

HIGH PRODUCTION VOLUME (HPV)
CHEMICALS CHALLENGE PROGRAM

REVISED TEST PLAN

For

4,5,6,7-TETRACHLORO-1,3-ISOBENZOFURANDIONE

CAS NO. 117-08-8

Prepared by:

Solutia, Inc. Registration No.

575 Maryville Centre Drive,
St. Louis, Missouri 63141

May 20, 2003

EXECUTIVE SUMMARY

Solutia, Inc. voluntarily submits the following Revised screening information data and Test Plan covering the chemical, 4,5,6,7-Tetrachloro-1,3-isobenzofurandione, also known as Tetrachlorophthalic Anhydride or TCPA (CAS No. 117-08-8), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

A substantial amount of data exists to evaluate the potential hazards associated with TCPA. Use of key studies or estimation models, available from data already developed, provide adequate support to characterize most of the Endpoints in the HPV Chemicals Challenge Program without the need for additional, unnecessary testing. If technically feasible, Solutia Inc has agreed to conduct an Aqueous Stability (hydrolysis) study according to OECD 111 guidance to complete the data needs for this assessment.

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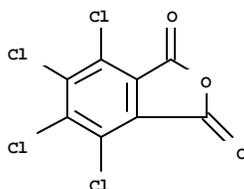
TEST PLAN FOR TETRACHLOROPHTHALIC ANHYDRIDE

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, Solutia Inc. has committed to voluntarily compile basic screening data on Tetrachlorophthalic Anhydride, also known as TCPA. The data included in this Revised Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of TCPA, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed on behalf of Solutia Inc. or found in the published scientific literature and, along with additional testing proposals, will fulfill Solutia's obligation to the HPV Challenge Program.

A. Structure and Nomenclature

Following is a structural characterization of TCPA and associated nomenclature.



Phthalic anhydride, tetrachloro-
CAS No. 117-08-8

Synonyms: 4,5,6,7-Tetrachloro-1,3-isobenzofurandione; TCPA;
TETRATHAL[®], Tetrachlorophthalic Anhydride; CP 626.

B. Manufacturing & Use

TCPA is manufactured by a single US producer, Solutia Inc., at a single manufacturing site and is produced in short production campaigns. The manufacturing operation is a closed, continuous process. Due to its potential to cause occupational asthma (Schlueter et al, 1978), Solutia has adopted an airborne exposure guideline of 0.5 mg/m³ 8-hour TWA and a 1 mg/m³ 15-minute TWA for this compound. Employees wear eye and skin protection to prevent contact and approved respiratory protection equipment, should airborne exposure limits be exceeded. Only a few employees are involved in the manufacturing process and thus have minimal potential for skin or airborne exposure, and those chiefly during drying and material transfer operations.

TCPA is sold to a limited number of customers at a few processing sites. Over 70% of annual production is exported from the US (NTP, 1993). T CPA is used primarily as (1) a chemical intermediate which undergoes chemical reaction to form chemicals used as dyes/pigments and as (2) a “reactive type” flame retardant in plastics (epoxy resins, polyesters, and polyurethanes). This designation is indicative that T CPA reacts to become chemically bound to the polymer backbone of the plastic (NTP, 1993). There are no known consumer uses of T CPA. Thus, potential exposure to T CPA resulting from TSCA-related activities is negligible. Airborne losses during manufacturing and during use have been estimated to be 0.05 pounds per 1000 pounds consumed (NTP, 1993). Hence, very limited occupational or environmental exposure is expected to occur.

II. TEST PLAN RATIONALE

The information obtained and included to support this Revised Test Plan have come from either 1) internal studies conducted by/or for Solutia Inc. (or its predecessor Monsanto Co.), 2) have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or 3) were estimated using environmental models accepted by the US EPA (1999b) for such purposes. This assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with T CPA. The data used to support this program include those Endpoints identified by the US EPA (1998); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VI. of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:

1. Reliable without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,
2. Reliable with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well

documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).

3. Not Reliable – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.

4. Not Assignable – Used to identify Supplemental studies conducted according to methodology insufficient to fully support an Endpoint in the HPV assessment program.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier. A few additional studies with TCPA have been identified during our literature search on the referenced HPV Endpoints but have not been summarized in this Dossier. The data herein presented is considered typical of additional information located in our literature review.

III. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion: Nearly all HPV Endpoints have been satisfied with data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation modeling programs. In those cases where data were not available, use of the weight-of-evidence has been applied to support a conclusion that no additional information is needed. Hence, with the exception of an aqueous stability (hydrolysis) study, no further testing for any of the HPV Endpoints is deemed necessary, as summarized in Table 1.

In summary:

Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) were obtained from reputable reference books and further cited as an Accepted or Peer Reviewed value in the Hazardous Substances Data Bank - Tetrachlorophthalic Anhydride (2002) and/or summarized in the NTP Toxicity Report No. 28 – Tetrachlorophthalic Anhydride (1993). Thus, these values were classified as “2-Reliable with restrictions”.

Environmental Fate values for Photodegradation, and Transport (Fugacity) were obtained using a computer estimation –modeling program (EPIWIN, 2002) recommended by EPA; as such, they were designated “2-Reliable with restrictions”.

The EPIWIN program was unable to estimate Stability in Water (Hydrolysis). Due to its limited environmental exposure potential and the stated recognition of hydrolysis from the anhydride to its acid form (US EPA, 1982), no additional Hydrolysis testing was deemed needed initially by Solutia to fill this Endpoint. After consideration of EPA comments, Solutia agrees to conduct such a study using OECD guideline 111. In so doing we note the potential difficulty in conducting such a study with a substance of low water solubility (as Tetrachlorophthalic anhydride); thus, a “best effort” will be given to development of this data. Due to its insolubility, Biodegradation testing (SCAS test) of TCPA could not be conducted even after several trials. Therefore, a biodegradation study was conducted with the sodium salt of tetrachlorophthalic acid. That study was well-documented and was conducted using methodology that preceded, but is considered consistent with, methodology recommended in OECD test guideline 301.

Ecotoxicity - A study conducted according to OECD guidelines for Acute Invertebrate Toxicity (OECD 202) and designated “2- Reliable with restrictions” fulfilled this Endpoint requirement. No acceptable studies were found to address either the Acute Plant Toxicity or the Acute Fish Toxicity Endpoint. Based on estimated levels of toxicity in fish and invertebrates occurring only above the level of TCPA water solubility, no additional testing is warranted for these two Endpoints.

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames and Chromosomal Aberration Testing, and Reproductive Toxicity) have all been filled with tests that either conformed directly with OECD test guidance or followed test designs similar to OECD guidance.

The Acute Toxicity Endpoint was supported by an oral toxicity study which was conducted preceding codification of OECD and GLP guidance but was well documented and followed methodology consistent with later guidance; it is considered “2- Reliable with restrictions”.

The Repeated Dose Toxicity Endpoint was met with a 90-Day Subchronic rat study (similar to OECD guideline 408) conducted in accordance with GLPs. It also was codified as “2- Reliable with restrictions” due to minor deviations in methodology.

Both the Ames test and the *in vitro* Chromosomal Aberration assay used to support their respective Endpoints were conducted by the US National Toxicology Program (NTP). The Ames test followed a study design equivalent to OECD guideline # 471 while the cytogenetics study was similar to, but not identical with, OECD guideline # 473. Thus, the Ames test was categorized as “1- Reliable without restriction” while the Cytogenetics study was classified as “2- Reliable with restrictions”.

The Reproductive Toxicity HPV Endpoint has been filled using a combination of the 90-day Subchronic Rat study previously cited along with a Rat Developmental Toxicity study, the latter considered “1- Reliable without restriction”. Both studies

met respective OECD test guidelines, i.e. OECD 408 and 414 and were conducted according to GLP guidance. No effects on male or female reproductive organs were observed in the Subchronic study. Therefore, according to EPA Guidance (US EPA, 1998), use of this combination of tests can fulfill this HPV Reproductive Toxicity Endpoint.

Following is a tabular summary of the Test Plan developed for Tetrachlorophthalic Anhydride.

