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Item ID Number	04260	☐ **Not Scanned**
Author	Albert, Roy E.	
Corporate Author		
Report/Article Title	The Carcinogen Assessment Group's Preliminary Report on Cacodylic Acid	
Journal/Book Title		
Year	0000	
Month/Day		
Color	☐	
Number of Images	0	
Description Notes	Alvin L. Young filed these documents together under the label, "Arsenic/Cacodylic Acid and Herbicide Blue".	

ALBERT, ROY E.

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THE CARCINOGEN ASSESSMENT GROUP'S

PRELIMINARY REPORT ON

CACODYLIC ACID

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EPA Literature on Cacodylic Acid.

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I. SUMMARY

Cacodylic acid (dimethylarsinic acid) is a non-selective herbicide used for the control of weeds, cotton defoliation, hard wood trees and suppression of bark beetles. It is not mutagenic to Salmonella typhimurium strains either with or without the mammalian metabolic activation system. Cacodylic acid is rapidly absorbed and excreted in the rat without extensive molecular alteration following a single intravenous injection, intratracheal instillation or gavage. However, slight but statistically significant demethylation was demonstrated by detecting ^{14}C-carbon dioxide, a metabolite of ^{14}C-dimethylarsinic acid in the expired air.

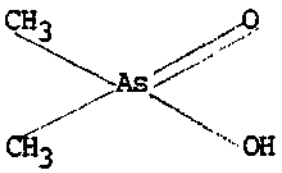
The carcinogenicity of cacodylic acid was examined by Innes, et al. in a study (1969) sponsored by the National Cancer Institute. In the Innes feeding study, utilizing two strains of mice, a statistically significant difference in the total number of tumor-bearing animals or of tumors produced at specific sites did not exist between the cacodylic acid treated and control groups of mice. In the Innes subcutaneous study, using the same two strains of mice, the incidence of tumors in treated groups was again not found to be significantly different than the control groups.

While there is no direct evidence that cacodylic acid is a carcinogen, there is room for apprehension in this regard on the following grounds. There is substantial evidence that the inorganic arsenic is carcinogenic in humans for the skin by ingestion and lung and skin by inhalation. The evidence is strongest for trivalent inorganic arsenic but also suggestive for pentavalent inorganic arsenic. Inorganic arsenic has been tested extensively in rodents for carcinogenicity with negative results. This raises the question whether rodents are an appropriate test organism for any form of arsenic, whether inorganic or organic. The extent to which cacodylic acid is degraded in the body to inorganic arsenic is not clearly established, although there is some evidence that, if such a metabolic pathway exists, it is not large. In the absence of epidemiological data, the extent of metabolism of cacodylic acid to inorganic arsenic is the central issue in the risk assessment because negative animal bioassay is not convincing that cacodylic acid is innocuous. It should also be noted that there is a possibility that inorganic arsenic derived from cacodylic acid may significantly elevate the inorganic arsenic in food.

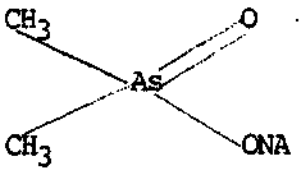
II. INTRODUCTION

The organoarsenical compound, cacodylic acid is a widely used non-selective herbicide. The prefix "cac" or "caco" is derived from the Greek word Kakos meaning bad. The Greek word kakodes means maloderous. Cacodyl refers to an arsenical radical $As(CH_3)_2$ whose compounds are noted for their vile smell and poisonous properties. Thus cacodylic acid has become a common name for dimethylarsinic acid. It is a colorless, crystalline compound. Its melting point is 195-196°C. It is very soluble in water and ionizes to cacodylate anion $(CH_3)_2\ AsO_2$ which is very stable and readily interchanges with cations to form salts.

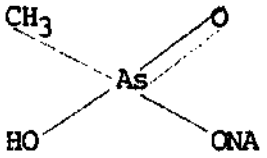
The technical product is 65% aqueous cacodylic acid. Water is the principal solvent in formulations and sodium cacodylate is usually the minor active ingredient. The commercial formulations contain 20 to 50% cacodylic acid. The formulation containing 50% cacodylic acid is used as a arborocide. Another formulation available contains cacodylic acid in combination with monosodium methane arsonate (MSMA) as the active ingredients. The chemical structure of these ingredients are:



Cacodylic acid



Sodium Cacodylate



Monosodium methane arsonate

Cacodylic acid is a non-selective herbicide used for the control of weeds, grasses along roads, rights-of-way, for cotton defoliation, for control of hardwood trees and for suppression of bark beetles. The Code of Federal Regulations (section 180, 311) specifies the tolerance levels for cacodylic acid, calculated as As_2O_3. They are: 28 ppm in or on cotton seed; 1.4 ppm in the kidney and liver of cattle, and 0.7 ppm in the meat, fat and meat products (except kidney and liver) of cattle.

