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Subject o,p-TSA HPV Submission

Day-Glo Color Corporation has sponsored benzenesulfonamide, ar-methyl- (CAS# 1333-07-9) also known as o,p-TSA in the U.S. EPA High Production Volume (HPV) Challenge program. On behalf of Day-Glo Color Corporation, Akzo Nobel Services Inc. is submitting the attached test plan, robust summaries as well as use and exposure information on o,p-TSA. Akzo Nobel Services Inc. will enter the data into EPA's HPV Information System (HPVIS).

Please note that this submission was inadvertently submitted to the EHPV program at EHPV-Program-Submissions@epa.gov on Wednesday, July 23, 2008.

Please contact me with any questions.

Best Regards

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**o,p-TSA
HPV TEST PLAN**

**Submitted to the U.S. Environmental Protection
Agency**

By

Day-Glo Color Corp.

July, 2008

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SUMMARY

Day-Glo Color Corporation has sponsored benzenesulfonamide, ar-methyl-, (CAS# 1333-07-9), also known as o,p-TSA, in the U.S. EPA High Production Volume (HPV) program. Experimental and modeling data exist on several SIDS endpoints for o,p-TSA.

Robust summaries of available studies on o,p-TSA are included in this submission (see Appendix A). Data on o,p-TSA from the EPISuite computer model were used in the absence of experimental data for physical/chemical characteristics. The ECOSAR computer model was used in the absence of experimental data on ecotoxicity endpoints as was data from studies conducted on the ortho and para isomers of TSA. The table below summarizes the endpoints of interest in the HPV program, the available data, and indicates proposed testing.

Endpoint	Sufficient Data Available	Testing Proposed
Physical/Chemical Characteristics	Yes	No
Photodegradation	Yes	No
Hydrolysis	Yes	No
Biodegradation	Yes	No
Transport	Yes	No
Acute Fish Toxicity	Yes	No
Acute Daphnia Toxicity	Yes	No
Acute Alga Inhibition	Yes	No
Acute Toxicity	Yes	No
Genetic Toxicity	Yes	No
Repeated Dose	Yes	No
Reproductive Toxicity	Yes	No
Developmental Toxicity	Yes	No

1.0 INTRODUCTION

Day-Glo Color Corp. has sponsored benzenesulfonamide, ar-methyl- (CAS# 1333-07-9), also known as o,p-TSA (indicating a mixture of ortho and para isomers), in the U.S. HPV program to assess its potential health and environmental hazards, including selected physical/chemical characteristics. Additional synonyms include Ketjenflex® 9 and Santicizer® 9. Data, to support various HPV endpoints, were taken from studies conducted on Ketjenflex® 9 and Santicizer® 9. Typical percent ratios of ortho/para isomers at the time these tests were performed were 30/70 (o/p) for Santicizer® 9 and 40/10/50 (o/m/p) for Ketjenflex® 9. The percent ratios of ortho/para isomers for current commercial products are 20/80 or 40/60. The slight difference in the ratios of isomers between former and current commercial products is not expected to affect the toxicity based on the data for the mixed and individual isomers presented in this test plan.

In the absence of measured environmental and ecotoxicity test data, on o,p-TSA, U.S. EPA validated computer models were used to generate estimated values. In the absence of test data, for health effects endpoints, data from studies conducted on o-TSA (CAS# 88-19-7) and p-TSA (CAS# 70-55-3) isomers were summarized. This is justified since the HPV substance is a combination of these two isomers. The hazard(s) of the HPV substance would not be expected to be greater than the most hazardous endpoint of an individual TSA isomer.

Based on the availability of model and measured data, no testing is proposed for o,p-TSA.