Table 1. Test Plan Matrix for Tetrachlorophthalic Anhydride

	Info. Avail.	OECD	GLP	Other Study	Estimat. Method	Accept-Able ?	Testing Recomm.
PHYSICAL CHEMICAL							
Melting Point	Y	R	N	N	-	Y	N
Boiling Point	Y	R	N	N	-	Y	N
Vapor Pressure	Y	R	N	N	-	Y	N
Partition Coefficient	Y	R	N	N	-	Y	N
Water Solubility	Y	R	N	N	-	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	N	N	Y	Y	N
Stability in Water	N	-	-	N	-	N	Y
Biodegradation	Y	N	N	Y	-	Y	N
Transport between Environmental Compartments (Fugacity)	Y	N	N	N	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	N	Y	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	Y	N	-	Y	N
Toxicity to Aquatic Plants	Y	-	-	-	Y	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	N	N	Y	-	Y	N
Repeated Dose Toxicity	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Mutation (Ames)	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Chromosomal	Y	N	Y	Y	-	Y	N

Chromosomal Aberrations							
Developmental Toxicity	Y	Y	Y	N	-	Y	N
Reproductive Toxicity	Y	-	-	Y	-	C	N

Y = Yes; N = No; R = Reference value; C = Completed through combination of Developmental Toxicity and Subchronic Toxicity Endpoints; - = Not applicable

III. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VI of this Dossier.

A. Chemical/Physical Properties

Table 2. Selected Chemical/Physical Properties of Tetrachlorophthalic Anhydride (TCPA)

Chemical	Boiling Pt. (°C.)	Melting Pt.(° C.)	Vapor Pressure (hPa @ 145 °C)	Water Solubility (mg/L)	Partition Coefficient (Log Kow)
TCPA CAS No. 117-08-8	371	254.5	0.21	< 1.0 @ 21 °C.	3.57

All HPV Endpoints for Physical-Chemical Properties have been completed with reliable information and taken from reputable textbook-references (Table 2). The values, which have been designated as “2-Reliable with restrictions”, are included in the Robust Summary section of this Dossier, have been accepted as accurately depicting the properties of TCPA and are cited as peer-reviewed references in the Hazardous Substances Data Bank for Tetrachlorophthalic Anhydride (HSDB, 2002) and/or the NTP Technical Report on Toxicity of Tetrachlorophthalic Anhydride (1993).

In summary, these data indicate that TCPA is a solid at room temperature and has a low vapor pressure. It has a moderate octanol:water partition coefficient and very low solubility in water.

Conclusion – Adequate reference values are available to provide needed information on the Physical-Chemical Properties associated with TCPA. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Biodegradation

In-house attempts to conduct a Semi-Continuous Activated Sludge (SCAS) Biodegradability study with TCPA proved unsuccessful, due to its very low water solubility. Therefore, a SCAS test was conducted with the sodium salt of TCPAcid. That study is summarized in the Robust Summary section of this Dossier and cited in Table 3 below. While conducted prior to inception of standardized international guidelines for **Biodegradability** testing and GLPs, this study followed similar standards for conduct subsequently codified into OECD guideline 301 and GLP documentation. Due to the technical difficulties to be encountered to conduct such a study with TCPA, no future attempts at testing are planned.

No information could be located regarding Photodegradation, Stability in Water (Hydrolysis) and Transport (Fugacity) for TCPA following an extensive literature search. Thus, we have incorporated the use of the estimation models found in EPIWIN (2002) for determination of these HPV Endpoints and have been designated “2-Reliable with restrictions”. Estimated **Photodegradation Rate** and **Fugacity** values are cited with the Robust Summaries and also are included in Table 3; thus, these HPV Endpoints are considered complete and each judged as “2-Reliable with restrictions”. At the request of EPA, we have also provided a Fugacity Level III assessment of the likely hydrolysis product of TCPA, tetrachlorophthalic acid. This estimation has been provided in the Robust Summary section of this dossier. In deference to this estimated Photodegradation rate, we note the information reported by Yu and Atallah (1978) with a structurally similar chemical, Tetrabromophthalic anhydride (TBPA)(CAS No. 632-79-1). When TBPA was applied to silica gel surfaces and irradiated with UV light, it was demonstrated to hydrolyze rapidly (half life of less than 5 min.) to the dicarboxylic acid; this result is also consistent with its degradation pattern in moist soil (Butz and Atallah, 1979). A similar, rapid hydrolysis after UV exposure, would be expected to occur with TCPA.

