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Provisional Peer-Reviewed Toxicity Values for

p-Phthalic Acid
(Terephthalic Acid)
(CASRN 100-21-0)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

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https://www.epa.gov/pprtv

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Center for Public Health and Environmental Assessment
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Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) CPHEA website at https://www.epa.gov/pprtv/forms/contact-us-about-pprtvs.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

DRAFT PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *P*-PHTHALIC ACID (TPA) (CASRN 100-21-0)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

Currently available PPRTV assessments can be accessed on the U.S. Environmental Protection Agency's (EPA's) PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of the chemical's potential for causing adverse human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two Center for Public Health and Environmental Assessment (CPHEA) scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVS

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) CPHEA website at https://www.epa.gov/pprtv/forms/contact-us-about-pprtvs.

INTRODUCTION

p-Phthalic acid, CASRN 100-21-0, also commonly known as terephthalic acid (TPA), is an aromatic acid with a structure consisting of a benzene ring substituted with two carboxylic acid groups at the 1 and 4 (para) positions. TPA is used for polyester fibers, films, and polyethylene terephthalate solid state resins and engineering resin production and manufacture (OECD, 2001). TPA is listed on the U.S. EPA's Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2018b) and registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2018).

TPA is made from *p*-xylene through a liquid-phase air oxidation process, in which manganese and cobalt acetate are used as catalysts and sodium bromide is used as a promoter. Purification of crude TPA is performed using hot water under pressure and selective catalytic hydrogenation of contaminants (OECD, 2001).

The empirical formula for TPA is $C_8H_6O_4$ (see Figure 1). A table of physicochemical properties for TPA is provided below (see Table 1). TPA is a white solid, with moderate water solubility. In the air, TPA will exist in the particulate phase based on a vapor pressure of 9.2×10^{-6} mm Hg. TPA will be degraded in the atmosphere by a reaction with photochemically produced hydroxyl radicals with a half-life of 8.6 days, calculated from an estimated reaction rate constant of 3.32×10^{-12} cm^3/molecule-second at 25°C. Because of TPA's low vapor pressure, negligible volatilization from dry soil surfaces is expected. Low volatilization from water or moist soil surfaces is expected based on an estimated Henry's law constant of 1.63×10^{-9} atm-m^3/mole. The estimated K_{oc} for TPA indicates potential for mobility in soil and negligible potential to adsorb to suspended solids and sediment in aquatic environments. TPA does not contain functional groups that are likely to hydrolyze under environmental conditions; therefore, hydrolysis is not expected to be an important fate process.

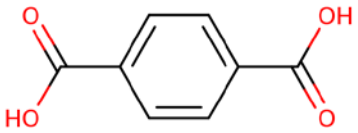

Figure 1. TPA (CASRN 100-21-0) Structure

Table 1. Physicochemical Properties of TPA (CASRN 100-21-0)

Property (unit)	Value[a]
Physical state	Needles, white crystals, or powder
Boiling point (°C)	341 (predicted average)
Melting point (°C)	368 (experimental average)
Density (g/cm^3 at 25°C)	1.47 (predicated average)
Vapor pressure (mm Hg at 25°C)	9.2×10^{-6} (experimental average)
pH (unitless)	3.88[b]
pKa (unitless)	3.54 and 4.46[b]
Solubility in water (mg/L at 25°C)	9.03×10^{-5} (experimental average)
Octanol-water partition constant (log K_{ow})	2.00 (experimental average)
Henry's law constant (atm-m^3/mol at 20°C)	1.63×10^{-9} (predicted average)
Soil adsorption coefficient K_{oc} (L/kg)	24.5 (predicted average)
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	3.32×10^{-12} (predicted average)
Atmospheric half-life (d)	8.6[c]
Relative vapor density (air = 1)	NV
Molecular weight (g/mol)	166.13
Flash point (open cup in °C)	205 (predicted average)

[a]Unless otherwise noted, data were extracted from the U.S. EPA CompTox Chemicals Dashboard (terephthalic acid; CASRN 100-21-0; https://comptox.epa.gov/dashboard/DTXSID6026080. Accessed August 5, 2020).
[b]ECHA (2018). At saturation in water; pH varies with concentration.
[c]U.S. EPA (2012b) (with user-entered inputs for water solubility = 17 mg/L, vapor pressure = 6×10^{-11} mm Hg, and log K_{ow} = 2; SMILES: C1=CC(=CC=C1C(=O)O)C(=O)O.

NV = not available; SMILES = simplified molecular input line entry system; TPA = terephthalic acid.

A summary of available toxicity values for TPA from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for TPA (CASRN 100-21-0)			
Source (parameter)[a, b]	**Value (applicability)**	**Notes**	**Reference[c]**
Noncancer			
IRIS	NV	NA	U.S. EPA (2018c)
HEAST (RfD)	1 mg/kg-d	Based on bladder hyperplasia in a chronic oral study in rats	U.S. EPA (2011a)
HEAST (sRfD)	1 mg/kg-d	Based on bladder hyperplasia in a chronic oral study in rats	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2018a)
ATSDR	NV	NA	ATSDR (2019)
IPCS	NV	NA	IPCS (2018)
CalEPA	NV	NA	CalEPA (2016a); CalEPA (2016b); CalEPA (2018)
OSHA	NV	NA	OSHA (2018); OSHA (2018); OSHA (2020)
NIOSH	NV	NA	NIOSH (2016)
ACGIH (TLV-TWA)	10 mg/m^3	Based on analogy to the TLV for particulates (insoluble) not otherwise specified	ACGIH (2018)
DFG (MAK)	5 mg/m^3	Based on absence of effects in an unpublished 28-d rat inhalation study	MAK-Commission (2015)
Cancer			
IRIS	NV	NA	U.S. EPA (2018c)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2018a)
NTP	NV	NA	NTP (2016)
IARC	NV	NA	IARC (2018)
CalEPA	NV	NA	CalEPA (2016b); CalEPA (2017); CalEPA (2018)

Table 2. Summary of Available Toxicity Values for TPA (CASRN 100-21-0)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference[c]
ACGIH	NV	NA	ACGIH (2018)
HEEP (WOE)	Group C: Possibly carcinogenic to humans	Based on limited animal evidence for bladder tumors	U.S. EPA (1986)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DFG = German Research Foundation; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.
[b]Parameters: MAK = maximum allowable concentration; RfD = reference dose; sRfD = reference concentration for subchronic oral exposure; TLV = threshold limit value; TWA = time-weighted average; WOE = weight of evidence.
[c]Reference date is the publication date for the database and not the date the source was accessed.

NA = not applicable; NV = not available; TPA = terephthalic acid.

METHODS

Literature Search

Four online scientific databases (PubMed, Web of Science [WOS], TOXLINE, and Toxic Substances Control Act Test Submissions [TSCATS] via TOXLINE) were searched by U.S. EPA's Health and Environmental Research Online (HERO) staff and stored in the HERO database.[1] The literature search focused on chemical name and synonyms (identified as "valid/validated" or "good" via the CompTox[2] Chemicals Dashboard and ChemSpider[3]) with no limitations on publication type, evidence stream (i.e., human, animal, in vitro, in silico), or health outcomes. Full details of the search strategy for each database are presented in Appendix A. The initial database searches were conducted in February 2018 and updated in July 2018, May 2019 and March 2020. Further details are given below, and a schematic of the literature search and disposition is shown as Figure 2.

Screening Process

Two screeners independently conducted a title and abstract screen of the search results using DistillerSR[4] to identify study records that met the Population, Exposure, Comparator, and Outcome (PECO) eligibility criteria (see Appendix B for a more detailed summary):

[1]U.S. EPA's HERO database provides access to the scientific literature behind U.S. EPA science assessments. The database includes more than 2,500,000 scientific references and data from the peer-reviewed literature used by U.S. EPA to develop its regulations.
[2]CompTox Chemicals Dashboard: https://comptox.epa.gov/dashboard/DTXSID6026080.
[3]ChemSpider: http://www.chemspider.com/Chemical-Structure.7208.html.
[4]DistillerSR is a web-based systematic review software used to screen studies available at https://www.evidencepartners.com/products/distillersr-systematic-review-software.

- Population: Humans, laboratory mammals, and other animal models of established relevance to human health (e.g., *Xenopus* embryos); mammalian organs, tissues, and cell lines; and bacterial and eukaryote models of genetic toxicity.
- Exposure: In vivo (all routes), ex vivo, and in vitro exposure to the chemical of interest, including mixtures to which the chemical of interest may contribute significantly to exposure or observed effects.
- Comparator: Any comparison (across dose, duration, or route) or no comparison (e.g., case reports without controls).
- Outcome: Any endpoint suggestive of a toxic effect on any bodily system, or mechanistic change associated with such effects. Any endpoint relating to disposition of the chemical within the body.

Records that were not excluded based on title and abstract screening advanced to full-text review using the same PECO eligibility criteria. Studies that have not undergone peer review were included if the information could be made public and sufficient details of study methods and findings were included in the report. Full-text copies of potentially relevant records identified from title and abstract screening were retrieved, stored in the HERO database, and independently assessed by two screeners using DistillerSR to confirm eligibility. At both title/abstract and full-text review levels, screening conflicts were resolved by discussion between the primary screeners with consultation by a third reviewer to resolve any remaining disagreements. During title/abstract or full-text level screening, studies that were not directly relevant to the PECO criteria, but could provide supplemental information, were categorized (or "tagged") relative to the type of supplemental information they provided (e.g., review, commentary, or letter with no original data; conference abstract; toxicokinetics and mechanistic information aside from in vitro genotoxicity studies; studies on routes of exposure other than oral and inhalation; acute exposure studies only; etc.). Conflict resolution was not required during the screening process to identify supplemental information (i.e., tagging by a single screener was sufficient to identify the study as potential supplemental information).

LITERATURE SEARCH AND SCREENING RESULTS

The database searches yielded 420 unique records that were captured in DistillerSR. Of the 420 studies identified, 93 were included following title and abstract screening. These 93 were reviewed at the full-text level, and 54 were considered relevant to the PECO eligibility criteria (see Figure 2). This included 42 in vivo animal studies, 2 human studies, and 10 in vitro genotoxicity studies. The detailed search approach, including the query strings and PECO criteria, are provided in Appendix A and Appendix B, respectively.

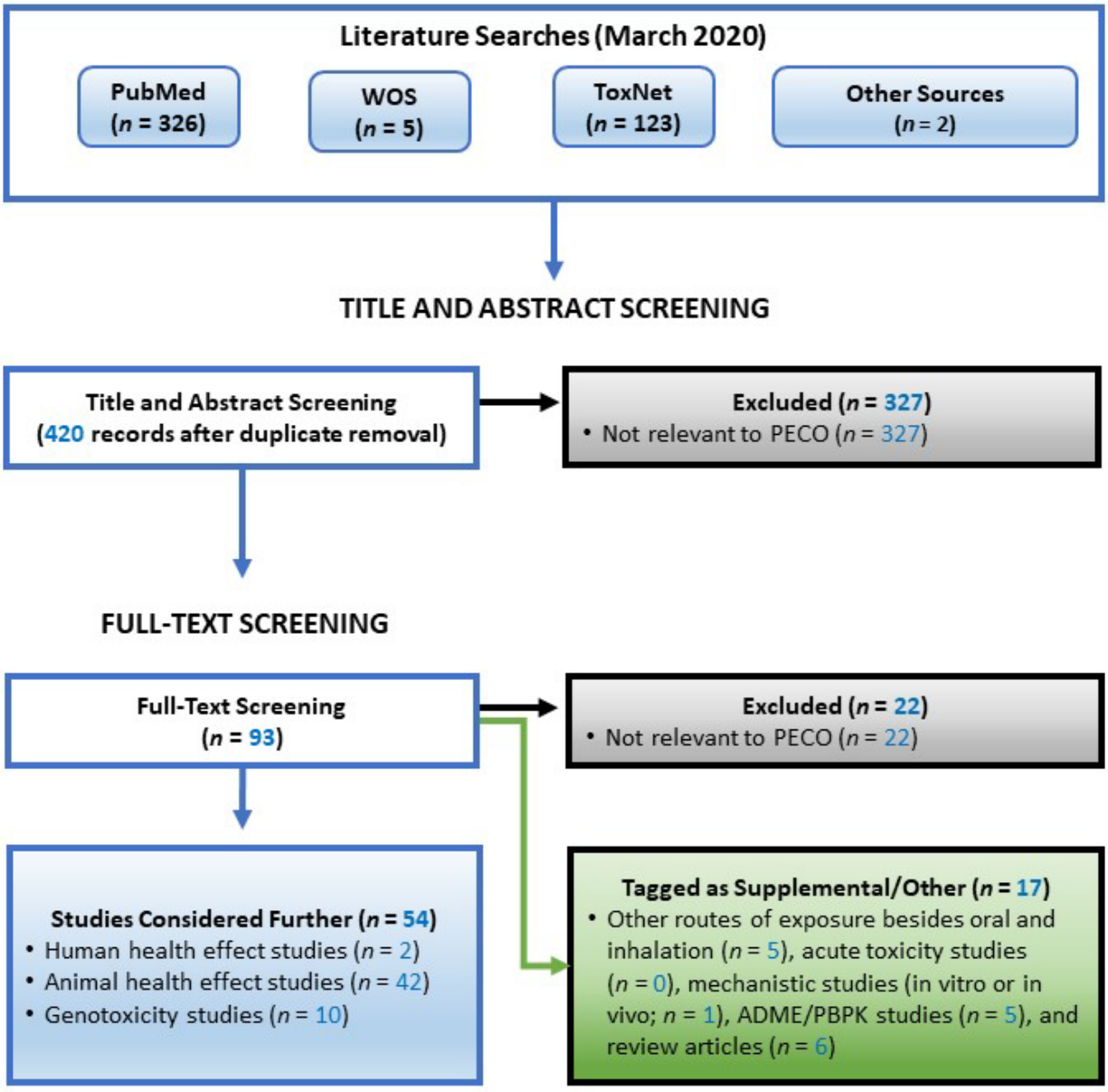

Figure 2. Literature Search and Screening Flow Diagram for TPA (CASRN 100-21-0)

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer databases, respectively, for TPA and include all potentially relevant repeated short-term, subchronic, and chronic studies, as well as reproductive and developmental toxicity studies. Principal studies are identified in bold. The phrase "statistical significance" and the term "significant," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for TPA (CASRN 100-21-0)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
Subchronic to chronic	141 workers (47% male) occupationally exposed to TPA. Average duration of employment 6.2 yr.	Three cumulative exposure categories: not-detected, ~50 mg/m^3, and ~80 mg/m^3 (low, medium, and high, respectively)	Slight increase in SACE activity in the exposed workers (12, 17, and 15% increase over controls).	NDr	NDr	Dai et al. (2005b)	PR
Animal							
1. Oral (mg/kg-d)							
Short term	30 M/30 F, weanling F344, rat, diet, 14 d Reported doses: 0, 0.5, 1.5, 3, 4, or 5% TPA in the diet	M: 0, 658, 1,904, 3,740, 4,860, 5,710 F: 0, 599, 1,836, 3,760, 4,770, 5,520	Reduced body weight and increased incidence of bladder calculi and associated gross and histopathological lesions in both males and females. Urinary pH and electrolyte concentrations were altered at lower doses.	3,760	4,770	Chin et al. (1981); Heck (1981)	PR
Short term	10 M, weanling F344, rat, diet, 14 d Reported doses: 0 or 4% TPA in the diet	0, 4,900	Reduced body weight and increased incidence of bladder calculi. Alterations in urinary pH and electrolyte concentrations were also observed.	NDr	4,900	Wolkowski-Tyl and Chin (1983)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for TPA (CASRN 100-21-0)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Subchronic	12−52 M/12−23 F, S-D, rat, diet, 90 d Reported doses: 0, 0.04, 0.2, 1, or 5% TPA in the diet	M: 0, 36.0, 179, 906, 4,550 F: 0, 40.0, 197, 997, 4,970	Increased incidences of bladder calculi and hyperplasia in males. Urinary acidosis in both sexes. Sediment in the urine and changes in urinary electrolytes were observed in males and females at lower doses.	906	4,550	Dai et al. (2006a); Dai et al. (2005c)	PR
Subchronic	6 M/6 F, weanling, albino rat (strain NS), diet, 90 d Reported doses: 0, 1, 3.2, or 10% TPA in the diet	M: 0, 859, 2,754, 10,500 F: 0, 992, 3,170, 11,200	Four of six males died. Other observed effects were hematuria, depressed body weights, and renal injury (2/12) associated with the presence of calculi in the urinary tract (all severe in males, less so in females).	2,754	10,500 (FEL)	Dupont Chem Co (1955)	NPR
Subchronic	30 M/30 F, Wistar, rat, diet, 90 d Reported doses: 0, 0.03, 0.154, 0.5, 2, or 5% TPA in the diet	M: 0, 15.3, 79.09, 266, 1,020, 2,650 F: 0, 19.3, 114.5, 313, 1,280, 3,100	Low incidences of bladder and urethra calculi, chronic cystitis, chronic urethritis, and transitional cell hyperplasia of the bladder and urethra in males and females.	3,100	NDr	Ledoux and Reel (1982); Ball et al. (2012)	NPR
Subchronic	30 M/30 F, CD, rat, diet, 90 d Reported doses: 0, 0.03, 0.154, 0.5, 2, or 5% TPA in the diet	M: 0, 14.6, 76.15, 247, 976, 2,590 F: 0, 17.6, 86.57, 286, 1,260, 2,840	Reduced body weight in females. Low incidences of urinary bladder calculi, chronic cystitis, and chronic urethritis and transitional cell hyperplasia in the bladder and urethra.	1,260	2,840	Ledoux and Reel (1982); Ball et al. (2012)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for TPA (CASRN 100-21-0)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Subchronic to chronic	30 M, Wistar, rat, diet, 22 wk Prior to TPA feeding, treated animals received i.p. injections of vehicle (5% citrate buffer) 2 times/wk for 4 wk; control animals did not receive vehicle injections Reported doses: 0, 1, or 5% TPA in the diet	0, 829, 4,280	Reduced body weight, increased absolute and relative bladder weights, and increased bladder hyperplasia. Sediment in urine and changes in urinary pH and electrolyte levels were seen in both dose groups.	829	4,280	Cui et al. (2006a)	PR
Chronic	20−38 M, Wistar, rat, diet, 48 wk Reported doses: 0 or 5% TPA in the diet	0, 3,680	Increased incidences of bladder calculi and hyperplasias at 12, 24, and 48 wk. Elevated absolute and relative bladder weights and reduced body weights were also reported, although the data were not shown.	NDr	3,680	Cui et al. (2007); Cui et al. (2006b); Shi et al. (2006)	PR
Chronic	50 M/50 F, Wistar, rat, diet, 24 mo Reported doses: 0, 1, 2, or 5% TPA in the diet	M: 0, 736, 1,470, 3,680 F: 0, 842, 1,680, 4,210	Body weight reduced by ≥10% in males and females. At higher doses in both sexes, increased incidences of high blood urea levels, nephropathy, and urinary tract calculi were observed.	736	1,470	Gross (1977)	NPR
Chronic	126 M/126 F, F344, rat, diet, 24 mo Doses reported as ADDs by study authors	M: 0, 19.5, 138.2, 995.4 F: 0, 19.2, 136.6, 989.8	Bladder hyperplasia in females.	995.4	NDr	Grubbs (1979); Preache (1983); ICI Americas Inc (1992)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for TPA (CASRN 100-21-0)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Reproductive/ Developmental	10 breeding pairs/group, Wistar, rat, diet, 90 d prior to mating through postweaning and PNDs 21−51 for weanlings Reported doses: 0, 0.03, 0.154, 0.5, 2, or 5% TPA in the diet	M: 0, 15.3, 79.09, 266, 1,020, 2,650 F: 0, 19.3, 114.5, 313, 1,280, 3,100	Significantly decreased pup body weight. Significantly increased renal and bladder calculi in pups upon necropsy (PNDs 21−51).	313	1,280	Ledoux and Reel (1982)	NPR
Reproductive/ Developmental	**9−10 breeding pairs/group, CD, rat, diet, 90 d prior to mating through postweaning and PNDs 21−51 for weanlings Reported doses: 0, 0.03, 0.154, 0.5, 2, or 5% TPA in the diet.**	**M: 0, 14.6, 76.15, 247, 976, 2,590 F: 0, 17.6, 86.57, 286, 1,260, 2,840**	**Significantly decreased pup body weight; decreased proportion of pups surviving to PND 21. Significantly increased renal and bladder calculi in pups at necropsy (PNDs 21−51).**	**NDr**	**17.6**	**Ledoux and Reel (1982)**	**NPR, PS**
Reproductive	10 M, S-D, rat, diet, 90 d Reported doses: 0, 0.2, 1, or 5% TPA in the diet	0, 172, 861, 4,310	Significant reductions in sperm head counts and in several other sperm motility parameters. Ultrastructural changes in cells from several stages of spermatogenesis. Some sperm motility parameters were affected at lower doses.	861	4,310	Cui et al. (2004)	PR
Reproductive	5 M, S-D, rat, gavage (dissolved in corn oil), daily for 4 wk	0, 10, 100, 1,000	Significant reduction in sperm progressive motility.	100	1,000	Kwack and Lee (2015)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for TPA (CASRN 100-21-0)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
2. Inhalation (mg/m^3)							
Developmental	22−25 F, S-D, rat, whole-body aerosol inhalation, 6 hr/d on GDs 6−15 Reported exposures: 0, 0.90, 4.73, or 10.40 mg/m^3	0, 0.59, 2.96, 6.240	Maternal: No effects. Fetal: No effects.	Maternal: 6.240 Fetal: 6.240	NDr NDr	Chemical Manufacturers Association (2000)	NPR

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Doses are presented as ADDs (mg/kg-day) for oral noncancer effects and as HECs (mg/m^3) for inhalation noncancer effects.
[c]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; F = female(s); FEL = frank effect level; GD = gestation day; HEC = human equivalent concentration; i.p. = intraperitoneal; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; PND = postnatal day; SACE = serum angiotensin-converting enzyme; S-D = Sprague-Dawley; TPA = terephthalic acid.

Table 3B. Summary of Potentially Relevant Cancer Data for TPA (CASRN 100-21-0)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**Reference (comments)**	**Notes[b]**
Human					
1. Oral (mg/kg-d)					
ND					
1. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
Carcinogenicity	20−38 M, Wistar, rat, diet, 48 wk Reported doses: 0 or 5% TPA in the diet	0, 1,090	Increased transitional cell carcinoma and papilloma in bladder in treated group.	Cui et al. (2006b)	PR
Carcinogenicity	50 M/50 F, Wistar, rat, diet, 24 mo Reported doses: 0, 1, 2, or 5% TPA in the diet	M: 0, 210, 419, 1,050 F: 0, 215, 429, 1,070	Increased bladder and ureter tumors (primarily transitional cell tumors or squamous cell carcinomas) in high-dose males and females.	Gross (1977)	NPR
Carcinogenicity	126 M/126 F, F344, rat, diet, 24 mo Reported doses: M: 0, 19.5, 138.2, 995.4 mg/kg-d; F: 0, 19.2, 136.6, 989.8 mg/kg-d	M: 0, 5.41, 38.49, 274.2 F: 0, 4.98, 35.41, 255.8	Increased transitional cell adenomas in bladder in high-dose females.	ICI Americas Inc (1992); Preache (1983)	NPR

Table 3B. Summary of Potentially Relevant Cancer Data for TPA (CASRN 100-21-0)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**Reference (comments)**	**Notes[b]**
2. Inhalation (mg/m^3)					
ND					

[a]Dosimetry: Oral exposures are expressed as HEDs (mg/kg-day); HEDs are calculated using DAFs, as recommended by U.S. EPA (2011b): HED = ADD (mg/kg-day) × DAF. The DAF is calculated as follows: DAF = $(BW_a \div BW_h)^{1/4}$, where DAF = dosimetric adjustment factor, BW_a = animal body weight, and BW_h = human body weight, using study (if available) or reference body-weight values for BW_a and the reference value of 70 kg for BW_h.
[b]Notes: NPR = not peer reviewed; PR = peer reviewed.

ADD = adjusted daily dose; BW = body weight; DAF = dosimetric adjustment factor; F = female(s); HED = human equivalent dose; M = male(s); ND = no data; TPA = terephthalic acid.

HUMAN STUDIES

Oral Exposures

No oral studies have been identified.

Inhalation Exposures

Dai et al. (2005b)

In a cohort study, Dai et al. (2005b) investigated the potential health effects of inhaled TPA in an industrial setting. Some of the data in this study appear to be identical to data presented in a study available only in Chinese (Li et al., 1999). One hundred forty-one workers (47% males) occupationally exposed to TPA dust and 77 unexposed workers (48% males) were recruited from two Chinese fiber factories. Workers had an average age of 30.3 years and an average duration of employment of 6.2 years. TPA concentrations were monitored in air for all exposed workers and in 10% of the unexposed workers using personal dust samplers, apparently each for a single 8-hour day. Cumulative exposure levels of TPA for each worker were calculated based on job history duration and mean concentration of TPA exposure, based on the location for each job. Blood and urine samples were collected in the morning prior to the 8-hour monitoring period, and an additional urine sample was collected after the shift. Blood samples were subject to hematological analysis (hemoglobin [Hb] and red blood cell [RBC], white blood cell [WBC], lymphocyte, and platelet counts) and serum chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], γ-glutamyl transferase [GGT], lactate dehydrogenase [LDH], albumin, and electrolytes). Urine was analyzed for TPA concentration by high-performance liquid chromatography (HPLC). The urine was also analyzed for ALP, GGT, LDH, α_1- and β_2-microglobulins, pH, and Ca^{2+}, Na^{+}, and K^{+} electrolytes. All workers underwent pulmonary function tests (inspiratory vital capacity [VC], forced vital capacity [FVC], forced expiratory volume in the first second [FEV_1], FEV_1/FVC, peak expiratory volume [PEV], and maximal expiratory flow rate at 75% [MEF_{75}], 50% [MEF_{50}], and 25% [MEF_{25}] of VC were measured) and had chest radiographs. Statistical analysis included two-way analyses of variance (ANOVAs) for comparison of means with a χ^2 test. Comparisons were made between unexposed and tertiles of cumulative TPA exposure (based on measured concentrations of TPA in air or urinary TPA levels). Nonparametric tests were used when variables were not normally distributed.

Monitoring results indicated that geometric mean air levels of TPA were 8.03 mg/m^3 (range 0.15−138.32 mg/m^3) in Plant I and 2.19 mg/m^3 (range 0.30−14.21 mg/m^3) in Plant II. After calculation of cumulative exposures, exposed workers were grouped into three cumulative exposure categories: not-detected (detection limit not reported), ~50 mg/m^3, and ~80 mg/m^3 (low, medium, and high, respectively). Similar categories were formed based on urine TPA concentrations: not detected, ~1 mmol/mol creatine, and ~5 mmol/mol creatine (low, medium, and high, respectively). The results of pulmonary function tests were similar in exposed and unexposed workers. The only difference was a slight increase in serum angiotensin-converting enzyme (SACE) activity in the exposed workers (12, 17, and 15% increase over the unexposed workers in low-, medium-, and high-cumulative-exposure groups, respectively) that was significant in the medium- and high-cumulative-exposure groups but did not increase with exposure level. No evidence of lung disease was detected by radiography. No differences were found between unexposed workers and exposed workers for any of the hematological indices. Significant increases in serum AST (27%) and LDH (11%) occurred in the medium-cumulative-exposure group, but the changes were within reference values and were not seen in the high-exposure group (see Table D-1). There was also a slight significant decrease in

serum albumin (−3%) in the high-exposure group. In urine, the only changes were slight increases in the concentrations of sodium and calcium in the exposed workers (see Table D-1). Serum TPA levels were comparable to those measured in the urine.

ANIMAL STUDIES

Oral Exposures

Short-Term Studies

Chin et al. (1981); Heck (1981)

In a published, peer-reviewed study, Chin et al. (1981) investigated the induction of bladder calculi by TPA (reported to be "high-purity") in commercially obtained weanling Fischer 344 (F344) rats. Additional data on urine electrolyte concentrations were reported by Heck (1981). Twenty-eight-day-old weanling F344 rats (30 males and 30 females/group) were fed diets containing 0, 0.5, 1.5, 3, 4, or 5% TPA for 14 consecutive days. Chin et al. (1981) reported the average daily doses of rats exposed to 3, 4, and 5% TPA in feed to be 3,740, 4,860, and 5,710 mg/kg-day, respectively, for males, and 3,760, 4,770, and 5,520 mg/kg-day, respectively, for females. Average daily doses for the 0.5 and 1.5% TPA levels in food were not provided but were calculated for this review to be 658 and 1,904 mg/kg-day for males and 599 and 1,836 mg/kg-day for females.[5] The study did not indicate whether validation or quantification of TPA in the food was done nor describe the frequency of dietary preparation. Individual body weights, food, and water intake per cage were monitored every other day throughout the study. Urine collected just prior to sacrifice was analyzed for pH, and for concentrations of calculus-forming materials (e.g., calcium, phosphate) and TPA. The entire urinary system, including the urethra, bladder, ureters, and kidneys, was visually analyzed for calculi. The composition of the calculi collected from four samples, each containing 14−18 calculi from the bladders of TPA-exposed rats, was analyzed. Urinary tract tissues from 10 control male rats and 10 male rats on the 4% TPA diet were collected for histologic examination (hematoxylin and eosin staining). Statistical analysis was performed by the study authors and comparison of means was done using either one-way ANOVA with a Dunnett's test or a Student-Newman-Keuls test, when appropriate.

Animals in the high-dose treatment groups developed diarrhea, which the study authors attributed to incomplete absorption of TPA. Male and female body weights in each exposure group were plotted graphically during three different time periods: Exposure Days 0−2, 6−8, and 12−14. The mean values were extracted for this review using GrabIT! Software.[6] Compared with controls, significant (≥10%) decreases in body weights occurred at Days 6−8 and 12−14 in both males and females exposed to 4 (males only) and 5% dietary TPA (see Table D-2). Food intake was significantly reduced during the first 2 days of exposure in highest-dose males and in females from the two highest dose groups but was similar to controls at the later time periods. Water intake was significantly increased in a dose-related manner in the three highest dose groups in both males and females on Days 6−8 and 12−14.

[5]Reported dietary intakes (% TPA in food) were converted to adjusted daily doses (ADDs) using the following equation: ADD = [% TPA in food × 10,000 (mg TPA/kg food) × food intake (kg food/day)] ÷ average body weight (BW; kg) and data for body weight and food intake provided in the study (graphically reported body-weight and food-intake data were extracted using GrabIT! software).

[6]GrabIT! software is a free software product (© 1999−2020) from shemes.com—all rights reserved. GrabIt!, Shemes, and each of their logos are trademarks of shemes.com.

The incidence of calculi increased in a dose-related manner (see Table D-3). In the two highest dose groups, calculi were significantly increased occurring in 57 and 93% of males and in 20 and 73% of females, respectively. No calculi were observed in controls, and only the occasional calculus was found in the lower dose groups. The calculus mass increased with dose and was greater in males than in females given the same dose. Calculi were made up primarily of TPA, but also included significant amounts of calcium and phosphate. Grossly observable lesions in the urinary tract occurred primarily in animals with calculi. These included an irregularly thickened bladder wall in all affected rats, hydronephrosis in some rats, and frequent hematuria in high-dose (exactly which dose[s] not reported) rats.

Urinary acidosis was observed in both sexes fed diets containing 0.5, 3, and 4% TPA (urinalysis of the 1.5 and 5% TPA groups was not reported) (see Table D-4). Hypercalcemia was also observed in all exposed groups examined, and the increases were significant ($p < 0.01$) over controls in the 3- and 4%-TPA groups. Further analysis of a subset of the tested rats by Heck (1981) showed significant increases in urinary ammonium concentrations in all treated groups and generally significant decreases in urinary sodium, potassium, and sulfate in the 3- and 4%-TPA groups (see Table D-5).

Chin et al. (1981) provided representative images of some histological lesions in urinary tract tissues from controls and animals fed 4% TPA diets. The authors described urinary bladder, ureters, and kidney tissues from control rats as normal, except for a few small foci of mineralization in the tubules of the outer medulla. Six out of the 10 treatment animals in the 4%-TPA group had macroscopic calculi, and histological lesions were primarily observed in these animals. Bladder lesions consisted of diffusely hyperplastic transitional epithelium with varying degrees of severity. Ulceration of the hyperplastic epithelium and neutrophil infiltration of the lamina propria were described as frequent. Ureters in the treated group were normal except for one animal that showed a dilated ureter with a thinned epithelial layer. This animal also exhibited severe hydronephrosis in one kidney and minimal hydronephrosis in the other. According to the study authors, most of the animals in the 4%-TPA group contained more mineralized foci in the kidneys than did the controls.

The NOAEL of 3,760 mg/kg-day and the LOAEL of 4,770 mg/kg-day are identified for this study based on increased incidence of bladder calculi and associated gross and histopathological lesions in weanling female F344 rats fed TPA in their diets for 14 days. Significant changes in urine pH and electrolyte levels were observed at lower doses and may be suggestive of mechanisms leading to calculi formation.

Wolkowski-Tyl and Chin (1983)

TPA at 4% in the diet was used as positive control for calculus formation in a follow-up study conducted by Wolkowski-Tyl and Chin (1983) using a protocol similar to that of the Chin et al. (1981) study. Weaned 28-day-old F344/CrlBr inbred albino rat pups (10 males/group) were administered TPA powder at a concentration of 0 or 4% (4,900 mg/kg-day)[7] in the diet for 14 consecutive days. The control and TPA treatment groups were also given a daily gavage of 0.5% carboxymethyl cellulose in tap water, which was used as a vehicle for additional treatment

[7]The reported dietary intake (% TPA in food) was converted to an ADD using the following equation:
ADD = [% TPA in food × 10,000 (mg TPA/kg food) × food intake (kg food/day)] ÷ time-weighted average (TWA) BW (kg) and data for food intake and body weight reported in the study (graphically reported body-weight data were extracted using GrabIT! software).

groups not reported here (additional treatment groups included sodium bicarbonate, chlorothiazide, allopurinol, and Neutra-Phos). The study did not indicate whether validation or quantification of TPA in food was done; diets were prepared fresh weekly. Individual body weights, and food and water intake per cage were recorded every other day beginning on Postnatal Day (PND) 28. On PND 42, the animals were sacrificed, and blood and urine samples were collected for determination of hematocrit and for measurements of calcium and magnesium ions. Urine pH and TPA concentrations were also recorded. The complete urinary system was examined macroscopically for the presence of calculi. Calculi from the urethra, bladder, ureters, and kidney were counted, dried, weighed, and stored for further analysis not described in this report. Statistical analysis performed by the study authors included Student's *t*-test with *f*-test for equality of variance and χ^2. Only data for negative control and TPA-treated rats receiving vehicle gavages are described below.

Diarrhea and crystalline encrustation at the urogenital orifice and papilla were observed in animals treated with TPA (the number of animals affected was not reported). Compared with controls, statistically significant depressions in mean body weights ranging from 8 to 17% (data extracted from graphical images using GrabIT! Software)[6] were observed in treated rats throughout the study (see Table D-6). The study authors indicated body-weight reductions of 20% in TPA-exposed rats at termination. Total food intake in treated animals was significantly decreased (15% decrease) and water intake was significantly increased (see Table D-7). Compared with control rats, urine from treated rats was hyperacidic. Significant increases in urinary calcium (~160% increase) and magnesium (~150% increase) (data displayed graphically), and serum calcium (6% increase) and magnesium (27% increase) were also observed. Hematocrit levels remained comparable to controls (see Table D-8). Calculi, primarily found in the bladder lumen, were significantly increased (5/10) in rats fed 4,900 mg TPA/kg-day; none were observed in controls (see Table D-9).

The only dose tested, 4,900 mg/kg-day, is a LOAEL in this study for significantly increased incidence of calculi in the bladder and decreased body weights. Significant changes in urine pH and levels of electrolytes were also observed. A NOAEL could not be determined.

Subchronic Studies

Dai et al. (2005c); Dai et al. (2006a)

In two published, peer-reviewed reports, Dai et al. (2005c) and Dai et al. (2006a) evaluated the effects of TPA (≥99.99% purity) exposure on Sprague-Dawley (S-D; Shanghai Animal Center) rats in a subchronic feeding study. Male and female S-D rats (12−23 females/group and 12−52 males/group) were fed diets containing 0, 0.04, 0.2, 1, or 5% TPA for 90 days. Adjusted daily doses (ADDs) were estimated in this report to be 0, 36.0, 179, 906, and 4,550 mg/kg-day for males and 0, 40.0, 197, 997, and 4,970 mg/kg-day for females.[8] Details of dietary preparation or whether validation of dietary concentrations was done were not reported. It is unknown whether animals were monitored for clinical signs or mortality. Initial and final body weights were measured. No information on feed or water intake was included in the report. Blood and urine were collected from rats prior to sacrifice (Day 90) for analysis.

