201-15310A

High Production Volume (HPV) Challenge Program

FINAL SUBMISSION
for
HEXAMETHOXYMETHYLMELAMINE

Melamine, hexakis(methoxymethyl)- (CAS # 3089-11-0)

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Prepared by

HMMM Coalition

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A. INTRODUCTION

The HMMM Coalition has voluntarily agreed to provide information under the U.S. EPA HPV Initiative for melamine, hexakis (methoxy methyl)- (CAS No. 3089-11-0), commonly known as hexamethoxymethylmelamine, and hereafter referred to as HMMM. By participating in this program, the Coalition has agreed to assess the adequacy of existing data on HPV endpoints, design and submit test plans to fill data gaps where necessary and appropriate, provide test results, and prepare summaries of the data characterizing HMMM.

HMMM is a methylated melamine formaldehyde resin used as a crosslinker in thermoset coatings such as beverage can coatings and automotive paint finishes. HMMM cannot be manufactured in pure form and cannot be isolated. Rather, commercial products contain a polymer mixture, and the HMMM itself can be present within the mixture as a monomer (CAS No. 3089-11-0) or as a low-molecular-weight polymer (methylated melamine-formaldehyde polymer, CAS No. 68002-20-0). The exact proportion of HMMM monomer to polymer varies with the manufacturing process, but commercial products are usually about 28-50% HMMM monomer. The balance is primarily the methylated melamine-formaldehyde polymer. Thus, while certain properties can be estimated for a hypothetical 100% monomeric product, the test data presented here are from testing of commercial products containing HMMM in a monomeric/polymeric mixture.

The HMMM Coalition submitting this Test Plan consists of Borden Chemical Inc., Cytec Industries Inc., and Surface Specialties, Inc., a subsidiary of UCB Chemicals Corporation, which has assumed the interests of former member Solutia Inc. in HMMM. Solutia manufactured, and UCB now produces, products containing HMMM in polymeric form, and hence is not covered by the HPV program. However, Solutia agreed to provide data regarding its HMMM-containing product. Its low-molecular-weight polymeric HMMM is very similar to the monomeric form of HMMM produced by Borden Chemical and Cytec Industries, and the data are representative of the CAS number listed in the HPV program.

Available data show HMMM has little or no toxicity to aquatic or mammalian organisms. Adequate data are now available for all of the HPV endpoints.

- Data on physical and chemical properties, including boiling point, vapor pressure, and partition coefficient are estimated from the EPA's EPIWIN model, assuming a 100% concentration of HMMM monomer. Measured values for melting point and water solubility of a commercial product containing 52% HMMM (the highest concentration product that is commercially produced) are now available.

- With regard to environmental fate, a recently conducted OECD Test Guideline 301B study shows that HMMM is not readily biodegradable, but it is expected to be inherently biodegradable. HMMM is estimated to have a half-life of minutes in sunlight. Fugacity modeling shows it most likely would be found in soil and to a lesser extent water, rather than air. Results of a recently conducted hydrolysis study (following OECD Test Guideline 111) indicate that the material is not stable in water at neutral or acidic pH, but is stable at high pH.

- For the ecotoxicological endpoints, adequate data are available for acute toxicity to fish, invertebrates and algae. In two separate tests of bluegill sunfish, no mortality was observed at any doses tested after 96 hours. Similarly, rainbow trout exposed to HMMM showed no mortality after 96 hours at any dose tested. A 48-hour test in daphnia magna also showed no mortality at any dose tested. The limit dose tested in a recently conducted algal toxicity study did not have any effect on the growth rate. ECOSAR modeling for freshwater fish produced estimates similar to the bluegill sunfish experimental results. In short, HMMM is not toxic to aquatic organisms.

