CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Fosamine Ammonium Salt

Chemical Code # 1921, **Document Processing Number (DPN)** 50097
SB 950 # 312
July 16, 2014, revised 10/21/2014

DATA GAP STATUS

Chronic toxicity, rat:	No study submitted*
Chronic toxicity, dog:	No study submitted*
Oncogenicity, rat:	No study submitted*
Oncogenicity, mouse:	No study submitted*
Reproduction, rat:	Data gap, no study submitted
Developmental toxicity, rat:	No data gap, no adverse effect indicated
Developmental toxicity, rabbit:	No data gap, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect indicated
Chromosome effects:	No data gap, possible adverse effect indicated
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	No data gap, no adverse effect indicated

Toxicology one-liners are attached.
All record numbers for the above study types through 279585 (Document No. 50097-0075) were examined. This includes all relevant studies indexed by DPR as of 10/15/14.

* The proposed use of the active ingredient is as an herbicide for the control of plant growth along rights-of-way and other non-agricultural areas and in pine plantations. These studies are not presently required for the registration of the active ingredient.

In the 1-liners below:
indicates an acceptable study.

Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: t20141021
Revised by T. Moore, 7/16/14, by Aldous on 10/21/2014
NOTE: The following symbols may be used in the Table of Contents which follows:
** = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

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METABOLISM AND PHARMACOKINETICS

50097-0011; 28814; "Metabolism of [^{14}C] Fosamine Ammonium in the Rat"; (R.L. Chrzanowski, J.C-Y. Han, C.L. McIntosh; Biochemicals Department, Research Division, Experimental Station, E.I. de Nemours & Co., Wilmington, DE; Publication: Agricultural and Food Chemistry, 27: 550-554; Date: May/June, 1979); Two male Charles River-CD rats were dosed orally by gavage with 57 mg/kg of [^{14}C]-Fosamine Ammonium (radiochemical purity: >99%, specific activity: 1.6 mCi/mmol) after having received 1000 ppm of unlabeled Fosamine Ammonium (purity not reported) in the diet for 18 days. Urine, feces and expired air were collected from both animals up to 72 hours post-dose. Tissue distribution of the radiolabel was determined. Radiolabelling was assessed by means of liquid scintillation counting. GC/MS was used to identify chemical structures. Eighty six to 88% of the administered dose was recovered in the feces and twelve to 14% of the dose was in the urine. Ninety eight to 99% of the administered dose had been excreted by 48 hours post-dose. Very little of the radiolabel was retained in the tissues at 72 hours post-dose. The parent compound was largely unmetabolized with 73 to 85% of the administered dose being unchanged. The only other metabolite which was isolated was carbamoylphosphonic acid diammonium which constituted 9 to 16% of the administered radiolabel. No characterization of the absorption profile was provided. **Summary report.** (Moore, 7/16/14)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat (No study on a.i. Accepted study on product with 41.5% a.i.)

No study submitted.

Acute dermal toxicity (No study on a.i. Accepted study on product with 41.5% a.i.)

No study submitted.

Acute inhalation toxicity, rat (No study on a.i. Accepted study on product with 41.5% a.i.)

No study submitted.

Primary eye irritation, rabbit (No study on a.i. Accepted study on product with 41.5% a.i.)

No study submitted.

Primary dermal irritation (No study on a.i. Data gap may be filled by other studies.)

No study submitted.

Dermal sensitization (No study on a.i. Accepted study on product with 41.5% a.i.)

No study submitted.