[8]Reported dietary intakes (% TPA in food) were converted to ADDs using the following equation: ADD = [% TPA in food × 10,000 (mg TPA/kg food) × food intake (kg food/day)] ÷ BW (kg). Average body weights were calculated from initial and final body weights provided in the study report. Food intake was calculated from body weight using the allometric equation (food consumption in kg/day = 0.056 × [body weight in $kg^{0.6611}$]) from U.S. EPA (1988).

Urine volume was recorded, and urine was analyzed for calcium, magnesium, zinc, potassium, sodium concentrations, pH, and presence of TPA sediment. Alpha 2u-globulin (α2u-g), a major urinary protein secreted by the liver in male rats, was measured in both urine and serum; however, precipitates were not analyzed to determine whether α2u-g was a component of the crystals. The brain, heart, liver, kidney, spleen, lung, and bladder were weighed. Bladders were inspected for calculi and micro calculi, and collected tissues were fixed for histopathological analysis, PCNA immunohistological (bladder) analysis, and for measurements of superoxide dismutase (SOD), malondialdehyde (MDA), and total antioxidative capability (T-AOC). Student's *t*-tests were used to test for significant differences between treated and control groups.

TPA exposure had no significant dose-related effects on body weight or body-weight gain. Sporadic changes not related to treatment occurred in some serum endpoints (total protein, albumin, and triglycerides; data not shown). Urine pH decreased in males and females at the highest dose and in females at the lowest dose and second highest dose (see Table D-10). Significant changes in urinary electrolytes were observed primarily in the two highest dose groups. Statistically significant organ weight changes appeared to be random and not related to exposure (see Table D-11). At necropsy, one male exhibited an enlarged bladder. A white urinary sediment appeared in all male treatment groups and in the highest three female treatment groups (see Table D-12). Bladder calculi were statistically significant in males in the highest dose group (21/52) but not in females at any dose. Incidences of simple (9/52) and atypical (5/52) bladder hyperplasias occurred in highest-dose males but were not statistically significant; no hyperplasia was observed in any other dose group in males. One highest-dose female bladder had simple hyperplasia. The majority of hyperplasias were PCNA positive (86.7%) and generally coincided with the presence of sediment and calculi; three cases of hyperplasia, however, had no calculi. See the "Mode-of-Action/Mechanistic Studies" section for additional discussion of relevant mechanistic results from these studies. However, in brief, because α2u-g crystals are male-specific, and crystals were found in females, the α2u-g mechanism is less likely. Furthermore, because α2u-g was not demonstrated to be a component of the crystals, there is insufficient evidence to consider an α2u-g-related mechanism of action.

A NOAEL of 906 mg/kg-day and a LOAEL of 4,550 mg/kg-day are identified for increased incidences of bladder calculi and hyperplasia in male S-D rats exposed to TPA in the diet for 90 days. Urinary acidosis was also observed in both males and females at the highest dose tested. Sediment in urine and alterations in urine electrolytes were observed at lower doses in both sexes.

Dupont Chem Co (1955)

In a 90-day feeding study performed by Haskell Laboratory (Dupont Chem Co, 1955), the potential effects of TPA exposure were investigated in weanling albino rats. Few study details were available in the unpublished, non-peer-reviewed summary. Commercially obtained albino rats (6 males and 6 females/treatment group; were fed diets containing 0, 1.0, 3.2, or 10% TPA). TPA concentrations in the diets were converted to ADDs of 0, 859, 2,754, and 10,500 mg/kg-day for males and 0, 992, 3,170, and 11,200 mg/kg-day for females.[9] The animals

[9]Reported dietary intakes (% TPA in food) were converted to ADDs using the following equation: ADD = [% TPA in food × 10,000 (mg TPA/kg food) × food intake (kg food/day)] ÷ BW (kg). TWA body weights were calculated from body-weight data provided in the study report. Food intake was calculated from body weight using the allometric equation from U.S. EPA (1988).

were observed for clinical signs (paleness, cyanosis, weakness, condition of body fur, frequency of urine, and diarrhea). Body weights were measured three times weekly through the fourth week of treatment, and twice weekly thereafter. Food consumption was recorded daily and presented as weekly averages; rough estimations of water consumption were made periodically. Urine samples were collected from four rats in the 10%-TPA group to estimate the amount of TPA recovered. Hematological analysis was done prior to dosing, once during treatment, and at sacrifice. Necropsies were performed at sacrifice, and the animals were examined for gross pathology; blood was also collected for measuring blood urea nitrogen (BUN) and plasma calcium and phosphorus. Major organs were weighed and examined for micropathology. Urinary calculi collected from the bladder and kidney were counted and analyzed for content. The available summary did not describe any statistical analyses performed by the study authors.

Four out of six male rats fed 10,500 mg TPA/kg-day died; the deaths were attributed to concretions of TPA in the urinary tract. By Treatment Day 11, five out of the six high-dose males had exhibited hematuria (blood in the urine), with the last male developing hematuria 2 weeks later. No females died. The study authors described the females as being affected by hematuria much less frequently, and with less severity, than males. They attributed blood in the urine as a direct result of damage to the urinary tract from the formation of calculi composed principally of calcium phosphate. Other clinical signs that the study authors noted included drying and cracking of the skin and mild to severe diarrhea (incidences were not reported). No clinical symptoms were described in the 1.0 and 3.2% treatment groups.

Compared with controls, body-weight gains and body weights were severely depressed at 30, 60, and 90 days in high-dose males (45−51% decreased body weight) and females (33−36% decreased body weight) (statistical analyses were not provided) (see Table D-13). The study authors indicated that significant reductions in food consumption were observed in high-dose males and females and that water intake was approximately twice that of controls. No changes outside of the normal range were observed in BUN or plasma calcium or phosphorus concentrations in any treatment group. The available summary indicated a slight tendency toward anemia in all TPA treatment groups at the end of the study and possible moderate hyperphosphatemia in the high-dose rats (the data for these effects were not available). Organ-weight measurements were not reported. At necropsy, calculi and related injury to the urinary tract was observed in 2/12 and 11/11 rats in the 2,754- and 10,500-mg/kg-day dose groups, respectively. Renal injury was consistently severe in the males of the high-dose group (less so in females) and attributed to the presence of calculi. Females were apparently able to eliminate the calculi more easily than males. Pathology of the urinary tract in the affected mid-dose animals was considered mild. No pathology was observed in low-dose rats.

A frank effect level (FEL) of 10,500 mg/kg-day is determined based on the death of 4/6 males and accompanying clinical signs (hematuria), reduced body weights, and severe renal injury associated with the presence of calculi in the urinary tract. The next lower dose of 2,754 mg/kg-day appears to be a NOAEL, although mild renal injury was observed in 2/12 animals at this dose. Confidence is reduced because of limited details available in the report.

Ledoux and Reel (1982); Ball et al. (2012)

In an unpublished, non-peer-reviewed study, Chemical Industry Institute of Toxicology (CIIT) initiated a 90-day TPA feeding study with a follow-on, one-generation reproductive range-finding study in two rat strains (Ledoux and Reel, 1982). Commercially obtained Wistar

and CD rats (30 males and 30 females/strain/dose) were fed TPA in the diet at target dietary exposure levels of 0, 0.03, 0.125, 0.5, 2.0, and 5% for 90 days (diets prepared by Zeigler Brothers, Gardners, PA). The study authors indicated that weekly analysis of feed samples identified a consistently higher than expected TPA concentration in the 0.125%-group feed, with an average, instead, of 0.154% TPA (the other samples were consistent with the target dietary concentrations). Based on the time-weighted average (TWA) body weights and the mean total TPA levels consumed/rat cited in the study, dietary exposure levels are determined to be equivalent to 0, 15.3, 79.09, 266, 1,020, and 2,650 mg/kg-day in Wistar males, 0, 19.3, 114.5, 313, 1,280, and 3,100 mg/kg-day in Wistar females, 0, 14.6, 76.15, 247, 976, and 2,590 mg/kg-day in CD males, and 0, 17.6, 86.57, 286, 1,260, and 2,840 mg/kg-day in CD females.[10] Observations for clinical signs, morbidity, and mortality were conducted twice daily. Physical examinations and measurements of food consumption and body weight were performed weekly. Sacrifices were done on five rats/strain/dose group on Study Days 30 and 60, and on 10 rats/strain/group on Study Day 90. Ten breeding pairs were maintained for the one-generation reproductive study; these animals were continued on their respective diets from mating through postweaning periods. Weaned offspring were fed the same diet as their parents up to PND 51. Additional details and results of the reproductive portion of the study are described later in the "Reproductive and Developmental Studies" section.

The study report indicates that for animals in the subchronic study group, urine was collected prior to sacrifice for measurements of pH, specific gravity, electrolyte concentrations, and levels of TPA. At each sacrifice, the animals were necropsied; the kidneys were weighed, and the kidneys, lower urinary tract structures, and any tissues with gross abnormalities were fixed for histological examination. The study authors performed statistical analysis using ANOVA and Dunnett's test, with each cage of rats as the experimental unit and the average effects per cage as dependent variables.

One male and one female high-dose Wistar rat died on Study Days 34 and 60, respectively. Three highest-dose CD females died on Study Days 59, 75, and 90. No deaths in the other groups were observed. During the first 4 weeks of the study, the number of animals showing clinical signs, including diarrhea, weight loss, or urogenital discharge was greater in highest-dose male (37 vs. 3% in controls) and female (43 vs. 10% in controls) Wistar rats, and in female (57 vs. 20% in controls) CD rats, compared with their respective controls. However, there were no significant clinical differences between groups by the end of the study.

Statistically significant reductions in mean body weights were observed primarily in highest-dose animals of both strains and sexes (see Table D-14). Except for CD female rats at 13 weeks (with 15% decreased body weight, compared with controls), the magnitudes of change were small (<10% of controls). Significant decreases in total average body weight gains appeared to be dose related with the greatest decreases in CD females (see Table D-15). Decreased total weight gains in Wistar rats were significant only in the highest-dose group at 13 weeks. Reduced body weights were generally attributed to reductions in food consumption (see Table D-16).

[10]Reported dietary intakes (% TPA in food) were converted to ADDs in mg/kg-day using the following equation: ADD =[% TPA in food × 10,000 (mg TPA/kg food)] ÷ BW (kg), based on TWA body weights and TPA consumption reported in the study.

Presentation of results in the available study report was incomplete. For example, kidney weight data were not provided. Furthermore, general results of histological examinations were discussed in text, but no histopathology incidence tables were provided. Observations included distention and enlargement of the urinary bladder, calculi, and distention of the caecum and colon in male and female rats of both strains given 5% dietary TPA. Calculi were observed in 1/5 male Wistar rats at 2,650 mg/kg-day at the 30-day sacrifice, and in 3/10 Wistar males, 1/10 Wistar females, and 1/10 CD females, all from the highest-dose groups, at the 90-day sacrifice. Other noted histological changes included frequent chronic inflammation in the urinary bladder submucosa and the renal cortex, medulla, and pelvis, that appeared more often in treated animals. In the bladder, inflammation was apparently associated with minimal to moderate hyperplasia of the transitional epithelium and was greatest in rats given 5% TPA in their diets. The study authors noted that these lesions were more frequently observed in females, and that lesions of the bladder and urethra were more common in Wistar versus CD rats. However, the study authors indicated that the low incidences (less than half the animals) of lesions overall prevent drawing any definitive conclusions of a potential relation to treatment. Some of the incidence data from this study were summarized in a secondary assessment (Ball et al., 2012) and are presented in Table D-17.

For Wistar rats, a NOAEL of 3,100 mg/kg-day is identified in female rats. A LOAEL cannot be established due to lack of statistically significant effects of bladder and urethra calculi, chronic cystitis, chronic urethritis, and transitional cell hyperplasia of the bladder and urethra in males and females, as reported by Ball et al. (2012). Although there were statistically significant decreases in body weight, a LOAEL was not identified for this effect because the changes were not considered biologically significant (i.e., changes were <10%).

In CD rats, a NOAEL of 1,260 mg/kg-day and a LOAEL of 2,840 mg/kg-day are identified for decreased body weight (>10%) in female rats treated with TPA in the diet for 90 days. As indicated by Ball et al. (2012), other findings at this dose were low incidences of urinary bladder calculi, chronic cystitis, chronic urethritis, and transitional cell hyperplasia in the bladder and urethra.

Chronic/Carcinogenicity Studies

Cui et al. (2006a)

In a published, peer-reviewed study, Cui et al. (2006a) reported the effects of repeated exposure to dietary TPA (99.9% purity) in Wistar rats, with a focus on understanding the development of urinary bladder carcinogenesis. Male Wistar rats (30 males/group) were treated in the following manner: Group 1: control (rats maintained on basal diets); Group 2: animals received intraperitoneal (i.p.) injections of vehicle (5% citrate buffer) twice/week for 4 weeks, followed by 22 weeks exposure to 1% dietary TPA; and Group 3: i.p. vehicle twice/week (as above), followed by 22 weeks of exposure to 5% dietary TPA. Control animals (Group 4, 20 males) did not receive vehicle injections. Average daily doses corresponding to 1 and 5% dietary TPA were determined to be 829 and 4,280 mg/kg-day as calculated for this review.[11] Additional groups of rats (Groups 5−7, 15 per group) were pretreated with

[11]Reported dietary intakes (% TPA in food) were converted to ADDs using the following equation: ADD = [% TPA × 10,000 (mg TPA/kg food) × food intake (kg food/day)] ÷ BW (kg). In the absence of TWA or starting body-weight data in the rat study, the reference body weight of 0.217 kg for male Wistar rats in a subchronic study from U.S. EPA (1988) was used. Food intake data reported in the study were used.

N-methyl-*N*-nitrosourea (MNU in citrate buffer) by injection for 4 weeks prior to TPA exposure in order to initiate urinary bladder carcinogenesis.

The study did not indicate whether animals were observed for clinical signs or morbidity. Body weights and food consumption were measured weekly for the first 20 weeks, then once every 2 weeks, and at termination. Freshly voided urine was collected from eight rats/group at Study Week 12 for analysis of electrolytes (calcium, sodium, chloride, and potassium) pH, and urinary TPA concentration. Necropsies were performed at sacrifice (26 weeks). Absolute and relative bladder weights were measured. Organs including brain, heart, liver, spleen, lung, kidneys, and bladder were fixed for histopathological analysis. Urinary tracts were observed for calculus formation. Sections from all animals were processed for proliferating cell nuclear antigen (PCNA) immunohistochemical analysis to detect clonal cell proliferation. Differences between means were analyzed by the study authors using ANOVA with least significance difference tests. Fisher's exact or χ^2 tests were used to assess differences in incidences of lesions.

No mortalities in the TPA treatment groups were reported. Significant decreases in mean final body weights were observed in both dose groups (8 and 12% decreased, relative to controls at 829 and 4,280 mg/kg-day, respectively). Absolute and relative bladder weights were significantly increased by 60 and 82%, respectively, at the high dose (see Table D-18). Results from urinalysis are shown in Table D-19. Significant dose-related decreases in urinary pH, sodium, potassium, and chloride, and increases in calcium and phosphorus were observed in both treatment groups. Urinary volume was significantly increased by 76% over controls at the high dose and increasing amounts of urine precipitate were observed in a dose-related manner. Macroscopically, 4/15 rats fed 4,280 mg/kg-day had numerous calculi versus none in controls. Moderate precipitates (incidence not reported), but no calculi, were observed at the low dose, but these incidences were not statistically significantly increased. Simple hyperplastic lesions in the bladder occurred in 2/15 low-dose and 5/15 high-dose animals and were statistically significant at the high dose. Animals receiving 4,280 mg TPA/kg-day in their diets also had incidences of papillary or nodule bladder hyperplasia (4/15 vs. 0/15 in controls) that were not significantly elevated. Hyperplastic lesions in high dose animals had increased PCNA indices compared with bladder tissues collected from control rats. No treatment related papillomas or transitional cell carcinomas were observed (see Table D-20).

A NOAEL of 829 mg/kg-day and a LOAEL of 4,280 mg/kg-day are determined for significantly decreased body weights (>10% change from controls), increased relative and absolute bladder weights, and increased incidences of simple hyperplasia in the bladder. Near significant incidences of calculi and papillary or nodule hyperplasia in the bladder were also reported. Significant changes in urinary pH and electrolyte levels, as well as sediment in the urine, were observed in both dose groups.

No evidence of carcinogenic effects in the bladder was noted in this study in any treatment group. The lack of concordance between urine precipitates, bladder calculi, and hyperplastic lesions of the bladder makes the cause and effect relationships unclear as there are animals with precipitates but no calculi, and animals with hyperplasia but no calculi. It is thus unclear whether calculi are a key event in the progression of downstream effects.

Cui et al. (2006b); Cui et al. (2007); Shi et al. (2006)

Three peer-reviewed publications by the same group reported separate, mechanistically focused results from a single study in rats (Cui et al., 2007; Cui et al., 2006b; Shi et al., 2006). Male Wistar rats (20/control group, 38/treatment group) were fed diets containing 0 or 5% TPA (>99.9% purity) for 48 weeks. A 5% dietary intake of TPA is determined to be equivalent to an ADD of 3,680 mg/kg-day.[12] Additional treatment groups included diets with 5% TPA plus 4% $NaHCO_3$, or 4% $NaHCO_3$ alone. Interim sacrifices (four controls and eight treated) were performed at Weeks 12 and 24. Body weights were measured once per week for the first 13 weeks, and then biweekly thereafter. The study report did not indicate whether measurements of food and water consumption or observations for clinical signs were included in the study design. At each sacrifice, complete necropsies were performed. Urinary bladders were excised, weighed, and fixed for histopathology. PCNA immunohistochemical analysis was done on all lesions to detect clonal cell proliferation. At 48 weeks, tumor incidence was recorded; the largest tumors were removed for various molecular assessments to investigate the potential mechanisms of cancer development (Cui et al., 2007; Shi et al., 2006). See the "Mode-of-Action/Mechanistic Studies" section. The study authors performed statistical analysis using one-way ANOVA, followed by least significant difference tests.

Two animals in the treatment group died from urethral obstruction. Hematuria was found in "some" treated rats after 2 weeks of exposure (incidences were not provided). Mean body weights of treated rats were described as "consistently lower than controls." Mean absolute and relative urinary bladder weights of rats fed TPA were significantly increased as reported by the study authors (data not provided). Bladder calculi and papillary or nodular hyperplasias were significantly increased in treated rats at the 12-, 24-, and 48-week time points, respectively, compared with none in the controls (see Table D-21).

Statistically significant incidences of bladder papillomas were observed at 24 (8/8) and 48 (18/20) weeks, and a significant incidence of transitional cell carcinomas in the bladder (16/20) occurred in TPA-treated rats at the end of the study, indicating that TPA acts as a bladder carcinogen in rats following oral exposure. At all time points, bladder lesions had significantly higher PCNA labeling indices than corresponding control tissues and labeling increased from papillary or nodular hyperplasia to papilloma to transitional cell carcinomas.

For non-neoplastic endpoints, the single exposure level of 3,680 mg/kg-day is identified as a LOAEL based on increased incidences of bladder calculi and hyperplasias at 12, 24, and 48 weeks. Because 3,680 mg/kg-day is the only dose tested, a NOAEL cannot be identified. Elevated absolute and relative bladder weights and reduced body weights were also reported, although the data were not shown.

Gross (1977)

An unpublished, non-peer-reviewed study performed at Hebrew University-Hadassah Medical School for EI DuPont de Nemours and Company reported the effects of chronic feeding of TPA (97.3% purity) in rats (Gross, 1977). Groups of Wag/Rij (Wistar) rats (50 males and

[12]The reported dietary intake of 5% TPA in food was converted to an ADD by applying the following equation: ADD = [% TPA × 10,000 (mg TPA/kg food) × food intake (kg food/day)] ÷ BW (kg). In the absence of body-weight or food-intake values in the study report, reference values from U.S. EPA (1988) for body weight (0.462 kg) and food intake (0.034 kg/day) for male Wistar rats in a chronic study were used.

50 females/dose group) were fed chow containing 0, 1, 2, or 5% TPA for 24 months. These diets are equivalent to ADDs of 0, 736, 1,470, and 3,680 mg/kg-day in males and 0, 842, 1,680, and 4,210 mg/kg-day in females, based on reference body-weight and food-consumption values for male and female Wistar rats in a chronic study (U.S. EPA, 1988).[13] Limited description of methods was provided in the available report. The animals were observed daily. Body weights were recorded weekly for the first 3 months, and then biweekly thereafter until Study Week 40. All animals found moribund or dead throughout the study were subject to necropsy and histopathological examination except for those with advanced autolysis. At sacrifice, blood was collected for hematology and limited serum chemistry (blood urea) analysis. The liver, kidney, heart, spleen, submaxillary, and adrenal glands were weighed. Histological examination was done on these and other tissues (pituitary, thyroid, bladder, bone marrow, stomach, small intestine, pancreas, and others). Limited statistical analysis of some data was performed by the study authors, although complete description of the statistical methods used was not provided.

Graphically depicted cumulative mortality curves for male and female rats in the low- and mid-dose groups did not differ appreciably from those of the controls; some of the animals in each group died, with an upward trend beginning at ~19 months. As indicated by the study authors, the predominant cause of death in all groups (except high dose TPA), including controls, was tumors of the pituitary. In the high-dose TPA treatment group, a significant number of animals died throughout the experiment beginning in the second month; at 24 months, the percent survival of high-dose males and females was 32 and 30%, respectively, compared with 66 and 74% survival in controls (see Table D-22). The study authors indicated that the formation of calculi in the urinary tract was the main cause of death in the high-dose animals. No data on food or water consumption were provided. Growth curves were generated and presented in an appendix that was not available for independent review. At the end of the experiment, final body weights of males fed 1,470 and 3,680 mg/kg-day were significantly decreased, relative to controls, by 10 and 22%, respectively. Female body weights were significantly reduced by 20% in the 4,210-mg/kg-day group (see Table D-23). No significant changes in any of the hematological endpoints measured (hemoglobin, and RBC and WBC counts) were observed. Compared with controls, the percent of animals with increased blood urea levels of ≥40 mg % (40 mg/dL) was significantly ($p < 0.05$) elevated in high-dose animals (females: 26 vs. 5% in controls; males: 23 vs. 17% in controls; data not shown).

Changes in organ weights were generally consistent with the observed reduction in body weight, with absolute organ weights decreasing and relative organ weights increasing, most notably in mid- and high-dose males and high-dose females (see Table D-24). An exception was the adrenal gland, which showed increases in both absolute and relative weights in high-dose males and females, but not significantly so in females. Statistically significant decreases in both absolute and relative liver, kidney, and heart weight in low- and mid-dose females in the absence of significant body-weight changes in these groups are of uncertain toxicological significance because the relative weights were not decreased in the high-dose group and no similar changes were seen in males.

[13]Reported dietary intakes (% TPA in food) were converted to ADDs using the following equation:
ADD = [% TPA × 10,000 (mg TPA/kg food) × food intake (kg food/day)] ÷ BW (kg). In the absence of sufficiently reported body weight and food consumption data in the study, reference values recommended by U.S. EPA (1988) for body weight (0.462 kg M/0.297 kg F) and food intake (0.034 kg/day M/0.025 kg/day F) for male and female Wistar rats in a chronic study were used.

Urinary tract calculi were observed almost exclusively in high-dose animals of both sexes. Ninety-three percent of high-dose females and 89% of high-dose males had calculi, compared with single incidences or none in the other treatment groups or controls; incidence of calculi was significantly increased in both sexes at the highest dose (see Table D-25). Calculi were found both filling and distending the urinary bladder and were also present in the pelvis of the kidney. The incidences were 0%, 0%, 0% and 89% in males and 0%, 2%, 0% and 93% in females. Analysis of kidneys from high-dose animals indicated a significant increase in incidences of nephropathy, ranging from focal areas of destruction to overall loss of kidney structure with infiltration of inflammatory cells and papillary necrosis. Other pathological changes, described by the study authors as being nearly exclusive to high-dose animals, included hyperplasia of the pelvis, ureteral, and/or bladder epithelium; infiltration of transitional cells; and epithelial squamous metaplasia.

Tumor incidences in various tissues for this study are provided in Table D-26. Treatment-related tumors were present in the bladder and ureter in 1/43, 1/48, and 21/37 males and in 0/48, 2/47, and 21/34 females in the low-, medium-, and high-dose groups, respectively. The bladder and ureter tumors were significantly increased in both sexes at the highest dose. No bladder or ureter tumors were observed in the controls (0/45 males and 0/46 females). The discussion within the available text of the Gross (1977) report indicates that these lesions were primarily transitional cell tumors or squamous cell carcinomas. The study authors reported that spontaneous tumors (where incidence in controls exceeded incidence in treatment groups) occurred primarily in the pituitary and thyroid in both sexes and in mammary glands in females; incidences of tumors in the adrenal medulla at the same level (2/46 in females) as the low dose were also noted. There was an unexplainable decrease in several spontaneous tumors primarily in the high-dose animals.

For non-neoplastic endpoints, a LOAEL of 1,470 and a NOAEL of 736 mg/kg-day are determined for this study based on a 10% decrease in body weight, which is considered to be biologically significant, in male Wag/Rij Wistar rats exposed to dietary TPA for 24 months. At higher doses in both sexes, increased incidences of high blood urea levels, nephropathy, and urinary tract calculi were observed.

Grubbs (1979); Preache (1983)

The Industry Institute of Toxicology (ITT) conducted a 24-month bioassay in rats to evaluate the toxicologic and carcinogenic potential of TPA (Preache, 1983; Grubbs, 1979). A portion of the pathological samples were later reanalyzed by Experimental Pathology Laboratories, Inc. (EPL), along with additional samples that had been stored for future analysis (ICI Americas Inc, 1992). The results from both unpublished, non-peer-reviewed reports (original and reanalyzed/revised) are discussed here. F344 rats (126/sex/dose) were fed target dietary levels of TPA (Amoco Chemicals Corp., "purified grade") equaling 0, 20, 142, and 1,000 mg/kg-day for 24 months. ADDs for the first 12 months of the study, based on recorded body weights and food consumption rates, were reported by the study authors to be 0, 19.5, 138.2, and 995.4 mg/kg-day in males and 0, 19.2, 136.6, and 989.8 mg/kg-day in females. For the purposes of this review, the reported doses at 12 months are adopted as the doses for the full duration of the study. The animals were observed twice daily for general physical appearance, morbidity, and mortality. Food consumption and body weights were measured approximately weekly for the first 13 weeks, biweekly for an additional 12 weeks, and monthly thereafter. Hematology, clinical chemistry, and urinalysis were performed on 5 animals/sex/group sacrificed

at 6 and 12 months, on 20 animals/group at 18 months, and on the remaining surviving animals at 24 months. Each animal was evaluated for neurological function and subjected to ophthalmologic examinations of both eyes prior to sacrifice, whereupon necropsies were performed. At each sacrifice, including any animals sacrificed due to a moribund state, brain, heart, liver, kidneys, lungs, testes, and ovaries, were weighed; these and >30 other tissues were preserved for histopathology. Histopathological examination was originally performed on control and high-dose animals, and only low- and mid-dose groups that died or had evidence of gross masses. Later, EPL re-evaluated the urinary bladders from a portion of these samples (234 males and 210 females from either control or high-dose groups), along with urinary bladders and eyes from an additional 214 male and 203 female rats exposed to low- and mid-dose levels that were sacrificed at 6, 12, 18, or 24 months. The original study authors conducted statistical analysis of the data using ANOVA and Tukey's procedure to determine the differences between control and treated groups. All comparisons were limited to within-sex analysis.

Experimental issues were reported that could affect the interpretation of the study results. First, there was a possibility that animals were exposed to continuous light during an undefined period of the study; the study authors thought this may have contributed to the high incidence of cataracts observed in both test and control animals of both sexes. An alternative explanation is that animals could have been exposed to an ocular virus. There was also an uncharacteristically high incidence of uterine adenocarcinomas in females from all groups that could not be explained; the authors suspected that this could also be related to continuous lighting and its effects on hormones. Second, animals were exposed to excess levels of vitamins, resulting from lack of autoclaving of the animal diets; the effect of this exposure is unknown. The study authors noted that interpretation of animal body-weight data was confounded by significant differences in initial (Day 0) body weights between rats designated for treatment groups versus those marked for controls, with significantly lower starting weights in the treated rats. Control and treated rats were also not weighed on the same day. Finally, the study authors indicated that the concentrations of TPA in the diet were not as carefully controlled as desired, and considerable deviations from the intended dose were observed during the first 24 weeks of the study. Analytical analysis of TPA recovered from feed was done on Weeks 1, 5, 9, 12, 13, 18, and 24, but not at later time points. The results indicated that the low-dose concentrations varied from the target level mean by 16.7% over the first 24 weeks. On Week 24, a deviation of +71% was observed. The study authors indicated that when this data point was dropped, the mean deviation fell to within 9% of target. Mean variations in the mid- and high-dose concentrations equaled 9.1 and 7.7%, respectively. It is unknown what potential deviations occurred throughout the duration of the study. Therefore, because of this uncertainty, confidence in the dosing provided by the study authors is low. In summary, because of experimental errors, confidence in this study is too low to be considered as a principal study.

6- and 12-Month Interim Sacrifices:

At 6 months, 5 animals/group were examined, and there were no gross lesions in any of the control or treated rats. There were also no treatment-related histopathologic tissue alterations. A variety of spontaneous lesions were observed in all groups, but the study authors reported that the lesions were not due to the treatment regimen. At 52 weeks (12 months), mortalities and/or sacrifices due to morbidity were as follows: controls (five females), low dose (three females, one male), mid dose (nine females, one male), and high dose (five females). Several females that died (in all groups) were found to have ovarian abscesses containing

Escherichia coli. During the first 12 months, no overt treatment-related clinical signs were observed. At 6 months, ophthalmological examinations indicated that 3/5 high-dose males had cataracts, and a high incidence of cataracts was again observed in TPA-treated males at 12 months (incidence not available), and to a lesser degree in treated females. Neurological evaluations were found to be within normal limits for all animals sacrificed at 6 and 12 months. There were significant decreases in mean body weights of both male and female rats of all groups compared with controls throughout the first 12 months of treatment (see Tables D-27 and D-28). However, these decreases may have been influenced by differences in initial body weights between groups and an unexplained period of weight loss in the control females. At times, the body-weight decreases exceeded 10% in females of all groups. Food consumption was also significantly varied throughout the study in all treated male and female groups relative to controls (see Tables D-29 and D-30). Six-month terminal sacrifice weights were significantly reduced in low- and high-dose females, with decreases of 14, 6, and 13% compared with controls at 19.2, 136.6, and 989.8 mg/kg-day, respectively (see Table D-31). Female terminal body weights at 12 months and final body weights in males at 6 and 12 months were not statistically different from controls. Furthermore, body weight in females was biologically significantly (≥10%) reduced at 6 months, but not at 12 months.

Absolute and relative organ weights were measured from only five animals per group at both the 6- and 12-month time points. Absolute and relative heart weights in high-dose males were significantly decreased at 6 months by 10 and 17%, respectively, relative to controls, but not at 12 months (see Table D-31). In females, absolute and relative liver weights were significantly increased (23 and 30%) in the mid-dose group at 6 months and relative liver weight was also increased (23%) in the high-dose group at that time. Relative liver weight was also significantly increased at 12 months in high-dose females, although the magnitude of change was <10%. Finally, absolute, but not relative, ovary weight was significantly increased in high-dose females at 12 months. No significant changes in kidney weights were observed in males or females. Urinalysis (pH, specific gravity, and urine output), hematology (RBC, Hb, hematocrit, and WBC), and clinical chemistry (glucose, BUN, ALT, and ALP) measurements were also done on a small number of animals (n = 5) and showed no clear dose-related effects.

There were no consistent gross pathology findings in any treatment group at 6 or 12 months. Several spontaneous histological lesions were observed in both the control and high-dose rats, but the incidences were not significant and not considered by the study authors to be treatment related, although the number of animals evaluated was low. Lesions relating to the bladder are shown in Table D-32. Histological analysis of other tissues was not performed in the low- and mid-dose groups.

18- and 24-Month Findings:

Available data for the 18- and 24-month sacrifices are limited to summary descriptions written by the study authors that could not be independently evaluated. By 24 months, several mortalities or sacrifices due to morbidity were described. Between 18 and 24 months, 75 males and 105 females died, and an additional 36 males and 33 females were sacrificed (dose groups were not specified). The numbers of surviving animals were comparable across groups in males, and although there were more female survivors in the control group, no dose-related effect on survival was observed. In females, the study authors indicated that uterine adenocarcinomas were the primary cause of death in 8/24, 17/43, 23/34, and 21/37 animals that died in the control, low-, mid-, and high-dose groups, respectively. The most prominent clinical signs among all

groups were ocular effects. At 18 months, all animals (including controls) had cataracts, although differences in severity were observed. The cataracts in males treated with TPA were considered "mature," whereas only 50% of the control males had this cataract designation. Although the severity appeared to be slightly less in female rats, the incidences were higher in treated animals than in controls. At 24 months, cloudy or opaque eyes occurred in >95% of all males (including controls) and in 91% of female controls and 96−100% of those treated with TPA. The frequency of matter-crusted eyes was slightly higher in mid- and high-dose females (15−20%) than those in the control and low-dose groups (<6%). Other ocular effects noted included dark brown hemorrhagic staining around eyelids, the presence of corneal crystals, vascular evidence of anemia, iris-corneal adhesions, and one instance of eyelid tumor (further details and data for these effects were not available). No treatment-related neurological effects were observed.

The decreases in body weights observed during the first 12 months of treatment were not biologically significant and were only maintained in high-dose males and females, and a concomitant increase in water intake was reported. At 24 months, high-dose females were described as having more moderate to heavy sediment in their urine compared with controls. Reduced urine pH was noted in treated male animals as well as those lacking triple phosphates (crystals) in the urine. At the 18- and 24-month necropsies, 2/27 and 11/86 high-dose females, respectively, showed evidence of urinary bladder calculi (data not reported). No exposure-related clinical chemistry or hematological changes were noted. Kidney weights of high-dose males were reduced at 18 months. At 24 months, heart and kidney weights were reduced in mid- and high-dose females, but the authors did not indicate whether these were absolute or relative organ weights. Other sporadic organ-weight changes were described, which the study authors attributed to changes in body weight, rather than to organ-specific toxicity. Gross necropsy indicated that sand-like particles, or calculi, occurred in 16/126 high-dose females over the course of the study.

The initial histopathological evaluation showed a nonsignificant increase in the incidence of bladder hyperplasia in high-dose females at 18 months (5/27 vs. 0/22 in controls) and 24 months (14/79 vs. 8/83 in controls) (see Table D-32). The incidence of bladder hyperplasia in high-dose males did not differ from controls at either time point. At 24 months, females also exhibited significantly increased incidence of squamous metaplasia (9/79 vs. 0/83 controls). Squamous metaplasias were always seen adjacent to a tumor.

A follow-up reanalysis was done on a portion of bladder, uterus, and eye tissues from control and high-dose animals from sacrifices at 6, 12, 18, and 24 months, as well as samples from low- and mid-dose animals. The available report (ICI Americas Inc, 1992) did not include revised incidence tables. Data from the pathologist summary text are included in Table D-32 where possible but reporting of data in the text was incomplete. In the bladder, noted findings were hyperplasia in 1 mid-dose female and 4 high-dose females (and no males) at 18 months and in 9 low-, 3 mid-, and 0 high-dose males and 7 low-, 2 mid-, and 24 high-dose females at 24 months. Discrepancies in the numbers of animals and some of the findings between the reanalysis and the original report were not specifically addressed. In the reanalysis several lesions were recategorized from transitional cell adenomas to hyperplasias. Ocular changes, including retinal degeneration and cataracts, were observed in low- and mid-dose male and female rats at 18 months, and in all animals at 24 months. Incidences of other non-neoplastic lesions in the spleen, kidney, adrenal glands, pituitary, testes, and ovaries were within the

expected range for F344 rats. The study authors reported that at 18 months, uterine abnormalities occurred more frequently in treated females, and uterine masses occurred only in treated groups. There were no treatment-related microscopic changes in animals from any treatment group sacrificed at 6 or 12 months.