- Regarding the mammalian toxicity endpoints, adequate data now exist for all of the required endpoints, including acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive and developmental toxicity. Multiple acute tests with oral doses show essentially no toxicity. A 28-day dermal repeat-dose test on HMMM is available. No effects were seen at 250 mg/kg/day, and no effects clearly related to treatment were seen at 750 and 1,000 mg/kg/day. Results of a recently conducted OECD 422 Test Guideline Study indicate that the repeated dose oral NOAEL also is 250 mg/kg/day. The NOAELs for reproductive toxicity, fetal toxicity and teratogenicity in this study were 250 mg/kg/day, 500 mg/kg/day and 1,000 mg/kg/day, respectively. The Ames test showed that HMMM is not mutagenic. While *in vitro* testing of Chinese hamster ovary cell line showed some effect, an *in vivo* chromosome aberration test was negative. Thus, HMMM is not considered clastogenic, and it displays little or no toxicity in mammalian studies.

B. GENERAL SUBSTANCE INFORMATION

Chemical Name: Melamine, hexakis(methoxymethyl)-

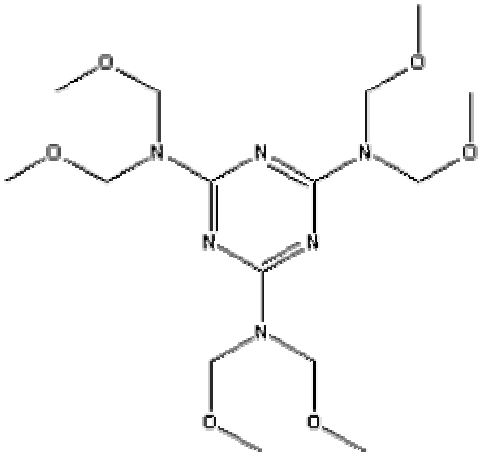
HMMM is formed as a reaction product in addition to several other reaction products when melamine crystal is methylolated and methylated. Commercial products containing HMMM do not exist as a pure material. These products are mixtures that contain HMMM in monomeric and polymeric forms.

Chemical Abstract Service Registry Number: CAS # 3089-11-0

Common Name: HEXAMETHOXYMETHYLMELAMINE (HMMM)

Structural Formula: $C_{15}H_{30}N_6O_6$
Molecular Weight: 390.44

Structure:



Synonyms:
1,3,5-Triazine-2,4,6-triamine, N,N,N',N',N'',N''-hexakis(methoxymethyl)-
Hexakis(methoxymethyl)melamine
Hexakis(methoxymethyl)melamin
hexakis(metoximetil)melamina Hexamethoxy methylmelamine
1,3,5-Triazine-2,4,6-triamine, N,N,N',N',N'',N''-hexakis(methoxymethyl)-
2,4,6-[N,N-Bis(methoxymethyl)amino]-1,3,5-triazine
N,N,N',N',N'',N''-Hexakis(methoxymethyl)-1,3,5-triazine-2,4,6-triamine
TRIAZINE [1,3,5]-2,4,6-TRIAMINE, N,N,N',N',N'',N''- HEXAKIS(METHOXYMETHYL)-
HEXAMETHOXYMETHYL MELAMINE

Other Name(s):
1,3,5-Triazine-2,4,6-triamine, N,N,N',N',N'',N''-hexakis(methyoxymethyl)-
Hexa(methoxymethyl)melamine
Hexamethyl methylolmelamine
Hexamethylolmelamine hexamethyl ether
Melamine, hexakis(methoxymethyl)-
N,N,N',N',N'',N''-Hexakis(methoxymethyl)-1,3,5-triazine-2,4,6-triamine
Pidifix 330

C. MANUFACTURE AND DISTRIBUTION OF HMMM

Commercial methylated melamine formaldehyde resins are complex mixtures of dimers, trimers and higher oligomers. No direct industrial synthesis of neat (100%), commercial HMMM has been reported. HMMM-containing resins are formed by methylolation of melamine with formaldehyde in the presence of acid or alkali, followed by methylation with methanol in the presence of acid.

HMMM containing resins are not sold directly to the consumer market. This material is reacted into the coatings in which they are added, limiting potential exposure in the finished consumer products.

HMMM is not sold as 100% HMMM. It is generally a mixture of HMMM, dimers and higher oligomers, and a smaller amount of less methylolated/methylated species. The typical commercial form is either a solid wax or liquid at ambient temperatures. The solid wax can be heated back to liquid form.

