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Provisional Peer-Reviewed Toxicity Values for

p-Chlorobenzenesulfonic Acid
(CASRN 98-66-8)

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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
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
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
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
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
NCEA	National Center for Environmental Assessment
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	glutamic oxaloacetic transaminase, also known as AST
SGPT	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_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *p*-CHLOROBENZENESULFONIC ACID (CASRN 98-66-8)

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. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

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.

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

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 EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

p-Chlorobenzenesulfonic acid (*p*-CBSA), CASRN 98-66-8, belongs to the class of compounds known as benzenesulfonic acids. *p*-CBSA is produced by the sulfonation of chlorobenzene with sulfuric acid and involves the continuous removal of water during the reaction and is used as an intermediate in the manufacture of 4-chloro-3-nitrobenzenesulfonic acid (Linder and Rodefeld, 2012). *p*-CBSA is listed on the public inventory of the U.S. EPA's Toxic Substances Control Act (U.S. EPA, 2015); it is not, however, registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2016).

The empirical formula for *p*-CBSA is $C_6H_5ClO_3S$. The chemical structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of *p*-CBSA. *p*-CBSA exists as deliquescent needles at room temperature (Linder and Rodefeld, 2012). *p*-CBSA's low estimated vapor pressure and low estimated Henry's law constant indicate that it is not expected to volatilize from either dry or moist surfaces. *p*-CBSA's vapor pressure indicates that it will exist in both the vapor and particulate phases in the atmosphere. The estimated half-life of vapor-phase *p*-CBSA in air by reaction with photochemically produced hydroxyl radicals is 25 days. The estimated high water solubility and low soil adsorption coefficient for *p*-CBSA indicate that it may leach to groundwater or undergo runoff after a rain event.

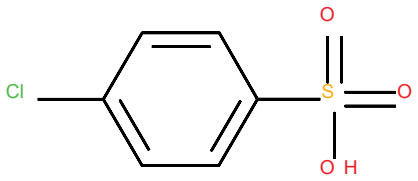

Figure 1. *p*-Chlorobenzenesulfonic Acid Structure

Table 1. Physicochemical Properties of *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8)

Property (unit)	Value
Physical state	Solid
Boiling point (°C at 25 mm Hg)	147[a]
Melting point (°C)	67[b]
Density (g/cm^3 at 20°C)	ND
Vapor pressure (mm Hg at 25°C)	4.3×10^{-6} (estimated)[b]
pH (unitless)	ND
pKa (unitless)	ND
Solubility in water (mg/L at 25°C)	3.1×10^{5} (estimated)[b]
Octanol-water partition coefficient (log K_{ow})	−0.52 (estimated)[b]
Henry's law constant (atm-m^3/mol at 25°C)	1.9×10^{-9} (estimated)[b]
Soil adsorption coefficient K_{oc} (L/kg)	16 (estimated)[b]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	4.3×10^{-13} (estimated)[b]
Atmospheric half-life (d)	25 (estimated)[b]
Relative vapor density (air = 1)	NA
Molecular weight (g/mol)	193[b]
Flash point (closed cup in °C)	ND

[a]Haynes (2014).
[b]U.S. EPA (2012b).

NA = not applicable; ND = no data.

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

Table 2. Summary of Available Toxicity Values for *p*-Chlorobenzenesulfonic Acid and Its Sodium Salt (CASRNs 98-66-8 and 5138-90-9)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2016)
IPCS	NV	NA	IPCS (2016); WHO (2016)
IARC	NV	NA	IARC (2016)
Cal/EPA	Acute Acceptable Daily Dose = 0.80 mg/kg-d; Chronic Acceptable Daily Dose = 0.27 mg/kg-d	Based on $BMDL_{1SD}$ of 797 mg/kg-d for reduced body-weight gain in a 32-d rat study by American Biogenics Corporation (1985) and total UF of 1,000 for the acute acceptable daily dose and 3,000 for the chronic acceptable daily dose	Cal/EPA (2015)
MiDEQ	Chronic RfD = 1 mg/kg-d	Based on a NOAEL of 1,000 mg/kg-d in a 32-d rat study by American Biogenics Corporation (1985) and total UF of 1,000	Michigan DEQ (2006)
OSHA	NV	NA	OSHA (2006); OSHA (2011)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2015)
DOE (PAC)	PAC-3: 99 mg/m^3; PAC-2: 17 mg/m^3; PAC-1: 1.5 mg/m^3 (for *p*-CBSA)	PAC-1 and PAC-2 based on adjustments to 1-hr TEEL-1 and TEEL-2; PAC-3 based on rat oral LD_{50}	DOE (2016)
USAPHC (air-MEG)	1-hr critical: 200 mg/m^3; 1-hr marginal: 40 mg/m^3; 1-hr negligible: 6 mg/m^3 (for *p*-CBSA)	Based on 1-hr TEELs. Documentation of the TEEL derivations was not located	U.S. APHC (2013)

Table 2. Summary of Available Toxicity Values for *p*-Chlorobenzenesulfonic Acid and Its Sodium Salt (CASRNs 98-66-8 and 5138-90-9)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Cancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2015)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2016a); Cal/EPA (2016b)
ACGIH	NV	NA	ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DOE = Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; MiDEQ = Michigan Department of Environmental Quality; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; USAPHC = U.S. Army Public Health Center.
[b]Parameters: MEG = military exposure guideline; PAC = protective action criteria.

BMDL = benchmark dose lower confidence limit; *p*-CBSA = *p*-chlorobenzenesulfonic acid; LD_{50} = median lethal dose; NA = not applicable; NOAEL = no-observed-adverse-effect level; NV = not available; RfD = reference dose; SD = standard deviation; TEEL = temporary emergency exposure limit; UF = uncertainty factor.

