APPENDIX A

O,P-TSA
HPV ROBUST SUMMARIES

o,p-TSA

HPV Robust Summaries
Day-Glo Color Corp.

July, 2008

1. Substance Information

CAS Number:	1333-07-9
Chemical Name:	Benzenesulfonamide, ar-methyl-
Structural Formula:	$C_7H_9NO_2S$
Other Names:	Mixture of 4-methyl-benzene sulfonamide and 2-methyl-benzene sulfonamide; Mixture of p-toluenesulfonamide and o-toluenesulfonamide; o,p-TSA; Ketjenflex® 9; Santicizer® 9
Exposure Limits:	Not established

2. Physical – Chemical Properties

2.1. Melting Point:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	KTM-01227 Determination of the Freezing Point (The method is based on European Pharmacopoeia II, Method V 6.12, but the temperatures of the oil baths were adjusted.
GLP:	No
Year:	1989
Value:	106 deg C
Decomposition:	No data available .
Conclusions:	The melting point is 106 deg C for a mixture of ortho: para-TSA (40:60)
Reliability:	4 (not assignable) Detailed report is not available. However, protocol for the method is available.
Reference:	1
Remarks:	The dried sample is brought into a test tube and molten at 170°C after which the tube is placed into an oil bath at 110°C (para toluene sulfonamide) or 130 - 135°C (ortho toluene sulfonamide). During the cooling period the temperature of the melt is measured. The freezing point is defined as the maximum temperature occurring during the solidification of the melt. The lowest melting point was achieved for the o:p ratio of 40:60.

	Although the study lacks details, the value is in agreement with that predicted by the EPISuite model, 91.19 deg C.
Additional References for Melting Point Studies:	4

2.2. Boiling Point:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Not provided
GLP:	No
Year:	1962
Value:	215 deg C
Pressure:	P = 10 mmHG
Pressure Unit:	Not known
Decomposition:	No data available
Conclusions:	The boiling point of o,p-TSA is 215 deg C
Reliability:	4 (not assignable) A formal written report and protocol are not available.
Reference:	2
Remarks:	Boiling points of various isomers were measured. The value is estimated based on the range between the value for the ortho and para isomers, 210-220 deg C. Although the study lacks details, the value is in agreement with the experimental database match from the EPISuite model, 214 deg C (ortho and para).
Additional References for Boiling Point Studies:	4

2.3. Density:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	No data available
GLP:	No data available
Year:	No data available
Value:	No data available
Conclusions:	No data available
Reliability:	No data available
Reference:	No data available
Remarks:	None
Additional References for Density Studies:	None

2.4. Vapor Pressure:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Gas Saturation Method (OECD 104)
GLP:	Yes - Signed GLP statement not included in report. However, reference is made to FDA GLP regulations and the study was audited and signed by QA.
Year:	1983
Value:	$< 3 \times 10^{-7}$ mm Hg
Temperature° C:	22°C
Pressure Unit:	mmHg
Decomposition:	Not available
Conclusions:	The vapor pressure of Santicizer® 9 was $< 3 \times 10^{-7}$ mm HG
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Santicizer® 9. For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o,p-TSA, ~30:70 ratio.
Reference:	3
Remarks:	The study was conducted on Santicizer® 9 (mixture of o- and p- TSA ~30:70 ratio), purity > 95%. The test system consisted of a regulated nitrogen supply at 35 psig, a thermally insulated test chamber equipped with a recording thermometer, two 600 mm X 30 mm I.D. saturation columns, vapor trap and flow meter. A one kilogram portion of acid washed, ignited white quartz sand was mixed with 10 g of the test article to achieve a 1% test material loading of the saturator sand. Dry nitrogen gas was passed through the saturator column, vapor trap containing 1 gram of Florisil and a bubble flow meter. The experiment was run several times. Run times were 7, 8, and 17 days. Flow rates were regulated to approximately 4.5 cm^3/min and 5.6 cm^3/min. The test article trapped on the Florisil was removed by extraction with methanol/water (45/55) and analyzed by HPLC. The estimated vapor pressure from the EPISuite model was 3.06×10^{-4} mm Hg at 25°C.
Additional Reference for Vapor Pressure Studies:	4

2.5. Partition Coefficient (log Kow):

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	EPI Suite Computer Model
GLP:	Not applicable
Year:	Not applicable
Log Kow:	0.92
Temperature°C:	No data available
Conclusions:	The log Kow of o,p-TSA is 0.92 based on the KOWWIN v1.67 in the EPI Suite Computer model
Reliability:	2 (valid with restrictions) Value estimated from validated EPA computer model
Reference:	4
Remarks:	Estimated value based on accepted model
Additional References for Partition Coefficient Studies:	Log Kow = 0.85 from experimental database match in EPI Suite from Hansch, C et al, 1995

2.6. Water Solubility:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	HPLC Analysis of a Saturated Solution
GLP:	Yes – Signed GLP statement not included in report. However, reference is made to FDA GLP regulations and study was audited and signed by QA.
Year:	1983
Value at temperature°C:	5 g/l at 25 deg C
Description of solubility:	Soluble
PH value and concentration at temperature °C:	Not available
Pka value at 25°C:	Not available
Conclusions:	The water solubility of a saturated solution of Santicizer® 9 is 5 g/l
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Santicizer® 9. For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o,p-TSA, ~30:70 ratio.
Reference:	5
Remarks:	The study was conducted on Santicizer 9 (mixture of o- and p- TSA ~30:70 ratio), purity > 95%. Twenty grams of the test article were mixed with 800 ml of deionized water.

	Replicate aliquots of the test solutions were taken for analysis of dissolved test article on day two and once each day for 5 days. Samples were centrifuged to remove undissolved test article. Duplicate 1 ml portions of the solution were analyzed by HPLC analysis. Calculations of the concentrations were done using normalized standard curves which were determined using the linear regression function of a Texas Instruments TI-55 calculator. The estimated water solubility = 7810 mg/l from experimental database match in EPI, Stephen, H & Stephen, T, 1963
Additional References for Water Solubility Studies:	4

2.7. Flash Point:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	No data available
GLP:	No data available
Year:	No data available
Results:	No data available
Conclusions:	No data available
Reliability:	No data available
Reference:	No data available
Remarks:	None
Additional References for Flash Point Studies:	None

2.8. Flammability:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	No data available
GLP:	No data available
Year:	No data available
Results:	No data available
Conclusions:	No data available
Reliability:	No data available
Reference:	No data available
Remarks:	None
Additional References for Flammability Studies:	None

3. Environmental Fate

3.1. Photodegradation:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	EPI Suite Computer Model
GLP:	Not applicable
Type:	Not applicable
Year:	Not applicable
Light Source:	No data available
Light Spectrum (nm):	No data available
Half-life:	Atmospheric oxidation (25 deg C): Half-Life = 8.7 days (12-hr day; 1.5E6 OH/cm^3); 104.8 hrs
Breakdown Products:	No data available
Conclusions:	The half-life of o,p-TSA is 8.8 days
Reliability	2 (valid with restrictions) Value estimated from validated EPA model
Reference:	4
Remarks:	Estimated value based on accepted model (AOPWIN) within EPISuite. It estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The rate constants estimated by the program are expressed as the half-life, the amount of time required for ½ of the material to degrade.
Additional References for Photodegradation Studies:	None