2.0 EVALUATION OF EXISTING DATA AND PROPOSED TESTING

The available data on o,p-TSA has been evaluated and summarized. Data on o,p-TSA from the EPISuite computer model (Ref. 1) were used in the absence of experimental values for physical/chemical properties. The ECOSAR computer model (Ref. 2) was used to estimate toxicity in the absence of measured data for algae. Data for mammalian toxicity was available from Axcentive SARL owned studies as well as from submissions made to the U.S. EPA under TSCA section 8(e). Robust summaries of the studies are included in this submission. The Klimisch (Ref. 3) reliability code was used to determine the reliability of the available studies. The Klimisch rating of 1, 2, 3 and 4 signifies valid without restriction, valid with restriction, not reliable and not assignable, respectively. A literature search of online databases included: TOXNET (TOXLINE, HSDB, IRIS, GENETOX, and CCRIS), PubMed, RTECS, European Chemicals Bureau (IUCLID), SIDS, EPA HPV, NTP, NIEHS, IARC, CIS (Aquire, Datalog, Envirofate, and BIODEG), EPA TSCA 8(e), TSCATS and STN. Several literature articles, on the o-TSA and p-TSA isomers, were identified to satisfy/support endpoints.

Physical/Chemical Properties:

Measured values for o,p-TSA are available for the physical/chemical properties provided in Table 2 below.

Table 2. Measured o,p-TSA Physical/Chemical Data

MW	MP °C (Ref. 4)	BP °C (Ref. 5)	VP mmHg (Ref. 6)	Water Sol. g/L (Ref. 7)
171.22	106	215	< 3x 10 ⁻⁷	5

The EPISuite model was used to estimate the Log Kow. Using the CAS# for o,p-TSA (1333-07-9) a Log Kow of 0.92 was obtained. A Log Kow of 0.85, from an experimental database match, was also provided in the EPISuite output.

It should be noted that the physical/chemical values and structure in EPISuite were identical for m-TSA (CAS# 1899-94-1) and o,p-TSA. As Table 3 below demonstrates, endpoint values are comparable for m-TSA (CAS# 1899-94-1), o,p-TSA (CAS# 1333-07-9), p-TSA (CAS# 70-55-3) and o-TSA (CAS# 88-19-7).

Table 3. Comparison of Physical/Chemical EPISuite Model Values of TSA Isomers

Endpoint	m-TSA CAS# 1899-94-1	o,p-TSA CAS# 1333-07-9	p-TSA CAS# 70-55-3	o-TSA CAS# 88-19-7
Log Kow	0.92 (0.85 exper. database match)	0.92 (0.85 exper. database match)	0.92 (0.82 exper. database match)	0.92 (0.84 exper. database match)
Water Solubility	7810 mg/l	7810 mg/l	3160 mg/l	1620 mg/l
MP deg C	91.19	91.19	91.19 (138.5 exper. database match)	91.19 (156.3 exper. database match)
BP deg C	307.16	307.16	307.16 (214 exper. database match)	307.16 (214 exper. database match)
VP mm Hg 25 deg C	3.06 E-004	3.06 E-004	9.56E-005	6.06E-005

According to the EPISuite classification, substances with a Log Kow of < 1 are highly water soluble. The Log Kow values, in Table 3, indicate that all isomers or the combination of o- and p- are water soluble (hydrophilic). In fact this is confirmed by the water solubility values (measured and model values). While the measured water solubility for o,p-TSA (Table 2) is somewhat different from model values (Table 3), all values are within the soluble range classification of EPISuite (>1,000-10,000). Therefore, based on the similarity between the Log Kow values for the individual isomers and confirmation of water solubility from the measured o,p-TSA value, it is appropriate to use the Log Kow value cited in the EPISuite output.

Recommendation: No additional chemical/physical property testing is proposed.

Environmental Fate:

Measured photodegradation rates are not available. However the Atmospheric Oxidation Program (AOPWIN), in EPISuite, was used to estimate the time required for the material to degrade in the atmosphere. AOPWIN estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The OH

half-life, for all isomers including o,p-TSA, was estimated to be 8.7 days (12-hr day; 1.5E6 OH/cm³). The photodegradation half-life of p-TSA and o-TSA were reported to be 132 days and 315 hours, respectively (Ref. 8 and 9). Table 4 summarizes photodegradation rates.

Table 4. Photodegradation of o,p-TSA and Isomers

Endpoint	Test Substance	Result	Reliability	Reference
Atmospheric Oxidation	o,p-TSA	8.7 days	2	1
Photodegradation	p-TSA	132 days	4 (secondary reference)*	8
Photodegradation	o-TSA	315 hours	4 (secondary reference)*	9

*OECD/SIDS document

The EPISuite model indicates that a hydrolysis half-life cannot be estimated for o,p-TSA or any of the individual isomers.