The original study reported transitional cell adenomas in the bladder's of 15/79 high-dose females and 1/83 controls at 24 months, which was identified as a statistically significant difference by Fisher's exact test performed for the purposes of this PPRTV assessment. In the reanalysis, as noted above, several lesions were recategorized from transitional cell adenomas to hyperplasias. This occurred primarily in high-dose females. Bladder tumors reported in the reanalysis (all at 24 months) were transitional cell adenomas in 10 high-dose females and 1 control female, transitional cell carcinoma in 1 high-dose female, and transitional cell papillomas in 2 low-dose females. Based on the data reported for the reanalysis, the incidence of bladder adenomas was significantly increased in high-dose females by a Fisher's exact test performed for the purposes of this PPRTV assessment.

Nine of the 15 animals (females) with transitional cell adenomas and both animals with transitional cell carcinoma (as reported in the original study) had calculi in the bladder at 24 months. Uterine adenocarcinomas occurred in 30/81 and 32/75 low- and mid-dose females combined over all sacrifice periods. The study authors reported that these aggressive metastatic uterine adenomas or adenocarcinomas appeared be treatment related (statistical significance not reported). Forty percent of high-dose females (vs. none in controls) at 18 months exhibited uterine neoplasias. However, the study authors also noted that similar tumors were observed in control animals from a different study that were housed in the same room as the TPA control animals. By 24 months, uterine masses did in fact appear in all groups, occurring in 17% controls, and in 22, 24, and 25% of females in low-, mid-, and high-treatment groups, respectively. The study authors indicated that the high incidence of uterine tumors could potentially be due to light-induced increases in estrogen, although there is little evidence to support this.

For non-neoplastic findings, a LOAEL cannot be determined because significant effects were not consistently observed throughout the 24-month study. Therefore, the highest dose of 995.4 mg/kg-day is identified as the NOAEL. As discussed previously, confidence in this study is low because of experimental deficiencies (i.e., exposure to continuous light during an undefined period of the study, exposure to excess levels of vitamins, the concentrations of TPA in the diet were not as carefully controlled as desired).

Reproductive and Developmental Studies

Ledoux and Reel (1982)

Exposure details for this unpublished, non-peer-reviewed 90-day feeding study and following one-generation reproductive range-finding study was described above under "Subchronic Studies." In brief, Wistar and CD rats (9−10 breeding pairs/group) that had already been on TPA exposure diets for ~90 days were continued on their diets through mating, gestation, and lactation until scheduled sacrifice. Calculated doses (equivalent to 0, 0.03, 0.154, 0.5, 2, and 5% TPA in feed) were 0, 15.3, 79.09, 266, 1,020, and 2,650 mg/kg-day (males) and 0, 19.3, 114.5, 313, 1,280, and 3,100 mg/kg-day (females) in Wistar rats, and 0, 14.6, 76.15, 247, 976, and 2,590 mg/kg-day (males) and 0, 17.6, 86.57, 286, 1,260, and 2,840 mg/kg-day (females) in CD rats (calculation details were described in the 90-day summary). At weaning,

litter sizes were reduced to 2 males and 2 females/litter from 5 litters (equaling 20 pups/strain/group) for continued exposure to the same diet as their parents for 30 days (until PND 51). Reproductive and developmental endpoints, including fertility index, litter size, sex, viability, and survivability were recorded. All animals were observed twice daily for clinical signs and mortality. Offspring body weights were recorded on PND 1 and at weaning (PND 21). Gross necropsies were performed on all offspring and on parental animals. The animals were examined for lesions in the thoracic and abdominal viscera, with a focus on renal and urinary systems. The study authors performed statistical analysis using ANOVA and Dunnett's test, using the litter as the experimental unit and average effects per litter as dependent variables.

Five treated Wistar dams, one treated CD dam, and two treated CD parental males died between TPA Exposure Days 116 and 148. The deaths were not attributed to treatment by the study authors, although they primarily occurred at the 2 and 5% dietary TPA levels. Four of the animals died due to hair in the intestinal tract; in one case, a dam died during labor. Clinical signs in parental control and treated animals during Experimental Days 91−147 primarily included weight loss (quantitative body-weight-gain data were not provided), which the study authors indicated was evenly distributed across groups, without correlation with TPA exposure level. The study authors reported that reproductive performance was not significantly affected by TPA exposure. There were no significant changes in the fertility index or litter size between respective controls and treated Wistar or CD rats (data not shown).

Seventeen Wistar and 23 CD pups (approximately 5% of the total number of pups) across all treatment groups were born dead. Of the pups found dead, the study authors reported that a total of 76% of Wistar and 96% of CD stillborn pups were clustered in the two highest dietary concentrations of TPA. There was no significant effect on the number of pups per litter alive on PND 0, 1, or 21. However, the proportions of CD rat male and female pups surviving to PND 21 were significantly decreased in the high-dose group (see Table D-33). Nonsignificant decreases were seen in Wistar rats. From birth to weaning, there were no notable treatment-related clinical signs in F_1 offspring of either strain. On PND 1, body weights of Wistar high-dose male, female, and combined sexes were significantly reduced by 17−19% from controls (see Table D-34). In CD rats, pup weight was biologically significantly (≥5%) reduced in males and females at ≥1,260 mg/kg-day and in combined sexes at the highest dose on PND 1. On PND 21, pup weights of Wistar male, female, and combined sexes were biologically significantly (≥5%) reduced at ≥1,280 mg/kg-day. In CD rat pups, body weights of male, female, and combined sexes were biologically significantly (≥5%) reduced at all doses at PND 21.

Postweaning, a number of unscheduled deaths occurred from PNDs 24 to 36 in high-dose weanlings of both strains. The presence of calculi in the bladder was associated with 10/19 and 12/18 deaths in high-dose weanling Wistar and CD rats, respectively. Gross necropsy of F_1 offspring between PNDs 21 and 51 indicated no notable findings in the bladder of animals fed 0.03, 0.154, 0.5, or 2% TPA in their diets. At the highest dose, the primary findings were significantly increased incidences of renal calculi and thickened bladder walls, occurring in 8/18 male and 16/31 female Wistar weanlings and in 5/9 male and 9/13 female CD weanlings (see Table D-35). Other gross observations reported by the study authors in high-dose animals included enlarged caecum and bladders, kidney dilation, and spots on the kidney.

This study identifies a LOAEL of 1,280 mg/kg-day and a NOAEL of 313 mg/kg-day in Wistar rats for biologically significant (≥5%) decreases in pup body weights on PND 21. There

were also significant increases in renal and bladder calculi in pups upon necropsy (PNDs 21−51) at higher doses. In CD rats, a LOAEL of 17.6 mg/kg-day (the lowest dose) is identified for biologically significant (≥5%) reduced pup body weights at PND 21. Because 17.6 mg/kg-day is the lowest dose tested, a NOAEL cannot be identified for CD rats.

Cui et al. (2004)

In a published, peer-reviewed study, Cui et al. (2004) investigated the effects of TPA (≥99.99% purity) on testicular function in rats. Commercially obtained male S-D rats (10 males/group) were fed daily diets containing 0, 0.2, 1, or 5% TPA for 90 days. Doses were determined for this review to be equivalent to 0, 172, 861, and 4,310 mg TPA/kg-day based on reference body-weight and food-consumption values for male S-D rats in a subchronic study.[14] Recordings of clinical signs or water consumption were not included in the study methods. Feed consumption (data not shown) and body-weight gain were monitored. At sacrifice (Day 91), blood was collected for serum testosterone measurements and testes were removed and weighed. Left testes were used for sperm head counts and biochemical assays; the right testes from six males were preserved for histopathological analysis. Three testes from the control and high-dose males were used for electron microscopic observation. Sperm from the cauda epididymides were measured for multiple motility parameters using Computer-Assisted Sperm Analysis (CASA). The study authors applied Duncan's test to evaluate the data for statistical significance.

TPA treatment up to 4,310 mg/kg-day did not cause any significant changes in food consumption (data not shown), body-weight gains, or absolute or relative testis weights, compared with controls (see Table D-36). Significant reductions in sperm head counts and daily sperm gain production (19% decrease from controls) were reported at the high dose. TPA treatment significantly affected several sperm motility parameters in a dose-related manner (see Table D-37). Straight line velocity (VSL) (27−39% decrease) and percent straightness (STR) (18−24% decrease) were significantly reduced from control values in all treatment groups. Linearity (LIN), and beat cross frequency (BCF) also decreased with increasing exposure to TPA and were significant starting at 861 (LIN only) and 4,310 mg/kg-day, respectively. No obvious histological changes were observed. Electron microscopic evaluation identified aberrations in cells from several stages of spermatogenesis (data displayed in images only). Observations included abnormal distribution of heterochromatin in spermatogonia, spermatocytes, and Sertoli cells; indistinction of the nuclear membrane in spermatogonia, spermatocytes, spermatozoa, and Sertoli cells; vacuolization and/or loss of mitochondrial cristae in spermatogonia, spermatocytes, and Sertoli cells; and liposome hyperplasia in spermatogonia. No changes were observed in Leydig cells. Testicular enzymes were largely unaffected, except for sorbitol dehydrogenase (SDH), which was significantly reduced by 16%, compared with controls. Serum testosterone was also unchanged with TPA treatment. The study did not evaluate fertility or reproductive performance.

Given the absence of histological findings, and lack of fertility assessment, in male Wistar rats, a NOAEL of 861 mg/kg-day and a LOAEL of 4,310 mg/kg-day with low confidence are determined for significant reductions in sperm head counts, several sperm motility

[14]Reported dietary intakes (% TPA in food) were converted to ADDs using the following equation: ADD = [% TPA in food × 10,000 (mg TPA/kg food) × food intake (kg/day)] ÷ average BW (kg). Body-weight and food-intake values were not reported, so reference values from U.S. EPA (1988) of 0.267 kg (BW) and 0.023 kg/day (food intake) for male S-D rats in a subchronic study were used.

parameters, daily sperm gain production, and abnormal changes in sperm cell structure throughout spermatogenesis observed by electron microscopy following exposure to TPA in the diet for 90 days. Collectively, these changes indicate the potential for TPA to affect male reproductive performance. Although significant reductions in some sperm motility parameters were observed at lower doses (i.e., 172 and 861 mg/kg-day), the biological significance of these findings is uncertain because fertility does not appear to be affected in other studies. Electron microscopy was only performed on controls and high-dose samples, and therefore, it cannot be determined whether any structural changes occurred at lower dose levels.

Kwack and Lee (2015)

The effects of TPA exposure on male reproductive organs were further investigated by Kwack and Lee (2015). S-D rats (five males/group, 6 weeks old at the start of the study) were treated by daily gavage with TPA doses of 0, 10, 100, or 1,000 mg/kg-day for 4 weeks. Similar treatments were done using other phthalic acid isomers. In vitro studies on mouse testis Sertoli cells, human testis cancer cells, and human fetal liver cells were also performed. No clinical observations, body weights, or measurements of food and water consumption were recorded. At 4 weeks, the testes, cauda epididymides, and spermaducts were dissected from rats under anesthesia. Absolute and relative testis and epididymis weights were recorded, and CASA was used to evaluate semen parameters in the controls and the rats treated with 1,000 mg/kg-day. The percentage of mobile, static, progressive, and rapid sperm were determined for all treatment groups. The study authors analyzed the data by one-way ANOVA and Tukey's post-hoc comparisons.

The authors reported no significant changes in relative or absolute testis or epididymis weights (data not shown), or total sperm counts in rats treated with 1,000 mg/kg-day TPA, compared with controls (see Table D-38). Sperm progressive motility (a measure of forward progression) was significantly reduced by 26% at the high dose, compared with controls. A general decline in other sperm motility parameters measured using CASA (amplitude of lateral head displacement, beat cross frequency, linearity, straightness, velocity average path, velocity curved line, and velocity straight line) were observed, but decreases were determined not to be statistically significant.

Based on decreased sperm motility, this study identifies LOAEL and NOAEL values of 1,000 and 100 mg/kg-day, respectively, in rats treated with TPA by gavage for 4 weeks.

Inhalation Exposures

No primary reports of short-term, subchronic, or chronic inhalation studies of TPA in animals have been located.

Reproductive and Developmental Studies

Chemical Manufacturers Association (2000)

In an unpublished, non-peer-reviewed study, Chemical Manufacturers Association (2000) investigated the teratological effects of inhaled TPA in female rats. Gravid S-D rats (22−25/group) were exposed to a purified TPA particulate aerosol by whole-body inhalation for 6 hours/day, 7 days/week on Gestation Days (GDs) 6−15; analyzed TWA concentrations reported by the study authors were 0, 0.90, 4.73, and 10.40 mg/m^3. The mass median aerodynamic diameters (MMAD) were 4.16, 4.87, and 5.39 for the low-, medium-, and high-exposure concentrations, respectively, with associated respirable fractions of 91.1, 89.4, and

85.0%. Geometric standard deviations (GSD; σ_g) were not reported. Control rats were exposed to filtered air only. The rats were observed twice daily on weekdays, and once daily on weekends, and for 3 hours after exposures for signs of toxicity. Body weights were recorded on GDs 0, 5, 6, 11, 16, and 20 (study termination). Dams were sacrificed on GD 20 and subjected to gross necropsies. Any lesions or abnormalities were noted, and uterine horns, fetuses, and ovaries were removed and weighed. Gross observations of fetuses were recorded, and one-half of each litter was randomly selected for either a skeletal or wet visceral examination. All anomalies were recorded and given a severity score based on historical control data. For statistical analysis, the study authors used a multilevel linear model to analyze log-transformed pup body weights using the pup as a nested factor within the dam. Log-transformed dam body weights were analyzed by multivariate ANOVA. Other statistical methods included ANOVA with Dunnett's test and a log-linear model for analysis of fetal anomalies.

No maternal deaths occurred during the study. Except for slightly higher, yet nonsignificant, incidences of scaly tail in TPA-exposed groups, clinical signs were sporadic in nature and not related to exposure. Dam body weights, body-weight gain, uterine weights, and corrected body weights (body weights minus uterine weights) were comparable to controls. No notable gross necropsy findings in dams were reported. There were no signs of maternal toxicity at the exposure concentrations tested.

TPA had no effect on litter viability; numbers of live and dead fetuses, total and live implants, and resorptions; or fetal sex ratio. Fetal body weights in all treatment groups, measured by sex, or combined, were comparable to controls. There were no significant gross external findings that the study authors considered treatment related. One fetus in the 4.73-mg/m^3 group, and one in the 10.40-mg/m^3 group, had short and/or filamentous tails. A second fetus in the 10.40-mg/m^3 group had agnathia (absence of a portion or the entirety of one or both jaws). Visceral anomalies (variations and malformations) were also not considered by the study authors to be treatment related and differences were not statistically significant. Visceral variations were observed primarily in the kidneys of all treatment groups, including the controls, with hydroureter and hydronephrosis being the most common defects. One fetus in the 10.40-mg/m^3 group also had fused kidneys with mispositioned ureters and ovaries.

Several anomalies were observed in the ribs, including ribs that were wavy, bulbous, and incompletely ossified, and reduced 13th and rudimentary 14th ribs. The study authors classified most of these anomalies as normal variations based on occurrences in in-house historical controls (one rib anomaly, the appearance of gnarled ribs in a fetus in the 4.73-mg/m^3 group, was considered a malformation). When combined, a statistically significant increase in total rib anomalies was observed in the mid-dose group, compared with controls (see Table D-39). This, however, was primarily due to a high incidence of bulbous ribs in a single litter (eight fetuses in one litter) in this group. Incidence of rib anomalies was not significantly increased in the high-dose group. Statistical analysis between controls and treated groups indicated no significant differences in the incidences of any individual skeletal anomalies. Three other skeletal malformations (in areas other than the ribs) were noted, including a misaligned sacral vertebrae, which was consistent with a filamentous tail, in a fetus in the 4.73-mg/m^3 group; a malformed skull in a 10.40-mg/m^3 group fetus; and a reduced jaw in one control animal. The study authors concluded that the skeletal rib anomalies, although statistically significant at the mid-exposure level, were not an indicator of TPA teratogenicity, citing these as common

anomalies based on in-house historical values, a lack of dose-response, and absence of other signs of embryotoxicity.

In this study, the high-exposure concentration of 10.40 mg/m^3 is a NOAEL for both maternal and fetal effects in female S-D rats exposed by inhalation to TPA particulates for 6 hours/day, 7 days/week on GDs 6−15. LOAEL values are not identified. The TWA concentrations of 0, 0.90, 4.73, and 10.40 mg/m^3 in this study correspond to human equivalent concentrations for extrarespiratory effects (HEC_{ERS}) of 0.59, 2.96, and 6.240 mg/m^3, respectively.[15]

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Table 4A provides an overview of genotoxicity studies of TPA and Table 4B provides an overview of other supporting studies on TPA.

Genotoxicity Studies

The genotoxicity of TPA has been evaluated in a limited number of in vitro and in vivo studies (see Table 4A for more details). The genotoxicity tests for TPA were negative. No mutagenicity was detected in *Salmonella typhimurium* with and without metabolic activation (Lee and Lee, 2007; Lerda, 1996; Brooks et al., 1989; Zeiger et al., 1985; Zeiger et al., 1982; Florin et al., 1980). TPA did not induce clastogenic effects in vitro or in vivo; no chromosomal aberrations (CAs) were observed in Chinese hamster ovary (CHO) cells [Ishidate et al. (1988) as reported in Ball et al. (2012); Lee and Lee (2007)], and there were no increases in micronuclei (MN) in binucleate human lymphocytes (Lerda, 1996) or in bone marrow from ICR mice administered up to 2,100 mg/kg TPA by i.p. injection [Bioreliance (2001) as reported in OECD (2001); Lee and Lee (2007)]. The urinary bladder is a primary target of TPA-induced toxicity. No deoxyribonucleic acid (DNA) damage was detected by comet assays on cells isolated from the bladders of rats exposed to doses as high as 2,000 mg/kg (Kyoya et al., 2018). Finally, there was no evidence of TPA-induced unscheduled DNA synthesis (UDS) in HeLa cells (Lerda, 1996), and no induction of *umu* gene expression, a bacterial operon induced by DNA damage, was observed when incubated with TPA-treated rat liver microsomes and a *S. typhimurium* NM2009 bacterial suspension (Dai et al., 2006b).

[15]HECs were calculated per U.S. EPA (1994) methodology for particulates as follows: 6-hour TWA exposure concentration (mg/m^3) × 6-hour daily exposure period/24 hour × the regional deposited dose ratio (RDDR) for extrarespiratory effects (2.6, 2.5, or 2.4 for the low-, medium-, or high-exposure groups, respectively). RDDR values were calculated by U.S. EPA software using MMAD and body-weight data from the study and assumed values for sigma g (which was not reported in the study) ranging from low (monodisperse) to high (polydisperse). It was found that choice of sigma g had little influence on the RDDR calculation.

Table 4A. Summary of TPA (CASRN 100-21-0) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1538	0−400 µg/plate; 5 doses	−	−	Ames assay. No evidence of mutagenicity in any of the strains tested, with or without S9 activation.	Brooks et al. (1989)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmol/plate	−	−	Preincubation assay. No evidence of mutagenicity or cytotoxicity with or without S9 activation in any of the strains tested.	Florin et al. (1980)
Mutation	*S. typhimurium* TA98, TA100, TA102, TA1535, TA1537	0, 20, 100, 500, 2,500, or 12,500 µM	−	−	Ames assay. No evidence of cytotoxicity or mutagenicity in any of the strains tested, with or without S9 activation.	Lee and Lee (2007)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0, 0.5, 5, 50, 500, 5,000 µg/plate	−	−	Ames assay. No evidence of mutagenicity in any of the strains tested, with or without S9 activation.	Lerda (1996)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	0, 100, 133, 1,000, 3,333, 100,000 µg/plate	−	−	Preincubation assay. No evidence of mutagenicity in any of the strains tested, with or without S9 activation.	Zeiger et al. (1982); Zeiger et al. (1985)
DNA damage (induction of *umu* gene expression)	*S. typhimurium* NM2009 Isolated S-D rat liver microsomes containing TPA and an NADPH-generating system were incubated with the NM2009 bacterial suspension, and *umu* gene expression was measured as the specific galactosidase activity per unit per protein	0.025, 0.05, 0.1 µmol/L	−	−	No dose-related induction of *umu* gene expression was detected with or without phenobarbital, or 3-methylcholanthrene-induced or diet control rat liver microsomes.	Dai et al. (2006b)

Table 4A. Summary of TPA (CASRN 100-21-0) Genotoxicity						
Endpoint	**Test System**	**Doses/ Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**References**
Genotoxicity studies in mammalian cells—in vitro						
CA	CHO cells	0, 20, 100, 500, 2,500, 12,500 µM	−	−	No increase in CA with or without S9 activation. There was no evidence of cytotoxicity.	Lee and Lee (2007)
CA	CHL cells	Up to 2,000 µg/mL or 12 mM	−	−	No increase in CAs without activation using a 48-hr treatment with no recovery.	Ishidate et al. (1988) as reported in Ball et al. (2012)
MN	Binucleate human lymphocytes	0, 0.5, 5, 50, 500 µg/mL	−	ND	No increase in MN/1,000 binucleated cells.	Lerda (1996)
UDS	HeLa heteroploidy human cells	0, 0.5, 5, 50, 500 µg/mL	−	−	No DNA repair was observed with or without activation with hydroxyurea.	Lerda (1996)
Genotoxicity studies—mammalian species in vivo						
MN (bone marrow)	Male ICR mice were administered TPA by single i.p. injection; mice were sacrificed 24 hr after dosing; bone marrow was evaluated for MN	0, 20, 100, 500, 2,500, 12,500 µmol/kg (~0, 3.3, 17, 83, 400, 2,100 mg/kg)	−	NA	The percent of MNPCEs was 0.28% in control and 0.54% average in treated groups. Effects occurred without a dose-response relationship and results were considered negative.	Lee and Lee (2007)
MN (bone marrow)	Male and female ICR mice (5/sex/group) were administered TPA by a single i.p. injection; animals were sacrificed at 24 or 48 hr after dosing; bone marrow was evaluated for MN	0, 200, 400, 800 mg/kg	−	NA	1 high-dose male died and was replaced. No dose-related increases in MN, compared with controls, at 24 hr. At 48 hr, control and high-dose groups had 2 and 8 MN per 20,000 PCEs, respectively. The results were considered negative by the researchers. No differences between males and females were observed.	Bioreliance (2001) as reported in OECD (2001)

Table 4A. Summary of TPA (CASRN 100-21-0) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
DNA damage (comet assay)	Male Wistar or S-D rats were administered TPA by gavage at 3 and 24 hr before sacrifice; cells from the urinary bladder were isolated for a comet assay	0, 500, 1,000, 2,000 mg/kg	–	NA	No significant increases in the average tail length were observed.	Kyoya et al. (2018)

[a]– = negative.

CA = chromosomal aberration; CHL = Chinese hamster lung; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; i.p. = intraperitoneal; MN = micronuclei; MNPCE = micronucleated polychromatic erythrocyte; NA = not applicable; NADPH = reduced form of nicotinamide adenine dinucleotide phosphate; ND = no data; PCE = polychromatic erythrocyte; S-D = Sprague-Dawley; TPA = terephthalic acid; UDS = unscheduled DNA synthesis.

Supporting Toxicity Studies

A number of supporting acute, short-term, subchronic, chronic, and reproductive/developmental studies are summarized in Table 4B. These include inadequately reported studies (primarily from secondary sources), studies that evaluated only one endpoint, studies published in a foreign language with limited English translations, and studies conducted via routes of exposure other than oral or inhalation (e.g., injection). These studies support that the bladder is a target of TPA toxicity. Studies that evaluated only a single endpoint were not considered as principal studies for the derivation of provisional reference values given the availability of comprehensive studies that evaluated multiple endpoints for *p*-phthalic acid.

Table 4B. Other TPA (CASRN 100-21-0) Studies				
Test[a]	**Materials and Methods[b, c]**	**Results**	**Conclusions**	**References**
Supporting evidence—noncancer effects in animals following oral exposure				
Acute	Male and female S-D rats (5/sex) received a single oral dose of 5,000 mg/kg TPA in water by gavage and were observed for 14 d. Endpoints evaluated included clinical signs, body weights, and gross necropsy.	No deaths were noted. Within 48 hr of dosing, all animals exhibited diarrhea. Redness around the nose occurred in 3/5 males and 2/5 females. Increased mean body weights were reported (data not shown).	Rat LD_{50}: >5,000 mg/kg.	Amoco Corporation (1990) as cited in OECD (2001)
Acute	Rat (no other details provided).	ND	Rat LD_{50}: >15,300 mg/kg.	Amoco Corporation (1975) as cited in OECD (2001)
Acute	10−20 F Wistar rats were given TPA via gavage to determine the LD_{50}.	ND	Rat LD_{50} = 1,960 mg/kg.	Cauiolle et al. (1991) as cited in OECD (2001)
Acute	Rat; acute lethality study.	ND	Rat LD_{50} = 18,800 mg/kg.	NIOSH (1985) as cited in U.S. EPA (1986)
Acute	30 F Swiss albino mice were administered by gavage suspensions of 10 and 20% TPA in 0.5% sodium carboxymethylcellulose solution to determine the LD_{50}.	Animals that died did so within 48 hr of treatment. Surviving animals had no abnormal behavior except lethargy.	Mouse LD_{50}: >5,000 mg/kg.	Hoshi et al. (1968)
Acute	Swiss mouse; acute lethality study.	ND	Mouse LD_{50}: 1,470 mg/kg.	BG Chemie (1990) as cited in MAK-Commission (2012)
Acute	Male S-D rats were administered 2 doses (at 21-hr intervals) of 0 or 2,000 mg/kg TPA via gavage. 2 animals were sacrificed at 3, 6, and 9 hr after the final dose (controls sacrificed at 6 hr only). Endpoints evaluated included mortality, clinical signs, body weight, and scanning electron microscopy analysis of bladder tissues.	Micro crystals were observed in the bladder 6 and 9 hr after dosing (4/6 animals). Raised ridges (1/6) and pleated surfaces was visible in the bladder epithelium 9 hr after dosing.	TPA induced formation of microcrystals and changes to the bladder epithelium within 6−9 hr of acute gavage exposure to 2,000 mg/kg.	Kyoya and Terada (2018)

Table 4B. Other TPA (CASRN 100-21-0) Studies

Test[a]	Materials and Methods[b, c]	Results	Conclusions	References
Subchronic	Male and female Wistar rats (number/group NS) were administered 0 or 5% TPA in the diet for 1 wk, followed by 3% dietary TPA through Exposure D 90 [~1,400 and 1,700 mg/kg-d for males and females, respectively, as reported in Ball et al. (2012)].	Increased incidence of bladder calculi in 11/18 males and 3/19 females. Moderate to mild transitional cell hyperplasia in 13/18 males and 3/19 females.	TPA was reported to induce calculi and hyperplasia in the bladder by subchronic dietary exposure. Primary study report not available.	Amoco Corporation (1972) as cited in OECD (2001); Ball et al. (2012)
Subchronic	S-D rats (17−18 M or F/group) received 0, 50, 500, or 5,000 mg/kg-d TPA in the diet for 90 d.	Incidences in the bladder at 0, 50, 500, and 5,000 mg/kg-d, respectively: Simple hyperplasia: 1/18, 10/17, 5/18, 7/17; Atypical hyperplasia: 0/18, 0/17, 10/18, 5/17; Calculi: 0/18, 0/17, 2/18, 10/17; Transitional cancer: 0/18, 0/17, 0/18, 4/17.	TPA was reported to induce calculi, hyperplasia and cancer in the bladder by subchronic dietary exposure. Primary study report not available.	Qi et al. (2002) foreign language study as cited in MAK-Commission (2012)
Chronic	Albino rats (30/sex/group; strain NS) were fed 0, 0.05, 0.16, 0.50, 1.5, or 5% TPA in the diet for 15 wk. Treatments correspond to approximately 0, 37.9, 122, 393, 1,220, and 3,837 mg/kg-d in males and 0, 46, 147, 447, 1,456, and 4,523 mg/kg-d in females.	Significant increases in bladder calculi (9/17 males), chronic inflammation, and proliferative hyperplasia. Males were more affected than females.	TPA was reported to induce calculi, inflammation, and hyperplasia in the bladder by subchronic dietary exposure. Primary study report not available. Reliability was decreased because of the age of the study, according to OECD (2001).	Amoco Corporation (1970) as cited in OECD (2001)
Chronic	F344 rats (4 F/group) were fed diets containing 0, 0.5, 2, or 5% TPA in the diet (~0, 565, 2,260, and 5,650 mg/kg-d) for 6 mo.	A decrease in urinary pH and significant changes in urinary electrolytes were observed in all dose groups. Two high-dose females developed calculi in the bladder; the incidence was not significant.	TPA was reported to produce low incidence of calculi in the bladder by 6-mo dietary exposure. Primary study report not available.	Heck (1979)

Table 4B. Other TPA (CASRN 100-21-0) Studies				
Test[a]	**Materials and Methods[b, c]**	**Results**	**Conclusions**	**References**
Supporting evidence—reproduction and development effects in animals following oral exposure				
Gestational/ lactational/feeding exposure of pups	Gravid F344 rats (5−7/group) were administered 0, 0.5, or 5% TPA in the diet (~0, 560, or 4,700 mg/kg-d) from GD 7 through parturition and weaning. A separate group of 4 dams received 5% (~4,700 mg/kg-d) TPA from PND 1 through weaning. Pups were sacrificed starting on PND 5 and continuing every 5 d until PND 45.	No calculi were seen in pups of any group during lactation (i.e., up to PND 20). From PND 25−45, when pups were self-feeding, a high incidence of calculi was found in pups of both 5% TPA groups (similar incidence in both). No calculi occurred in pups from the control or low-dose groups. No calculi were found in dams.	Appearance of calculi coincided with onset of self-feeding. Weanling rats were susceptible to calculus formation only when TPA is ingested at high concentrations in the diet. Transport of TPA to the fetus by the placenta or through the milk is insufficient to induce calculi. Incidence of bladder calculi was the only endpoint evaluated.	Wolkowski-Tyl et al. (1982)
Gestational/ lactational/feeding exposure of pups	Pregnant F344 rats (7 controls and 5 treated) were administered 0 or 5% TPA (~4,700 mg/kg-d) in the diet beginning on GD 7 for up to 54 d. 1 dam/group was sacrificed on GDs 18 and 20; the remaining dams were allowed to litter and were sacrificed on PND 35.	Increased pup mortality compared with controls (14% mortality by PND 2). Pups exposed in utero and through lactation to PND 35 had high incidences of calculi in urinary tract tissues. Pup weight was also reduced.	TPA was reported to induce calculi in pup, increase pup mortality, and decrease pup weight. Primary study report not available.	Heck (1979)

Table 4B. Other TPA (CASRN 100-21-0) Studies

Test[a]	Materials and Methods[b, c]	Results	Conclusions	References
Multigeneration reproduction study	Alpk:AP$_f$SD (Wistar derived) breeding pairs (26 M and 26 F/group) were fed diets containing 0, 1,000, 5,000, or 20,000 ppm TPA from 10 wk prior to mating through weaning F_1 litters. Exposure and breeding were repeated to generate the F_2 generation. Treatments were equivalent to 0, 92.2, 461, and 1,840 mg/kg-d for males, and 0, 103, 513, and 2,050 mg/kg-d for females.	Decreased F_0 and F_1 parental body weights at high dose; decreased absolute and relative kidney weights in males and increased relative male and female liver weights in both generations. Bladder changes in high-dose males and females were greater in F_1 than in F_0. No effects on any reproductive endpoints including sperm number, motility, or morphology. Developmental effects include decreased anogenital distance in high-dose F_1 and F_2 females and delayed preputial separation in mid- and high-dose males. These were considered to be related to decreased pup body weights.	TPA was reported to affect pup body weights and developmental milestones. Primary study report not available.	Milburn (2003)
1-generation reproduction study	Male and female C3H/He mice (numbers NS) were fed a control diet or a diet containing 0.5% TPA from weaning, through mating, to death.	No treatment effects on the estrous cycle, growth during premating and between mating and parturition, litter size, average body weight of pups at birth or on PNDs 12 and 20, or on pup growth and rearing rates were observed (data were not shown).	TPA was reported not to affect reproduction in mice. The study was available only as an abstract. Primary study report not available.	Nagasawa and Fujimoto (1973)
Supporting evidence—noncancer effects in humans following inhalation exposure				
Occupational	Industrial hygiene study in workers of a chemical fiber factory (further details not available). Endpoints evaluated: liver and kidney function.	Regression analysis indicated that liver and renal injury (based on serum and urine analysis) correlated with exposure to TPA after adjustment for multiple confounding factors.	TPA was reported to affect serum biomarkers for liver and kidney injury in exposed workers. This is a foreign language study with an English abstract. Primary study report not available in English.	Yao et al. (2002)

Table 4B. Other TPA (CASRN 100-21-0) Studies

Test[a]	Materials and Methods[b, c]	Results	Conclusions	References
Supporting evidence—noncancer effects in animals following inhalation exposure				
Acute	Male and female S-D rats (5/sex) were exposed to 2.02 mg/L TPA as a particulate for 2 hr, and were observed for 14 d. Endpoints evaluated included mortality, clinical signs, body weights, and gross necropsy.	No deaths occurred. Clinical signs included diarrhea, redness around the nose, and discolored fur. Increased mean body weights were described (data not shown). 1 male had dark lungs; enlarged mandibular lymph nodes occurred in 1 male and 1 female.	Rat LC_{50}: >2.02 mg/L (>2,020 mg/m^3).	Amoco Corporation (1987) as cited in OECD (2001) and MAK-Commission (2012)
Acute	Male F344 rats (12/group) were exposed nose only to 0, 55.0, 109.0, or 235.0 mg/m^3 for 30 min. Sacrifices were done 24 hr and 14 d postexposure. Rats were evaluated for clinical signs and signs of pulmonary toxicity.	No treatment-related effects were observed.	TPA was reported not to have produced any effects in this acute inhalation study.	Thomson et al. (1988)
Acute	Male rats (10/group; strain NS) were exposed nose only to target TPA concentrations of 30, 100, or 1,000 mg/m^3 for 4 hr.	No treatment-related abnormalities were observed.	TPA was reported not to have produced any effects in this acute inhalation study. Primary study report not available.	ICI Internal Report CTL/R/909 (1987) as cited in OECD (2001)
Short term	Male rats (number and strain NS) were exposed to 21.5 mg/m^3 TPA by inhalation for 6 hr/d, 5 d/wk, for 4 wk (continuous concentration ~3.8 mg/m^3).	No deaths were recorded, and no signs of toxicity or gross pathological changes were noted. Histopathology was not conducted.	TPA was reported not to have produced any effects in this short-term inhalation study. Primary study report not available.	Amoco Corporation (1973) as cited in OECD (2001)
Short term	Male and female rats (number and strain NS) were exposed by inhalation to 0, 0.52, 1.2, or 3.3 mg/m^3 TPA for 6 hr/d for 4 wk (continuous concentration of ~0.13, 0.3, or 0.83 mg/m^3).	No exposure-related deaths, clinical chemistry, hematology, body, or organ weight changes were observed. Tracheal epithelial lining degeneration occurred in 19/20 high-exposure rats, compared with 1/20 controls. Incidences of trachea epithelial lining degeneration occurred in 5, 30, 65, and 95% of animals at 0, 0.52, 1.3, and 3.3 mg/m^3, respectively.	TPA was reported to produce degeneration of the tracheal epithelial lining in this short-term inhalation study. Primary study report not available.	Amoco Corporation (1973) and Jernigan et al. (1988) as cited in OECD (2001)

Table 4B. Other TPA (CASRN 100-21-0) Studies

Test[a]	Materials and Methods[b, c]	Results	Conclusions	References
Short term	Male and female S-D rats (10/sex/group) were exposed to TPA aerosol concentrations of 0, 1, 3, or 10 mg/m^3 nose only for 28 d.	No clinical signs or effects on body weight, food or water intake, eyes, locomotor activity, grip strength, righting reflex, body temperature, hematology, serum chemistry, urinalysis, organ weights, or gross or histological pathology, including the lung, larynx, trachea, and nasal tissues.	TPA was reported not to have produced any effects in this apparently comprehensive short-term inhalation study. Primary study report not available.	Plastics Europe (2008) as cited in MAK-Commission (2015)
Chronic	Male S-D rats and Hartley guinea pigs were exposed by inhalation to TPA dusts (10 mg/m^3, "respirable" dust concentration 5 mg/m^3) for 6 hr/d, 5 d/wk for 6 mo.	No effects on body weight, organ (lung, liver, kidney, or spleen) weights, clinical chemistry, or urinalysis. No gross or histological changes outside of normal limits were described.	TPA was reported not to have produced any effects in this 6-mo inhalation study. Primary study report not available.	Lewis et al. (1982) as cited in OECD (2001); Heck and Tyl (1985)

Table 4B. Other TPA (CASRN 100-21-0) Studies				
Test[a]	**Materials and Methods[b, c]**	**Results**	**Conclusions**	**References**
Supporting evidence—noncancer effects in animals following other exposure routes				
Acute (i.p)	Male and female rat; acute lethality study.	ND	Rat LD_{50} = 1,210 mg/kg (F) and 2,250 mg/kg (M).	BG Chemie (1990) as cited in MAK-Commission (2012)
Acute (i.p)	Mouse; acute lethality study.	ND	Mouse LD_{50} = 880−1,900 mg/kg.	BG Chemie (1990) as cited in MAK-Commission (2012)
One-generation reproduction study (i.p.)	Female CF1 mice were dosed via i.p. injection with 0, 20, 50, or 100 mg/kg-d TPA for a total of 6 wk (3 wk prior to mating and 3 wk during mating). Endpoints evaluated included percent pregnancy, number of live births, deaths, and birth weights. Pup weights, percent survival, and sex were measured 3 wk after birth. Histological analysis of kidney, liver, and spleen was done in dams.	No effects on fertility, reproduction, or pup growth were observed. Pup survival (number/litter) was reduced at 50 mg/kg-d (5.59 vs. 9.20 in controls), but not at the higher dose.	TPA was reported not to have affected reproduction or pup growth.	Hall et al. (1993)

[a]Acute = exposure for ≤24 hours; short term = repeated exposure for >24 hours ≤30 days; subchronic = repeated exposure for >30 days ≤10% lifespan (>30 days up to approximately 90 days in typically used laboratory animal species); chronic = repeated exposure for >10% lifespan for humans (more than approximately 90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]When doses in mg/kg-day were not provided, reported dietary intakes (% TPA in food) were converted to ADDs (mg/kg-day) using the following equation: ADD = [TPA (mg/kg food) × food intake (kg food/day)] ÷ BW (kg) using appropriate reference body-weight and food-intake values (U.S. EPA, 1988).
[c]When applicable, reported exposure concentrations were converted to continuous concentrations using the following equation: exposure concentration (mg/m^3) × hours/day × days/week.

