B4-1.0 CACODYLIC ACID

B4-1.1 Background Information

CACODYLIC ACID Sodium salt **Phytar 560G**

IUPAC: dimethylarsinic acid

CAS: dimethylarsinic acid

CASRN: 75-60-5 CASRN **Sodium salt 124-65-2**

CACODYLIC ACID USAGE

Cacodylic acid, which is also known as dimethylarsinic acid, is an arsenical non-selective contact herbicide which defoliates or desiccates a wide variety of plant species. Historically it has been used as a cotton defoliant, for lawn renovation, weed control in non-crop areas, and in forest management.

Cacodylic acid was only applied on designated plots in CFB Gagetown during the 1966/67 U.S. trials as Phytar 160 or Phytar 560G.

Table B4-1 Cacodylic Acid Usage at CFB Gagetown[a]

Year	Total Cacodylic Acid Applied (kg)	Total Area Treated (ha)
1966	129.9	31.1
1967	20.4	2.4
Total	**1.5E+02**	**3.4E+01**

[a] Adapted from Demaree and Haws, 1968; Demaree and Creager, 1968; and, Demaree *et al*., 1966.
[b] Average maximum yearly application rate (kg/ha).

B4-2.0 CHEMICAL AND PHYSICAL PROPERTIES

Formula: $C_2H_7AsO_2$

Activity: herbicides (arsenical herbicides)

Notes: There is no ISO common name for this substance; the name “cacodylic acid” is approved by the Weed Science Society of America.

Structure:

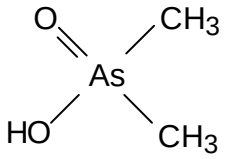

Figure B4-1 Cacodylic acid CASRN 75-60-5

Table B4-2 Chemical and Physical Properties of Cacodylic Acid

Chemical/Physical Property	Result	Reference
Boiling Point	>200°C	Ahrens, 1994
Colour/Form	Colourless to white Crystals	Weast, 1979; Lewis, 1997
Dissociation Constant (pKa)	1.57	Lide, 1996; JW, 2006
Henry's Law constant	$1.8x10^{-14}$ atm·m^3/mol at 25°C	JW, 2006
	0 (non-volatile)	U.S. EPA, 2006a
Log K_{ow}	-1.55	U.S. EPA, 2006a
	0.36	JW, 2006
Melting Point	192-194°C	U.S. EPA, 2006a
	192-198 °C	U.S. National Library of Medicine, 1995
	195 °C	Lide, 2000
Molecular Weight	138 g/mol	EXTOXNET, 1996; Lide, 2000; JW, 2006
Odour	Odourless	Lewis, 1997
Vapour Pressure	0 (non-volatile)	U.S. EPA, 2006a
	$4.6x10^{-3}$ mm Hg at at 25°C[a]	Lyman, 1985
	$1.0x10^{-7}$ mm Hg at 25°C	JW, 2006
Water Solubility	~ 1 to $3x10^6$ mg/L	U.S. EPA, 2006a
	$2x10^6$ mg/L at 25°C	Yalkowsky and Dannenfelser, 1992; JW, 2006

[a] Estimated vapour pressure using the fragment constant method/

Table B4-3 Chemical and Physical Properties of Sodium Cacodylate

Chemical/Physical Property	Result	Reference
Boiling Point	200°C	Farm Chemicals Handlbook, 2001
Colour/Form	Colourless to light yellow Crystalline soild	U.S Coast Guard, 1984; Farm Chemicals Handlbook, 2001
Dissociation Constant (pKa)	6.29	Tomlin, 1997
Molecular Weight	159.98 g/mol	Budavari, 1996
Odour	Odourless	U.S Coast Guard, 1984
Specific Gravity	>1 at 20°C	U.S Coast Guard, 1984
Water Solubility	$2x10^6$ mg/L at 25°C	Tomlin, 1997

B4-3.0 PMRA EVALUATION

No data found.

B4-4.0 TOXICOLOGICAL SUMMARY

B4-4.1 Human Health Effects

Acute dermal exposure to cacodylic acid may cause irritation, burning, itching, skin thickening and colour changes immediately or shortly after exposure (New Jersey Department of Health and Senior Services, 1999). Eye contact may cause irritation and burns, where as breathing cacodylic acid can irritate the nose and throat resulting in coughing and wheezing. Repeated acute exposure can cause a metallic or garlic taste, poor appetite, nausea and vomiting, difficulty swallowing, stomach pain, diarrhea, seizures and death (New Jersey Department of Health and Senior Services, 1999).

Chronic exposure to cacodylic acid can cause an ulcer or hole to form in the bone dividing the inner nose (New Jersey Department of Health and Senior Services, 1999). Hoarseness and sore eyes may also occur. Repeated dermal contact can cause thickened skin and/or patchy areas of darkening and loss of pigmentation. Some people will develop white lines on the nails. Exposure to high concentrations of cacodylic acid and repeated exposure may damage the nerves causing weakness, 'pins and needles', and poor coordination in the arms and legs. Chronic exposure may also damage the liver (New Jersey Department of Health and Senior Services, 1999).

