

201-15125A

High Production Volume (HPV) Challenge Program

Data Analysis and Test Plan

For

Phenol, 2,4,6-tris[(dimethylamino)methyl]-

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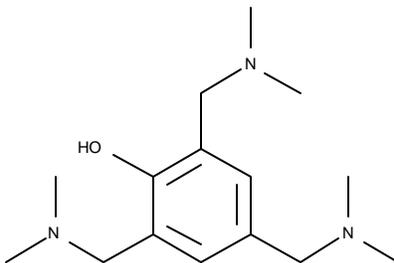
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1.0 INTRODUCTION

Phenol, 2,4,6-tris[(dimethylamino)methyl]- is a Mannich base that is used as a delayed-action gelation catalyst for rigid foams, as a curing agent and as a tertiary amine activator for epoxy resins cured with a wide variety of hardener types. Phenol, 2,4,6-tris[(dimethylamino)methyl]- has the following structure:



Air Products and Chemicals, Inc. has committed to provide basic chemistry, environmental fate, ecotoxicity and health effects information on phenol, 2,4,6-tris[(dimethylamino)methyl]- (CAS 90-72-2) listed under the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program. By participating in this voluntary program, Air Products and Chemicals, Inc., agreed to assess the adequacy of existing data; prepare summaries of the data characterizing the chemical; determine data needed to fulfill the HPV data requirements; and design and submit a test plan to satisfy these testing requirements.

2.0 EVALUATION OF DATA

2.1 Physico-chemical Data

- 2.1.1 Melting Point:** -20° C (-4° F) [Ref. 1]
- 2.1.2 Boiling Point:** started to decompose at approximately 156° C (313° F) [Ref. 2]
- 2.1.3 Vapor Pressure:** 7.5×10^{-2} Pa @ 25°C (5.6×10^{-4} mm Hg) [Ref. 3]
- 2.1.4 Partition Coefficient:** $\log Pow = -0.660$ at 21.5°C [Ref. 4]
- 2.1.5 Water Solubility:** >85% w/w (>850 g/l) at 20±0.5°C [Ref. 5]

2.1.6 Summary of Physico-chemical Data

Scientifically reliable data exists for all SIDS physico-chemical endpoints. No additional testing is recommended.

2.2 Environmental Fate and Biodegradation Data

2.2.1 Photodegradation:

Estimation Programs Interface for Microsoft® Windows (EPIWIN V3.10, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C.), Atmospheric Oxidation Program (v1.90) modeling component was used to calculate the rate of photodegradation for phenol, 2,4,6-tris[(dimethylamino)methyl]-. The half-life was calculated to be 0.042 days (or approx. 1/24 hour), assuming the reaction occurred over a 12-hour day with an average atmospheric concentration of 1.5×10^6 OH/cm³ [Ref. 6].

2.2.2 Hydrolysis:

For hydrolysis reactions to occur, there must be an electrophilic carbon atom, which is 'attacked' by oxygen, and a 'leaving group', which departs from the attacked carbon atom. The most electropositive carbon in the phenol, 2,4,6-tris[(dimethylamino)methyl]- molecule is the carbon attached to the phenolic OH group due to the electron withdrawing effect of the phenolic OH group.

The hydrolysis reaction of phenol, 2,4,6-tris[(dimethylamino)methyl]- if it were to occur, would occur by attack of water or OH at the carbon attached to the phenolic OH group. The product of such a reaction would be phenol, 2,4,6-tris[(dimethylamino)methyl]- itself, indicating that there would be no net hydrolysis reaction.

Phenol, 2,4,6-tris[(dimethylamino)methyl]- would be hydrolytically stable under the conditions of the OECD hydrolysis test (OECD Guideline 111), and laboratory testing is not required.

2.2.3 Biodegradation:

Phenol, 2,4,6-tris[(dimethylamino)methyl]- degraded approximately 4% in 28 days in the Closed Bottle test (OECD 301D). Phenol, 2,4,6-tris[(dimethylamino)methyl]- is therefore not readily biodegradable [Ref. 7].

2.2.4 Transport/Distribution:

The Level III fugacity model (from EPIWIN V3.10, US EPA) was used for predicting partitioning of phenol, 2,4,6-tris[(dimethylamino)methyl]- among air, water, soil and sediment compartments. The following are the concentration results using a soil K_{oc} of 0.0897 as calculated by the model and a $\log K_{ow}$ of -0.66 as determined through octanol water partition coefficient testing [Ref. 8]:

| | |
|------------|--------|
| - Air | <0.01% |
| - Water | 51.9% |
| - Soil | 48% |
| - Sediment | <0.1% |

2.2.5 Summary of Environmental Fate and Biodegradation Data

Scientifically reliable data exists for most SIDS environmental fate and biodegradation endpoints. No additional testing is recommended.

