AMINOTRI(METHYLENEPHOSPHONIC ACID)

Document History
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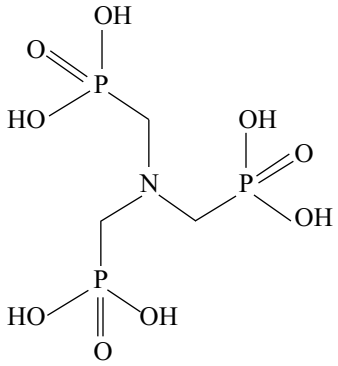
I. IDENTIFICATION[1-3]

Chemical Name: Aminotri(methylenephosphonic acid)
Synonyms: ATMP; Aminotris(methylenephosphonic acid), Briquest 302-500; Briquest 301-32S; Dequest 2000; Dequest 2001; Nitrilotrimethanephosphonic acid; NTMP; NTPA, NTF
CAS Number: 6419–19–8
Molecular Formula: C_3-H_{12}-N-O_9-P_3
Chemical Structure:



DOT #: UN3265

II. CHEMICAL AND PHYSICAL PROPERTIES[1-3]

Physical State: Liquid
Molecular Weight: 299.07
Conversion Factors: 1 ppm = 12.2 mg/m^3
1 mg/m^3 = 0.08 ppm at 20°C (68°F)
Melting Point: -14°C (24.8°F)
Boiling Point: 105°C (221°F)
Vapor Pressure: 1 x 10^{-7} mm Hg at 20°C (68°F)
Saturated Vapor Concentration: 0.00013 ppm (calc.)
Vapor Density: Not available
Odor Description and Threshold: Not available
Flammability Limits: LEL: not available UEL: not available
Flash Point: Not applicable, aqueous solution
Autoignition Temperature: Not applicable, aqueous solution
Specific Gravity: 1.33 at 20°C (68°F) (water = 1)
Solubility: Soluble in water (610 g/L @ 35°C)
Reactivity: Not available; product is sold as an aqueous solution containing 50% w/w or less of the acid at pH <2 and pH neutral solution (sodium salt solution). Decomposition takes place at 200–250°C. Will give off phosphine if heated >200°C.
Log K_{ow}: -3.53

III. USES AND VOLUMES[2-3]

Used for industrial water treatment, bleach stabilizer, cleaning/washing agent, corrosion inhibitor, anti-scaling agent, complexing agent.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Oral

LD_{50} >10 g/kg of the tested solution, rat (Sprague-Dawley, OECD 401 GLP study with Briquest 310-32S, 6.6 g/kg of sodium salt, 4.4 g/kg of neutralized acid)[2,3]

LD_{50} = 2910 mg/kg, rat (Sprague-Dawley, Monsanto, non-GLP study, 25% aqueous solution of acid)[2,3]

LD_{50} = 2100 mg/kg, rat (sex and strain not specified)[1]

2. Eye Irritation

The eyes of New Zealand rabbits were exposed to Briquest 301-32S (32% w/w solution) in an OECD 405 (GLP) study. Under the conditions of this study no significant irritation reactions were observed (max. scores at 1 hr were: 0 for cornea, 1 for iris and 1 for chemosis).[4] In a Draize test[5], ATMP, as dried Dequest 2000 powder, was applied to rabbit eyes. The maximum score 24 hrs after administration of the test material was 53.6/110. Edema, copious discharge, moderate conjunctival redness, and mild corneal cloudiness were observed within one hour.

Based on this study, the test material was considered a moderate eye irritant.

3. Skin Absorption

LD_{50} > 6310 mg/kg, rabbit (New Zealand White, Monsanto, non-GLP study, 25% aq. solution)[1,3]

LD_{50} > 10 ml/kg of the tested solution, rat (Sprague-Dawley, OECD 402 GLP study with Briquest 310-32S, 32% w/w as acid).[2]

4. Skin Irritation

The dermal irritancy of Briquest 310-32S (50% w/w aq. sol'n of ATMP) was tested in New Zealand white rabbits in accordance with OECD test guideline 404. Under the conditions of this GLP study, the test material was classified as a mild irritant, with a Primary Irritiation Index (PII) of 0.1. The maximum score for erythema and edema one hr. after removal of the test substance was 1.[2,3]

In a Draize skin irritation test with New Zealand white rabbits[2,3], ATMP was applied as a dry powder or a 25% aqueous solution. It was non-irritating when applied as a powder (PII = 0/8) and a moderately severe irritiant (PII = 4.6/8) when applied as a 25% aqeous solution.

5. Skin Sensitization

ATMP was judged negative in a Magnusson and Kligman maximization test with guinea pigs[6] (no further details available).

6. Inhalation Toxicity

No data found for ATMP

7. Other

No data found for ATMP

B. Subacute Toxicity

No data found for ATMP

C. Subchronic Toxicity

Groups of 5 Long-Evans rats/sex/dose were orally exposed via the feed for 34 days to 0, 125, 240, 500, 750, or 1000 mg/kg/day of ATMP (as Dequest 2000 dried acid), in a study conducted in accordance with OECD test guideline 407.[7] No treatment-related effects were observed on body weights, food consumption, survival, or gross pathology findings. There were no hematology or clinical chemistry assessments made during this study. The NOAEL for the study was set at 1000 mg/kg/d.