Non-date-limited literature searches were conducted in May 2015 and updated in June 2016 for studies relevant to the derivation of provisional toxicity values for *p*-CBSA (CASRN 98-66-8) and its sodium salt (CASRN 5138-90-9). Searches were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related data: ACGIH, ATSDR, Cal/EPA, EPA IRIS, EPA HEAST, EPA Office of Water (OW), EPA TSCATS2/TSCATS8e, EPA High Production Volume (HPV), ECETOC, Japan Existing Chemical Data Base (JECDB), European Chemicals Agency (ECHA), Organisation for Economic Cooperation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, NIOSH, NTP, OSHA, and Defense Technical Information Center (DTIC).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

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

Table 3A. Summary of Potentially Relevant Noncancer Data for *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8)								
Category[a]	**Number of Male/Female, Strain Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL**	**BMDL/ BMCL**	**LOAEL**	**Reference (comments)**	**Notes[c]**
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								
Animal								
1. Oral (mg/kg-d)								
Subchronic	**10 M/10 F, S-D rat, gavage administration of 0, 10, 50, 500, 1,000, or 2,000 *p*-CBSA sodium salt for 31−32 consecutive d**	**0, 9.0, 45, 449, 898, 1,800 as *p*-CBSA**	**No effects clearly related to *p*-CBSA exposure were observed.**	**1,800**	**NDr**	**NDr**	**American Biogenics Corporation (1985)** **Observations in rats included: Increased (8.5−11% compared to control) group mean relative kidney weight, clinical signs of toxicity (salivation, gasping, irregular breathing), and decreased body-weight gain in two males, as well as ileal enteritis in one male. These effects may have all been confounded by issues unrelated to *p*-CBSA exposure.**	**NPR, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8)

Category[a]	Number of Male/Female, Strain Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL	BMDL/ BMCL	LOAEL	Reference (comments)	Notes[c]
Chronic	Rabbit; number, sex, strain, frequency and mode of administration, and formulation not reported; 0, 0.1, 1, 10 mg/kg for 7 mo	ND	Authors reported significant changes in hematology, clinical chemistry, and liver and kidney function tests; however, study design details and quantitative data were lacking.	NDr	NDr	NDr	Kryatov (1970) (Lack of study design details and quantitative data preclude affirmation of actual dosimetry [e.g., ADD] or effect level identification)	PR
Developmental	25 F, CD rat, gavage administration of 0, 1,000, or 2,000 *p*-CBSA sodium salt on GDs 7−16	0, 898, 1,800 as *p*-CBSA	No effects on maternal weight gain, average litter size, or pup weight on PNDs 1 or 3.	1,800 (based on very limited evaluations)	NDr	NDr	Chernoff and Rosen (1985) as cited in U.S. EPA (1986)	NPR
2. Inhalation (mg/m^3)								
ND								

[a]Treatment/exposure duration (unless otherwise noted): Short-term = repeated exposure for 24 hours to ≤30 days; long-term (subchronic) = repeated exposure for >30 days and ≤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 values are presented as ADDs (mg/kg-day) for oral noncancer studies. In contrast to other repeated dose studies, dosimetry values from gestational exposure studies are not adjusted for duration in the calculation of an ADD. Where applicable, the dose of *p*-CBSA was calculated from the dose of *p*-CBSA sodium salt by multiplying the ratio of the molecular weights of the two compounds (192.6 g/mol *p*-CBSA:214.6 g/mol *p*-CBSA sodium salt).

[c]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; *p*-CBSA = *p*-chlorobenzenesulfonic acid; F = female(s); GD = gestation day; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8)								
Category	**Number of Male/Female, Strain, Species, Study Type and Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**BMDL/BMCL**	**LOAEL**	**Reference**	**Notes**
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								
Animal								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								

BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; LOAEL = lowest-observed-adverse-effect level; ND = no data; NOAEL = no-observed-adverse-effect level.

HUMAN STUDIES

No relevant data have been located regarding the toxicity of *p*-CBSA to humans following oral or inhalation exposure.

ANIMAL STUDIES

Oral Exposures

Subchronic-Duration Studies

American Biogenics Corporation (1985)

In an unpublished, good laboratory practice (GLP)-compliant study, American Biogenics Corporation (1985) examined the effects of *p*-CBSA sodium salt (purity not reported) administered by gavage in distilled water to Sprague-Dawley (S-D) rats. Groups of 10 rats/sex/dose were given doses of 0, 10, 50, 500, 1,000, or 2,000 mg/kg-day for 31 or 32 consecutive days (beginning at 45 days of age). Equivalent doses of *p*-CBSA are 0, 9.0, 45, 449, 898, or 1,800 mg/kg-day[1]. In-life evaluations included twice-daily observations and weekly detailed examinations for clinical signs and weekly body-weight and food-consumption measurements. On study Day 28, all rats were given ophthalmologic examinations. At the end of exposure, blood samples were collected for evaluation of hematology (red blood cell [RBC] count, hemoglobin [Hb], hematocrit [Hct], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin count [MCHC], platelet count, and total and differential leukocyte counts) and serum chemistry (electrolytes, glucose, blood urea nitrogen [BUN], creatinine, aspartate aminotransaminase [AST], alanine aminotransaminase [ALT], γ-glutamyl transferase [GGT], total protein, albumin, globulin, and total bilirubin). At sacrifice on study Days 32 or 33, gross necropsies were performed on all animals, and the following organs were weighed: adrenals, testes with epididymides, ovaries, kidneys, and liver. Microscopic examination of the following organs was performed in control and animals in the highest-dose group: adrenals, bone and marrow, brain, gonads, heart, small and large intestines, kidneys, liver, pancreas, spleen, stomach, thyroid and parathyroid, urinary bladder, uterus, and cervix, and any other tissue exhibiting grossly observed changes. Statistical analyses consisted of analysis of variance (ANOVA) with the Tukey or Scheffe's test of multiple comparisons for parametric data and the Kruskal-Wallis test with the Kruskal-Wallis multiple comparison test for nonparametric data; these tests are considered to be appropriate for the nature of the data.