SUBCHRONIC STUDIES

Rat 10-Day Oral Toxicity Study

50097-0007; 24121; "Ten-Dose Subacute Oral Test"; (E.N. Miles; E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine; Report No. 268-68; 11/7/68); Six Chr-CD male rat/group were dosed orally by gavage with 0 or 2200 mg/kg/day with INR 1108 (Carbamoyl-Phosphonic Acid Monoethyl Ester, Ammonium Salt) (code no. INR-1108-3; a.i. content not reported) 5 days/week for a total of 10 doses. Three animals/group/time point were euthanized at 4 hour and 14 days post-final dose. No deaths resulted from the treatment. Mild diarrhea was noted as a clinical sign. The necropsy examination did not reveal any treatment-related lesions. **No adverse effect indicated**. Summary data. No NOEL established. **Supplemental study**. (Moore, 6/3/14)

Rat Subchronic Dietary Toxicity Study

50097-0007; 24997; "Three Month Dietary Feeding with One-Generation Reproduction Study – Rats"; (no study director identified; Hazleton Laboratories, Inc., Falls Church, VA; Report No. HLO-362-69; 11/14/69); (**phase I: 3-month study**) Sixteen albino rats (strain not identified) received 0, 200, 1000 or 5000 ppm of R 1108 (Ammonium Ethyl Carbamoylphosphonate) (no lot no.; purity of test material not identified) in the diet for 13 weeks. The treatment level of the high dose group was adjusted to 10000 ppm after 8 weeks of treatment. No unscheduled deaths resulted from the treatment. There was no treatment-related effect on the mean body weights or food consumption. The hematological evaluation did not reveal any treatment-related effects. No apparent treatment-related effects were evident in the clinical chemistry evaluation. No parameters in the urinalysis exhibited a treatment-related effect. In the necropsy, there was no treatment-related effect upon the organ weights. Swelling and/or irregularity of epithelium was noted in the proximal tubules of the 1000 and 5000/10000 ppm males. **No adverse effect indicated. Reported Rat Subchronic Dietary NOEL:** (M) 200 ppm (based upon the lesions noted in kidneys of the 1000 ppm treated males), (F) 5000/10000 ppm (based upon the lack of treatment-related effects noted for the 5000/10000 ppm females); **Study unacceptable**, not upgradeable (based upon the lack of analysis of the dietary preparations and the absence of an ophthalmological examination) (Moore, 5/30/14)

Rat 4-Week Inhalation Toxicity Study

50097-0069; 277257; "A 4-Week Nose-Only Inhalation Toxicity Study of Fosamine Ammonium in Sprague-Dawley Rats"; (J.M. Randozzo; WIL Research, Ashland, OH and Vet Path Services, Inc., Mason, OH; Project ID No. WIL-925003; 8/7/13); Ten Crl:CD (SD) rats/sex/group were exposed nose-only to 0, 0.1, 0.3 or 1.0 mg/l (gravimetric) for 6 hours/day for a total of 20 (males) or 21 (females) exposures over a 4-week period. The mean MMAD (GSD) values were 2.5 (2.20), 2.7 (2.42), 2.8 (2.16) um, respectively. No unscheduled deaths occurred during the study. There was no treatment-related effect noted on the mean body weights or food

consumption. The hematology and clinical chemistry evaluations did not reveal any treatment-related effects. There were no apparent treatment-related effects noted in the urinalysis or ophthalmological examination. In the necropsy examination, the mean absolute and relative thymus weights for the 1.0 mg/l males were greater than the control group values ($p<0.05$ or 0.01). The mean relative kidney and adrenal weights of the 0.3 and 1.0 mg/l females were greater than the values for the control group ($p<0.05$). In the histopathology examination, mucous cell hyperplasia was evident in the nasal turbinate, levels IV (females only), V and VI of all of the treated groups of both sexes. Hypertrophy of the adrenal gland and sinusoidal erythrocytosis in the bronchial lymph node were also noted for the females in the 1.0 mg/l group. **No adverse effect indicated. Rat 4-Week Inhalation Toxicity NOEL:** (M/F) < 0.1 mg/l (based upon the incidence of mucosal hyperplasia in the nasal turbinate of both sexes in the 0.1 mg/l exposure group); **Study supplemental** (non-guideline study). (Moore, 5/28/14)