Table B4- 4 Human Health Effects Resulting from Acute and Chronic Exposure to Sodium Cacodylate[a,b]

Exposure	Effects	Response
Acute	Vital Signs	Rapidly hypotensive; tachycardia; pain; hypovolemia; cardiac effects; and, anxiety.
	HEENT	Headache; conjuncitivits; photophobia; dimness of vision; diplopia; lacrimation; irritating and corrosive to the eyes and mucous membranes; and, garlic-odour may be detected on breath.
	Cardiovascular	Ventricular tachycardia; and, ventricular fibrillation.
	Respiratory	Acute respiratory failure; pulmonary edema; and, adult respiratory distress syndrome (ARDS).
	Neurologic	Toxic delirium; encephalopathy; and, peripheral neuropathy.
	Gastrointestinal	Abdominal pain; vomiting; profuse bloody or watery diarrhea; pain in the extremities and muscles; weakness; and, flushing of the skin.
	Hepatic	Hepatocellular damange may occur; and, mitotic activity of hepatocytes.
	Genitournary	Anuria; hematuria; proteinuria; acute tubular necrosis; renal failure; and, chronic renal insufficiency from cortical necrosis.
	Fluid-Electrolyte	Electrolyte imbalances.
	Hematologic	Hemolysis; pancytopenia; isolated leucopenia; and, anemia.
	Dermatologic	Irritating and corrosive to the skin; flusing; diaphoresis; palmar hyperkeratosis; peripheral edema; hyperpigmentation; brawny desquamation; exfoliative dermatitis; transverse white stria of the nails; and, shingles.
Chronic	HEENT	Hair loss; conjunctivitis; photophobia; dimness of vision; diplopia; lacrimation; sensation of burning, dryness and constriction of the oral and nasal cavaties; garlic odour on the breath; and, chronic laryngitis.
	Respiratory	Upper respiratory tract irritation.
	Gastrointestinal	Sensation of burning and dryness of the oral and nasal cavities; and, vomiting.
	Hepatic	Enlarged livers; hepatic cirrhosis; or, noncirrhotic portal hypertension.
	Hematologic	Pancytopenia; isolated leucopenia; anemia; aplastic anemia; and, acute myelogenous leukemia.
	Nuerologic	Toxic delirium; encephalopathy; and, peripheral neuropathy.
	Dermatologic	Irritating and corrosive to the skin; flusing; diaphoresis; palmar hyperkeratosis; peripheral edema; hyperpigmentation; brawny desquamation; exfoliative dermatitis; basal cell and squamous cell cancers of the skin may occur; and, painful irritation or ulceration of the skin (especially wrists and scrotum).

[a] Rumack and Hall, 2006.
[b] MEDITEXT®, 2006.

B4-4.2 Health Effects by Route of Exposure

B4-4.2.1 Oral Exposure

B4-4.2.1.1 Death

Table B4-5 Mammalian Acute LD_{50} Values Resulting from Oral Exposure to Cacodylic Acid

Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Rat	644	Kidd and James, 1991
Rat	830	Weed Science Society of America, 1994
Rat	1,350	Verschueren, 1983
Not specified	2,800	U.S. EPA, 2006b

Table B4-6 Mortality Resulting from Oral Exposure to Cacodylic Acid

Test Organism (Species)	Dose (Duration)	Response	Reference
Acute			
Rabbit (New Zealand white)	48 mg/kg/day (11 days)	Mortality	Rubin and Nyska, 1988

B4-4.2.1.2 Systemic Effects

Table B4-6 Systemic Effects Resulting from Oral Exposure to Cacodylic Acid

Test Organism (Species)	Daily Dose (Duration)	Response	Reference
Chronic			
Mice (B6C3F1)(F)	8.65 mg/kg	Increased vacuolar degeneration of bladder epithelium.	Gur *et al*., 1990
Mice (B6C3F1)(M)	35.25 mg/kg	Increased vacuolar degeneration of bladder epithelium.	Gur *et al*., 1990
Mice (B6C3F1)(M)	91.95 mg/kg	Decreased body weight gains; nephrocalcinosis of the kidney.	Gur *et al*., 1990
Rat (Fischer F344)	0.73-0.79 (2 years)	Increased height of thyroid follicular epithelium (M).	Gur *et al*., 1989
Rat (Fischer F344)	2.8-3.2 (2 years)	Submucosal lymphocytic infiltration (F); transitional cell hyperplasia of the bladder; kidney lesions (pyelonephritis, medullary nephrocalcinosis, medullary tubular cystic dilatation); and, Increased height of thyroid follicular epithelium (F).	Gur *et al*., 1989
Rat (Fischer F344)	7.3-8.0 (2 years)	Decreased %HCT, HGB and RBC (M); decreased %HCT and HGB (F); increased urine volume; increased kidney weights; vacoular degeneration of bladder transitional epithelium; submucosal lymphocytic infiltration (M); pelvic transitional hyperplasia increased (M); and, increased incidence of hyperplasia of epithelium lining in renal papilla.	Gur *et al*., 1989
Dog (Beagle)	40 mg/kg	Increased salivation, vomiting and diarrhea; decreased body weight gains; decreased HCT%, RBC counts; and, total protein albumin concentration (M).	Zomber *et al.*, 1989

B4-4.2.1.3 Neurological Effects

No data found.

B4-4.2.1.4 Reproductive/Developmental Effects

Table B4-7 Reproductive and Developmental Effects Resulting from Oral Exposure to Cacodylic Acid

Test Organism (Species)	Exposure	Dose (Duration)	Response	Reference
Rat (pregnant F)	Oral	0.35 mg/kg/day	Fetal effects: Smaller fetus size; decreased body weight.	Weed Science of America, 1994
Rat (Charles River SD)	Gavage	36 mg/kg/day (days 6 through 15 of gestation)	Fetal effects: decreased weight; shorter crown rump length, suggestion of disaphragmatic hernia; and, delayed ossification of numerous bones.	Gal and Rubin, 1988
			Maternal effects: decreased body weight, body weight gains, food consumption and gravid uterine weights.	
Rat (Charles River CD)	Diet	15.5-17.9 mg/kg/day	Parental effects: lower absolute and relative ovarian weights; and, increased incidence of thyroid follicles line with cuboidal to columnar epithelium (F).	Rubin *et al*., 1989
Rat (M)	Diet	226 mg/kg/day (21 days)	Reduced sperm production.	Weed Science of America, 1994
Rabbit (New Zealand white)	Gavage	48 mg/kg/day	Maternal effects: mortality; abortions; body weight loss; and, reduced food consumption.	Rubin and Nyska, 1988
Rabbit	Oral	48 mg/kg/day	Maternal effect: decreased food intake	Weed Science of America, 1994
			Fetal effect: decreased body weight.	

