HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN FOR CYCLIC ANHYDRIDES

Submitted to the U.S. EPA

BY

The Industrial Health Foundation, Inc. Cyclic Anhydrides Committee

Consortium Registration Number:

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MEMBER COMPANIES OF THE CYCLIC ANHYDRIDES COMMITTEE:

Buffalo Color Corporation

Dixie Chemical Company, Inc.

Lindau Chemicals, Inc.

Lonza Group
(formerly Lonza Inc./Lonza Spa)

Milliken Chemical

CYCLIC ANHYDRIDE TEST PLAN

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INTRODUCTION

"Cyclic anhydrides" are being submitted as a category of chemicals under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge program by the Industrial Health Foundation Cyclic Anhydride Committee. Hereafter within this document, the term "cyclic anhydrides" will be used to denote only the anhydrides contained within this group.

Cyclic anhydrides are primarily "destructive industrial use" chemicals. They are not sold in consumer markets. Aside from occupational exposure, exposure of the general public would be limited to accidental release. Cyclic anhydrides are mainly used as curing agents (also called hardeners) in epoxy resin systems. The cured resins characteristically have high chemical resistance as well as good electrical insulation capacity and adhesive strength. Some of these chemicals are also used in the manufacture of alkyd and polyester resins.

As will be discussed in greater detail in the following test plan, anhydrides within the group have similar structure and physicochemical properties. Low molecular weight carboxylic acid anhydrides are also recognized to have similar toxicological properties. Of the more extensively studied anhydrides, phthalic anhydride is most structurally similar to the cyclic anhydrides. Within this report a toxicological analogy will be made to phthalic anhydride.

Available data indicates that the cyclic anhydrides have a low acute toxicity, are respiratory and skin sensitizers and can cause corrosive eye damage. Since these compounds are considered to be sensitizers at low concentrations, exposures in the workplace are controlled to lowest possible levels.

Relying on factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program, in which the use of chemical categories is encouraged, the IHF Cyclic Anhydride Committee concluded that hexahydrophthalic anhydride (CAS No.: 85-42-7), methyl-hexahydrophthalic anhydride (CAS No.: 25550-51-O; 571 I-02-99) tetrahydrophthalic anhydride (CAS No.: 85-43-8), methyltetrahydrophthalic anhydride (CAS No.: 34090-76-I ; 11070-44-3), and nadic methyl anhydride (CAS No.: 25134-21-8) constitute a "chemical category".

Two of the chemicals within the group, MHHPA and MTHPA are on the EPA's 1994 Inventory Update Rule (IUR) List of HPV Additions and are not formally included in the current HPV Challenge Program. One of the two chemicals, MTHPA has been sponsored by Hitachi Chemical Co. under the ICCA Program. As test data for MTHPA (CAS No.: 11070-44-3) is or will soon be available through the ICCA Testing Program, testing is not planned for MTHPA.

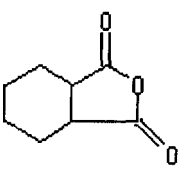
1. CATEGORY JUSTIFICATION

A. Structural Similarity

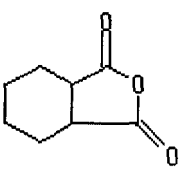
A key factor supporting grouping these chemicals in a single category is their structural similarity. All chemicals in this group contain a bicyclic ring structure with the carboxylic acid anhydride group as the single reactive and toxic functional moiety. This reactive moiety hydrolyses to form the diacid in water and is responsible for the irritant as well as sensitizing properties of the cyclic anhydrides. Two of the five bicyclic ring structures are saturated and three are partially unsaturated. One of the saturated and two of the partially unsaturated are substituted methyl derivatives. While the compounds with substituted methyl groups may exist as several isomeric forms (with different CAS numbers), there is no reason to believe this should affect the toxic potential of these compounds in any way.

Structures for chemicals within the chemical category are presented below.