D. USES OF HMMM

HMMM-containing resins are used as crosslinkers in thermoset coatings. Their principal function is to crosslink the molecules of the primary film-forming vehicle in a coating, in order to build a three-dimensional thermoset polymer network with high performance properties. This involves the reaction of the functional groups (such as the methoxymethyl groups on HMMM) to the complementary reactive groups on the vehicle, typically in the presence of an acid catalyst. This imparts characteristics such as hardness and mar resistance to the coating finishes. The thermoset coating formed from HMMM-containing resins is considered excellent for solvent resistance, chemical resistance and exterior durability. Examples of applications are automotive paint finishes and beverage can coatings. HMMM is also used in methylated melamine formaldehyde resins, which are approved by FDA for use in food packaging.

E. EXPOSURE INFORMATION

HMMM resin is the predominant crosslinking agent for thermoset coatings. Thermoset coatings undergo chemical reactions during the curing process so that the molecular weight is built up and crosslinking takes place. Thus, upon curing, the parent methylated melamine formaldehyde material is no longer present.

The only potential routine worker contact comes from sampling procedures for quality control, and in some instances, during packaging. Exposure would be by skin contact. Inhalation exposure is extremely low due to the use of ventilation and the material's low vapor pressure. Ingestion would not be expected.

No consumer exposure is expected, as unreacted HMMM would not be present in the coated products.

F. SUMMARY OF AVAILABLE DATA

Data on HMMM are now available for all of the HPV endpoints. These data are summarized in Table 1. Table 2 provides a summary of the adequacy of data for required endpoints.

As noted above, neat (100%) HMMM cannot be produced in isolation. Commercial products containing 28-52% HMMM have been tested for some physical and environmental chemistry endpoints and all aquatic and mammalian toxicity endpoints. Recently conducted studies have been performed with a commercial product (CYMEL® 300 Resin) containing 52% HMMM, 47% melamine-formaldehyde resin (CAS No. 68002-20-0), < 1% methanol (CAS No. 7732-18-5), 0.15% formaldehyde (CAS No. 50-00-0) and 0.09% water. The following paragraphs briefly summarize the available data, which are then presented in tabular form and in robust summaries.

Recently conducted OECD test guideline studies indicate that the melting point and water solubility of CYMEL® 300 Resin are 28-33 °C and 69.5 g/l, respectively. The boiling point (448.2 °C), vapor pressure (.00000014 hPa at 25 °C) and partition coefficient (log Pow = 1.61) were estimated from the EPA EPIWIN model assuming a 100% concentration of HMMM.

With regard to environmental fate, a recently conducted OECD test Guideline 301 B study with CYMEL® 300 Resin showed that this material is not readily biodegradable, but is expected to be inherently biodegradable. Under conditions of the study, 23% of the material degraded after 28 days. Neat HMMM is estimated to have a half-life of minutes in sunlight. Fugacity modeling shows it most likely would be found in soil and to a lesser extent water, rather than air. Results of a recently conducted OECD Test Guideline 111 hydrolysis study with CYMEL (TM) 300 Resin show that the half life of this material in water at pH 7 and 25 °C is 67 days, and that the rate of hydrolysis increases with decreasing pH.

For the ecotoxicological endpoints, adequate data are now available for acute toxicity of HMMM to fish, invertebrates, and algae. In two separate tests of bluegill sunfish, no mortality was observed at any doses tested (up to 1000 mg/l) after 96 hours. Similarly, rainbow trout exposed to HMMM showed no mortality after 96 hours at any dose tested (up to 1000 mg/l). A 48-hour test in daphnia magna also showed no mortality at any dose tested (up to 1000 mg/l). ECOSAR modeling for daphnia magna produced estimates similar to the bluegill sunfish experimental results The limit dose tested in a recently conducted algal toxicity study with CYMEL® 300 Resin did not have any effect on the growth rate.

Regarding the mammalian toxicity endpoints, adequate data exist on all of the endpoints, including acute toxicity, repeat dose, reproductive and developmental toxicity, and genotoxicity. Multiple acute tests with oral doses show LD50 values of 1,600-7,400 mg/kg. A 28-day dermal repeat-dose test on HMMM is available. No effects were seen at 250 mg/kg/day. At 750 and 1,000 mg/kg/day, there were some effects on organ weights in males and liver enzyme values in females that were not clearly related to treatment. No clinical signs of dermal irritation or toxicity were observed. There were no macro or microscopic changes in any of the male or female reproductive organs.

