Method Version: GreenScreen® Version 1.2

Verified or Non-Verified: VERIFIED

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	Date: October 22, 2013
	Verification Review Plan Prepared By: Dr. Eric Rosenblum
Verified GreenScreen® Prepared by Licensed Profiler:	Organization: ToxServices LLC
	Date: October 15, 2013

Terephthalic Acid (CAS# 100-21-0) GreenScreen® Assessment

Prepared for:

Clean Production Action

Date:

October 15, 2013 (Verified)

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GreenScreen® Executive Summary for Terephthalic Acid (CAS #100-21-0)

Terephthalic acid is a chemical that functions as a monomer for polyester which has a variety of applications including adhesives, tire cord, beverage bottles and magnetic recording tapes. In addition, terephthalic acid is used as an OH trap in the fluorescent detection of hydroxylated terephthalate for monitoring OH generation in plant tissue under heavy metal stresses.

TPA was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it has Moderate (M) Toxicity (T) for Carcinogenicity, Endocrine Activity, Reproductive Toxicity and Developmental Toxicity (Group I Human) (Appendix B). This corresponds to GreenScreen® benchmark classification 2e in CPA 2011. A data gap (DG) exists for Respiratory Sensitization (SnR*). Although a data gap exists, TPA meets requirements for a GreenScreen® Benchmark Score of 2 as outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), even with its hazard data gap. In the worst case scenario, TPA would still be categorized as a Benchmark 2 chemical even if it were assigned a High score for the data gap for Respiratory Sensitization.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
All exposure routes (oral, dermal and inhalation) were evaluated together, as a standard approach for GreenScreen® evaluations, so the GreenScreen® Benchmark Score of 2 ("Use but search for safer substitutes") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Terephthalic Acid

Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
M	L	M	M	*M*	L	M	L	M	L	L	DG	L	M	L	L	*vL*	*vL*	M	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M and L) instead of three (i.e., H, M and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Assessment for Terephthalic Acid (CAS #100-21-0)

GreenScreen® Version 1.2 Assessment

Chemical Name: Terephthalic Acid

CAS Number: 100-21-0

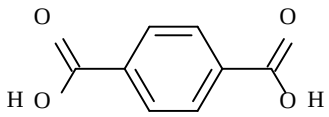
GreenScreen® Assessment Prepared By:
Name: Bingxuan Wang, Ph.D.

Title: Toxicologist
Organization: ToxServices LLC
Date: April 8, 2013; October 7, 2013 (Revision #1)

Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: April 11, 2013; October 15, 2013 (Revision #1)

Confirm application of the *de minimus* rule[1]: not applicable, terephthalic acid is not a mixture

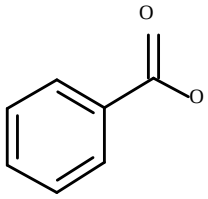
Chemical Structure(s):



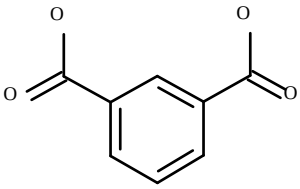
Terephthalic Acid (CAS #100-21-0)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:

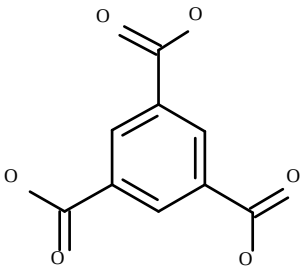
In order to fill the data gaps, surrogates were sought using the AIM software (U.S. EPA 2012). Pass 1 search identified 3 structurally similar analogs for TPA, as listed below:



Benzoic Acid
(CAS #65-85-0)



Isophthalic acid
(CAS #121-91-5)



1,3,5-Benzenetricarboxylic acid
(CAS #554-95-0)

Notes related to production-specific attributes[2]: No information disclosed.

[1] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

[2] Note any composition or hazard attributes of the chemical product relevant to how it is manufactured. For example, certain synthetic pathways or processes result in typical contaminants, by-products or transformation

Also called: 1,4-Benzenedicarboxylic acid; p-Benzenedicarboxylic acid; p-Carboxybenzoic acid; p-Dicarboxybenzene; p-Phthalic acid; para-Phthalic acid; Tephthol

Identify Applications/Functional Uses:
1. Almost exclusively used as a monomer component of polyester with a variety of applications including adhesives, tire cord, beverage bottles and magnetic recording tapes (HSDB 2012)
2. Used as an OH trap in the fluorescent detection of hydroxylated terephthalate for monitoring OH generation in plant tissue under heavy metal stresses (HSDB 2012)

GreenScreen® Summary Rating for Terephthalic Acid (TPA)[3]: TPA was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it has Moderate (M) Toxicology (T) for Carcinogenicity, Endocrine Activity, Reproductive Toxicity and Developmental Toxicity (Group I Human) (Appendix B). This corresponds to GreenScreen® benchmark classification 2e in CPA 2011. A data gap (DG) exists for Respiratory Sensitization (SnR*). Although a data gap exists, TPA meets requirements for a GreenScreen® Benchmark Score of 2 as outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), even with its hazard data gap. In the worst case scenario, TPA would still be categorized as a Benchmark 2 chemical even if it were assigned a High score for the data gap for Respiratory Sensitization.

Figure 1: GreenScreen® Hazard Ratings for Terephthalic Acid

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
M	L	M	M	*M*	L	M	L	M	L	L	DG	L	M	L	L	vL	*vL*	M	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M and L) instead of three (i.e., H, M and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[4,5]

products. Explain any differences between the manufactured chemical product and the GreenScreen™ assessment of the generic chemical by CAS #.

[3] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

[4] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

[5] The assessment of transformation products depends on the Benchmark Score of the parent chemical (see CPA Guidance 2013).

Terephthalic acid (TPA) is expected to exist solely in the particulate phase in the a®osphere and may be susceptible to direct photolysis by sunlight, as predicted by the EPISuite program. However, no photodegradation products are predicted. When released to soil, TPA will partially exist in anion form. TPA may be disposed of in an approved chemical incinerator or a waste chemical landfill. Dilute TPA is amenable to biological trea®ent at a municipal sewage trea®ent plant. When heated to decomposition, it emits acrid smoke and irritating fumes (HSDB 2012), which are composed of carbon monoxide and carbon dioxide. These two compounds are naturally occurring in the environment and therefore are not relevant to the assessment of terephthalic acid.

Introduction

Terephthalic acid (TPA) is primarily used as a monomer in the manufacture and production of polyester fibers, films, polyethylene terephthalate solid-state resins and polyethylene terephthalate engineering resins. Polyester fibers have been used to manufacture carpet, apparel, fill fibers for consumer products and industrial filaments. Polyethylene terephthalate solid-state resins are primarily used as containers for food and beverages. Polyester films are used as photographic films and magnetic tape base. Polyethylene terephthalate and polytubylene terephthalate engineering resins are primarily used in automobile parts (UNEP 2001).

ToxServices assessed TPA against GreenScreen® Version 1.2 (CPA 20113) following procedures outlined in ToxServices' SOP 1.37 (GreenScreen Hazard Assessment)(ToxServices 2013). In order to identify relevant environmental fate, environmental toxicity, and human health effects data, multiple sources were searched for data. These sources include on-line databases such as: ChemIDplus (which indexes databases such as HSDB, DART, EMIC, CCRIS, IRIS, Medline, and Toxline), TSCATS (which catalogs toxicity studies submitted to EPA under TSCA), ExPub (which indexes databases such as RTECS, NICNAS and ECHA. In addition, the World Wide Web is also used to search for material safety data sheets (MSDS) and other relevant data.

GreenScreen® List Translator Screening Results[6]

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2013) is an online list-searching tool that is used to screen chemicals against some of the lists in the List Translator electronically. Results of other lists will be captured under the Hazard Summary Classification Section. The output identifies the lists on which the chemical appears in addition to a hazard score that corresponds to the endpoint represented by that list. Using these automated hazard outputs, chemicals with possible Benchmark 1 scores can be identified immediately. The output for terephthalic acid can be found in Appendix C and a summary of the results can be found below:

Reproductive

GHS-Japan: Toxic to reproduction category 2

Mammalian

GHS-Japan: Systemic toxicity following repeated exposure category 1

[6] The GreenScreen™ List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen™ benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2013) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.

