Doc. No. 009775]

Animals at 5000 ppm died or were sacrificed in extremis within 8 weeks of the start of the study. No mortality was noted at the lower dose levels. At the 2000 ppm dose level, a decrease in the rate of body weight gain of approximately 30% in males and 15% in females occurred together with a 17% increase in food consumption in the females versus the controls. A decrease in the efficiency of food conversion was seen in the males at the 500 and 2000 ppm dose levels. An increased water intake occurred in males at 500 ppm. Males at 200 ppm and females at 500 ppm showed periodic increases in water intake. Urine output was not measured. Vacuolar degeneration of the superficial cells of the transitional epithelium of the urinary bladder was seen in both sexes at 500 and 2000 ppm. Under the conditions of this study, the NOEL was 500 ppm. The LOEL of 500 ppm was based on histopathological lesions of the urinary bladder.

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Reference: Cacodylic Acid: Toxicity in Dietary Administration to Rats for 13 Weeks. MRID No. 427677-01; HED Doc. No. 010550

Cacodylic acid was incorporated into the diet of 6 groups of 60 Fischer F344 rats per sex at concentrations, respectively, of 0, 5, 50, 500, 2000 or 5000 ppm for at least 13 weeks [MRID 427677-01; HED Doc. No. 010550].

All rats treated with 2,000 or 5,000 ppm died or were sacrificed during the first 5 weeks of treatment. Body weight gains in both sexes were depressed at 500 ppm. Slightly decreased hematological parameters (hematocrit, hemoglobin, red blood cell count and MCHC and MCV (females) occurred in both sexes at 500 ppm. Females at 50 ppm showed a slight decrease in hemoglobin and red blood cell values versus the controls. A compensatory increase in the reticulocyte count occurred at 500 ppm in both sexes. The thyroid gland in the female showed a dose related decrease in the absolute and relative weights. At 50 and 500 ppm the thyroid presented hypertrophic follicular epithelium in both sexes. At 500 ppm, a reduced volume of smooth muscle of the uterus occurred; hyperplasia of the epithelium lining the renal papilla associated with papillary necrosis was seen. Pathological changes were also seen at 500 ppm in the aorta (focal medial mineralization), bone marrow (reduced cellularity), heart (subchronic myocarditis). The absolute weight of the testes was decreased and germinal epithelium degeneration and reduced sperm occurred. In this study, the NOEL was 5 ppm. The LOEL of was 50 ppm was based on alterations in hematology parameters, organ weight changes and histopathological changes of the urinary bladder.

Reference: Cacodylic Acid: Combined Chronic Feeding and Oncogenicity Study in the Rat. Study No. PAL/010/CAC. Report Issued: October 30, 1989, Life Science Research Israel, Ltd. [MRID 418621-01, HED Doc. No[s]. 009391, 010550].

In the chronic toxicity/carcinogenicity study in rats discussed in detail earlier, cacodylic acid did not cause toxicological [no adverse effects on survival, body weight or clinical signs] or pharmacological [no changes in hematology or clinical chemistry] effects. Treatment caused non-neoplastic lesions in the urinary bladder, kidneys and thyroid gland. Under the conditions of this study, for chronic toxicity, the NOEL was 2 ppm [0.14 mg/kg/day] for males and 10 ppm [0.79 mg/kg/day] for females. The LOEL, based on non-neoplastic lesions of the urinary bladder was 10 ppm [0.73 mg/kg/day] for males and 40 ppm [3.2 mg/kg/day] for females.

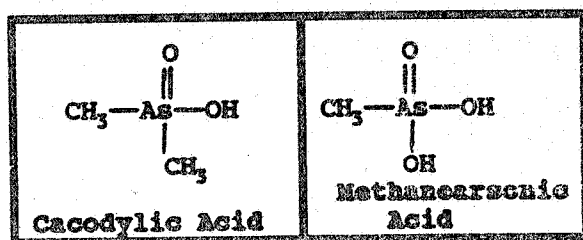
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Reference: Cacodylic Acid: 52-Week Oral Toxicity Study in Beagle Dogs. MRID No. 414909-01; HED Doc.No. 010630

In a chronic toxicity study, beagle dogs [4/sex/dose] received gelatin capsules containing cacodylic acid at 0, 6.5, 16 or 40 mg/kg/day, 6 days/week for 52 weeks. Decreases in body weight gain occurred in males at 40 mg/kg/day while body weight and body weight gain decreased in females at this dose. Males at 40 mg/kg/day exhibited decreases in total protein and albumin at 12, 25, 39 and 51 weeks while females at this dose showed decreases in albumin on week 39 and total protein on week 51. Decreases in HCT, HgB and RBC occurred in males at 40 mg/kg/day at weeks 12 and 25 [dose-related] and in week 51. Based on these results, the NOEL was 16 mg/kg/day and the LOEL, based on clinical signs, body weight changes and alterations in hematology and clinical chemistry parameters, was 40 mg/kg/day.

4. Structural Activity Correlation

Methanearsonic acid [$\text{CH}_3\text{AsO}(\text{OH})\text{OH}$], a monomethyl arsenic compound, related to the dimethyl arsenic compound, cacodylic acid [$(\text{CH}_3)_2\text{AsO}(\text{OH})$] was the only organic arsenical found in the literature that is currently used as a herbicide.



A structurally related compound, methanearsonic acid, administered for 24 months in feed to male and female C3B6F1 mice, respectively, at 0, 1.8, 9.3, 38 and 83 mg/kg/day and 0, 2.2, 12, 46 and 104 mg/kg/day showed no carcinogenic effect. Signs of toxicity occurred in the high dose males and intermediate and high dose females after 10-12 months of treatment (decrease in body weight gain, increased food consumption in the females, and slight, diffuse cuboidal and squamous metaplasia in the rectum).

