B8-1.0 FOSAMINE AMMONIUM SALT

B8-1.1 Background Information

IUPAC: Ammonium ethylcarbamoylphosphonate

CAS: Ammonium ethyl (aminocarbonyl) phosphonate

CASRN: 25954-13-6

FOSAMINE AMMONIUM USES:

Fosamine ammonium can be used to control brush and herbaceous plants on non-cropland. It can be applied to nonagricultural rights-of-way (such as highways, railroads, and utilities), industrial sites, and fencerows.

Fosamine ammonium was the active ingredient of herbicide product Krenite Brush Control®. It was applied at the CFB Gagetown between 1991 to 2000 (JW, 2006).

Table B8-1 Fosamine Ammonium Usage at CFB Gagetown[a]

Year	Amount of Fosamine Ammonium Applied (kg)	Total Area Treated (ha)
1989	No information available	No information available
1990	213.1	25
1991	540	75
Total	**7.5E+02**	**1.0E+02**

[a] Adapted from JW, 2006

B8-2.0 CHEMICAL AND PHYSICAL PROPERTIES

Formula: $C_3H_{11}O_4N_2P$

Activity: Herbicides; Organophosphonate, subclass of organophosphate (U.S. EPA, 1995).

Notes: limitations have been applied to the use of fosamine ammonium by the U.S. EPA. It is not recommended to apply fosamine ammonium directly to water, areas where surface water is present, intertidal areas below the mean high water mark, or to wash equipment contaminated with fosamine ammonium using water that may come in contact with a body of water. Furthermore, fosamine ammonium is not recommended to be applied on food crops, irrigation systems, or by air (U.S. EPA, 1995; PMRA, 2004).

Structure:

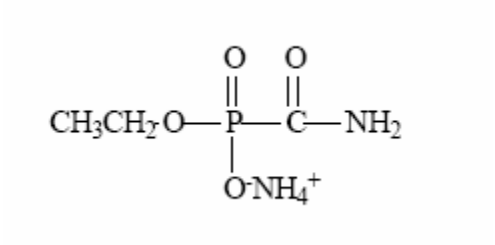

Figure B8-1 Fosamine Ammonium CASRN: 25954-13-6 Structure

Table B8-2 Chemical and Physical Properties of Fosamine Ammonium

Chemical/Physical Property	Result	Reference
Colour/Form	White, crystalline solid	U.S. EPA, 1995
Dissociation Constant (pKa)	9.25	JW, 2006
Henry's Law constant	8.37×10^{-23} atm-m^3/mole	JW, 2006
Log K_{ow}	-2.92	JW, 2006
	0.0012	U.S. EPA, 1995
Melting Point	173 – 175ºC (decomposition)	U.S. EPA, 1995
Molecular Weight	170.10g	JW, 2006
	170.11g	U.S. EPA, 1995
Odour	Alcoholic	U.S. EPA, 1995
Specific Gravity	1.24g/ml at 25ºC	U.S. EPA, 1995
Vapour Pressure	3.98×10^{-6}mm Hg	JW, 2006
	4×10^{-6} mm Hg	U.S. EPA, 1995
Water Solubility	1.00×10^{6} mg/L	JW, 2006

B8-3.0 PMRA EVALUATION

The PMRA (2004) determined that fosamine ammonium is acceptable for continued registration.

B8-4.0 TOXICOLOGICAL SUMMARY

B8-4.1 Human Health Effects

Most prominent cases of exposure to fosamine ammonium are occupational. These usually occur either through dermal contact or inhalation of dust and sprays, especially to workers applying the compound as an herbicide.