GHS-Japan: Acute toxicity (oral) category 4
GHS-Japan: Systemic toxicity following single exposure category 3

Eye irritation
GHS-Japan: Serious eye damage category 2B

Skin irritation
GHS-Japan: Skin corrosion category 3

PhysioChemical Properties of TPA

TPA is a white crystal or powder at room temperature. It has a very low vapor pressure (6×10^{-11} mm Hg), indicating that it is mostly in the solid phase with little potential to volatize. It is slightly soluble in water (15 mg/L). As an acid, it can be dissociated into ionic forms in water.

Table 1: Physical and Chemical Properties of TPA

Property	Value	Reference
Molecular formula	C8-H6-O4	HSDB 2012
SMILES Notation	c1(C(O)=O)ccc(C(O)=O)cc1	ChemIDplus 2013
Molecular weight	166.131	ChemIDplus 2013
Physical state	Solid	HSDB 2012
Appearance	White crystals or powder	HSDB 2012
Melting point	427℃	HSDB 2012
Vapor pressure	6×10^{-11} mm Hg at 25℃	HSDB 2012
Water solubility	15 mg/L at 20℃	HSDB 2012
Dissociation constant	$pK_1 = 3.54$, $pK_2 = 4.46$ at 25℃	HSDB 2012
Density/specific gravity	1.522 at 25℃	HSDB 2012
Partition coefficient	2.00	HSDB 2012

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M or L): *M*
TPA was assigned a score of *M* for carcinogenicity based on limited evidence of carcinogenicity in rodents (GHS Category 2). Level of confidence was low due to the use of expert judgment based on limited available data for this endpoint. GreenScreen® criteria classify chemicals as an *M* hazard for carcinogenicity when they are classified as GHS Category 2 for carcinogenicity (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- TPA was not listed as a known carcinogen by U.S. EPA, EU, GHS, IARC, NIOSH, NTP or Prop 65.
- ECHA 2013
  - In a non-GLP compliant study, Wag/Rij Wistar rats (50/sex/dose) were fed diets containing 1, 2, or 5% TPA (97.3% purity) for 2 years, which were equivalent to doses of

500, 1000, or 2500 mg/kg/day. Clinical observations and body weights were monitored throughout the study. At sacrifice, blood parameters were determined. Organs were weighed and examined histologically. Survival and body weights were statistically significantly affected at the highest dose. Blood urea was statistically significantly reduced in the mid dose males, but statistically significantly increased in high dose males and females. Liver, kidney and heart weights were reduced at the two lowest doses in females. Limited pathology findings were tabulated, showing a large number of animals with urolithiasis (89 and 93% in males and females, respectively), nephropathy (97 and 80% in males and females, respectively) and bladder tumors (57% and 62% in males and females, respectively) mainly at the highest dose, and there was no indication of severity of nephropathy. Hyperplasia of the pelvis and/or ureteral and/or bladder epithelium were present (dose unspecified). The epithelium also showed squamous metaplasia. The authors concluded that the presence of stones changed the urinary tract epithelium and resulted in the findings stated above. These findings are considered precursors to papillomas, infiltrating transitional cell tumors, and squamous cell carcinomas, although none of these malignant tumors were found in this study.

- In a non-GLP compliant study similar to OECD Guideline 453 (combined Chronic Toxicity/Carcinogenicity Studies), Fischer 344 rats (126/sex/dose) were fed diets containing 0, 20, 142 or 1000 mg/kg/day TPA for 2 years. Satellite groups of animals were sacrificed and necropsied at 6, 12 and 18 months. Food consumption, body weight, clinical observations were made periodically during the study. Hematology, clinical chemistry and urinalyses, eye examination, neurological function evaluations were performed for all the animals sacrificed at different time points. At the end of the study, organs were excised and examined histopathologically. Survival rates and body weight were decreased in some treated groups compared to controls without dose-dependence. Increased relative liver and brain weights, decreased heart and kidney weights were seen in some treated groups at certain time points without dose-dependence. A reduction of urine pH was noted for males fed the high dose TPA sacrificed at 24 months. TPA induced bladder stones or sand-like particles in 13/126 females at the high dose and microconcretions or calculi were seen at histopathologic evaluation in 3 other animals in this group. Bladder tumor (transitional cell adenoma) incidence in the high dose group was increased to 19/118 in females (incidence in other groups not reported), and no gross or histologic evidence of urolith formation was found in 6 of the 19 tumor-bearing females. Squamous metaplasia was seen in the bladder of 11/118 females in the high dose but not in controls, and it was never seen in the absence of a bladder tumor. Bladder hyperplasia incidence was increased in females at the high dose of TPA, although it was also noted in control females and in males. No statistics were reported. An abnormally high incidence of eye lesions, cataracts and associated lesions, as well as retinal lesions were found in all the animals of the study, possibly due to continuous lighting for a large portion of the study. In addition, a high incidence of uterine adenocarcinomas was also found in both treated and control animals. There was a large variation in dietary dose levels of TPA, which may result in the lack of clear dose-response relationships in the study. The authors concluded that evidence of carcinogenic effect was seen at the high dose level in this study. Transitional cell tumors were increased in high dose females, which were associated with a chronic proliferative response to urolithiasis.
- Microscopic re-evaluations on urinary bladder and eyes were performed by another laboratory for the Fischer rat study described above. At 6 and 12 months, no trea®ent related changes were present in the urinary bladders of either sex. At 18 months, no trea®ent-related changes were present in the urinary bladders of the high dose males.

Squamous metaplasia was found in 8 high dose females. Focal epithelial hyperplasia was found in 3 low dose and 1 high dose females. Diffuse epithelial hyperplasia was found in 4 low dose, 2 mid dose and 23 high dose females. Transitional cell papillomas were found in 2 low dose females. Transitional cell adenomas were found in 1 control female and 10 high dose females. One high dose female had a transitional cell carcinoma. No statistics were reported. The authors concluded that evidence of bladder carcinogenicity was seen in females at the highest dose level in this study.

  - Groups of 31 female mice were fed diets containing 0 or 0.5% TPA (3940 mg/kg/day)[7] for 16 months. Chronic feeding of TPA (> 6months) resulted in a statistically significantly decreased incidence of spontaneous mammary tumors in mice.
  - In a review article, it was concluded that low levels of TPA (<1%) do not seem to induce carcinogenic effects, while 5% TPA (780 mg/kg/day)[8] was associated with the formation of bladder and ureteral neoplasms in male and female rats.
- UNEP 2001
  - It is believed that the calculi injure the bladder epithelium and induce cell proliferation, which is probably a critical factor in bladder tumor induction by TPA in rodents. This mechanism of action has a threshold because bladder calculi only occur when the solubility of the stone components (Calcium ions and TPA) is exceeded. The document concluded that based on the urinary solubility of Ca-TPA (8 – 16 mM), assuming the average volume of urine excreted by humans is 1.5 L/day, the amount of TPA absorbed to produce the minimum saturating concentration would be 2,400 mg/day. Therefore, the carcinogenic risk for TPA in humans is low.

- Based on the weight of evidence, although no human studies have established that TPA is carcinogenic in humans and no regulatory agencies have classified TPA with regard to its carcinogenicity, results in more than one rodent study indicate that TPA is tumorigenic through a non-genotoxic mode of action which may be relevant to humans. However, due to the lack of statistical analysis and the lack of dose-response relationship, ToxServices assigned TPA as a GHS Category 2 chemical (suspected) based on limited or marginal evidence of carcinogenicity in animals.

Mutagenicity/Genotoxicity (M) Score (H, M or L): L

TPA was assigned a score of L for mutagenicity/genotoxicity based on mostly negative results in *in vitro* and *in vivo* studies. GreenScreen® criteria classify chemicals as a L hazard for mutagenicity/genotoxicity when adequate data are available and are negative for both chromosomal aberrations and gene mutations, the chemicals have no structural alerts and GHS grouping has not been classified (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- ECHA 2013
  - *In vitro:* TPA tested negative for mutagenicity in Ames tests using *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 in the presence and absence of metabolic activation up to the limit concentration (10,000 µg/plate)

[7] Food factor for female mice in chronic studies is 0.188 kg/kg/day (U.S. EPA 1988). Therefore 0.5% in the diet is equivalent to 0.5% x 0.188 kg/kg/day x 1,000,000 mg/kg = 3,940 mg/kg/day

[8] Food factor for rats in average in chronic studies is 0.078 kg/kg/day (U.S. EPA 1988). Therefore 1% in the diet is equivalent to 0.078 kg/kg/day x 1% x 1,000,000 mg/kg = 780 mg/kg/day.