B4-4.2.1.5 No Observed Adverse Effect Levels

Table B4-8 NOAELs and LOAELs for Oral Exposure to Cacodylic Acid

Test Organism (Species)	Effect	Value	Endpoint	Reference
Acute				
Rat	NOAEL	0.4 mg/kg/day	Systemic toxicity	Crown *et al*., 1987
Rat	LOAEL	4 - 4.5 mg/kg/day	Increased incidence of cuboidal to columnar epithelial lining thyroid follicles; increased water consumption and urine output; decreased specific gravity; and, decreased hematology parameters (F).	Crown *et al*., 1987
Chronic				
Mice (B6C3F1)(F)	LOAEL	8.65 mg/kg/day	Systemic toxicity (vacuolar degeneration of bladder epithelium).	Gur *et al*., 1990
Mice (B6C3F1)(M)	LOAEL	35.35 mg/kg/day	Systemic toxicity (vacuolar degeneration of bladder epithelium).	Gur *et al*., 1990

Table B4-8 NOAELs and LOAELs for Oral Exposure to Cacodylic Acid

Test Organism (Species)	Effect	Value	Endpoint	Reference
Mice (B6C3F1)(F)	NOAEL	1.8 mg/kg/day	Systemic toxicity.	Gur *et al*., 1990
Mice (B6C3F1)(M)	NOAEL	7 mg/kg/day	Systemic toxicity.	Gur *et al*., 1990
Mice (B6C3F1)	NOAEL	92-97 mg/kg/day	Survival; food consumption; food efficiency; differential cell counts; and, organ weights.	Gur *et al*., 1990
Rat (Fischer F344)	NOAEL	7.3-8.0 mg/kg/day	Mortality; food consumption; food efficiency; body weight; and, body weight gains.	Gur *et al*., 1989
Dog (Beagle)	LOAEL	40 mg/kg/day	Systemic toxicity (salivation; vomiting; diarrhea; decreased body weight gains; decreased HCT%, RBC counts; and, total protein albumin concentration (M))	Zomber *et al.*, 1989
Dog (Beagle)	NOAEL	16 mg/kg/day	Systemic toxicity.	Zomber *et al.*, 1989
Dog (Beagle)	NOAEL	40 mg/kg/day	Food consumption; ophthalmology; neurology; organ weights.	Zomber *et al.*, 1989

Obtained from U.S. EPA, 2006b,c; U.S. EPA, 2005.

Table B4-9 Cacodylic Acid Reproductive and Developmental NOAEL and LOAEL Values[a]

Test Organism (Species)	Effect	Daily Value	Endpoint	Reference
Rat (Charles River SD)	LOAEL	36 mg/kg	Maternal toxicity (decreased body weight, body weight gains; food consumption; and, gravid uterine weights).	Gal and Rubin, 1988
Rat (Charles River SD)	LOAEL	36 mg/kg	Developmental toxicity (decreased fetal weights; shorter crown rump length; suggestion of disaphragmatic hernia; and, delayed ossification of numerous bones).	Gal and Rubin, 1988
Rat (Charles River CD)	NOAEL	2.16-2.48 mg/kg/day	Parental toxicity.	Rubin *et al*., 1989
Rat (Charles River SD)	NOAEL	12 mg/kg	Maternal and developmental toxicity.	Gal and Rubin, 1988
Rat (Charles River CD)	NOAEL	15.5-17.9 mg/kg/day	Reproductive toxicity.	Rubin *et al*., 1989
Rabbit (New Zealand white)	LOAEL	48 mg/kg	Maternal toxicity (mortality; abortions; body weight loss; and, reduced food consumption).	Rubin and Nyska, 1988
Rabbit (New Zealand white)	NOAEL	12 mg/kg	Maternal and developmental toxicity	Rubin and Nyska, 1988
Rat (Charles River CD)	NOAEL	147 ppm	Parental toxicity (lower absolute and relative ovarian weights and increased incidence of thyroid follicles line with cuboidal to columnar epithelium (F))	Rubin *et al*., 1989

[a] Obtained from U.S. EPA, 2006c.

B4-4.2.2 Dermal Exposure

B4-4.2.2.1 Death

Table B4-10 Mammalian Acute LD_{50} Value Resulting from Dermal Exposure to Cacodylic Acid

Test Type	Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute	--	> 2,000	U.S. EPA, 2006b

B4-4.2.2.2 Systemic Effects

Table B4-11 Systemic Effects Resulting from Dermal Exposure to Cacodylic Acid

Test Type	Test Organism (Species)	Dose (Duration) (mg/kg/day)	Response	Reference
Sub-chronic	Rabbit (New Zealand white)	1,000 (21 days)	Decreased body weight gains (F); decreased testicular weights associated with hypospermia; and, tubular hypoplasica (M).	Margitich and Ackerman, 1991

(M) Effects observed in males only
(F) Effects observed in females only

B4-4.2.2.3 Neurological Effects

No data found.