No rats in any exposure group died prior to study termination (American Biogenics Corporation, 1985). Clinical signs possibly related to *p*-CBSA exposure were salivation, gasping, and irregular breathing observed in one highest-dose male rat on Day 8 (only), and irregular breathing observed in a second male from the highest-dose group, along with crusty nose and eye, on Day 33 (the day of sacrifice for this rat). Necropsy findings in the latter rat (a fractured snout and black crusted material around nose and mouth) suggest that the animal may have experienced trauma, which may have been responsible for, or contributed to, the irregular breathing in this animal. Due to the low incidence of affected animals, the transitory occurrence of signs in one animal, and possible confounding cause of signs (potentially related to physical trauma) in the other, these clinical signs are not considered to be related to *p*-CBSA exposure. Further, crusty nose or eye and misaligned or missing incisor(s) were also noted in two male rats exposed to 898 mg/kg-day, one male rat exposed to 449 mg/kg-day, and one

[1]The dose of *p*-CBSA sodium salt was multiplied by the ratio of molecular weights (192.6 g/mol *p*-CBSA:214.6 g/mol *p*-CBSA sodium salt) to yield an equivalent dose of *p*-CBSA.

female rat exposed to 45 mg/kg-day, and were considered by the study authors to be unrelated to exposure.

The same two male rats from the highest-dose group that showed clinical signs of toxicity (and trauma in one) also exhibited lower body-weight gain than others in their group (90 and 117 g total weight change compared with 141−194 g in the remaining rats), as well as markedly lower total food consumption (572 and 650 g total food consumed vs. 725−839 g for the remaining rats). Thus, while the lower body-weight gain was likely attributable to lower food intake, it is unclear whether the reduction in food intake reflected generalized diminished health in one of these animals, and a more traumatic physical condition (e.g., fractured snout) in the other. There were no statistically significant differences among the groups in mean body weight or food consumption at any time point. Although the American Biogenics Corporation (1985) ANOVA analysis of total body-weight change in males indicated a statistically significant difference among the mean values for all of the groups, there were no biologically significant (difference ≥10% compared with control) changes in body weight in any group. Mean Week 4 and terminal (fasted) body weights were within 5% of control means in all exposure groups (see Tables B-1 and B-2).

Hematology and clinical chemistry results did not reveal any treatment-related changes; a significant increase in white blood cell (WBC) count was seen in females exposed to 449 mg/kg-day, but not at higher doses or in males (see Tables B-1 and B-2) (American Biogenics Corporation, 1985). Ophthalmology examinations were unremarkable. At gross necropsy, one of the two males from the highest-dose group, exhibiting clinical signs and body-weight decrements, was observed to have dark contents in the stomach, ileum, and cecum, as well as a discolored testis, enlarged lymph node, fractured snout, and black crusted material about the nose and mouth.

The only statistically significant organ-weight changes were decreases in the absolute and relative weights of the left adrenal gland in males exposed to 449 mg/kg-day; these effects were not seen at higher doses, in the right adrenal weights, or in female rats (see Tables B-1 and B-2). An increase of 11% (compared with controls; not statistically significant) in mean relative left kidney weight was observed in male rats of the highest dose; mean relative right kidney weight was increased by 8.5% at the same dose. Absolute left and right kidney weights were increased by 5 and 3%, respectively, in highest dose males. In contrast, absolute and relative kidney weights were decreased at lower doses in males and at all doses in females.

Fluctuations in relative and absolute ovary weights as high as 31% difference from control were also observed; these changes did not exhibit a dose-response relationship and were not statistically significant (p-values > 0.05 for Jonckheere-Terpstra tests and linear regression analyses performed for this review) (American Biogenics Corporation, 1985). Further, the biological significance of ovarian-weight changes can be difficult to interpret because ovarian weights are highly variable in control populations and are influenced by both reproductive cycling and stress (Sellers et al., 2007).

One male rat from the highest-dose group exhibited slight bilateral testicular tubular degeneration and epididymal aspermia. Another male rat from the highest-dose group exhibited slight ileal enteritis. The study authors considered these and other observed changes to be common in rats and unrelated to exposure.

In summary, observations at the highest dose included clinical signs of toxicity and decreased body-weight gain in 2/10 males, a marginally biologically significant increase in group mean relative kidney weight in males, testicular tubular degeneration (1/10 males vs. 0/10 male controls), and enteritis of the ileum (1/10 males vs. 0/10 male controls). As described above, the relationship between clinical signs potentially indicative of an effect (salivation, gasping, and irregular breathing) and exposure to *p*-CBSA is uncertain due to the low incidence of affected animals, transitory occurrence of signs in one animal, and possible confounding signs of physical trauma in the other. Decreased body-weight gain was seen only in the two males exhibiting clinical signs of toxicity, and there were no statistically or biologically significant differences among treatment groups in mean body weight at any time during the study. The increase in relative kidney weight was observed only in males, was not statistically significant, was only marginally biologically significant (11% increase in the left kidney and 8.5% increase in the right kidney), and reflects, in part, 4% decreased body weight in males from the highest-dose group (increases in absolute kidney weight were only 3−5% in males from the highest-dose group). It should be noted that the increases in kidney weight in males from the highest-dose group stand in contrast to decreases in kidney weight in lower dose males and in females. However, histopathology findings in individual male rats from the highest-dose group were not correlated with organ-weight changes; the study authors characterized the findings as common and unrelated to treatment.