The EPISuite Level III fugacity model was used to estimate the distribution of o,p-TSA. The modeling results indicate that when distributed equally to air, water and soil, o,p-TSA is primarily distributed to water and soil. Table 5 summarizes the environmental distribution of o,p-TSA and isomers.

Table 5. Environmental Distribution of o,p-TSA and Isomers

Transport/Distribution	m-TSA CAS# 1899-94-1	o,p-TSA CAS# 1333-07-9	p-TSA CAS# 70-55-3	o-TSA CAS# 88-19-7
Air	2.7	2.7	2.7	2.69
Water	46.7	46.7	46.9	46.8
Soil	50.5	50.5	50.3	50.4
Sediment	0.096	0.096	0.096	0.096

o,p-TSA was degraded very slowly in the Shake Flask CO₂ Evolution Test (Ref. 10). This test is similar to OECD 301B Modified Sturm Test. However, there are several deviations from the current guideline. o,p-TSA biodegraded 92.9% in a SCAS Test (similar to OECD 302A) (Ref. 11). p-TSA was classified as readily biodegradable in the Closed Bottle Test (OECD 301D) (Ref. 12). p-TSA and o-TSA were not readily biodegradable in MITI (I) (OECD 301C) (Ref. 8 and 9). p-TSA biodegraded 106% by day 28 in the (Repetitive Die Away (RDA) test while o-TSA degraded 27% (Ref. 13). Table 6 summarizes biodegradation of o,p-TSA and isomers.

Table 6. Biodegradation of o,p-TSA and Isomers

Study	Test Substance	Result	Reliability	Reference
SCAS	o,p-TSA	Inherently Biodegradable	2	11
Modified Sturm	o,p-TSA	Not Readily Biodegradable	4 (protocol deviations)	10
Closed Bottle Test	p-TSA	Readily Biodegradable	2	12
RDA	p-TSA	Readily Biodegradable	4 (English translation not available)	13
MITI	p-TSA	Not Readily Biodegradable	4 (secondary reference)*	8
RDA	o-TSA	Not Readily Biodegradable	4 (English translation not available)	13
MITI	o-TSA	Not Readily Biodegradable	4 (secondary reference)*	9

*OECD/SIDS document

Based on the SCAS test, o,p-TSA is considered inherently biodegradable.

Recommendation: No additional environmental fate testing is proposed.

Aquatic Toxicity:

Aquatic studies indicate that o,p-TSA has a low order of acute toxicity to fish and Daphnia as does model data for algae. The ECOSAR model estimated a low order of toxicity, for o,p-TSA to algae using an estimated Log Kow of 0.92. Measured data from algae studies, briefly summarized in the OECD SIDS documents on p-TSA and o-TSA, indicate moderate toxicity to algae. Table 7 below contains available acute aquatic studies on o,p-TSA with the Klimisch reliability code.

Table 7. Ecotoxicity Data of o,p-TSA and Isomers

STUDY	TEST SUBSTANCE	RESULT	RELIABILITY	REFERENCE
96-hr LC50 (Trout)	Santicizer® 9 (o,p-TSA)	120 mg/l	2	14
	p-TSA	100 mg/l	2	15
96-hr LC50 (Bluegill)	Santicizer® 9 (o,p-TSA)	260 mg/l	2	16
	p-TSA	370 mg/l	2	17
96-hr LC50 (Killifish)	p-TSA	435 mg/l	4 (secondary reference)**	8
96-hr LC50 (Killifish)	o-TSA	> 100 mg/l	4 (secondary reference)**	9
48-hr EC50 (Daphnia)	Santicizer® 9 (o,p-TSA)	>1000 mg/l	2	18
24-hr EC50 (Daphnia)	p-TSA	150 mg/l	4 (secondary reference)**	8
48-hr EC50 (Daphnia)	o-TSA	210 mg/l	4 (secondary reference)**	9
21-day LOEL (Daphnia)	p-TSA	150 mg/l	4 (secondary reference)**	8
21-day EC50 (Daphnia)	o-TSA	79 mg/l	4 (secondary reference)**	9
96-hr EC50 (Algae)*	o,p-TSA	768 mg/l	2	2
Algae ChV*	o,p-TSA	41.140 mg/l	2	2
144-hr EC50 (Chlorella pyrenoidosa)	p-TSA	80 mg/l	4 (summary only)	19
72-hr EC50 (S. capricornutum)	p-TSA	23 mg/l	4 (secondary reference)**	8
72-hr EC50 S. capricornutum)	o-TSA	57 mg/l	4 (secondary reference)**	9