  - *In vitro:* The clastogenicity of TPA was investigated in primary cultures of human peripheral blood lymphocytes in a GLP study according to OECD Guideline 473. The results showed that TPA was clastogenic in the absence of S-9 mix. However, in a separate study of the same design, sodium terephthalate was non-clastogenic at concentrations up to 2,100 µg/ml. This suggests that the clastogenicity of TPA in the first study is not associated with the terephthalate anion itself, as sodium terephthalate also has the terephthalate anion, but is not clastogenic.
  - *In vivo*: In a DNA damage and repair test conducted under GLP according to OECD Guideline 486, a single oral dose of TPA at 2,000 mg/kg was given to male rats via gavage. No unscheduled DNA synthesis was found in the liver.
  - *In vivo*: In a micronucleus assay conducted according to OECD Guideline 474 under GLP, male and female mice (5/dose/sex) were given a single intraperitoneal injection of TPA at doses of 200, 400 or 800 mg/kg. TPA trea®ent did not increase the incidence of micronucleated polychromatic erythrocytes from bone marrow in any of the treated groups.
- UNEP 2001
  - *In vitro*: TPA was not mutagenic in multiple Ames tests using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 at the doses up to 10,000 µg/plate with and without metabolic activation.
  - *In vitro:* TPA tested negative in a cytogenetic assay in human peripheral blood lymphocytes. No more details were provided.
  - *In vitro:* TPA tested negative in a DNA amplification test. No more information was provided.
  - *In vitro:* TPA tested negative in Chinese hamster lung fibroblasts at the concentration of 2,000 µg/ml without metabolic activation.
  - *In vitro:* TPA tested negative in a micronucleus assays in human peripheral blood lymphocytes. No more information was provided
  - *In vitro:* TPA did not induce DNA single strand breaks in primary rat hepatocytes. No more information was provided.
  - *In vivo:* In a micronucleus assay, mice received single i.p. doses of TPA of 0.09 – 4.3 mmol/kg (15 - 714 mg/kg). Increased micronuclei were found in bone marrow polychromatic erythrocytes which peaked at 24 hours. No further information was provided to substantiate the validity of the study, as data from this reference were available in abstract form only. In addition, as DMSO was used in this study as a solvent, and DMSO is known to result in excess mortality and elevated micronuclei in the negative control group. UNEP concluded that "poor study design and reporting along with solvent toxicity make interpretation of this study problematic."

- TPA tested positive for clastogenicity in one study without metabolic activation in *in vitro* primary cultures of human peripheral blood lymphocytes (ECHA 2013). Another similar study with sodium terephthalate demonstrated negative results for clastogenicity, indicating that the possible clastogenic effect noted in the first study may not be related to the terephthalate anion (ECHA 2013). TPA increased micronucleus formation *in vivo* in mice in a poorly reported and designed study (UNEP 2001), but was found non-genotoxic for the same endpoint in another GLP study (ECHA 2013). All the other *in vivo* and *in vitro* studies showed negative results for its mutagenicity and clastogenicity. Based on the weight of evidence, TPA is not likely to be genotoxic.

Reproductive Toxicity (R) Score (H, M, or L): M

TPA was assigned a score of M for reproductive toxicity based on classification to GHS category 2. GreenScreen® criteria classify chemicals as M hazard for reproductive toxicity when they are classified to GHS category 2 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* NITE 2006 (GHS-Japan)
    - GHS-Japan classified TPA as Category 2 for toxicity to reproduction, based on the evidence of decreased weight gain and reduced viability in pups described below in the study in CD and Wistar rats and is discussed further in the developmental toxicity section below.
- ECHA 2013
  - In a GLP-compliant two-generation reproductive toxicity study in Wistar rats performed according to OECD Guideline 416, TPA (purity 100%) was given without a vehicle at 0, 1,000, 5,000 or 20,000 ppm in the diet (equivalent to 0, 100.5 - 116.2, 502.7 – 581.1 or 2010.9 – 2324.3 mg/kg/day, respectively, according to ECHA) to animals (26/sex/dose). F0 animals were exposed from 5 weeks of age to termination of the F2 generation. They were initially exposed for 10 weeks and then mated for 14 days. F1 offspring were exposed to the diet from birth (retained with their dams until day 29 post-partum) until termination. Body weights were reduced (statistical significance not reported) in F0 and F1 animals of both sexes at the highest dose only. Food consumption and utilization were also reduced in at this dose (statistical significance not reported). No effects were found on smear cycle and pattern, pre-coital interval, gestation length, proportion of successful matings, pups borne live, litter size, pup survival, pup sex distribution or pup clinical observations in any exposed group. Body weights of F2 animals of both sexes at the highest dose were lower than control (statistical significance not reported), which correlated with increased litter sizes, and total litter weight was not affected. Body weights of F1 males at the mid dose were lower than controls on day 29 post-partum, and body weight of F2 pups at the mid dose were lower than control from day 15 post-partum. A statistically significant decrease in the ano-genital distance was found in females in the F1 and F2 litters at the highest dose only. Vaginal opening was slightly delayed (i.e. by 1.6 days) in F1 females at the highest dose. Preputial separation was delayed in F1 males at the mid and high doses (by 0.8 days and 1.6 days, respectively). These differences were related to the reduced body weight of these animals. Kidney weights (absolute and relative) decreased in males from all treated males in both generations. In females, only absolute kidney weight was reduced. Relative liver weight was increased in both sexes and both generations at the highest dose only. No effects were noted on sperm number, sperm motility or sperm morphology. No effects were observed on the number of mated F0 or F1 animals failing to produce litters, and on the reproductive organs. A variety of changes were noted in the urinary bladder of male and female rats at the highest dose, with higher incidences in the F1 animals compared to the F0 generation. The authors considered these changes associated with the irritant effect on the bladder mucosa. Minimal or slight renal papillary necrosis was found in the grossly abnormal kidneys of a few F0 and F1 males at the highest dose. The authors concluded that no effects on reproductive performance or reproductive system were found in this study. Irritant changes were found in the bladders at the highest dose and there was some evidence of kidney toxicity at this dose. Reductions in pup body weight generally occurred from D15 post-partum, when the offspring had started consuming solid diet and

therefore considered to be a direct dietary effect on the pups rather than developmental toxicity. Decreased pup body weight in the F2 generation at the highest dose from parturition was considered to be related to the larger litter size. ECHA established the NOAEL at 2010.9 – 2324.3 mg/kg/day for reproductive and developmental toxicities, and the NOAEL at 502.7 – 581.1 mg/kg/day for the F0 and F1 animals and the respective offspring for systemic toxicity based on kidney and urinary bladder changes.

- In a subchronic feeding study, male Sprague-Dawley rats (10/dose) received TPA in the diet at 0, 0.2, 1 or 5% (equivalent to 0, 172, 860, 4,300 mg/kg/day, respectively[9]) for 90 days. Testicular functions were evaluated by histopathology, testicular sperm head counts, daily sperm production, sperm motility, biochemical indices (marker testicular enzymes), and serum testosterone. No effects on body weight gain or food consumption were found attributable to exposure. Damages to spermatogenic cells and Sertoli cells were found by electron microscope. Testicular sperm head counts, daily sperm production and activity of sorbitol dehydrogenase (SDH) were statistically significantly decreased at the highest dose. Sperm motility was significantly reduced in all treated groups dose-dependently. It was concluded that the 90-day administration of TPA at a very high dose of 5% in the diet caused adverse effects on sperm cells.