Based on the lack of a clear (nonconfounded) relationship between potential toxic effects and *p*-CBSA exposure, a no-observed-adverse-effect level (NOAEL) of 1,800 mg/kg-day is identified for this study.

Chronic-Duration Studies

Kryatov (1970)

In a chronic-duration toxicity study, originally published in Russian but with an available English translation, Kryatov (1970) administered 0, 0.1, 1.0, or 10 mg/kg of *p*-CBSA (purity and formulation not reported) orally (presumably by gavage based on the description of the short-term-duration experiment described elsewhere in the report) to rabbits for 7 months. The strain, sex, number of rabbits per group, vehicle, and frequency of administration were not reported. Parameters measured include body weight, behavior, conditioned reflexes, hematology (RBC, WBC, Hb, phagocytic activity) and clinical chemistry (AST, ALT, serum cholesterol), liver and kidney function tests (bromosulfophthalein [BSP] in the liver and phenol red [phenolsulfonphthalein] in the kidney), organ weight, and vitamin C content of organs. Histopathology was not conducted. No mortality data were presented, and no quantitative values were presented for any of the results. Statistical analyses were limited to Student's t-tests.

Apart from graphical reporting of BSP retention data, no quantitative results were provided. The study author reported that exposure to 10 mg/kg-day *p*-CBSA significantly decreased erythrocyte counts and hemoglobin, and increased reticulocyte counts, plasma transaminase activities, serum urea, and serum cholesterol (Kryatov, 1970). The text of the translation reported that treatment with the high dose also decreased BSP retention in the liver; however, data shown graphically indicate that BSP retention was increased. Kryatov (1970) also reported decreased phenol red in the kidneys and decreased vitamin C content in the adrenal glands at this dose. Observations at the mid dose of 1 mg/kg-day included nonsignificant increases in the activity of plasma transaminases and a significant increase in

BSP retention in the liver in the third and sixth months on study. The study author considered 1 mg/kg-day to be a "threshold" dose for *p*-CBSA in rabbits and 0.1 mg/kg-day to be a "subliminal" (i.e., ineffective) dose. The methods and results were not presented with enough detail to allow for a full evaluation of this study; in addition, quantitative results were presented graphically (and without any measure of variability) and only for BSP retention, not for other endpoints. Therefore, effect levels cannot be identified for this study.

Developmental Studies

Chernoff and Rosen (1985) as cited in U.S. EPA (1986)

Chernoff and Rosen (1985) as cited in U.S. EPA (1986) conducted a screening-level teratology study of *p*-CBSA sodium salt in rats. Mated female CD rats were given gavage doses of 0, 1,000, or 2,000 mg/kg-day *p*-CBSA sodium salt on Gestation Days (GDs) 7−16. Equivalent doses of *p*-CBSA are 0, 898, and 1,800 mg/kg-day[1]. Maternal-weight gain during pregnancy was recorded, as were average litter sizes and average pup weights on Postnatal Days (PNDs) 1 and 3; no other endpoints were evaluated. No differences in maternal-weight gain, average litter size, or pup weights were observed among the exposed and control groups. While a NOAEL of 1,800 mg/kg-day is identified for the study, the lack of detailed maternal and offspring evaluations limits the confidence in this effect level determination.

Inhalation Exposures

No relevant data have been located regarding the toxicity of *p*-CBSA to animals following inhalation exposure.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Other supporting studies on *p*-CBSA include an acute lethality study in multiple species, two poorly reported acute or short-term-duration oral toxicity studies, and genotoxicity data; these are described below. Table 4 provides an overview of genotoxicity studies of *p*-CBSA.

Supporting Animal Studies

Kryatov (1970) reported oral median lethal dose (LD_{50}) values of 8,350 (white mice), 11,100 (albino rats), 7,100 (rabbits), and 16,000 mg/kg (guinea pigs) for *p*-CBSA; no details of the study design were reported. Mortalities occurred within 2 days of administration. The author also briefly reported repeated-dose experiments in rats and rabbits (numbers of animals not reported) exposed to *p*-CBSA by gavage to doses of 1/5th and 1/10th the animals' LD_{50} values (equivalent to ~2,220 and 1,110 mg/kg-day, respectively, in rats and ~1,400 and 710 mg/kg-day, respectively, in rabbits) for 20 days (Kryatov, 1970). No "marked cumulative properties" were observed, although at necropsy the author did indicate evidence of hemorrhage in the gastrointestinal tract and visceral hyperemia; however, it is unclear in the original report whether this was in reference to *p*-CBSA exposure or another chemical (chloral) evaluated in the study. One animal in the highest-dose group died (species not reported). No additional information on this experiment was provided in the report. In addition, Kryatov (1970) briefly noted an experiment in rats exposed to 0.1 or 1 mg/kg *p*-CBSA and tested for effects on conditioned reflexes; the results of this experiment were either not reported or of unclear biological relevance (e.g., 'slower fixation of differentiation reaction').