B4-4.2.2.4 Reproductive/Developmental Effects

No data found.

B4-4.2.2.5 No Observed Adverse Effect Level

Table B4-12 NOAELs and LOAELs for Dermal Exposure to Cacodylic Acid[a]

Test Organism (Species)	Effect	Value	Endpoint	Reference
Subchronic				
Rabbit (New Zealand white)	LOAEL	1,000 mg/kg/day	Systemic toxicity (body weight changes (F); and,changes in testicular weights and histopathology (M).	Margitich and Ackerman, 1991
Rabbit (New Zealand white)	NOAEL	300 mg/kg/day	Systemic toxicity.	Margitich and Ackerman, 1991
Rabbit (New Zealand white)	NOAEL	1,000 mg/kg/day	Dermal irritation.	Margitich and Ackerman, 1991

[a] Obtained from U.S. EPA, 2006c.
(M) Effects observed in males only.
(F) Effects observed in females only.

B4-4.2.3 Inhalation Exposure

B4-4.2.3.1 Death

Table B4-13 Mammalian LD_{50} Value Resulting from Inhalation Exposure to Cacodylic Acid

Test Type	Test Organism (Species/Sex)	LD_{50}	Reference
Acute	Rat	3.9 mg/L	Weed Science Society of America, 1994
Acute (2 hours)	Rat (F)	3.9 mg/L[a]	Verschueren, 1983
Acute	Not specified (M/F)	4.9 mg/L	U.S. EPA, 2006b
Acute (2 hours)	Rat (M/F)	6.4 mg/L[a]	Verschueren, 1983
Acute (2 hours)	Rat (M)	> 6.9 mg/L[a]	Verschueren, 1983

[a] Phytar®138 used for exposures; exposure to dust atmospheres.

B4-4.2.3.2 Systemic Effects

No data found.

B4-4.2.3.3 Neurological Effects

No data found.

B4-4.2.3.4 Reproductive/Developmental Effects

No data found.

B4-4.2.3.5 No Observed Adverse Effect Level

Table B4-14 NOAELs and LOAELs for Inhalation Exposure to Cacodylic Acid[a]

Test Organism (Species)	Effect	Value	Endpoint	Reference
Subchronic				
Rat	LOAEL	0.034 mg/L/day	Moderate and marked intracytoplasmic eosinophilic granues (IEG) in the cells of the nasal turbinates.	Whitman, 1994
Rat	NOAEL	0.01 mg/L/day	Systemic toxicity.	Whitman, 1994
Rat	NOAEL	1 mg/L/day	Mortality; body and organ weights; ocular abnormalities; clinical chemistry; hematology; and, respiratory tract.	Whitman, 1994

[a] Obtained from U.S. EPA, 2006b.

B4-4.3 Carcinogenicity

In 1996, the U.S. EPA classified cacodylic acid as category D: not classifiable to human carcinogenicity based on inadequate animal data and no human data. Conversely, IARC (1987) has classified arsenic and arsenic compounds as carcinogenic to humans (Group 1). This classification is based upon limited evidence of carcinogenicity in animals and sufficient evidence of carcinogenicity to humans. However, this evaluation applies to the group of chemicals as a whole, and not necessarily to all individual chemicals within the group.

The U.S. EPA (2005) published a special report on the mode of action for the development of bladder tumours in rats and supports a linear dose-response assessment. The mode of action found in rats is expected to also occur in humans. One requirement for this mode of action is that a large enough concentration of dimethylarsinic acid (DMA) be available at the target site to cause cell killing. In addition, cytotoxicity must be sustained to cause regenerative proliferation. Both of these steps are required in order for DMA to induce bladder tumours in rats. Therefore, DMA is not considered carcinogenic up to doses causing regenerative proliferation, which is believed to be the rate limiting step (U.S. EPA, 2005).

Table B4-15 Animal Carcinogenicity Data for Exposure to DMA^V (Cacodylic Acid)[a]

Test Subjects	Exposure Medium	Dose (ppm) Weeks of Exposure	Response	Reference
Mice ($B6C3F_1$ and $B6AKF_1$)	Gavage; Diet	46.4 mg/kg/day (days 7-28); (121 ppm) 80 weeks	No significant differences in tumour incidence.	NCI, 1968; Innes *et a*l., 1969
Mice ($B6C3F_1$)	Diet	94 mg/kg/day (500 ppm); 104 weeks	No preneoplastic degenerative changes, cell death, inflammation, hyperplasia or neoplasia in the bladder.	Arnold *et al*., 2006
Mice ($B6C3F_1$)	Diet	94 mg/kg/day (500 ppm)	No tumorigenic response	Gur *et al*., 1990
Mice ($B6C3F_1$ and $B6AKF_1$)	Subcutaneous injection	464 mg/kg	Tumour incidences were not significantly increased over controls.	NCI, 1968
Rat (F344)(M)	Water	$\geq$2.7 mg/kg/day (50 ppm)	Dose dependent increase in urinary bladder tumours (papillomas and carcinomas).	Wei *et al*., 1999
Rat (F344)	Water	8.68 mg/kg/day (100 ppm) 32 wks	No bladder tumours were found.	Wanibuchi *et al.*, 1996
Rat (F344)	Diet	7.8 mg/kg/day 100 ppm (104 weeks)	60 rats/sex/dose fed DMA^V. Urothelial hyperplasia at 40 ppm (F more sensitive); and, bladder tumours in M & F at 100 ppm.	Arnold *et al*., 2006
Rat (Fischer F344)	Diet	7.3-8.0 mg/kg/day (100 ppm) 104 weeks	Treatment related urinary bladder tumours; significant response was found for papillomas and carcinomas combined	Gur *et al*., 1989