Table B8-3 Human Health Effects Resulting from Acute and Chronic Exposure to Fosamine Ammonium[a]

Exposure	Effects	Response
Acute	Dermal	Rash and skin irritation, itching, burning, redness, swelling or rash. At excessive dermal exposure levels, significant dermal and systemic effects after contact are unlikely to occur.
	Ophthalmic	Eye irritation, discomfort, tearing, blurring of vision.
	Respiratory	Irritation of the upper respiratory passages, with cough, difficulty breathing or shortness of breath and nonspecific discomfort, nausea, headache, or weakness.
	Non specific	Ingestion of high doses of fosamine ammonium may cause nonspecific discomfort, such as nausea, headache, or weakness.

[a] Dupont, 2006.

B8-4.2 Health Effects by Route of Exposure

B8-4.2.1 Oral Exposure

B8-4.2.1.1 Death

Table B8-4 Mammalian LD_{50} Values Resulting from Oral Exposure to Fosamine Ammonium

Test Type	Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute	Rat	24,400	Miles, 1968; E.I. du Pont de Nemours and Company, 1979

B8-4.2.1.2 Systemic Effects

Table B8-5 Mammalian Systemic Effects Resulting from Oral Exposure to Fosamine - Ammonium

Test Organism (Species)	Daily Dose (Duration)	Response	Reference
Sub-chronic			
Rats	0, 10, 50, 250, or 500 mg/kg/day for 90 days	Swollen deep proximal convoluted tubules of the kidney in male rats were observed at the 50 mg/kg/day dose level and above. On vacuolated and degenratively affected deep proximal convoluted tubules of the kidneys, epithelial hyperplasia of the urinary bladder and slight decreases in body weight, body weight gain and food consumption in males at doses of 250 and 500 mg/kg/day.	Holsing *et al*., 1969
Dogs	0, 5, 25, 125, 187.5 or 250 mg/kg/day for 6 months	Statistically significant increase in serum glucose was observed in high-dose female dogs.	Cox. 1993.

No chronic mammalian toxicology studies were provided by the U.S. EPA, 1995 or by the PMRA, 2004.

B8-4.2.1.3 Neurological Effects

Delayed acute perineural lymphoid proliferations were observed, but results were equivocal and needed to be resolved (Fletcher, 1993).

Table B8-6 Mammalian Neurological Effects Resulting from Oral Exposure to Fosamine – Ammonium

Test Organism (Species)	Dose (mg/kg/day) (Duration)	Response	Reference
Sub-chronic			
Male rats	299, 604, 1193 mg/kg/day for 96-98 days	Diarrhea in males at all dose levels, no neurotoxic effects at any dose level.	Christoph, 1993
Female rats	398, 779, 1567 mg/kg/day for 96-98 days	Diarrhea in females at dose of 1567 mg/kg/day. No neurotoxic effects at any dose level.	

B8-4.2.1.4 Mammalian Reproductive/Developmental Effects

Table B8-7 Reproductive and Developmental Effects Resulting from Oral Exposure to Fosamine Ammonium

Test Organism (Species)	Exposure	Dose (Duration)	Response	Reference
Crl:CD®BR rats	Gavage on days 7-17 of gestation	0, 50, 350, 1,000, 3000 mg/kg/day for 96-98 days	Maternal: diarrhea, and decreases in body weight gain/ food consumption	Alvarez, 1992.
			Developmental toxicity observed at 3,000 mg/kg/day.	

B8-4.2.1.5 No Observed Adverse Effect Levels in Mammals

Table B8-8 Mammalian NOELs and LOELs from Oral Exposure to Fosamine-Ammonium

Test Organism (Species)	Effect	Value (mg/kg)	Endpoint	Reference
Acute				
Rats	NOEL	500	Increases in palpebral closure (non statistical)	Christoph, 1993
	LEL	1,000		
Sub-chronic				
Rats	NOEL	10	Swollen deep proximal convoluted tubules of the kidney in male rats. On vacuolated and degenratively affected deep proximal convoluted tubules of the kidneys, epithelial hyperplasia of the urinary bladder and slight decreases in body weight, body weight gain and food consumption in males.	Holsing *et al.*, 1969
	LEL	50		
Rats	NOEL	299	Diarrhea in males at all dose levels and females at 1,567 mg/kg/day. There were no neurotoxicity at any dose level.	Christoph, 1993
	LEL	299		
Rats	NOEL	299	Diarrhea in males at all dose levels and females at 1,567 mg/kg/day dose level.	McKenzie, 1991
	LEL	299		
Dogs	NOEL	125/187.5/250	Statistically significant increase in serum glucose was observed in high-dose female dogs.	Cox. 1993