- Hexahydrophthalic anhydride (CAS No.: 85-42-7), referred to in this report as HHPA

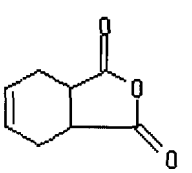


- Methylhexahydrophthalic anhydride (CAS No.: 25550-51-0)referred to in this report as MHHPA

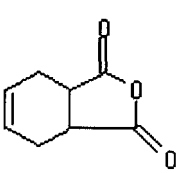


D1-Me

- Tetrahydrophthalic anhydride (CAS No.: 85-43-8), referred to in this report as THPA



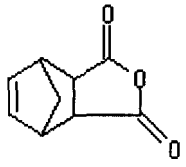
- Methyltetrahydrophthalic anhydride (CAS No.: 34090-76-l; 11070-44-3), referred to in this report as MTHPA



Dl-Me

A. Structural Similarity (continued)

- Nadic methyl anhydride (CAS No.: 25134-21-8), referred to in this report as NMA.



Ill-Me

Note: Dl-Me indicates that for NMA, MTHPA, and MHHPA, the location of the methyl group may vary.

B. Chemical and Physical Similarity

The physicochemical properties of cyclic anhydrides suggest many general similarities. Molecular weight of anhydrides within the group varies from 152 to 178 classifying these compounds as low molecular weight (< 500) carboxylic acid anhydrides. All have relatively high boiling points and low vapor pressures indicating that vapor concentrations would be low under ambient conditions. All of the compounds will hydrolyze rather easily in water to produce the corresponding diacid. This indicates that solubility of the hydrolysis products and resultant pH is expected to be most relevant in the assessment of potential toxicity. Solubility data for the compounds themselves (which has been stated to be “low” or “negligible” on data sheets) is not of much value in the assessment of potential toxicological hazards. Aside from acidic pH resulting from hydrolysis to the diacid, other physical properties do not suggest a potential for environmental or toxicity concerns.

C. Toxicological Similarity

Review of existing published and unpublished test data for the cyclic anhydride category confirms similarity in toxicity. Workers exposed to cyclic anhydrides have occasionally developed conjunctivitis, skin sensitization, urticaria, rhinitis, occupational asthma, and an eczematous response. Respiratory sensitization is a major concern for all cyclic anhydrides.

All of the cyclic anhydrides which have been tested, as well as the closely related analogue, phthalic anhydride (PA), have a low acute toxicity. Oral LD50s for cyclic anhydrides in rats are relatively high, ranging from 958 to 4460 mg/kg. Dermal toxicity is also relatively low as indicated by dermal LD50s of > 2000 mg/kg in rabbits for HHPA, MTHPA, and NMA. These values suggest a low order of acute oral and dermal toxicity. The four-hour inhalation LC50 for HHPA in rats is cited as > 1100 mg/m^3 (aerosol). In a limited inhalation study on NMA, a concentration of 750 mg/m^3 for 4 hours was lethal to 8 of 10 rats.

As demonstrated by animal testing and human experience, anhydrides within the group can cause mild to moderate skin irritation and moderate to severe eye irritation with possible corrosive effects. For European labeling purposes (Directive 67/548/EEC, Annex I) risk (R) phrases for HHPA, MHHPA, MTHPA, and THPA are: “Risk of serious damage to the eyes. May cause sensitization by inhalation and skin contact,” Studies in rabbits indicate that NMA also causes severe eye irritation with the possibility of permanent damage. HHPA, MTHPA, THPA, and NMA all have caused mild skin irritation in rabbits. In one test, NMA was found to be moderately irritating and no studies were found indicating potential irritant effects MHHPA may have on the skin.

C. Toxicological Similarity (continued)

Similarities in toxicity of cyclic anhydrides has been recognized by the EPA's Office of Pollution Prevention and Toxics by designation of "anhydrides, carboxylic acid' as a valid chemical category for PMN review purposes. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers. Documentation for sensitization was available for all anhydrides within the group with the exception of NMA. Based on analogy to other acid anhydrides and verbal industrial reports, NMA is expected to produce sensitization.

Allergic response to cyclic anhydrides is triggered by the ability of cyclic anhydrides to bind covalently to free amino groups; in particular, to the amino group of lysine. An immunologic hapten-protein conjugate is formed which stimulates specific immunological responses. PA and cyclic anhydrides have been associated with occupational asthma.