Genotoxicity

p-CBSA has been tested for genotoxicity in Ames assays, in a mammalian cell mutagenicity assay, and in rats exposed in vivo [all tests conducted by Pharmakon Research

International (1985) as cited in U.S. EPA (1986)], with uniformly negative results (see Table 4). *p*-CBSA did not increase the frequency of mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 or in L5178Y mouse lymphoma cells when tested with or without metabolic activation, or the frequency of chromosomal aberrations (CAs) in bone marrow in male rats given a single oral gavage dose of 2,000 mg/kg *p*-CBSA.

Table 4. Summary of *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results Without Activation[a]	Results With Activation[a]	Comments	Reference
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538	50, 167, 500, 1,667, 5,000 mg/plate	–	–	Positive and solvent controls gave expected responses.	Pharmakon Research International (1985) as cited in U.S. EPA (1986)
Genotoxicity studies in mammalian cells—in vitro						
Mutation	L5178Y mouse lymphoma	50, 125, 250, 500, 1,000 mg/mL	–	–	Positive and solvent controls gave expected responses.	Pharmakon Research International (1985) as cited in U.S. EPA (1986)
Genotoxicity studies—in vivo						
CAs	Male rats given single dose by gavage and sacrificed 6, 12, and 24 hr after dosing for scoring of CAs in bone marrow smears	2,000 mg/kg	–	–	Positive and solvent controls gave expected responses.	Pharmakon Research International (1985) as cited in U.S. EPA (1986)

[a]– = negative.

CA = chromosomal aberration.

Mode-of-Action/Mechanistic Studies

p-CBSA gave uniformly negative results in a large number of high-throughput screening assays under the National Toxicology Program's (NTP's) Tox21 program[2]: 21 cell cycle assays, 86 nuclear receptor assays, 2 cell morphology assays, 78 deoxyribonucleic acid (DNA) binding assays, 2 growth factor assays, 3 cytochrome assays, and 1 hydrolase assay. These high-throughput assays are designed to survey the potential for a given xenobiotic to be bioactive across a broad array of modes of action (MOAs) known to be associated with altering the structure and/or function of mammalian cells. The negative results for *p*-CBSA across the specific assays listed here suggest a low potential for bioactivity in MOAs involving direct/indirect interaction with DNA, cell cycle activation/deactivation, or nuclear or growth factor-dependent cell signaling.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively.

Table 5. Summary of Noncancer Reference Values for *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	S-D rat/M	No effects clearly related to *p*-CBSA exposure were observed.	1	NOAEL	432	300	American Biogenics Corporation (1985)
Screening chronic p-RfD (mg/kg-d)	S-D rat/M	No effects clearly related to *p*-CBSA exposure were observed.	1×10^{-1}	NOAEL	432	3,000	American Biogenics Corporation (1985)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

HED = human equivalent dose; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; *p*-CBSA = *p*-chlorobenzenesulfonic acid; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; S-D = Sprague-Dawley; UF_C = composite uncertainty factor.

[2]Data are available online at http://actor.epa.gov/dashboard/#chemical/98-66-8.

Table 6. Summary of Cancer Reference Values for *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	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.

DERIVATION OF ORAL REFERENCE DOSES

No data have been located on the effects of oral exposure to *p*-CBSA in humans. Information on the toxicity of repeated oral exposure to *p*-CBSA is limited to an unpublished 32-day gavage study (although referred to in various literature as a "28-day" study, the actual length of gavage exposure was 31–32 days) in rats (American Biogenics Corporation, 1985), an unpublished screening-level developmental toxicity study in rats exposed by gavage [Chernoff and Rosen (1985) as cited in U.S. EPA (1986)], and the translated version of a paper published in Russian describing a 7-month study in rabbits (Kryatov, 1970). Kryatov (1970) did not report the sex or strain of rabbit exposed, nor the frequency or mode of *p*-CBSA administration. In addition, Kryatov (1970) reported data on BSP retention graphically and without any measure of variability, while quantitative results for other endpoints were not reported. Thus, effect levels could not be determined. The available studies were unpublished and/or not peer reviewed and thus were determined to be unsuitable for use in deriving provisional toxicity values. However, the unpublished study by American Biogenics Corporation (1985) was well conducted and reported adequate information with which to derive screening subchronic and chronic provisional reference doses (p-RfDs) for *p*-CBSA (see Appendix A).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

There are no studies of *p*-CBSA toxicity in humans or animals exposed by inhalation, thus precluding derivation of provisional reference concentrations (p-RfCs).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No studies were located examining possible associations between exposure to *p*-CBSA and cancer in humans or animals. Studies in animals (one 32-day study in rats, a poorly reported 7-month study in rabbits, and a developmental toxicity screening study in rats) are inadequate to assess the carcinogenicity of *p*-CBSA. In vitro bacterial and mammalian mutagenicity assays and an in vivo CA assay were uniformly negative. The cancer weight-of-evidence (WOE) descriptor for *p*-CBSA is provided in Table 7.

Table 7. Cancer WOE Descriptor for *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no sufficient animal studies to support this.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are no sufficient animal studies to support this.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No carcinogenicity studies of *p*-CBSA are available.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

NA = not applicable; NS = not selected; *p*-CBSA = *p*-chlorobenzenesulfonic acid; WOE = weight of evidence.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of *p*-CBSA following oral or inhalation exposure precludes the derivation of quantitative estimates of carcinogenic potency.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main provisional peer-reviewed toxicity value (PPRTV) document, it is inappropriate to derive provisional toxicity values for *p*-chlorobenzenesulfonic acid (*p*-CBSA). However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center 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 PPRTV documents 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 is considerably 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 Superfund Health Risk Technical Support Center.