Rabbit 14-Day Oral Toxicity Study

50097-0065; 277250; "An Oral (Gavage) 14-Day Tolerability Study of Fosamine Ammonium in Non-Pregnant New Zealand White Rabbits"; (C.J. Kappeler; WIL Research, Ashland, OH; Project ID No. WIL-925006; 1/15/13); Three female non-pregnant New Zealand White rabbits/group were dosed orally by gavage with 100, 300, 700 or 1000 mg/kg/day of Fosamine, Ammonium Technical (lot no. 20120805, purity: 95.3%) for 14 days. No unscheduled deaths occurred during the study. There was no apparent treatment-related effect upon the mean body weight gain or food consumption. No treatment-related clinical signs were apparent. The necropsy examination did not reveal any treatment-related lesions. Treatment up to 1000 mg/kg/day was well tolerated by the study animals. **Study supplemental.** (Moore, 5/15/14)

Rabbit 10-Day Repeated Dose Dermal Toxicity Study

50097-0007; 24120; "Ten-Day Subacute Exposure of Rabbit Skin to INR-1108 Plant Growth Modifier"; (J.W. McAlack; Laboratory not identified; Report No. 112-73; 3/21/73); The skin of 6 male albino rabbits/group was treated with 0 (distilled water), 600 or 1200 mg/kg of INR-1108 Plant Growth Modifier (no lot no. provided; a.i.: 42%) 6 hours/day for 10 days under an occlusive wrap. No deaths resulted from the treatment. There was no treatment-related effect upon mean bodyweights or clinical signs. No treatment-related effect was noted in the hematology evaluation. No lesions were noted in the histopathological examination. Summary data were reported. **No adverse effect indicated.** No NOEL established. **Study supplemental.** (Moore, 6/2/14)

Rabbit 21-Day Repeated Dosing Dermal Toxicity

** 50097-0056; 277237; "Repeated Dose Dermal Toxicity: 21-Day Study with DPX-R1108-100 (Fosamine Ammonium) in Rabbits"; (S.A. MacKenzie; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 431-91; 8/13/91). The skin of 5 New Zealand White rabbits/sex/group was treated with 0, 50, 500 or 1500 mg/kg/day of DPX-R1108-100 (Fosamine Ammonium Technical) (no batch no. provided; purity: 97.7%) 6 hours per day for 21 days. The test material was moistened with deionized water. There were no treatment-related deaths. There was no treatment-related effect upon the body weight gain or food consumption. No treatment-related systemic clinical signs were evident throughout the treatment period. Localized irritation at the application site was quite minimal at the highest treatment level. No treatment-related effects were noted in the

hematological evaluation. Although there were statistically-significant differences between the treated and control animals for some of the clinical chemistry parameters, there was no apparent treatment-related effect on these parameters. In the necropsy examination, there was no treatment-related effect upon the mean absolute or relative organ weights. The histological examination did not reveal any treatment-related lesions. **No adverse effect was evident. 21-Day Repeated Dose Dermal Toxicity NOEL:** (M/F) 1500 mg/kg/day (based upon the lack of any treatment-related effects noted for the 1500 mg/kg treatment group); **Dermal Irritation NOEL:** (M/F): 1500 mg/kg/day (based upon the lack of an apparent treatment-related effect at the site of application for the 1500 mg/kg treatment group); **Study acceptable** (Moore, 5/13/14)

Dog 6-Month Dietary Toxicity Study

50097-0067; 277255; "Subchronic Oral Toxicity: Six-Month Study with DPX-R1108-76 (Fosamine Ammonium) Feeding Study in Dogs"; (A.M. Kaplan; revision: L.R. Cox; E.I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Project ID No. 406-78; 7/18/78, revision, 7/26/93); Four beagle dogs/sex/group received 0, 200, 1000 and 5000 ppm of Fosamine, Ammonium Technical (DPX-R1108-76) (no batch no.; purity: 99%) in the diet for 6 months. For the high dose group, the treatment level was adjusted to 7500 ppm after one week and to 10000 ppm by the beginning of the 4th week of treatment ((M) 0, 6.16, 33.2, 281 mg/kg/day, (F) 0, 5.97, 30.1, 284 mg/kg/day). No unscheduled deaths occurred during the study. There was no treatment-related effect upon the mean body weights or food consumption. The hematological evaluation did not reveal any treatment-related effects. Although some values for certain clinical chemistry parameters of the treated groups were statistically different from those of the control, there were no apparent treatment-related effects. The urinalysis did not reveal any treatment-related effects. In the necropsy, there were no treatment-related effects upon either the absolute or relative organ weights. Microscopic examination of tissues and organs did not reveal any treatment-related lesions. **No adverse effect indicated. Reported Dog Subchronic Dietary NOEL:** (M/F) 10000 ppm ((M) 281 mg/kg/day, (F) 284 mg/kg/day) (based upon the lack of a treatment-related effect on the animals in the 10000 ppm group); **Study unacceptable** (ophthalmological examination was not performed). (Moore, 5/22/14)