[a] Obtained from U.S. EPA, 2005; U.S. EPA, 1996; U.S. EPA, 2006c

Cacodylic acid has been tested for mutagenicity and genotoxicity in bacteria, yeast, Drosophila, and mammalian cell cultures with positive and negative results (Reviewed by Cohen *et al*., 2006). In reverse mutation assays using *Escherichia coli* and *Salmonella typhimurium* strains, cacodylic acid was negative in either the presence or absence of S9 (Simmon *et al*., 1977; Jones *et al*., 1984; Andersen *et al*., 1972). The results of DNA repair assays in *S. typhimurium* were negative (Jones *et al.*, 1984) and in *Bacillus subtilus* and *E. coli* were inconclusive (Simmon *et al*., 1977; Jones *et al*., 1984); these assays were performed both with and without S9. In mitotic recombination and mitotic crossing over assays using *Saccharomyces cerevisiae* cacodylic acid was positive both with and without S9 (Jones *et al*., 1984; Simmon *et al*., 1977; Riccio *et al*.,

1981). Tests for non-disjunction and loss of sex chromosomes in Drosophila were negative (Ramel and Magnusson, 1979) as was the sex-linked recessive lethal test (Valencia, 1981).

Results from mammalian cell tests were both positive and negative. In both a sister chromatid exchange assay in Chinese hamster ovary (CHO) cells (Jones *et al.*, 1984) and a reverse mutation assay also in CHO cells (Taylor *et al.*, 1984) cacodylic acid tested negative. In a forward mutation assay using mouse lymphoma L5178Y $TK^{+/-}$ cells, cacodylic acid tested positive in the presence of S9 (Jones *et al.*, 1984) but was negative in an unscheduled DNA synthesis assay in human fetal lung fibroblast cells (WI-38 cells) (Simmon *et al.*, 1977). A bone marrow micronucleus test (Jones *et al.*, 1984) was positive at the highest dose tested (750 mg/kg initially and 1,500 mg/kg 1 day later) when mice were administered cacodylic acid.

In a 2-year bioassay, male rats were treated with 12.5, 50, or 200 ppm DMA^V in the drinking water (Wei *et al.*, 2002). There was a dose-responsive increase in urinary bladder tumours in the rats treated with 50 or 200 ppm DMA^V, but there was no evidence of urinary bladder cytotoxicity, proliferation, or neoplasms in the rats treated with 12.5 ppm DMA^V.
Salim *et al.* (2003) treated p53 heterozygous ($^{+/}$) knockout mice and wild type ($^{+/+}$) C57BL/6J mice with 50 and 200 ppm DMA^V in the drinking water for 18 months. They reported a significant increase in the total number of all tumours per mouse in both the wild type ($p53^{+/+}$) mice and in the heterozygous ($p53^{+/}$) mice treated with 200 ppm DMA^V. There was no evidence of tissue-specific induction of tumours in any of these mice.

Carcinogenic mode-of-action for cacodylic acid (DMA^V)

Although there are insufficient data to unequivocally assign a mechanism or mode of action to DMA^V-induced rat bladder tumourigenesis, the weight of evidence is sufficient to support the proposed mode of action of cytotoxicity and regenerative cell proliferation, and there are no inconsistencies (Cohen *et al.*, 2006). The key observation with all of the proposed mechanisms, including effects related to indirect genotoxicity, is that the dose response for both genotoxicity and tumourigenesis is nonlinear (Cohen *et al.*, 2006).

What are the key events in DMA^V-induced carcinogenicity in the rat?

In DMA^V carcinogenicity studies in the rat, the dose response clearly demonstrates nonlinearity and a likely threshold (no effect level) that is substantially higher than human exposures.

Is the mode of action observed in animals plausible for humans?

The rat is particularly susceptible to DMA^V-induced cytotoxicity and tumourigenicity because of its unique metabolism and disposition of DMA^V, namely, the extensive binding of DMA^{III} to hemoglobin (Lu *et al.*, 2004) and retention in red blood cells and the generation of high levels of TMAO (Vahter, 1999). The extensive binding and retention of DMA^{III} in the rat compared to other species effectively prolongs the half-life of these compounds *in vivo* and may contribute to the higher levels of TMAO generated in the rat (Cohen *et al.*, 2006).

DMA^V produced a dose-related increase in carcinogenic activity in one species (the rat) and one target organ (urothelium) with an apparent threshold level. The doses used in these bioassays. Reported by Arnold *et al.* (2006) were several orders of magnitude greater than any plausible human exposure. The metabolism and toxicokinetics of DMA^V differ significantly between rats

and mice, and between both of these species and humans. In contrast to observations in humans, the rat sequestered significant concentrations of DMA^{III} in the red blood cells as the trivalent form bound to hemoglobin (Shiobara *et al.*, 2001; Lu *et al.*, 2004). In addition, TMAO is a major metabolite of orally administered DMA^{V} in rats, whereas in humans it is present at extremely low levels, if at all (Arnold *et al.*, 2006). The mode of action for DMA^{V}-induced carcinogenicity in the rat clearly appears to involve the production of increased levels of the reactive metabolite DMA^{III} resulting in cytotoxicity with cell necrosis followed by increased cell proliferation (hyperplasia) and eventually tumor formation. The cytotoxicity occurs only at high exposure concentrations of DMA^{V}, and is consistent with a threshold, non-linear dose response.