Table B8-9 Fosamine Ammonium Mammalian Reproductive and Developmental NOEL and LOEL Values

Test Organism (Species)	Effect	Daily Value (mg/kg)	Endpoint	Reference
Crl:CD®BR rats	NOEL	1,000	Maternal: diarrhea, and decreases in body weight gain/ food consumption	Alvarez, 1992.
	LEL	3,000		
	NOEL	3,000	Developmental toxicity	

B8-4.2.2 Dermal Exposure

B8-4.2.2.1 Death

Table B8-10 Mammalian Acute LD_{50} Value Resulting from Dermal Exposure to Fosamine Ammonium

Test Organism (Species/Sex)	LD_{50} (mg/kg)	Reference
Acute		
Rabbit	1,682	McAlack, 1973

B8-4.2.2.2 Systemic Effects

Table B8-11 Mammalian Systemic Effects Resulting from Dermal Exposure to Fosamine - Ammonium

Test Organism (Species)	Dose (mg/kg/day) (Duration)	Response	Reference
Sub-chronic			
Rabbits	0, 50, 500, 1,500 mg/kg/day for 21 days	Intermittent, minimal dermal irritation was observed in all treatment groups in both male and female rabbits. Mild erythema was observed more often in the test group than in the controls, it was not clearly related to exposure to the test material.	McKenzie, 1991

B8-4.2.2.3 Neurological Effects

No data found.

B8-4.2.2.4 Reproductive/Developmental Effects

No data found.

B8-4.2.2.5 No Observed Adverse Effect Level

Table B8-12 Mammalian NOELs and LOELs from Dermal Exposure to Fosamine-Ammonium

Test Organism (Species)	Effect	Value	Endpoint	Reference
Sub-chronic				
Rabbits	NOEL	1,500 mg/kg/day	Dermal irritation was observed in all treatment groups in both male and female rabbits. Mild erythema was observed more often in the test group than in the controls.	McKenzie, 1991

B8-4.2.3 Inhalation Exposure

B8-4.2.3.1 Death

Table B8-13 Mammalian LC_{50} Value Resulting from Inhalation Exposure to Fosamine Ammonium

Test Organism (Species/Sex)	LC_{50}	Reference
Acute		
Rat (male)	>56.6 mg/L	Brown, 1993a; Brown, 1993b; Brittelli, 1981
Rat (Female)	>42.0 mg/L	

B8-4.2.3.2 Systemic Effects

No data found.

B8-4.2.3.3 Neurological Effects

No data found.

B8-4.2.3.4 Reproductive/Developmental Effects

No data found.

B8-4.2.3.5 No Observed Adverse Effect Level

No data found.

B8-4.3 Carcinogenicity

No mammalian carcinogenicity studies were provided by the U.S. EPA, 1995 or by the PMRA, 2004.

U.S. EPA (1995) reviewed various *in vitro* mutagenicity studies during their re-evaluation of fosamine ammonium. While a chromosome aberration study was reported to be strongly positive in Chinese hamster ovaries (CHO), all other assays were negative. The studies reviewed, included a gene mutation assay in *S. Typhimurium*, a CHO/HGPRT assay for gene mutation, an *in vivo* bone marrow cytogenetic assay in rats, an *in vitro* assay for chromosome aberrations in CHO, and an unscheduled DNA synthesis/rat hepatocytes study *in vitro*. U.S. EPA came to a conclusion that additional testing with germ cells is required as a follow up to the positive results from the CHO chromosome aberration study. U.S. EPA suggested using an *in vivo* cytogenetics assay in spermatogonia/spermatocytes or micronucleus assay with spermatids as confirmatory studies.