3.2. Stability in Water:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	EPI Suite Computer Model
GLP:	Not applicable
Type:	Not applicable
Year:	Not applicable
Half-life at a specific pH:	Not applicable
Breakdown Products:	Not applicable
Conclusions:	Rate constants can not be estimated for this structure based on the EPISuite model
Reliability:	Not applicable
Reference:	4

Remarks:	None
Additional References for Stability in Water Studies:	None

3.3. Transport (Fugacity):

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	EPI Suite Computer Model
GLP:	Not applicable
Type:	Not applicable
Year:	Not applicable
Media:	Air, Water, Soil, Sediment

Distributions:

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	13.2	0.025	0.473
Water	29.4	99.7	27.6
Soil	57.3	0.109	71.8
Sediment	0.0605	0.205	0.0568

Adsorption Coefficient:	No data available
Desorption:	No data available
Volatility:	No data available
Conclusions:	Partitions primarily to soil and water
Reliability:	2 (valid with restrictions) Values estimated based on validated EPA model
Reference:	4
Remarks:	When distributed equally to air, water and soil, is distributed 3% to air, 47% to water and 50% to soil.
Additional References for Transport (Fugacity) Studies:	None

3.4. Biodegradation:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Shake Flask CO2 Evolution : ASTM Draft No. 3 for the "Proposed Standard Practice for the Determination of the Ultimate Biodegradability of Organic Chemicals", 1980 (OECD 301B type)
Type:	CO2 Evolution
GLP:	Yes
Year:	1981
Degradation% after time:	13% after 35 days

Breakdown Products:	Not available
Concentration Of Test Chemical:	25.3 mg/l
Analytical Method:	Barium hydroxide titration with 0.1N HCL
Conclusions:	Moderate degree of biodegradation
Reliability:	4 (not assignable) Concentration of suspended solids not provided, sludge was acclimated for 14 days, CO2 production was not reported for every day of sampling. The study was conducted on, what was at the time, a commercial batch of Santicizer® 9 (purity not provided). For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o,p-TSA, ~30:70 ratio.
Reference:	6
Remarks:	The study was conducted on Santicizer® 9 (mixture of o- and p- TSA ~30:70 ratio). An acclimated inoculum (derived from soil, raw sewage and activated sludge mixed liquor) is prepared by the stepwise addition of test compound to a defined medium over a 14-day period. Following the acclimation period, 100 ml of the inoculum are mixed with 900 ml of minimal salts media in a flask, aerated (70% oxygen) and incubated the test article. An open reservoir containing 10 ml of 0.15N barium hydroxide is suspended via a glass tube inserted in a neoprene stopper. Flasks are sealed, agitated on a rotary shaker in the dark at ambient temperature. On days 3, 7, 14, 21, 28 and 35, barium hydroxide solution is removed from the flasks and titrated to determine the CO2 evolved. Fresh barium hydroxide is added back at each sampling point. Control values are subtracted from values for the test article. Barium hydroxide solutions removed from the shake flask reservoir were analyzed by titration with standard 0.1N HCL to a pH 8.5 endpoint using a Fisher Automatic Titrimeter II Titration System. CO2 evolution data were calculated as follows: Mg CO2 Evolved = (Titer – Mean Control Titer) x 2.200 $\text{CO2 Evolution (\% of Theory)} = \frac{\sum \text{Mg Co2 Evolved}}{\text{Mg of Test Compd x \%C X 3.664}} \times 100$ Sodium citrate (50 mg/l) was included in the study as a control and exhibited 71% degradation.

Additional References for Biodegradation Studies:	8, 9, 32, 36 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.
Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Soap and Detergent Association, Test Procedure and Standards – ABS and LAS Biodegradability. Scientific and Technical Report No. 3, January, 1966, as outlined by U.S. EPA Federal Register, March 16, 1979, 16275-16277 (OECD 302A type).
Type:	Semi-continuous Activated Sludge (SCAS) Biodegradation
GLP:	Yes - Signed GLP statement not included in report. However, reference is made to FDA GLP regulations and the study was audited and signed by QA.
Year:	1983
Degradation% after time:	92.9% after a twenty-one day biodegradation period.
Breakdown Products:	Not available
Concentration Of Test Chemical:	56.9 ppm
Analytical Method:	Dichloromethane extraction with quantification by HPLC
Conclusions:	Inherently Biodegradable
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Santicizer® 9 (purity not provided). For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o,p-TSA, ~30:70 ratio.
Reference:	7

Remarks: The study was conducted on Santicizer® 9 (mixture of o- and p- TSA ~30:70 ratio). Activated sludge used in the study was obtained for a waste water treatment plant. Solids concentration of the sludge was adjusted to approximately 3000 mg/l. The initial microbial population had an average of 2.1 x 10^6 organisms/ml of mixed liquor. A 14 day acclimation period was employed following a daily draw and fill routine during which dose rates increased from 0 to 50 ppm. Determination of suspended solids in the mixed liquor were performed at each draw and fill as well as measurement of dissolved oxygen levels. Aliquots of the influent from each control and test chamber were taken for dissolved organic carbon (DOC) analysis on days 6, 9, and 13. Aliquots of the effluent from each of the control and test chambers were taken for DOC analysis on days 7, 10, and 14. The DOC was obtained as the difference between the total carbon and inorganic carbon. The values obtained for the DOC levels in the influent and effluent samples were used to calculate the percent organic carbon removal.

$$\% \text{ removal} = 100 - \frac{(\text{DOC of influent}) - (\text{DOC of effluent})}{(\text{DOC of influent})} \times 100$$

The 21-day biodegradation period was initiated with a dose of 50 ppm. During this phase analyses included test material specific analysis on days 0 and 21 and dissolved organic carbon level monitoring. Analyses for levels of the test article were conducted by HPLC. The DOC levels were monitored on biodegradation days 1, 3, 7, 14, and 21. Examination of the percent of DOC removal values obtained during the acclimation phase of the study indicates a possibility of inhibition of the test article. The inhibition appears to be insignificant by the end of the acclimation period. Examination of the microbial population data shows no evidence of adverse effects of the test compounds upon

	the microflora present in the sludge. Therefore it was concluded that the test article had no adverse effects on sludge microflora and had no effect on the wastewater treatment process when present at of below the 70 ppm level. Measurements of the test article during the biodegradation phase indicted the 92.9% of the 56.9 ppm of the test article had biodegraded with 4.03 ppm remaining after 21 days. Percent DOC removal on day 21 was 24.8%, 55.4% and 48.1 percent for the negative control, positive control (triethylene glycol) and test article, respectively. Two protocol deviations were noted: sludge was characterized as to percent organic matter at the end of the study as opposed to study initiation and the study temperatures exceeded nominal ranges on some days. These deviations did not impact the study.
Additional References for Biodegradation Studies:	8, 9, 32, 36 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

3.5 Bioconcentration:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	EPI Suite Computer Model
Type:	Not applicable
GLP:	Not applicable
Year:	Not applicable
Results:	Log BCF = 0.500 (BCF = 3.162)
Conclusions:	Not expected to bioaccumulate
Reliability:	2 (valid with restrictions) Value estimated based on validated EPA model
Reference:	4
Remarks:	Estimated value based on accepted model using log Kow 0.85
Additional References for Bioconcentration Studies:	None