ADD = adjusted daily dose; BW = body weight; F = female(s); GD = gestation day; i.p. = intraperitoneal; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; M = males(s); ND = no data; NS = not specified; PND = postnatal day; S-D = Sprague-Dawley; TPA = terephthalic acid.

Acute oral lethality studies with TPA reported median lethal dose (LD_{50}) values ranging from 1,960−18,800 mg/kg in rats [Cajolle et al. (1991) and Amoco Corporation (1975, 1990) as cited in OECD (2001); NIOSH (1985) as cited in U.S. EPA (1986)], and from 1,470−>5,000 mg/kg in mice [BG Chemie (1990) as cited in MAK-Commission (2012); Hoshi et al. (1968)]. Deaths typically occurred within 48 hours of exposure. A single inhalation lethality study in rats reported in a median lethal concentration (LC_{50}) of >2,020 mg/m^3 [Amoco Corporation as cited in MAK-Commission (2012); OECD (2001)]. Additional acute inhalation studies reported no effects. Reported LD_{50} values by i.p. injection were 1,210 and 2,250 mg/kg in rats and between 880 and 1,900 mg/kg in mice.

Several supporting animal studies evaluated bladder effects after oral exposure. A two-dose acute exposure by gavage showed the formation of microcrystals in the bladder starting as early as 6 hours after dosing (Kyoya and Terada, 2018). Calculi in the bladder were observed in weanling F344 rats fed 5% TPA, but not 0.5% TPA, in the diet from weaning to PND 45 (Wolkowski-Tyl et al., 1982), and after 90 days of 5% TPA exposure (~3,680−4,210 mg/kg-day) in feed, incidences of hyperplasia, in conjunction with calculi, were reported in male and female Wistar rats, with males appearing to be more sensitive [Amoco Corporation (1972) as cited in Ball et al. (2012); OECD (2001)]. Similar findings were reported in a foreign language study [Qi et al. (2002) as summarized in MAK-Commission (2012)] in a 90-day feeding study in S-D rats. Calculi and atypical hyperplasia in the bladder occurred at 500 mg/kg-day; simple hyperplasia did occur at a lower dose (50 mg/kg-day), but in the absence of visible calculi. At the highest dose (5,000 mg/kg-day), 4/17 animals were reported to have transitional epithelial cancer [Qi et al. (2002) as cited in MAK-Commission (2012)]. Highlighting the fact that females may be less sensitive to TPA-induced bladder effects, Heck (1979) found only two individuals with bladder calculi in female F344 rats administered 5% TPA (~5,650 mg/kg-day) for 6 months in the diet, and [Amoco Corporation (1970) as cited in OECD (2001)] also noted that males rats were more affected than females in a 15-week feeding study.

A few supporting studies evaluated the potential effects of TPA on reproduction and development. Evidence indicates that TPA administered either orally, or by i.p. injection, does not affect female reproductive endpoints in mice (Hall et al., 1993; Nagasawa and Fujimoto, 1973) or rats (Milburn, 2003; Heck, 1979). However, Milburn, (2003) and Heck (1979) did report TPA-decreased pup weights, supporting the findings from Ledoux and Reel (1982). An abstract by Nagasawa and Fujimoto (1973) indicates that 0.5% dietary TPA from weaning to 16 months-of-age caused no changes to the pattern of estrous cycle, growth during the virginial stage, or the interval between mating and parturition, and no changes in litter size, the average weight of pups at birth and PNDs 12 and 20, or in pup growth and rearing rates, compared with controls. Six weeks of i.p. injections of up to 100 mg/kg-day also had no impact on fertility, reproduction, or pup growth; limited details suggest pup survival may have been reduced (Hall et al., 1993). Both Heck (1979) and Wolkowski-Tyl et al. (1982) looked at calculi formation in rats exposed during different developmental stages. Both studies indicate that exposure in utero, or in utero through lactation, does not lead to calculi formation in offspring. Bladder calculi were only observed once pups began self-feeding.

A number of inhalation studies, all with extremely limited details, were summarized in OECD (2001). One study indicated incidence of degeneration of the tracheal epithelial lining in rats exposed to 3.3 mg/m^3, 6 hours/day, for 4 weeks [Amoco Corporation (1973) and Jernigan et al. (1988) as cited in OECD (2001)]. The remaining studies reported no exposure-related effects

[Amoco Corporation (1973), Lewis et al. (1982), and ICI Internal Report CTL/R/909 (1989) all as cited in OECD (2001)]. A seemingly comprehensive study of rats exposed to TPA aerosols at up to 10 mg/m^3 for 28 days found no lesions in the trachea or other respiratory tissues and no systemic effects, but only a brief summary was located [Plastics Europe (2008) as cited in MAK-Commission (2015)].

Absorption, Distribution, Metabolism, and Excretion Studies

Based on excretion in urine and feces, it is estimated that ~97% of TPA administered orally is rapidly absorbed by the gastrointestinal (GI) tract (Hoshi and Kuretani, 1967). Following oral exposure via gavage in rats, approximately 64% of administered TPA remained in the stomach, small intestine, caecum, and to a lesser degree, in the large intestine 2 hours after exposure. TPA was no longer detectable by 24 hours after exposure (Hoshi and Kuretani, 1967). A single dermal 5-hour application in rats resulted in negligible absorption; repeated dermal dosing resulted in recovery of ~13% of the administered dose, indicating that some absorption through the skin did occur (Moffitt et al., 1975). Similarly, a longer ocular exposure (24 hours) in rabbits yielded a 37% recovery, indicating some absorption through ocular tissues (Moffitt et al., 1975).

Distribution is rapid following oral exposure, with a blood distribution half-life of 2.43−3.4 hours in rats and 27 hours in rabbits [Hoshi et al. (1966) as cited in Ball et al. (2012)]. Estimated half-lives are notably shorter after intravenous (i.v.) dosing; the computer-estimated value for terminal TPA half-life was 1.2 hours in rats following an i.v. injection, suggesting that GI absorption has some rate-limited effect (Wolkowski-Tyl et al., 1982). Plasma clearance was approximately equal to glomerular filtration rate, with the highest concentrations of TPA in urine occurring within hours of exposure (Wolkowski-Tyl et al., 1982). TPA is transported through the placenta in pregnant rats and distributed into fetal tissues; radioactivity was tracked through the placenta, to the fetus, and then to amniotic fluid. Similar to dams, radioactivity in fetuses was highest in the bladder, with a half-life in the fetal bladder of approximately 3 hours. However, TPA concentrations in fetal tissues were approximately two orders of magnitude lower than in dams, indicating that in utero exposure levels are likely to be low (Wolkowski-Tyl et al., 1982). Some distribution has also been noted in other tissues, primarily the liver and kidney in rats either fed diets containing 0.5% TPA or given a single oral dose, but the TPA is rapidly excreted and does not accumulate (Hoshi and Kuretani, 1968).

Studies on TPA metabolism found only the parent TPA compound present in the urine in rats dosed either orally or via i.v. injections, indicating that TPA is not metabolized (Wolkowski-Tyl et al., 1982; Heck, 1979; Hoshi and Kuretani, 1967). Another study in chickens where TPA was infused into the renal portal also failed to identify any TPA metabolites (Tremaine and Quebbemann, 1985).

Rapid elimination of unchanged TPA given orally, or by i.v. injection, has been described above. In rats gavaged with 85 mg/kg radioactive TPA, 93.8 and 3.3% of the dose was excreted in urine and feces, respectively (Hoshi and Kuretani, 1967). Similar recovery levels were described by Moffitt et al. (1975). In both studies, near 100% elimination was evident within 48 hours of dosing.

No information on absorption, distribution, metabolism, or excretion (ADME) following inhalation of TPA has been identified.

Mode-of-Action/Mechanistic Studies

Bladder calculi associated with TPA exposure were hypothesized to be the primary cause of urinary tract irritation, lesions, and regenerative cell proliferation that could eventually lead to tumors in the bladder (Cohen et al., 2002; Heck and Tyl, 1985). Several researchers have focused their attention on the physical characteristics of bladder calculi in TPA exposed rodents, and the mechanisms of TPA-induced calculi formation (Cui et al., 2006a; Dai et al., 2005a; Dai et al., 2005c; Heck and Tyl, 1985; Chin et al., 1981; Heck, 1981; Heck, 1979). Heck (1979) and Chin et al. (1981) studied the composition of TPA-induced bladder calculi, identifying calcium terephthalate (Ca-TPA) as the principal component, particularly in weanling rats. Heck (1981) studied the equilibria and concentrations of components required for calculus formation, as well as the solubility properties of Ca-TPA. Results from this study indicate that a urinary concentration of approximately 100 mM TPA is required to induce calculi formation, but that other kinetic factors influence the speed of calculus formation once saturation is reached. Extrapolating to humans, Heck (1979) estimated that an 8-mM concentration of TPA would be required to saturate a human urine sample, which the study author calculated to require an exposure of 2.4 g of TPA/day. Hypercalciuria and aciduria were also determined to be necessary, but not sufficient, for TPA-induced calculi (Wolkowski-Tyl and Chin, 1983).

Other studies focused on downstream mechanisms occurring once calculi were formed that could potentially lead to tumor formation. Hyperplastic bladder lesions in TPA-treated rats had positive indices for PCNA (Cui et al., 2006b); the lesions also showed increases in positive indices for cyclin D1 and CDk4. Importantly, none of the transitional cell carcinoma (TCC) tumors that formed had detectable mutations in the *K-ras* and *H-ras* genes, providing support that TPA exposure may lead to changes in components of the anti-oncogenic Rb pathway (Cui et al., 2006b). The same study authors also performed proteomics on normal bladder tissues and TPA-induced TCCs to identify potential proteins that may be involved in TPA-induced tumorigenesis (Cui et al., 2007). They found an elevation in prostaglandin E_2 (PGE_2), which is known to be involved in carcinogenesis, in TPA-TCC tissues (Shi et al., 2006).

DERIVATION OF PROVISIONAL VALUES

DERIVATION OF PROVISIONAL ORAL REFERENCE DOSES

Derivation of a Subchronic Provisional Reference Dose

The database of potentially relevant studies for deriving an oral subchronic reference value for TPA includes several oral feeding studies in rats (Dai et al., 2006a; Dai et al., 2005c; Cui et al., 2004; Ledoux and Reel, 1982; Dupont Chem Co, 1955). Collectively, these studies identify the urinary tract, and in particular the bladder, as a target of TPA toxicity, as indicated most notably by increased incidences of bladder calculi and associated urinary tract histopathology. Decreased body weight was also reported in several studies, both in adults and in pups exposed in utero and via lactation. There is limited evidence for an effect on sperm count, motility, and ultrastructure in two studies (Kwack and Lee, 2015; Cui et al., 2004). Single- or multiple-generation reproduction studies (Milburn, 2003; Hall et al., 1993; Ledoux and Reel, 1982) however, did not report a change in fertility following TPA treatment. The interpretation of the observed changes is unclear, because of the small number of studies that reported TPA-induced sperm effects and the lack of consistency across studies. The sperm motility endpoint is not considered further as the critical effect.

The most sensitive, potential POD for bladder effects is a NOAEL (ADD) of 906 mg/kg-day for increased incidence of bladder calculi in male rats [Dai et al. (2005c); see Table D-12]. The NOAEL (ADD) of 197 mg/kg-day for increased incidence of white sediment in the urine in female rats (Dai et al., 2005c) is lower than the NOAEL for bladder calculi in male rats from the same study, but the biological relevance of the sediment effect is unclear. As discussed previously, there is an inconsistent cause–effect relationship between precipitates, calculi and hyperplastic lesions.

For effects on body weight, the most sensitive, potential PODs were in Wistar and CD rat pups in the developmental portion of the Ledoux and Reel (1982) study (see Table D-34). In Wistar rats, a NOAEL (ADD) of 313 mg/kg-day is identified for biologically significant (≥5%), decreased pup weight on PND 21. In CD rats, a LOAEL (ADD) of 17.6 mg/kg-day is identified for biologically significant (≥5%), decreased pup weight on PND 21.

To provide a common basis for comparing potential points of departure (PODs) and critical effects for deriving a subchronic p-RfD for TPA, data sets representing the most sensitive endpoints (i.e., bladder effects and pup weight effects) were selected for benchmark dose (BMD) analysis. All available continuous or dichotomous-variable models in the Benchmark Dose Software (BMDS, Version 2.7) were fit to the data sets for the most sensitive endpoints. Appendix E contains details of the modeling results for these data sets. The HED, in mg/kg-day, was used as the dose metric. The standard reporting benchmark response (BMR) of 10% extra risk for bladder incidence data was used. The BMR for decreased fetal body weight used was 5% RD change from control means, which is considered a biologically significant response for developmental aged animals. The incidence data for bladder calculi from Dai et al. (2005c) were not amenable to modeling because the lesions were seen only at the highest dose (see Table D-12). For decreased pup weight in Wistar and CD rats (Ledoux and Reel, 1982), one or more available BMD models provided adequate fit to the data. Candidate PODs are presented in Table 5.

In U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, U.S. EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for deriving an oral reference dose (RfD) under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite, but not for portal-of-entry effects. A validated human physiologically based toxicokinetic model for TPA is not available for use in extrapolating doses from animals to humans. Furthermore, the most sensitive endpoints being considered are not portal-of-entry effects and TPA does not readily metabolize. Therefore, scaling by $BW^{3/4}$ is relevant for deriving HEDs for the considered effects.

Following U.S. EPA (2011b) guidance, the doses administered resulting in the most sensitive endpoints are converted to an HED through application of a dosimetric adjustment factor (DAF) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Study-specific body weight is used to calculate the DAF for each dose group (U.S. EPA, 2011b). Calculated HEDs are presented in Table D-12 for male rats exposed subchronically to TPA (Dai et al., 2005c) and Table D-34 for female rats exposed to TPA during pregnancy (Ledoux and Reel, 1982).

Table 5. Candidate PODs in Rats Administered TPA for the Derivation of the Subchronic p-RfD

Endpoint	POD (HED) (mg/kg-d)
Dai et al. (2005c)	
Increased bladder calculi in males	220 (NOAEL)[b]
Ledoux and Reel (1982)	
Decreased pup weight in combined sexes in Wistar rats at PND 21	59.9 ($BMDL_{05}$)
Decreased pup weight in male Wistar rats at PND 21	58.8 ($BMDL_{05}$)
Decreased pup weight in female Wistar rats at PND 21	61.8 ($BMDL_{05}$)
Decreased pup weight in combined sexes in CD rats at PND 21	55.5 ($BMDL_{05}$)
Decreased pup weight in male CD rats at PND 21	54.6 ($BMDL_{05}$)
Decreased pup weight in female CD rats at PND 21	54.4 ($BMDL_{05}$)

[a]Modeling results are described in more detail in Appendix E.
[b]Data were not amenable to BMD modeling.

BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NDr = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; POD = point of departure; p-RfD = provisional reference dose; TPA = terephthalic acid.

Among all the sensitive endpoints evaluated, the lowest POD (HED) following oral exposure to TPA is for decreased pup weight in female CD rats (Ledoux and Reel, 1982). The $BMDL_{05}$ (HED) of 54.4 mg/kg-day for decreased pup weight is expected to be protective of all developmental effects during a susceptible life stage, as well as any systemic effects (e.g., bladder calculi observed following subchronic TPA exposure). The choice of decreased pup weight as the critical effect is supported by observations of TPA-induced pup weight effects in other studies [i.e., Milburn (2003); Heck (1979)] and in two rat strains (i.e., Wistar and CD rats) from the Ledoux and Reel (1982) study. In summary, the Ledoux and Reel (1982) study is selected as the principal study because it identified the most sensitive POD and was adequate in its experimental design and protocol. However, because the study is not peer reviewed, a screening-level subchronic p-RfD is derived for TPA in Appendix C, in lieu of a subchronic p-RfD.

Derivation of a Chronic Provisional Reference Dose

Chronic oral studies on TPA are limited to a group of papers published on a 48-week study in rats that are primarily mechanistic in nature and a 22-week study in rats (Cui et al., 2006a). There were also two, unpublished, non-peer-reviewed 2-year studies in rats (Preache, 1983; Grubbs, 1979; Gross, 1977). In addition to the aforementioned chronic studies, the developmental/reproductive study from Ledoux and Reel (1982) is also considered relevant to the derivation of the chronic p-RfD.

The 48-week study (Cui et al., 2007; Cui et al., 2006b; Shi et al., 2006) evaluated a single exposure dose and reported on limited endpoints. Given the availability of more comprehensive studies that evaluated multiple effects at various doses, the 48-week study (Cui et al., 2007; Cui

et al., 2006b; Shi et al., 2006) was not considered for deriving the chronic p-RfD. In addition, the 2-year study (Preache, 1983; Grubbs, 1979) in rats conducted by the ITT was not considered further because of experimental issues described above (e.g., dosing uncertainty). The remaining two studies in the chronic TPA database (Cui et al., 2006a; Gross, 1977) were considered adequate for deriving a chronic p-RfD. A NOAEL (ADD) and LOAEL (ADD) of 829 and 4,280 mg/kg-day, respectively, were identified for increased bladder hyperplasia, increased bladder weight, and decreased body weight in male Wistar rats exposed to TPA in the diet for 22 weeks (Cui et al., 2006a). In the 2-year feeding study by Gross (1977), urinary tract effects (calculi, nephropathy, increased blood urea levels) were seen only at the high dose in both sexes (3,680−4,210 mg/kg-day) of Wistar rats; the most sensitive effect was decreased body weight in male rats, which defines a LOAEL and a NOAEL of 1,470 (ADD) and 736 mg/kg-day (ADD), respectively. In the developmental portion of the Ledoux and Reel (1982) study (see Table D-34) as discussed above, a NOAEL (ADD) of 313 mg/kg-day is identified for biologically significantly (≥5%) decreased pup weight on PND 21 in Wistar rats. In CD rats, a LOAEL (ADD) of 17.6 mg/kg-day is identified for biologically significantly (≥5%) decreased pup weight on PND 21.

Following U.S. EPA (2011b) guidance, the doses administered resulting in the most sensitive endpoints are converted to an HED through application of a DAF derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Calculated HEDs are presented in Tables D-18 and D-23 for male rats exposed chronically to TPA (Cui et al., 2006a; Gross, 1977) and Table D-34 for female rats exposed to TPA during pregnancy (Ledoux and Reel, 1982).

To provide a common basis for comparing potential points of departure (PODs) and critical effects for deriving a chronic p-RfD for TPA, data sets representing the most sensitive endpoints were selected for benchmark dose (BMD) analysis. Data for simple hyperplasia from Cui et al. (2006a) were suitable for modeling, which was performed using the available dichotomous models in U.S. EPA's Benchmark Dose Software (BMDS; Version 2.7). HEDs were used as the dose metric. The standard reporting benchmark response (BMR) of 10% extra risk for incidence data was used. Other sensitive endpoints in the Cui et al. (2006a) study (i.e., reduced body weight and increased absolute and relative bladder weights) could not be modeled because the type of variance data shown in the study report was not identified. For decreased body weight observed in the 2-year feeding study in male and female Wistar rats (Gross, 1977), a benchmark response (BMR) of 10% relative deviation (RD) was used because a 10% change in body weight for adult animals is generally considered to be biologically significant. The BMR for decreased fetal body weight used was 5% RD change from control means, which is considered a biologically significant response in developmentally aged animals. For decreased pup weight in Wistar and CD rats (Ledoux and Reel, 1982) and decreased body weight in adult Wistar rats (Gross, 1977), one or more available BMD models provided adequate fit to the data as described above. Candidate PODs are presented in Table 6.

Table 6. Candidate PODs in Rats Administered TPA for the Derivation of the Chronic p-RfD[a]

Endpoint	POD (HED) (mg/kg-d)
Cui et al. (2006a)	
Increased bladder hyperplasia in males	95.0 ($BMDL_{10}$)
Decreased body weight in males	196 (NOAEL)[b]
Increased absolute bladder weight in males	196 (NOAEL)[b]
Increased relative bladder weight in males	196 (NOAEL)[b]
Gross (1977)	
Decreased body weight in males	373 ($BMDL_{10}$)
Ledoux and Reel (1982)	
Decreased pup weight in combined sexes in Wistar rats at PND 21	59.9 ($BMDL_{05}$)
Decreased pup weight in male Wistar rats at PND 21	58.8 ($BMDL_{05}$)
Decreased pup weight in female Wistar rats at PND 21	61.8 ($BMDL_{05}$)
Decreased pup weight in combined sexes in CD rats at PND 21	55.5 ($BMDL_{05}$)
Decreased pup weight in male CD rats at PND 21	54.6 ($BMDL_{05}$)
Decreased pup weight in female CD rats at PND 21	54.4 ($BMDL_{05}$)

[a]Modeling results are described in more detail in Appendix E.
[b]Data could not be BMD modeled because the type of variance data shown in the study report was not identified.

BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NDr = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; POD = point of departure; p-RfD = provisional reference dose; TPA = terephthalic acid.

When the BMD results in Table 6 are compared, the lowest POD (HED) is for decreased pup weight in female CD rats (Ledoux and Reel, 1982). The $BMDL_{05}$ (HED) of 54.4 mg/kg-day for decreased pup weight in female CD rats is expected to be protective of all developmental effects during a susceptible life stage, as well as any potential systemic effects observed following chronic TPA exposure. However, because the Ledoux and Reel (1982) study is not peer reviewed, a screening-level chronic p-RfD is derived for TPA in Appendix C, in lieu of a chronic p-RfD.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The database of inhalation studies on TPA is inadequate for deriving a provisional reference concentration (p-RfC). Available inhalation studies on TPA are limited to an unpublished, non-peer-reviewed developmental toxicity study in rats, which reported no maternal or fetal effects at the exposure levels tested (Chemical Manufacturers Association, 2000). There are a number of other inhalation studies but they were not available for independent review and are only briefly cited in various secondary sources (MAK-Commission, 2015; Ball et al., 2012; MAK-Commission, 2012; OECD, 2001). These studies also only tested a single exposure (MAK-Commission, 2012), and thus can only be considered as supporting. Most of these studies report no effects (see Table 4B). The short duration of exposure in the

Chemical Manufacturers Association (2000) study (i.e., 9 days) makes extrapolation to subchronic or chronic durations highly uncertain, particularly because no effects were seen at the high dose, even though the exposures are in a sensitive life stage. It is unclear whether the selection of the highest concentration from the Chemical Manufacturers Association (2000) study to derive p-RfCs would be protective of toxicity following long-term exposure to TPA. Given this uncertainty, derivation of p-RfCs or screening p-RfCs is precluded.

Table 7 summarizes the subchronic and chronic values derived for TPA.

Table 7. Summary of Noncancer Reference Values for TPA (CASRN 100-21-0)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	CD Rat/F	Decreased pup weight	5×10^{-1}	$BMDL_{05}$	54.4	100	Ledoux and Reel (1982)
Screening chronic p-RfD (mg/kg-d)	CD Rat/F	Decreased pup weight	5×10^{-1}	$BMDL_{05}$	54.4	100	Ledoux and Reel (1982)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

BMDL = 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); F = female(s); HEC = human equivalent concentration; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NDr = not determined; POD = point of departure p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor; TPA = terephthalic acid.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Following U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, the database for TPA provides *"Suggestive Evidence of Carcinogenic Potential"* by oral exposure (see Table 8). There are no pertinent human data, but several studies in laboratory animals have evaluated TPA for carcinogenicity. Male Wistar rats treated by TPA in the diet at 3,680 mg/kg-day for 48 weeks had significantly elevated incidence (16/20) of transitional cell carcinomas in the bladder, versus 0/12 in controls; no other doses were tested in this study (Cui et al., 2006b). A study of male and female Wistar rats exposed to TPA in the diet for 2 years found significant increases in bladder and ureter tumors (primarily transitional cell tumors or squamous cell carcinomas) in the high-dose group fed 3,680−4,210 mg/kg-day with incidences of 57% (21/37) in males and 62% (21/34) in females, in comparison to 0% incidence in controls (n = 45−46/group) and 0−4% incidence in lower dose groups (n = 43−48) fed 736−1,680 mg/kg-day (Gross, 1977). A second 2-year study (ICI Americas Inc, 1992; Preache, 1983) conducted in male and female F344 rats, was performed at lower doses. In this study, incidence of transitional cell bladder tumors (primarily adenomas) in high-dose females fed (10/73) 989.8 mg/kg-day was significantly increased versus controls. Although the available data for TPA are consistent with one of the examples provided in the U.S. EPA's Cancer Guidelines (U.S. EPA, 2005) for the descriptor *"Likely to Be Carcinogenic to Humans"* (which states that supporting data for this descriptor include "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without

evidence of carcinogenicity in humans"), tumors were only significant at the highest doses tested and the only tumor site observed was the urinary tract. As stated in the Cancer Guidelines (U.S. EPA, 2005), one of the examples for a chemical to be considered to have *"Suggestive Evidence of Carcinogenic Potential"* is "a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend." The Cancer Guidelines (U.S. EPA, 2005) further state that the descriptor *"Suggestive Evidence of Carcinogenic Potential"* is appropriate when "the weight of evidence is suggestive of carcinogenicity, a concern for potential carcinogenic effects is raised, but the data are not judged sufficient for a stronger conclusion." The mechanistic data for urinary bladder tumors also provide support for the descriptor *"Suggestive Evidence of Carcinogenic Potential"* for TPA. Mode-of-action (MOA) information indicates that the induction of urinary bladder tumors in rats by dietary TPA exposure is a high-dose phenomenon that might be related to the formation of urinary bladder calculi. The relevance of calculi-associated bladder tumors to humans has come into question given the following considerations: (1) rodents may be more prone to calculi formation or to prolonged presence of calculi due to their horizontal anatomy (although humans spend a significant fraction of the day horizontal while sleeping) and the ureter of humans is at the bottom of the bladder (when standing), leading to passage of calculi, while in the rodent, the ureter is on the side, leading to retention of calculi (2) calculi formation in rodents appears to be a high-dose phenomenon, based on the necessity to have enough calculus-forming constituents for precipitation to occur; it is unclear whether such a dose could be reached in humans (Cohen et al., 2002; Heck, 1981). Thus, based on the Cancer Guidelines (U.S. EPA, 2005) and the carcinogenicity data from available animal studies and mechanistic studies, the WOE descriptor of *"Suggestive Evidence of Carcinogenic Potential"* is appropriate for TPA for the oral route of exposure.

There is *"Inadequate Information to Assess the Carcinogenic Potential"* of TPA by inhalation exposure. No suitable human or animal data are available by this route (see Table 8).

Table 8. Cancer WOE Descriptors for TPA (CASRN 100-21-0)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.
"Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.
"Suggestive Evidence of Carcinogenic Potential"	**Selected**	**Oral**	**The available studies, described above, suggest that TPA at high doses in the diet can induce bladder tumors in rats. However, the relevance of these data to humans at environmental exposure levels is uncertain because humans would unlikely be exposed at these levels. Mechanistic data informing the formation of bladder tumors following TPA exposure that would lead to a plausible mode of action is unclear.**
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Inhalation**	**This descriptor is selected due to the lack of any information on the carcinogenicity of TPA by inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.

NA = not applicable; NS = not selected; TPA = terephthalic acid; WOE = weight of evidence.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005) define MOA "…as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation." Examples of possible modes of carcinogenic action for any given chemical include "mutagenicity, mitogenesis, programmed cell death, cytotoxicity with reparative cell proliferation, and immune suppression."

Evidence from genotoxicity tests (see Table 4A) were mostly negative. It has been proposed that TPA-associated tumor formation in the bladder may be a secondary response to the formation of calcium-TPA calculi following TPA exposure (Heck and Tyl, 1985), leading to cytotoxicity and reparative cell proliferation. One hypothesis is that urolith-caused irritation to the bladder epithelium contributes to hyperplastic proliferative lesions that could then progress to papillomas, squamous cell metaplasias, and eventually tumors (Gross, 1977). In several TPA studies, calculi in the bladder were nearly always present in animals that also exhibited lesions (Cui et al., 2006b; Cui et al., 2006a; Dai et al., 2005c; Preache, 1983; Ledoux and Reel, 1982; Gross, 1977). Several reviews have discussed the potential relationship between urinary tract calculi, cell proliferation, and carcinogenesis (Cohen, 2002; Cohen et al., 2002; Cohen et al., 2000; Cohen, 1998, 1995a, b). Several chemicals are capable of causing urinary calculi when administered at high doses that also induce bladder tumors (Cohen et al., 2002). Similarly, there

appears to be a relatively high dose threshold for TPA-induced calculi (see Table 3A). Finally, some hyperplastic lesions are found in bladders that do not have calculi; thus, it is possible that calculi are correlated with hyperplasia and not causal (Cui et al., 2006a).

A second hypothesis of TPA-induced bladder tumors that may be independent of calculi formation has also been proposed. Dai et al. (2005c) proposed that TPA may interact with α2u-g, a protein secreted by the male rat liver to form white sediment in the bladder that could also give rise to bladder cell proliferation and possibly cancer. While this mechanism is usually only found in male rats exposed to certain hydrocarbons, it could be a partial explanation, leading to higher incidence in males than females (although the incidence rate in males and females is similar in other studies). Another related hypothesis is that the TPA/α2u-g crystals may create a "concentrated reservoir" of the chemical, and that the effects would be seen in animals that do not form crystals, but at higher doses due to the lack of the "reservoir." Thus, the crystals themselves might not be the toxic entity, but rather a concentrated form of the chemical. This mechanism does not account for the increase in tumors found in females, which do not form α2u-g. In S-D rats, Dai et al. (2005c) demonstrated an increase in α2u-g in serum and urine in a TPA dose-dependent manner, along with the appearance of white sediment (precipitates); however, the presence of α2u-g was not demonstrated in the crystals. There were, however, instances of hyperplasia without calculi. Other researchers also reported the appearance of sediment in the urine (Cui et al., 2006a; Preache, 1983). Additional evidence, however, to support this hypothesis, including staining of the proposed crystals to show the presence of α2u-g, and a male-only pattern of expression, would be required to discount the relevance of this partial mechanism to humans, who do not form α2u-g. As mentioned previously, the evidence suggests the calculi are composed of Ca-TPA, not α2u-g, thus this potential mechanism for the formation of calculi is unclear.

In any case, the MOA is unclear. Some hyperplastic lesions are found in bladders that do not have calculi; thus, it is possible that calculi are correlated with hyperplasia and not causal Cui et al. (2006a). It is also unclear which, if any, of the hyperplastic lesions are preneoplastic, or whether the eventual neoplastic lesions arise from some other subset of cells. These hyperplastic lesions have thus not been shown to be preneoplastic, and the relationships between the various cell types is unclear. Finally, although there is no evidence that TPA is genotoxic, the data that would characterize a nongenotoxic MOA are inconsistent. There is insufficient/inconsistent data to support a nongenotoxic MOA because there are occurrences of hyperplasia without calculi suggesting that calculi may not be a key event in the progression. Thus, important considerations in the Bradford-Hill rationale (consistency, temporality) are not met.

DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

The WOE of the available data for TPA constitutes only *"Suggestive Evidence of Carcinogenic Potential,"* with tumors at only one site and in one species. This descriptor is based on rat data from three studies (two unpublished) showing TPA induction of bladder tumors. The tumors were increased at high doses (the single highest doses in each study), and mechanistic data are unclear whether the carcinogenic potential of TPA is associated with a key event (calculus formation) that itself only occurs at high doses. It is unclear whether calculus formation is a key event in the progression because hyperplastic lesions are found in animals without calculi [e.g., Cui et al. (2006a)]. Considering the inconsistent data supporting this hypothesized relationship, discussed above, and the appropriateness of using bladder tumor incidence data obtained in rats fed high doses of TPA to derive quantitative estimates of cancer

risk for humans, who are expected to experience much lower exposure levels, is questionable. For chemicals with *"Suggestive Evidence of Carcinogenic Potential,"* cancer risk estimates may or may not be derived, depending on strengths and weaknesses of the particular database. In light of the uncertainties discussed here, provisional cancer risk estimates were not derived for TPA (see Table 9). If the bladder calculi MOA is operating and responsible for the TPA-induced bladder tumors, the POD [$BMDL_{05}$ of 54.4 mg/kg-day for decreased pup weight in female rats; Ledoux and Reel (1982)] used for the derivation of the subchronic and chronic p-RfDs is lower than that of the bladder hyperplasia POD [$BMDL_{10}$ of 95.0 mg/kg-day in male rats; Cui et al. (2006a)] indicating that the p-RfDs derived are protective of cancer.

Table 9. Summary of Cancer Risk Estimates for TPA (CASRN 100-21-0)

Toxicity Type (units)	Species/Sex	Tumor Type(s)	Cancer Risk Estimate	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor; TPA = terephthalic acid.