Similarity in mechanism for allergic response to cyclic anhydrides within this group is also demonstrated by cross-sensitization potential. Workers sensitized to MTHPA, HHPA or HHPA/MHHPA have shown marked cross-reactivity to MTHPA-human serum albumin (HAS), HHPA-HAS, and MHHPA-HAS as demonstrated by radioallergosorbent test (RAST), RAST inhibition and skin prick tests. Ring structure, methyl group substituents and position of double bonds may all affect sensitizing potential of cyclic anhydrides; however differences are quantitative rather than qualitative.

2. PHYSICOCHEMICAL PROPERTIES

The majority of the physicochemical properties for the cyclic anhydrides were taken from various manufacturer's MSDSs and product specification sheets. In most cases full documentation of the test value including information concerning methodology and GLP was unavailable. In the following tables, testing is proposed for values which are not in good agreement with each other as well as for values that appear to be taken from a single undocumented source. As MTHPA is currently sponsored under the ICCA Program, testing is not planned for this compound.

A. Melting Point

CAS No.	Melting Point	Reference	Year	Remarks
25134-21-8 NMA	< *18°C*	Buffalo Color Corp.	1995; 1997	None
85-42-7 HHPA	*34-38* °C	Dixie Chemical Co., Inc.	1999	None
	35-36 °C	Hawley's Chemical Dictionary, 12th Ed.	1993	Glassy solid @ 35-36 °C.
	35-37 °C	Buffalo Color Corp.	1996	None
	37 °C	Lonza Inc./Lonza Spa	1995	None
85-43-8 THPA	*99-101* °C	Hawley's Chemical Dictionary, 12th Ed.	1993	Solidification point.
	99 °C	Dixie Chemical Co., Inc.	1998	None
	100 °C	EUCLID Data Sheet	1994	None
	102°C (minimum)	Lonza Inc/Lonza Spa	1995	None
34090-76-I *(11070-44-3)* MTHPA	- *38* °C	Lonza Inc./Lonza Spa/ Hedset Data Sheet	1997/1995	Value is for mixture of 3- and 4-MTHPA. No decomposition or sublimation.
25550-51-o MHHPA *(57 11-02-99)*	- *30* °C	Lonza Inc./Lonza Spa	1995	None

Summary:
Values were obtained from manufacturer's MSDSs, product specification sheets, and a standard reference source. Values for HHPA and THPA appear to be in good internal agreement. Limited data exists for the three remaining anhydrides – NMA, MTHPA, and MHHPA. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. Years stated are for references rather than date of test value determination.

Reliability:
[2] Valid with Restrictions (Klimisch)

Test recommendations: Testing is recommended for NMA to determine a specific value. Testing to determine the melting point for MTHPA and MHHPA is not recommended as these anhydrides have melting points well below 0 °C (OECD, Section 3.4 *Guidance for Meeting the SIDS Requirements,* Part 2.1. OECD Guideline 1021.

B. Boiling Point

CAS No.	Boiling Point	Reference	Year	Remarks
25134-21-8 NMA	140 °C	Buffalo Color Corp.	1997	Approximate value @ 10 mm Hg.
	140 °C	Lonza Inc./Lonza Spa	1998	Approximate value @ 10 mm Hg.
85-42-7 HHPA	158 °C	Buffalo Color Corp.	1996	@ 17 mm Hg
	158 °C	Hawley's Chemical Dictionary, 12th Ed.	1993	@ 17mmHg
	144 °C	Dixie Chemical Co., Inc.	1999	@ 17 mm Hg
	296 °C	Lonza Inc./Lonza Spa	1995	@ 760 mm Hg.
	285 °C	Buffalo Color Corp.	1996	None
85-43-8 THPA	195 °C	Lonza Inc./Lonza Spa	1995	@ 50 mm Hg
	195 °C	EUCLID Data Sheet	1994	@ 1013 hPa. No decomposition,
34090-76-I (11070-44-3) MTHPA	150 °C	HEDSET Data Sheet	1995	@ 13.5 hPa. No decomposition
	> 585 °F > 307.5%	Lindau Chemicals, Inc.	1995	ASTM D-86
	283 °C	Dixie Chemical Co., Inc.	2000	@ 760 mm Hg
	290 °C	Lonza Inc./Lonza Spa	1996	@ 760 mm Hg
25550-51-o (571 I-02-99) MHHPA	290 °C	Lonza Inc./Lonza Spa	1995	None