CHRONIC STUDIES

Chronic, rat (study not required for limited uses proposed as of Sept. 2014)

No study submitted.

Chronic, dog (study not required for limited uses proposed as of Sept. 2014)

No study submitted.

Oncogenicity, rat (study not required for limited uses proposed as of Sept. 2014)

No study submitted.

Oncogenicity, mouse (study not required for limited uses proposed as of Sept. 2014)

No study submitted.

GENOTOXICITY

Bacterial reverse mutation assay **

NOTE: Neither bacterial reverse mutation study was independently acceptable, but both of the following Haskell studies tested to high levels with no mutagenic response. Considering also the negative accepted mammalian cell assay, the collective studies for gene mutation are adequate. Aldous, 10/21/2014.

50097-008 34795 Haskell Laboratories; "*In vitro* microbial mutagenicity studies of carbamoylphosphonic acid, monoethyl ester, ammonium salt - base-pair substitution and frame-shift mutations in *Salmonella typhimurium*, 01/01/1976. Unacceptable - no repeat trial, individual plate counts are not included, test article not described. No mutagenic effect. Five strains exposed to 0 to 10,000 µg/plate, with and without activation. A. Apostolou, 8/6/85.

50097-013 36492 Haskell; "*In vitro* microbial mutagenicity studies of carbamoylphosphonic acid, monoethyl ester, ammonium salt (fosamine, ammonium salt, formulation with 42% active ingredient) in *Salmonella typhimurium*, 02/01/1976. Unacceptable - no repeat trial, no individual plate counts. No increase in mutation frequency. 0, 500, 1000, 2000, 2500, 5000, 7500 and 10,000 µg/plate with and without activation. Five strains. J. Gee, 3/17/86.

Mutagenicity: *In vitro* mammalian cell assay **

** 50097-0004; 17064; "CHO/HGPRT Assay for Gene Mutation"; (K. Fitzpatrick; E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 676-82; 9/27/82); Chinese Hamster Ovary (CHO-K_1-BH_4) cells were exposed to H# 14,506 (Phosphonic Acid, (Aminocarbonyl)- Monoethyl Ester, Ammonium Salt) (lot no.S60406-86; a.i.: 41.5%) at concentrations ranging from 3.3 to 33.3 µl/ml (Trial 1) or to 30.0 µl/ml (Trials 2 and 3) for 18 to 19 hours at 37° C w/o activation and from 3.3 to 40 µl/ml for 5 hours with activation. Three trials (non-activation) or two trials (activation) were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related statistically significant increase in the mutant frequency of the treated cells. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 6/6/14)

Mutagenicity: *In vivo* cytogenetics ** †

** 50097-0004; 17065; "Unscheduled DNA Synthesis/Rat Hepatocytes *in Vitro*"; (K.T. McCooey; E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 680-82; 10/20/82); Primary rat hepatocyte cultures were exposed to H# 14,506 (Phosphonic Acid, (Aminocarbonyl)- Monoethyl Ester, Ammonium Salt) (lot no. S60406-86; a.i.: 41.5%) at concentrations ranging from 0.01 to 10000 µM for 18 hours at 37° C. Vehicle control (phosphate-buffered saline) and positive control (DMBA, 500 or 1000 µM) cultures were included in the assay. There were 2 cultures/treatment level. There was no treatment-related increase in unscheduled DNA synthesis. **No adverse effect indicated.** The positive control was functional. **Study acceptable**. (Moore, 6/9/14)