DERIVATION OF A SCREENING SUBCHRONIC PROVISIONAL REFERENCE DOSE

Information on the toxicity of repeated oral exposure to *p*-CBSA is limited to a 32-day gavage study in rats (American Biogenics Corporation, 1985), a screening-level developmental toxicity study in rats exposed by gavage [Chernoff and Rosen (1985) as cited in U.S. EPA (1986)], and a 7-month study in rabbits (Kryatov, 1970) with significant deficiencies in reporting. In the study by Kryatov (1970), the methods and results were not presented with enough detail to allow for a full evaluation of the findings; quantitative results were presented graphically (and without any measure of variability) and only for bromosulfophthalein (BSP) retention, not for other endpoints. Thus, effect levels could not be determined from this study. The developmental toxicity study in rats [Chernoff and Rosen (1985) as cited in U.S. EPA (1986)] identified a no-observed-adverse-effect level (NOAEL) of 1,800 mg/kg-day (as *p*-CBSA) based on limited toxicological evaluations. The unpublished 32-day rat study by American Biogenics Corporation (1985) provided repeat-dose information on the potential effects of *p*-CBSA on body weight, clinical toxicity (e.g., salivation, gasping, and irregular breathing), and changes in organ weight (e.g., adrenals, ovaries, and kidneys). However, none of these effects could be attributed solely to *p*-CBSA exposure. For example, decreased body-weight gain was associated primarily with two males in the highest-dose group that consumed significantly less food than control rats and were reported to be in poor physical condition (e.g., fractured snout). Further, total body weights were not significantly different between treatment groups in general. Similarly, clinical signs of toxicity were observed in the same two male rats that suffered apparent trauma, which confounds interpretation of potential exposure-related effects. Lastly, adrenal-weight changes occurred only in the left adrenal, only in males, and did not exhibit a dose-response relationship. Similarly, while ovary weights were increased in treated females, this effect did not have a dose-response relationship and was not statistically significant compared to control females. Increased relative kidney weight occurred only in male rats, did not exhibit a dose-response relationship, was not statistically significant, and may be more an artifact of decreased body weight than an increase in actual kidney weight (e.g., absolute kidney weights increased by 3−5% and were not biologically significant). As such, a NOAEL of 1,800 mg/kg-day (as *p*-CBSA) was identified for the 32-day gavage study (American Biogenics Corporation, 1985) based on the lack of effects clearly related to exposure;

this study was selected as the principal study for the screening subchronic provisional reference dose (p-RfD).

The NOAEL of 1,800 mg/kg-day for lack of effects following 32 days of oral gavage exposure was used to derive the screening subchronic p-RfD for *p*-CBSA. The NOAEL was converted to a human equivalent dose (HED) according to current U.S. EPA (2011b) guidance. In *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 body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD from effects that are not portal-of-entry.

Following U.S. EPA (2011b) guidance, the point of departure (POD) is converted to an HED through the 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

Using a reference BW_a of 0.25 kg for rats and a reference BW_h of 70 kg for humans, the resulting DAF is 0.24 (U.S. EPA, 2011b). Applying this DAF to the NOAEL of 1,800 mg/kg-day yields a POD (HED) as follows:

$$\begin{aligned} \text{POD (HED)} &= \text{NOAEL (mg/kg-day)} \times \text{DAF} \\ &= 1{,}800 \text{ mg/kg-day} \times 0.24 \\ &= 432 \text{ mg/kg-day} \end{aligned}$$

The screening subchronic p-RfD for *p*-CBSA was derived using the POD (HED) and a composite uncertainty factor (UF_C) of 300 (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 10):

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= \text{POD (HED)} \div UF_C \\ &= 432 \text{ mg/kg-day} \div 300 \\ &= \textbf{1 mg/kg-day} \end{aligned}$$

Table A-1 summarizes the uncertainty factors for the screening subchronic p-RfD for *p*-CBSA.

Table A-1. Uncertainty Factors for the Screening Subchronic p-RfD for *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8)

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 *p*-CBSA exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *p*-CBSA in humans.
UF_D	10	A UF_D of 10 is applied to account for the limited toxicity database for *p*-CBSA, which consists of an unpublished 32-d rat study, an unpublished screening-level teratogenicity study in rats (which does not suffice for evaluating the potential developmental effects of *p*-CBSA exposure), and a poorly reported chronic-duration toxicity study in rabbits from the Russian literature.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was selected as the principal study.
UF_C	300	Composite Uncertainty Factor = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

HED = human equivalent dose; NOAEL = no-observed-adverse-effect level; *p*-CBSA = *p*-chlorobenzenesulfonic acid; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor.

DERIVATION OF A SCREENING CHRONIC PROVISIONAL REFERENCE DOSE

The screening chronic p-RfD for *p*-CBSA was derived using the same POD (HED) as the screening subchronic p-RfD (432 mg/kg-day) and a UF_C of 3,000 (reflecting a UF_A of 3, a UF_H of 10, a UF_D of 10, and a UF_S of 10 for extrapolation from a subchronic to a chronic duration):

$$\begin{aligned} \textbf{Screening Chronic p-RfD} &= \text{POD (HED)} \div UF_C \\ &= 432 \text{ mg/kg-day} \div 3{,}000 \\ &= \mathbf{1 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

Table A-2 summarizes the uncertainty factors for the screening chronic p-RfD for *p*-CBSA.