APPENDIX A. LITERATURE SEARCH STRATEGY

Non-date-limited literature searches were conducted in February 2018 and updated in July 2019, May 2019, and March 2020 for studies relevant to the derivation of provisional toxicity values for terephthalic acid (TPA; CASRN 100-21-0). Synonyms included in the search included terephthalic acid and para-dicarboxylic acid. Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE (including the Toxic Substances Control Act Test Submissions [TSCATS] database), and Web of Science (WOS). In addition, the following databases were searched outside of HERO: U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Health Effects Assessment Summary Tables (HEAST), International Programme on Chemical Safety (IPCS) INCHEM, U.S. EPA Integrated Risk Information System (IRIS), Japan Existing Chemical Data Base (JECDB), National Toxicology Program (NTP), and Organisation for Economic Co-operation and Development (OECD), including eChemPortal. The following additional sources were checked for regulatory values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

LITERATURE SEARCH STRINGS

PubMed

("P-PHTHALIC ACID"[TW] OR "100-21-0"[EC/RN NUMBER] AND ("2019/05/01"[PDAT] : "3000"[PDAT]))"

WOS

((TS="P-PHTHALIC ACID" AND ((WC=("TOXICOLOGY" OR "ENDOCRINOLOGY & METABOLISM" OR "GASTROENTEROLOGY & HEPATOLOGY" OR "GASTROENTEROLOGY & HEPATOLOGY" OR "HEMATOLOGY" OR "NEUROSCIENCES" OR "OBSTETRICS & GYNECOLOGY" OR "PHARMACOLOGY & PHARMACY" OR "PHYSIOLOGY" OR "RESPIRATORY SYSTEM" OR "UROLOGY & NEPHROLOGY" OR "ANATOMY & MORPHOLOGY" OR "ANDROLOGY" OR "PATHOLOGY" OR "OTORHINOLARYNGOLOGY" OR "OPHTHALMOLOGY" OR "PEDIATRICS" OR "ONCOLOGY" OR "REPRODUCTIVE BIOLOGY" OR "DEVELOPMENTAL BIOLOGY" OR "BIOLOGY" OR "DERMATOLOGY" OR "ALLERGY" OR "PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH") OR SU=("ANATOMY & MORPHOLOGY" OR "CARDIOVASCULAR SYSTEM & CARDIOLOGY" OR "DEVELOPMENTAL BIOLOGY" OR "ENDOCRINOLOGY & METABOLISM" OR "GASTROENTEROLOGY & HEPATOLOGY" OR "HEMATOLOGY" OR "IMMUNOLOGY" OR "NEUROSCIENCES & NEUROLOGY" OR "OBSTETRICS & GYNECOLOGY" OR "ONCOLOGY" OR "OPHTHALMOLOGY" OR "PATHOLOGY" OR "PEDIATRICS" OR "PHARMACOLOGY & PHARMACY" OR "PHYSIOLOGY" OR "PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH" OR "RESPIRATORY SYSTEM" OR "TOXICOLOGY" OR "UROLOGY & NEPHROLOGY" OR "REPRODUCTIVE BIOLOGY" OR "DERMATOLOGY" OR "ALLERGY")) OR (TS="RAT"

OR TS=“RATS” OR TS=“MOUSE” OR TS=“MURINE” OR TS=“MICE” OR TS=“GUINEA” OR TS=“MURIDAE” OR TS=RABBIT* OR TS=LAGOMORPH* OR TS=HAMSTER* OR TS=FERRET* OR TS=GERBIL* OR TS=RODENT* OR TS=“DOG” OR TS=“DOGS” OR TS=BEAGLE* OR TS=“CANINE” OR TS=“CATS” OR TS=“FELINE” OR TS=“PIG” OR TS=“PIGS” OR TS=“SWINE” OR TS=“PORCINE” OR TS=MONKEY* OR TS=MACAQUE* OR TS=BABOON* OR TS=MARMOSET* OR TS=“CHILD” OR TS=“CHILDREN” OR TS=ADOLESCEN* OR TS=INFANT* OR TS=“WORKER” OR TS=“WORKERS” OR TS=“HUMAN” OR TS=PATIENT* OR TS=MOTHER OR TS=FETAL OR TS=FETUS OR TS=CITIZENS OR TS=MILK OR TS=FORMULA OR TS=EPIDEMIO* OR TS=POPULATION* OR TS=EXPOSURE* OR TS=QUESTIONNAIRE OR SO=EPIDEMIO*) OR TI=TOXIC*)) AND (PY=2019-2020))OS

APPENDIX B. DETAILED PECO CRITERIA

Table B-1. Population, Exposure, Comparator, and Outcome (PECO) Criteria

PECO Element	Evidence
Population	Humans, laboratory mammals, and other animal models of established relevance to human health (e.g., *Xenopus* embryos); mammalian organs, tissues, and cell lines; and bacterial and eukaryote models of genetic toxicity.
Exposure	In vivo (all routes), ex vivo, and in vitro exposure to the chemical of interest, including mixtures to which the chemical of interest may contribute significantly to exposure or observed effects.
Comparator	Any comparison (across dose, duration, or route) or no comparison (e.g., case reports without controls).
Outcome	Any endpoint suggestive of a toxic effect on any bodily system, or mechanistic change associated with such effects. Any endpoint relating to disposition of the chemical within the body.

APPENDIX C. SCREENING PROVISIONAL VALUES

For reasons discussed in the main Provisional Peer Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional toxicity values for terephthalic acid (TPA) because the principle study is not peer reviewed. However, information is available for this chemical, which although insufficient to support deriving a provisional toxicity value under current guidelines, may be of use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the provisional reference values to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there could be more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the CPHEA.

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCE DOSES

As discussed in the main body of the report, the reproductive/developmental study by Ledoux and Reel (1982) was chosen as the principle study and the corresponding 5% benchmark dose lower confidence limit ($BMDL_{05}$) human equivalent dose (HED) of 54.4 mg/kg-day for decreased pup weight in female CD rats was identified as the most sensitive point of departure (POD) for deriving screening-level provisional reference dose (p-RfD) values. The choice of decreased pup weight as the critical effect is supported by observations of TPA-induced pup weight effects in other studies [i.e., Milburn (2003); Heck (1979)] and in two rat strains (i.e., Wistar and CD rats) from the Ledoux and Reel (1982) study.

Derivation of Screening Subchronic Provisional Reference Dose

The screening subchronic p-RfD is derived by applying a composite uncertainty factor (UF_C) (see Table C-1) of 100 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 3) to the selected POD of 54.4 mg/kg-day.

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= \text{POD (HED)} \div UF_C \\ &= 54.4 \text{ mg/kg-day} \div 100 \\ &= \mathbf{5 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

Table C-1 summarizes the uncertainty factors for the screening subchronic p-RfD for TPA.

Table C-1. Uncertainty Factors for the Screening Subchronic p-RfD for TPA (CASRN 100-21-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following TPA exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 1988).
UF_D	3	A UF_D of 3 ($10^{0.5}$) is applied to account for deficiencies in the database. Numerous repeated-dose oral studies of TPA are available, and findings are consistent across studies, although a number of studies are unpublished and/or poorly reported and some others included only a single dose level. Although both key chronic studies are unpublished and not peer reviewed, they both included adequate numbers of male and female rats and multiple dose groups; investigated a range of endpoints, including the target urinary tract; identified dose-response relationships; and provided useable documentation. Single- and multiple-generation reproductive studies are available, but of reduced utility due to poor reporting or non-peer-reviewed status (Milburn, 2003; Hall et al., 1993; Ledoux and Reel, 1982). None of these studies has reported any effect on fertility, although studies of testicular and sperm effects (Kwack and Lee, 2015; Cui et al., 2004) have found some sperm changes of uncertain toxicological significance. Effects on pup body weights and developmental milestones have been reported in the developmental/reproductive studies, as has some evidence for an effect on pup survival. No oral teratogenicity studies were located.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of TPA in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a $BMDL_{05}$.
UF_S	1	A UF_S of 1 is applied because developmental toxicity was used as the critical effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	100	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; TPA = terephthalic acid; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of Screening Chronic Provisional Reference Dose

The screening chronic p-RfD is derived using the same POD ($BMDL_{05}$ [HED] of 54.4 mg/kg-day for decreased pup weight in female CD rats from the Ledoux and Reel (1982) study as the screening subchronic p-RfD and applying a UF_C of 100 (reflecting a UF_A of 3, a UF_H] of 10, and a UF_D of 3).

Screening Chronic p-RfD = POD (HED) ÷ UF_C
= 54.4 mg/kg-day ÷ 100
= **5×10^{-1} mg/kg-day**

Table C-2 summarizes the uncertainty factors for the screening chronic p-RfD for TPA.

Table C-2. Uncertainty Factors for the Screening Chronic p-RfD for TPA (CASRN 100-21-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following TPA exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 1988).
UF_D	3	A UF_D of 3 ($10^{0.5}$) is applied to account for deficiencies in the database. Numerous repeated-dose oral studies of TPA are available, and findings are consistent across studies, although a number of studies are unpublished and/or poorly reported and some others included only a single dose level. Although both key chronic studies are unpublished and not peer reviewed, they both included adequate numbers of male and female rats and multiple dose groups; investigated a range of endpoints, including the target urinary tract; identified dose-response relationships; and provided useable documentation. Single- and multiple-generation reproductive studies are available, but of limited utility due to poor reporting or nonoral exposure (Milburn, 2003; Hall et al., 1993; Ledoux and Reel, 1982). None of these studies has reported any effect on fertility, although studies of testicular and sperm effects (Kwack and Lee, 2015; Cui et al., 2004) have found some sperm changes of uncertain toxicological significance. Effects on pup body weights and developmental milestones have been reported in the developmental/reproductive studies, as has some evidence for an effect on pup survival. No oral teratogenicity studies were located.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of TPA in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a $BMDL_{05}$.
UF_S	1	A UF_S of 1 is applied because developmental toxicity was used as the critical effect. The developmental period is recognized as a susceptible life stage when exposure during a time window of development is more relevant to the induction of developmental effects than lifetime exposure (U.S. EPA, 1991).
UF_C	100	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; TPA = terephthalic acid; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies variability uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

APPENDIX D. DATA TABLES

Table D-1. Serum Chemistry and Urine Endpoints in Chinese Fiber Factory Workers Exposed to Ambient TPA Dust[a]

Cumulative Exposure Group (mg/m^3)				
Serum Endpoint	**Control (*n* = 77)**	**Not Detected (*n* = 52)**	**~50 (*n* = 59)**	**~80 (*n* = 30)**
ALB (g/L)	48.81 ± 2.78[b, c]	48.99 ± 2.44 (0%)	48.58 ± 2.68 (0%)	47.39 ± 2.74* (−3%)
ALT (U/L)	13.96 ± 15.07	11.85 ± 8.63 (−15%)	15.4 ± 22.6 (+10%)	13.67 ± 9.39 (−2%)
AST (U/L)	14.16 ± 5.37	15.4 ± 4.85 (+9%)	17.96 ± 12.45* (+27%)	16.57 ± 5.79 (+17%)
GGT (U/L)	15.05 ± 10.81	12.94 ± 10.74 (−14%)	14.1 ± 8.17 (−6%)	12.77 ± 5.45 (−15%)
ALP (U/L)	72.31 ± 24.11	78.6 ± 28.5 (+9%)	75.93 ± 26.01 (+5%)	68.57 ± 19.19 (−5%)
LDH (U/L)	280.25 ± 73.38	286 ± 56.14 (+2%)	309.78 ± 63.45* (+11%)	279.73 ± 49.45 (0%)
Urine Endpoint	**Control (*n* = 71)**	**Not Detected (*n* = 46)**	**~50 (*n* = 57)**	**~80 (*n* = 24)**
pH	5.71 ± 0.4	5.74 ± 0.6	5.71 ± 0.84	5.63 ± 0.91
K^+ (mmol/mol Cr)	4.5 ± 2.18	5.02 ± 2.13 (+12%)	4.24 ± 1.20 (−6%)	4.54 ± 1.72 (+1%)
Na^+ (mmol/mol Cr)	19.84 ± 10.3	23.53 ± 11.12 (+19%)	24.42 ± 8.75* (+23%)	25.22 ± 11.33* (+27%)
Ca^{2+} (mmol/mol Cr)	0.19 ± 0.1	0.3 ± 0.19* (+58%)	0.33 ± 0.14* (+74%)	0.3 ± 0.11* (+58%)

[a]Dai et al. (2005b); Li et al. (1999).
[b]Data are mean ± SD.
[c]Value in parentheses is percent change relative to control = [(treatment mean – control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors.

ALB = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Cr = creatinine; GGT = γ-glutamyl transferase; LDH = lactate dehydrogenase; SD = standard deviation; TPA = terephthalic acid.

Table D-2. Body Weights of F344 Weanlings Rats Exposed to TPA (CASRN 100-21-0) for 14 Days[a]

	Male: ADD (HED) in mg/kg-d[b]					
Exposure Days	**0**	**658 (121)**	**1,904 (354.4)**	**3,740 (690)**	**4,860 (877)**	**5,710 (993)**
0–2	57.3[c, d]	57.7 (+0.6%)	61.1* (+7%)	59.6 (+4%)	56.2 (−2%)	53.9 (−6%)
6–8	80.6	80.2 (−0.5%)	83.2 (+3%)	80.0 (−0.8%)	72.8* (−10%)	61.2* (−24%)
12–14	104.8	101.9 (−3%)	107.8 (+3%)	103.4 (−1%)	93.4* (−11%)	77.2* (−26%)
	Female: ADD (HED) in mg/kg-d					
Exposure Days	**0**	**599 (108)**	**1,836 (330.4)**	**3,760 (669)**	**4,770 (842)**	**5,520 (954)**
0–2	51.8	56.0* (+8%)	54.6* (+5%)	52.9 (+2%)	54.1 (+4%)	51.8 (+0.02%)
6–8	70.6	73.9 (+5%)	73.4* (+4%)	69.8 (−1%)	66.0* (−7%)	59.5* (−16%)
12–14	87.9	92.5* (+5%)	92.4* (+5%)	87.2 (−1%)	84.0* (−4%)	76.2* (−13%)

[a]Chin et al. (1981).
[b]Doses correspond to 0, 0.5, 1.5, 3, 4, and 5% TPA in the diet.
[c]Data are mean values (g) based on graphically reported body-weight data extracted using GrabIT! software; variance values were not extracted.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-3. Incidence and Mass of Calculi in the Bladders of F344 Weanlings Rats Exposed to TPA (CASRN 100-21-0) for 14 Days[a]

	Males: ADD (HED) in mg/kg-d[b]					
Effect	**0**	**658 (121)**	**1,904 (354.4)**	**3,740 (690)**	**4,860 (877)**	**5,710 (993)**
Incidence of calculi[c]	0/30	0/30	0/30	3/30 (+10%)	17/30* (+57%)	28/30** (+93%)
Mean mass[d]	NA	NA	NA	9.4 ± 2.4	10.1 ± 1.4	38.8 ± 7.1
	Females: ADD (HED) in mg/kg-d					
Effect	**0**	**599 (108)**	**1,836 (330.4)**	**3,760 (669)**	**4,770 (842)**	**5,520 (954)**
Incidence of calculi	0/30	0/30	1/30 (+3%)	1/30 (+3%)	6/30* (+20%)	22/30** (+73%)
Mean mass	NA	NA	NDr	2.1	4.3 ± 1.9	20.3 ± 7.1

[a]Chin et al. (1981).
[b]Doses correspond to 0, 0.5, 1.5, 3, 4, and 5% TPA in the diet.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
[d]Values are mean ± SE.
*Significantly different from control ($p < 0.05$), by two-tailed Fisher's exact test, as conducted for this review.
**Significantly different from control ($p < 0.01$), by two-tailed Fisher's exact test, as conducted for this review.

ADD = adjusted daily dose; HED = human equivalent dose; NA = not applicable; NDr = not determined; SE = standard error; TPA = terephthalic acid.

Table D-4. Urinary Endpoints of F344 Weanlings Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 14 Days[a]

Endpoint	Male: ADD (HED) in mg/kg-d[b]					
	0	**658 (121)**	**1,904 (354.4)**	**3,740 (690)**	**4,860 (877)**	**5,710 (993)**
pH	6.30 ± 0.10[c, d]	5.88 ± 0.05**	ND	5.77 ± 0.03**	5.73 ± 0.02**	ND
Ca^{2+} (mM)	5.5 ± 0.6	11.1 ± 1.1 (+102%)	ND	22.5 ± 2.2** (+309%)	22.2 ± 1.9** (+304%)	ND
PO_4^{3-} (mM)	96 ± 13	68 ± 8 (−29%)	ND	88 ± 11 (−8%)	113 ± 11 (+18%)	ND
TPA (mM)	NA	46 ± 3	ND	68 ± 7	81 ± 6	ND
Endpoint	**Female: ADD (HED) in mg/kg-d**					
	0	**599 (108)**	**1,836 (330.4)**	**3,760 (669)**	**4,770 (842)**	**5,520 (954)**
pH	6.22 ± 0.08	5.8 ± 0.04**	ND	5.73 ± 0.03**	5.74 ± 0.03**	ND
Ca^{2+} (mM)	4.9 ± 0.7	11 ± 1.5 (+124%)	ND	23.8 ± 1.3** (+386%)	23.5 ± 2.7** (+380%)	ND
PO_4^{3-} (mM)	99 ± 19	59 ± 5* (−40%)	ND	109 ± 11 (+10%)	128 ± 11 (+29%)	ND
TPA (mM)	NA	37 ± 4	ND	81 ± 2	101 ± 9	ND

[a]Chin et al. (1981).
[b]Doses correspond to 0, 0.5, 1.5, 3, 4, and 5% TPA in the diet.
[c]Data are mean ± SEM; n = 10−28.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$) by Dunnett's test, as reported by the study authors.
**Significantly different from control ($p < 0.01$), by Dunnett's test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; ND = no data; SEM = standard error of the mean; TPA = terephthalic acid.

Table D-5. Urinary Electrolyte and TPA (CASRN 100-21-0) Concentrations in Weanling F344 Rats Exposed to TPA in the Diet for 14 Days[a]

Endpoint	Sex	Male/Female: ADD (HED) in mg/kg-d[b]			
		0/0 (0/0)	**658/599 (121/108)**	**3,740/3,760 (690/669)**	**4,860/4,770 (877/842)**
Number of animals	*n*	18 M, 10 F	9 M, 14 F	17 M, 10 F	19 M, 13 F
pH	M	6.35 ± 0.11[c, d]	5.79 ± 0.04**	5.75 ± 0.03**	5.74 ± 0.02**
	F	6.19 ± 0.12	5.73 ± 0.03**	5.65 ± 0.03**	5.78 ± 0.04**
Na^+ (mM)	M	149 ± 16	192 ± 28 (+29%)	103 ± 8* (−31%)	77 ± 6** (−48%)
	F	120 ± 9	155 ± 22 (+29%)	130 ± 18 (+8%)	61 ± 7* (−49%)
NH_4^+ (mM)	M	109 ± 23	324 ± 41** (+197%)	308 ± 28** (+183%)	422 ± 26** (+287%)
	F	111 ± 21	347 ± 42** (+213%)	372 ± 14** (+235%)	458 ± 24** (+313%)
K^+ (mM)	M	256 ± 34	223 ± 24 (−13%)	116 ± 15** (−55%)	126 ± 9** (−51%)
	F	312 ± 53	168 ± 17** (−46%)	139 ± 9** (−55%)	138 ± 14** (−56%)
Ca^{2+} (mM)	M	5.6 ± 0.7	11.7 ± 1.3 (+109%)	22.5 ± 2.2** (+302%)	22.4 ± 2** (+300%)
	F	4.9 ± 0.7	11 ± 1.5 (+124%)	25 ± 1.2** (+410%)	22.4 ± 3.1** (+357%)
Mg^{2+} (mM)	M	37.6 ± 4.7	34.4 ± 2.4 (−9%)	29.7 ± 3.7 (−21%)	34.3 ± 2.9 (−9%)
	F	44.1 ± 5.8	28.5 ± 2* (−35%)	36.1 ± 2.4 (−18%)	37 ± 4.2 (−16%)
Cl^- (mM)	M	162 ± 13	194 ± 23 (+20%)	144 ± 15 (−11%)	135 ± 12 (−17%)
	F	169 ± 18	200 ± 20 (+18%)	183 ± 6 (+8%)	142 ± 12 (−16%)
PO_4^{3-} (mM)	M	92 ± 13	71 ± 11 (−23%)	88 ± 11 (−4%)	113 ± 11 (+23%)
	F	107 ± 19	59 ± 5* (−45%)	108 ± 6 (+1%)	121 ± 12 (+13%)

Table D-5. Urinary Electrolyte and TPA (CASRN 100-21-0) Concentrations in Weanling F344 Rats Exposed to TPA in the Diet for 14 Days[a]

Endpoint	Sex	Male/Female: ADD (HED) in mg/kg-d[b]			
		0/0 (0/0)	**658/599 (121/108)**	**3,740/3,760 (690/669)**	**4,860/4,770 (877/842)**
Number of animals	*n*	18 M, 10 F	9 M, 14 F	17 M, 10 F	19 M, 13 F
SO_4^{2-} (mM)	M	32.1 ± 3.4	34.2 ± 1.8 (+7%)	16.3 ± 1.8** (−49%)	21.6 ± 1.7** (−33%)
	F	34.2 ± 3.7	41.9 ± 3.9 (+23%)	24.1 ± 2.2* (−30%)	24 ± 1.9* (−30%)

[a]Heck (1981).
[b]Data are mean ± SEM.
[c]Doses correspond to 0, 0.5, 3, and 4% TPA in the diet.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$) by Dunnett's test, as reported by the study authors.
**Significantly different from control ($p < 0.01$) by Dunnett's test, as reported by the study authors.

ADD = adjusted daily dose; F = female(s); HED = human equivalent dose; M = male(s); SEM = standard error of the mean; TPA = terephthalic acid.

Table D-6. Body Weights of Male F344 Rat Pups Exposed to TPA (CASRN 100-21-0) in the Diet for 14 Days[a]

Exposure Day	ADD (HED) in mg/kg-d[b]	
	0	4,900 (874)
0	50.87[c, d]	49.55 (−3%)
2	60.47	55.86* (−8%)
4	68.53	61.72* (−10%)
6	78.78	69.57* (−12%)
8	84.87	71.93* (−15%)
10	93.37	80.43* (−14%)
12	102.31	87.39* (−15%)
14	108.84	90.85* (−17%)

[a]Wolkowski-Tyl and Chin (1983).
[b]Doses correspond 0 and 4% TPA in the diet.
[c]Data are mean values based on graphically reported body-weight data extracted using GrabIT! software; accurate variance values could not be extracted due to overlapping data points.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*The study authors indicated in the text that significant depressions in body weight were observed beginning on Day 2 of the study.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-7. Food and Water Intake of Male F344 Rat Pups Exposed to TPA (CASRN 100-21-0) in the Diet for 14 Days[a]

Endpoint	ADD (HED) in mg/kg-d[b]	
	0	4,900 (874)
Water (mL/cage-d)	5.86 ± 0.19[c, d]	7.80 ± 0.34* (+33%)
Food (g/cage-d)	51.46 ± 1.59	43.50 ± 1.85* (−15%)

[a]Wolkowski-Tyl and Chin (1983).
[b]Doses correspond 0 and 4% TPA in the diet.
[c]Data are mean ± SEM; n = 10.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), by Student's t-test with f-test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SEM = standard error of the mean; TPA = terephthalic acid.

Table D-8. Serum and Urinary Endpoints in Male F344 Rat Pups Exposed to TPA (CASRN 100-21-0) in the Diet for 14 Days[a]

Endpoint[c, d]	ADD (HED) in mg/kg-d[b]	
	0	4,900 (874)
Urinary endpoint		
pH	7.00 ± 0.15	5.74 ± 0.04*
Blood/serum endpoint		
Calcium	3.12 ± 0.02	3.31 ± 0.02* (+6%)
Magnesium	0.73 ± 0.02	0.93 ± 0.03* (+27%)
Hematocrit	42.1 ± 0.5	41.0 ± 0.5 (−3%)

[a]Wolkowski-Tyl and Chin (1983).
[b]Doses correspond 0 and 4% TPA in the diet.
[c]Data are mean ± SEM; n = 10.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), by Student's t-test with f-test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SEM = standard error of the mean; TPA = terephthalic acid.

Table D-9. Incidence of Calculi in Male F344 Rat Pups Exposed to TPA (CASRN 100-21-0) in the Diet for 14 Days[a]

Endpoint[c]	ADD (HED) in mg/kg-d[b]	
	0	4,900 (874)
Incidence of calculi	0/10 (0%)	5/10* (50%)

[a]Wolkowski-Tyl and Chin (1983).
[b]Doses correspond 0 and 4% TPA in the diet.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$), by two-tailed Fisher's exact test, as conducted for this review.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-10. Urinary Endpoints in Male and Female S-D Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

Endpoint	Male: ADD (HED) in (mg/kg-d)[b]				
	0	**36.0 (8.77)**	**179 (43.8)**	**906 (220)**	**4,550 (1,100)**
Number examined (*n*)	*n* = 12	*n* = 12	*n* = 10	*n* = 12	*n* = 9
Ca^{2+} (g/mol Cr)	0.39 ± 0.31[c, d]	0.45 ± 0.48 (+15%)	0.52 ± 0.36 (+33%)	8.23 ± 7.6** (+2,010%)	124.56 ± 15.72** (+31,839%)
Mg^{2+} (g/mol Cr)	16.2 ± 7.62	30.37 ± 11.06 (+88%)	41.65 ± 11.61** (+157%)	43.38 ± 21.2** (+168%)	119.65 ± 55.69** (+639%)
Zn^{2+} (g/mol Cr)	0.1 ± 0.11	0.16 ± 0.07 (+60%)	0.1 ± 0.06 (0%)	0.18 ± 0.12 (+80%)	0.74 ± 0.72** (+640%)
K^{+} (g/mmol Cr)	0.11 ± 0.04	0.4 ± 0.05 (+264%)	0.29 ± 0.13 (+164%)	0.4 ± 0.28** (+264%)	0.31 ± 0.26 (+182%)
Na^{+} (g/mmol Cr)	0.26 ± 0.16	0.48 ± 0.14 (+85%)	0.34 ± 0.18 (−31%)	0.39 ± 0.32 (+50%)	0.91 ± 1.28* (+250%)
pH (*n* = 11)	6.53 ± 0.47	6.05 ± 0.25	6.39 ± 0.45	5.92 ± 0.38	5.66 ± 0.18**
Endpoint	**Female: ADD (HED) in (mg/kg-d)**				
	0	**40.0 (9.03)**	**197 (44.9)**	**997 (225)**	**4,970 (1,130)**
Number examined (*n*)	*n* = 12	*n* = 12	*n* = 10	*n* = 12	*n* = 9
Ca^{2+} (g/mol Cr)	8.61 ± 6.46	9.69 ± 6.15 (+13%)	9.93 ± 3.98 (+15%)	25.92 ± 23.22 (+201%)	44.12 ± 25.78** (+412%)
Mg^{2+} (g/mol Cr)	25.64 ± 16.66	44.45 ± 14.48 (+73%)	47.26 ± 15.02 (+84%)	49.94 ± 15.68 (+95%)	86.85 ± 68.57** (+239%)
Zn^{2+} (g/mol Cr)	0.05 ± 0.02	0.08 ± 0.06 (+60%)	0.11 ± 0.07 (+120%)	0.18 ± 0.26 (+260%)	0.22 ± 0.17* (+340%)
K^{+} (g/mmol Cr)	0.26 ± 0.14	0.27 ± 0.14 (+4%)	0.21 ± 0.07 (−19%)	0.58 ± 0.3** (+123%)	0.33 ± 0.28 (+27%)
Na^{+} (g/mmol Cr)	0.50 ± 0.25	0.5 ± 0.22 (0%)	0.23 ± 0.11 (−54%)	0.6 ± 0.4 (+20%)	0.75 ± 0.14** (+50%)
pH (*n* = 11)	6.56 ± 0.06	6.2 ± 0.56**	6.27 ± 0.54	6.08 ± 0.77*	5.77 ± 0.22**

[a]Dai et al. (2005c); Dai et al. (2006a).
[b]Doses correspond to 0, 0.04, 0.2, 1, and 5% TPA in the diet.
[c]Data are mean ± variance (specified by the study authors as "*s*").
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$) by Student's *t*-test, as reported by the study authors.
**Significantly different from control ($p < 0.01$) by Student's *t*-test, as reported by the study authors.

ADD = adjusted daily dose; Cr = creatinine; HED = human equivalent dose; S-D = Sprague-Dawley; TPA = terephthalic acid.

Table D-11. Relative Organ Weights of Male and Female S-D Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

Endpoint (g/100 g BW)	Male: ADD (HED) in mg/kg-d[b]				
	0	**36.0 (8.77)**	**179 (43.8)**	**906 (220)**	**4,550 (1,100)**
Number examined (*n*)	*n* = 12	*n* = 12	*n* = 11	*n* = 12	*n* = 52
Liver	2.998 ± 0.431[c,d]	3.27 ± 0.193 (+9%)	3.218 ± 0.118 (+7%)	3.383 ± 0.363* (+13%)	2.94 ± 0.295 (−2%)
Spleen	0.185 ± 0.031	0.169 ± 0.029 (−9%)	0.173 ± 0.017 (−7%)	0.178 ± 0.021 (−4%)	0.167 ± 0.03 (−10%)
Kidney	0.719 ± 0.13	0.776 ± 0.044 (+8%)	0.748 ± 0.077 (+4%)	0.781 ± 0.034 (+9%)	0.778 ± 0.115 (+8%)
Adrenal gland	0.014 ± 0.003	0.012 ± 0.004 (−14%)	0.017 ± 0.005 (+21%)	0.015 ± 0.004 (+7%)	0.014 ± 0.003 (0%)
Brain	0.507 ± 0.047	0.463 ± 0.079 (−9%)	0.433 ± 0.078* (−15%)	0.487 ± 0.099 (−4%)	0.474 ± 0.113 (−7%)
Endpoint (g/100 g BW)	**Female: ADD (HED) in mg/kg-d**				
	0	**40.0 (9.03)**	**197 (44.9)**	**997 (225)**	**4,970 (1,130)**
Number examined (*n*)	*n* = 12	*n* = 12	*n* = 12	*n* = 12	*n* = 23
Liver	3.16 ± 0.295	3.329 ± 0.427 (+5%)	3.128 ± 0.354 (−1%)	3.295 ± 0.376 (+4%)	3.125 ± 0.359 (−1%)
Spleen	0.205 ± 0.026	0.202 ± 0.036 (−2%)	0.193 ± 0.027 (−6%)	0.235 ± 0.023** (+15%)	0.208 ± 0.05 (+2%)
Kidney	0.776 ± 0.065	0.751 ± 0.135 (−3%)	0.728 ± 0.139 (−6%)	0.848 ± 0.037** (+9%)	0.78 ± 0.073 (+1%)
Adrenal gland	0.031 ± 0.009	0.04 ± 0.035 (+29%)	0.027 ± 0.005 (−13%)	0.03 ± 0.006 (−3%)	0.03 ± 0.005 (−3%)

[a]Dai et al. (2005c); Dai et al. (2006a).
[b]Doses correspond to 0, 0.04, 0.2, 1, and 5% TPA in the diet.
[c]Data are mean ± variance (specified by the study authors as "*s*").
[d]Value in parenthesis is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$) by Student's *t*-test, as reported by the study authors.
**Significantly different from control ($p < 0.01$) by Student's *t*-test, as reported by the study authors.

ADD = adjusted daily dose; BW = body weight; HED = human equivalent dose; S-D = Sprague-Dawley; TPA = terephthalic acid.

Table D-12. Incidence of Calculi, Sediment, and Non-neoplastic Lesions in Bladders of Male and Female S-D Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

Endpoint		Male: ADD (HED) in (mg/kg-d)[b]				
		0	**36.0 (8.77)**	**179 (43.8)**	**906 (220)**	**4,550 (1,100)**
Bladder calculi	Amount[c]	0/12 (0%)[d]	0/12 (0%)	0/11 (0%)	0/12 (0%)	21/52* (40%)
Urine white sediment	+	0/12 (0%)	5/12* (42%)	5/11* (46%)	6/12* (50%)	13/52 (25%)
Urine white sediment	++	0/12 (0%)	0/12 (0%)	0/11 (0%)	4/12* (33%)	9/52 (17%)
Urine white sediment	+++	0/12 (0%)	0/12 (0%)	0/11 (0%)	2/12 (17%)	8/52 (15%)
Bladder hyperplasia	Simple	0/12 (0%)	0/12 (0%)	0/11 (0%)	0/12 (0%)	9/52 (17%)
Bladder hyperplasia	Atypical	0/12 (0%)	0/12 (0%)	0/11 (0%)	0/12 (0%)	5/52 (10%)
Endpoint		**Female: ADD (HED) in (mg/kg-d)**				
		0	**40.0 (9.03)**	**197 (44.9)**	**997 (225)**	**4,970 (1,130)**
Bladder calculi	Amount	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	1/23 (4%)
Urine white sediment	+	0/12 (0%)	0/12 (0%)	2/12 (17%)	4/12* (33%)	8/23* (35%)
Urine white sediment	++	0/12 (0%)	0/12 (0%)	0/12 (0%)	1/12 (8%)	4/23 (17%)
Urine white sediment	+++	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	3/23 (13%)
Bladder hyperplasia	Simple	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	1/23 (4%)
Bladder hyperplasia	Atypical	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/23 (0%)

[a]Dai et al. (2005c); Dai et al. (2006a).
[b]Doses correspond to 0, 0.04, 0.2, 1, and 5% TPA in the diet.
[c]+ = minor, ++ = moderate, +++ = large.
[d]Values denote number of animals showing changes/total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$), by two-tailed Fisher's exact test, as conducted for this review.

ADD = adjusted daily dose; HED = human equivalent dose; S-D = Sprague-Dawley; TPA = terephthalic acid.