- UNEP 2001
  - In a GLP-compliant one-generation combined repeated dose toxicity and reproductive toxicity study in CD and Wistar rats, TPA was given to the animals in the diet at 0.03, 0.125. 0.5, 2.0 and 5.0% (equivalent to 14, 59, 240, 940 and 2499 mg/kg/day in male CD rats, 17, 67,282, 1107 and 2783 mg/kg/day in female CD rats, 14, 61, 249, 960 and 2480 mg/kg/day in male Wistar rats, and 19, 78, 307, 1219 and 3018 mg/kg/day in female Wistar rats). Males were on the diets for 90 days prior to and throughout mating while females were exposed further through gestation and lactation. Offspring were observed for 51 days including from birth through lactation and 30 days post lactation. Following 90-day exposure to TPA, statistically significant decreases in food consumption were observed in CD females treated with 2% and 5%, and in both sexes of Wistar rats on 5% TPA diet. Body weights were statistically significantly decreased in CD rats on 2% and 5% diets, in males on 0.03% diet, and in Wistar rats on the 5% diet. Five animals died (3CD females, 1 Wistar/sex) during weeks 4 – 13 in animals on the 5% diet. During the reproductive toxicity component of the study,7 animals (1 male CD at 2%, 1 CD/sex at 5%, 2 Wistar females at 0.03% and 2 at 5%) died. No effects were seen on fertility index and litter size in either strain. No effects of trea®ent were found on sex ratio or total number of offspring. Survivability on Day 21 was reduced in both sexes of offspring in CD rats whose parents had been exposed to 5% TPA in the diet. Body weights of offspring from Wistar dams on the 5% TPA diet were reduced at Day 1. On Day 21, body weight was reduced in both strains of offspring from dams exposed to 5% TPA in the diet. Increased postnatal deaths on Day 1 and decreased survivability to Day 21 were noted in the 2% and 5% groups of both strains. Unscheduled deaths during postweaning period (Day 21-51) in both strains were confined to the 5% TPA group and were associated with very high incidences of renal and bladder calculi. The NOAEL for reproductive toxicity was > 5% in the diet (approximately 2,480 – 3,018 mg/kg/day). The NOAEL for parental toxicity and systemic toxicity in the F1 generation was 0.5% TPA in the diet (approximately 240 – 307 mg/kg/day). The reduced weight gain and reduced viability in pups is considered a developmental effect for the purposes of this

[9] According to U.S. EPA (1988), food factor for male Sprague-Dawley rats in a subchronic study is 86 g/kg/day. Therefore, 1% in the diet is equivalent to 1% x 86 g/kg/day x 1,000 mg/g = 860 mg/kg/day.

assessment.
  - In groups of female C3H mice fed a diet containing 0.5% TPA (750 mg/kg/day) throughout life, animals were mated after approximately 50 days of trea®ent. Reproduction indices (interval between mating and birth of the pups, litter size, put weights, growth rate) were normal.
  - Feeding TPA at 0.5% in the diet to chickens reduced body weight, inhibited sperm formation, induced testes damage and affected the pituitary and thyroid. No more information was provided.

- The GHS-Japan classification of this chemical is based on its developmental toxicity (effects on the pups), rather than a reproductive toxicity. In 3 of the 5 studies identified above, no reproductive effects were found. However, in one 90-day feeding study in male Sprague-Dawley rats, a high dose of TPA (4,300 mg/kg/day) led to damages to spermatogenic cells and Sertolic cells and decreased testicular sperm head counts, daily sperm production and SDH activity (second study described under ECHA 2013). This is supported by the study in chickens indicating a potential for TPA to induce reproductive toxicity (third study under UNEP 2001). ToxServices classified TPA to GHS category 2 (suspected) based on the available data.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M or L): M
TPA was assigned a score of M for developmental toxicity based on limited evidence of increased mortality and reduced body weight in the offspring of rats exposed to TPA in the diet. GreenScreen® criteria classify chemicals as M hazard for developmental toxicity when available data indicate GHS Category 2 classification (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* NITE 2006 (GHS-Japan)
    - GHS-Japan classified TPA as Category 2 for toxicity to reproduction, based on evidence of decreased weight gain and reduced viability in pups at doses toxic to parental animals or in the absence of data on parental toxicity in the studies described in the reproduction toxicity section.
- UNEP 2001
  - In a GLP-compliant one-generation study in CD and Wister rats, TPA was given in the diet at the doses and according to the protocol described above (the first study under reproductive toxicity endpoint). Survivability on Day 21 was reduced in both sexes of offspring in CD rats whose parents had been exposed to 5% TPA in the diet. Body weights of offspring from Wistar dams on the 5% TPA diet were reduced at Day 1. On Day 21, body weight was reduced in both strains of offspring from dams exposed to 5% TPA in the diet. Increased postnatal deaths on Day 1 and decreased survivability to Day 21 were noted in the 2% and 5% groups of both strains. Unscheduled deaths during postweaning period (Day 21-51) in both strains were confined to the 5% TPA group and were associated with very high incidences of renal and bladder calculi. The NOAEL for F1 generation was 0.5% TPA in the diet (approximately 240 – 307 mg/kg/day). The reduced weight gain and reduced viability in pups is considered a developmental effect for the purposes of this assessment.
  - In a developmental toxicity study similar to OECD Guideline 414 conducted in Sprague-Dawley rats under GLP, females were exposed to TPA (< 99%) via inhalation at the doses of 1.0, 5.0 and 10.0 mg/m^3 for 6 hours/day for 10 consecutive days from Gestation Day 6 to 15. No signs of maternal toxicity were observed. No statistically significant

differences were noted in mean litter weights, pup viability or number of fetal malformations. External soft tissue examinations did not reveal any differences from controls. Internal examinations showed a slight increase in the incidence of rib anomalies in the middle dose group. This was only statistically significant when all the various types of rib anomalies were added up. It was concluded that rib anomalies were common variations and occurred at a rate within the range of the laboratories own historical controls. No other signs of embryotoxicity were observed that were associated with this change. As a result, rib anomalies were not considered biologically significant as an indicator of teratogenesis in this study. The maternal and fetal NOAELs were both greater than the highest dose tested (10 mg/m^3).

- The weight of evidence indicates that TPA administered in the diet to rats is toxic to the developing fetuses as exemplified by reduced survival rate and pup body weight at doses that were toxic and doses that were non-toxic to the parental rats (first study under UNEP 2001).

Endocrine Activity (E) Score (H, M or L): *M*

TPA was assigned a score of *M* for endocrine disruption based on limited evidence of pituitary and thyroid changes in chickens fed TPA, and on limited evidence of glucagon and insulin secretion changes caused by the surrogate benzoic acid, leading to it being listed by TEDX. Level of confidence was low due to the limited evidence available. GreenScreen® criteria classify chemicals as M hazard for endocrine activity when there is evidence of endocrine activity. In addition, listing by TEDX translates to H or M for this endpoint (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
  - *Screening:* The surrogate benzoic acid is listed by TEDX as a potential endocrine disruptor. This was based on the impact of benzoic acid and its analogues on insulin and glucagon secretion in one sheep study. Neither isophthalic acid nor 1,3,5-benzenetricarboxylic acid is listed by TEDX.
- Neither TPA nor any of the surrogates is listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Neither TPA nor any of the surrogates is listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- U.S. FDA 2010
  - TPA has a Log RP value of -10,000 in an estrogen receptor (ER) reporter gene assay, indicating low potency of estrogen receptor binding activity.
- UNEP 2001
  - Feeding TPA at 0.5% in diet to chickens reduced body weight, inhibited sperm formation, induced testes damage and affected the pituitary and thyroid. No more information was provided.
- There are no appropriate models to predict TPA's impact on glucagon and insulin secretion.