Summary:

Values were obtained from manufacturer's MSDSs, product specification sheets, IUCLID document, and a standard reference source. The variance in boiling points for MTHPA are probably due to different mixtures of 3- and 4-MTHPA produced by the manufacturers. As MTHPA is currently sponsored under the ICCA, testing will not be proposed for this substance. Boiling point for HHPA was obtained from a reliable reference source. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. The date given reflects the reference year rather than the date of test value determination.

Reliability:
[2] Valid with Restrictions (Klimisch)

Test Recommendations:

Testing to obtain boiling point values using OECD Test Guideline 103 are recommended for THPA and MHHPA and NMA.

C. Vapor Pressure

CAS No.	Vapor Pressure	Reference	Year	Remarks
25134-21-8 NMA	0.1 mm Hg	Buffalo Color Corp.	Not Available	@ 20 °C
	1.5 mm Hg	Buffalo Color Corp.	Not Available	Estimated @ 30 °C
	5.0 mm Hg	Buffalo Color Corp.; Lonza Inc./Lonza Spa	1997; 1998	@ 120 °C.
85-42-7 HHPA	0.0068	Dixie Chemical Co., Inc.	1999	@ 25 °C
	0.25 mm Hg	Buffalo Color Corp.	1996	Calculated @ 30 °C
	5.0 mm Hg	Buffalo Color Corp.	Not Available	@ 106 °C
	10.0 mm Hg	Buffalo Color Corp.	1996	@ 125 °C
85-43-8 THPA	< 0.01 mm Hg	Dixie Chemical Co., Inc.	1998	@ 20 °C, calculated
	0.01 mm Hg	Lonza Inc./Lonza Spa	1995	@ 20 °C
	50.0 mm Hg	Dixie Chemical Co., Inc.	1998	@ 195 °C
34090-76-I (11070-44-3) MTHPA	0.002 mm Hg	Dixie Chemical Co., Inc.	2000	@ 25 °C
	< 0.01 mm Hg	Lonza Inc./Lonza Spa	1995	@ 20 °C
	6.8 hPa	HEDSET Data Sheet	1995	@ 137 °C
	136 hPa	HEDSET Data Sheet	1995	@ 216 °C
25550-51-o (571 I-02-99) MHHPA	5.00 mm Hg	Lonza Inc./Lonza Spa	1995	@ 137 °C
	3.00 mm Hg	Dixie Chemical Co., Inc.	1999	@ 145 °C

Summary:

Values were obtained from manufacturer's MSDSs, product specification sheets, technical data sheets, and IUCLID documents. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. The date given reflects the reference year rather than the date of test value determination. Values indicate that airborne vapor concentrations would be extremely low and aside from sensitization or respiratory irritation are unlikely to pose an acute or chronic inhalation hazard.

Reliability:

[2] Valid with Restrictions (Klimisch)

Test Recommendations: None recommended.

D. Partition Coefficient

CAS No.	Partition Coefficient	Reference	Year	Remarks
25134-2 1-8 NMA	1.35 ± 0.03	Buffalo Color Corp.	1997	Octanol/Water Partition Coefficient; Log,,, Pow; P = 22.4
85-42-7 HHPA	1.33 ± 0.14	Buffalo Color Corp.	1996	Octanol/Water Partition Coefficient; Log,, Pow; P = 21.4
85-43-8 THPA	0.02	Hansch, L.	1989*	Calculated value from EUCLID data sheet.
34090-76-l (11070-44-3) MTHPA	No Data			
25550-51-O (571 I-02-99) MHHPA	No Data			

Summary:

Values taken from manufacturer's occupational and environmental health hazard summaries and IUCLID Documents. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. With the exception of the value for THPA, the date given reflects the reference year rather than the date of test value determination.