4. Ecotoxicity

4.1. Acute Toxicity to Fish:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	American Public Health Association, 1975. Standard Methods for the Examination of Water and Wastewater. 14th ed. Washington, DC. 1193 p. and Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians. Environmental Protection Agency, Ecological Research Series EPA-66-/3/75/009, April, 1975. 61 p.
Type:	Acute toxicity to Rainbow Trout-Static Bioassay
GLP:	Yes
Year:	1983
Species/Strain/:	Rainbow Trout (Salmo gairdneri)
Supplier:	Trout Lodge, Inc. McMillin, Washington
Analytical Monitoring:	Dissolved oxygen and pH
Exposure Period:	96 hours
Nominal/Measured Concentrations:	Nominal: 56, 100, 180, 320 and 560 mg/l
LC50:	120 mg/L (95% confidence limits 56-180 mg/l)
Conclusions:	The 96-hr LC50 = 120 mg/l
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Santicizer® 9. For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o,p-TSA, ~30:70 ratio. GLP study conducted in accordance with OECD 203. While test concentrations were not verified analytically, the solubility of the test article is 5 g/l and the preparation of the dosing solutions were verified by QA.
Reference:	10

Remarks:	The study was conducted on Santicizer® 9 (mixture of o- and p- TSA ~30:70 ratio), purity > 95%. The static fish bioassay was conducted in five gallon glass vessels containing 15 liters of well water. The dilution water contained 9.5 mg/l of dissolved oxygen (dissolved oxygen saturation at the test temperature was 10.8 mg/l) and had a pH of 8.1 and total hardness ($CaCO_3$) of 255 ppm. The test vessels were maintained in a 12 degree C water bath. The fish were acclimated to the water for 48 hours prior to testing. The mean fish weight and length was 1.4 g and 46 mm. The definitive study consisted of five concentrations of the test compound, ranging in a logarithmic series from 56 to 560 mg/l, with ten fish per concentration. The test concentrations were achieved by adding the appropriate weights of the test article directly to the test chambers. The fish were added 30 minutes after the addition of the test material. Mortality and abnormal effects were monitored and recorded once every 24 hours. Antimycin A was used as a positive control. The 96-hr LC50 of Antimycin A was 3.9 x 10^{-5} The percent mortality at 96 hours was 0, 0, 20, 100, 100, and 100 for the control, 56, 100, 180, 320 and 560 mg/l groups, respectively. The 96-hr LC50 was calculated using the Binomial Method.
Additional References for Acute Toxicity to Fish Studies:	11, 32, 36 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.
Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	American Public Health Association, 1975. Standard Methods for the Examination of Water and Wastewater. 14th ed. Washington, DC. 1193 p. and Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians. Environmental Protection Agency, Ecological Research Series EPA-66-/3/75/009, April, 1975. 61 p.
Type:	Acute toxicity to Bluegill Sunfish-Static Bioassay

GLP:	Yes
Year:	1983
Species/Strain/:	Bluegill Sunfish (Lepomis macrochirus)
Supplier:	Fattig Fish Hatchery, Brady, Nebraska
Analytical Monitoring:	Dissolved oxygen and pH
Exposure Period:	96 hours
Nominal/Measured Concentrations:	Nominal: 56, 100, 180, 320 and 560 mg/l
LC50:	260 mg/L (95% confidence limits 180-320 mg/l)
Conclusions:	The 96-hr LC50 = 260 mg/l
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Santicizer® 9. For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o,p-TSA, ~30:70 ratio. GLP study conducted in accordance with OECD 203. While test concentrations were not verified analytically, the solubility of the test article is 5 g/l and the preparation of the dosing solutions were verified by QA.
Reference:	12
Remarks:	The study was conducted on Santicizer® 9 (mixture of o- and p- TSA ~30:70 ratio), purity > 95%. The static fish bioassay was conducted in five gallon glass vessels containing 15 liters of well water. The dilution water contained 9.6 mg/l of dissolved oxygen (dissolved oxygen saturation at the test temperature was 8.8 mg/l) and had a pH of 8.3 and total hardness ($CaCO_3$) of 255 ppm. The test vessels were maintained in a 22 degree C water bath. The fish were acclimated to the water for 48 hours prior to testing. Mean fish weight and length was 0.37 g and 25 mm, respectively.

	The definitive study consisted of five concentrations of the test compound, ranging in a logarithmic series from 56 to 560 mg/l, with ten fish per concentration. The test concentrations were achieved by adding the appropriate weights of the test article directly to the test chambers. The fish were added 30 minutes after the addition of the test material. Mortality and abnormal effects were monitored and recorded once every 24 hours. Antimycin A was used as a positive control. The 96-hr LC50 of Antimycin A was 6.2 x 10^{-5}. The percent mortality at 96 hours was 0, 0, 0, 0, 90, and 100 for the control, 56, 100, 180, 320 and 560 mg/l groups, respectively. The 96-hr LC50 was calculated using the Binomial Method. Mortality was accompanied by surfacing, dark discoloration and loss of equilibrium. The No-effect concentration was 56 mg/l. An oily film was noted in the two highest concentrations.
Additional References for Acute Toxicity to Fish Studies:	13, 32, 36 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

4.2. Acute Toxicity to Invertebrates:.

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Grueber, D.J. and W.J. Adams, 1980. MIC Environmental Assessment Method for Conducting Acute Tests with Daphnia magna. Environmental Sciences Report ES-80-M-6. and U.S. EPA (1975) Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians. Ecological Research Series, EPA 660/3-75-009, 61 pp.
Type:	Acute Toxicity to Daphnia magna-Static Test
GLP:	Yes
Year:	1981
Species/Strain/:	Daphnia magna
Supplier:	Cultured at the Monsanto Industrial Chemicals Company (MIC) aquatic laboratory
Analytical Monitoring:	Dissolved oxygen, pH, alkalinity, hardness and temperature.
Exposure Period:	48 hours

Nominal/Measured Concentrations:	Nominal: 1000 mg/l
LC50:	> 1000 mg/L
Conclusions:	The 48-hr EC50 was > 1000 mg/l.
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Santicizer® 9 (purity not provided). For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o,p-TSA, ~30:70 ratio. GLP study conducted in accordance with OECD 202. Test concentrations were not verified analytically. However, the solubility of the test article is 5 g/l.
Reference:	14
Remarks:	The study was conducted on Santicizer® 9 (mixture of o- and p- TSA ~30:70 ratio). The static test was conducted in 250 ml beakers which contained 200 ml of test solution. The dilution water used was well water. For each test concentration, the appropriate amount of test article, dissolved in dimethylformamide (DMF), was added to 1000 ml of dilution water and shaken for 1 minute. This solution was divided into three 200 ml aliquots. Therefore, there were three replicates per concentration. A negative control (dilution water and 1.0 ml/l of DMF) was included in the study. Ten daphnids, (< 24 hours old), were assigned to each test vessel 30 minutes after the test article was added. The range finder test was conducted with controls, 62, 125, 250, 500 and 1000 mg/l. No immobilization was observed at any test concentration. During the 48 hour test, the pH ranged from 6.9 to 8.5, and the dissolved oxygen from 5.1 to 9.2 mg/l. The average temperature was 22 degrees C. The alkalinity and hardness ranged from 280 to 342 mg/l and 240 to 358 mg/l, respectively. There were no effects at 1000 mg/l the highest and only concentration tested in the definitive test.