Cohen *et al.*, (2006) have concluded that DMA^{V} is a threshold carcinogen with a mode-of-action in rats that may be theoretically possible in humans, but not at the anticipated human exposures. The DMA^{V}-induced rat bladder tumors are a rat-specific phenomenon, due to the unique rat metabolism and disposition of DMA^{V}. This mechanism is consistent with a mode of action in which DMA^{V}-induced cytotoxicity occurs *only* at high levels, resulting in cell necrosis, followed by increased cell proliferation, with a nonlinear dose-response relationship and with a threshold. Arnold *et al.* (2006) conclude that the carcinogenicity of DMA^{V} to rat bladder has a clear mode-of-action, that has no relevance to humans at plausible levels of oral exposure.

Populations at Special Risk

No data found.

B4-4.4 Toxicokinetics

B4-4.4.1 Absorption

The dermal absorption factor for a ten hour exposure period is 3.5% (Hauswald, 1994).

The major routes of arsenic absorption are ingestion and inhalation (WHO, 2000). Cacodylic acid is readily absorbed into the bloodstream when ingested (U.S. National Library of Medicine, 1995). For example, 75 to 85% of oral doses of organic arsenics were absorbed by the gastrointestinal tract (WHO, 2000).

Studies of the metabolism of cacodylic acid (DMA^{V}) in various species show that most of the dose of DMA^{V} is readily absorbed from the gastrointestinal tract. In most species (with the exception of the rat) dimethylarsinate (DMA^{V}) is rapidly excreted as unchanged parent compound mainly in the urine (WHO, 2000; Arnold *et al.*, 2006) (Figure B4-3-1). For most species, very little DMA^{V} undergoes additional metabolism to form the trimethylated arsenical trimethylarsine oxide (TMAO). On the other hand, in the rat there is extensive metabolism of DMA^{V} to TMAO, which is then excreted in the urine (Cohen *et al.*, 2002). The methylation of DMA^{V} to TMAO first requires reduction of DMA^{V} to the highly reactive trivalent metabolite dimethylarsinous acid (DMA^{III}) which undergoes oxidative methylation to form TMAO (Le *et al.*, 2000). The dimethylated arsenical is retained in the red blood cells of the rat and slowly excreted over time (Shiobara *et al.*, 2001; Lu *et al.*, 2004). The retention occurs primarily by binding of the trivalent metabolite (DMA^{III}) to hemoglobin (Lu *et al.*, 2004).

B4-4.4.2 Distribution

Blood is the major vehicle for transporting arsenic throughout the body after absorption occurs; however, arsenic is cleared quite rapidly from it (WHO, 2000). Arsenic tends to accumulate in the muscles, bones, kidneys and lungs which have the highest absolute amounts of arsenic. However, the skin and excretory storage organs such as nails and hair have the highest concentrations (WHO, 2000). For instance, cacodylic acid has been shown to accumulate in the skin, finger and toe nails and hair (U.S. National Library of Medicine, 1995). Transplacentel transfer of arsenic appears to occur in humans (WHO, 2000).

B4-4.4.3 Metabolism

It is unclear whether humans metabolize DMA^V to TMAO, or whether DMA^{III} is produced in humans from exposure to exogenous DMA^V; if so, it is only after extremely high exposure and to a very limited extent.

Upon human oral ingestion of cacodylic acid greater than 99% of total arsenic excreted was the unchanged parent compound (Buchet *et al*., 1981). However, cacodylic acid can be broken down and metabolized in the liver (Figure B4-3-1) (U.S. National Library of Medicine, 1995). For instance, after oral administration of cacodylic acid to one human volunteer 4% of the dose was excreted as trimethanearsinic oxide (TMAO) (Marafante *et al*., 1987)

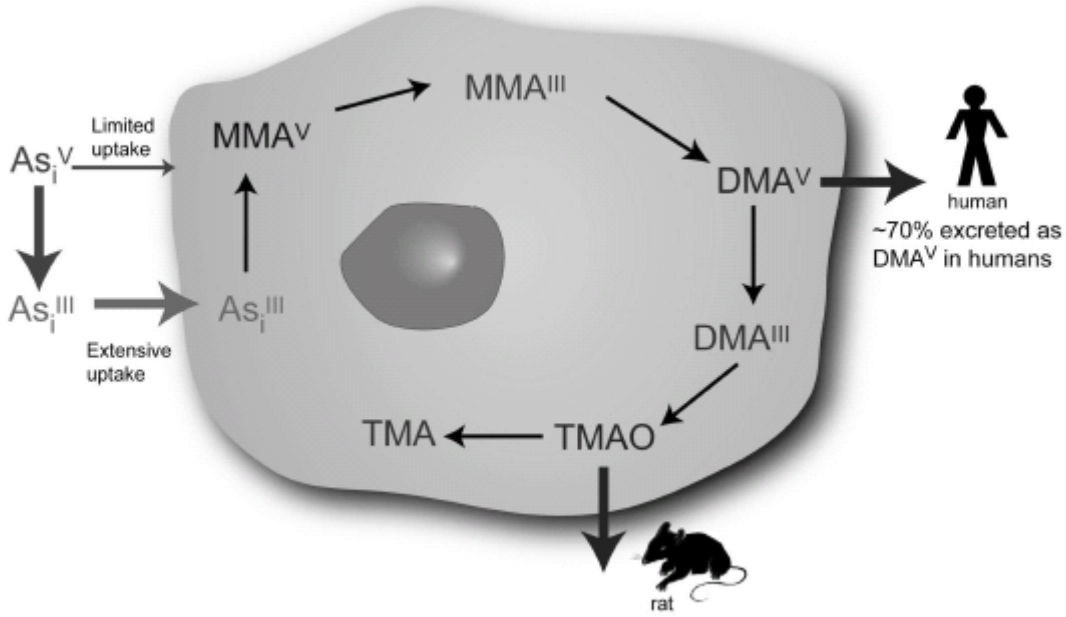

Figure B4-2 **General metabolic profile following direct exposure to inorganic arsenic and cacodylic acid (DMA^V) in humans and rats. In humans, a small amount of TMAO (~4%) appears in urinary excretions. By contrast, ~20 to 40% of urinary excretion in rats exposed to DMA^V is excreted as TMAO. Adapted from Cohen *et al*., 2006; U.S. EPA, 2005**

B4-4.4.4 Elimination and Excretion

Most of the absorbed dose was excreted in urine and feces (Hauswald, 1994).