Reliability:

[4] Not assignable

Test Recommendations:

Octanol/water partition coefficients will be calculated for all of the cyclic anhydrides with the exception of MTHPA in accordance with accepted methods.

E. Water Solubility

CAS No.	Water Solubility	Reference	Year	Remarks
25134-21-8 NMA	No Data			Hydrolyzes to diacid in water
85-42-7 HHPA	No Data			Hydrolyzes to diacid in water
85-43-8 THPA	10 g/L	EUCLID Data Sheet	1994	@ 20 °C. Slowly hydrolyzes to diacid in water.
34090-76-1 (11070-44-3) MTHPA	176.4 g/L	HEDSET Data Sheet	1995	@ 10°C
25550-51-O (57 11-02-99) MHHPA	36 g/L	HEDSET Data Sheet	1995	@ 20 °C
	< 0.1%	Lonza Inc./Lonza Spa	1995	Hydrolyzes to diacid in water.

Summary:

Values were cited in manufacturer's MSDSs and IUCLID Documents. Cyclic anhydrides characteristically hydrolyze to form diacid in water. Solubility of the anhydrides is stated in various manufacturers' reference sources as low or negligible; however quantitative data is limited. High values are believed to reflect the solubility of the diacids following hydrolysis of the anhydride. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. The date given reflects the reference year rather than the date of test value determination.

Reliability:

[4] Not assignable

Test Recommendations:

Water solubility testing for all members of the group with the exception of MTHPA in accordance with OECD Test Guideline 105 is proposed for all anhydrides in the group due to inadequacy of available data.

F. pH/pKa

CAS No.	pH/pKa	Reference	Year	Remarks
25134-21-8 NMA	pH = 2.4	FDRL Report 6771 F	1981	pH of 10% aqueous solution. By analogy to HHPA, pH of diacid was estimated at approximately 4
85-42-7 HHPA	pH = 4.2	FDRL Report	1981	Calculated value for 1% aqueous mixture.
85-43-8 THPA	pH = 2.1	EUCLID Data Sheet	1994	pH at 20 °C and 10 g/L.
34090-76-l (11070-44-3) MTHPA	No Data			
25550-51-O (571 l-02-99) MHHPA	No Data			

Summary:

Values taken from manufacturer's MSDSs and IUCLID Documents. Characteristically anhydrides will hydrolyze to form the diacid in water. Information concerning purity of test material, test method, GLP, and year of testing was unavailable for the majority of the test data. The date given reflects the reference year rather than the date of test value determination.

Reliability:
[3] Not valid

Test Recommendations:

As these substances hydrolyze to form the diacid in water, testing for acids including dissociation constants (pKa) and conditions under which they were measured (OECD Guideline 112) will be conducted for all members of the group with the exception of MTHPA.

3. ENVIRONMENTAL FATE

Fate and Transport Characteristics

Limited environmental fate and distribution data is available for the five anhydrides. Due to the reactive nature of the carboxylic acid anhydride group, these chemicals are expected to hydrolyze in moist soils rather than adsorb to the soil. This conclusion is based on analogy to another closely-related cyclic anhydride, phthalic anhydride (PA). By analogy to PA, the cyclic anhydrides would not be expected to bioconcentrate in aquatic organisms, adsorb to sediments, or evaporate if released into water. Hydrolysis is expected to be a major fate process based on an estimated half-life for PA of 1.5 minutes. Release into the atmosphere is expected to result in direct photolysis via ring addition of photochemically produced hydroxyl radicals. The vapor-phase half-life of PA in the atmosphere is approximately 32 days. Limited photolysis data on HHPA suggests that it has an even shorter atmospheric half-life of about 7 days.

Biodegradation studies following OECD guidelines (i.e.: Method 301) have been conducted on four category members: HHPA, MHHPA, THPA, and NMA. Results showed no evidence of biodegradation potential for MHHPA and THPA as measured by BOD. NMA showed no biodegradation by BOD but did show a 1 .O% biodegradation as measured by total organic carbon (TOC). HHPA also exhibited slight biodegradation potential (1 .O-6%) as measured by BOD. All four cyclic anhydrides were hydrolyzed to their respective corresponding acids.