B8-4.4 Populations at Special Risk

No data found.

B8-4.5 Toxicokinetics

Pharmacokinetic studies in rats conducted by Chrzanowski *et al*., 1979 showed that 87% of the administered dose of fosamine ammonium was recovered from the feces and 13% from the urine (Chrzanowski *et al*., 1979). Trace amounts of radioactivity detected within the animal indicated that fosamine ammounium is not absorbed systemically (Chrzanowski *et al*., 1979). No radioactivity was detected in the body tissues after 72 hours, which indicated that fosamine ammonium is almost completely eliminated from the animal (Chrzanowski *et al*., 1979).

Unchanged fosamine ammonium (86%) and a metabolite carbamoylphsphonic acid (CPA) diammonium salt (14%) were detected in feces (Chrzanowski *et al*., 1979). Both of these metabolites are polar. Likewise, similar metabolite composition was found in the urine. Overall, on average, fosamine ammonium was rapidly eliminated unchanged from the animals (79%) while only a small amount (13%) of the compound was hydrolytically degraded to CPA. Some of the feces residue that was unable to be extracted was assumed to be fosamine acid (Chrzanowski *et al*., 1979).

The pattern of metabolic degradation products of fosamine ammonium was found to be consistent with known metabolic pathways of organophosphorus agrichemicals in animals (Menn *et al*., 1974). The C-O-P bonds in fosamine ammonium were found to be easily hydrolyzed, whereas the C-P bond resisted metabolic cleavage.

Table B8-14 Existing RfD Values (Exposure Limits) for Fosamine Ammonium Exposures

Reference Dose (mg/kg/day)	Route of Exposure	Reference	Endpoint	Study	Reference	NOEL (mg/kg/day)	Uncertainty Factor
Acute/Short-term (1-7 days)							
Not required	Dermal Inhalation	U.S.EPA, 1995	No known significant acute or chronic toxicological endpoints	--	--	--	--
Intermediate-term (7 days- Several months)							
Not required	Dermal Inhalation	U.S.EPA, 1995	No known significant acute or chronic toxicological endpoints	--	--	--	
Long-term (6 months to lifetime)							
0.01	Oral	U.S.EPA, 1995	Kidneys: Swollen tubules[a] , Bladder hyperplasia. Weight loss[a]	90-day feeding study in rats	Holsing, *et al*., 1969	10	1,000

[a] Observed in males only.

A chronic RfD of 0.01 mg/kg/day (U.S. EPA, 1995) was selected for the purposes of this risk assessment. Based on the current use pattern of fosamine ammonium (worst case scenario in handlers), the U.S. EPA conceded that fosamine ammonium does not pose as a serious threat through the dermal and/or inhalatory routes of exposure (U.S. EPA, 1995). The U.S. EPA stated that there were no known significant acute or chronic toxicological endpoints that warrant the

establishment of risk mitigation measures or minimum personal protective equipment (PPE) requirements to protect handlers of the pesticide (U.S. EPA, 1995).

B8-5.0 ENVIRONMENTAL FATE AND EXPOSURE

B8-5.1 Air

Fosamine ammonium has low vapour pressure and thus volatilization would only occur to a minor extent. Furthermore, fosamine ammonium also has a low Henry's Law constant of 8.37 x 10^{-23} atm-m^3/mole (JW, 2006). This indicates that it would have little tendency to escape from an aqueous solution. Hence, fosamine ammonium will not be expected to be found in air with the exception of potential aerial spray drift. PMRA has restricted fosamine ammonium from aerial application (PMRA, 2004).