** 50097-0004; 17062; "*In Vivo* Bone Marrow Cytogenetic Assay in Rats"; (M.G. Farrow; Hazleton Laboratories America, Inc., Vienna, VA; Project No. 201-572; 11/1/82); Twelve Sprague Dawley rats/sex/group were dosed orally by gavage with 0 (vehicle: isotonic saline),

1000, 3000 or 10000 mg/kg of H# 14,506 (Carbamoyl-Phosphonic Acid Monoethyl Ester, Ammonium Salt) (no lot no.; a.i.: 41.5%). Three animals/sex/group/time point were euthanized at 6, 12, 24 and 48 hours post-dose and bone marrow was recovered from the femurs of each animal. The animals received an ip injection of colchicine, 2 mg/kg, at 2 hours prior to sacrifice. A positive control group of 3 animals/sex received a dose of 40 mg/kg of cyclophosphamide and were euthanized at 24 hours post-dose. Fifty bone marrow cells in metaphase/animal if possible were analyzed for chromosomal aberrations. There was no apparent treatment-related increase in the incidence of chromosomal aberrations in the bone marrow cells. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 6/4/14)

**** 50097-0004; 17063**; "*In Vitro* Assay for Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells"; (D. Vlachos; E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 683-82; 10/19/82); Chinese Hamster Ovary cells (CHO-K_1) (BH-4 clone) were incubated with H# 14,506 (Phosphonic Acid, (Aminocarbonyl)- Monoethyl Ester, Ammonium Salt) (lot no. S60406-86; a.i: 41.5%) at concentrations ranging from 0.3 to 33.3 µg/ml under conditions of non-activation and from 1.5 to 60.0 µg/ml under conditions of activation at 37° C. The non-activated samples received 10 hours of treatment. The activated samples received 2 hours of treatment followed by 8 hours of additional incubation. In both assays, the cells were incubated the last 2 hours with Colcemid prior to fixation. Two trials were performed with duplicate cultures for each treatment. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was an increased incidence in the percentage of cells with chromosomal aberrations with and w/o activation. **Possible adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 6/5/14)

50097-0066; 277254; "Rat Spermatid Micronucleus Assay of Fosamine-Ammonium (DPX-R1108-100) following Acute Oral Exposure"; (K.S. Bentley; E.I. du Pont de Nemours and Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 357-96; 4/26/96); Twenty male Crl:CD (SD) BR rats/group were dosed orally by gavage with 0 (vehicle: sterile water) or 5000 mg/kg/day of Fosamine, Ammonium Technical (DPX-R1108 technical) (batch no. DPX-R1108-100; purity: 97.7%) for 5 days. Five animals/group/time point were euthanized at 1, 3, 18 and 20 days post-final dose. In a positive control group, 10 animals were dosed by ip injection with 100 mg/kg/day of methyl methanesulfonate on study days 4 and 5. Five animals/time point were euthanized on 18 and 20 days post-final dose. The sampling times of 1, 3, 18 and 20 days post final dose corresponded to diakinesis MI and MII (metaphase), late pachytene (G2 phase) and preleptotene (G1 and S phase) stages of spermatocyte development. The incidence of micronucleated spermatids was ascertained. Four of the treated animals died prior to study day 5. Five of the positive control animals died, necessitating the dosing of an additional 8 animals, 3 more of which died. There was no apparent increase in the incidence of micronucleated spermatids in the treated animals. However, the response of the positive control group was also equivocal. **No adverse effect indicated. Study supplemental** (study was not performed according to an approved guideline for assessing chromosomal aberrations) (Moore, 5/23/14)