Due to limited environmental fate data available for members of the cyclic anhydride group, the IHF Cyclic Anhydride Committee proposes to complete environmental fate information for HHPA, MHHPA, THPA, and NMA by testing or modeling. As MTHPA is currently sponsored under the ICCA, testing is not proposed for this substance. The following tests are proposed:

NAME	ENDPOINT			
	PHOTODEGRADATION	HYDROLYSIS (stability in water)	TRANSPORT & DISTRIBUTION	BIODEGRADATION
HHPA	Data available [1]	OECD 111 (or estimation method)	Fugacity-based modeling	Data available*
MHHPA	Estimation via model	OECD 111 (or estimation method)	Fugacity-based modeling	Data Available*
THPA	Estimation via model	OECD 111 (or estimation method)	Fugacity-based modeling	Data Available [2]
NMA	Estimation via model	OECD 111 (or estimation method)	Fugacity-based modeling	Data Available*

[1] Test data (computer modeling) is acceptable without restrictions (Klimisch Criteria = 1); however study details were unavailable.
[2] Tests similar to OECD Method 301A have been conducted and appear adequate (Klimisch Criteria = 2).

4. ECOTOXICITY

HHPA and THPA were tested using adequate (Klimisch Criteria = 2) test methods for freshwater fish, *Leuciscus idis (DIN 38412,* Teil 15), *Daphnia magna,* (DIN 38412, Teil 1 I), and algae, *Scenedesmus subspicatus,* (Algenwochstums-Hemmtest nach UBA, 1984). MHHPA, HHPA and THPA showed 48-hour LC50s in fish of > 500 mg/L, 600 mg/L and 610 mg/L, respectively. THPA and HHPA showed 24-hour EC50s Of 103 and *117* mg/L in *Daphnia,* and 72-hour EC50s of 95.6 and 65.7 mg/L for algae, respectively. Under the ICCA program, MTHPA was reported to have a 96-hour LC50 of 100 mg/L (Ricefish), a 48-hour EC50 of *130* mg/L for *Daphnia,* and a 72- hour EC50 of 79 mg/L for algae. HHPA and THPA had 24- hour EC50s of 103 and *117* mg/L in *Daphnia* and 72-hour LC50s of 95.6 and 65.7 mg/L in algae respectively. These results suggest a low order of ecotoxicity and are in agreement with similar studies indicating that phthalic anhydride also has a low order of ecotoxicity. As ecotoxicity data is available for three of the five anhydrides within the group, the IHF Cyclic Anhydride Committee plans to conduct ecotoxicity testing on one member of the group, NMA. NMA will be tested for acute toxicity to *Pimephales promelas* (OECD Method 203), *Daphnia magna* (OECD Method 202) and *Selenastrum capricornufum* (OECD Method 201) to provide more definitive ecotoxicity data to better evaluate the cyclic anhydride category.

5. TOXICITY

A. Acute

Acute oral mammalian toxicity data is available for all five anhydrides within the group. Some dermal and inhalation data were also available. Oral LD50s in rats ranged from 958 to 4460 mg/kg reflecting a low order of acute oral toxicity. Dermal absorption toxicity was also low as indicated by dermal LD50s of > 2000 mg/kg in rabbits for HHPA, MTHPA, and NMA. Oral toxicity data on a comparable anhydride (PA) showed LD50s ranging from 800 to 4000 mg/kg in rats. Acute inhalation testing, available for two members of the group also indicates a relatively low order of acute toxicity. The four-hour LC50 for HHPA in rats is cited as > 1100 mg/m^3 (aerosol) which was the maximum attainable concentration under optimal conditions. In a limited study on NMA, a concentration of 750 mg/m^3 for 4 hours was lethal to 8 of 10 rats. It is important to note that respiratory sensitization is a major aspect of all cyclic anhydrides and probably occurs at exposure levels at or below 1 ppm. Any acute inhalation toxicity testing would most likely have to be conducted at concentrations of 1 to 2 orders of magnitude above those associated with respiratory sensitization. Since oral toxicity data are available for all five chemicals, dermal toxicity data are available for three chemicals in the group, and inhalation data is available for two members of the group, the IHF Committee believes that no additional acute toxicity testing is warranted. Available data is believed to be adequate to properly evaluate the cyclic anhydride group.