Additional References for Acute Toxicity to Invertebrates Studies:	32, 36 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

4.3. Acute Toxicity to Aquatic Plants:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	ECOSAR Model
Type:	Not applicable
GLP:	Not applicable
Year:	Not applicable
Species/Strain/ Supplier:	Green algae
Analytical Monitoring:	Not applicable
Exposure Period:	96 hours
Nominal/Measured Concentrations:	Not applicable
EC50:	767.2 mg/l
Conclusions:	96-hr EC50 was 767.2 mg/l
Reliability:	2 (valid with restrictions) Value estimated based on EPA validated model
Reference:	15
Remarks:	Value estimated from EPA validated model
Additional References for Acute Toxicity to Aquatic Plants Studies:	16, 32, 36 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

5. Mammalian Toxicity

5.1. Acute Toxicity:

5.1.1. Oral

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	OECD 401
Type:	Acute Oral Toxicity Study
GLP:	Yes
Year:	1986

Species/Strain:	Wistar
Sex:	Male and female
No. Of Animals Per Sex Per Dose:	5
Vehicle:	Corn Oil
Route Of Administration:	Oral gavage
Time Of Observation Period:	14 days
Doses Administered:	1800, 2100 and 2400 mg/kg
LD50:	2400 mg/kg
Conclusions:	The acute oral LD50 to rats (combined sexes) was 2400 mg/kg
Reliability:	1 (valid without restrictions) Apparently well conducted GLP study
Reference:	17
Remarks:	The study was conducted on Ketjenflex® 9 (a mixture of toluene sulfonamides o/m/p = 41/8/51)

The test article was suspended in corn oil and administered to rats as a single dose using a plastic stomach tube at dose levels of 1800, 2100 or 2400 mg/kg. Animals were evaluated for clinical signs of toxicity and mortality.

Five of 10 animals in the high dose group died. All deaths occurred within 3 days of dosing. Clinical signs of toxicity in the mid and low dose groups included lethargy, unbalanced gait, and dyspnea. These signs were also noted in the high dose group as well as coma, bloody encrustation around the eye, absent or bloody stool and slimy salivation. All animals which became comatose died within 48 hours. Survivors appeared normal by day 4 and throughout the remaining 14-day observation period.

Macroscopic examination of dead animals revealed GI tract hemorrhages and hematuria. Macroscopic examination of survivors did not reveal any test article related effects.

The LD50 was calculated by probit analysis (Finney, 1971).

Additional References for Acute Oral Toxicity Studies:	18, 19, 20, 32, 36 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

5.1.2. Dermal

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Not Provided
Type:	Acute Dermal Toxicity
GLP:	No
Year:	1957
Species/Strain:	New Zealand Rabbit
Sex:	Male and Female
No. Of Animals Per Sex Per Dose:	1
Vehicle:	Corn oil
Route Of Administration:	Applied as a 25% suspension to the intact skin
Time Of Observation Period:	Five days
Doses Administered:	2-7.5 g/kg
LD50:	> 7.5 g/kg
Conclusions:	The test article was not acutely toxic when applied to the skin of rabbits.
Reliability:	4 (not assignable) Inadequate study details and results were provided. Only one rabbit was dosed per dose level. Non-GLP.
Reference:	21
Remarks:	The study was conducted on Santicizer® 9 (mixture of o- and p- TSA). A 25% suspension in corn oil was applied to the closely clipped, intact skin of New Zealand rabbits and observations made for evidence of toxicity. The treated areas were covered with plastic shields and a leather collar placed around the neck of each animal to prevent access to the sample.

Additional References for Acute Dermal Toxicity Studies:	None

5.1.3. Irritation

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	U.S. FDA (Fed. Reg. 28 (119), 5582, 1963)
Type:	Skin Irritation
GLP:	No
Year:	1978
Species/Strain:	New Zealand White Albino Rabbits
Sex:	Not provided
No. Of Animals Per Sex Per Dose:	6
Vehicle:	None reported
Route Of Administration:	0.5 grams were applied to the intact and abraded skin under a surgical patch, fixed to the application site by means of adhesive tape. The test article was removed 24 hours later.
Time Of Observation Period:	72 hours post application
Concentration Of Test Material:	Applied as received
Results:	Very slight erythema was noted on two intact sites and 6 abraded sites after patch removal. After 72 hours, very slight erythema was noted on three intact and three abraded sites. The average score (erythema plus edema) for 24 and 72 hours on intact skin was 0.4 and 0.5, respectively. The average score (erythema plus edema) for 24 and 72 hours on abraded skin was 1.0 and 0.5, respectively. Maximum score for erythema was 4. Maximum score for edema was 4. Total possible score for primary irritation was 8 (4 + 4).
Conclusions:	Ketjenflex® 9R was a very slight skin irritant.
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Ketjenflex® 9R (purity not provided). For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o/m/p-TSA, ~40/10/50 ratio. Apparently well conducted study.
Reference:	22
Remarks:	The test article was Ketjenflex® 9R (a mixture of o/m/p-TSA, ~40/10/50% ratio). The skin reactions were evaluated according to the method of Draize (J. Pharmacol 82: 377-390, 1944).

Additional References for Acute Dermal Irritation Studies:	23 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

5.1.4. Sensitization

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Not available
Type:	Not available
GLP:	Not available
Year:	Not available
Species/Strain:	Not available
Sex:	Not available
No. Of Animals Per Sex Per Dose:	Not available
Vehicle:	Not available
Route Of Administration:	Not available
Time Of Observation Period:	Not available
Concentration Of Test Material:	Not available
Results:	Not available
Conclusions:	Not available
Reliability:	Not available
Reference:	Not available
Remarks:	Not available
Additional References for Acute Dermal Sensitization Studies:	None

5.1.5. Eye Irritation

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	U.S. FDA (Fed. Reg. 28 (119), 5582, 1963)
Type:	Eye irritation
GLP:	No
Year:	1978
Species/Strain:	New Zealand White Albino rabbits

Sex:	Not provided
No. Of Animals Per Sex Per Dose:	6
Vehicle:	None
Route Of Administration:	100 mg of the test article were instilled into the everted lower lid of one eye of each rabbit. Eyes were washed 24 hours after instillation.
Time Of Observation Period:	7 days post instillation
Concentration Of Test Material:	Applied as received
Results:	The test article caused very slight corneal (score of 1/4) and iridal effects (score of 1/2) in one rabbit after 24 hours and moderate to slight redness and chemosis in all rabbits. After 7 days, three of the six rabbits exhibited slight redness (score of 1/ 3). All other scores were zero.
Conclusions:	Ketjenflex® 9R was not considered an eye irritant.
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Ketjenflex® 9R (purity not provided). For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o/m/p-TSA, ~40/10/50 ratio. Apparently well conducted study.
Reference:	24 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.
Remarks:	The test article was Ketjenflex® 9R (a mixture of o/m/p-TSA, ~40/10/50 ratio). The eye reactions were evaluated according to the method of Draize and Kelley (Drug Cosmet. Industr. 71: 36, 1952).
Additional References for Acute Eye Irritation Studies:	25 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