Table A-2. Uncertainty Factors for the Screening Chronic p-RfD for *p*-Chlorobenzenesulfonic Acid (CASRN 98-66-8)

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 *p*-CBSA exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *p*-CBSA in humans.
UF_D	10	A UF_D of 10 is applied to account for the limited toxicity database for *p*-CBSA, which consists of an unpublished 32-d rat study, an unpublished screening-level teratogenicity study in rats (which does not suffice for evaluating the potential developmental effects of *p*-CBSA exposure), and a poorly reported chronic-duration toxicity study in rabbits from the Russian literature.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	10	A UF_S of 10 is applied because a subchronic-duration study was selected as the principal study.
UF_C	3,000	Composite Uncertainty Factor = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$

HED = human equivalent dose; NOAEL = no-observed-adverse-effect level; *p*-CBSA = *p*-chlorobenzenesulfonic acid; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor.

APPENDIX B. DATA TABLES

Table B-1. Selected Results in Male S-D Rats Administered *p*-CBSA Sodium Salt by Gavage for 31−32 Days[a]

Endpoint	Dose in mg/kg-d as *p*-CBSA Sodium Salt (mg/kg-d as *p*-CBSA)[b]					
	0	**10 (9.0)**	**50 (45)**	**500 (449)**	**1,000 (898)**	**2,000 (1,800)**
Total body-weight change (g)	165 ± 20.9	170 ± 21.3 (+3.0%)	176 ± 9.8 (+6.7%)	160 ± 14.9 (−3.0%)	153 ± 19.6 (−7.3%)	150 ± 29.2 (−9.1%)
Wk 4 body weight (g)	379 ± 26	378 ± 30.4 (−0.3%)	392 ± 18.5 (+3.4%)	365 ± 31.3 (−3.7%)	364 ± 35.5 (−4.0%)	365 ± 36.1 (−3.7%)
Terminal (fasted) body weight (g)	360.5 ± 25.98	357.4 ± 29.08 (−0.9%)	374.9 ± 20.19 (+4.0%)	349.9 ± 29.58 (−2.9%)	349.2 ± 34.29 (−3.1%)	344.7 ± 34.65 (−4.4%)
WBC count (thousand/mm^3)	13.43 ± 3.14	12.46 ± 2.16 (−7.2%)	12.48 ± 4.07 (−7.1%)	14.01 ± 3.81 (+4.3%)	13.57 ± 4.88 (+1.0%)	14.15 ± 2.53 (+5.4%)
Adrenal weight						
Right absolute (g)	0.0308 ± 0.0109	0.0302 ± 0.0062 (−1.9%)	0.0316 ± 0.0081 (+2.6%)	0.0314 ± 0.0098 (+1.9%)	0.0312 ± 0.0077 (+1.3%)	0.0301 ± 0.0064 (−2.3%)
Right relative (% body weight)	0.0086 ± 0.0033	0.0084 ± 0.0015 (−2.3%)	0.0085 ± 0.0023 (−1.2%)	0.0090 ± 0.0029 (+4.7%)	0.0089 ± 0.002 (+3.5%)	0.0089 ± 0.0026 (+3.5%)
Left absolute (g)	0.0375 ± 0.0042	0.0313 ± 0.0062 (−17%)	0.0336 ± 0.0048 (−10%)	0.0252 ± 0.003** (−33%)	0.0323 ± 0.0086 (−14%)	0.0320 ± 0.0044 (−15%)
Left relative (% body weight)	0.0105 ± 0.0014	0.0088 ± 0.002 (−16%)	0.0090 ± 0.0016 (−14%)	0.0072 ± 0.0009** (−31%)	0.0092 ± 0.0022 (−12%)	0.0093 ± 0.0014 (−11%)

Table B-1. Selected Results in Male S-D Rats Administered *p*-CBSA Sodium Salt by Gavage for 31−32 Days[a]						
Endpoint	**Dose in mg/kg-d as *p*-CBSA Sodium Salt (mg/kg-d as *p*-CBSA)[b]**					
	0	**10 (9.0)**	**50 (45)**	**500 (449)**	**1,000 (898)**	**2,000 (1,800)**
Kidney weight						
Right absolute (g)	1.6435 ± 0.199	1.6129 ± 0.2155 (−1.9%)	1.6685 ± 0.1918 (+1.5%)	1.5122 ± 0.159 (−8%)	1.5799 ± 0.1807 (−3.9%)	1.6979 ± 0.1974 (+3.3%)
Right relative (% body weight)	0.4557 ± 0.0408	0.4503 ± 0.0389 (−1.2%)	0.4455 ± 0.0504 (−2.2%)	0.4326 ± 0.0343 (−5.1%)	0.4528 ± 0.0319 (−0.6%)	0.4945 ± 0.0579 (+8.5%)
Left absolute (g)	1.6012 ± 0.1813	1.6132 ± 0.1784 (+0.7%)	1.6327 ± 0.1769 (+2%)	1.5026 ± 0.1415 (−6.2%)	1.5482 ± 0.1827 (−3.3%)	1.6835 ± 0.1332 (+5.1%)
Left relative (% body weight)	0.4441 ± 0.0362	0.4518 ± 0.0429 (+1.7%)	0.4362 ± 0.0497 (−1.8%)	0.4295 ± 0.0184 (−3.3%)	0.4443 ± 0.0424 (+0.0%)	0.4913 ± 0.0483 (+11%)

[a]American Biogenics Corporation (1985).
[b]Data reported as mean ± standard deviation (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100.
**Statistically significantly different from control ($p \leq 0.01$), as reported by the study authors.

p-CBSA = *p*-chlorobenzenesulfonic acid; S-D = Sprague-Dawley; WBC = white blood cell.