No data is available on Stability of TCPA in Water and the EPIWIN (2002) program is not capable of estimating a hydrolysis value for cyclic esters, including TCPA. Thus, the water stability of TCPA is best estimated from analogy with related compounds, as it is exceedingly difficult to conduct the recommended OECD 111 test with this material. The OECD 111 test requires the test material to be soluble at a level of 20 mM, and the actual water solubility of TCPA is < 1 mg/L, or < 0.004 mM, thus rendering this study impractical to conduct. After review of EPA comments on our initial submission, Solutia has agreed to provide a “best effort” in conduct of an OECD 111 study, using recommended modifications needed for low water solubility chemicals like TCPA.

TCPA is an anhydride, a reactive species known to be readily hydrolysable (Smith and March, 2001). The presence of the electron-withdrawing chloro groups are also expected to increase the susceptibility to base hydrolysis by reducing electron density at the carbonyl carbon and making the meta carboxyl group a better leaving group. Thus, the tetrachloro compound should hydrolyze even more rapidly than phthalic anhydride,

which is reported to have a $T_{1/2}$ in water of about 90 seconds (Jones, HR, 1972). TCPA is already expected to hydrolyze to its acid (US EPA, 1982). While the acid itself is only slightly soluble and has shown little biodegradation potential in the SCAS test (Table 3), it is considered biodegradable in the environment under both aerobic and anaerobic conditions (Bosma et al, 1996).

By way of comparison, the structurally similar TBPA (Tetrabromophthalic anhydride) has been assessed for its capacity to hydrolyze in moist soils (Butz and Atallah, 1979). Rapid hydrolysis occurred to the halogenated phthalic acid, where further degradation ceased.

Table 3. Environmental Fate and Biodegradation Parameters for Tetrachlorophthalic Anhydride (TCPA)

Chemical	Biodegradation Rate	Stability in Water	Fugacity (%)	Photodegrad. Rate ($T_{1/2}$)
TCPA CAS No. 117-08-8	0.2 %	Not calculatable In EPIWIN, but Considered rapid	Air – 1.25 Water – 13.4 Soil – 83.9 Sediment – 1.42	338.4 days-EPIWIN. Hydrolysis - rapid

The Environmental Fate and Biodegradability of TCPA can be summarized as follows. Direct photolysis in water or water droplets occurs when a photon is absorbed by a compound, which leads to the formation of an excited form, which in turn can react in a variety of ways to form more stable products. Only a small portion of synthetic organics absorb UV light above 295 nm, the sunlight region of the spectrum. Absorbance of sunlight in this range is needed for a compound to undergo direct photolysis. Aliphatic and oxygenated compounds including acids absorb only below 220 nm and would not be considered able to directly photolyze. Compounds that may be candidates for direct photolysis include polyhalogenated benzenes that do absorb UV light at 295 nm and higher. The presence of a polyhalogenated benzene ring with either the tetrachlorophthalic anhydride or the acid to which it hydrolyzes in water indicates that both are candidates for direct photolysis (Weast, 1985). In regards to hydrolysis or direct photolysis in airborne water droplets, the fact that the tetrachlorophthalic anhydride is a flaked solid at room temperature precludes much, if any, from entering the atmosphere. This is further supported by fugacity modeling of the anhydride that shows that less than 1.5% would be found in air and of the acid (assuming complete hydrolysis of the anhydride to the acid) which would indicate availability of $\ll 0.1\%$ or that chemical form.

So, upon release to the air, TCPA is expected to react photochemically only to a minimal extent by reaction with photochemically-produced hydroxyl radicals; the half-life for this

reaction in air is estimated to be 338 days (Table 3 - Photodegradation). It is anticipated that rapid hydrolysis would occur. The majority of airborne TCPA or its acid equivalent would be expected to precipitate in the soil (Table 3 – Fugacity). If still in its parent form it would undergo rapid hydrolysis in a moist soil environment, and much would become soil-bound. Significant volatilization from soil or water to air is not expected, based on its Vapor Pressure (Table 2) and Henry's Law constant (EPIWIN, 2002). In aqueous solution, TCPA is expected to hydrolyze to its acid form and thereafter undergo further aerobic and anaerobic degradation (Bosma et al, 1996). Due to TCPA's low water solubility and high binding capacity, the potential for persistence or bioaccumulation has been judged as minimal (US EPA, 1982).