REPRODUCTIVE TOXICITY, RAT

50097-0007; 24997; "Three Month Dietary Feeding with One-Generation Reproduction Study – Rats"; (no study director identified; Hazleton Laboratories, Inc., Falls Church, VA; Report No. HLO-362-69; 11/14/69); (**phase II: one generation reproductive toxicity**) Sixteen albino rats (strain not identified) received 0, 200, 1000 or 5000 ppm of R 1108 (Ammonium Ethyl Carbamoylphosphonate) (no lot no.; purity of test material not identified) in the diet for 13 weeks. The treatment level of the high dose group was adjusted to 10000 ppm after 8 weeks of treatment. At the end of thirteen weeks of treatment, 10 animals/sex/group were euthanized for the subchronic toxicity study. The remaining 6 animals/sex/group were treated through the mating, gestation and lactation periods of two litters of offspring (F1a and F1b). There was no apparent treatment-related effect upon fetal development. **No adverse effect indicated.** No NOEL established. **Study supplemental.** (Moore, 6/2/14)

DEVELOPMENTAL TOXICITY

Rat **

** 50097-0057; 277238; "Developmental Toxicity Study of DPX-R1108-100 in Rats"; (L. Alvarez; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 43-92; 5/8/91); Twenty five mated Crl:CD BR females/group were dosed orally by gavage with 0 (vehicle: deionized water), 50, 350, 1000 or 3000 mg/kg/day of DPX-R1108-100 (Fosamine Ammonium Technical) (no batch no.; purity: 97.7%) on days 7 through 16 of gestation. No unscheduled deaths resulted from the treatment. The mean body weight gain of the dams in the 3000 mg/kg group was less than that of the control group on gestation days 7 to 9 ($p<0.05$). The mean food consumption of the dams in the 1000 and 3000 mg/kg groups was less than that of the control group from gestation days 7 to 9 ($p<0.05$). The lower food consumption of the 3000 mg/kg dams persisted through day 17 of gestation ($p<0.05$). There was no treatment related effect upon litter size, number of resorptions, number of live fetuses, or fetal body weight. **No adverse effects were evident. Maternal NOEL:** 350 mg/kg/day (based on the incidence of diarrhea and reduced food consumption of the dams in the 1000 mg/kg treatment group); **Developmental NOEL:** 3000 mg/kg/day (based on the lack of treatment-related effects on the fetuses in the 3000 mg/kg group); **Study acceptable**. (Moore, 5/14/14)

50097-0007; 24998; "Teratogenic Study in Rats with Carbamoyl-Phosphonic Acid Monoethyl Ester, Ammonium Salt (INR-1108)"; (R. Culik; E.I. du Pont de Nemours and Co., Inc., Haskell Laboratory; Report No. 605-73; 12/11/73); Twenty eight or twenty seven mated CR-CD females rats/group received 0, 200, 1000 or 10000 ppm of INR 1108 (Carbamoyl-Phosphonic Acid Monoethyl Ester, Ammonium Salt) (code no. INR-1108-28; a.i.: 42%) in the diet from gestation day 6 through 15 (reported a.i. uptake: 18.9, 92.2, 944.0 mg/kg/day). There was no treatment-related effect upon the mean body weights or food consumption of the dams. The development of the fetuses was not apparently affected by the treatment. **No adverse effect indicated.** Summary data only. No NOEL established. **Supplemental Study** (Moore, 6/3/14)

Rabbit **

**50097-0074 279584 Kappeler, C. J., "An oral (gavage) prenatal developmental toxicity study of fosamine ammonium in rabbits," WIL Research, Ashland, OH, June 5, 2013. Laboratory

Study No. WIL-925002. Groups of 25 timed-mated NZW females were dosed by gavage with fosamine ammonium, Batch 20120805, purity 95.3% on gestation days 7-28 in a guideline developmental toxicity study. Maternal NOEL = 100 mg/kg/day, based mainly on "decreased defecation," which indicated a strong dose-response over the range of 300 to 700 mg/kg/day. Developmental NOEL = 700 mg/kg/day (no effects at highest dose tested). Common findings in 700 mg/kg/day rabbits included "brown material in anogenital area" (wet or dried), and soft stool. Study is acceptable, with no adverse effects. Aldous, 10/21/14.