5.2. Repeated Dose Toxicity:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Not provided

Type:	90-day oral
GLP:	No
Year:	1974
Species/Strain:	Albino rats
Sex:	Male and Female
No. Of Animals Per Sex Per Dose:	15
Vehicle:	
Route of Administration:	Oral dietary
Time of Observation Period:	90 days
Doses Administered:	300, 1000 and 3000 ppm
Frequency of Treatment:	Daily
NOEL:	3000 ppm
LOEL:	> 3000 ppm
Toxic Response By Dose Level:	
Conclusions:	No effects on survival, hematology, clinical chemistry, gross or microscopic parameters were reported when rats were fed up to 3000 ppm.
Reliability:	3 (not reliable) This report was generated by a laboratory of questionable reputation (Industrial Bio-Test) prior to GLPs and cannot be considered reliable as the data cannot be verified.
Reference:	26
Remarks:	The study was conducted on Santicizer® 9 (a mixture of o/p-TSA ~30:70 ratio)
Additional References for Repeated Dose Toxicity Studies:	31, 32, 42 These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Not provided
Type:	90-day oral
GLP:	N0
Year:	1974
Species/Strain:	Beagle dog
Sex:	Males and Females
No. Of Animals Per	4

Sex Per Dose:	
Vehicle:	
Route of Administration:	Oral dietary
Time of Observation Period:	90 days
Doses Administered:	300, 1000 and 3000 ppm
Frequency of Treatment:	Daily
NOEL:	3000 ppm
LOEL:	> 3000 ppm
Toxic Response By Dose Level:	
Conclusions:	No effects on survival, hematology, clinical chemistry, gross or microscopic parameters were reported when dogs were fed up to 3000 ppm.
Reliability:	3 (not reliable) This report was generated by a laboratory of questionable reputation (Industrial Bio-Test) prior to GLPs and cannot be considered reliable as the data cannot be verified.
Reference:	27
Remarks:	The study was conducted on Santicizer® 9 (a mixture of o/p-TSA ~30/70 ratio)
Additional References for Repeated Dose Toxicity Studies:	31, 32, 42 These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

Identity:	p-TSA (CAS# 70-55-3)
Method:	OECD 422
Type:	Combined Repeat Dose and Reproductive/Developmental Toxicity Screening
GLP:	Yes
Year:	1994
Species/Strain:	Rat: Crj:CD(SD)
Sex:	Males and Females
No. Of Animals Per Sex Per Dose:	13
Vehicle:	5% gum Arabic solution
Route of Administration:	Gavage
Time of	Clinical signs: daily; Body weight and Food consumption:

Observation Period:	weekly; Clinical Laboratory: prior to scheduled sacrifice; Macroscopic and Microscopic: scheduled sacrifice.
Doses Administered:	0 (vehicle), 120, 300, and 750 mg/kg/day.
Frequency of Treatment:	Males were dosed daily for 42 days. Males were sacrificed day 43. Females from 14 days before mating to day 3 of lactation. Females were sacrificed day 4 of lactation.
NOEL:	< 120 mg/kg/day
LOEL:	120 mg/kg/day
Toxic Response By Dose Level:	A dose related hyper-salivation in all treated groups; body weight reduction in high dose males and in mid and high dose females during gestation and/or lactation; reduced food consumption during week 1 (high dose males) and during gestation (mid and high dose females); necropsy findings included: dark-colored liver (6/13 high dose males), decrease thymus weight (mid and high dose females), significant increases in relative kidney and testicular weights (high dose males), increase in relative kidney and liver weights (high dose females); Hematology findings included: dose-related increase in white blood cell count (mid and high dose males), significant increase in proportion of neutrophils (high dose males); Clinical chemistry findings included: significantly elevated blood urea nitrogen, GOT, and chloride (mid and high dose males), elevated GPT and decrease potassium (high dose males); Histopathology revealed: thickened urinary bladder epithelium (6/13 low and 11/13 mid and high dose males and 1/13 low, 12/13 mid and 7/13 high dose females), dose dependent acceleration of involution of the thymus (mid and high dose females).
Conclusions:	Repeated oral administration of p-TSA to rats caused clinical signs of toxicity, urinary bladder hyperplasia (both sexes) and involution of the thymus (females).
Reliability:	2 (valid with restrictions) English translation
Reference:	28
Remarks:	The study was conducted on p-TSA (99.9% pure) by the Ministry of Health and Welfare (MHW), Japan and is considered a key study under OECD SIDS. The original report was translated from Japanese.
Additional References for Repeated Dose Toxicity Studies:	31, 36, 42 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

Identity:	o-TSA (CAS# 88-19-7)
Method:	OECD 422
Type:	Combined Repeat Dose and Reproductive/Developmental Toxicity Screening
GLP:	Yes
Year:	1999
Species/Strain:	Rat: Crj:CD(IGS)
Sex:	Males and Females
No. Of Animals Per Sex Per Dose:	13
Vehicle:	5% CMC Na
Route of Administration:	Gavage
Time of Observation Period:	Clinical signs: daily; Body weight and Food consumption: weekly; Clinical Laboratory: prior to scheduled sacrifice; Macroscopic and Microscopic: scheduled sacrifice.
Doses Administered:	0 (vehicle), 20, 100, and 500 mg/kg/day
Frequency of Treatment:	Males were dosed daily for 42 days. Males were sacrificed day 43. Females from 14 days before mating to day 3 of lactation. Females were sacrificed day 4 of lactation.
NOEL:	< 20 mg/kg/day (males) and 20 mg/kg/day (females)
LOEL:	20 mg/kg/day
Toxic Response By Dose Level:	Mortality: three females in the high dose group, and two sacrificed in moribund condition during pre-mating; Clinical signs: decreased locomotor activity, prone position and salivation and significant low body weights in both sexes in the mid and high dose; Hematology: increased total cholesterol in mid and high dose, decrease in glucose and triglyceride in the (high dose males); Macroscopic examination: significantly increased liver weight (high dose males and mid and high dose females), significantly increased relative kidney weight (mid and high dose males and high dose females); Histopathology: hypertrophy of centrilobular hepatocytes with cytoplasm having a glass appearance (mid and high dose of both sexes), dose dependent increase incidence and severity of renal eosinophilic body (all males), significantly increased incidence of fibrosis and cellular infiltration of the pericardium and fibrosis and cellular infiltration of the capsule and atrophy of the thymus (high dose females).
Conclusions:	Repeated oral administration of o-TSA to rats caused clinical signs of toxicity, centrilobular hepatocyte hypertrophy, renal eosinophilic bodies (males) and atrophy of the thymus (females).

Reliability:	2 (valid with restrictions) An English translation of the original report is not available. However, a summary of the report, in English, was provided by the Hatano Research Institute, the laboratory which conducted the study.
Reference:	29
Remarks:	The study was conducted on o-TSA (99.95% pure) by the Ministry of Health and Welfare (MHW), Japan and is considered a key study under OECD SIDS.
Additional References for Repeated Dose Toxicity Studies:	32 These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