Over a 7 day period 90 to 98% of the total dose was excreted. The total radioactivity recovered in the urine, feces and exhaled air at 28 to 82, 4 to 33 and 0 to 0.1%, respectively (Gibson *et al.*, 1992). Cacodylic acid is excreted fairly rapidly from the body. For example, 24 hoursafter four male human subjects ingested the compound 57% of the dose had been excreted in urine. Furthermore, 4 days following the dose, 75% of the dose had been excreted in the urine (Buchet *et al*., 1981).

Cacodylic acid accumulates in skin, nails and hair, which also serves as a means of excretion (U.S. National Library of Medicine, 1995)

B4-4.5 Exposure Limits

Table B4-16 Existing RfD Values for Cacodylic Acid Exposures

Reference Dose (mg/kg/day)	Exposure Route	Reference	Endpoint	Study	Reference	Dose (mg/kg/day)	Uncertainty factor	Study Classification
Acute/Short-term								
0.12	Oral	U.S. EPA, 2006d	a) Decreased fetal weights, shorter crown-rump length; suggestion of diaphragmatic hernia; delayed/lack of ossification	a) Rat developmental toxcity	Gal and Rubin, 1988	(NOEL) 12	100	Acceptable
			b) Mortality; abortions; body weight loss; reduced food consumption	b) Rabbit developmental toxicity	Rubin and Nyska, 1988			Acceptable
Intermediate-term								
No available values								
Long-term								
0.014	Oral	U.S. EPA, 2006d	BrdU labeling	--	Arnold *et al*., 1999	($BMDL_{10}$) 0.43	30	--

Table B4-B17 Summary of Toxicological Doses and Endpoints for Cacodylic Acid Used in Human Risk Assessments by the U.S. EPA (2006b)

Exposure Scenario	Reference Dose	Endpoint	Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	LOC for Risk Assessment	Reference
Incidental Oral Acute-Term (1 day)	0.12	Decreased fetal weight; shorter crown-rump length; suggestion of diaphragmatic hernia; delayed ossification of numerous bones	Rat developmental toxicity	12	36	100	Gal and Rubin, 1988
		Mortality; abortions; body weight loss; reduced food consumption	Rabbit developmental toxicity	12	48		Rubin and Nyska, 1988

Table B4-B17 Summary of Toxicological Doses and Endpoints for Cacodylic Acid Used in Human Risk Assessments by the U.S. EPA (2006b)

Exposure Scenario	Reference Dose	Endpoint	Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	LOC for Risk Assessment	Reference
Incidental Oral Short – term (1-30 days) Intermediate- term (1-6 mouths)	0.014	BrdU labeling	--	0.43 ($BMDL_{10}$)	0.92 (BMD_{10})	30	
Dermal Short-term (1-30 days) Intermediate-term (1-6 mouths)	3.0	Decreased body weight gain (F); decreased testicular weights, hypospermia and tubular hypoplasia (M)	21 days Dermal Rabbit	300	1,000	100	Margitich and Ackerman, 1991
Dermal Long-term (>6 mouths)	Not required						
Inhalation Short- (1-30 days) and Intermediate-term (1-6 mouths)	0.044	Presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the nasal turbinate cells	90 days Inhalation Rat	4.38 (0.01 mg/L)	14.95 (0.034 mg/L)	100	Whitman, 1994
Inhalation Long-term (>6 mouths)	Not required						

Based on the available general population (B4-16) and occupational reference doses (Table B4-17) the following exposure limits were selected for the risk assessment purposes of this report (Table B4-18).

Table B4-18 Summary of Selected TRVs for Cacodylic Acid

COC	TRV Type	Route	TRV value (mg/kg/day)	Major Health Effects	Route of Exposure in Primary Study	Reference
Cacodylic Acid	Acute/Short-term RfD (1-30 days)	Oral	0.12	Decreased fetal weight; shorter crown-rump length; suggestion of diaphragmatic hernia; delayed ossification of numerous bones		U.S. EPA, 2006b,d
		Dermal	3.0	Decreased body weight gain (F); decreased testicular weights, hypospermia and tubular hypoplasia (M)	Dermal	U.S. EPA, 2006b
		Inhalation	0.044	Presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the nasal turbinate cells	Inhalation	U.S. EPA, 2006b
	Intermediate-term RfD (1to 6 months)	Oral	0.014	BrdU labeling		U.S. EPA, 2006b
		Dermal	3.0	Decreased body weight gain (F); decreased testicular weights, hypospermia and tubular hypoplasia (M)	Dermal	U.S. EPA, 2006b
		Inhalation	0.044	Presence of moderate and marked intracytoplasmic eosinophilic granules (IEG) in the nasal turbinate cells	Inhalation	U.S. EPA, 2006b
	Long-term RfD (>6 months to lifetime)	Oral	0.014	BrdU labeling		U.S. EPA, 2006d
		Dermal	Not required			U.S. EPA, 2006b
		Inhalation	Not required			U.S. EPA, 2006b

B4-5.0 ENVIRONMENTAL FATE AND EXPOSURE

B4-5.1 Air

B4-5.1.1 Transport and Partitioning

Cacodylic acid is expected to exist solely as a vapour in the ambient atmosphere based on its vapour pressure (Table B4-3) (Bidleman, 1988).