50097-0055; 277236; "An Oral (Gavage) Dose Range-Finding Prenatal Developmental Toxicity Study of Fosamine Ammonium in Rabbits"; (C.J. Kappeler; WIL Research, Ashland, OH; Study No. WIL-925001; 3/27/13); Six mated female New Zealand White rabbits/group were dosed orally with 0 (vehicle: deionized water), 100, 300, 700 or 1000 mg/kg/day of Fosamine Ammonium Technical (lot no. 20120805; purity: 95.3%) from gestation day 7 through 28. Two does in the 1000 mg/kg group were euthanized *in extremis* on gestation days 18 and 21 due to excessive body weight loss and inappetence. One doe in the 700 mg/kg group was found dead on gestation day 28. She too had lost weight over the previous week. The body weight gain and food consumption of the 700 and 1000 mg/kg groups were less than the control values of the control group over the course of the study. The mean fetal weight of the 700 and 1000 mg/kg groups were less than the mean control fetal weight. There was no apparent treatment-related effect on other fetal developmental parameters. **No adverse effect indicated. Maternal and Developmental NOELs were not established due to the incompleteness of the study protocol. Study supplemental** (the number of does/group was too few for a guideline study and the fetal examination only included an external assessment). (Moore, 5/12/14)

50097-0075 279585 is a re-submission of Record No. 277236, above.

NEUROTOXICITY

Acute neurotoxicity, rat **

**50097-0072 279582 Christoph, G. R., "Acute neurotoxicity study of DPX-R1108-100 (fosamine ammonium) in rats," Haskell Laboratory (Du Pont), Newark DE, 9/22/93. DuPont HLR 431-93. Twelve Crl:CD®BR rats/sex/group were dosed once by gavage with DPX-R1108-100 (fosamine ammonium), Batch R1108-100, purity 97.7%, at 0, 500, 1000, or 2000 mg/kg. All rats were examined pre-test and on days 1, 8, and 15 for FOB and motor activity. After day 15 FOB and motor activity tests, 6 rats/sex/group were perfused *in situ*, embedded with methacrylate (peripheral nerves and Gasserian ganglia), or paraffin (other protocol tissues), stained, and evaluated for neurohistopathology. NOEL = 500 mg/kg, based primarily on clinical signs of diarrhea in 1000-2000 mg/kg males and females on day 1. Irregular respiration in 1000-2000 mg/kg males on day 1 appeared to be also treatment-related. FOB was negative, except to confirm diarrhea noted in clinical signs. Subsequent FOB's, motor activity, and histopathology were uneventful. Study is acceptable, with no adverse effects. Aldous, Oct. 9, 2014.

90-day neurotoxicity, rat **

**50097-0073 279583 Christoph, G. R., "Subchronic neurotoxicity study of DPX-R1108-100 (fosamine ammonium) in rats," Haskell Laboratory (Du Pont), Newark DE, 9/24/93. Study No. DuPont HLR 438-93. Twelve Crl:CD®BR rats/sex/group were dosed in diet with 0, 5000,

10000, or 20000 ppm of DPX-R1108-100 (fosamine ammonium), Batch R1108-100, purity 96.9%, in the diet for 96-98 days in a guideline subchronic neurotoxicity study. Estimated achieved dose levels, calculated by DPR reviewer based on nominal exposures together with averages of reported achieved concentrations, were 285, 531, and 1018 mg/kg/day for increasing dose groups in males, and 379, 684, and 1337 mg/kg/day for respective females. NOEL < 5000 ppm (males), due to increased diarrhea in all dose groups at clinical observations. NOEL in females = 5000 ppm, based on increased incidence of diarrhea. Diarrhea in 5000 ppm males was seen only once or twice in the majority of affected rats. There were no changes relating to the key parameters of this study type, such as in FOB, motor activity, or neurohistopathology. Study is acceptable, with no adverse effects. Aldous, 10/10/14.

Developmental neurotoxicity, rat

No study submitted.