Identity:	o-TSA (CAS# 88-19-7)
Method:	Lifetime (Two Generation)
Type:	Oral (Dietary)
GLP:	No
Year:	1980
Species/Strain:	Rat: Sprague-Dawley
Sex:	Males and Females
No. Of Animals Per Sex Per Dose:	50 males and 50 females per dose group
Vehicle:	Appropriate amount of the test article was premixed with 500 g of ground rat chow.
Route of Administration:	Dietary
Time of Observation Period:	Clinical signs: daily; Body weight and Food consumption: weekly; Hematology: at various intervals up to 98 weeks of age (F0) or 45.5 weeks of age (F1); Urine: 6- month intervals; Macroscopic and Microscopic: study termination.
Doses Administered:	0 (control), 2.5, 25, 250 mg/kg/day
Frequency of Treatment:	Rats were exposed to the chemical from 90 days before mating in the first generation (for 142 weeks) and after weaning in the second generation (for 127 weeks).
NOEL:	25 mg/kg/day
LOEL:	250 mg/kg
Toxic Response By Dose Level:	Growth rates decreased in the 250 mg/kg dose group. Food consumption was less in this group for animals surviving at least 80 weeks on test. There was no effect on reproduction, lifespan or hematological parameters in any dose group or generation when compared to controls. Some animals had

	bladder and kidney stones but these were determined to non-treatment related.
Conclusions:	The dietary exposure of up to 250 mg/kg/day of o-TSA, had no adverse effects on reproduction, hematology, or survival and did not increase the tumor incidence.
Reliability:	4 (not assignable) Non-GLP; only histopathology data were reported.
Reference:	30
Remarks:	The study was conducted on o-TSA and contained less than 100 ppm total impurities. The concentration of o-TSA in the diets was changed weekly to maintain a constant dosage. An appropriate amount of the test article was premixed with 500 g of ground rat chow. The premix was added to an appropriate amount of basal diet plus corn oil and mixed thoroughly on the day prior to use. Weighed amounts of the feed were distributed to the animals on a weekly basis.
Additional References for Repeated Dose Toxicity Studies:	32 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

5.3. Reproductive Toxicity:

Identity:	p-TSA (CAS# 70-55-3)
Method:	OECD 422
Type:	Combined Repeat Dose and Reproductive/Developmental Toxicity Screening
GLP:	Yes
Year:	1994
Species/Strain:	Rat: Crj:CD(SD)
Sex:	Males and Females
No. Of Animals Per Sex Per Dose:	13
Vehicle:	5% gum Arabic solution
Route Of Administration:	gavage
Time Of Observation Period:	Mating: checked daily during cohabitation (from mating results mating rate, conception rate were calculated); Pregnancy periods: day 0 to delivery; Pup data: from delivery to day 4 lactation; Autopsy: day 4 of lactation

Doses Administered:	0 (vehicle), 120, 300 and 750 mg/kg/day
Frequency Of Treatment:	Males were dosed daily for 42 days. Males were sacrificed day 43. Females from 14 days before mating to day 3 of lactation. Females were sacrificed day 4 of lactation.
Premating Exposure For Males:	14 days
Premating Exposure For Females:	14 days
P NOEL:	300 mg/kg/day (reproduction); < 120 mg/kg/day (non-reproductive)
P LOEL:	750 mg/kg/day (reproduction); 120 mg/kg/day (non-reproductive)
F1 NOEL:	300 mg/kg/day
F1 LOEL;	750 mg/kg/day
F2 NOAEL (NOEL):	No data available
F2 LOAEL (LOEL):	No data available
P/F1/F2 Toxic Response By Dose Level:	Clinical signs of toxicity, (salivation, reduced weight gain and urinary bladder changes), were observed in groups receiving 120 mg/kg/day or more. Mating performance and fertility were not affected. Reproduction parameters were comparable among all groups including controls. There was no significant difference in birth rate and the period of pregnancy when compared to controls. A difficult labor was observed in two of the high dose females (all pups died by day 2 in these two litters) as well as a decrease in lactation index. There was no significant difference in the numbers of corpora lutea and implantations and implantation rate between the control and treated groups. Viability rate for lactation day one was significantly reduced. Delivery rate, birth rate and viability rate for day four was comparable to controls. Body weights on lactation day one in the high dose group were reduced but not on day four. There were no significant visceral or skeletal findings when compared to controls.
Conclusions:	The NOEL for reproductive/developmental toxicity is 300 mg/kg/day.
Reliability:	2 (valid with restrictions) English translation
Reference:	28
Remarks:	The study was conducted on p-TSA (99.9% pure) by the Ministry of Health and Welfare (MHW), Japan and is considered a key study under OECD SIDS. The original

	report was translated from Japanese.
Additional References for Reproductive Toxicity Studies:	33 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

Identity:	o-TSA (CAS# 88-19-7)
Method:	OECD 422
Type:	Combined Repeat Dose and Reproductive/Developmental Toxicity Screening
GLP:	Yes
Year:	1999
Species/Strain:	Rat: Crj:CD(IGS)
Sex:	Males and Females
No. Of Animals Per Sex Per Dose:	13
Vehicle:	0.5% CMC Na
Route Of Administration:	gavage
Time Of Observation Period:	Mating: checked daily during cohabitation (from mating results mating rate, conception rate were calculated); Pregnancy periods: day 0 to delivery; Pup data: from delivery to day 4 lactation; Autopsy: day 4 of lactation
Doses Administered:	0 (vehicle), 20, 100 or 500 mg/kg/day
Frequency Of Treatment:	Males were dosed daily for 42 days. Males were sacrificed day 43. Females from 14 days before mating to day 3 of lactation. Females were sacrificed day 4 of lactation.
Premating Exposure For Males:	14 days
Premating Exposure For Females:	14 days
P NOEL:	500 mg/kg/day (reproduction); < 20 mg/kg/day (non-reproductive)
P LOEL:	Not determined (reproduction); 20 mg/kg/day (non-reproductive)
F1 NOEL:	100 mg/kg/day

F1 LOEL;	500 mg/kg/day (low birth index and weights of pups)
F2 NOEL:	No data available
F2 LOEL:	No data available
P/F1/F2 Toxic Response By Dose Level:	Three females died and two females were sacrificed in moribund condition during the pre-mating period at 500 mg/kg/day. Decreased locomotor activity and appearance of prone position and salivation were observed in the mid and high dose groups of both sexes. There were no effects on copulation, ovulation and fertility, delivery and lactation at doses up to and including 500 mg/kg/day. There was no effect on viability, sex ratio and body weights in mid and low dose groups. In the high dose group, the number of live pups on days 0 and 4 of lactation and birth index tended to be low (not statistically significant) and weights of pups of both sexes on days 0 and 4 were significantly reduced.
Conclusions:	The NOEL for reproduction and developmental toxicity is 500 mg/kg/day and 100 mg/kg/day, respectively.
Reliability:	2 (valid with restrictions) An English translation of the original report is not available. However, a summary of the report, in English, was provided by the Hatano Research Institute, the laboratory which conducted the study.
Reference:	29
Remarks:	The study was conducted on o-TSA by the Ministry of Health and Welfare (MHW), Japan and is considered a key study under OECD SIDS.
Additional References for Reproductive Toxicity Studies:	None

Identity:	o-TSA (CAS# 88-19-7)
Method:	Lifetime (Two Generation)
Type:	Oral (Dietary)
GLP:	No
Year:	1980
Species/Strain:	Rat: Sprague-Dawley
Sex:	Males and Females
No. Of Animals Per Sex Per Dose:	50 males and 50 females per dose group
Vehicle:	Appropriate amount of the test article was premixed with 500 g of ground rat chow.
Route of Administration:	Dietary
Time of Observation	Clinical signs: daily; Body weight and Food consumption: weekly; Hematology: at various intervals up to 98 weeks of