Table D-13. Body-Weight Data for Male and Female Albino Weanling Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

Endpoint[c, d]	Male: ADD (HED) in (mg/kg-d)[b]			
	0	**859 (217)**	**2,754 (693.5)**	**10,500 (2,290)**
Body weight (g)[c]				
Initial body weight	104.3[e, f]	105	105	105
30 d	252.3	242 (−4%)	251 (−1%)	138.4 (−45%)
60 d	351.3	346 (−2%)	343 (−2%)	172 (−51%)
90 d	421.3	415 (−1%)	396 (−6%)	226 (−46%)
Body-weight gain (%)				
30 d	142	130 (−8%)	139 (−2%)	32 (−79%)
60 d	237	230 (−3%)	227 (−4%)	64 (−73%)
90 d	304	295 (−3%)	277 (−9%)	115 (−62%)
Endpoint	**Female: ADD (HED) in (mg/kg-d)**			
	0	**992 (225)**	**3,170 (719.2)**	**11,200 (2,320)**
Body weight (g)[e]				
Initial body weight	94.3	94	94	94
30 d	177	178 (+0.6%)	180 (+2%)	118 (−33%)
60 d	216.3	210 (−3%)	212 (−2%)	142 (−34%)
90 d	240.3	239 (−0.5%)	235 (−2%)	154 (−36%)
Body-weight gain (%)				
30 d	88	89 (+1%)	91 (+2%)	26 (−71%)
60 d	129	123 (−5%)	126 (+2%)	51 (−60%)
90 d	155	154 (−1%)	150 (−3%)	64 (−59%)

[a]Dupont Chem Co (1955).
[b]Doses correspond to 0, 1, 3.2, and 10% TPA in the diet.
[c]Body weights at 30, 60, and 90 days were calculated from body-weight-gain data provided in the study.
[d]Statistical analysis was not performed by the study authors.
[e]Data are mean values; variance values were not reported; n = 6/sex/group.
[f]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-14. Adjusted Mean Body Weights of Male and Female Wistar and CD Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

	Male: ADD (HED) in (mg/kg-d)[b]					
Wistar	**0**	**15.3 (4.44)**	**79.09 (22.81)**	**266 (76.0)**	**1,020 (293)**	**2,650 (750)**
4 wk	401.8[c, d]	396.9 (−1%)	402 (0%)	399.9 (0%)	393.2 (−2%)	374.1** (−7%)
8 wk	401.4	410.5 (+2%)	400.9 (0%)	393.3 (−2%)	386.4 (−4%)	369.8** (−8%)
13 wk	471.6	468 (−1%)	483 (+2%)	464.1 (−2%)	448.9 (−5%)	431.6** (−8%)
CD	**0**	**14.6 (4.23)**	**76.15 (21.99)**	**247 (71.5)**	**976 (282)**	**2,590 (741)**
4 wk	396.2	387.8 (−2%)	390.6 (−1%)	384.6* (−3%)	385.5* (−3%)	375.5** (−5%)
8 wk	429.8	415.1 (−3%)	428.7 (0%)	415 (−3%)	418 (−3%)	418 (−3%)
13 wk	485.8	447.9 (−8%)*	458.7 (−6%)	458.6 (−6%)	450.2* (−7%)	440.5** (−9%)
	Female: ADD (HED) in (mg/kg-d)					
Wistar	**0**	**19.3 (4.84)**	**114.5 (27.89)**	**313 (78.7)**	**1,280 (321)**	**3,100 (773)**
4 wk	377.8	375.8 (−1%)	376 (0%)	373.7 (−1%)	371.4** (−2%)	360.6** (−5%)
8 wk	395.7	398.6 (+1%)	400.6 (+1%)	397.1 (0%)	390.8 (−1%)	379.2** (−4%)
13 wk	404.7	391.1 (−3%)	404.7 (0%)	400.8 (−1%)	394.6 (−2%)	383.9** (−5%)
CD	**0**	**17.6 (4.65)**	**86.57 (22.83)**	**286 (75.0)**	**1,260 (321)**	**2,840 (732)**
4 wk	379.9	376.8 (−1%)	380.5 (0%)	369.9 (−3%)	366.9** (−3%)	351.5** (−7%)
8 wk	401.4	410.5 (+2%)	400.9 (0%)	393.3 (−2%)	386.4 (−4%)	369.8** (−8%)
13 wk	426.8	427.1 (0%)	411.4 (−4%)	409.6 (−4%)	390.6** (−8%)	362** (−15%)

[a]Ledoux and Reel (1982).
[b]Doses correspond to 0, 0.03, 0.154, 0.5, 2, and 5% TPA in the diet.
[c]Data are adjusted means (g) extracted from graphically reported data using GrabIT! software; variance values were not reported; n = ~30/sex/treatment group.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), based on Dunnett's two-tailed t-test, as reported by the study authors.
**Significantly different from control ($p < 0.01$), based on Dunnett's two-tailed t-test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-15. Adjusted Mean Body-Weight Gains of Male and Female Wistar and CD Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

	Male: ADD (HED) in (mg/kg-d)[b]					
Wistar	**0**	**15.3 (4.44)**	**79.09 (22.81)**	**266 (76.0)**	**1,020 (293)**	**2,650 (750)**
Body-weight gain (g)	130[c, d]	125 (−4%)	137 (+5%)	130 (0%)	108 (−17%)	75** (−43%)
CD	**0**	**14.6 (4.23)**	**76.15 (21.99)**	**247 (71.5)**	**976 (282)**	**2,590 (741)**
Body-weight gain (g)	131	106* (−19%)	117 (−11%)	101** (−23%)	99** (−24%)	82** (−37%)
	Female: ADD (HED) in (mg/kg-d)					
Wistar	**0**	**19.3 (4.84)**	**114.5 (27.89)**	**313 (78.7)**	**1,280 (321)**	**3,100 (773)**
Body-weight gain (g)	73	70 (−4%)	71 (−2%)	69 (−6%)	63 (−14%)	44** (−40%)
CD	**0**	**17.6 (4.65)**	**86.57 (22.83)**	**286 (75.0)**	**1,260 (321)**	**2,840 (732)**
Body-weight gain (g)	92	87 (−5%)	81 (−12%)	64** (−30%)	54** (−41%)	19** (−79%)

[a]Ledoux and Reel (1982).
[b]Doses correspond to 0, 0.03, 0.154, 0.5, 2, and 5% TPA in the diet.
[c]Data are adjusted means (g) extracted from graphically reported data using GrabIT! software; variance values were not reported, n = ~30/sex/treatment group.
[d]Value in parenthesis is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), based on Dunnett's two-tailed t-test, as reported by the study authors.
**Significantly different from control ($p < 0.01$), based on Dunnett's two-tailed t-test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-16. Adjusted Mean Cumulative Food Consumption of Male and Female Wistar and CD Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

Male: ADD (HED) in (mg/kg-d)[b]						
Wistar	**0**	**15.3 (4.44)**	**79.09 (22.81)**	**266 (76.0)**	**1,020 (293)**	**2,650 (750)**
4 wk	625.6[c, d]	615.2 (−2%)	620.3 (−1%)	634.7 (+1%)	599.9 (−4%)	563.5** (−10%)
8 wk	1,277.5	1,254.7 (−2%)	1,260.2 (−1%)	1,285.8 (+1%)	1,228.2 (−4%)	1,188.3* (−7%)
13 wk	2,095.8	2,051.1 (−2%)	2,074.6 (−1%)	2,107.5 (+1%)	2,008 (−4%)	1,992.5 (−5%)
CD	**0**	**14.6 (4.23)**	**76.15 (21.99)**	**247 (71.5)**	**976 (282)**	**2,590 (741)**
4 wk	593.9	581.5 (−2%)	573 (−4%)	582.5 (−2%)	565.4 (−5%)	561 (−6%)
8 wk	1,223.6	1,170.9 (−4%)	1,186.5 (−3%)	1,175.2 (−4%)	1,154.2 (−6%)	1,183.9 (−3%)
13 wk	2,036.3	1,920.1 (−6%)	1,953.6 (−4%)	1,944.8 (−4%)	1,914.9 (−6%)	1,991.1 (−2%)
Female: ADD (HED) in (mg/kg-d)						
Wistar	**0**	**19.3 (4.84)**	**114.5 (27.89)**	**313 (78.7)**	**1,280 (321)**	**3,100 (773)**
4 wk	602.4	606.5 (+1%)	601.2 (0%)	593.5 (−1%)	587.1 (−3%)	529.3** (−12%)
8 wk	1,206.3	1,212.9 (+1%)	1,207.4 (0%)	1,175.3 (−3%)	1,183.9 (−2%)	1,111.5** (−8%)
13 wk	1,970.5	1,945.7 (−1%)	1,962.7 (0%)	1,909.2 (−3%)	1,926.8 (−2%)	1,834.5** (−7%)
CD	**0**	**17.6 (4.65)**	**86.57 (22.83)**	**286 (75.0)**	**1,260 (321)**	**2,840 (732)**
4 wk	605.5	585.3 (−3%)	583 (−4%)	583.2 (−4%)	567.5** (−6%)	508.1** (−16%)
8 wk	1,196.5	1,178.1 (−2%)	1,170.2 (−2%)	1,162.5 (−3%)	1,149.2 (−4%)	1,077.6** (−10%)
13 wk	1,962.5	1,917.8 (−2%)	1,889.6 (−4%)	1,878.3 (−4%)	1,860.2* (−5%)	1,746.8** (−11%)

[a]Ledoux and Reel (1982).
[b]Doses correspond to 0, 0.03, 0.154, 0.5, 2, and 5% TPA in the diet.
[c]Data are adjusted means (g) extracted from graphically reported data using GrabIT! software; variance values were not reported; n = ~30/sex/treatment group.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), based on Dunnett's two-tailed t-test, as reported by the study authors.
**Significantly different from control ($p < 0.01$), based on Dunnett's two-tailed t-test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-17. Incidence of Urinary Tract Effects in Male and Female Wistar and CD Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

Observation[c]	ADD (HED) in (mg/kg-d)[b]	
	Wistar	CD
	2,650 M, 3,100 F (750, 773)	2,590 M, 2,840 F (741, 732)
Urinary bladder calculi	4/9 M, 1/9 F	1/7 F
Chronic cystitis	3/10 M, 4/10 F	1/9 M, 4/10 F (1/10 F control)
Transitional cell hyperplasia (bladder)	3/10 M, 5/10 F	1/9 M, 4/10 F (1/10 F control)
Urethra calculi	2/7 M	ND
Chronic urethritis	2/7 M, 4/10 F	4/9 F
Transitional cell hyperplasia (urethra)	2/7 M, 5/10 F	4/9 F (1/10 F control)

[a]Data as reported in Ball et al. (2012) regarding Ledoux and Reel (1982); the only data provided on controls are shown.
[b]Doses correspond to 5% TPA in the diet.
[c]Values denote number of animals showing changes ÷ total number of animals examined.

ADD = adjusted daily dose; F = female(s); HED = human equivalent dose; M = male(s); ND = no data; TPA = terephthalic acid.

Table D-18. Body and Bladder Weights in Male Wistar Rats Treated with TPA (CASRN 100-21-0) in the Diet for 22 Weeks[a]

Endpoint	ADD (HED) in (mg/kg-d)[b]		
	0	**829 (196)**	**4,280 (1,010)**
Body weight (g)	424.6 ± 36.33[c, d]	389.13 ± 37.35* (−8%)	375.4 ± 28.36** (−12%)
Absolute bladder weight (g)	0.094 ± 0.035	0.1 ± 0.045 (+6%)	0.15 ± 0.075** (+60%)
Relative bladder weight (% BW)	0.022 ± 0.006	0.025 ± 0.009 (+14%)	0.04 ± 0.02** (+82%)

[a]Cui et al. (2006a).
[b]Doses correspond to 0, 1, and 5% TPA in the diet.
[c]Data are mean ± variance (type of variance not specified by the study authors); n = 30 (controls), n = 15 (treatment groups).
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), based on ANOVA and least significance difference tests, as reported by the study authors.
**Significantly different from control ($p < 0.01$), based on ANOVA and least significance difference tests, as reported by the study authors.

ADD = adjusted daily dose; ANOVA = analysis of variance; BW = body weight; HED = human equivalent dose; TPA = terephthalic acid.

Table D-19. Urinary Endpoints in Male Wistar Rats Treated with TPA (CASRN 100-21-0) in the Diet for 22 Weeks[a]

Urinary Endpoint	ADD (HED) in (mg/kg-d)[b]		
	0	829 (196)	4,280 (1,010)
pH	6.43 ± 0.25[c, d]	5.98 ± 0.38*	5.43 ± 0.21**
Volume (mL)	5.83 ± 1.06	7.89 ± 0.85 (+35%)	10.24 ± 1.57** (+76%)
Sodium (mM)	119.26 ± 18.77	104.55 ± 3.27* (−12%)	88.79 ± 5.71** (−26%)
Potassium (mM)	286.2 ± 55.94	225.83 ± 36.63* (−21%)	79.78 ± 26.55** (−72%)
Calcium (mM)	4.2 ± 1.54	9.81 ± 2.17** (+134%)	14.83 ± 3.96** (+253%)
Chloride (mM)	151.35 ± 30.85	122.91 ± 16.01** (−19%)	90.41 ± 17.04** (−40%)
Phosphorus (mM)	29.63 ± 1.43	33.25 ± 1.12** (+12%)	31.77 ± 2.2** (+7%)
Urine precipitate	± or −[e]	++	+++

[a]Cui et al. (2006a).
[b]Doses correspond to 0, 1, and 5% TPA in the diet.
[c]Data are mean ± variance (type of variance not specified by the study authors); n = 30 (controls), n = 15 (treatment groups).
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
[e]– = no change; ± = trace; + = slight; ++ = moderate; +++ = marked.
*Significantly different from control ($p < 0.05$), based on ANOVA and least significance difference tests, as reported by the study authors.
**Significantly different from control ($p < 0.01$), based on ANOVA and least significance difference tests, as reported by the study authors.

ADD = adjusted daily dose; ANOVA = analysis of variance; HED = human equivalent dose; TPA = terephthalic acid.

Table D-20. Incidences of Calculi and Histopathological Findings in the Urinary Bladders of Male Wistar Rats Treated with TPA (CASRN 100-21-0) in the Diet for 22 Weeks[a]

Endpoint	ADD (HED) in (mg/kg-d)[b]		
	0	**829 (196)**	**4,280 (1,010)**
Calculi	0/15[c]	0/15 (0%)	4/15 (27%)
Simple hyperplasia	0/15ǂ	2/15 (13%)	5/15* (33%)
PN hyperplasia	0/15	0/15 (0%)	4/15 (27%)
Papilloma	0/15	0/15 (0%)	0/15 (0%)
Transitional cell carcinoma	0/15	0/15 (0%)	0/15 (0%)

[a]Cui et al. (2006a).
[b]Doses correspond to 0, 1, and 5% TPA in the diet.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$), by two-tailed Fisher's exact test, as conducted for this review.
ǂSignificant test for trend ($p < 0.05$), by χ^2 test, as conducted for this review.

ADD = adjusted daily dose; HED = human equivalent dose; PN = papillary or nodule hyperplasia; TPA = terephthalic acid.

Table D-21. Calculi and Histopathological Changes in the Urinary Bladder of Male Wistar Rats Exposed to TPA (CASRN 100-21-0) in the Diet for up to 48 Weeks[a]

		Dose: ADD (HED) in (mg/kg-d)[b]	
Treatment	**Endpoint**	**0**	**3,680 (1,090)**
12 wk	Calculi	0/4 (0%)[c]	7/8* (88%)
	PN hyperplasia	0/4 (0%)	7/8* (88%)
24 wk	Calculi	0/4 (0%)	8/8** (100%)
	PN hyperplasia	0/4 (0%)	8/8** (100%)
	Papilloma	0/4 (0%)	8/8** (100%)
48 wk	Calculi	0/12 (0%)	20/20** (100%)
	PN hyperplasia	0/12 (0%)	20/20** (100%)
	Papilloma	0/12 (0%)	18/20** (90%)
	Transitional cell carcinoma	0/12 (0%)	16/20** (80%)

[a]Cui et al. (2006b).
[b]Doses correspond to 0 and 5% TPA in the diet.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
*Significantly different from control ($p < 0.05$), by two-tailed Fisher's exact test, as conducted for this review.
**Significantly different from control ($p < 0.01$), by two-tailed Fisher's exact test, as conducted for this review.

ADD = adjusted daily dose; HED = human equivalent dose; PN = papillary or nodule hyperplasia; TPA = terephthalic acid.

Table D-22. Survival of Male and Female Wistar Rats Fed TPA (CASRN 100-21-0) in the Diet for 24 Months[a]

	Male: ADD (HED) in (mg/kg-d)[b]			
Endpoint	**0**	**736 (210)**	**1,470 (419)**	**3,680 (1,050)**
Survival at 24 mo	33/50 (66%)[c]	26/50 (52%)	37/50 (74%)	16/50** (32%)
	Female: ADD (HED) in (mg/kg-d)			
Endpoint	**0**	**842 (215)**	**1,680 (429)**	**4,210 (1,070)**
Survival at 24 mo	37/50 (74%)	38/50 (76%)	42/50 (84%)	15/50*** (30%)

[a]Gross (1977).
[b]Doses correspond to 0, 1, 2, and 5% TPA in the diet.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
**Statistically different from control ($p < 0.01$), by Fisher's exact test performed for this review.
***Statistically different from control ($p < 0.0001$), by Fisher's exact test performed for this review.

ADD = adjusted daily doses; HED = human equivalent dose; TPA = terephthalic acid.

Table D-23. Mean Body Weights of Male and Female Wistar Rats Fed TPA (CASRN 100-21-0) in the Diet for 24 Months[a]

Endpoint	Male: ADD (HED) in (mg/kg-d)[b]			
	0	**736 (210)**	**1,470 (419)**	**3,680 (1,050)**
Number of animals (*n*)	*n* = 34	*n* = 32	*n* = 40	*n* = 17
Final body weight (g)	331.1 ± 9.1[c, d]	330.6 ± 9.3 (0%)	298.7 ± 6.9** (−10%)	257.8 ± 7.8** (−22%)
Endpoint	**Female: ADD (HED) in (mg/kg-d)**			
	0	**842 (215)**	**1,680 (429)**	**4,210 (1,070)**
Number of animals (*n*)	*n* = 40	*n* = 38	*n* = 42	*n* = 20
Final body weight (g)	190.2 ± 5.6	188.6 ± 4 (−1%)	181.3 ± 3.9 (−5%)	151.8 ± 3.3** (−20%)

[a]Gross (1977).
[b]Doses correspond to 0, 1, 2, and 5% TPA in the diet.
[c]Data are mean ± SE.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
**Significantly different from control ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SE = standard error; TPA = terephthalic acid.

Table D-24. Absolute and Relative Organ Weights of Male and Female Wistar Rats Fed TPA (CASRN 100-21-0) in the Diet for 24 Months[a]

Endpoint	Male: ADD (HED) in (mg/kg-d)[b]			
	0	**736 (210)**	**1,470 (419)**	**3,680 (1,050)**
Number of animals (*n*)	*n* = 34	*n* = 32	*n* = 40	*n* = 17
Absolute Organ Weights (mg)				
Liver	9,938 ± 407[c, d]	9,708 ± 447 (−2%)	8,733 ± 329* (−12%)	8,201 ± 486*** (−18%)
Kidney	1,239 ± 31	1,143 ± 29 (−8%)	1,078 ± 23*** (−13%)	1,205 ± 57 (−3%)
Heart	904 ± 17	937 ± 23 (+4%)	877 ± 17*** (−3%)	839 ± 38*** (−7%)
Spleen	538 ± 20	516 ± 25 (−4%)	455 ± 23*** (−15%)	433 ± 40* (−20%)
Submaxillary gland	277 ± 9	218 ± 8 (−21%)	209 ± 7 (−25%)	188 ± 8*** (−32%)
Adrenal	23 ± 0.9	22 ± 0.8 (−4%)	24 ± 0.9 (+4%)	31 ± 3** (+35%)
Testis	1,860 ± 34	1,906 ± 58 (+3%)	1,772 ± 46 (−5%)	1,712 ± 61* (−8%)
Relative Organ Weights (mg/100 g BW)				
Liver	2,981 ± 74	2,906 ± 74 (−3%)	2,923 ± 94 (−2%)	3,150 ± 121 (+6%)
Kidney	381 ± 12	351 ± 9 (−8%)	368 ± 12 (−3%)	472 ± 24*** (+24%)
Heart	296 ± 7	287 ± 7 (−3%)	293 ± 7 (−1%)	326 ± 10** (+10%)
Spleen	163 ± 5	154 ± 5 (−6%)	151 ± 7 (−7%)	165 ± 13 (+1%)
Submaxillary gland	69 ± 2.6	66 ± 1.9 (−4%)	70 ± 1.7 (+1%)	73 ± 25 (+6%)
Adrenal	7.3 ± 0.47	7 ± 0.37 (−4%)	8.2 ± 0.39 (+12%)	12.1 ± 1.2*** (+66%)
Testis	571 ± 17	585 ± 19 (+3%)	601 ± 18 (+5%)	646 ± 35 (+13%)

Table D-24. Absolute and Relative Organ Weights of Male and Female Wistar Rats Fed TPA (CASRN 100-21-0) in the Diet for 24 Months[a]

	Female: ADD (HED) in (mg/kg-d)			
Endpoint	**0**	**842 (215)**	**1,680 (429)**	**4,210 (1,070)**
Number of animals (*n*)	*n* = 40	*n* = 38	*n* = 42	*n* = 20
Absolute Organ Weight (mg)				
Liver	7,950 ± 350	6,950 ± 200** (−13%)	6,650 ± 190*** (−16%)	6,430 ± 210*** (−19%)
Kidney	961 ± 35	776 ± 14*** (−19%)	748 ± 13*** (−22%)	877 ± 85 (−9%)
Heart	704 ± 19	659 ± 14 (−6%)	616 ± 10*** (−13%)	588 ± 12*** (−17%)
Spleen	389 ± 21	407 ± 31 (+5%)	341 ± 10 (−12%)	375 ± 44 (−4%)
Submaxillary gland	182 ± 5	179 ± 4 (−2%)	178 ± 3 (−2%)	153 ± 5 (−16%)
Adrenal	22 ± 1	20 ± 0.7 (−9%)	20 ± 0.6 (−9%)	24 ± 0.7 (+9%)
Relative Organ Weights (mg/100 g BW)				
Endpoint	**0**	**842 (215)**	**1,680 (429)**	**4,210 (1,070)**
Liver	4,173 ± 146	3,965 ± 92*** (−5%)	3,673 ± 79*** (−12%)	4,245 ± 128 (+2%)
Kidney	518 ± 24	418 ± 11*** (−19%)	419 ± 10*** (−19%)	587 ± 63 (+13%)
Heart	377 ± 10	353 ± 7* (−6%)	343 ± 5*** (−9%)	390 ± 10 (+3%)
Spleen	206 ± 12	213 ± 13 (+3%)	189 ± 4 (−8%)	248 ± 29 (+20%)
Submaxillary gland	98 ± 3.4	96 ± 2.5 (−2%)	100 ± 2.1 (+2%)	100 ± 3.4 (+2%)
Adrenal	12 ± 0.7	11 ± 0.4 (−8%)	11 ± 0.4 (−8%)	16 ± 0.6* (+33%)

[a]Gross (1977).
[b]Doses correspond to 0, 1, 2, and 5% TPA in the diet.
[c]Data are mean ± SE.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors.
**Significantly different from control ($p < 0.02$), as reported by the study authors.
***Significantly different from control ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; BW = body weight; HED = human equivalent dose; SE = standard error; TPA = terephthalic acid.

Table D-25. Incidence of Urinary Tract Calculi and Nephropathy in Wistar Rats Fed TPA (CASRN 100-21-0) in the Diet for 24 Months[a]

	Male: ADD (HED) in (mg/kg-d)[b]			
Endpoint	**0**	**736 (210)**	**1,470 (419)**	**3,680 (1,050)**
Calculi	0/45 (0%)[c]	0/48 (0%)	0/50 (0%)	42/47** (89%)
Nephropathy	0/45 (0%)	1/43 (2%)	0/48 (0%)	32/37** (87%)
	Female: ADD (HED) in (mg/kg-d)			
Endpoint	**0**	**842 (215)**	**1,680 (429)**	**4,210 (1,070)**
Calculi	0/46 (0%)	1/48 (2%)	0/50 (0%)	39/42** (93%)
Nephropathy	0/46 (0%)	0/48 (0%)	1/47 (2%)	27/34** (80%)

[a]Gross (1977).
[b]Doses correspond to 0, 1, 2, and 5% TPA in the diet.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
**Statistically different from control ($p < 0.01$), by Fisher's exact test (two-tailed), performed for this review.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-26. Tumor Incidences in Wistar Rats Fed TPA (CASRN 100-21-0) in the Diet for 24 Months[a]

	Male: ADD (HED) in (mg/kg-d)[b]			
Tumor location	**0**	**736 (210)**	**1,470 (419)**	**3,680 (1,050)**
Pituitary	36/45 (80%)[c]	37/43 (86%)	43/48 (90%)	21/37 (57%)
Thyroid	19/45 (42%)	14/43 (33%)	17/48 (35%)	7/37 (19%)
Adrenal medulla	0/45 (0%)	1/43 (2%)	1/48 (2%)	1/37 (3%)
Bladder and ureter	0/45 (0%)	1/43 (2%)	1/48 (2%)	21/37** (57%)
	Female: ADD (HED) in (mg/kg-d)			
Tumor location	**0**	**842 (215)**	**1,680 (429)**	**4,210 (1,070)**
Pituitary	33/46 (72%)	36/48 (75%)	37/47 (79%)	14/34 (41%)
Thyroid	19/46 (41%)	14/48 (29%)	18/47 (38%)	7/34 (21%)
Mammary gland	11/46 (24%)	8/48 (17%)	8/47 (17%)	1/34 (3%)
Adrenal medulla	2/46 (4%)	2/48 (4%)	0/47 (0%)	0/34 (0%)
Bladder and ureter	0/46 (0%)	0/48 (0%)	2/47 (4%)	21/34** (62%)

[a]Gross (1977).
[b]Doses correspond to 0, 1, 2, and 5% TPA in the diet.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
**Statistically different from control ($p < 0.01$), by Fisher's exact test performed for this review.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-27. Mean Body Weights of Male F344 Rats Fed TPA (CASRN 100-21-0) in the Diet for 52 Weeks[a]

Study week	ADD (HED) in (mg/kg-d)[b]			
	0	**19.5 (5.30)**	**138.2 (37.54)**	**995.4 (268.2)**
0	205 ± 11[c, d]	195 ± 14* (−5%)	195 ± 11* (−5%)	196 ± 12* (−4%)
1	235 ± 11	223 ± 11 (−5%)	222 ± 13 (−6%)	221 ± 11 (−6%)
2	255 ± 14	245 ± 11 (−4%)	242 ± 13 (−5%)	241 ± 11 (−5%)
3	269 ± 12	262 ± 11* (−3%)	260 ± 12* (−3%)	253 ± 11* (−6%)
4	283 ± 13	274 ± 10 (−3%)	279 ± 11 (−1%)	268 ± 11 (−5%)
5	297 ± 13	288 ± 12 (−3%)	286 ± 36 (−4%)	280 ± 12 (−6%)
6	308 ± 16	298 ± 13 (−3%)	299 ± 14 (−3%)	291 ± 15 (−6%)
7	317 ± 16	306 ± 13* (−3%)	305 ± 14* (−4%)	296 ± 18* (−7%)
8	325 ± 15	313 ± 14 (−4%)	316 ± 14 (−3%)	307 ± 14 (−6%)
9	340 ± 16	321 ± 15 (−6%)	322 ± 15 (−5%)	313 ± 30 (−8%)
10	343 ± 17	337 ± 15 (−2%)	339 ± 15 (−1%)	325 ± 16 (−5%)
11	362 ± 20	338 ± 15* (−7%)	343 ± 15* (−5%)	332 ± 15* (−8%)
12	362 ± 17	342 ± 15 (−6%)	345 ± 16 (−5%)	333 ± 15 (−8%)
13	359 ± 21	351 ± 16 (−2%)	349 ± 15 (−3%)	336 ± 14 (−6%)
15	375 ± 21	360 ± 19* (−4%)	361 ± 15* (−4%)	348 ± 17* (−7%)
17	374 ± 20	362 ± 16 (−3%)	361 ± 16 (−3%)	350 ± 16 (−6%)
19	390 ± 20	378 ± 17* (−3%)	380 ± 19* (−3%)	365 ± 16* (−6%)
21	401 ± 21	383 ± 18 (−4%)	383 ± 17 (−4%)	376 ± 17 (−6%)
23	426 ± 33	393 ± 19* (−8%)	397 ± 17* (−7%)	385 ± 17* (−10%)
25	415 ± 28	439 ± 24 (+6%)	400 ± 18 (−4%)	398 ± 19 (−4%)
30	414 ± 21	411 ± 21 (−1%)	410 ± 21 (−1%)	397 ± 17* (−4%)
34	422 ± 24	411 ± 24* (−3%)	419 ± 20 (−1%)	399 ± 18* (−5%)
39	432 ± 22	418 ± 25* (−3%)	425 ± 20* (−2%)	409 ± 20* (−5%)
43	440 ± 23	429 ± 20* (−3%)	434 ± 20 (−1%)	419 ± 20* (−5%)
47	447 ± 22	432 ± 20* (−3%)	440 ± 21 (−2%)	425 ± 20* (−5%)
52	456 ± 23	442 ± 21* (−3%)	449 ± 22* (−2%)	428 ± 20* (−6%)

[a]Grubbs (1979).
[b]ADD (mg/kg-day) were reported by the study authors.
[c]Data are mean ± SD (g).
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors; statistics were only performed at monthly intervals.

ADD = adjusted daily dose; HED = human equivalent dose; SD = standard deviation; TPA = terephthalic acid.

Table D-28. Mean Body Weights of Female F344 Rats Fed TPA (CASRN 100-21-0) in the Diet for 52 Weeks[a]

Study week	ADD (HED) in (mg/kg-d)[b]			
	0	**19.2 (4.40)**	**136.6 (31.18)**	**989.8 (223.8)**
0	137 ± 6[c, d]	130 ± 6* (−5%)	130 ± 13* (−5%)	131 ± 5* (−4%)
1	146 ± 6	136 ± 6 (−7%)	135 ± 6 (−8%)	137 ± 6 (−6%)
2	155 ± 6	143 ± 7 (−8%)	145 ± 6 (−6%)	140 ± 7 (−10%)
3	163 ± 7	150 ± 8* (−8%)	149 ± 6* (−9%)	147 ± 7* (−10%)
4	169 ± 7	155 ± 7 (−8%)	163 ± 11 (−4%)	164 ± 7 (−3%)
5	173 ± 7	160 ± 7 (−8%)	159 ± 7 (−8%)	157 ± 6 (−9%)
6	178 ± 7	163 ± 7 (−8%)	163 ± 7 (−8%)	160 ± 7 (−10%)
7	183 ± 10	165 ± 8* (−10%)	164 ± 7* (−10%)	161 ± 6* (−12%)
8	184 ± 8	168 ± 8 (−9%)	167 ± 8 (−9%)	164 ± 7 (−11%)
9	193 ± 8	170 ± 8 (−12%)	169 ± 16 (−12%)	164 ± 7 (−15%)
10	192 ± 7	185 ± 11 (−4%)	172 ± 8 (−10%)	170 ± 9 (−11%)
11	204 ± 12	176 ± 9* (−14%)	174 ± 8* (−15%)	172 ± 7* (−16%)
12	207 ± 8	179 ± 9 (−14%)	176 ± 9 (−15%)	171 ± 7 (−17%)
13	202 ± 14	179 ± 9 (−11%)	176 ± 9 (−13%)	171 ± 7 (−15%)
15	208 ± 11	185 ± 14* (−11%)	184 ± 9* (−12%)	180 ± 8* (−13%)
17	203 ± 8	186 ± 9 (−8%)	184 ± 9 (−9%)	172 ± 8 (−15%)
19	214 ± 9	190 ± 10* (−11%)	188 ± 9* (−12%)	184 ± 8* (−14%)
21	217 ± 12	196 ± 9 (−10%)	189 ± 9 (−13%)	184 ± 9 (−15%)
23	238 ± 27	196 ± 10* (−18%)	194 ± 20* (−18%)	192 ± 11* (−19%)
25	230 ± 11	203 ± 11 (−12%)	197 ± 10 (−14%)	192 ± 9 (−17%)
30	212 ± 14	204 ± 12* (−4%)	201 ± 11* (−5%)	196 ± 10* (−8%)
34	210 ± 11	210 ± 12* (0%)	199 ± 13* (−5%)	190 ± 10* (−10%)
39	217 ± 11	208 ± 12* (−4%)	204 ± 12* (−6%)	197 ± 12* (−9%)
43	220 ± 12	211 ± 12* (−4%)	207 ± 13* (−6%)	199 ± 12* (−10%)
47	223 ± 13	213 ± 13* (−4%)	208 ± 12* (−7%)	200 ± 11* (−10%)
52	227 ± 13	223 ± 18* (−2%)	217 ± 15* (−4%)	207 ± 18* (−9%)

[a]Grubbs (1979).
[b]ADD (mg/kg-day) were reported by the study authors.
[c]Data are mean ± SD (g).
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control ($p < 0.05$), as reported by the study authors; statistics were only performed at monthly intervals.

ADD = adjusted daily dose; HED = human equivalent dose; SD = standard deviation; TPA = terephthalic acid.

Table D-29. Food Consumption of Male F344 Rats Fed TPA (CASRN 100-21-0) in the Diet for 52 Weeks[a]

Study weeks	ADD (HED) in (mg/kg-d)[b]			
	0	**19.5 (5.30)**	**138.2 (37.54)**	**995.4 (268.2)**
0−1	17.2 ± 0.8[c, d]	15.3 ± 0.8** (−11%)	15.8 ± 0.9** (−8%)	15.8 ± 0.9** (−8%)
1−2	17.7 ± 0.5	16.4 ± 0.6** (−7%)	15.7 ± 0.9** (−11%)	15.8 ± 0.8** (−11%)
2−3	17.1 ± 0.5	16.7 ± 0.8 (−2%)	15.9 ± 1.1** (−7%)	15.5 ± 0.7** (−9%)
3−4	17.7 ± 0.7	16.0 ± 0.6** (−10%)	16.0 ± 0.5** (−10%)	15.8 ± 0.8** (−11%)
4−5	17.0 ± 1.5	16.1 ± 0.6** (−5%)	16.4 ± 0.6** (−4%)	16.0 ± 0.6** (−6%)
5−6	16.7 ± 0.8	16.4 ± 1.0 (−2%)	15.7 ± 1.4** (−6%)	15.8 ± 1.2** (−5%)
6−7	16.6 ± 0.6	15.9 ± 0.7** (−4%)	15.7 ± 0.9** (−5%)	15.9 ± 0.6** (−4%)
7−8	16.4 ± 0.7	15.5 ± 0.8** (−5%)	15.4 ± 1.0** (−6%)	15.5 ± 0.8** (−5%)
8−9	16.4 ± 0.5	15.5 ± 1.1** (−5%)	15.9 ± 0.9** (−3%)	15.4 ± 0.7** (−6%)
9−10	16.3 ± 1.3	15.2 ± 1.0** (−7%)	15.9 ± 1.3 (−2%)	15.5 ± 0.7** (−5%)
10−11	15.1 ± 1.5	15.6 ± 0.8 (+3%)	15.5 ± 1.7 (+3%)	15.3 ± 0.7 (+1%)
11−12	15.6 ± 1.2	14.9 ± 0.6** (−4%)	15.4 ± 0.7 (−1%)	15.1 ± 0.6 (−3%)
12−13	15.8 ± 0.7	15.1 ± 0.8** (−4%)	15.1 ± 0.6** (−4%)	15.1 ± 0.7** (−4%)
14−15	16.4 ± 0.8	16.4 ± 1.6 (0%)	15.3 ± 1.5** (−7%)	15.5 ± 1.1 (−5%)
16−17	16.3 ± 1.1	16.5 ± 1.9 (+1%)	16.3 ± 0.7 (0%)	15.8 ± 0.8 (−3%)
18−19	16.4 ± 1.4	14.6 ± 0.9** (−11%)	14.5 ± 0.6** (−12%)	14.6 ± 0.6** (−11%)
20−21	16.3 ± 1.1	15.0 ± 0.7** (−8%)	15.3 ± 0.9** (−6%)	15.4 ± 1.2** (−6%)
22−23	15.1 ± 1.9	16.2 ± 0.8* (+7%)	15.5 ± 0.6 (+3%)	15.4 ± 0.6 (+2%)
25−26	15.0 ± 1.4	18.1 ± 1.1* (+21%)	16.3 ± 0.8* (+9%)	16.8 ± 1.3* (+12%)
29−30	15.1 ± 1.0	17.5 ± 1.3* (+16%)	15.4 ± 1.1 (+2%)	15.4 ± 1.1 (+2%)
34−35	14.9 ± 0.7	14.6 ± 1.2 (−2%)	14.9 ± 0.8 (0%)	15.0 ± 1.0 (+1%)
38−39	15.8 ± 1.7	17.5 ± 1.3* (+11%)	16.2 ± 1.1 (+3%)	15.7 ± 1.2 (−1%)
42−43	15.1 ± 1.1	15.5 ± 1.2 (+3%)	16.3 ± 1.0* (+8%)	15.6 ± 1.0 (+3%)
46−47	18.3 ± 1.0	17.4 ± 0.9** (−5%)	17.5 ± 0.9** (−4%)	17.3 ± 1.0** (−5%)
51−52	16.7 ± 1.2	17.5 ± 1.2* (+5%)	17.4 ± 1.3* (+4%)	17.2 ± 1.2 (+3%)

[a]Grubbs (1979).
[b]ADD (mg/kg-day) were reported by the study authors.
[c]Data are mean ± SD (g/animal-day).
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly higher from control ($p < 0.05$), as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SD = standard deviation; TPA = terephthalic acid.