B. Repeated Dose

MTHPA, under the ICCA program, has been tested by oral gavage using OECD Method No. 422. Rats were dosed subchronically at 0, 30, 100 and 300 mg/kg/day. On terminal sacrifice, both male and female rats dosed at 300 mg/kg exhibited evidence of irritation at the site of administration, the forestomach. Less severe indications of irritation were evident in male rats at 100 mg/kg. No irritation was evident in males dosed at 30 mglkglday or females dosed at 30 mglkglday or 100 mglkglday. Aside from transient salivation in the animals dosed at 300 mg/kg/day, no adverse effects on body weight, food consumption, or other clinical signs were apparent. At termination, blood chemistry determinations indicated decreased total cholesterol and BUN as well as increased triglyceride level and adrenal weight in males. Aside from irritation at the site of administration, no specific target organ for MTHPA was elucidated. The NOELs were reported to be 30 mg/kg/day for males and 100 mg/kg/day for females. Other than the preceding subchronic data for MTHPA, adequate repeated-dose studies have not been conducted for the remaining cyclic anhydrides within this group.

B. Repeated Dose (continued)

Phthalic anhydride, a comparable analogue, has been the subject of an NCI lifetime oral bioassay in rats (≤ 15,000 ppm in the diet) and mice (≤ 32,692 ppm in the diet). Under this chronic dosing regimen, there were decreased body weight gains at all doses but no adverse effect on survival. PA was not carcinogenic in either species. Since data reflecting a low order of repeated exposure toxicity is available for one member of the category (MTHPA), and for a comparable analog (phthalic anhydride), repeated dose testing for one additional anhydride is expected to adequately characterize the subchronic toxicity potential within the proposed chemical category. The IHF Cyclic Anhydride Committee proposes to sponsor repeat dose testing for one category member, NMA. NMA will be tested in a 90-day oral toxicity study (OECD #408) in rats in conjunction with a one-generation reproductive study (OECD #415). NMA has been selected as the test compound on the basis of acute toxicity data suggesting that NMA is expected to be more toxic than other members of the group in repeat dose testing. If physicochemical, ecotoxicity, and environmental fate data for other members provide results which indicate these chemicals may differ significantly relative to mechanism of toxic action, then additional mammalian toxicity testing will be considered.

C. Genotoxicity (in vitro – Bacterial-Point mutation and Chromosomal aberration)

Using the standard Ames Test procedures as cited in OECD Test Guideline number 471, HHPA, THPA, and MTHPA were negative in Salmonella *typhimurium*, with and without metabolic activation. Phthalic anhydride, a closely-related analogue, also tested negative in the Ames Test with and without metabolic activation. *In* vitro chromosomal aberration studies conducted for PA were negative and results for MTHPA were equivocal.

Since gene mutation assays have been conducted on three of the five category members and in vitro chromosomal aberration studies have been conducted on MTHPA as well as the closely-related PA, additional testing for two chemicals will be conducted. The IHF Cyclic Anhydrides Committee proposes to conduct a chromosomal aberration assay (OECD Method 473) for HHPA and both a point mutation assay (Ames Test; OECD Method 471) and a chromosomal aberration assay (OECD Method 473) for NMA. Data from these assays combined with existing genotoxicity test data for MTHPA, THPA, HHPA, and PA are expected to provide sufficient data to adequately assess *in vitro* genotoxicity for the anhydrides as a category.