Period:	age (F0) or 45.5 weeks of age (F1); Urine: 6- month intervals; Macroscopic and Microscopic: study termination
Doses Administered:	0 (control), 2.5, 25, 250 mg/kg/day
Frequency of Treatment:	Rats were exposed to the chemical from 90 days before mating in the first generation (for 142 weeks) and after weaning in the second generation (for 127 weeks).
Premating Exposure for Mates:	90 days
Premating Exposure for Females:	90 days
P NOEL:	250 mg/kg/day (reproduction); 25 mg/kg/day (non-reproductive)
P LOEL:	250 mg/kg/day (reduced growth rate)
F1 NOEL:	25 mg/kg/day
F1 LOEL:	250 mg/kg/day (decreased litter size)
P/F1 Toxic Response By Dose Level:	Growth rates decreased significantly in the 250 mg/kg dose group. Food consumption in this group was less for animals surviving at least 80 weeks on test. There was no effect on lifespan or hematological parameters in any dose group or generation when compared to controls. Some animals had bladder and kidney stones but these were determined to non-treatment related. There was no effect on reproductive parameters (details not provided). However, there was a statistically significant decrease in litter size on day 1 and 4 postpartum in the 250 mg/kg/day group. When adjusted for litter size on day 4 postpartum, the average pup body weight was significantly lower in this group.
Conclusions:	The NOEL for reproductive and developmental toxicity was 250 mg/kg/day and 25 mg/kg/day, respectively.
Reliability:	4 (not assignable) Details of reproductive parameters such as ovulation, implantation, delivery and lactation analyses were not provided.
Reference:	30
Remarks:	The study was conducted on o-TSA and contained less than 100 ppm total impurities. The concentration of o-TSA in the diets was changed weekly to maintain a constant dosage. An appropriate amount of the test article was premixed with 500 g of ground rat chow. The premix was added to an appropriate amount of basal diet plus corn oil and mixed thoroughly on the day prior to use. Weighed amounts of the feed were distributed to the animals on a weekly basis.

Additional References for Repeated Dose Toxicity Studies:	None

5.4. Genetic Toxicity

5.4.1. *In Vitro* Gene Mutations

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Salmonella/Microsome Plate Test
Type:	*in vitro* Microbial Assay
GLP:	No
Year:	1978
Cell Type:	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100 and Saccharomyces D4
Metabolic Activation:	S9 from Sprague-Dawley rat liver induced by Aroclor 1254
Concentrations Tested:	Solvent control, 1, 10, 100, 500 and 1000 ug/plate
Vehicle:	DMSO
Cytotoxic Concentration:	Not specifically indicated
Genotoxic Effects With Metabolic Activation:	No significant increase in revertants when compared to controls.
Genotoxic Effects Without Metabolic Activation:	No significant increase in revertants when compared to controls.
Conclusions:	Not mutagenic to Salmonella typhimurium or Saccharomyces D4 with or without metabolic activation.
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Ketjenflex® 9R (purity not provided). For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o/m/p-TSA, 40/10/50 ratio. Apparently well conducted study.
Reference:	34
Remarks:	The study was conducted on Ketjenflex® 9R (mixture of o/m/p-TSA, 40/10/50 ratio). The test article was tested over a series of concentrations such that there was quantitative or qualitative evidence of some chemically induced

	physiological effect at the highest dose level. The low dose was below a concentration that demonstrated any toxic effect. Appropriate positive controls were included in the study and significantly increased the number of revertants when compared to controls demonstrating the validity of the test.
Additional References for In Vitro Gene Mutation Studies:	32, 36, 42, 43 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	Salmonella/Microsome Plate Test
Type:	*in vitro* Microbial Assay
GLP:	No
Year:	1976
Cell Type:	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100 and Saccharomyces D4
Metabolic Activation:	S9 from Sprague-Dawley rat liver induced by Aroclor 1254
Concentrations Tested:	Solvent control, 0.5, 5, 50 and 250 ug/plate
Vehicle:	DMSO
Cytotoxic Concentration:	Not specifically indicated
Genotoxic Effects With Metabolic Activation:	No significant increase in revertants when compared to controls.
Genotoxic Effects Without Metabolic Activation:	No significant increase in revertants when compared to controls.
Conclusions:	Not mutagenic to Salmonella typhimurium or Saccharomyces D4 with or without metabolic activation.
Reliability:	2 (valid with restrictions) The study was conducted on, what was at the time, a commercial batch of Santicizer® 9E (purity not provided). For the US HPV program, the test article, identified by trade name in the report, was chemically identified by contemporaneous documents (i.e. MSDS, memos, product bulletins etc.) as o,p-TSA, ~30:70 ratio. There was no indication that phenotypic characteristics or growth requirements were verified.
Reference:	35
Remarks:	The study was conducted on Santicizer® 9E (mixture of o,p-

	TSA, ~30:70 ratio). The test article was tested over a series of concentrations such that there was quantitative or qualitative evidence of some chemically induced physiological effect at the highest dose level. The low dose was below a concentration that demonstrated any toxic effect. Appropriate positive controls were included in the study and significantly increased the number of revertants when compared to controls demonstrating the validity of the test.
Additional References for In Vitro Gene Mutation Studies:	32, 36, 42, 43 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

5.4.2. *In Vitro* Chromosome Aberrations

Identity:	p-TSA (CAS# 70-55-3)
Method:	Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) OECD 473
Type:	Non-bacterial *in vitro* Chromosomal Aberration Test
GLP:	Yes
Year:	1994
Cell Type:	Chinese hamster CHL cells
Metabolic Activation	Rat liver induced with Phenobarbital and 5,6-benzoflavone
Concentrations Tested:	Solvent control, 0.33, 0.65 and 1.3 mg/ml without activation, (continuous treatment for 24 and 48 hours) and solvent control, 0.43, 0.85 and 1.7 mg/ml with and without activation (6 hour treatment and 18 hours of culturing)
Vehicle:	DMSO
Cytotoxic Concentration:	>1.7 mg/ml with activation; >1.3 mg/ml without activation
Genotoxic Effects With Metabolic Activation:	Did not induce chromosomal aberrations.
Genotoxic Effects Without Metabolic Activation:	Did not induce chromosomal aberrations.
Conclusions:	The test article was negative under the conditions of the test.
Reliability:	2 (valid with restrictions) English translation
Reference:	37
Remarks:	The study was conducted on p-TSA (99.9% purity) for the

	Ministry of Health and Welfare (MHW), Japan and is considered a key study under OECD SIDS. The original report was translated from Japanese. Chromosomes were analyzed for aberrations following 24 and 48 hours of continuous treatment without activation and following 18 hours of culturing after 6 hours of treatment with and without activation. Structural aberrations were classified according to the Japanese Environmental Mutagen Society Mammalian Mutagenicity Study Group. Two hundred cells at mitotic metaphase from each group were analyzed for structural aberrations and 800 mitotic metaphase cells from each group for polyploidy. Numbers of observed cells, types and number of structural aberrations and number of polyploids were recorded. Appropriate positive and negative controls were included in the study. Fischer's Exact probability test was used to determine significance. The frequency of cells with chromosomal aberration less than 5% were considered negative, 5%-10% as pseudo-positive and >10% as positive.
Additional References for *In Vitro* Chromosome Aberration Studies:	44, 45 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Identity:	o-TSA (CAS# 88-19-7)
Method:	Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) OECD 473
Type:	Non-bacterial *in vitro* Chromosomal Aberration Test
GLP:	Yes
Year:	1999
Cell Type:	Chinese hamster CHL cells
Metabolic Activation	Rat liver induced with Phenobarbital and 5,6-benzoflavone
Concentrations Tested:	Solvent control, 375, 750, 1500 2250 and 3000 ug/ml without activation, (continuous treatment for 24 and 48 hours) and Solvent control, 375, 750, 1500 and 3000 ug/ml with and without activation (6 hour treatment and 18 hours of culturing)
Vehicle:	DMSO
Cytotoxic Concentration:	2250 ug/ml for continuous treatment. No cytotoxicity for short-term treatment with or without activation.
Genotoxic Effects With Metabolic	Did not induce chromosomal aberrations.