B4-5.1.2 Transformation and Degradation

Vapour phase cacodylic acid is degraded in the atmosphere by reacting with photo-chemically produced hydroxyl radicals.

Table B4-19 Half-life of Cacodylic Acid in Air

Conditions	Half-life	Reference
Presence of hydroxyl radicals	31 days[a]	Meylan and Howard, 1993

[a] Estimated half-life for the reaction of cacodylic acid and photo-chemically produced hydroxyl radicals, calculated using a rate constant of 5.2×10^{-13} cm^3/molecule·sec at 25°C.

B4-5.2 Water

B4-5.2.1 Transport and Partitioning

Significant leaching of cacodylic acid or its metabolites to groundwater is not expected to occur from agricultural use (U.S. EPA, 2006a). However, runoff and erosion of surfaces where cacodylic acid has been applied may contaminate surface water and sediments (U.S. EPA, 2006a).

Cacodylic acid is a non-volatile solid that is very soluble in water. It has a pKa of 1.57 causing it to ionize in water. Therefore, volatilization of the parent compound is not expected to be a significant route of dispersal (U.S. EPA, 2006a).

B4-5.2.2 Transformation and Degradation

Cacodylic acid was found to degrade in river sediments producing arsenate (Holm *et al.*, 1980)

Table B4-20 Half-life of Cacodylic Acid in Water

Conditions	Half-life	Reference
River sediments	30 days	Holm *et al*., 1980

B4-5.3 Sediment and Soil

B4-5.3.1 Transport and Partitioning

Cacodylic acid has low to moderate persistence in soil and has a soil adsorption coefficient of 48.64 (JW, 2006). The compound is quickly inactivated upon contact with soil by adsorption to soil particles and ion exchange (U.S. National Library of Medicine, 1995; Weed Science Society

of America, 1994). The U.S. EPA (2006a) calculated soil Kds for cacodylic acid/cacodylate which ranged between 8.2 to 33 mL/g, with a median value of 16 mL/g. Sorption did not correlate with organic matter content of the soil, but rather with clay and iron and aluminum oxide content.

Cacodylic acid is not expected to volatilize from dry soil surfaces based upon its vapour pressure (Lyman, 1985).

B4-5.3.2 Transformation and Degradation

Arsenicals undergo microbial metabolism in soil under aerobic and anaerobic conditions (Weed Science Society of America, 1994; U.S. EPA, 2006d). The rate at which this metabolism occurs depends on environmental conditions. Parent compounds can remain in the soil for days to years after application depending on soil moisture, temperature, chemical concentration, bacterial population and the amount of organic matter (U.S. EPA, 2006d). Arsenic from pesticides is never removed from the environment, but is redistributed and transformed throughout the environment into other arsenic-containing substances.

The principle metabolites of microbial demethylation are arsenate, carbon dioxide, and the volatile compounds dimethylarsine and trimethylarsine (U.S. EPA, 2006a). Another minor product that may be detected is methanearsonic acid.

Table B4-21 Half-life of Cacodylic Acid in Soil

Conditions	Half-life	Reference
Aerobic	75 ± 40 days	U.S. EPA, 2006a
Anaerobic (flooded)	128 ± 38 days	U.S. EPA, 2006a

B4-5.4 Other Environmental Media

B4-5.4.1 Transport and Partitioning

The Log K_{ow} value (Table B4- 2-2) for cacodylic acid indicates that there is little potential for bioconcentration in aquatic or terrestrial environments (U.S. EPA, 2006a). Furthermore, cacodylic acid has a BCF of 21 for mosquito fish suggesting its bioaccumulation potential is low (Isensee *et al*., 1973). JW (2006) reported a BCF of 3.162 for cacodylic acid. In many species, humans included, cacodylic acid is a major final waste product from the metabolism of arsenic compounds ingested from natural sources.

B4-5.4.2 Transformation and Degradation

Refer to Section B4-4.4 Toxicokinetics.

B2-6.0 SUMMARY

Cacodylic acid, which is also known as dimethylarsinic acid, is an arsenical non-selective contact herbicide that can be used to defoliate or desiccate a wide variety of plant species. Historically, cacodylic acid has been used in forest management, and as a cotton defoliant.

Cacodylic acid was applied on designated plots at CFB Gagetown during the 1966 and 1967 U.S. trials. Approximately 150 kg of cacodylic acid was applied over an area of 34 hectares (Demaree and Haws, 1968; Demaree and Creager, 1968; and, Demaree *et al*., 1966).

Cacodylic acid has low acute toxicity *via* the oral route. Chronic administration of cacodylic acid will cause adverse kidney and bladder effects. Furthermore, cacodylic acid has also caused significant developmental/reproductive effects (decreased fetal weights, delayed ossification of bones, decreased maternal body weights, lowered relative ovarian weights, decreased sperm production) in rodents. *Via* the dermal route of exposure, cacodylic acid has exhibited low acute and intermediate-term toxicity in rodents. However, moderate acute toxicity of cacodylic acid was observed in rodents through the inhalation route of exposure. In 1996, the U.S. EPA classified cacodylic acid as a group D carcinogen (not classifiable as to human carcinogenicity) based on inadequate animal studies and no human data (U.S. EPA, 1996).

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