D. Reproductive/Developmental Toxicity

A combined screening study (OECD Method No. 422) was conducted to assess repeated dose toxicity, reproductive performance and developmental toxicity potential on MTHPA. Results from this study indicates that at doses less than or equal to 300 mg/kg/day, MTHPA had no adverse effects on reproductive performance in either male or female rats and no indications of developmental toxicity were evident. Limited studies on other carboxylic acid anhydrides (i.e.: phthalic anhydride) raise the question of possible reproductive toxicity concerns. To adequately characterize the cyclic anhydrides category, the IHF Cyclic Anhydrides Committee proposes to conduct an oral gavage one-generation reproduction study (OECD #415) in conjunction with a 90-day study on one of the category members, NMA (See Section B. above). The committee proposes these studies as opposed to conducting a screening study (OECD 422) which only provides limited information on chronic toxicity potential, reproductive performance and developmental toxicity potential. If any suggestion of developmental toxicity (i.e.: malformations, implantation difficulties, etc.) is noted in the reproductive study, a developmental toxicity study (OECD #414) will be conducted on that material. Coupled with similar data on MTHPA from the ICCA Program, the preceding proposed studies on NMA are expected to provide sufficient data to characterize the cyclic anhydrides category relative to reproductive/developmental toxicity potential.

7. SUMMARY

The following tests and/or computer modeling are planned for the Cyclic Anhydride Category:

- HHPA (84-42-7): Partition coefficient and water solubility/pKa; hydrolysis and transport/distribution; an *in* vitro chromosomal aberration study

- MHHPA (25550-51-O): Boiling point, partition coefficient, and water solubility/pKa; photodegradation, hydrolysis and transport/distribution

- THPA (85-43-8): Boiling Point, partition coefficient, and water solubility/pKa; photodegradation, hydrolysis and transport/distribution

- MTHPA (34090-76-I): Testing is not planned for this compound as MTHPA (11070-44-3) is currently sponsored under the ICCA program.

- NMA (255134-21-8): Melting point, boiling point, partition coefficient and water solubility/pKa; photodegradation, hydrolysis and transport/distribution; acute fish, acute Daphnia and acute algae; 90-day oral toxicity study in conjunction with a one-generation reproduction study, *in vitro* point mutation and *in vitro* chromosomal aberration study
  Note: Additional developmental toxicity studies will be conducted if developmental toxicity is suggested by the reproductive study.

As this test plan was developed, the IHF Cyclic Anhydride Committee considered the animal usage required and has, therefore, recommended only a minimal amount of animal testing – one combined 90-day toxicity study in conjunction with a one-generation reproduction study. By keeping the number of animals used in the proposed test plan to a minimum, the committee feels that animal welfare concerns have been properly addressed.

MATRIX OF APPLICABLE DATA ON CYCLIC ANHYDRIDE CATEGORY DATA AND PROPOSED TESTING						
TEST	**CATEGORY MEMBER; CAS NUMBER**					**REMARKS**
	HHPA; 85-42-7	**MHHPA; 25550-51-0 (5711-02-99)**	**THPA; 85-43-8**	**MTHPA; 34090-76-1 (11070-44-3)**	**NMA; 25134-21-8**	
PHYSICOCHEMICAL PROPERTIES						
Melting Point	A	A	A	(A)	T	
Boiling Point	A	T	T	(A)	T	
Vapor Pressure	A	A	A	A	A	
Partition Coefficient	T	T	T	(A)	T	
Water Solubility	T	T	T	(A)	T	Solubility and pKa testing will be done
ENVIRONMENTAL FATE						
Photodegradation	A	T	T	(A)	T	
Hydrolysis	T	T	T	(A)	T	
Transport and Distribution	T	T	T	(A)	T	
Biodegradation	A	A	A	A	A	
ECOTOXICITY						
Acute Fish	A	C	A	A	T	
Acute Daphnia	A	C	A	A	T	
Algae	A	C	A	A	T	
MAMMALIAN TOXICITY						
Acute Toxicity	A	A	A	A	A	
Repeated Dose	C	C	C	A	T	
Genotoxicity (in vitro – bacterial)	A	C	A	A	T	
Genotoxicity (in *vitro* – non-bacterial)	T	C	C	A	T	
Reproductive/Developmental Toxicity	C	C	C	A	T	

A- Endpoint requirement fulfilled with adequate existing data
C – Endpoint requirement fulfilled using Category Approach
T Endpoint requirement to be fulfilled by testing.
(A) – Endpoint requirement to be fulfilled with data from ICCA Test Program.