Activation:	
Genotoxic Effects Without Metabolic Activation:	Did not induce chromosomal aberrations.
Conclusions:	The test article was negative under the conditions of the test.
Reliability:	2 (valid with restrictions) An English translation of the original report is not available. However, a summary of the report, in English, was provided by the Hatano Research Institute. Tables, in the original report are in English.
Reference:	38
Remarks:	The study was conducted on o-TSA (99% purity) for the Ministry of Health and Welfare (MHW), Japan and is considered a key study under OECD SIDS. Chromosomes were analyzed for aberrations following 24 and 48 hours of continuous treatment without activation and following 18 hours of culturing after 6 hours of treatment with activation. Structural aberrations were classified according to the Japanese Environmental Mutagen Society Mammalian Mutagenicity Study Group. Two hundred cells at mitotic metaphase from each group were analyzed for structural aberrations and 800 mitotic metaphase cells from each group for polyploidy. Numbers of observed cells, types and number of structural aberrations and number of polyploids were recorded. Appropriate positive and negative controls were included in the study. Fischer's Exact probability test was used to determine significance. The frequency of cells with chromosomal aberration less than 5% were considered negative, 5%-10% as pseudo-positive and >10% as positive.
Additional References for *In Vitro* Chromosome Aberration Studies:	45 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

5.5. Developmental Toxicity:

Identity:	o,p-TSA (CAS# 1333-07-9)
Method:	U.S. EPA Pesticide Assessment Guidelines Series 83-3, 1982
Type:	Developmental
GLP:	Yes
Year:	1985
Species/Strain:	Rat:Charles River COBS CD
Sex:	Mated Females
No. Of Animals Per Sex Per Dose:	25
Vehicle:	Corn Oil
Route Of Administration:	Gavage
Time Of Observation Period:	Twice daily for mortality and once daily for clinical signs of toxicity on gestation days 6-15. Body weights were recorded at various intervals throughout gestation. Cesarean section on day 20 of gestation. Fetuses were examined for external malformations and variations. One-half were subjected to soft tissue examination and the other half to skeletal examination.
Doses Administered:	0 (vehicle), 50, 250, and 500 mg/kg/day. Doses were prepared daily. The dosage volume was 10 ml/kg.
Frequency Of Treatment:	Daily on gestation days 6-15
Maternal NOEL:	50 mg/kg/day
Maternal LOEL:	250 mg/kg/day (reduced body weights)
Fetal NOEL:	50 mg/kg/day
Fetal LOEL;	250 mg/kg/day
Maternal Toxic Response By Dose Level:	There were no maternal mortalities. Body weights were recorded on gestation days 0, 6, 9, 12, 16 and 20. There was a statistically significant reduction in maternal body weight gain at the mid and high dose during the treatment interval. Weight loss was observed during this interval. Pregnancy rates in the low and mid dose group were lower when compared to controls. This was not treatment related as dosing did not begin until after mating.
Fetal Toxic Response By Dose Level:	Fetal body weight was statistically significantly less than control in the mid and high dose groups and slight in the low dose group. Fetotoxicity was exhibited by an increase in

	postimplantation loss in the mid and high dose groups which was significant in the high dose. All other parameters (corpora lutea, total implantations, viable litter size, and sex distribution) were comparable to controls. The incidence of fetal malformations, were comparable to controls. Developmental variations, (unossification of sternebrae #5 and #6), were increased in the high dose group which was correlated with fetal body weight reduction. All remaining variations were comparable to controls or occurred as an isolated incidence.
Conclusions:	The test article was not teratogenic when administered up to 500 mg/kg/day.
Reliability:	2 (valid with restrictions) No verification of dose levels, and no information on food consumption.
Reference:	39
Remarks:	The study was conducted on Santicizer® 9C (a mixture of 32% o-TSA and 68% p-TSA), > 99% purity. Dose levels were selected based on a range-finding study. In the range-finding study, dams were administered 100, 500, 1000, 1500, or 2000 mg/kg/day by oral gavage during gestation. There was a dose-response reduction in maternal weight gain. Embryolethality (increase in postimplantation losses/dam) with a concurrent decrease in viable fetuses/dam, was observed in the 1500 and 20000 mg/kg/day dose groups.
Additional References for Reproductive Toxicity Studies:	40, 41 Data from additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database or were determined to be inadequate.

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APPENDIX B

O,P-TSA
USE AND EXPOSURE INFORMATION

Use and Exposure Information for o,p-TSA

1.0 Production Volume, Physical Form of Marketed Product and Use Pattern

Day-Glo Color Corp., has agreed to sponsor the substance o,p-TSA or benzenesulfonamide, ar-methyl- (CAS# 1333-07-9), under the Extended HPV Program. o,p-TSA is imported into the U.S. at one site as a fine white powder in 25 kg bags. o,p-TSA has a measured melting point of 106°C, a measured boiling point of 215°C, a measured vapor pressure of $< 3 \times 10^{-7}$, and a measured water solubility of 5 g/l.

Importation of o,p-TSA meets or exceeds the HPV criteria of 1 million pounds.

In general, o,p-TSA is used in an industrial setting as a chemical intermediate monomer to produce fluorescent pigment powder and colorant and is completely consumed in the manufacturing process of final products.

o,p-TSA is not used in consumer products.

2.0 Environmental Exposure and Fate

2.1. Sources of Environmental Exposure

There is limited opportunity for environmental release during the use of o,p-TSA. During loading and processing, any free particulate matter is trapped, via a suction vent attached to the reactor vessel. The resulting air stream is carried through a series of aqueous scrubbers preventing release of any particulate matter into the atmosphere. There is essentially no residual o,p-TSA following processing into the final products and therefore no release from clean-up of the reaction vessels. Empty bags which contained o,p-TSA are burned in an on-site incinerator.

2.2. Transportation between Environmental Compartments

When distributed equally to air, water, and soil, o,p-TSA primarily distributed to water and soil based on the EPISuite Computer Model.

2.3 Biodegradation and Bioaccumulation

o,p-TSA was biodegradable in the SCAS test.

o,p-TSA is not expected to bioaccumulate based on EPISuite Computer Model.

2.4 Stability in Water

Rate constants cannot be estimated for this structure.

2.5 Atmospheric Degradation

The half-life of o,p-TSA, in the atmosphere, is estimated to be 8.7 days by the EPISuite Computer Model.

3.0 Human Exposure

3.1. Occupational Exposure

In an occupational setting, exposure to o,p-TSA could occur during the following workplace situations:

Task	Number of Workers
• Charging reactor vessels	8 (maximum)
• Handling empty bags	2 (maximum)

The primary routes of occupational exposures are through skin, eye, oral and inhalation contact. However, there is limited opportunity for exposure during the use of o,p-TSA. When o,p-TSA is charged into reactor vessels, the charging is accomplished by cutting the bags and pouring the material into the open manway of the reactor. Exposure to the powder is minimized by using a suction vent attached to the reactor vessel. When handling the bags, workers use chemical gloves and respirators with HEPA filters as protective equipment.

3.2 Consumer Exposure

o,p-TSA is manufactured for use as a chemical intermediate and is totally consumed in the manufacture of the final product. Therefore, no exposure to the general public is expected through the use of commercial or consumer products.