Based on the TPA-induced changes in endocrine organs in chickens and on the TEDX listing of one of its surrogates, benzoic acid, but not the other surrogates (which have more than one carboxylic acid substitutions on the benzene ring), ToxServices determined that TPA may have a moderate potential for endocrine activity.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M or L): L

TPA was assigned a score of L for acute toxicity based on oral and dermal LD_{50} values of over 2,000 mg/kg. GreenScreen® criteria classify chemicals as L hazard for acute toxicity when Oral and Dermal LD_{50} values are greater than 2,000 mg/kg and inhalation-Dust LD_{50} is greater than 5 mg/L where data available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* NITE 2006 (GHS-Japan)
    - Category 4 for acute oral toxicity, based on the rat LD_{50} (oral) value of 1,960 mg/kg, representing the lower of the two testing data (i.e. 1,960 and 18,800 mg/kg) available to the agency.
- ECHA 2013
  - Oral LD_{50} (rats) > 15,380 mg/kg
  - Inhalation LC_{50} (rats, 2h, aerosol) > 2.02 mg/L
  - Inhalation LC_{50} (rats, 4h, dust) > 1 mg/L
  - Inhalation LC_{50} (rats, 30 min, pyrotechnically disseminated[10]) > 0.235 mg/L
  - Dermal LD_{50} (rabbits) > 2,000 mg/kg
- ChemIDplus 2013
  - Oral LD_{50} (mice) = 3,200 mg/kg
  - Oral LD_{50} (rats) > 6,400 mg/kg
- UNEP 2001
  - Oral LD_{50} (rats) values range from 1,960 to > 15,380 mg/kg
  - Oral LD_{50} (mice) values range from 1,470 to 6,400 mg/kg

- GHS-Japan classified the compound based on limited available data. Based on the weight of evidence, the oral LD_{50} values of TPA are generally over 2,000 mg/kg in rodents and the dermal LD_{50} is greater than 2,000 mg/kg in rabbits. Inhalation LC_{50} values were higher than 1 mg/L, but there is insufficient data to determine if they are greater than 5 mg/L.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)

***Group II Score (single dose)*(vH, H, M or L)**: **M**

TPA was assigned a score of M for systemic toxicity (single dose) based on classification to GHS category 3. GreenScreen® criteria classify chemicals as an M hazard for systemic toxicity (single dose) when they are classified as GHS category 3 for Single Exposure (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* NITE 2006 (GHS-Japan)
    - TPA is classified as a GHS Category 3 chemical for specific target

[10] The pyrotechnic devices contained 54% TPA, 15% sugar, 26% potassium chlorate, 3% magnesium chlorate and 2% nitrocellulose along with a small amount of starter mix.

organs/systemic toxicity following single exposure based on human evidence including mild irritation of the respiratory tract (HSDB 2012).

- UNEP 2001
  - In an acute toxicity study conducted under GLP, a single dose of 5,000 mg/kg TPA (diluted with water to form a 50% w/v suspension) was given to Sprague-Dawley rats (5/sex) via gavage. Animals were continuously observed for 14 days after dosing before necropsy. Clinical signs consisted of diarrhea, redness around nose and discolored inguinal fur. These signs diminished in most animals by 48 hours and all the animals completely recovered at study termination. Mean body weights increased during the study and no adverse events were noted during gross necropsy.
  - In an acute oral (unspecified) toxicity study in mice (GLP status unknown), single doses of 500, 5,000 or 10,000 mg/kg (in 5% starch) TPA was administered. At 10,000 mg/kg, TPA disturbed movement coordination, damaged gastrointestinal tract, caused fluid retention and tissue death in internal organs. Of the treated animals, 40% died within 6 – 12 days. At 5,000 mg/kg, pronounced vascular disorders, and effects on the nervous system function were observed. At 500 mg/kg, only mild transient nervous system effects of excitation and depression were observed. ToxServices assigned a LOAEL of 5,000 mg/kg for systemic toxicity based on pronounced vascular disorders.
  - In an acute inhalation toxicity study conducted under GLP, Sprague-Dawley rats (5/sex) were exposed to 2.02 mg/L TPA as a particulate aerosol for 2 hours. No deaths occurred in the study. Clinical observations revealed diarrhea, redness around nose, wet and discolored fur and hair loss. Mean body weights increased during the 14-day study period. At necropsy, dark lungs (in 1 male rat) and enlarged mandibular lymph nodes (in 1 male and one female rat) were noted. Particle size was not determined during the exposure due to technical difficulties, and therefore the gravimetric time weighted average concentration of 2.02 mg/L was not corrected for respirable particle size. The number of animals with dark lungs (1/10) and enlarged mandibular lymph nodes (2/10) was low and the total number of animals used (i.e., 10) was low. The concentration based on respirable particle size is not known. Therefore, these observations were of questionable toxicological significance and no LOAEL/NOAEL was established for this study.
  - In an acute dermal toxicity study conducted under GLP, New Zealand rabbits (5/sex) received 2,000 mg/kg TPA on the shaved skin under occlusive conditions. Animals were observed for 14 days post exposure. No deaths occurred. The only clinical signs noted were erythema at the application site immediately after unwrapping in some animals.
- HSDB 2012
  - TPA is mild irritant to respiratory tract. It may cause irritation to the mouth, nose or throat.

- Available data from animal studies indicate that at extremely high doses, potential adverse effects may occur, such as the pronounced vascular disorders observed in rats at the oral dose of 5,000 mg/kg (second study under UNEP 2001), and darkened lungs and enlarged lymph nodes in mice at the inhalation concentration of 2.02 mg/L (although with questionable toxicological significance due to low occurrence and unknown respirable particle size) (third study under UNEP 2001). TPA is a mild irritant to the respiratory tract (HSDB 2012) and was classified to GHS category 3 based on respiratory tract irritation in humans by GHS-Japan. ToxServices determined that the available data support this GHS classification.

Group II* Score (repeated dose)**(H, M, L): L**

TPA was assigned a score of L for systemic toxicity (repeated dose) based on the lowest oral LOAEL of 1,000 mg/kg/day for bladder calculus and the absence of significant toxicity in inhalation studies tested up to the dose of 10.05 mg/m^3. GreenScreen® criteria classify chemicals as a L hazard for systemic toxicity (repeated dose) when oral critical values are greater than 100 mg/kg/day (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* NITE 2006 (GHS-Japan)
    - TPA was classified as GHS Category 1 (respiratory organs, based on degeneration of the bronchial mucosal epithelium in animal studies) and Category 2 (bladder, based on bladder calculus) in Specific target organs/systemic toxicity following repeated exposure by Japan.
- UNEP 2001
  - Oral
    - In a pre-GLP 15-week feeding study, male and female Albino rats (30/sex/dose) were fed diets containing 0.05, 0.16, 0.5, 1.6 and 5.0% (37.9, 122, 393, 1220 and 3837 mg/kg/day in males and 46, 147, 447, 1456 and 4523 mg/kg/day in females) TPA (> 99% pure). Survival, clinical observations, growth, food consumption, hematology, serum clinical chemistries, urinalysis, gross pathology, weights and histology of a full range or organs were examined. Four animals (1 male at 0.5% TPA and 3 females at 5% TPA died during the study of unknown etiology. Hematuria was noted sporadically in the latter 2/3 of the study duration in males at 5% dietary TPA. Body weights from both sexes were mildly depressed at 5% TPA. Calculi in the urinary bladder were noted in males treated with 5% TPA in the diet. Hyperplasia was found in the urinary bladder and occasionally the kidney pelvis epithelium of all test and control groups, but the incidences and severities were statistically significantly increased in males in the highest dose group. These conditions were inconclusive in females at the highest dose. The bladder hyperplasia is believed to be secondary to calculi and subsequent inflammation in these animals. The NOAEL was established at 1.6% in the diet (1,220 and 1,456 mg/kg/day in males and females, respectively) based on the critical effect of bladder calculi and subsequent hyperplasia observed at the LOAEL of 5% in the diet (3,837 and 4,523 in males and females, respectively).
    - In a 90-day feeding study, male and female Wistar rats were fed 5% TPA in the diet for 1 week and then 3% (2760 and 3090 mg/kg in males and females, respectively)[11] for the remainder of the study. Pathological effects were limited to the kidney and bladder. TPA induced formation of bladder stones in 11/18 males and 3/19 females. Mild to moderate hyperplasia of the bladder urothelium was found in 13/18 males and 3/19 females. A strong correlation was found between the presence of uroliths and the development of bladder hyperplasia: 8/13 in males and 3/3 in females diagnosed as having transitional cell hyperplasia also had bladder stones. It is possible that microscopic calculi were passes or were lost during sectioning of the bladder tissue that could account for the failure to detect uroliths in all the hyperplastic bladders.

[11] According to U.S. EPA (1988), Food factor for male and female Wistar rats in subchronic studies are 0.092 and 0.103 kg/kg/day, respectively. Therefore, for males, 3% in the diet is equivalent to 0.092 kg/kg/day x 3% x 1,000,000 mg/kg = 2760 mg/kg/day. Similarly, 3% is equivalent to 3090 mg/kg/day in females.