Delayed neurotoxicity, hen **

**50097-0071 279581 Fletcher, D. W., "H18642: 21-day acute delayed neurotoxicity study in mature leghorn hens," Bio-Life Associates, Ltd. (BLAL), Neillsville, WI, 6/22/93. BLAL Study No. 124-001-13. DuPont HLO No. 434-93. Leghorn hens were assigned to groups as follows: (1) Twenty received 2000 mg/kg fosamine ammonium [also designated as DPX-R1008-100 (technical)], 97.7% purity; (2) Sixteen received 500 mg/kg TOTP as positive controls, and (3) Sixteen negative controls received empty capsules. From each group, 4 were sacrificed at 24 hrs and an additional 4/group at 48 hrs for brain esterase assays (NTE and AChE). The remaining hens (12 fosamine hens: 8 in other groups) were examined for clinical signs for 21 days (reduced to 17 days for TOTP hens due to declining condition). Hens were perfused with fixative at sacrifice, after which 6/group were randomly selected for neurohistopathology (mid-saggital section of brain, proximal and distal sections of spinal cord cervical, thoracic, and lumbosacral regions, and sciatic nerves were examined by longitudinal section (distal) or cross-section (proximal), each bilaterally. There were no neurological clinical signs due to fosamine. TOTP hens began to show generalized weakness beginning on day 13, with ataxia beginning on day 14 in one hen. Seven of eight remaining TOTP hens showed some level of ataxia by the last examination on day 16. Fosamine had no influence on NTE or on AChE activities in brain or spinal cord. The positive control, TOTP, in contrast, markedly inhibited NTE (about 90% reduction in brain and about 70% reduction in spinal cord), with no effect on AChE. Characteristic neurohistopathology of TOTP was observed in 2 of the 6 TOTP hens examined, namely myelin bubbles, myelin debris, and Schwann cell proliferation in proximal and distal sections of the tibial nerve. Fosamine hens and negative controls showed no such responses. Study is acceptable, and negative for acute delayed neurotoxicity. Aldous, 9/11/14.

IMMUNOTOXICITY **

** 50097-0068; 277256; "A 28-Day Oral Gavage Immunotoxicity Study of Fosamine Ammonium in CD-1 Mice"; (J. Bultman; WIL Research, Ashland, OH and ImmunoTox, Inc., Richmond, VA; Project ID No. WIL-925005; 4/22/13); Ten CD-1 female mice/group were dosed orally by gavage with 0, 100, 500 or 1000 mg/kg/day of Fosamine, Ammonium Technical (lot no. 20120805; purity: 95.3%) for 28 days. Another 10 females were dosed by intraperitioneal injection with 50 mg/kg of cyclophosphamide on study days 24 through 27 as the positive control group. On day 24, each animal received an iv injection of $1x10^8$ sheep red blood cells (SRBC) (0.2 ml volume). SRBC specific IgM plaques were determined for each animal by

incubating a spleen cell suspension preparation with guinea pig complement and SRBC. No deaths occurred during the treatment period. There was no apparent treatment-related effect upon the mean body weights or food consumption. There were no treatment-related lesions noted in the necropsy examination. There was no treatment-related effect upon the thymus or spleen weights. There was no treatment- related effect evident in the plaque-forming cell assay. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 5/27/14)

ENDOCRINE DISRUPTOR STUDIES

No Study submitted.

SUPPLEMENTAL STUDIES

Mechanistic Study

50097-0042; 277214; "Cholinesterase Inhibition Study with DPX-R1180-100 (Fosamine Ammonium) in Rats"; (S.A. MacKenzie; **:** E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 599-93; 9/15/93); Ten male Crl:CD BR rats/group were dosed orally by gavage with either 0 (vehicle: deionized water) or 2000 mg/kg/day of DPX-R1108-100 (Fosamine, Ammonium Technical) (batch no. R1108-100; purity: 97.7%) for 5 days. At the conclusion of the dosing interval, blood was collected from the orbital sinus at 3 hours post-final dose. The animals were then euthanized at 4 to 6 hours post-final dose and the brains were dissected. Cholinesterase (ChE) activity was assayed in the plasma, red blood cell and brain (cerebellum, hippocampus and neocortex). No treatment-related effect was evident on ChE activity in the plasma, red blood cell or brain. **No adverse effect indicated. Study supplemental.** (Moore, 5/8/14).