Groups of 5 Sprague-Dawley rats/sex were exposed to diets containing 0 or 6000 ppm (~300 mg/kg/d) ATMP (as Briquest 301-32S, 32% expressed as acid) for 90 days.[8] One of ten controls died during the test but there were no mortalities among the ATMP-exposed rats. Food consumption and body weight gains were comparable in treated and control animals. No macroscopic abnormalities were noted, however histopathological examinations were not performed. No differences between treated and control groups were noted in the limited clinical chemistry assessments included in this study. The authors set the NOAEL for this study at 6000 ppm (~300 mg/kg/d).

D. Chronic Toxicity/Carcinogenicity

A study designed to evaluate the chronic toxicity/carcinogenicity of ATMP was conducted using groups of 70 Long-Evans rats/sex/dose exposed via the feed to 0, 50, 150 or 500 mg/kg/d for 2 years.[9, 10] Groups of 10 rats/sex were sacrificed after 6 and 12 months exposure. No treatment related-effects on survival were noted, nor were there any significant differences in hematological or clinical chemistry parameters between the control and exposed groups. Male rats from the high dose group had decreased body, liver, spleen and kidney weights, in the absence of decreased food consumption. No histopathological effects related to test material exposure were observed in rats at the interim or final sacrifices, and the incidences of neoplastic and non-neoplastic lesions were similar for all test groups. One unusual tumor (osteosarcoma-axilla) was observed in one of the high dose male rats. However the biological relevance of this finding could not be determined. Based on the non-neoplastic effects observed in males at 500 mg/kg/d, a chronic NOAEL of 150 mg/kg/d was established from this study.

E. Developmental/Reproductive Toxicity

In a Segment II FDA guideline teratology study, 0, 100, 500, or 1000 mg/kg/d ATMP (as Dequest 2000) was administered by gavage to groups of pregnant CD-1 rats from Days 6–15 of gestation.[2,11] A slight reduction in weight gain of dams was observed at 1000 mg/kg/d. A significant increase in resorptions and the number of dams with ≥2 resportions was noted at 100 and 1000 mg/kg. However, the incidence of these parameters were within the historical control range, and no similar increase was observed in dams of the 500 mg/kg group. Consequently, this was not considered an effect of treatment. No teratogenic effects were observed in litters from the low- and mid-dose groups. In the high-dose

group, six pups from a single litter had multiple malformations including flexed forepaws, shortened torso, abdominal distension and exaggerated flexure of the head. Two of these six pups also had a malrotation defect of the heart. All other high-dose pups were unremarkable. The authors concluded that no significant developmental or embyro/fetotoxicity occurred at 100 or 500 mg/kg. At 1000 mg/kg, no embyro/fetotoxicity was observed, however a possible teratogenic effect could not be discounted. The authors set the maternal NOEL at 500 mg/kg and the developmental LOEL at 1000 mg/kg.

ATMP was also tested in a three-generation reproduction study with Long-Evans rats.[2,11] F_0 groups were composed of 12 male and 24 female rats, and were exposed via the diet to 300, 1000, or 3000 ppm (15, 50 or 150 mg/kg/d) ATMP. No adverse effects were observed on fetal, pup or adult survival, or on pup or adult body weights. Mating and fertility indices were normal for all test groups. Histopathologic examination of selected tissues from F3 pups indicated no treatment-related effects.

F. Genotoxicity/Mutagenicity

ATMP (as Dequest 2000) was tested in *S. typhimurium* strains TA1535, TA1537, TA100, and TA98 with and without S-9 in a GLP Ames test. ATMP was negative in all strains with and without metabolic activation.[2]

ATMP (as Dequest 2000) was also tested for gene mutations in L5178Y mouse lymphoma cells with and without S-9. It was positive in this assay with metabolic activation but produced negative results without metabolic activation. The authors considered the positive result in the presence of S-9 consistent with the effect of low pH in this type of bioassay. Consequently, the test with metabolic activation was repeated with neutralized ATMP and under those conditions the result was negative.[2]

ATMP was also tested in a GLP mouse micronucleus assay conducted in accordance with OECD guideline 474.[2,12] Male and female mice were dosed by gavage with aqueous solutions 0, 120, 600, or 1200 mg/kg ATMP. Bone marrow smears were prepared from each animal 24 hrs. after dosing, and in the case of high dose animals, also 48 and 72 hrs after administration of the test material. At 1200 mg/kg, the group mean micronucleated cell count at 24, 48 and 72 hrs did not differ significantly from the control group. Consequently, the bone marrow smears from the 120 and 600 mg/kd groups were not evaluated. The authors concluded that ATMP did not show any evidence of mutagenic potential in the mouse micronucleus assay.