*ECOSAR

**OECD/SIDS document

Although there is no measured data, the toxicity of o,p-TSA to algae would not be expected to be greater than the toxicity of the individual isomers. Therefore o,p-TSA would, at the most, be expected to be moderately toxic to algae, the most sensitive species, based on studies conducted on the individual isomers.

Recommendation: No additional aquatic testing proposed.

Acute Mammalian Toxicity:

Acute mammalian toxicity studies are available on o,p-TSA. Valid studies indicate a low order of acute toxicity by the oral route and slight irritation to skin and eyes. An acute study also demonstrates a low order toxicity by the dermal route. The report lacks sufficient details. However, based on the lack of toxicity at such a high dose, further testing would not be

substantially additive to the database. Table 8 below contains available acute studies on o,p-TSA with the Klimisch reliability code.

Table 8. Acute Mammalian Toxicity Studies on o,p-TSA

STUDY	TEST SUBSTANCE	RESULT	RELIABILITY	REFERENCE
Acute Oral LD50 (rat)	Ketjenflex® 9	2400 mg/kg	1	20
Acute Oral LD50 (rat)	Ketjenflex® 9	1790 mg/kg	4 (inadequate details)	21
Acute Oral LD50 (rat)	Santicizer® 9	3800 mg/kg	4 (inadequate details)	22
Acute Dermal LD50 (rabbit)	Santicizer® 9	> 7.5 g/kg	4 (inadequate details)	23
Skin and Eye Irritation	Ketjenflex® 9	Slightly Irritating	2	24

Acute studies are also available on the ortho and para isomers. The acute oral LD50 (rat) for o-TSA and p-TSA was greater than 2000 mg/kg in several studies (Refs. 25, 26, 27, and 8). In one study, the LD50 of o-TSA in female rats was reported to be between 1000 and 2000 mg/kg (Ref. 9). The acute dermal LD50 (rabbits), of o-TSA, was reported to be > 7940 mg/kg (Ref. 27). In irritation studies, o-TSA and p-TSA caused slight irritation to skin and eyes (Refs. 24 and 23).

Recommendation: No additional acute mammalian toxicity testing proposed.

Repeated Dose

There are no valid repeat dose studies available on the o,p-TSA mixture. There are 90-day feeding studies in rats and dogs with Santicizer® 9 (o,p-TSA). No effects on survival, hematology, clinical chemistry, gross or microscopic parameters were reported when rats and dogs were fed up to 3000 ppm. However these studies were generated by a laboratory of questionable reputation and cannot be considered valid as the data cannot be verified (Ref. 28 and 29). Repeat dose studies do exist for o-TSA and p-TSA.

A 90-day dietary study with p-TSA, was submitted to US EPA under TSCA section 8(e). Urinary bladder hyperplasia was noted in two males in the high dose group (738 mg/kg/day) and significant reduction in weight gain (males and females) (Ref. 30). In another study submitted on a combined repeat dose oral gavage study, urinary bladder hyperplasia was reported at dose levels of 120, 300 and 750 mg/kg/day as well as involution of the thymus in females in the 300 and 750 mg/kg/day groups (Ref. 31).

The National Toxicology Program (NTP) had conducted a 2-week study with p-TSA in rats and mice. Animals were administered the test article at 750, 1500, 3000, 10000 or 30000 ppm. No treatment related adverse effects were reported (Ref. 32). A 90-day oral gavage study in rats is currently in progress.

In a combined oral gavage study with o-TSA, hepatic centrilobular hypertrophy was noted in rats administered 100 and 500 mg/kg/day. Enhanced incidences and grade of eosinophilic bodies in the kidneys of males in all dose groups (20, 100 and 500 mg/kg/day) and atrophy of the thymus in females in the 500 mg/kg/day group was also reported (Ref. 33). When fed to rats over their lifetime, o-TSA, did not significantly increase the incidence in bladder tumors over controls (Ref. 34).