B8-5.2 Water

Fosamine ammonium has low probability to impact ground-water quality when properly applied. It is possible that fosamine ammonium could move to surface water through spray drift and to a lesser extent through surface water runoff. However, there is a low probability that fosamine ammonium would be found in runoff waters because it readily degrades in aerobic and anaerobic environments through microbial mediated processes at a rapid rate (U.S. EPA, 1995). However, fosamine ammonium can be found in surface waters with low microbiological activities or long hydrological residence times. U.S. EPA concluded that, the available data in which they have attained indicated fosamine ammonium will not impact the quality of surface waters significantly. Hence, no drinking water health advisories have been established for fosamine ammonium, and its degradates (U.S. EPA, 1995).

Table B8-15 Half-life of Fosamine Ammonium in Water

Conditions	Half-life	Reference
Pond water, anaerobic conditions	4 days	U.S. EPA, 1995

B8-5-3 Sediment and Soil

Fosamine ammonium was found to be highly mobile in various types of soils, but not persistent under aerobic or anaerobic conditions (U.S. EPA, 1995). The rapid degradation of fosamine ammonium that takes place reduces the likelihood that it will move through the aerobic soil layer without any degradation (U.S. EPA, 1995). Fosamine ammonium dissipation is predominantly dependent on rapid, microbial-mediated degradation. Supplemental soil column leaching studies indicated that fosamine ammonium residues will not leach (U.S. EPA, 1995). Hence, fosamine ammonium will not pose a threat to groundwater or surface waters because it will be rapidly degraded in aerobic and anaerobic environments in soil (U.S. EPA, 1995). The degradates of fosamine ammonium in soil are carbamoylphosphonic acid, carboxylphosphonic acid, unidentified polar compounds and carbon dioxide. Mobility and persistence of these degradates are not known (U.S. EPA, 1995).

Table B8-16 Half-life of Fosamine Ammonium in Soil

Conditions	Half-life	Reference
Field, and laboratory	1-6 weeks	JW, 2005
Microbial degradation	0.5-11 days	U.S. EPA, 1995

B8-5-4 Other Environmental Media

Fosamine ammonium has a bioconcentraion factor of 3.162 in fish (JW, 2006).

B8-5.5 Plant Residues and Metabolism

Fosamine ammonium will act as bud break inhibitors and it has minimal effects on existing foliage except for certain types of pines which can show a response soon after application (Chrzanowski *et al*., 1979). Susceptible plants will fail to refoliate and either die or suffer severe growth retardation (Chrzanowski *et al*., 1979). Once fosamine ammonium comes in contact with plants, it will be absorbed through the leaf slowly (WSSA, 1994). Out of the amount of fosamine ammonium absorbed through the leaves, around 50% will be translocated throughout the whole plant (WSSA, 1994). Tolerant plants do not have the ability to translocate fosamine ammonium as effective as susceptible plants (WSSA, 1994). In the plant tissues, fosamine ammonium salt will hydrolyze into fosamine acid, and will subsequently be broken down to carbamoylphosphonic acid within weeks (WSSA, 1994).

B8-6.0 SUMMARY

Fosamine ammonium is in the organophosphonate (subclass of organophosphate) family of herbicides (U.S. EPA, 1995). As an herbicide, fosamine ammonium can be used to control brush and herbaceous plants on non-agricultural areas. Between 1991 and 2000 approximately 750 kg of fosamine ammonium was applied over an area of 100 ha at CFB Gagetown (JW, 2006).

Most of the fosamine ammonium toxicity studies produced systemic effects, especially in the kidneys and the lower urinary tract in rodents. Similarly, signs of acute neurotoxicity in the form of increased incidence of palpebral closure were also observed. Furthermore, long-term feeding studies revealed that fosamine ammonium would cause adverse developmental/reproductive effects in rodents as well. No mammalian carcinogenicity studies were provided by the U.S. EPA, (1995) or by the PMRA, (2004).

B8-7.0 REFERENCES

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