G. Metabolism and Pharmacokinetics

A toxicokinetics study with ^{14}C-labelled ATMP (as Dequest 2000) was conducted with male Sprague-Dawley rats administered the test material via the oral (150 mg/kg) and intravenous (15 mg/kg) routes.[2] Absorption of ATMP following a single oral dose was 2.15%. Approximately 1.14% of the oral dose was excreted in the urine and 83% was excreted in the faeces. Elimination via expired gases accounted for <0.05% of the oral dose. The half-life of ATMP in the plasma showed a bi-phasic pattern with $t_{1/2}$ of 0.53 and 38.4 hr. Clearance was calculated as 0.28 mL/hr. When administered i.v., 53% of the dose was eliminated in the urine with 4.6% eliminated in the feces. Approximately 21% of the dose remained in the carcass. Autoradiographic analysis of both orally and intravenously dosed rats showed that very little ^{14}C remained in any tissues 10 days after dosing, except for the bone of i.v. dosed animals.

In another study, the cutaneous absorption of labelled ATMP (1% solution) was 0.6% in male rats and 0.9% in female rats, 48 hrs. after exposure.[2] ATMP was excreted mainly in the urine during the first 24 hrs. after dermal application.

V. HUMAN USE AND EXPERIENCE

No adverse effects have been reported in >20 years of use aside from those related to the known irritancy of ATMP.[2]

VI. RATIONALE

ATMP is a liquid with a low vapor pressure at room temperature. It is normally sold/used as an aqueous solution. Consequently, inhalation exposure is unlikely to occur unless it is heated, or where aerosols are produced. As an aqueous solution it is a mild skin and eye irritant. As a solid powder it has produced moderate-severe eye irritation reactions. It has low acute toxicity via the oral route and dermal routes. It was negative for dermal sensitization reactions in a guinea pig maximization assay. ATMP was negative in the Ames, mouse lymphoma and mouse micronucleus assays. No significant adverse effects were observed in 34- and 90-day oral feeding studies in the rat in which NOAELs 1000 mg/kg/day and 6000 ppm (300 mg/kg/d) were established. Chronic dietary exposure to Long-Evans rats to up to 500 mg/kg/d had no effect on the incidence of neoplastic lesions and the NOAEL for systemic effects was 150 mg/kg/d. No adverse developmental or reproductive effects were noted in rats exposed to as much as 500 mg/kg/d by gavage and 3000 ppm (150 mg/kg/d) in the diet, respectively.

Based on the chronic NOAEL of 150 mg/kg/d, a OEL Guide of 10 mg/m^3 (aerosol) should provide

adequate protection against possible systemic or developmental toxicity.

VII. RECOMMENDED OEL

Based on its low vapor pressure, ATMP is not likely to be present in workplace air. An OEL Guide of 10 mg/m^3 (aerosol) is recommended.

VIII. REFERENCES

Databases consulted during this review include: RTECS; IUCLID; TSCATS; INCHEM

1. **RTECS:** Record SZ9860000, Phosphonic acid, (nitrilotris(methylene))tri-, last revised: 1997/10.
2. **IUCLID Dataset:** Nitrilotrimethylenetris(phosphonic acid), CAS 6419–19–8, European Commission, 18 Feb 2000.
3. **OECD SIDS Summary,** Phosphonic acid, (nitrilotris(methyelene)tris-), CAS 6419–19–8, IRPTC Data Profile.
4. **Albright & Wilson:** Internal report 678/8208, OECD 405 study with Briquest 301-32S (1982) [unpublished report summarized in refs 2 and 3].
5. **Monsanto Company:** Unpublished report Y-66-199, eye irritation study with ATMP as dried dequest 2000 acid powder (undated) [unpublished report summarized in refs 2 and 3].
6. **Henkel, K.A.:** unpublished data, Guinea Pig Maximization Test, archive no. 840016 and 840185 (1969) [unpublished report summarized in ref 2].
7. **Monsanto Company:** unpublished report BDN-75-117, Repeated Dose Oral Toxicity Study with Dequest 2000 (undated) [unpublished report summarized in ref 2].
8. **Abright & Wilson:** internal report 625/8208, OECD 408 study with Briquest 301-32S (1982) [unpublished report summarized in refs 2 and 3].
9. **Bio/dynamics Inc.:** A twenty-four month oral toxicity/carcinogenicity study of CP 42902 in rats, study no. BD-75-118, Monsanto Company, EPA/OTS0524047, 8EHQ-0490-0937 (1979).
10. **Stevens, M.W.:** Chronic Toxicity and Reproduction Studies on Aminotri(methylenephosphonic acid) [ATMP]. *Toxicologist 2*:35 (1982) [abstract].
11. **Bio/dynamics Inc.:** A segment II teratology study of FA 42902 (CAS#6419-19-8) in rats, study no. BD-78-54, Monsanto Company, EPA/OTS0524047-1, 8EHQ-0490-0937 (1979).
12. **Wallat, S.:** Prüfung auf Mutagenität im Mikrokern-Test *in vivo*. Henkel Inst. für Toxicologie, unpublished report number 840401 (1984) (summary in English, report in German).