Table D-30. Food Consumption of Female F344 Rats Fed TPA (CASRN 100-21-0) in the Diet for 52 Weeks[a]

Study weeks	ADD (HED) in (mg/kg-d)[b]			
	0	**19.2 (4.40)**	**136.6 (31.18)**	**989.8 (223.8)**
0–1	10.8 ± 0.8[c, d]	9.6 ± 0.5** (−11%)	9.2 ± 0.5** (−15%)	9.2 ± 0.5** (−15%)
1–2	11.7 ± 0.5	9.9 ± 0.7** (−15%)	9.8 ± 0.5** (−16%)	9.9 ± 0.5** (−15%)
2–3	11.8 ± 0.6	10.3 ± 0.6** (−13%)	10.1 ± 0.5** (−14%)	9.7 ± 0.7** (−18%)
3–4	11.8 ± 0.8	10.1 ± 0.9** (−14%)	9.8 ± 0.7** (−17%)	9.7 ± 0.6** (−18%)
4–5	11.5 ± 0.6	9.8 ± 1.0** (−15%)	10.5 ± 0.5** (−9%)	10.7 ± 0.7** (−7%)
5–6	11.1 ± 0.5	10.2 ± 0.7** (−8%)	9.8 ± 0.5** (−12%)	9.9 ± 0.7** (−11%)
6–7	10.9 ± 0.4	9.9 ± 0.9** (−9%)	9.8 ± 1.5** (−10%)	9.8 ± 0.5** (−10%)
7–8	10.4 ± 0.5	9.5 ± 1.0** (−9%)	9.3 ± 0.5** (−11%)	9.2 ± 0.7* (−12%)
8–9	10.4 ± 0.5	9.6 ± 1.0** (−8%)	9.4 ± 1.1** (−10%)	9.6 ± 1.1** (−8%)
9–10	10.8 ± 0.4	9.3 ± 1.0** (−14%)	9.6 ± 1.0** (−11%)	9.8 ± 1.3** (−9%)
10–11	9.5 ± 0.5	10.6 ± 0.9* (+12%)	9.2 ± 0.5 (−3%)	9.5 ± 0.6 (0%)
11–12	10.1 ± 0.7	8.7 ± 0.6** (−14%)	8.8 ± 0.5** (−13%)	9.0 ± 0.6** (−11%)
12–13	10.6 ± 0.7	9.5 ± 0.5** (−10%)	9.3 ± 0.5** (−12%)	9.2 ± 0.6** (−13%)
14–15	10.5 ± 0.5	10.3 ± 1.6 (−2%)	10.9 ± 3.5 (+4%)	9.5 ± 1.3 (−10%)
16–17	10.1 ± 0.9	10.0 ± 0.6 (−1%)	9.6 ± 0.6** (−5%)	9.3 ± 0.8** (−8%)
18–19	10.7 ± 1.0	9.5 ± 0.6** (−11%)	9.5 ± 0.5** (−11%)	9.1 ± 0.6** (−15%)
20–21	10.4 ± 0.6	9.5 ± 1.1** (−9%)	9.3 ± 0.8** (−11%)	9.5 ± 1.4** (−9%)
22–23	9.4 ± 1.1	9.7 ± 1.0 (+3%)	9.2 ± 0.6 (−2%)	8.6 ± 1.0** (−9%)
25–26	8.5 ± 0.9	10.5 ± 0.7* (+24%)	9.8 ± 1.4* (+15%)	9.7 ± 0.8* (+14%)
29–30	8.7 ± 0.8	12.1 ± 0.8* (+39%)	11.9 ± 1.3* (+37%)	11.7 ± 0.8* (+34%)
34–35	9.0 ± 0.8	8.8 ± 0.5 (−2%)	8.8 ± 0.5 (−2%)	8.9 ± 0.7 (−1%)
38–39	9.4 ± 0.5	10.9 ± 0.9 (+16%)	10.5 ± 0.9 (+12%)	10.8 ± 0.9 (+15%)
42–43	8.9 ± 0.8	9.4 ± 0.8* (+6%)	10.3 ± 1.0* (+16%)	9.4 ± 0.8* (+6%)
46–47	11.7 ± 1.1	10.6 ± 0.7** (−9%)	11.3 ± 0.7 (−3%)	11.2 ± 0.7 (−4%)
51–52	10.6 ± 0.8	11.7 ± 0.9* (+10%)	11.6 ± 1.0* (+9%)	11.3 ± 1.1* (+7%)

[a]Grubbs (1979).
[b]ADD (mg/kg-day) were reported by the study authors.
[c]Data are mean ± SD (g/animal-day).
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly higher from control ($p < 0.05$), as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SD = standard deviation; TPA = terephthalic acid.

Table D-31. Terminal Body Weights and Absolute and Relative Organ Weights of Male and Female F344 Rats Sacrificed at 6 and 12 Months Following Exposure to TPA (CASRN 100-21-0) in the Diet[a]

	Male: ADD (HED) in (mg/kg-d)[b]			
Endpoint	**0**	**19.5 (5.30)**	**138.2 (37.54)**	**995.4 (268.2)**
Terminal body weight				
6 mo	358 ± 20[c, d, e]	375 ± 19 (+5%)	384 ± 11 (+7%)	374 ± 10 (+4%)
12 mo	433 ± 16	422 ± 22 (−3%)	416 ± 19 (−4%)	412 ± 14 (−5%)
Absolute heart				
6 mo	1.02 ± 0.07	1.01 ± 0.06 (−1%)	1.02 ± 0.05 (0%)	0.92 ± 0.05* (−10%)
12 mo	1.43 ± 0.07	1.27 ± 0.1 (−11%)	1.43 ± 0.15 (0%)	1.23 ± 0.09 (−14%)
Relative heart				
6 mo	0.29 ± 0.02	0.27 ± 0.02 (−7%)	0.27 ± 0.01 (−7%)	0.24 ± 0.02* (−17%)
12 mo	0.33 ± 0.02	0.3 ± 0.02 (−9%)	0.35 ± 0.03 (+6%)	0.3 ± 0.02 (−9%)
Absolute kidney				
6 mo	2.24 ± 0.2	2.4 ± 0.16 (+7%)	2.58 ± 0.32 (+15%)	2.37 ± 0.5 (+6%)
12 mo	2.92 ± 0.14	2.81 ± 0.12 (−4%)	2.77 ± 0.07 (−5%)	2.64 ± 0.36 (−10%)
Relative kidney				
6 mo	0.63 ± 0.05	0.64 ± 0.06 (+2%)	0.67 ± 0.09 (+6%)	0.64 ± 0.14 (+2%)
12 mo	0.68 ± 0.03	0.67 ± 0.02 (−1%)	0.66 ± 0.02 (−3%)	0.64 ± 0.09 (−6%)
Absolute liver				
6 mo	8.33 ± 1.12	9.14 ± 0.23 (+10%)	9.65 ± 0.55 (+16%)	9.7 ± 0.26 (+16%)
12 mo	10.84 ± 0.76	11.9 ± 0.86 (+3%)	10.59 ± 0.54 (−2%)	11.13 ± 0.79 (+3%)
Relative liver				
6 mo	2.47 ± 0.33	2.44 ± 0.11 (−1%)	2.48 ± 0.12 (0%)	2.59 ± 0.05 (+5%)
12 mo	2.52 ± 0.13	2.65 ± 0.09 (+5%)	2.54 ± 0.06 (+1%)	2.7 ± 0.13 (+7%)

Table D-31. Terminal Body Weights and Absolute and Relative Organ Weights of Male and Female F344 Rats Sacrificed at 6 and 12 Months Following Exposure to TPA (CASRN 100-21-0) in the Diet[a]

Endpoint	Female: ADD (HED) in (mg/kg-d)			
	0	**19.2 (4.40)**	**136.6 (31.18)**	**989.8 (223.8)**
Terminal body weight				
6 mo	206 ± 15	177 ± 12* (−14%)	193 ± 6 (−6%)	180 ± 5* (−13%)
12 mo	216 ± 14	220 ± 15 (+2%)	216 ± 15 (0%)	203 ± 14 (−6%)
Absolute heart				
6 mo	0.65 ± 0.05	0.6 ± 0.04 (−8%)	0.65 ± 0.02 (0%)	0.58 ± 0.09 (−11%)
12 mo	0.86 ± 10	0.76 ± 0.04 (−12%)	0.77 ± 0.02 (−10%)	0.81 ± 0.04 (−6%)
Relative heart				
6 mo	0.32 ± 0.02	0.34 ± 0.03 (+6%)	0.34 ± 0.02 (+6%)	0.32 ± 0.04 (0%)
12 mo	0.4 ± 0.03	0.34 ± 0.02* (−15%)	0.36 ± 0.02 (−10%)	0.4 ± 0.04 (0%)
Absolute kidney				
6 mo	1.44 ± 0.44	1.36 ± 0.09 (−6%)	1.4 ± 0.09 (−3%)	1.31 ± 0.12 (−9%)
12 mo	1.66 ± 0.07	1.62 ± 0.12 (−2%)	1.61 ± 0.12 (−3%)	1.57 ± 0.08 (−5%)
Relative kidney				
6 mo	0.7 ± 0.06	0.77 ± 0.07 (+10%)	0.72 ± 0.03 (+3%)	0.73 ± 0.05 (+4%)
12 mo	0.77 ± 0.03	0.74 ± 0.03 (−4%)	0.75 ± 0.04 (−3%)	0.78 ± 0.03 (+1%)
Absolute liver				
6 mo	4.53 ± 0.57	4.46 ± 0.36 (−2%)	5.55 ± 0.16* (+23%)	4.89 ± 0.33 (+8%)
12 mo	5.85 ± 0.47	5.69 ± 0.42 (−3%)	5.66 ± 0.51 (−3%)	5.79 ± 0.36 (−1%)
Relative liver				
6 mo	2.21 ± 0.27	2.52 ± 0.2 (+14%)	2.87 ± 0.12* (+30%)	2.72 ± 0.13* (+23%)
12 mo	2.7 ± 0.08	2.59 ± 0.1 (−4%)	2.62 ± 0.16 (−3%)	2.86 ± 0.14* (+6%)
Absolute ovaries				
6 mo	NA	NA	NA	NA
12 mo	0.51 ± 0.07	0.46 ± 0.04 (−10%)	0.49 ± 0.03 (−4%)	0.66 ± 0.13* (+29%)
Relative ovaries				
6 mo	NA	NA	NA	NA
12 mo	0.24 ± 0.04	0.21 ± 0.02 (−13%)	0.23 ± 0.02 (−4%)	0.33 ± 0.08 (+38%)

[a]Grubbs (1979).
[b]ADD (mg/kg-day) were reported by the study authors.
[c]Data for absolute organ weight measurements are mean ± SD (g) for five animals/group.
[d]Data for relative organ weight measurements are mean ± SD (g/100 g BW) for five animals/group.
[e]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly higher from control ($p < 0.05$), as reported by the study authors.

ADD = adjusted daily dose; BW = body weight; HED = human equivalent dose; NA = not applicable; SD = standard deviation; TPA = terephthalic acid.

Table D-32. Incidences of Bladder Lesions in Male and Female F344 Rats Exposed to TPA (CASRN 100-21-0) in the Diet for up to 24 Months[a]

	Male: ADD (HED) in (mg/kg-d)[b]			
Endpoint	**0**	**19.5 (5.41)**	**138.2 (38.49)**	**995.4 (274.2)**
Number of bladders examined				
12 mo	5	0	1	7
18 mo	27	20	14	27
24 mo	87	0	0	82
18 mo, revised[c]	*26*	*11*	*15*	*26*
24 mo, revised	*85*	*84*	*85*	*80*
Hyperplasia				
12 mo	0/5 (0%)[d]	NA	0/1 (0%)	2/7 (29%)
18 mo	0/27 (0%)	1/20 (5%)	0/14 (0%)	0/27 (0%)
24 mo	2/87 (2%)	NA	NA	2/82 (2%)
18 mo, revised	*ND*	*0/11 (0%)*	*0/15 (0%)*	*0/26 (0%)*
24 mo, revised	*ND*	*9/84 (11%)*	*3/85 (4%)*	*0/80 (0%)*
Transitional cell papilloma				
12 mo	0/5 (0%)	ND	0/1 (0%)	1/7 (14%)
18 mo	0/27 (0%)	0/20 (0%)	0/14 (0%)	0/27 (0%)
24 mo	0/87 (0%)	NA	NA	0/82 (0%)
18 mo, revised	*ND*	*0/11 (0%)*	*0/15 (0%)*	*0/26 (0%)*
24 mo, revised	*ND*	*0/84 (0%)*	*0/85 (0%)*	*0/80 (0%)*
	Female: ADD (HED) in (mg/kg-d)			
Endpoint	**0**	**19.2 (4.98)**	**136.6 (35.41)**	**989.8 (255.8)**
Number of bladders examined				
12 mo	9	3	7	7
18 mo	22	16	12	27
24 mo	83	0	0	79
18 mo, revised	*21*	*12*	*16*	*23*
24 mo, revised	*71*	*81*	*75*	*73*
Hyperplasia				
12 mo	0/9 (0%)	0/3 (0%)	0/7 (0%)	0/7 (0%)
18 mo	0/22 (0%)	1/16 (6%)	0/12 (0%)	5/27 (19%)
24 mo	8/83 (10%)	NA	NA	14/79 (18%)
18 mo, revised	*ND*	*0/12 (0%)*	*1/16 (6%)*	*4/23 (17%)*
24 mo, revised	*ND*	*7/81 (9%)*	*2/75 (3%)*	*24/73 (33%)*
Squamous metaplasia				
12 mo	0/9 (0%)	0/3 (0%)	0/7 (0%)	0/7 (0%)
18 mo	0/22 (0%)	0/16 (0%)	0/12 (0%)	2/27 (0%)
24 mo	0/83 (0%)	NA	NA	9/79** (11%)
Transitional cell papilloma				
12 mo	0/9 (0%)	0/3 (0%)	0/7 (0%)	0/7 (0%)
18 mo	0/22 (0%)	0/16 (0%)	0/12 (0%)	0/27 (0%)
24 mo	1/83 (1%)	NA	NA	0/79 (0%)
18 mo, revised	*ND*	*0/12 (0%)*	*0/16 (0%)*	*0/23 (0%)*
24 mo, revised	*ND*	*2/81 (2%)*	*0/75 (0%)*	*0/73 (0%)*

Table D-32. Incidences of Bladder Lesions in Male and Female F344 Rats Exposed to TPA (CASRN 100-21-0) in the Diet for up to 24 Months[a]

Endpoint	Females: ADD (HED) in (mg/kg-d)			
	0	**19.2 (4.98)**	**136.6 (35.41)**	**989.8 (255.8)**
Transitional cell adenoma				
12 mo	0/9 (0%)	0/3 (0%)	0/7 (0%)	0/7 (0%)
18 mo	0/22 (0%)	0/16 (0%)	0/12 (0%)	2/27 (7%)
24 mo	1/83 (1%)	NA	NA	15/79** (19%)
24 mo, revised	*1/71 (1%)*	*0/81 (0%)*	*0/75 (0%)*	*10/73** (14%)*
Transitional cell carcinoma				
12 mo	0/9 (0%)	0/3 (0%)	0/7 (0%)	0/7 (0%)
18 mo	0/22 (0%)	0/16 (0%)	0/12 (0%)	0/27 (0%)
24 mo	0/83 (0%)	NA	NA	2/79 (3%)
24 mo, revised	*ND*	*0/81 (0%)*	*0/75 (0%)*	*1/73 (1%)*

[a]ICI Americas Inc (1992); Preache (1983); Grubbs (1979).
[b]Measured daily doses of TPA (mg/kg-day) during the first 12 months on treatment diets, as reported by the study authors.
[c]Data in italics indicate the new and/or reanalysis of histological data performed by ICI Americas Inc (1992).
[d]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
*Statistically different from control ($p < 0.05$), by Fisher's exact test (two-tailed) performed for this review.
**Statistically different from control ($p < 0.01$), by Fisher's exact test (two tailed) performed for this review.

ADD = adjusted daily dose; HED = human equivalent dose; NA = not applicable; ND = no data;
TPA = terephthalic acid.

Table D-33. Survival of Offspring of Wistar and CD of Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days Prior to Mating, and through Mating, Gestation, and Lactation[a]

			Proportion of Females Surviving		Proportion of Males Surviving	
Strain	**ADD (HED) in (mg/kg-d)[b]**	**Number of Litters**	**Day 1**	**Day 21**	**Day 1**	**Day 21**
Wistar	**0**	8	1 ± 0	0.93 ± 0.05	1 ± 0	0.9 ± 0.06
	19.3 (4.84)	9	0.97 ± 0.02 (−3%)[c, d]	0.85 ± 0.11 (−9%)	1 ± 0 (0%)	0.88 ± 0.11 (−2%)
	114.5 (27.89)	10	0.98 ± 0.01 (−2%)	0.95 ± 0.02 (+2%)	0.96 ± 0.04 (−4%)	0.96 ± 0.04 (+7%)
	313 (78.7)	10	0.88 ± 0.1 (−12%)	0.85 ± 0.1 (−9%)	0.88 ± 0.1 (−12%)	0.88 ± 0.1 (−2%)
	1,280 (321)	10	0.9 ± 0.1 (−10%)	0.8 ± 0.14 (−14%)	0.87 ± 0.1 (−13%)	0.76 ± 0.13 (−16%)
	3,100 (773)	7	0.95 ± 0.04 (−5%)	0.8 ± 0.14 (−14%)	0.95 ± 0.05 (−5%)	0.74 ± 0.14 (−18%)
CD	**0**	5	1 ± 0	0.97 ± 0.02	0.97 ± 0.02	0.98 ± 0.02
	17.6 (4.65)	7	1 ± 0 (0%)	1 ± 0 (+3%)	0.98 ± 0.02 (+1%)	0.95 ± 0.04 (−3%)
	86.57 (22.83)	4	1 ± 0 (0%)	1 ± 0 (+3%)	1 ± 0 (+3%)	0.96 ± 0.04 (−2%)
	286 (75.0)	6	1 ± 0 (0%)	0.97 ± 0.02 (0%)	1 ± 0 (+3%)	1 ± 0 (+2%)
	1,260 (321)	5	0.9 ± 0.07 (−10%)	0.7 ± 0.18 (−28%)	0.93 ± 0.04 (−4%)	0.73 ± 0.19 (−26%)
	2,840 (732)	4	0.96 ± 0.04 (−4%)	0.39 ± 0.21* (−60%)	1 ± 0 (+3%)	0.49 ± 0.21* (−50%)

[a]Ledoux and Reel (1982).
[b]Doses equivalent to 0, 0.03, 0.154, 0.5, 2, and 5% TPA in the diets of dams.
[c]Data are mean ± SE.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly higher from control ($p < 0.05$), as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SE = standard error; TPA = terephthalic acid.

Table D-34. Body Weights of Offspring of Wistar and CD Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days Prior to Mating, and through Mating, Gestation, and Lactation[a]

Mean BW (g)	Wistar Rat: ADD (HED) in (mg/kg-d)[b]					
	0	**19.3 (4.84)**	**114.5 (27.89)**	**313 (78.7)**	**1,280 (321)**	**3,100 (773)**
Number of litters	8	8	10	9	8	6
Combined						
Day 1	6.6 ± 0.21[c,d]	6.9 ± 0.27 (+5%)	7.1 ± 0.39 (+8%)	6.8 ± 0.24 (+3%)	6.4 ± 0.20 (−3%)	5.4 ± 0.22* (−18%)
Day 21	48.6 ± 1.86	52.8 ± 2.84 (+9%)	53.1 ± 3 (+9%)	48.2 ± 1.84 (−1%)	41.3 ± 2.28 (−15%)	31.6 ± 3.75** (−35%)
Male						
Day 1	6.7 ± 0.23	7.1 ± 0.28 (+6%)	7.3 ± 0.4 (+9%)	7.0 ± 0.24 (+4%)	6.6 ± 0.21 (−1%)	5.4 ± 0.18* (−19%)
Day 21	50.1 ± 1.82	54.3 ± 3.03 (+8%)	54.7 ± 3.23 (+9%)	49.6 ± 2.02 (−1%)	42.7 ± 2.22 (−15%)	32.0 ± 3.63* (−36%)
Female						
Day 1	6.4 ± 0.19	6.7 ± 0.27 (+5%)	7.0 ± 0.38 (+9%)	6.5 ± 0.26 (+2%)	6.2 ± 0.18 (−3%)	5.3 ± 0.24* (−17%)
Day 21	46.2 ± 2.00	51.6 ± 2.8 (+12%)	51.7 ± 2.86 (+12%)	46.3 ± 1.68 (0%)	39.8 ± 2.25 (−14%)	31.5 ± 3.83* (−32%)

Table D-34. Body Weights of Offspring of Wistar and CD Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 90 Days Prior to Mating, and through Mating, Gestation, and Lactation[a]

Mean BW (g)	CD Rat: ADD (HED) in (mg/kg-d)					
	0	**17.6 (4.65)**	**86.57 (22.83)**	**286 (75.0)**	**1,260 (321)**	**2,840 (732)**
Number of litters	5	7	4	6	4	3
Combined						
Day 1	7.7 ± 0.64	7.2 ± 0.26 (−6%)	8 ± 0.56 (+4%)	7.6 ± 0.23 (−1%)	7.4 ± 0.17 (−4%)	7 ± 0.66 (−9%)
Day 21	58.1 ± 5.23	50.7 ± 2.93 (−13%)	55.1 ± 8.49 (−5%)	52.2 ± 2.44 (−10%)	45.4 ± 3.18 (−22%)	25.2 ± 3.69** (−57%)
Male						
Day 1	8.0 ± 0.78	7.3 ± 0.26 (−9%)	8.1 ± 0.55 (+1%)	8.2 ± 0.30 (+2%)	7.6 ± 0.21 (−5%)	7.2 ± 0.70 (−10%)
Day 21	59.8 ± 5.87	51.0 ± 3.10 (−15%)	56.1 ± 9.26 (−6%)	54.9 ± 3.40 (−8%)	46.3 ± 3.12 (−23%)	25.9 ± 3.71* (−57%)
Female						
Day 1	7.5 ± 0.52	7.1 ± 0.26 (−5%)	7.8 ± 0.62 (4%)	7.2 ± 0.20 (−4%)	7.1 ± 0.16 (−5%)	6.8 ± 0.62 (−9%)
Day 21	57.5 ± 4.73	50.2 ± 2.84 (−13%)	54.1 ± 8.22 (−6%)	51.2 ± 2.44 (−11%)	44.4 ± 3.01 (−23%)	23.9 ± 3.76* (−58%)

[a]Ledoux and Reel (1982).
[b]Doses equivalent to 0, 0.03, 0.154, 0.5, 2, and 5% TPA in the diets of dams.
[c]Data are mean ± SE.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly higher from control ($p < 0.05$), as reported by the study authors.
** Statistically significantly higher from control ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; BW = body weight; HED = human equivalent dose; SE = standard error; TPA = terephthalic acid.

Table D-35. Incidence of Renal and Bladder Calculi in F_1 Rats Exposed to TPA (CASRN 100-21-0) from Gestation through Weaning and in the Diet for up to 30 Days[a]

Strain	ADD (HED) (mg/kg-d)[b]	Male	Female
Wistar	**0**	0/31 (0%)[c, d]	0/21 (0%)
	19.3 (4.84)	0/26 (0%)	0/31 (0%)
	114.5 (27.89)	0/31 (0%)	0/33 (0%)
	313 (78.7)	0/34 (0%)	0/33 (0%)
	1,280 (321)	0/34 (0%)	1/32 (3%)
	3,100 (773)	8/18* (44%)	16/31* (51%)
CD	**0**	0/17 (0%)	0/20 (0%)
	17.6 (4.65)	0/21(0%)	0/24 (0%)
	86.57 (22.83)	0/13 (0%)	0/12 (0%)
	286 (75.0)	0/21 (0%)	0/22 (0%)
	1,260 (321)	1/17 (6%)	1/16 (6%)
	2,840 (732)	5/9* (56%)	9/13* (70%)

[a]Ledoux and Reel (1982).
[b]Doses equivalent to 0, 0.03, 0.154, 0.5, 2, and 5% TPA in the diets of dams.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
[d]Incidence includes all weanling rats necropsied between Days 21−51.
*Statistically different from control ($p < 0.05$), by Fisher's exact test (two-tailed) performed for this review.

ADD = adjusted daily dose; HED = human equivalent dose; TPA = terephthalic acid.

Table D-36. Body-Weight Gain and Testicular Endpoints in Male S-D Rats Treated with TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

Endpoint	ADD (HED) in (mg/kg-d)[b]			
	0	**172 (42.7)**	**861 (214)**	**4,310 (1,070)**
Body-weight gain (g)	240.98 ± 34.8[c, d]	240.84 ± 34.45 (0%)	229.7 ± 33.07 (−5%)	211.44 ± 35.3 (−12%)
Absolute testis (g)	3.2 ± 0.27	3.13 ± 0.21 (−2%)	3.22 ± 0.19 (+1%)	3.12 ± 0.35 (−3%)
Relative testis (% of BW)	0.88 ± 0.121	0.89 ± 0.105 (+1%)	0.88 ± 0.076 (0%)	0.93 ± 0.097 (+6%)
Sperm head count (10^6/g)	113.32 ± 10.31	112.84 ± 11.69 (0%)	106.94 ± 13.11 (−6%)	91.43 ± 13.42** (−19%)
Daily sperm gain production (10^6/g-d)	18.58 ± 1.69	18.5 ± 2.15 (0%)	17.53 ± 1.92 (−6%)	14.99 ± 2.2** (−19%)

[a]Cui et al. (2004).
[b]Doses equivalent to 0, 0.2, 1, and 5% TPA in the diet.
[c]Data are mean ± SD; n = 10.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
**Significantly different from control ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; BW = body weight; HED = human equivalent dose; SD = standard deviation; S-D = Sprague-Dawley; TPA = terephthalic acid.

Table D-37. Sperm Motility Parameters in Male S-D Rats Treated with TPA (CASRN 100-21-0) in the Diet for 90 Days[a]

Parameter	ADD (HED) in (mg/kg-d)[b]			
	0	**172 (42.7)**	**861 (214)**	**4,310 (1,070)**
Number of animals (*n*)	*n* = 6	*n* = 5	*n* = 6	*n* = 6
VCL (µM/s)	398.97 ± 35.67[c, d]	369.48 ± 20.26 (−7%)	378.68 ± 28.93 (−5%)	365.28 ± 15.22 (−8%)
VAP (µM/s)	117.75 ± 11.85	112.9 ± 11.05 (−4%)	114.63 ± 10.23 (−3%)	103.77 ± 12.13 (−12%)
VSL (µM/s)	87.58 ± 22.19	63.92 ± 12.94* (−27%)	62.92 ± 15.34* (−28%)	53.17 ± 18.72** (−39%)
BCF (Hz)	7.58 ± 1.4	5.9 ± 1.47 (−22%)	5.82 ± 1.51 (−23%)	4.9 ± 1.49** (−35%)
ALH (µm)	50.53 ± 7.87	46.3 ± 5.58 (−8%)	46.63 ± 9.02 (−8%)	50.23 ± 10.11 (−1%)
LIN (%)	21.85 ± 5.23	16.5 ± 3.01 (−25%)	15.62 ± 3.26* (−29%)	14.1 ± 5.32* (−36%)
STR (%)	75.38 ± 11.65	61.86 ± 2.38* (−18%)	60.05 ± 7.96* (−20%)	57.17 ± 11.59** (−24%)

[a]Cui et al. (2004).
[b]Doses equivalent to 0, 0.2, 1, and 5% TPA in the diet.
[c]Data are mean ± SD.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; ALH = amplitude of lateral head displacement; BCF = beat cross frequency; HED = human equivalent dose; LIN = linearity; SD = standard deviation; S-D = Sprague Dawley; STR = straightness; TPA = terephthalic acid; VAP = average path velocity; VCL = curvilinear velocity; VSL = straight line velocity.

Table D-38. Sperm Parameters in Male Rats Exposed to TPA (CASRN 100-21-0) by Daily Gavage for 4 Weeks[a]

Parameter	ADD (HED) in (mg/kg-d)[b]	
	0	1,000 (249)
Sperm count (millions/mL)	7.66 ± 2.53[c, d]	7.72 ± 1.94 (+1%)
Sperm motility		
VAP (µm/s)	96.8 ± 7.35	73.5 ± 4.3 (−24%)
VSL (µm/s)	87.9 ± 17.7	66.6 ± 1.02 (−24%)
VCL (µm/s)	215 ± 22.8	175.8 ± 31.6 (−18%)
ALH (µm)	26.7 ± 2	23.8 ± 1 (−11%)
BCF (Hz)	35.2 ± 3.7	32.6 ± 2.9 (−7%)
STR (%)	90.8 ± 2.6	90.6 ± 1.2 (−0.2%)
LIN (%)	40.9 ± 2.5	37.9 ± 2 (−7%)

Parameter	ADD (HED) in (mg/kg-d)			
	0	10 (2.5)	100 (24.9)	1,000 (249)
Progressive motility (%)	54.18[e]	54.03 (0%)	55.52 (+2%)	39.87* (−26%)
Sperm mobility (%)	89.73	94.51 (+5%)	91.86 (+2%)	84.96 (−5%)

[a]Kwack and Lee (2015).
[b]Reported doses (mg/kg-day).
[c]Data are mean ± SD, n = 5 rats/group.
[d]Value in parentheses is percent change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
[e]Means were extracted from graphical images using GrabIT! software.
*Significantly different from control ($p < 0.05$) by ANOVA and Tuckey's post hoc comparisons, as reported by the study authors.

ADD = adjusted daily dose; ALH = amplitude of lateral head displacement; ANOVA = analysis of variance; BCF = beat cross frequency; HED = human equivalent dose; LIN = linearity; SD = standard deviation; STR = straightness; TPA = terephthalic acid; VAP = velocity average path; VCL = velocity curved line; VSL = velocity straight line.

Table D-39. Skeletal Anomalies in Fetuses of S-D Rats Exposed to TPA (CASRN 100-21-0) Aerosols on GDs 6−15[a]

Effect	Analytical Concentration (HEC_{ER}) (mg/m^3)[b]			
	0	**0.90 (0.59)**	**4.73 (2.96)**	**10.40 (6.240)**
Number examined	151/23[c]	162/24	147/22	171/25
Ribs				
Wavy	2/2	0/0	4/4[d]	5/4
Bulbous	4/3	0/0	11/4[e]	9/4
Reduced 13th	1/1	2/2	3/2	8/5
Rudimentary 14th	2/2	1/1	5/5	2/2
Incomplete ossification	2/2	0/0	7/2	4/3
All rib anomalies	7/5	3/3	19/8*	19/11
% Affected	4.6/22	1.9/13	13/36*	11/44
Summary of Skeletal Evaluation Scores				
Score[f]				
0	144/18	159/21	128/14	152/14
1	1/1	2/2	3/2	7/5
2	3/3	0/0	3/2	4/2
3	2/2	1/1	9/7	6/5
4	1/1	0/0	4/1	2/1
5	0/0	0/0	1/1[g]	0/0

[a]Chemical Manufacturers Association (2000).
[b]Corrected (i.e., respirable-sized particles) TWA concentrations for dams exposed 6 hours/day, 7 days/week on GDs 6−15; calculated extrarespiratory HECs appear in parentheses.
[c]Fetus/litter.
[d]One fetus had ribs that appeared gnarled; this was considered by the study authors to be a malformation.
[e]Eight fetuses from a single litter had bulbous ribs.
[f]0 = no visible abnormality; 1 = variation within normal limits; 2 = slight variation; 3 = moderate variation; 4 = severe variation; 5 = malformation.
[g]Pup exhibited both a variation and a malformation.
*Significantly different from controls ($p < 0.05$), as reported by the study authors.

ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration; S-D = Sprague-Dawley; TPA = terephthalic acid; TWA = time-weighted average.

APPENDIX E. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE

Dichotomous Noncancer Data

The benchmark dose (BMD) modeling of dichotomous data is conducted with U.S. EPA's Benchmark Dose Software (BMDS; Version 2.7 was used for this document). For these data, the Gamma, Logistic, Log-Logistic, Log-Probit, Multistage, Probit, and Weibull dichotomous models available within the software are fit using a benchmark response (BMR) of 10% extra risk. Alternative BMRs may also be used where appropriate, as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012a). In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate benchmark dose lower confidence limit (BMDL) estimates from different models (high model dependence). Adequacy of model fitting is judged by three criteria: (1) goodness-of-fit *p*-value ($p < 0.1$), (2) visual inspection of the dose-response curve, and (3) scaled residual at the data point (except the control) closest to the predefined BMR (absolute value < 2.0). Among all models providing adequate fit, the BMDL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential point of departure (POD), if the BMDLs are sufficiently close (less than approximately threefold); if the BMDLs are not sufficiently close (greater than approximately threefold), model-dependence is indicated, and the model with the lowest reliable BMDL is selected.

Continuous Data

BMD modeling of continuous data is conducted with U.S. EPA's BMDS (Version 2.7). All continuous models available within the software (Exponential, Hill, Linear, Polynomial, and Power models) are fit using a standard reporting BMR of 1 standard deviation (SD) relative risk. Alternate BMRs may also be used (e.g., BMR = 10% RD for body weight based on a biologically significant weight loss of 10%), as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012a). In general, the BMR should be near the low end of the observable range of increased risk in the study. BMRs that are too low can result in widely disparate BMDL estimates from different models (high model dependence). An adequate fit is judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR (absolute value < 2.0), and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination is made as to whether the variance across dose groups is homogeneous. If a homogeneous variance model is deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results are estimated from a homogeneous variance model. If the test for homogeneity of variance is rejected (*p*-value < 0.1), the model is run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model does not adequately fit the data (i.e., Test 3; *p*-value < 0.1), the data set is considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL is selected if the BMDL estimates from different models vary more than approximately threefold (indicating model dependence); otherwise, the BMDL from the model with the lowest AIC is selected as a potential POD from which to derive the reference value.

Decreased Pup Weight in Male and Female Wistar Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

The procedure outlined above for continuous data was applied to the data for decreased pup weight in male and female Wistar rats following TPA exposure via diet for 90 days prior to mating through postweaning [Ledoux and Reel (1982); see Table D-34]. The BMD modeling results are presented in Table E-1 and Figure E-1. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all available models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Exponential 2) is selected. Based on human equivalent doses (HEDs), the 5% benchmark dose (BMD_{05}) and 5% benchmark dose lower confidence limit ($BMDL_{05}$) for decreased pup weight in male and female Wistar rats were 78.7 and 59.9 mg/kg-day, respectively.

Table E-1. Decreased Pup Weight in Male and Female Wistar Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{05} (HED) (mg/kg-d)	$BMDL_{05}$ (HED) (mg/kg-d)
Constant variance						
Exponential (model 2)[c, *]	0.3833	0.5483	−0.355	249.0319	78.7234	59.944
Exponential (model 3)[c]	0.3833	0.3829	−0.3573	251.0318	79.0636	59.9441
Exponential (model 4)[c]	0.3833	0.3902	−0.308	250.9843	71.6596	35.4053
Exponential (model 5)[c]	0.3833	0.2466	−0.5254	252.7752	96.5983	36.3945
Hill[c]	0.3833	0.2498	−0.52	252.749182	95.4929	32.1315
Linear[d]	0.3833	0.4895	−0.425	249.399362	96.5738	78.1725
Polynomial (2-degree)[d]	0.3833	0.4895	−0.425	249.399362	96.5738	78.1725
Polynomial (3-degree)[d]	0.3833	0.4895	−0.425	249.399362	96.5738	78.1725
Power[c]	0.3833	0.4895	−0.425	249.399362	96.5738	78.1725

[a]Ledoux and Reel (1982).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be negative.
*Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; HED = human equivalent dose; TPA = terephthalic acid.

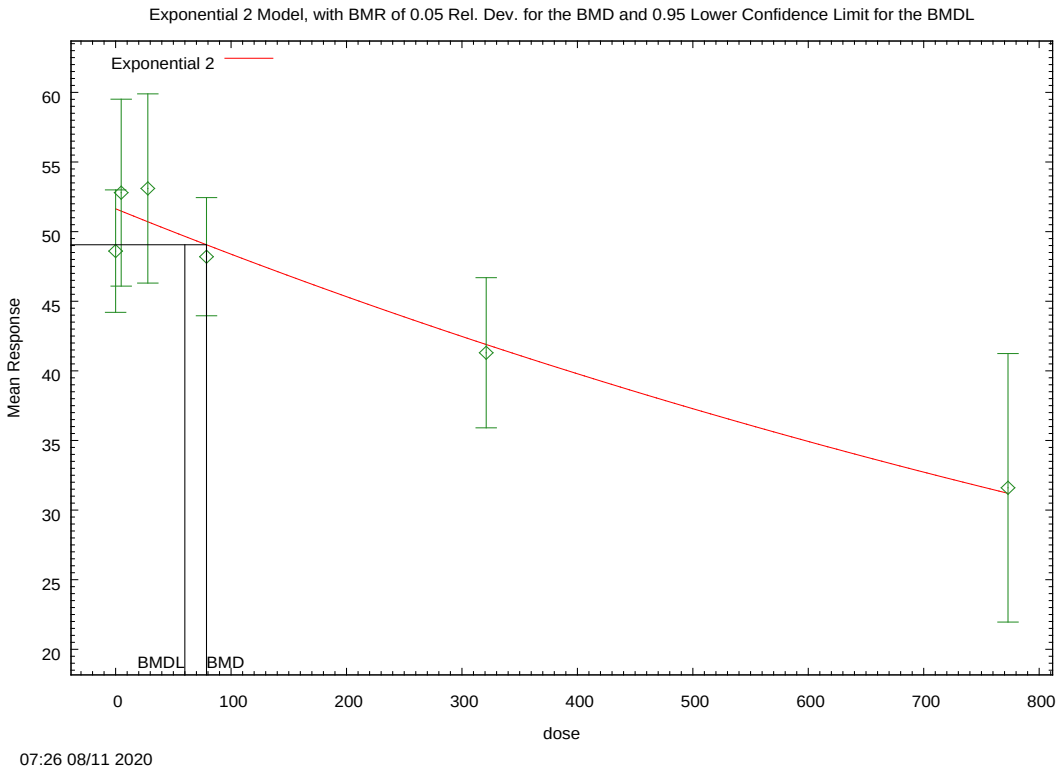

Figure E-1. Fit of Exponential 2 Model to Data for Decreased Pup Weight in Male and Female Wistar Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

Decreased Pup Weight in Male Wistar Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

The procedure outlined above for continuous data was applied to the data for decreased pup weight in male Wistar rats following TPA exposure via diet for 90 days prior to mating through postweaning [Ledoux and Reel (1982); see Table D-34]. The BMD modeling results are presented in Table E-2 and Figure E-2. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all available models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Exponential 2) is selected. Based on HEDs, the BMD_{05} and $BMDL_{05}$ for decreased pup weight in male Wistar rats were 77.1 and 58.8 mg/kg-day, respectively.