2.3 Ecotoxicology Data

2.3.1 Acute Toxicity to Fish:

Phenol, 2,4,6-tris[(dimethylamino)methyl]- was tested in both rainbow trout and carp [Ref. 9].

Rainbow trout (*Salmo gairdneri*) were exposed for 96 hours to concentrations of 0, 140, 180, 240, 280, and 320 mg/l of phenol, 2,4,6-tris[(dimethylamino)methyl]- in a static system. Ten fish were exposed at each concentration. The 24- and 96-hour LC_{50} values (concentration causing 50% of the fish to die) were determined. The 24-hour LC_{50} value was 222 mg/l with a 95 percent confidence interval of 174 to 283 mg/l. The 96-hour LC_{50} value was >180 mg/l but <240 mg/l. The 96-hour LC_{100} value was 240 mg/l. The 96-hour No Observed Effect Level (NOEL) was 180 mg/l.

Carp (*Cyprinus carpio*) were exposed for 96 hours to concentrations of 0, 140, 240, 320, and 420 mg/l of phenol, 2,4,6-tris[(dimethylamino)methyl]- in a static system. Ten fish were exposed at each concentration. The 24- and 96-hour LC_{50} values were determined. The 24-hour LC_{50} value was 249 mg/l with a 95 percent confidence interval of 204 to 305 mg/l. The 96-hour LC_{50} value was 175 mg/l with a 95 percent confidence interval of 131 to 235 mg/l. The 96-hour LC_{100} value was 240 mg/l. The 96-hour NOEL was 140 mg/l.

These results indicate that phenol, 2,4,6-tris[(dimethylamino)methyl]- is practically nontoxic to fish.

2.3.2 Acute Toxicity to Aquatic Invertebrates:

Phenol, 2,4,6-tris[(dimethylamino)methyl]- was tested in both mud crabs and grass shrimp [Ref. 10].

Mud crabs (*Neopanope texana*) were exposed for 96 hours to concentrations of 0, 320, 420, 560, 750, and 1000 mg/l. Ten mud crabs were exposed at each concentration. The 24- and 96-hour LC_{50} values were determined. The 24- and 96-hour LC_{50} values were >750 mg/l but <1000 mg/l. The 96-hour LC_{100} value was 1000 mg/l. The 96-hour NOEL was 750 mg/l.

Grass shrimp (*Palaemonetes vulgaris*) were exposed for 96 hours to concentrations of 0, 320, 420, 560, 750, and 1000 mg/l. Ten shrimp were exposed at each concentration. The 24- and 96-hour LC₅₀ values were determined. The 24-hour LC₅₀ value was >750 mg/l but <1000 mg/l. The 96-hour LC₅₀ was 718 mg/l with a 95 percent confidence interval of 524 to 984 mg/l. The 96-hour NOEL was 560 mg/l.

These results indicate that phenol, 2,4,6-tris[(dimethylamino)methyl]- is practically nontoxic to aquatic invertebrates.

2.3.3 Toxicity to Aquatic Plants:

Phenol, 2,4,6-tris[(dimethylamino)methyl]- has not been tested in algae.

2.3.4 Summary of Ecotoxicology Data

Phenol, 2,4,6-tris[(dimethylamino)methyl]- is practically nontoxic to fish and aquatic invertebrates. Scientifically reliable data exists for these two SIDS ecotoxicity endpoints. Phenol, 2,4,6-tris[(dimethylamino)methyl]- has not been tested in algae. Therefore algal growth inhibition testing according to OECD guideline 201 is recommended.

2.4 Health Effects Data

2.4.1 Acute Health Effects

2.4.1.1 Acute Oral Toxicity

Groups of ten Sprague-Dawley rats (five male and five female) were orally administered undiluted phenol, 2,4,6-tris[(dimethylamino)methyl]- at dose levels of 1333, 2000 and 3000 mg/kg body weight. Surviving animals were observed daily post-dose for 14 days. All animals in the low dose group survived. Three out of ten animals in the mid-dose group died. All animals in the high-dose group died. All surviving animals appeared normal within three days or less of dosing, gained weight, and the only findings seen at necropsy in the survivors were abnormalities of the non-glandular stomach epithelium. Since this material is corrosive, the stomach findings were not unusual. The oral LD₅₀ for phenol, 2,4,6-tris[(dimethylamino)methyl]- in rats was 2169 mg/kg body weight [Ref. 11].

2.4.1.2 Summary of Acute Toxicological Effects

Phenol, 2,4,6-tris[(dimethylamino)methyl]- is practically non-toxic following a single oral exposure. Scientifically reliable data exists for the SIDS acute toxicity endpoint. Additionally this material is corrosive, therefore no additional acute toxicity testing is recommended.