- In a 2-week oral study, weanling F344 rats (postnatal day 28) of both sexes were exposed to diets containing 0.5, 1.5, 3.0, 4.0 or 5.0% TPA (905, 2715, 5430 and 7240 mg/kg/day in males and 915, 2745, 5490 and 7320 mg/kg/day in females). Of the male pups on the 5% TPA diet, 93.3% developed bladder calculi. Females pups also developed stones, but at a lower frequency. No stones were induced at dietary concentrations of TPA below 1.5%. Extensive hyperplasia of the transitional epithelium was found only in the urinary bladders with calculi. The principal components of the calculi were TPA, calcium, phosphate and protein. TPA induced urinary acidosis and hypercalciuria in the range of doses used. The study suggests that critical saturating urinary concentrations of TPA and calcium are necessary for stones to develop following TPA exposure, and that calculus formation appears to be a prerequisite for the induction of TPA-induced bladder hyperplasia. ToxServices assigned a NOAEL of 0.5% (905 and 915 mg/kg/day in males and females, respectively)[12] and a LOAEL of 1.5% (2715 and 2745 mg/kg/day in males and females, respectively) for TPA in the diet, based on the development of bladder calculus.
- In the 2-year feeding study in F344 rats (as described in the carcinogenicity section), TPA was given at 20, 142, or 1,000 mg/kg/day. Bladder stones were found in 13/126 females in the high dose group. No bladder calculi were detected at 6 or 12 months, and at 18 months, sand-like particles or bladder calculi were only seen in 2 of the high dose females. The high dose corresponds to an approximate dietary concentration of 2.0 to 2.8% in adult F344 rats. Based on this description, ToxServices assigned a NOAEL and LOAEL of 142 and 1000 mg/kg/day based on the presence of bladder stones.
- In a 90-day feeding study in rats (strain unspecified), animals were put on diets containing 0, 1, 3.2 or 10% TPA. No effects on growth or adverse clinical signs of toxicity were found in rats at the low and mid dose levels. No adverse histopathology was found in animals on the low dose. Calculi-associated effects on the urinary tract were observed in 2/12 animals in the mid dose group. Marked depression of growth, hematuria and urinary calculi were observed in 8/12 animals in the high dose group that survived. ToxServices assigned the NOAEL and LOAEL of 1% (960 mg/kg/day) and 3.2% (3072 mg/kg/day)[13], respectively, based on histopathological findings in the mid dose (not specified).

o Inhalation

- In a 28-day inhalation study, male rats (strain unreported) were exposed to TPA at the dose of 21.5 mg/m^3 for 6 hours/day, 5 days/week. No deaths, signs of toxicity or gross pathological changes were observed. No histopathology was conducted.
- In a 28-day inhalation study, male and female rats (20/dose, strain not reported) were exposed to TPA at 0, 0.52, 1.2 or 3.3 mg/m^3 for 6 hours per day. No deaths occurred during the study. No changes in clinical chemistry, hematology, body or organ weight changes or physiological parameters were found. Minimal tracheal epithelial lining degeneration was observed at the rate of 5%, 30%, 65% and 95% at doses of 0, 0.52, 1.2 and 3.3 mg/m^3, respectively. The results of this study were further evaluated in a more detailed study, which is summarized below.

[12] According to U.S. EPA 1988, Food factors for weaning F344 rats are 0.181 (M) and 0.183 (F) kg/kg/day.
[13] According to U.S. EPA 1988, Food factor for rats in a subchronic study is 0.096 kg/kg/day on average.

  - In a 6-month inhalation study, Male Sprague-Dawley rats and Hartley guinea pigs were exposed to TPA at 10 mg/m^3 for 6 hours/day, 5 days/week. No effects were observed on body weights, organ (lung, liver, kidney, spleen) weights, clinical chemistry or tissue structure.
  - Inhalation exposure to TPA for 14- 20 days at the dose of 2 – 5 mg/m^3 produced skin redness, skin erosions, mucous membrane redness and increased respiration rate in rats. Effects were also noted on the vascular, respiratory and nervous system (unspecified). No more information was provided.

- ECHA 2013
  - To investigate the degeneration of the tracheal lining epithelium effect seen in the previous 28-day inhalation study (2nd study described under inhalation under UNEP 2001), another 28-day inhalation study was conducted under GLP according to OECD Guideline 412. Sprague-Dawley rats (10 or 15/sex/dose) was exposed nose-only to TPA (purity > 99.9%) at the doses of 0, 1.03, 2.93 and 10.05 mg/m^3 6 hours/day, 5 days/week for 4 weeks. One control and one high dose group were allowed a 14-day recovery period after the exposure. Clinical signs, mortality, body weight and weight gain, food and water consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, neurobehavior, organ weights, gross pathology and histopathology were evaluated. Male rats in the high dose group showed decreased cholinesterase levels indicative of decreased liver synthesis. Bilirubin levels were significantly decreased in the low dose group in both sexes but slightly increased in females in the high dose group. In males, plasma glucose levels were slightly increased in the low dose group while mildly decreased in the medium and high dose groups. The same trend was seen in females with the decrease in the high dose group statistically significant. The above changes were all reversed in the recovery group and thus considered not toxicologically significant. Trea®ent-related histopathological lesions were not observed in any group in any organ examined. All findings in the nasal and paranasal cavities were regarded as incidental. The incidence of inflammatory/mononuclear cell infiltration in the larynx was high, but similar for control and trea®ent groups, probably due to mild local irritation caused by the experimental setting (i.e. nose-only inhalation). The observed changes in the trachea were minimal and considered unrelated to inhalation of TPA. The degenerative lesions observed in the previous inhalation study could not be consistently reproduced in this study. Relatively high incidences of alveolar macrophage accumulations were found in the lungs, but were still within the limits of normal variation in Sprague-Dawley rats. Lesions observed in other organs including retrobulbar hemorrhage of the eyes, necrosis and inflammation in the Harderian glands and tubular mineralization in the kidneys were either related to the blood sampling procedure or spontaneous in origin, not unusual for this strain of rats. Transient effects in some of the locomotor activity parameters were found in all treated groups without dose-response relationship. They were considered to be of low toxicological relevance. In summary, no significant adverse effects were observed in this study and the NOAEL was established to be greater than 10.05 mg/m^3, the highest dose tested.

- Based on the weight of evidence, for the oral route of exposure, formation of urinary bladder calculi is the critical effect after repeated exposure. The lowest LOAEL for this endpoint is 1000 mg/kg/day in Fisher rats in a 2 year feeding study (third oral study under UNEP 2001). For the inhalation route of exposure, although older studies indicate some evidence of minimal tracheal epithelial lining degeneration (second inhalation study under UNEP 2001), a more recent GLP

study (ECHA 2013) could not reproduce the observations, and no significant toxicity was observed up to 10.05 mg/m^3, which was the highest dose tested. Although GHS-Japan classified the chemical as Category 1 (respiratory organs, based on degeneration of the bronchial mucosal epithelium in animal studies) and Category 2 (bladder, based on bladder calculus) in Specific target organs/systemic toxicity following repeated exposure, degeneration of the bronchial musical epithelium in the 28-day inhalation study could not be reproduced in a more recent GLP study (ECHA 2013), and bladder calculus were not observed in GLP studies at oral doses lower than 1000 mg/kg/day (UNEP 2001). As a result, ToxServices assigned a Hazard score of L for this endpoint.

Neurotoxicity (N)

***Group II Score (single dose)*(vH, H, M or L): M**

TPA was assigned a score of M for neurotoxicity (single dose) based on classification to GHS category 3 for its transient narcotic effects. GreenScreen® criteria classify chemicals as an M hazard for neurotoxicity (single dose) when they are classified to GHS category 3 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- ECHA 2013
  - In an acute oral toxicity study, TPA was given to male and female rats at single dose levels of 6,834, 10,250 and 14,380 mg/kg. Animals were observed for 14 days following dosing and hypoactivity and muscular weakness were observed at all dose levels. Animals with these effects recovered within 2 – 7 days post exposure.
- UNEP 2001
  - In an acute oral (unspecified, GLP status unknown) toxicity study in mice as described above in single dose systemic toxicity section), a single dose of 10,000 mg/kg TPA (in 5% starch) disturbed movement coordination. At 5,000 mg/kg, pronounced "vascular" disorders, effects on nervous system function and a reduced rate were observed. At 500 mg/kg, only mild transient nervous system effects of excitation and depression were observed. ToxServices assigned a LOAEL of 500 mg/kg for neurotoxicity based on mild nervous system effects which became more severe with higher doses.