Table E-2. Decreased Pup Weight in Male Wistar Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{05} (HED) (mg/kg-d)	$BMDL_{05}$ (HED) (mg/kg-d)
Constant variance						
Exponential (model 2)[c, *]	0.3103	0.5737	−0.3637	252.5633	77.0854	58.8168
Exponential (model 3)[c]	0.3103	0.4082	−0.4013	254.5518	82.7344	58.8488
Exponential (model 4)[c]	0.3103	0.4074	−0.3464	254.5567	74.4376	36.785
Exponential (model 5)[c]	0.3103	0.2556	−0.5415	256.3851	97.8234	37.6158
Hill[c]	0.3103	0.2582	−0.539	256.36507	97.1229	33.4038
Linear[d]	0.3103	0.5295	−0.439	252.828823	94.7266	76.9098
Polynomial (2-degree)[d]	0.3103	0.5295	−0.439	252.828823	94.7266	76.9098
Polynomial (3-degree)[d]	0.3103	0.5295	−0.439	252.828823	94.7266	76.9098
Power[c]	0.3103	0.5295	−0.439	252.828823	94.7266	76.9098

[a]Ledoux and Reel (1982).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be negative.
*Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; HED = human equivalent dose; TPA = terephthalic acid.

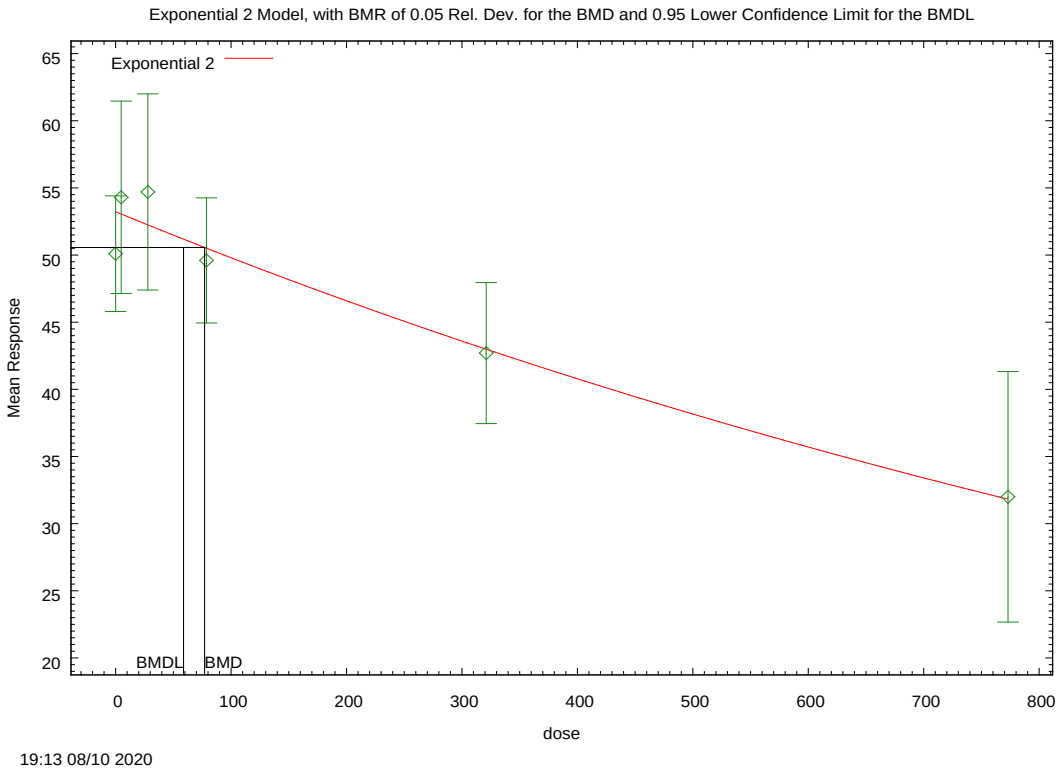

Figure E-2. Fit of Exponential 2 Model to Data for Decreased Pup Weight in Male Wistar Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

Decreased Pup Weight in Female Wistar Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

The procedure outlined above for continuous data was applied to the data for decreased pup weight in female Wistar rats following TPA exposure via diet for 90 days prior to mating through postweaning [Ledoux and Reel (1982); see Table D-34]. The BMD modeling results are presented in Table E-3 and Figure E-3. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all available models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the models with the lowest AICs (Exponential 2 and 3) are selected. Based on HEDs, the BMD_{05} and $BMDL_{05}$ for decreased pup weight in female Wistar rats were 82.4 and 61.8 mg/kg-day, respectively.

Table E-3. Decreased Pup Weight in Female Wistar Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{05} (HED) (mg/kg-d)	$BMDL_{05}$ (HED) (mg/kg-d)
Constant variance						
Exponential (model 2)[c, *]	0.4121	0.3238	−0.4693	248.8078	82.4489	61.7604
Exponential (model 3)[c, *]	0.4121	0.3238	−0.4693	248.8078	82.4489	61.7604
Exponential (model 4)[c]	0.4121	0.2137	−0.3761	250.6302	67.9907	32.2851
Exponential (model 5)[c]	0.4121	0.1209	−0.6034	252.3714	93.3897	33.4975
Hill[c]	0.4121	0.1235	−0.59	252.328388	91.3872	29.2144
Linear[d]	0.4121	0.2749	−0.527	249.269353	100.62	80.2109
Polynomial (2-degree)[d]	0.4121	0.2749	−0.527	249.269353	100.62	80.2109
Polynomial (3-degree)[d]	0.4121	0.2749	−0.527	249.269353	100.62	80.2109
Power[c]	0.4121	0.2749	−0.527	249.269353	100.62	80.2109

[a]Ledoux and Reel (1982).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be negative.
*Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; HED = human equivalent dose; TPA = terephthalic acid.

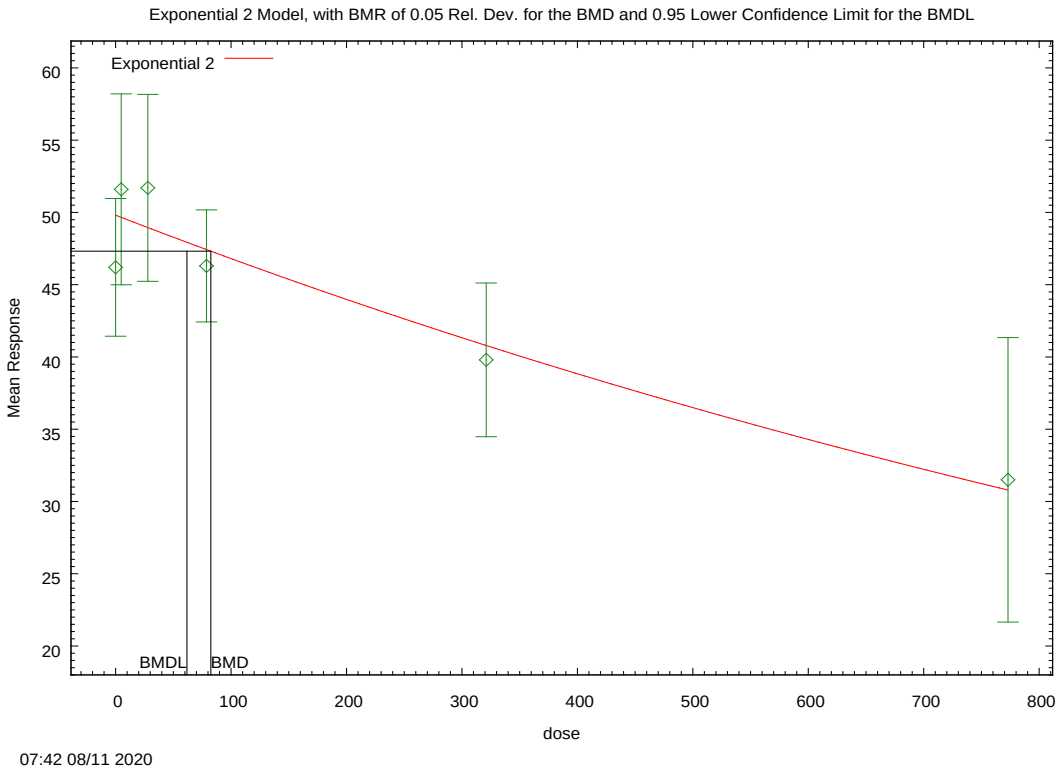

Figure E-3. Fit of Exponential 2 Model to Data for Decreased Pup Weight in Female Wistar Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

Decreased Pup Weight in Male and Female CD Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

The procedure outlined above for continuous data was applied to the data for decreased pup weight in male and female CD rats following TPA exposure via diet for 90 days prior to mating through postweaning [Ledoux and Reel (1982); see Table D-34]. The BMD modeling results are presented in Table E-4 and Figure E-4. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all available models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Linear) is selected. Based on HEDs, the BMD_{05} and $BMDL_{05}$ for decreased pup weight in male and female CD rats were 71.7 and 55.5 mg/kg-day, respectively.

Table E-4. Decreased Pup Weight in Male and Female CD Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{05} (HED) (mg/kg-d)	$BMDL_{05}$ (HED) (mg/kg-d)
Constant variance						
Exponential (model 2)[c]	0.1342	0.4796	0.1715	163.4117	57.6879	39.8961
Exponential (model 3)[c]	0.1342	0.5261	−0.2503	164.1524	158.293	43.8932
Exponential (model 4)[c]	0.1342	0.4796	0.1715	163.4117	57.6879	33.2875
Exponential (model 5)[c]	0.1342	0.328	−0.2503	166.1524	158.293	43.8932
Hill[c]	0.1342	0.3335	−0.187	166.118876	140.366	55.2759
Linear[d, *]	0.1342	0.6122	0.0536	162.605554	71.7181	55.4981
Polynomial (2-degree)[d]	0.1342	0.5414	−0.106	164.075162	121.581	56.8571
Polynomial (3-degree)[d]	0.1342	0.544	−0.0474	164.062316	107.468	56.8926
Power[c]	0.1342	0.5333	−0.181	164.11615	138.854	56.7445

[a]Ledoux and Reel (1982).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be negative.
*Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; HED = human equivalent dose; TPA = terephthalic acid.

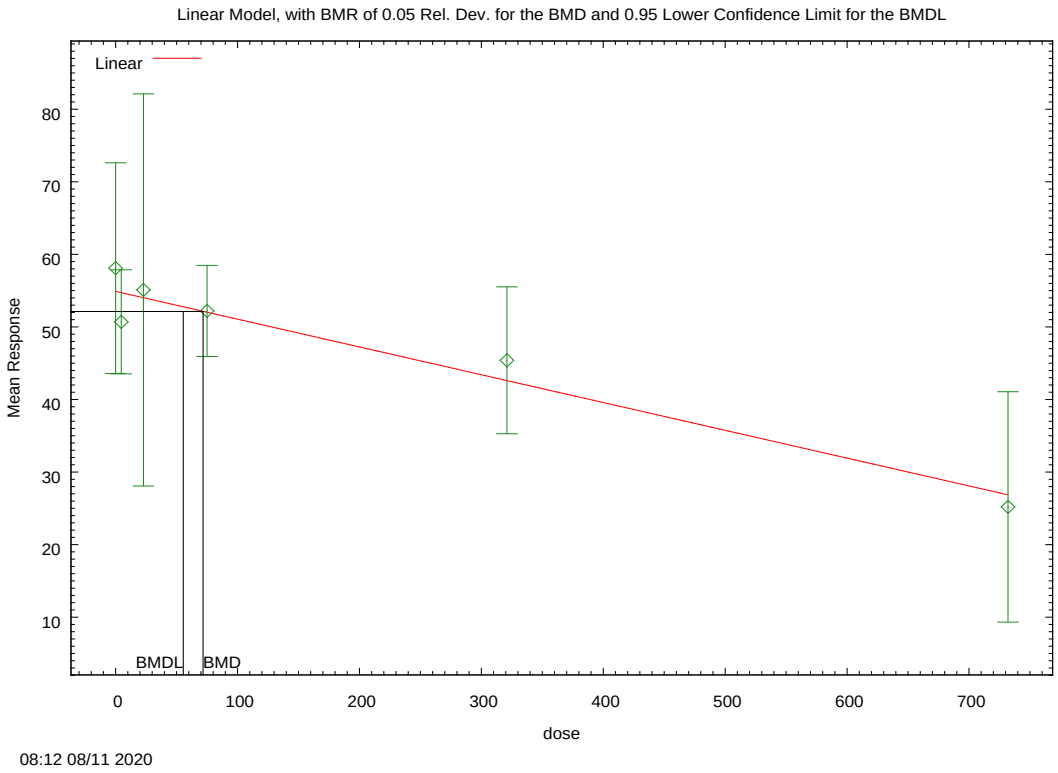

Figure E-4. Fit of Linear Model to Data for Decreased Pup Weight in Male and Female CD Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

Decreased Pup Weight in Male CD Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

The procedure outlined above for continuous data was applied to the data for decreased pup weight in male CD rats following TPA exposure via diet for 90 days prior to mating through postweaning [Ledoux and Reel (1982); see Table D-34]. The BMD modeling results are presented in Table E-5 and Figure E-5. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all available models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Linear) is selected. Based on HEDs, the BMD_{05} and $BMDL_{05}$ for decreased pup weight in male CD rats were 72.1 and 54.6 mg/kg-day, respectively.

Table E-5. Decreased Pup Weight in Male CD Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{05} (HED) (mg/kg-d)	$BMDL_{05}$ (HED) (mg/kg-d)
Constant variance						
Exponential (model 2)[c]	0.1482	0.4347	0.4889	169.9029	58.381	39.1203
Exponential (model 3)[c]	0.1482	0.4865	0.1016	170.5483	164.124	43.782
Exponential (model 4)[c]	0.1482	0.4347	0.4889	169.9029	58.381	32.3256
Exponential (model 5)[c]	0.1482	0.2954	0.1016	172.5482	164.133	43.7778
Hill[c]	0.1482	0.2981	4.99×10^{-5}	172.529938	213.31	38.8895
Linear[d, *]	0.1482	0.5488	0.386	169.163521	72.113	54.6046
Polynomial (2-degree)[d]	0.1482	0.4785	0.223	170.591947	133.189	56.1618
Polynomial (3-degree)[d]	0.1482	0.4785	0.223	170.591947	133.189	56.1618
Power[c]	0.1482	0.4825	0.158	170.570045	148.96	56.2269

[a]Ledoux and Reel (1982).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be negative.
*Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; HED = human equivalent dose; TPA = terephthalic acid.

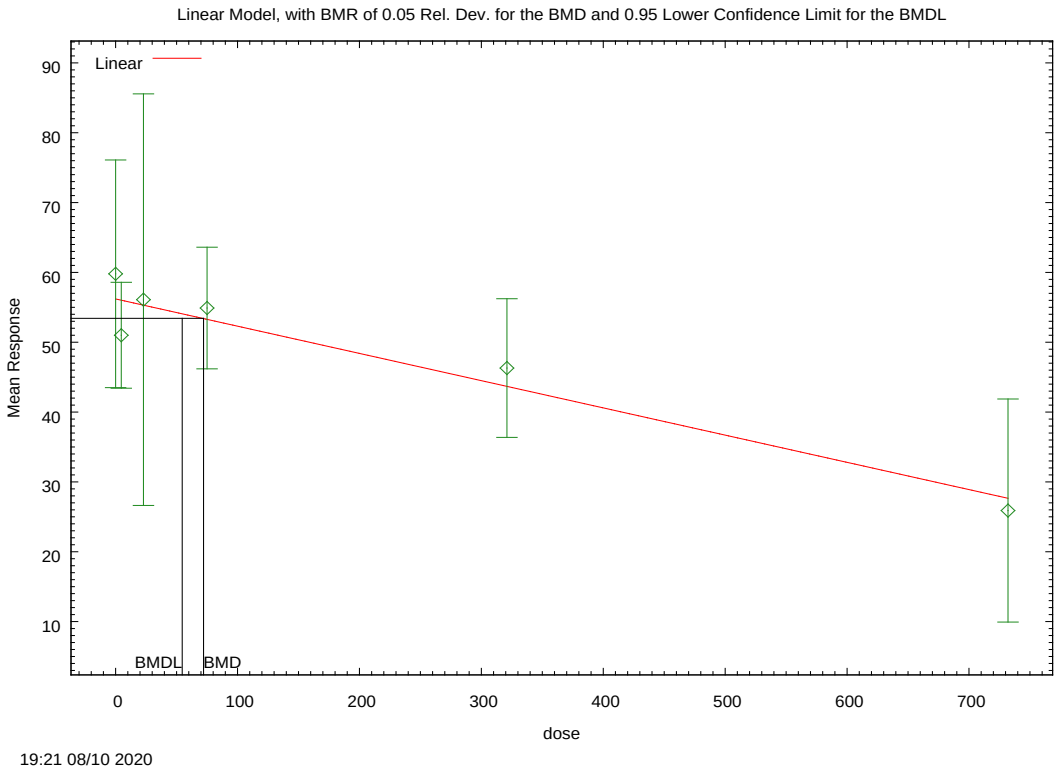

Figure E-5. Fit of Linear Model to Data for Decreased Pup Weight in Male CD Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

Decreased Pup Weight in Female CD Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

The procedure outlined above for continuous data was applied to the data for decreased pup weight in female CD rats following TPA exposure via diet for 90 days prior to mating through postweaning [Ledoux and Reel (1982); see Table D-34]. The BMD modeling results are presented in Table E-6 and Figure E-6. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all available models. The BMDLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Linear) is selected. Based on HEDs, the BMD_{05} and $BMDL_{05}$ for decreased pup weight in female CD rats were 69.2 and 54.4 mg/kg-day, respectively.

Table E-6. Decreased Pup Weight in Female CD Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{05} (HED) (mg/kg-d)	$BMDL_{05}$ (HED) (mg/kg-d)
Constant variance						
Exponential (model 2)[c]	0.1644	0.4495	0.1273	161.0159	55.0169	38.6817
Exponential (model 3)[c]	0.1644	0.4974	−0.3253	161.7049	151.545	42.5884
Exponential (model 4)[c]	0.1644	0.4495	0.1273	161.0159	55.0169	32.9356
Exponential (model 5)[c]	0.1644	0.3043	−0.3253	163.7049	151.545	42.5884
Hill[c]	0.1644	0.3136	−0.245	163.644549	130.142	54.9865
Linear[d, *]	0.1644	0.5963	−0.00487	160.099523	69.214	54.3605
Polynomial (2-degree)[d]	0.1644	0.5217	−0.164	161.577874	112.804	55.6005
Polynomial (3-degree)[d]	0.1644	0.5267	−0.107	161.551855	100.791	55.6673
Power[c]	0.1644	0.5091	−0.243	161.643124	129.641	55.4353

[a]Ledoux and Reel (1982).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]Coefficients restricted to be negative.
*Selected model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 5 = dose associated with 5% relative deviation); BMR = benchmark response; HED = human equivalent dose; TPA = terephthalic acid.

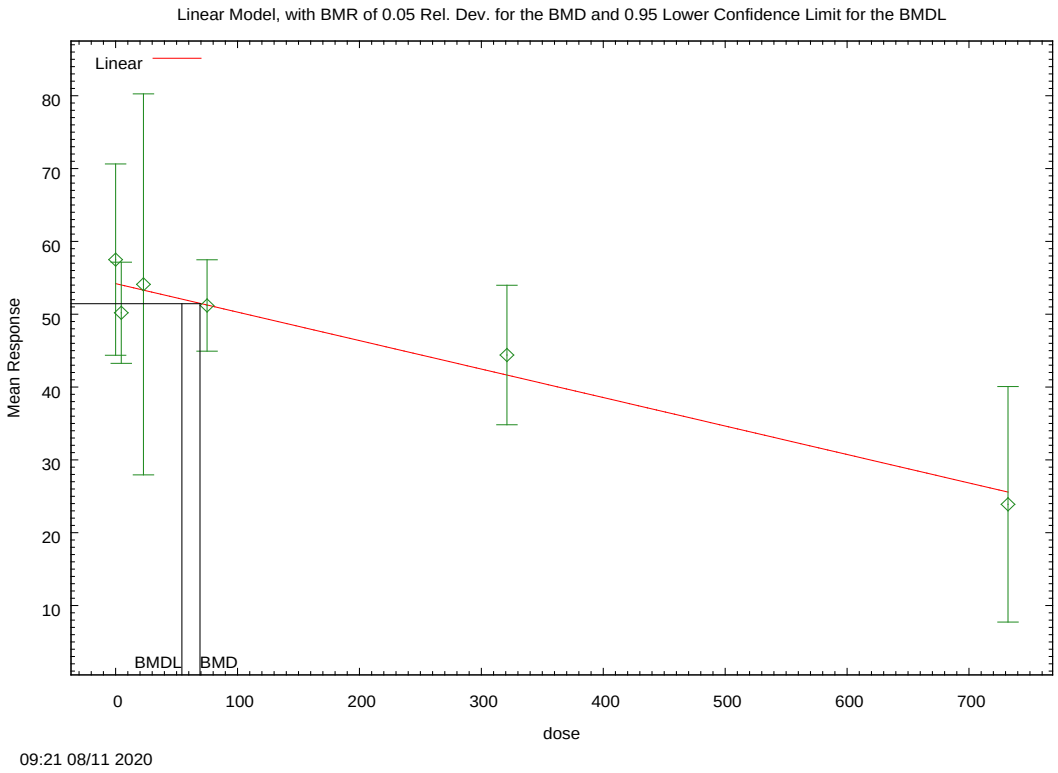

Figure E-6. Fit of Linear Model to Data for Decreased Pup Weight in Female CD Rats Following TPA Exposure via Diet for 90 Days Prior to Mating through Postweaning (Ledoux and Reel, 1982)

BMD Output for Figure E-6:

```
================================================================
        Polynomial Model. (Version: 2.21;  Date: 03/14/2017)
        Input Data File: C:/Users/JKaiser/Desktop/BMDS240/Data/lin_pupwt_f_CD_LR_Lin-
ConstantVariance-BMR05.(d)
        Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/lin_pupwt_f_CD_LR_Lin-ConstantVariance-BMR05.plt
                                                Tue Aug 11 15:02:40 2020
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Signs of the polynomial coefficients are not restricted
   A constant variance model is fit

   Total number of dose groups = 6
   Total number of records with missing values = 0
```

```
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                          alpha =      85.6196
                            rho =            0   Specified
                         beta_0 =      54.6853
                         beta_1 =   -0.0405127


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -rho
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

                    alpha       beta_0       beta_1

     alpha              1    -1.2e-007     7.5e-008

    beta_0    -1.2e-007            1        -0.53

    beta_1     7.5e-008        -0.53            1


                                Parameter Estimates

                                                                 95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
          alpha          74.7222           19.623             36.2618
113.183
         beta_0          54.1511          1.88608             50.4545
57.8477
         beta_1       -0.0391186       0.00708413          -0.0530032           -
0.025234


     Table of Data and Estimated Values of Interest

 Dose       N    Obs Mean     Est Mean   Obs Std Dev  Est Std Dev   Scaled Res.
------     ---   --------     --------   -----------  -----------   ----------

    0     5       57.5         54.2         10.6         8.64          0.866
 4.65     7       50.2           54         7.51         8.64          -1.15
22.83     4       54.1         53.3         16.4         8.64          0.195
   75     6       51.2         51.2         5.98         8.64       -0.00487
  321     4       44.4         41.6         6.02         8.64          0.649
  732     3       23.9         25.5         6.51         8.64         -0.324


 Model Descriptions for likelihoods calculated


 Model A1:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma^2
```

```
 Model A2:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma(i)^2

 Model A3:        Yij = Mu(i) + e(ij)
          Var{e(ij)} = Sigma^2
     Model A3 uses any fixed variance parameters that
     were specified by the user

 Model  R:         Yi = Mu + e(i)
           Var{e(i)} = Sigma^2


                     Likelihoods of Interest

            Model      Log(likelihood)   # Param's      AIC
             A1          -75.662630            7     165.325260
             A2          -71.734959           12     167.469918
             A3          -75.662630            7     165.325260
         fitted          -77.049762            3     160.099523
              R          -87.468813            2     178.937627


                   Explanation of Tests

 Test 1:  Do responses and/or variances differ among Dose levels?
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous? (A1 vs A2)
 Test 3:  Are variances adequately modeled? (A2 vs. A3)
 Test 4:  Does the Model for the Mean Fit? (A3 vs. fitted)
 (Note:  When rho=0 the results of Test 3 and Test 2 will be the same.)

                     Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df        p-value

   Test 1              31.4677         10       0.0004909
   Test 2              7.85534          5          0.1644
   Test 3              7.85534          5          0.1644
   Test 4              2.77426          4          0.5963

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


              Benchmark Dose Computation

Specified effect =          0.05

Risk Type        =     Relative deviation

Confidence level =          0.95
```

```
BMD =          69.214

BMDL =        54.3605

BMDU =        96.8278
```

Increased Incidence of Simple Bladder Hyperplasia in Male Wistar Rats Exposed to TPA in the Diet for 22 Weeks (Cui et al., 2006a)

Incidences of simple hyperplasia in the bladder of male Wistar rats exposed to terephthalic acid (TPA) in the diet for 22 weeks were fit to all dichotomous models in the BMDS (Version 2.7) using the procedure described above for dichotomous data. All models provided an adequate fit to the data (see Table E-7). The BMDLs for the models were not sufficiently close (differed by greater than approximately threefold), so the model with the lowest BMDL was selected (LogLogistic). This is also the best fitting model, with the lowest AIC. Figure E-7 shows the fit of the LogLogistic model to the data. Based on HEDs, the 10% benchmark dose (BMD_{10}) and 10% benchmark dose lower confidence limit ($BMDL_{10}$) for increased incidence of simple bladder hyperplasia in male Wistar rats were 194 and 95.0 mg/kg-day, respectively.

Table E-7. BMD Modeling Results for Simple Hyperplasia in the Urinary Bladders of Male Wistar Rats Treated with TPA (CASRN 100-21-0) in the Diet for 22 Weeks[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Gamma[c]	2	0.52	0.77	0.65	33.34	228.34	129.34
Logistic	1	1.55	0.21	0.88	37.00	515.89	342.36
LogLogistic[d, *]	2	0.24	0.88	0.42	33.11	194.44	95.03
LogProbit[d]	1	2.01	0.16	1.11	37.27	423.05	210.75
Multistage (1-degree)[e]	2	0.52	0.77	0.65	33.34	228.34	129.34
Multistage (2-degree)[e]	2	0.52	0.77	0.65	33.34	228.34	129.34
Probit	1	1.49	0.22	0.88	36.89	478.82	316.18
Weibull[c]	2	0.52	0.77	0.65	33.34	228.34	129.34

[a]Cui et al. (2006a).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
*Selected model. All models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (differed by >threefold), so the model with the lowest BMDL (LogLogistic) was selected.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); BMR = benchmark response; DF = degree(s) of freedom; HED = human equivalent dose; TPA = terephthalic acid.

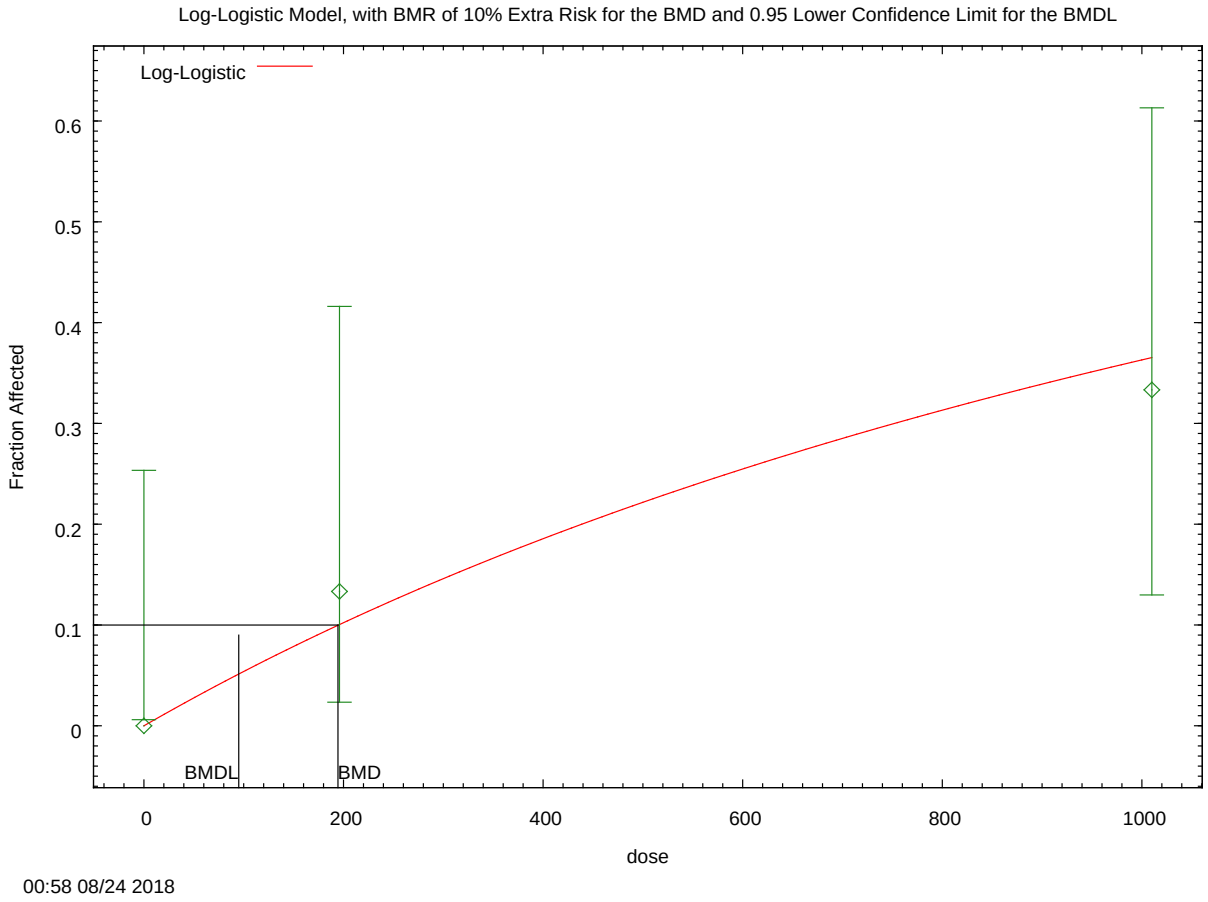

Figure E-7. Fit of LogLogistic Model to the Data for Increased Incidence of Simple Hyperplasia in the Urinary Bladders of Male Wistar Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 22 Weeks (Cui et al., 2006a)

Decreased Body Weight in Male Wistar Rats Exposed to TPA in the Diet for 24 Months (Gross, 1977)

The procedure outlined above for continuous data was applied to the data for decreased terminal body weight of male Wistar rats exposed to dietary TPA for 24 months (Gross, 1977). The constant variance model did not provide an adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model, all of the tested models except the Hill model provided adequate fit to the means (see Table E-8). The Hill model failed because there were insufficient degrees of freedom available in the data set. BMDLs for the models providing adequate fit were sufficiently close (differed by less than approximately threefold), so the model with the lowest AIC was selected (Linear model; 2- and 3-degree Polynomial models converged on the Linear model). Figure E-8 shows the fit of the Linear model to the data. Based on HEDs, the BMD_{10} and $BMDL_{10}$ for decreased body weight in male rats were 448 and 373 mg/kg-day, respectively.

Table E-8. BMD Modeling Results for Decreased Body Weight in Male Wistar Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 24 Months[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	Scaled Residual at Dose Nearest BMD	AIC	BMD_{10} (HED) (mg/kg-d)	$BMDL_{10}$ (HED) (mg/kg-d)
Nonconstant variance						
Exponential (model 2)[c]	0.99	0.25	−0.584	1,073.5	411.80	331.51
Exponential (model 3)[c]	0.99	0.12	−0.842	1,075.2	469.27	335.14
Exponential (model 4)[c]	0.99	0.25	−0.584	1,073.5	411.80	264.04
Hill[c, d]	0.99	NA	−0.041	1,074.7	422.74	317.26
Linear[e, *]	0.99	0.26	−0.765	1,073.4	448.78	372.76
Polynomial (2-degree)[e]	0.99	0.26	−0.765	1,073.4	448.78	372.76
Polynomial (3-degree)[e]	0.99	0.26	−0.765	1,073.4	448.78	372.76
Power[c]	0.99	0.10	−0.878	1,075.4	475.76	373.39

[a]Gross (1977).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to be ≥1.
[d]The degrees of freedom were less than or equal to 0, and the χ^2 test for fit was not valid.
[e]Coefficients restricted to be negative.
*Selected model. The constant variance model did not provide an adequate fit to the variance data, but the nonconstant variance model did. With the nonconstant variance model applied, all models except the Hill model provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (did not differ by more than approximately threefold), so the model with the lowest AIC was selected (Linear model). The 2- and 3-degree Polynomial models converged on the Linear model.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 10 = dose associated with 10% relative deviation); BMR = benchmark response; HED = human equivalent dose; NA = test for fit is not valid; TPA = terephthalic acid.

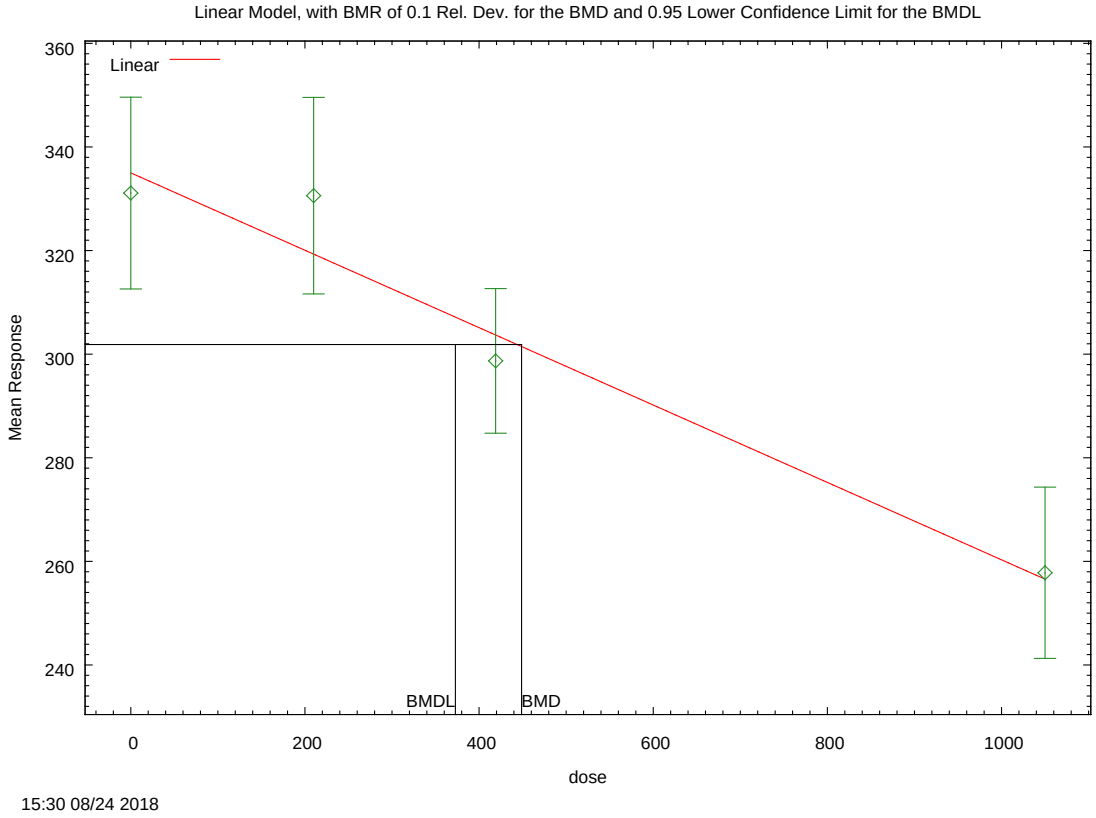

Figure E-8. Fit of Linear Model to Data for Body Weight in Male Wistar Rats Exposed to TPA (CASRN 100-21-0) in the Diet for 24 Months (Gross, 1977)

APPENDIX F. REFERENCES

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