Table 9 below contains available repeat dose studies on o- and p-TSA with the Klimisch reliability code.

Table 9. Repeat Dose Toxicity Studies on o/p-TSA Isomers

STUDY	Test Substance	RESULT	RELIABILITY	REFERENCE
90-day dietary (rat)	p-TSA	NOEL = 3000 ppm (214 and 248 mg/kg/day, males and females, respectively) LOEL = 10000 ppm (738 mg/kg urinary bladder hyperplasia males; 795 mg/kg/day reduced body weight gain females)	4 (TSCA 8(e) summary only)	30
Combined Repeat Dose Oral Gavage (rat)	p-TSA	NOEL = <120 mg/kg/day LOEL = 120 mg/kg/day (urinary bladder hyperplasia all groups; involution of thymus in 300 and 705 mg/kg/day females)	2	31
2-week Feeding Study	p-TSA	No treatment related adverse effects were reported up to 30000 ppm	2	32
Combined Repeat Dose Oral Gavage (rat)	o-TSA	NOEL = < 20 mg/kg/day LOEL= 20 mg/kg/day (males); 100 mg/kg/day (females) (increased incidence and severity of eosinophilic body in the male kidneys of all groups; centrilobular hepatocyte hypertrophy in 100 and 500 mg/kg/day; atrophy of female thymus in 500 mg/kg/day)	2	33
Two-Generation Lifetime Feeding (rats)	o-TSA	NOEL = 25 mg/kg/day LOEL = 250 mg/kg/day (reduced growth rate)	4 (Only histopathology examinations were reported)	34

Reproductive Toxicity

There is no reproductive study available on o,p-TSA mixture. However, there are studies available to evaluate reproductive endpoints on p-TSA and o-TSA.

In an OECD Combined Repeat Dose and Reproductive/Developmental rat study with p-TSA, there were no effects on mating performance and fertility. The number of corpora lutea and implantations and implantation rate was comparable between treated animals and control animals. Signs of parental toxicity were present in all dose groups (120, 300 and 750 mg/kg/day). Two females in the high dose group (750 mg/kg/day) exhibited a difficult labor (all pups died in these two litters) and a decrease in lactation index. Viability rate for lactation day one was significantly reduced. There were no significant visceral or skeletal findings.

In an OECD Combined Repeat Dose and Reproductive/Developmental rat study with o-TSA, there was no effect on copulation, ovulation and fertility, or on delivery and lactation at doses up to and including 500 mg/kg/day. Signs of parental toxicity were present in the mid (100 mg/kg/day) and high (500 mg/kg/day) dose groups. Males exhibited an increased incidence and severity of eosinophilic bodies in the kidneys in all groups (20, 100 and 500 mg/kg/day). The number of live pups, from this group, on days 0 and 4 of lactation and the birth index tended to be low but not statistically significant. Weights of the pups, were significantly reduced on lactation days 0 and 4.

In a submission to US EPA under TSCA section 8(e) on a two-generation dietary rat study with p-TSA, the NOEL for reproduction and breeding was 10000 ppm. Decrease body weight and organ weight changes resulted from exposure to diets containing 3000 and 10000 ppm. F1 pups from the 10000 ppm group exhibited lower body weight and organ weight changes and a delay in vaginal opening and balanopreputial separations. F2 pups exhibited lower body and organ weight changes in the 10000 ppm group. When corrected for mean test article intake 1000 ppm corresponds to 52-78 mg/kg/day and 75-161 mg/kg/day for males and females, respectively, 3000 ppm corresponds to 165-236 mg/kg/day and 232-499 mg/kg/day for males and females, respectively and 10000 ppm corresponds to 566-832 mg/kg/day and 733-1631 mg/kg/day for males and females, respectively.

In a two-generation life time feeding study with o-TSA, there was no effect on reproductive parameters when rats consumed 250 mg/kg/day. Adults exhibited a significant reduction in growth rate at 250 mg/kg/day. There was a statistically significant decrease in litter size on day 1 and 4 postpartum in the 250 mg/kg/day group.

Table 10 below contains available reproductive studies on o- and p-TSA with the Klimisch reliability code.