2.4.2 Genetic Toxicology Effects

2.4.2.1 Bacterial Gene Mutation Assay

Phenol, 2,4,6-tris[(dimethylamino)methyl]- diluted in sterile water was examined for mutagenic activity in a *Salmonella typhimurium*-*Escherichia coli* direct plate incorporation assay. The assay was performed using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 and *E. coli* strain WP2uvrA⁻ over a dose range of 50 to 5,000 ug/plate in both the presence and absence of a phenobarbitone/â-naphthoflavone-induced rat-liver S9 metabolic activation system. OECD guideline 471 was followed. Phenol, 2,4,6-tris[(dimethylamino)methyl]- was not mutagenic under the test conditions used in this bacterial assay. [Ref. 12]

2.4.2.2 In Vitro Chromosomal Aberration Assay

Phenol, 2,4,6-tris[(dimethylamino)methyl]- has not been tested for chromosomal aberrations.

2.4.2.3 Summary of Genetic Toxicology Effects

Phenol, 2,4,6-tris[(dimethylamino)methyl]- was not mutagenic when examined in a *Salmonella typhimurium-Escherichia coli* direct plate incorporation assay according to OECD guideline 471. Phenol, 2,4,6-tris[(dimethylamino)methyl]- has not been tested for chromosomal aberrations. Therefore an in vitro chromosomal aberration test according to OECD guideline 473 is recommended.

2.4.3 Repeated Dose Health Effects

2.4.3.1 Systemic Dermal Toxicity

Rats were exposed dermally to tris(dimethylaminomethyl)phenol at dose levels of 0, 5, 25, and 125 mg/kg/day, 5 days/week for 4 weeks. Treatment-related signs and symptoms included slight to moderate excitability and/or hypertonicity in the 25- and 125-mg/kg, dose groups. Slight to moderate erythema, occasionally accompanied by edema and necrosis, was observed in the 125-mg/kg, dose group. Histopathology revealed moderate to marked hydropic change and slight parakeratosis in the epidermis in the 125-mg/kg, dose group. Slight hydropic change without parakeratosis was noted in the 25-mg/kg, dose group. The no observed effect level (NOEL) was 5 mg/kg/day [Ref. 13].

2.4.3.2 Reproductive and Developmental Toxicity

Phenol, 2,4,6-tris[(dimethylamino)methyl]- has not been tested for reproductive or developmental effects.

2.4.3.3 Summary of Systemic, Reproductive and Developmental Toxicity Effects

Phenol, 2,4,6-tris[(dimethylamino)methyl]- has been evaluated for repeated dose effects via the dermal route of exposure. Due to the corrosive nature of the material, the dose levels employed were relatively low and the clinical and pathological findings were limited to the site of exposure. It is therefore unclear whether phenol, 2,4,6-tris[(dimethylamino)methyl]- would be systemically toxic via oral exposure where a higher dose may be feasible.

Phenol, 2,4,6-tris[(dimethylamino)methyl]- has not been tested for reproductive or developmental effects. Therefore a combined oral repeat dose/repro-screening test according to OECD guideline 422 is recommended.

3.0 CONCLUSIONS

The majority of the data needed to meet the requirements of the HPV program are available and of high quality for phenol, 2,4,6-tris[(dimethylamino)methyl]-. Data for several endpoints are not currently available, therefore additional studies have been recommended to assess the hazards of this chemical. Table 1 shows the studies that exist for phenol, 2,4,6-tris[(dimethylamino)methyl]- and the data that still need to be developed.

TABLE 1: HPV DATA REQUIREMENTS/CRITICAL STUDIES: Phenol, 2,4,6-tris[(dimethylamino)methyl]-

| HPV Data Category | Test Endpoint | | Acceptable Data Reference (Klimisch Rating) | Data to be Generated |
|----------------------------------|---|-----------------------|---|----------------------|
| Physical and Chemical Properties | Melting Point | | 1 (1) | No |
| | Boiling Point | | 2 (1) | No |
| | Vapor Pressure | | 3 (1) | No |
| | Partition Coefficient | | 4 (1) | No |
| | Water Solubility | | 5 (1) | No |
| Environmental Fate and Pathways | Photodegradation | | 6 (2) | No |
| | Hydrolysis | | NA | No |
| | Biodegradation | | 7 (1) | No |
| | Transport/Distribution | | 8 (2) | No |
| Ecotoxicity | Acute toxicity to Fish | | 9 (2) | No |
| | Acute toxicity to Aquatic Invertebrates | | 10 (2) | No |
| | Toxicity to Aquatic Plants | | No | Yes |
| Human Health Effects | Acute toxicity | | 11 (1) | No |
| | Repeated Dose | | 13 (2) | Yes |
| | Genetic Toxicity | Gene Mutation | 12 (1) | No |
| | | Chromosome Aberration | No | Yes |
| | Reproductive Toxicity | | No | Yes |
| | Developmental Toxicity | | No | Yes |

Notes:

Data listed are cross-referenced to a Robust Summary report [i.e. 1 (2)]; which identifies the reference number and Klimisch Rating ().