The acceptable daily intake (ADI) for cacodylic acid has not yet been established.

III. METABOLISM

Few investigators have studied the metabolism of cacodylic acid. In summarizing the conclusions of these studies, it should be possible to suggest the metabolic fate of cacodylic acid.

Hwang and Schanker (1973) studied the metabolic fate of cacodylic acid in rats after oral administration. The results indicated that cacodylic acid was absorbed from the small intestine and the half time of absorption was calculated to be 1.5 to 3.4 hrs. The cacodylic acid appeared to be absorbed by simple diffusion. The absorption process did not show evidence of saturation when the concentrations tested ranged from 1 to 100 mM (100 fold increase). The absorption rates of cacodylic acid and other organic arsenicals did not appear to be related to molecular size. Therefore, it was unlikely that passage through membrane pores was an important pathway.

In another study (Peoples 1963), excretion of cacodylic acid in the cow was found to occur primarily via the urine (75-80%). A balance between intake and output was established 30 days after feeding at 24.5 mg/day.

Overby and Frost (1962) demonstrated that arsenic found in swine liver in diets fed to rats was rapidly excreted by the rats. Three types of diets were used. The control diet was composed of acetone - dried liver powder. The tissue-arsenic diet consisted of liver powder obtained

from swine fed arsanilic acid. Control liver-powder plus 3.3 mg of As_2O_3/100g constituted the inorganic-arsenic diet. The amount of elemental arsenic contained in these diets was less than 0.1 ppm for the control, 6.0 ppm for the tissue bound arsenic and 6.5 ppm for the inorganic arsenic diet. Rats were fed ad libitum one of the three diets in a 7-day cycle. Feeding was continued with some animals for up to 42 days. The diets, the daily feces and urine were analyzed for total arsenic.

The metabolic inertness of arsenic bound to liver was demonstrated by the fact that 97% of the tissue-bound arsenic was excreted during the feeding period and the following 7-day control period. However, only about 50% of the inorganic arsenic was excreted during the same period under the same test conditions. The results of this investigation appear parallel to the results of an earlier study, (Coulson et al. 1935), in which "shrimp arsenic" was reported to be retained by rats at much lower levels than inorganic arsenic.

The strength of the tissue-arsenic bond is emphasized by the fact that liver-bound arsenic was not easily solubilized in vitro by the usual chemical or biochemical digestion methods. Combustion to ashes was necessary to convert tissue arsenic to a form that could be readily reduced as distilled arsine.

Jacobson et al. (1972) have demonstrated that cacodylic acid reacts with various SH-containing materials that are

commonly used in enzyme-catalyzed reactions, such as 2 mercaptoethanol, cysteine, glutathione and dithiothreitol. Further, authors have stated that cacodylic acid is in the arsenous class of compounds, with the arsenic in the 3+ oxidation state such as sodium arsenite which has also been shown to react with dithiothreitol.

Recently, Stevens et al. (preprint 1977) studied the distribution, excretion, and possible metabolism in rats of ^{14}C and/or ^{74}As cacodylic acid following a single intravenous injection, intratracheal instillation or gavage. Male Sherman rats were dosed at levels ranging from 120 mg/kg to 200 mg/kg.

The extent and rate of lung absorption was greater than gastrointestinal absorption. Concentrations in the liver and whole blood were found to be higher after oral dosing than intravenous administration. The levels of labelled cacodylic acid observed in plasma and other tissues were similar after all three routes following the absorptive phase. The percent dose found in the whole blood, red blood cells, and plasma was similar for all doses given by these routes. Less than 0.1% of the dose was recovered as $^{14}CO_2$ by any route 24 hours after administration. Twenty-four hours after intravenous, intratracheal, or oral administration, 71, 60, or 25% of the cacodylic acid was excreted respectively in the urine. After intravenous administration of 200 mg/kg, sufficient ^{14}C-cacodylic acid was recovered in the bile to account for the small

amount excreted in the feces. Cacodylic acid is probably not metabolized to inorganic arsenic since the disposition of ^{14}C and ^{74}As-cacodylic acid were identical.