Conclusion – Adequate studies are available to provide needed information for the HPV Designated Environmental Properties associated with TCPA. Biodegradation with its sodium salt used methodology consistent with OECD test guidance, while Fugacity and Photodegradation Endpoints were completed using EPIWIN, an accepted estimation-modeling program. While there would appear justification for no additional testing needs for Stability in Water based on generalized knowledge of hydrolysis of anhydrides and low solubility of TCPA specifically that may prevent conduct of a meaningful study, an OECD 111 guideline study will be attempted with TCPA.

C. Aquatic Toxicity

Limited information is available on the acute toxicity of TCPA on algae, invertebrates and fish. An acceptable study, summarizing effects in *D. magna* has been used to fulfill the Acute Invertebrate Toxicity Endpoint. While not conducted specifically to meet OECD guidelines, it used methodology recommended by the US EPA Committee of Methods for Toxicity Testing with Aquatic Organisms (1975). These recommendations are consistent with OECD guidelines; the study was conducted under GLPs. The study was conducted at and above levels of TCPA water solubility (<1 ppm) such that the test medium reached saturation; while this does not detract from the lack of toxicity seen up to that level, the final nominal LC0 (Minimum Lethal Dose) value reported of > 1,000 ppm is well above TCPA solubility and thus artificially elevated. Hence, this study has been designated as "2- Reliable with restrictions", selected for development of Robust Summaries, and is cited in Table 4. A computer-derived estimation of a 48-hr. *Daphnia* LC50 value with TCPA correctly indicated a toxicity value in excess of the water solubility of TCPA, as was determined in the present study.

Table 4. Aquatic toxicity parameters for Tetrachlorophthalic Anhydride (TCPA)

Chemical	Fish LC 50 (mg/L)	Invertebrate LC50 (mg/L)	Algae EC50 (mg/L)
TCPA CAS No. 117-08-8	7.086 (estim.)	> 1,000 (Daphnia-48 hr)	5.791 (estim.)

No adequate toxicity study data has been located to fulfill the Acute Fish Toxicity and the Acute Algae Toxicity Endpoints. A single preliminary acute fish toxicity study (Applegate et al, 1957) reported the lack of toxicity to sea lamprey larvae after static exposure to a nominal concentration of 5 ppm TCPA; this again was conducted at a level well above TCPA water solubility. This study is considered insufficient in design and documentation (Category 3) to justify use in completion of this HPV data set and has not been summarized further. However, the results reported, i.e. no effects of exposure at the test level reported, were consistent with results from the acute invertebrate study.

We have conducted a computer-derived (ECOSAR) toxicity value to aquatic species for TCPA. Levels of predicted toxicity for both fish and algae are cited in Table 4 and have been further summarized in section VI. Robust Summaries of this Dossier; TCPA-specific parameters used in the modeling are cited.

Additionally, acute static toxicity studies in fish (rainbow trout and bluegill sunfish) and water fleas (*D. magna*) have been reported for the structurally similar chemical tetrabromophthalic anhydride (TCBA) (US EPA 1986a, 1986b, 1986c). In all cases, the LC50 values were reported to be greater than 10 mg/L TBPA.

Based on the weight-of-information available on TCPA, we conclude that no additional testing for either of the Fish or Algae Toxicity Endpoints appears justified. We base this conclusion on the following lines of evidence: (1) TCPA is nearly insoluble (solubility level of <1ppm) in water, (2) TCPA is not toxic (LC0) at aqueous levels of saturation, (3) predictive modeling estimates that aquatic toxicity of TCPA could only occur above the level of TCPA water solubility, hence that limit already sets the upper bound of potential toxicity (4) TCPA's expected pattern and release scenarios and its projected environmental pathways indicate a negligible presence in the aquatic domain and (5) results of a close structural analog (TBPA) proved non toxic to fish and invertebrates.

Conclusion – An adequate study is available to meet the Acute Invertebrate Toxicity Endpoint for TCPA. Further, results of the lack of toxicity, coupled with low water solubility and insignificant environmental levels in the aquatic environment mitigates against any additional, unnecessary testing to complete additional HPV Endpoints in this category.

D. Mammalian Toxicity Endpoints

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Tables 5 and 6. Each report citation has been further summarized in the Robust Summary section of this Dossier.