Table 10. Reproduction Toxicity Studies on o/p-TSA Isomers

STUDY	TEST SUBSTANCE	RESULT	RELIABILITY	REFERENCE
Combined Repeat Dose Oral Gavage (rat)	p-TSA	NOEL (reproduction) = 300 mg/kg/day LOEL (reproduction) = 750 mg/kg/day (delivery dysfunction and suppression of embryos) LOEL (parental toxicity) = 120 mg/kg/day NOEL (developmental) = 300 mg/kg/day (decrease litter weight, lactation index, viability rate in 750 mg/kg day)	2	31
Two Generation Dietary (rat)	p-TSA	NOEL (reproduction) = 10000 ppm LOEL (parental toxicity) = 3000 ppm NOEL (developmental) = 3000 ppm LOEL(developmental) = 10000 ppm (delay vaginal opening and balanopreputial separation)	4 (TSCA 8(e) summary)	35
Combined Repeat Dose Oral Gavage (rat)	o-TSA	NOEL (reproduction) = 500 mg/kg/day LOEL (parental toxicity) = 20 mg/kg/day NOEL (developmental) = 100 mg/kg/day; (non-significant reduction in number of live pups and birth index on days 0 and 4 lactation and significantly reduced weights in 500 mg/kg/day group)	2	33
Two-Generation Dietary (rat)	o-TSA	NOEL (reproduction) = 250 mg/kg/day LOEL (parental toxicity) = 250 mg/kg/day NOEL (developmental) = 25 mg/kg/day (decreased litter size at 250 mg/kg/day and lower pup weight)	4 (Details of reproductive parameters such as ovulation, implantation, delivery and lactation analyses were not provided)	34

Developmental Toxicity

There is one valid developmental study available the on o,p-TSA mixture.

Santicizer® 9, a mixture of 32% o-TSA and 68% p-TSA was administered to pregnant rats during gestation days 6-15 at 50, 250 or 500 mg/kg/day. There was a significant reduction in maternal body weight gain in the mid and high dose group during treatment. Weight loss was noted during this interval. The test article was fetotoxic at 250 and 500 mg/kg/day as demonstrated by increased postimplantation loss in the presence of maternal toxicity. There was a significant difference in fetal body weight and an increase in unossification of sternebrae at 500 mg/kg/day but no teratogenic effects (Ref. 36). In the range finder to this study, pregnant rats were administered Santicizer® 9 at 100, 500, 1000, 1500 or 2000 mg/kg/day during gestation. Maternal toxicity was observed at dose levels of 500 mg/kg/day and greater. At 1500 and 2000 mg/kg/day signs of developmental toxicity included increased resorptions and postimplantation loss (Ref. 37).

While this is the only study available on the substance with mixed isomers, additional studies have been conducted on the individual ortho and para isomers (Table 11).

In a submission to US EPA under TSCA section 8(e) on a dietary study, pregnant rabbits were given diets, on gestations 7-29, containing p-TSA.

Reduced body weight and food consumption was noted in dams at dietary levels of 3000 ppm (113 mg/kg/day) and 11000 ppm (367 mg/kg/day). Dams exposed to the 1000 ppm (41 mg/kg/day) dietary level did not exhibit any toxicity. There was no effect on reproductive parameters in any treatment group.

There was a statistically significant increase in the mean litter proportion of fetuses with vertebral anomaly with or without associated rib anomaly in the 11000 ppm group. However, there was a confounding factor of environmental stress to dams, prior to treatment, resulting in a low pregnancy rate and subsequently an insufficient number of pregnant animals. Additional animals were therefore added to each group. Only fetuses from the initial pregnant dam group exhibited the vertebral anomaly. Fetuses from dams added to the study did not display the anomaly. Additionally, this vertebral anomaly was not observed in fetuses, from dams in the range-finding study, exposed to dietary levels up to 20000 ppm. Therefore, the results from this study are equivocal due to the confounding environmental stress (Ref. 38).

A developmental study was conducted to determine the effect of o-TSA on the urinary tract of rats exposed during gestation and postnatally (Ref. 39). The test article was administered to dams by oral gavage beginning day one of pregnancy until the pups were weaned, day 21 postpartum. After weaning the pups were fed diets containing equivalent dose levels of the test article as their mother, 40, 100 or 250 mg/kg/day.