Methanearsonic acid administered in the feed to SD rats for 24 months at 0, 25, 50, 100 and 200 ppm produced a statistically significant increase ($p < 0.01$) in thyroid adenomas in the male at the high dose level. No lesions were seen in the females. Hemosiderin deposition, ovarian follicular cysts and nephrosis also occurred at the highest dose tested.

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F. Weight of Evidence Considerations:

1. Male and female B6C3F1 mice were fed diets containing cacodylic acid at doses of 0, 8, 40, 200 or 500 ppm for 2-years. The high dose level [500 ppm] in the male [but not the female] was judged adequate for determining the carcinogenic potential. A markedly increased incidence of vacuolar degeneration [similar to that in the rat study below] occurred in males at 200 and 500 ppm and in females at all dose levels except the control. Neoplastic lesions [multiple organ fibroma and/or fibrosarcoma] occurred at 40, 200 and 500 ppm in the male and 500 ppm in the female. The neoplastic lesions showed a statistically significant trend [$p < 0.01$] in the females. When the incidence of the neoplastic lesions were combined [both sexes] at 200 and 500 ppm, a statistically significant trend [$p < 0.05$] was also seen; these increases were greater than the performing laboratory's range and NTP historical control range.
2. Male and female Fischer F344 rats were fed diets containing cacodylic acid at doses of 0, 2, 10, 40 or 100 ppm for 2-years. The males could have tolerated a higher dose; the high dose in the females were judged adequate for determining the carcinogenic potential.

In the male, an increased incidence of tumors as evidenced by papillomas/carcinomas of the transitional cell epithelium of the urinary bladder occurred at all dose levels except the controls. Even though statistical significance was not seen at any dose level, these tumors types were considered to be of toxicological significance because of their rarity in the rat population. A markedly increased incidence of hyperplasia and vacuolar degeneration of the transitional epithelium occurred at 100 ppm. Individual tumor incidences [papillomas, carcinoma] and the total combined incidences were greater than the performing laboratory's and NTP historical control ranges.

In the female rats at 100 ppm, an increased incidence of rare tumors similar to that in the male rat presented as carcinomas (statistically significant by pair-wise [$p < 0.05$] and trend [$p < 0.01$] analyses) and papillomas (statistically significant by trend [$p < 0.01$] analyses). A markedly increased incidence of vacuolar degeneration and hyperplasia of the transitional epithelium occurred at 40 and 100 ppm. Pairwise [$p < 0.01$] and trend [$p < 0.01$] analyses also showed a statistically significant increase when papillomas and carcinomas were combined. Individual tumor incidences [papilloma, carcinoma] and the total combined incidence were greater than the performing laboratory's and NTP historical control ranges.

3. Insufficient data on crystals or calculi existed to attribute the carcinogenic response as being secondary to the toxicity of the chemical.

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4. In a published study, no evidence of neoplasia was seen in mice at 121 mg/kg/day administered cacodylic acid in the diet for 18 months (J. Nat. Can. Inst. 42:1101-14, 1972). The dose used in this study was similar to the high dose used in the above mouse study.
5. Cacodylic acid was shown to be not mutagenic in the *in vitro* *Salmonella* and mouse lymphoma gene mutation assays with and without metabolic activation and in the *in vivo* mouse micronucleus test. Mutagenicity data for similar organic compounds was limited. Based on this evidence, there was little concern for the genotoxic potential of cacodylic acid. However, inorganic arsenic containing compounds [e.g. arsenic acid, arsenic pentoxide, potassium arsenite, sodium arsenate, sodium arsenite] all have been found to produce chromosomal aberrations in cultured mammalian cells.
6. A structurally-related compound, methanearsonic acid, administered for 24 months in feed to male and female C3B6F1 mice, respectively, at 0, 1.8, 9.3, 38 or 83 mg/kg/day and 0, 2.2, 12, 46 and 104 mg/kg/day showed no carcinogenic effect. Signs of toxicity occurred in the high dose males and intermediate and high dose females after 10-12 months of treatment and included diffuse cuboidal and squamous metaplasia in the rectum.
7. Methanearsonic acid administered in the feed to SD rats for 24 months at 0, 25, 50, 100 or 200 ppm produced a statistically significant increase ($p < 0.01$) in follicular cell adenomas of the thyroid in the male at 200 ppm. No alterations were seen in the females.
8. Carcinogenicity in animals -- Cacodylic Acid

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the Committee concludes that exposure to cacodylic acid resulted in an increased incidence of bladder tumors (malignant carcinomas and/or combined papillomas/carcinomas) in both sexes of rats. The relevance of these data to an evaluation of cacodylic acid's potential for human carcinogenicity is discussed elsewhere in this document.

G. Classification of Carcinogenic Potential:

The CPRC considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The CPRC agreed that cacodylic acid should be classified as a Group B2 - probable human carcinogen. This decision was based on increases in urinary bladder tumors in both sexes of the Fischer rat and increases in fibrosarcomas (multiple organs) in female B6C3F1 mice. In the female rat there were statistically significant increases in carcinomas of the urinary bladder; in males there was only a numerical increase for the same tumor, which was nevertheless considered to be significant, due to the rarity of this tumor type. Furthermore, the doses used in the rat study were considered to be adequate, but the rats could have tolerated a higher dose. There was also non-neoplastic pathology in the urinary bladders of male mice, similar to that seen in both sexes in the rat study, and the dosing in the female mouse was not considered to be adequate.

The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1^*), based on the total (papillomas and carcinomas) urinary tumors in the rat, both for females alone and for males and females combined.

The CPRC concluded that there is no need to repeat the mouse study, since there are adequate data for performing Risk Characterization, based on the urinary bladder tumors in the rat.