Table 5. Acute and Repeated Dose Mammalian Toxicity of Tetrachlorophthalic Anhydride (TCPA)

Chemical Name/ CAS no.	Acute Toxicity (LD50/LC50)			Subchronic (13-week) Toxicity	
	Oral (mg/kg)	Dermal (mg/kg)	Inhalation (mg/m ³)	Oral (gavage)	Inhalation
Tetrachloro phthalic Anhydride CAS No. 117-08-8	>15,800	>5,010	>3,600	Rat – LOAEL= 94 mg/kg (lowest level tested) Target tissue: kidneys Mice – NOEL 187 mg/kg Target tissue: none	Rat (dust) – LOAEL= 0.73 mg/m ³ (lowest level tested) Target tissue: lungs, liver Rat (fumes) – LOAEL=0.5 mg/m ³ (lowest level tested) Target tissue: lungs., liver

1.0 Acute Toxicity

Results of acute toxicity studies by the oral, dermal and inhalation routes of exposure have been conducted, as summarized in Table 5. The oral toxicity study has been selected to fulfill the HPV Acute Toxicity Endpoint, while the other studies are included as supplemental information. Both the oral and dermal studies were conducted using study designs consistent with OECD Test Guidelines 401 and 402, respectively, and GLP guidance, but were completed before such guidance was codified. They are considered well documented and thus have been classified as “2- Reliable with restrictions”. The inhalation study has been similarly classified, although its documentation is limited.

TCPA is considered to be “practically nontoxic” after acute oral or dermal exposure to rats or rabbits, respectively, and only “slightly toxic” after acute inhalation exposure. However, based on the ability of TCPA to produce allergic skin and

respiratory sensitization, this material is considered to be hazardous in the workplace, requiring adequate handling practices to avoid acute or repeated exposures.

Conclusion – A quality study is available to assess the Acute hazards associated with TCPA. Therefore, no additional data development is needed for the Acute Toxicity HPV Endpoint.

2.0 Repeated Dose Toxicity

TCPA has been adequately tested by several routes of exposure to define its Repeated Dose toxicity. The key study used for this HPV assessment is cited in Table 5 and summarizes a 90-day subchronic rat study by the oral route. This study was conducted using a study design consistent with OECD Test Guideline 408, and conducted under GLP auspices as part of the NTP Testing program; it is considered “2- Reliable with restrictions” having but minor deviations from Guideline # 408. Another 90-day subchronic oral study, this one conducted in mice, was also included in the NTP testing program and also has been referenced in Table 5. While not used to support the Repeated Dose HPV Endpoint, it too is considered “2- Reliable with restrictions”. Two subchronic studies conducted on behalf of Solutia Inc. with forms of TCPA dust have also been summarized in Table 5 and included in the Robust Summary section of this Dossier as Supplemental information. Each of these inhalation studies has been classified as “2- Reliable with restrictions” in that technical difficulties precluded a definitive dosage delivery determination at the lowest dosage level tested. Nevertheless, the toxicological effects reported in these studies are relevant. In all cases, no evidence of an effect on the male or female reproductive organs (including testes) was observed. Lungs and liver proved to be target tissues in the rat inhalation studies, while oral studies identified degenerative renal changes in rats, but not mice.

Conclusion - The Repeated Dose HPV Endpoint for TCPA has been fulfilled with a well-conducted and documented 90-Day Subchronic study in rats deemed “2- Reliable with restrictions”. No further testing is needed for completion of information related to the Repeat Dose HPV Endpoint.

3.0 Mutagenicity and Chromosomal Aberrations

Table 6. Mutagenic and Reproductive/Developmental Mammalian Toxicity of Tetrachlorophthalic Anhydride (TCPA)

Chemical Name/ CAS no.	Mutagenicity			Reprotoxicity	Developmental. Tox
	Ames	Chromos. Aberration In vitro	Other In vitro	Other	Rat - oral
Tetrachloro phthalic Anhydride CAS No. 117-08-8	Neg w/wo S9.	Neg. w/wo S9	Neg. SCE – .w/wo S9	Mouse Sperm morph & vaginal cytol. – Both negative	Maternal & Developmental NOEL – 1000 mg/kg

3.1 Ames/Point Mutation Testing

When tested in the standard Ames assay for point mutations, TCPA elicited no mutagenic response in any of the *S. Typhimurium* tester strains employed, either with or without inclusion of metabolic activation. The Zeiger et al, (1985) study, conducted on behalf of the NCI/NTP program, has been summarized in the Robust Summary section of this Dossier and referenced in Table 5. Its design and documentation are such that it is considered equivalent to OECD guideline # 471 and thus is considered “1- Reliable without restriction” for this assessment. Additionally, TCPA has been tested in the secondary tier *Drosophila* Sex-Linked Recessive Lethal assay; no mutagenicity was observed after either oral or injection dosing up to lethal doses by each route in this same NCI/NTP program (Valencia et al, 1985).