An OECD Test Guideline 422 study was recently conducted to fill the reproductive and developmental toxicity endpoints. In this study, male and female rats were given 0, 250, 500 or 1,000 mg/kg/day of CYMEL® 300 Resin by gavage, 14 days before mating and during mating. Treatment in females continued to day 4 of lactation. The exposure period was 28 days for males and 36-52 days for females. The NOAEL for systemic toxicity in the adult animals was 250 mg/kg/day. One female in each of the 500 and 1,000 mg/kg/day groups died or was euthanized in extremis, after exhibiting difficult delivery or changes in nesting and nursing behavior. Both of the deaths were attributed to administration of test material. Changes in blood chemistry and clinical signs such as lethargy, brown staining around the mouth and/or salivation were noted in animals given 500 mg/kg/day. These changes, along with prostration, impaired mobility and labored respiration were seen in a few animals given 1,000 mg/kg/day. Clinical signs were observed 1 hour after treatment, but were not observed during the 14-day recovery period. Body weights and food consumption of males in this group were lower than control, and adrenal gland weights of both males and females in this group were higher than control.

Histopathologic changes were found in the stomachs of most treated animals (including those treated with 250 mg/kg/day), which were considered to be due to irritation from the test material (and not reflective of systemic toxicity). With the exception of one male, the changes in the stomach were not observed in animals allowed to recover from treatment for 14 days before being necropsied.

There was no effect of treatment on any functional neurotoxicity test or on reproductive performance. Gross appearance of offspring was normal, with the exception of one control pup that had a major blood vessel variation and one pup in the 1,000 mg/kg/day group that had anury and tarsal flexure (bilateral). Both of these changes were not considered to be of any significance. Slight reductions in postnatal survival and mean body weight that may have been related to treatment were observed in pups from animals treated with 1,000 mg/kg bw/day. Therefore, the NOAELs for fetotoxicity and teratogenicity were 500 and 1,000 mg/kg bw/day, respectively.

The Ames test showed that HMMM is not mutagenic. Although *in vitro* testing of a Chinese hamster ovary cell line showed some effect, an *in vivo* chromosome aberration test (bone marrow cytogenetics rat metaphase analysis) was negative. Thus, HMMM is not considered clastogenic, and it displays little or no toxicity in mammalian studies.

Tables 1 and 2below summarize the available data. The tables are followed by robust summaries of the existing data.

TABLE 1 SUMMARY OF AVAILABLE DATA ON HMMM

CAS# 3089-11-0	Study Date	Results	Data Acceptable
Physical/Chemical Characteristics			
Melting Point[a]	2003	28-33 °C	Yes
Boiling Point[b]	2002	448.20 °C	Yes
Vapor Pressure[b]	2002	1.06 x 10^{-8} mm Hg @ 25 °C	Yes
Partition Coefficient[b]	2002	Log K_{ow} = 1.61	Yes
Water Solubility[a]	2003	69.5 g/L @ 20 °C	Yes
Environmental Fate			
Photodegradation[b]	2002	For reaction with hydroxyl radical, predicted rate constant = 323.5521 x 10^{-12} cm^3/molecule-sec Predicted half-life = 23.802 minutes	Yes
Hydrolysis[a]	2003	3.3 hours @ pH 4 and 25 °C 67 days @ pH 7 and 25 °C >1 year @ pH 9 and 25 °C	Yes