Kinetic analysis of the plasma curve for ^{14}C-cacodylic acid (high dose) yielded three half-times; 0.014, 0.214 and 3.42 hour with an apparent volume of distribution of 15.3 ml. The highest initial concentrations were found in the whole blood, muscle, kidney, liver and lung. Levels in all tissues decreased rapidly, but remained high in whole blood. The red blood cells were found to be the major site of cacodylic acid accumulation.

Woolson and Kearney (1973) conducted an extensive study on fate of cacodylic acid in soil. According to them, cacodylic acid appears to be degraded to inorganic arsenate. This inorganic arsenic may find its way into edible crops. There is evidence from clinical observation and occupational and population studies that inorganic arsenic is carcinogenic in humans for the skin by ingestion and lung and skin by inhalation. (National Academy of Sciences (1976).

IV. MUTAGENESIS

Anderson et al. (1972) studied the genetic effect of cacodylic acid in histidine-requiring mutants of Salmonella typhimurium (Ames test). Cacodylic acid did not induce reversion to histidine independence. The test results indicated that cacodylic acid did not possess a potential for causing gene (point) mutations in this system.

Two similar studies of the genetic effect of cacodylic acid -- one conducted by Microbiological Associates under the sponsorship of the Ansul Company Weslaco (1975) and another study performed by Stanford Research Institute for the E.P.A. (Simmon et al. 1976) - confirmed the Anderson Findings. Both studies observed negative results using the Ames test with or without metabolic activation using a mammalian microsomal enzyme system.

V. TOXICOLOGY

Animal Toxicity

The acute oral toxicity (LD_{50}) for rats reported for cacodylic acid ranged from 0.7 to 2.6 g/kg for males versus 1.28 g/kg for females (Palazzolo, 1975). When weanling rats were fed at diets containing 10, 20, and 40% of the estimated oral LD_{50}, (0.70 g/kg), little effect was noted on the various tissues examined except for reduced activity of spermatogonia cells at the 40% treatment level. Subacute toxicity tests (90 days) indicated that dietary cacodylic acid was nontoxic at 100 ppm to rats.

In rabbits given a dermal application of cacodylic acid, 77% exhibited mortality at lower dose levels when the skin was abraded than when it was intact. With abraded skin, a dose of 1.0 g/kg was lethal for the rabbit; whereas with intact skin, death did not occur until the dose reached 2.5 g/kg.

Subacute (dietary) toxicity tests were conducted in dogs (Derse, 1968). Thirty-two beagle puppies were divided into 4 groups of males and 4 groups of females, 4 in each group. One group of each sex was used as a control and the other 3 groups of each sex were given dietary levels of cacodylic acid of 3, 15, or 30 ppm. Both weights were recorded weekly; kidney and liver function tests and urinalysis were conducted after 90 days feeding. Mortality was not evident in any of the test groups. No differences in body weight at 30 ppm were observed with the exception of a slower weight gain for females.

Hematological differences between the treated and control groups were not detected and no apparent hematological differences between control and treated animals were discernible. Some lesions were observed in the brain, heart, liver, kidney, spleen, intestine and other organs, but the lesions were randomly scattered in both control and treated animals and were not considered to be associated with the dietary supplementation of cacodylic acid.

VI. CARCINOGENICITY STUDIES

Innes et al. Carcinogenicity study (1969)

Cacodylic acid [a/] was evaluated for possible carcinogenic activity in the Innes carcinogenesis study of 171 compounds (Bionetics 1968). In this study, they used two strains of mice: strain A mice were hybrids from a cross of C57Bl/6 and C3H/Anf mice; strain B mice were hybrids from a cross of C57Bl/6 and AKR mice. Two separate routes of administration were used: (1) a single subcutaneous injection, 464 mg/kg at 28 days of age and (2) oral feeding of the compound. Initially a daily dosage of 46.6 mg/kg of cacodylic acid was given in distilled water from 7 to 28 days. Thereafter, the test material was incorporated in food at a level of 121 ppm and fed ad libitum for nearly 18 months. At the end of this period, the animals were sacrificed and examined grossly. Histologic examinations were made of several organs and of all visible lesions.