NA= Not Applicable

4.0 REFERENCES

1. Melting Point: Air Products and Chemicals, Inc. (EXT-03/043). Phenol, 2,4,6-tris[(dimethylamino)methyl]-: Determination of General Physico-Chemical Properties. Testing Facility: Safepharm Laboratories Ltd., Shardlow Derbyshire, UK. Study year: 2003. Klimisch = 1
2. Boiling Point: Air Products and Chemicals, Inc. (EXT-03/043). Phenol, 2,4,6-tris[(dimethylamino)methyl]-: Determination of General Physico-Chemical Properties. Testing Facility: Safepharm Laboratories Ltd., Shardlow Derbyshire, UK. Study year: 2003. Klimisch = 1
3. Vapor Pressure: Air Products and Chemicals, Inc. (EXT-03/057). Phenol, 2,4,6-tris[(dimethylamino)methyl]-: Determination of the Vapor Pressure (OPPTS 830.7950). Safepharm Laboratories Ltd., Shardlow Derbyshire, UK. Study year: 2003. Klimisch = 1
4. Partition Coefficient: Air Products and Chemicals, Inc. (EXT-03/043). Phenol, 2,4,6-tris[(dimethylamino)methyl]-: Determination of General Physico-Chemical Properties. Testing Facility: Safepharm Laboratories Ltd., Shardlow Derbyshire, UK. Study year: 2003. Klimisch = 1
5. Water Solubility: Air Products and Chemicals, Inc. (EXT-03/043). Phenol, 2,4,6-tris[(dimethylamino)methyl]-: Determination of General Physico-Chemical Properties. Testing Facility: Safepharm Laboratories Ltd., Shardlow Derbyshire, UK. Study year: 2003. Klimisch = 1
6. Photodegradation: Estimation Programs Interface for Microsoft® Windows (EPIWIN V3.10, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C.) Atmospheric Oxidation Program (v1.90). Klimisch = 2
7. Biodegradation: Air Products and Chemicals, Inc. (EXT-99/104). Ancamine K54: Assessment of Ready Biodegradability: Closed Bottle Test. Testing Facility: Safepharm Laboratories Ltd., Shardlow Derbyshire, UK. Study year: 1996. Klimisch = 1
8. Transport/Distribution: Estimation Programs Interface for Microsoft® Windows (EPIWIN V3.10, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C.) Level III Fugacity Model. Klimisch = 2
9. Acute Toxicity to Fish: Air Products and Chemicals, Inc. (EXT-99/034). Acute Toxicity of DMP-30 to Carp (*Cyprinus carpio*), Rainbow Trout (*Salmo gairdneri*), Mud Crab (*Neopanope texana*), and Grass Shrimp (*Palaemonetes vulgaris*). Testing Facility: Bionomics, Inc., Wareham, Massachusetts, USA . Study year: 1973. Klimisch = 2
10. Acute Toxicity to Aquatic Invertebrates: Air Products and Chemicals, Inc. (EXT-99/034). Acute Toxicity of DMP-30 to Carp (*Cyprinus carpio*), Rainbow Trout (*Salmo gairdneri*), Mud Crab (*Neopanope texana*), and Grass Shrimp (*Palaemonetes vulgaris*). Testing Facility: Bionomics, Inc., Wareham, Massachusetts, USA . Study year: 1973. Klimisch = 2
11. Acute Oral Toxicity: Air Products and Chemicals, Inc. (EXT-92/042). Ancamine K54 (BX352): Acute Oral Toxicity Test in the Rat. Testing Facility: Safepharm Laboratories Ltd., Shardlow Derbyshire, UK. Study year: 1992. Klimisch = 1
12. Gene Mutation: Air Products and Chemicals, Inc. (EXT-03/071). Phenol, 2,4,6-Tris[(dimethylamino)methyl]-: Reverse Mutation Assay “Ames Test” Using *Salmonella typhimurium* and *Escherichia coli* (OECD 471). Testing Facility: SafePharm Laboratory, Shardlow, Derbyshire, UK. Study year: 2003. Klimisch = 1
13. Systemic Dermal Toxicity: Initial Submission: Final Report - TK 10433 - 28-Days Dermal Toxicity Study in Rats, EPA/OTS Doc # 88-920007287. Study year: 1986. Klimisch = 2