CAS# 3089-11-0	Study Date	Results	Data Acceptable
Fugacity[b]	2002	Predicted distribution using Level III Fugacity Model: Air: 0.0000645% Water: 36.1% Soil: 63.8% Sediment: 0.0996%	Yes
Biodegradation[a]	2004	Not readily biodegradable 23% biodegradation after 28 days	Yes
Ecotoxicity			
Acute Toxicity to Fish	 1993 1984 2002 1983	Lepomis macrochirus: LC50 (96 hr) > 603.1 mg/L [c] LC50 (96 hr) >1,000 mg/L [d] LC50 (96 hr) = 673.2 (estimated by ECOSAR) [b] Salmo gairdneri: LC50 (96 hr) = >1,000 mg/L [d]	 Yes Yes Yes Yes
Acute Toxicity to Invertebrates	 1983 2002	Daphnia magna LC50 (48hr) = >1,000 mg/L [d] LC50 (48hr) = 702.2 mg/L (estimated by ECOSAR) [b]	 Yes Yes
Acute Toxicity to Algae[a]	2004	Scenedesmus subspicatus NOEC = 100 mg/L EC50 > 100 mg/L	Yes

CAS# 3089-11-0	Study Date	Results	Data Acceptable
Mammalian Toxicity			
Acute Toxicity			
Oral LD50 (rat)	2001	oral LD50 (rat) = 2.0 g/kg [e]	Yes
Oral LD50 (rat)	1984	oral LD50 (rat) = 1.8 g/kg [e]	Yes
Oral LD50 (rat)	1976	oral LD50 (rat) = 7.4 g/kg [e]	Yes
Oral LD50 (rat)	1960	oral LD50 (rat) = >5 g/kg [f]	No
Dermal LD50 (rabbit)	1976	dermal LD50 (rat) = >7.9 g/kg [e]	Yes
Inhalation LC50	1976	6-hour inhalation LC50 = >0.6 mg/L [e]	No
Primary Eye Irritation	1976	Slight Eye Irritant [e]	Yes
Primary Skin Irritation	1976	Non-Irritating to Skin [e]	No
Primary Skin Irritation	1988	Mild to Non-Irritating to Skin [e]	Yes
Repeat Dose Toxicity			
OECD 422 (28-Day Oral, rat)	2003	NOAEL = 250 mg/kg/day (oral) [a]	Yes
28-Day Dermal (rat)	1990	NOEL = 250 mg/kg/day (dermal) [e] NOAEL = 1000 mg/kg/day [e]	Yes
ReproductiveToxicity[a]	2003	NOAEL (parental) = 250 mg/kg/day NOAEL (offspring) = 500 mg/kg/day	Yes
DevelopmentalToxicity[a]	2003	NOAEL (maternal) = 250 mg/kg/day NOAEL (fetotoxicity) = 500 mg/kg/day NOAEL (teratogenicity) = 1000 mg/kg/day	Yes
Genetic Toxicity:			
Gene Mutations	1988	Negative [e]	Yes
Chromosomal Aberration			
In Vitro (CHO Cell Assay)	1989	Positive (In Vitro) [e]	Yes
In Vivo (Bone Marrow Cytogenetics)	1989	Negative (In Vivo) [e]	Yes

[a] Test performed with commercial product (Cymel (TM) 300 Resin) containing 52% HMMM
[b] Estimated by modeling for hypothetical 100% concentration of HMMM.
[c] Test performed with commercial product containing 34-44% HMMM
[d] Test performed with commercial product containing 28±1% HMMM
[e] Test performed with commercial product containing 29±1% HMMM
[f] Test performed with commercial product containing approximately 50% HMMM

TABLE 2 SUMMARY OF TESTING

CAS # 3089-11-0	Data Available	Data Acceptable	Testing Required
Study	**Y/N**	**Y/N**	**Y/N**
Physical/Chemical Characteristics			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	N
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
Environmental Fate			
Photodegradation	Y	Y	N
Hydrolysis	Y	Y	N
Fugacity	Y	Y	N
Biodegradation	Y	Y	N
Ecotoxicity			
Acute Toxicity to Fish	Y	Y	N
Acute Toxicity to Invertebrates	Y	Y	N
Acute Toxicity to Algae	Y	Y	N
Mammalian Toxicity			
Acute Toxicity	Y	Y	N
Repeat Dose Toxicity	Y	Y	N
Developmental Toxicity	Y	Y	N
Reproductive Toxicity	Y	Y	N
Genetic Toxicity: Gene Mutations	Y	Y	N
Genetic Toxicity: Chromosomal Aberration	Y	Y	N