The observed tumor incidences are presented in Tables I, II, and III. In most of the cases, tumors were found in many sites in treated groups as well as in controls. The tumor incidences in the treated group were compared with matched and pooled controls. The matched control is defined to include all of the untreated control groups which were housed in the room where the chemical was tested plus the vehicle control group which received the solvent or medium that contained the test compound administered to the treated groups. The pooled control group is defined as the sum of all the untreated controls for the route of administration considered, plus the one vehicle control that corresponds to the vehicle used in the test compound.

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a/ Cacodylic acid obtained from Fisher Co. M.P. 192-198°C. Purity was not specified.

TABLE I. NUMBER OF MICE WITH TUMORS FROM ORAL ADMINISTRATION OF CACODYLIC ACID FOR 18 MONTHS

DOSE	STRAIN A MALE	FEMALE	STRAIN B MALE	FEMALE
121 ppm	3/18 (17%)	0/18 (0%)	1/18 (6%)	4/18 (22%)
0 (matched)	6/18 (33%)	2/18 (11%)	2/18 (11%)	0/18 (0%)
0 (pooled)	28/72 (39%)	24/72 (33%)	13/72 (18%)	5/72 (7%)

Table I presents the data for the number and percent of strain A and B mice having tumors after being fed 121 ppm of cacodylic acid in the diet for 18 months. The tumor incidence was slightly lower in the treated mice relative to the controls of both sexes of strain A and the male control mice of strain B was higher than that after matched and polled controls. Tumor incidence in this strain was, statistically, slightly less than significant with the following P-values: treated mice vs. matched control $p \leq 0.052$; treated mice vs. polled control, $p \leq 0.075$. Common tumors observed were leiomyosarcoma (uterus), pulmonary adenoma, and reticulum cell sarcoma type A.

TABLE II. NUMBER OF MICE WITH TUMORS FROM SUBCUTANEOUS INJECTION OF SINGLE DOSE OF CACODYLIC ACID

DOSE	STRAIN A MALE	FEMALE	STRAIN B MALE	FEMALE
464 mg/kg	4/18 (22%)	2/18 (11%)	3/18 (17%)	3/18 (17%)
0 (matched)	9/48 (19%)	5/54 (9%)	0/54 (0%)	5/54 (9%)
0 (matched)	16/102 (16%)	8/108 (7%)	5/108 (5%)	11/108 (10%)

The data in table II indicate the number and percent of mice with tumors following a single subcutaneous injection of 464 mg/kg of cacodylic acid. A slight increase in tumor incidence was observed in treated mice as compared to the controls. However, for the treated mice of both sexes of strain A and the treated female mice of strain B the increased tumors were not statistically significant for the number observed in the respective control groups. The treated male mice of strain B had an increase of tumors relative to the control mice. This increased tumor incidence was statistically significant for treated mice vs. matched control ($p \leq 0.03$) and statistically not significant for treated mice vs. pooled control ($p \leq 0.087$). The observed tumors were: 2 mice with reticulum cell sarcoma type A and one mouse with pulmonary adenoma.

TABLE III. NUMBER OF STRAIN B MICE WITH TUMORS FROM BOTH ORAL AND SUBCUTANEOUS ADMINISTRATION OF CACODYLIC ACID

STRAIN B MICE					
	ORAL			SUBCUTANEOUS	
DOSE	FEMALE	MALE	DOSE	FEMALE	MALE
121 ppm	4/18 (22%)	1/18 (5%)	464 mg/kg	3/18 (17%)	3/18 (17%)
0 (matched)	0/18 (0%)	2/18 (11%)	0 (matched)	5/54 (9%)	0/54 (0%)
0 (pooled)	5/72 (7%)	13/72 (18%)	0 (pooled)	11/108 (10%)	5/108 (5%)

Female Strain B mice oral dose

1 leiomyosarcoma (uterus)
1 pulmonary adenoma
2 reticulum cell sarcoma, type A

Female Strain B mice subcutaneous dose

1 leiomyosarcoma (uterus)
1 reticulum cell sarcoma type A
1 pulmonary adenoma

Male strain B mice subcutaneous dose

2 reticulum cell sarcoma type A
1 pulmonary adenoma

The number and type of tumors of strain B mice are described in Table III. The observed tumors were leimyosarcoma (uterus), pulmonary adenoma, and reticulum cell sarcoma type A. The pulmonary adenoma, reticulum cell sarcoma A and leiomyosarcoma (uterus) were found in female mice treated with cacodylic acid as well as in control mice.

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