- The available data indicate that narcotic effects may happen at oral doses of 5,000 mg/kg and higher (ECHA 2013, UNEP 2001). Mild reversible CNS effects occurred at 500 mg/kg in mice (UNEP 2001). This dose could potentially classify TPA to GHS category 2. However, according to GHS classification criteria, mild reversible CNS effects do not support classification for category 1 and 2. On the other hand, transient narcotic effects classify chemicals to GHS category 3, regardless of the dose. Therefore, ToxServices classified TPA to GHS category 3.

***Group II* Score (repeated dose)*(H, M, L): L**

TPA was assigned a score of L for neurotoxicity (repeated dose) based on the absence of significant neurotoxicity in any of the available studies. GreenScreen® criteria classify chemicals as a L hazard for neurotoxicity (repeated dose) when adequate data are available and negative for neurotoxicity (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- ECHA 2013
    - In a 28-day inhalation study (as described in the repeated dose toxicity studies section), rats received doses of 0, 1.03, 2.93 and 10.05 mg/m^3 6 hours/day, 5 days/week for 4 weeks. Neurobehavioral examinations were performed. In female rats, body temperature was significantly lower in the low dose group compared to control. In males, forelimb grip strength was significantly increased in the low dose group and the righting reflex score was significantly increased in the high dose group compared to control. No other trea®ent induced effects were observed. Most of the observed effects were transient and without any dose-response relationship. As a result, they were considered toxicologically insignificant.
- UNEP 2001
    - Chronic inhalation exposure to 0.08 mg/m^3 TPA decreased the intensity of noradrenaline uptake in rats (GLP status, rat strain, dose levels and length of exposure not reported). At 0.4 mg/m^3, the uptake was decreased by 25%. At 1 mg/m^3, the uptake decreased by 62%. Exposure to 0.08 and 0.4mg/m^3 caused some increase in monoamine oxidase of the cerebral hemisphere and the 1 mg/m^3 dose increased the enzyme by 26%. Catecholamine o-methyltransferase activity was also increased in the cerebral hemisphere at 0.4 mg/m^3 and was higher at 1 mg/m^3. These effects may presumably affect the catecholamine inactivation mechanism of the central nervous system (CNS). No more information was provided.
    - In the 2-year dietary study described above (2nd carcinogenicity study), evaluation of neurological function was performed on animals sacrificed at 6, 12, 18 and 24 months on at the TPA doses of 0, 20, 142 and 1,000 mg/kg/day. This included an assessment of posture and gait, tone of facial muscles and examination of pupillary, palpebral, extensor thrust and crossed extensor reflexes. No TPA-related effects were observed.
- Based on the weight of evidence, no significant neurotoxicity was observed after repeated inhalation or oral exposure to TPA.

Skin Sensitization (SnS) Group II* Score (H, M or L): L
TPA was assigned a score of L for skin sensitization based on the absence of allergic reactions in guinea pigs. GreenScreen® criteria classify chemicals as a L hazard for skin sensitization when adequate data are available and negative, chemicals have no structural alerts and GHS statuses have not been classified (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* not listed in any authoritative lists
    - *Screening:* not listed in any screening lists
- UNEP 2001
    - TPA was not sensitizing to the skin of guinea pigs. No further information was provided.

Respiratory Sensitization (SnR) Group II* Score (H, M or L): DG
TPA was assigned a score of DG for respiratory sensitization based on the lack of data.

- No relevant data were identified.
- No appropriate models are available to predict respiratory sensitization.
- No data were found on any of the surrogates.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L): L

TPA was assigned a score of L for skin irritation/corrosivity based on negative findings in rabbits. GreenScreen® criteria classify chemicals as a L hazard for skin irritation/corrosivity when adequate data are available and negative for skin irritation/corrosivity (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* NITE 2006 (GHS-Japan)
    - Category 3 for skin corrosion/irritation "based on the description in the report on skin irritation tests in rabbits and human volunteers: 'non-irritating' or 'slightly irritating'. The substance is thus considered to possess 'mild skin irritation' (though it is unclear whether the results are those of 4-hour application)".
- ECHA 2013
  - TPA (undiluted) was not corrosive or irritating to the rabbit skin in a non GLP-compliant study conducted according to OECD Guideline 404. The irritation score ranged from 0.7/8.0 at 30-60 min, to 0.0/8.0 at 72 hours. The Primary Dermal Irritation Score for TPA was 0.2.
  - TPA (undiluted) was not classified as a skin irritant in rabbits in a study conducted similar to OECD Guideline 404 prior to GLP: Of the 6 animals tested, 2 exhibited erythema at abraded application sites at 24 and 72 hours post exposure, and 1 showed erythema at the intact skin application site at 24 hours which returned to normal within 72 hours. The irritation scores (totaling erythema and edema) were 0.66 and 0.17 out of a possible score of 4 for abraded and intact skin, respectively.
  - TPA (undiluted) did not show skin corrosivity in rabbits in a non-GLP compliant study conducted according to a DOT corrosion screen guideline. 0.5 g TPA was applied to the shaved skin under semiocclusive conditions for 4 hours and the skin was evaluated at 0, 24 and 48 hours after the removal of the test substance. However, no judgment could be made regarding classification for irritation.
- According to GHS Criteria, chemicals that are Category 3 (Mild irritant) should have a mean value between 1.5 and 2.3 for erythema/edema in at least 2 of 3 tested animals at 24, 48 and 72 hours or, if reactions are delayed, on 3 consecutive days after the onset of skin reactions. None of the irritation scores in the above studies is greater than 1.5. The weight of evidence indicates that TPA is not a dermal irritant.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M or L): M

TPA was assigned a score of M for eye irritation/corrosivity based on its mild ocular irritating effects in rabbits and the GHS-Japan classification of Category 2B for this chemical. GreenScreen® criteria classify chemicals as a M hazard for eye irritation/corrosivity when they are mildly irritating (GHS Category 2B) (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* NITE 2006 (GHS-Japan)
    - Category 2B "based on the description in the report on rabbit eye irritation tests: 'non-irritating' or 'slightly irritating'. The substance is thus considered a 'mild irritant'".
- ECHA 2013
  - TPA (undiluted) is a mild eye irritant in rabbits in a study prior to GLP. Effects included Grade 1 conjunctival erythema and chemosis in all 6 rabbits, with Grade 1 corneal opacity also present in 1 rabbit at 24 hours. Conjunctival discharge was noted in 1 rabbit

at 24 hours only.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M or L): L
TPA was assigned a score of L for acute aquatic toxicity based on acute aquatic toxicity values of over 100 mg/L. GreenScreen® criteria classify chemicals as a L hazard for acute aquatic toxicity when acute L/EC_{50} values are greater than 100 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- ECHA 2013
  - 96h LC_{50} (freshwater fish, golden orfe) > 961 mg/L
  - 96h LC_{50} (freshwater fish, *Oryzias latipes*) > 18.6 mg/L
  - 96h LC_{50} (freshwater fish, fathead minnow) > 100 mg/L
  - 48h EC_{50} (*Daphnia magna*) > 967 mg/L
  - 48h EC_{50} (*Daphnia magna*) > 20.1 mg/L
  - 96h LC_{50} (*Daphnia magna*) > 100 mg/L
  - 96h EbC_{50} and ErC_{50} (freshwater algae) > 668 mg/L
  - 72h EbC_{50} and ErC_{50} (freshwater algae) > 19.0 mg/L
- Water solubility of TPA is 15 mg/L at 20ºC. Therefore, the available data indicate that TPA is not acutely toxic at concentrations below its water solubility.