Table B-2. Selected Results in Female S-D Rats Administered *p*-CBSA by Gavage for 31−32 Days[a]

Endpoint	Dose in mg/kg-d as *p*-CBSA Sodium Salt (mg/kg-d as *p*-CBSA)[b]					
	0	**10 (9.0)**	**50 (45)**	**500 (449)**	**1,000 (898)**	**2,000 (1,800)**
Total body-weight change (g)	66 ± 9.6	63 ± 10 (−4.5%)	69 ± 20.5 (+4.5%)	68 ± 12 (+3%)	66 ± 8.1 (0)	61 ± 12.4 (−7.6%)
Wk 4 body weight (g)	223 ± 16.6	217 ± 11 (−2.7%)	225 ± 26.9 (+0.9%)	220 ± 16.6 (−1.3%)	222 ± 16.8 (−0.4%)	216 ± 21.2 (−3.1%)
Final (fasted) body weight (g)	208.252 ± 14.0241	201.105 ± 11.6435 (−3.4%)	209.344 ± 25.2218 (0.5%)	206.477 ± 16.1061 (−0.9%)	209.687 ± 14.9094 (+0.7%)	202.877 ± 20.4691 (−2.6%)
WBC count (thousand/mm^3)	7.35 ± 1.5204	7.57 ± 1.82 (+3%)	9.21 ± 2.61 (+25%)	11.15 ± 4.78* (+52%)	8.70 ± 2.60 (+18%)	9.85 ± 2.12 (+34%)
Adrenal weight						
Right absolute (g)	0.0352 ± 0.0077	0.0417 ± 0.0082 (+18%)	0.0414 ± 0.0089 (+18%)	0.0364 ± 0.0066 (+3.4%)	0.0405 ± 0.0086 (+15%)	0.0357 ± 0.0068 (+1.4%)
Right relative (% body weight)	0.0169 ± 0.0035	0.0208 ± 0.0041 (+23%)	0.0200 ± 0.0047 (+18%)	0.0176 ± 0.0029 (+4.1%)	0.0193 ± 0.0039 (+14%)	0.0178 ± 0.0041 (+5.3%)
Left absolute (g)	0.0372 ± 0.0083	0.0407 ± 0.0081 (+9.4%)	0.0383 ± 0.0077 (+3%)	0.0372 ± 0.0084 (0)	0.0432 ± 0.008 (+16%)	0.0373 ± 0.0057 (+0.3%)
Left relative (% body weight)	0.0178 ± 0.0037	0.0203 ± 0.0044 (+14%)	0.0185 ± 0.004 (+3.9%)	0.0180 ± 0.0035 (+1.1%)	0.0206 ± 0.0038 (+16%)	0.0186 ± 0.0035 (+4.5%)
Kidney weight						
Right absolute (g)	0.9644 ± 0.1053	0.9648 ± 0.0818 (0)	0.9563 ± 0.1316 (−0.84%)	0.9404 ± 0.1107 (−2.5%)	0.959 ± 0.0782 (−0.56%)	0.901 ± 0.1082 (−6.5%)
Right relative (% body weight)	0.4631 ± 0.0383	0.48 ± 0.0332 (+3.6%)	0.4566 ± 0.0294 (−1.4%)	0.4548 ± 0.029 (−1.8%)	0.4577 ± 0.0255 (−1.2%)	0.45 ± 0.0584 (−3.5%)
Left absolute (g)	0.9527 ± 0.0906	0.9689 ± 0.812 (+1.7%)	0.9298 ± 0.1361 (−2.4%)	0.9149 ± 0.01333 (−4%)	0.9522 ± 0.0586 (−0.1%)	0.9006 ± 0.0948 (−5.5%)
Left relative (% body weight)	0.4574 ± 0.0286	0.4819 ± 0.0306 (+5.4%)	0.4436 ± 0.0355 (−3%)	0.4417 ± 0.0411 (−3.4%)	0.4561 ± 0.0411 (−0.3%)	0.45 ± 0.0471 (−2.5%)

Table B-2. Selected Results in Female S-D Rats Administered *p*-CBSA by Gavage for 31−32 Days[a]

Endpoint	Dose in mg/kg-d as *p*-CBSA Sodium Salt (mg/kg-d as *p*-CBSA)[b]					
	0	**10 (9.0)**	**50 (45)**	**500 (449)**	**1,000 (898)**	**2,000 (1,800)**
Ovary weight						
Right absolute (g)	0.0459 ± 0.012	0.0479 ± 0.0104 (+4.4%)	0.056 ± 0.0084 (+22%)	0.0554 ± 0.0198 (+21%)	0.0434 ± 0.0093 (−5.4%)	0.0534 ± 0.0125 (+16%)
Right relative (% body weight)	0.022 ± 0.0055	0.0238 ± 0.0046 (+8.2%)	0.0271 ± 0.0052 (+23%)	0.0265 ± 0.0076 (+20.5%)	0.0207 ± 0.0035 (−5.9%)	0.0264 ± 0.0058 (+20%)
Left absolute (g)	0.0436 ± 0.0115	0.0508 ± 0.0177 (+17%)	0.0494 ± 0.0123 (+13%)	0.0536 ± 0.0141 (+23%)	0.04 ± 0.0091 (−8.3%)	0.0557 ± 0.0119 (+28%)
Left relative (% body weight)	0.0209 ± 0.0052	0.0252 ± 0.0086 (+21%)	0.024 ± 0.0071 (+15%)	0.0258 ± 0.0053 (+23%)	0.0191 ± 0.0042 (−8.6%)	0.0274 ± 0.005 (+31%)

[a]American Biogenics Corporation (1985).
[b]Data reported as mean ± standard deviation (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.

p-CBSA = *p*-chlorobenzenesulfonic acid; S-D = Sprague-Dawley; WBC = white blood cell.

APPENDIX C. REFERENCES

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