Thus, it is concluded that adequate testing of sufficient quality to be designated “1- Reliable without restriction” has been performed on TCPA to evaluate the Ames Test (Point Mutation) requirement; no further testing is needed for this Endpoint.

3.2 - Chromosomal Aberrations

As part of the NCI/NTP program (Galloway et al, 1987), TCPA was tested in the CHO cell *in vitro* assay to determine its potential to induce chromosomal aberrations. A Robust

Summary has been prepared for this study as found in section VI of this Dossier and is referenced in Table 5. As part of the same study design, the effect of TCPA treatment on production of Sister Chromatid Exchanges (SCE's) was also evaluated in the same test system (Galloway et al, 1987). In both cases, with and without metabolic activation, TCPA was without effect. The quality of this study is considered to be "2- Reliable with restrictions", as it did not follow an established OECD protocol, yet was well documented and has been used for regulatory purposes.

TCPA has also been tested *in vivo* for induction of SCEs and Chromosomal Aberrations in mouse bone marrow cells. However, NTP has considered this study "incomplete" (NTP, 1993) and thus has not been further summarized.

The HPV Chromosomal Aberration Endpoint for testing of TCPA has, thus, been fulfilled with an adequately conducted and documented *in vitro* study; thus, no further testing is needed.

4.0 Reproductive and Developmental Toxicity

Sperm morphology and vaginal cytology evaluations were included as part of the 13-week rodent study program conducted by NTP with both mice and rats (NTP, 1993). Both studies were considered well documented but insufficient to provide definitive information to be used in this HPV assessment for TCPA and thus were designated as "4-Not assignable". Each study has been summarized in the Robust Summary section of this Dossier as Supplemental information and referenced in Table 6.

Of interest, it was concluded that there were no treatment-related changes in sperm morphology or vaginal cytology between TCPA-treated rats or mice and their respective controls (NTP, 1993).

Of direct relevance to completion of the Reproductive Toxicity Endpoint for this HPV assessment with TCPA, is identification of a well documented rat developmental toxicity study conducted according to OECD Guideline 414. This study has been assessed as "1- Reliable without restriction". It has been summarized in the Robust Summary section of this Dossier and is included in Table 6.

No maternal toxicity, embryotoxicity, fetotoxicity or teratogenic effects were observed at or below 1,000 mg/kg/d (NOEL). A low incidence of rib and vertebral malformations was observed at the maternally toxic level of 2,000 mg/kg/d. Hence, a wide margin (>10,000-fold) of safety exists at the recommended occupational exposure limit.

No evidence of morphological effects of either male or female reproductive organs was observed following subchronic TCPA testing (Table 5). No increases in organ weights or weight ratios of testes/epididymides or ovaries were seen after subchronic

testing in two mammalian species by two exposure routes. Further, there were no treatment-related microscopic findings observed after TCPA testing in adequately conducted 90-day subchronic studies in rats by both the oral and inhalation route and in mice exposed orally for the same duration.

In conclusion, the Reproductive Toxicity HPV Endpoint has been fulfilled using the EPA-accepted (US EPA, 1998) approach of dual consideration of a 90-day subchronic study (without effect on reproductive organs) and a rodent developmental toxicity study. The available data set on TCPA conforms to this approach. Multiple repeated dose studies have been conducted, none of which are indicative of an effect on reproductive organs, including the testes, of rodents. The Repeated Dose Study selected is of 90 days duration and of adequate quality. Similarly, a Developmental Toxicity study, assessed as “1-Reliable without restriction”, has been conducted with TCPA. Thus, the data requirements for this HPV Endpoint have been met and no further testing is required.

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V. ROBUST STUDY SUMMARIES -

IUCLID Data Sets are Appended