Chronic Aquatic Toxicity (CA) Score (vH, H, M or L): L
TPA was assigned a score of L for chronic aquatic toxicity based on a 21-day NOEC of 19.5 mg/L in daphnia. GreenScreen® criteria classify chemicals as a L hazard for chronic aquatic toxicity when these values are greater than 10 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- ECHA 2013
  - 21d NOEC (*Daphnia magna*) = 19.5 mg/L for reproduction and mortality.
- Water solubility of TPA is 15 mg/L at 20ºC. Therefore, the available data indicate that TPA is not a chronic aquatic toxicant at concentrations below its water solubility.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vL
TPA was assigned a score of vL for persistence based on meeting the 10-day window in ready biodegradation test in water. GreenScreen® criteria classify chemicals as a vL hazard for persistence when they meet the 10-day window in "Ready Biodegradation Test" (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- ECHA 2013
  - TPA was readily biodegradable (>60% degradation within 10 days) in a ready biodegradability test according to OECD 301B (Sturm Test) procedure at concentrations of 10 and 20 mg/L.

- TPA was readily biodegradable in a Japanese MITI I test which was adopted by OECD as Guideline 301C.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*
TPA was assigned a score of *vL* for bioaccumulation based on a calculated BCF of 3. The level of confidence was low because the BCF was calculated rather than measured. GreenScreen® criteria classify chemicals as a vL hazard for bioaccumulation when modeled BCF is less than 100 and log Kow is less than 4 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- HSDB 2012
  - An estimated BCF of 3 was calculated for TPA using a log Kow of 2.00, which indicates low bioconcentration potential in aquatic organisms.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M or L): M
TPA was assigned a score of M for reactivity based on GHS classification of Division 1.4. GreenScreen® criteria classify chemicals as a M hazard for reactivity when they are classified as GHS Division 1.4 or 1.5 chemicals (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- HSDB 2012
  - TPA can explode during preparation.
  - Dust may form an explosive mixture with air, may react with strong oxidizers such as chlorine or permanganates, and may form explosive compounds when exposed to nitric acid.
  - TPA mixtures with benzene close to the stoichiometric proportions of around 84% acid have very high sensitivity to mechanical shock.
  - National Fire Protection Association (NFPA) Hazard Classification for instability = 0: materials that are normally stable, even under fire exposure conditions, and do not react with water.
- ICSC 1994
  - Finely dispersed particles form explosive mixtures in air
  - Dust explosion possible if in powder or granular form, mixed with air
  - Reacts violently with strong oxidants

- Based on the weight of evidence, although NFPA classification of this compound indicates that it is normally stable even under fire exposure conditions, TPA may have explosive potentials when mixed with air. As a result, an M hazard was assigned for TPA for this endpoint.

Flammability (F) Score (vH, H, M or L): L
TPA was assigned a score of L for flammability based on the lack of flammability.

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists

    - *Screening:* not listed in any screening lists
- ECHA 2013
    - Ii a preliminary flammability screening test that ignited a loosely-packed linear pile of TPA, combustion self-terminated after 218 seconds and without propagating 200 mm along the pile. According to the UN Recommendations on the Transport of Dangerous Goods, TPA is not classified as a readily combustible solid of Division 4.1 and further flammability testing is therefore not required.
- HSDB 2012
    - NFPA Hazard Classification: Flammability :1.1 = materials that must be preheated before ignition will occur, such as Class IIIB combustible liquids and solids and semi-solids whose flash point exceeds 200 deg F, as well as most ordinary combustible materials.
    - Combustible

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APPENDIX A: Hazard Benchmark Acronyms (in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(Cr) Corrosion/ Irritation (Skin/ Eye)

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for TPA (CAS #100-21-0)

GreenScreen™ Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	TPA	100-21-0	*M*	**L**	**M**	**M**	*M*	**L**	**M**	**L**	**M**	**L**	**L**	DG	**L**	**M**	**L**	**L**	**vL**	*vL*	**M**	**L**

Table 3a: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	Yes	No	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen™ Benchmark Score
TPA	2

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

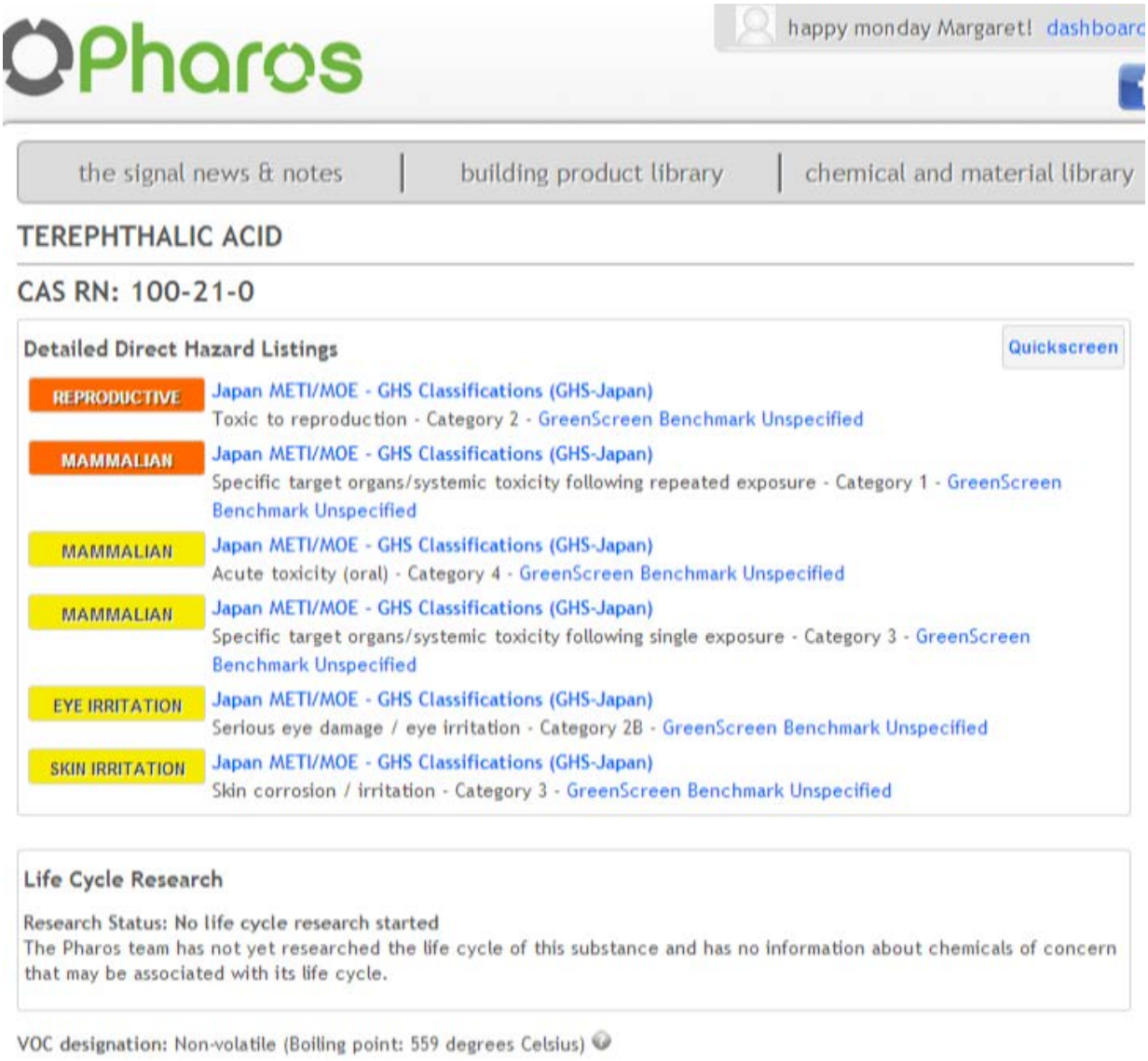
Chemical Name	Final GreenScreen™ Benchmark Score
TPA	2

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

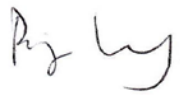
Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for TPA (CAS #100-21-0)



Authorized Reviewers

Terephthalic Acid GreenScreen® Evaluation Prepared By:



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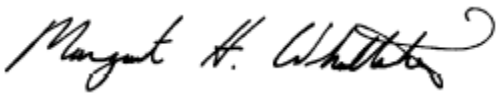

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