There were no clinical signs of maternal toxicity and no effect on reproductive parameters. Pups, of both sexes, exposed during gestation, lactation and up to 105 days postpartum, exhibited a dose related increase in the incidence of urinary calculi and in the 100 and 250 mg/kg/day dose groups, bladder hyperplasia in 105-day old males.

When the same study was conducted with dietary equivalents, there was a significant dose response for the incidence of renal calculi in 8-day old pups but not older pups. Eight-day old pups in the 250 mg/kg/day group had a significant increase in focal epithelial hyperplasia.

Table 11. Developmental Toxicity Studies on o,p-TSA and Isomers

STUDY	TEST SUBSTANCE	RESULT	RELIABILITY	REFERENCE
Developmental Oral Gavage (rats)	Santicizer® 9 (o,p-TSA)	NOEL (maternal) = 50 mg/kg/day LOEL (maternal) = 250 mg/kg/day NOEL (fetal) = 50 mg/kg/day LOEL (fetal) = 250 mg/kg/day (fetotoxic at 250 and 500 mg/kg/day; unossification of sternebrae at 500 mg/kg/day; Not teratogenic)	2	36 and 37
Developmental Dietary (rabbits)	p-TSA	NOEL (maternal) = 1000 ppm (41 mg/kg/day) LOEL (maternal) = 3000 ppm (113 mg/kg/day) NOEL (fetal) = 3000 ppm LOEL (fetal) = 11000 ppm (367 mg/kg/day-vertebral anomalies)	4 (TSCA 8(e) summary and equivocal results due to confounding environmental stress)	38
Developmental Oral Gavage (rats)	o-TSA	NOEL (maternal) = 250 mg/kg/day NOEL (fetal) = 250 mg/kg/day for 8 and 15 day old pups LOEL (fetal) = 40 mg/kg/day for 21 and 105 day old pups (dose related urinary calculi at 40, 100 and 250 mg/kg/day; epithelial hyperplasia in the bladder in the males at 100 and 250 mg/kg/day)	4 (non-guideline study, no maternal toxicity)	39

It should be emphasized that the only study which reported malformations was the 8(e) submission conducted with p-TSA on rabbits. However, the results from this study are equivocal due to confounding factors of environmental stress as noted in the 8(e) letter. No such findings were reported in any of the combined repeat dose reproductive/developmental studies or in the reproductive studies, conducted on o-TSA and p-TSA summarized above.

Recommendation: No additional testing proposed for repeated dose/reproductive/developmental toxicity.

Mutagenicity/Genotoxicity:

Two valid *in vitro* microbial assays were conducted with o,p-TSA products. Both were negative, with and without metabolic activation, in *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100 and *Saccharomyces D4* (Ref 40 and 41).

In a study conducted by the Japanese Ministry of Health and Welfare, p-TSA was not mutagenic to *Salmonella typhimurium* or *Escherichia coli* with and without metabolic activation when tested up to 5000 ug/plate (Ref. 8). In a National Toxicology Program (NTP) *Salmonella/E. coli* mutagenicity test, p-TSA was not mutagenic when tested up to 10000 ug/plate (Ref. 42)

The OECD/SIDS document, for o-TSA, cites seven bacterial *in vitro* mutation assays. Six were negative and one was weakly positive. In the weakly positive study there was a non-dose response 2-3 fold increase in TA98 with activation. The weakly positive result could not be confirmed when the study was duplicated (Ref. 9).

p-TSA was negative in the Mouse Lymphoma Forward mutation assay when tested without metabolic activation and positive with activation (high dose only) when tested up to 2000 ug/plate (Ref. 45).

While no chromosomal aberration studies have been conducted on the mixture of o- and p-TSA isomers, mammalian (CHL cells) *in vitro* chromosomal aberrations studies have been conducted on o-TSA and p-TSA with and without metabolic activation (Ref 43 and 44). Both were negative. Therefore, the o,p-TSA mixture is not expected to induce chromosomal aberrations.

o-TSA was also negative in the Ouabain-resistant mutation assay with human R5a Cells and did not induce chromosomal aberrations in CHO-K1 cells (Ref. 9).

p-TSA was negative in three micronucleus assays (Ref. 42 and 46, 47).

o-TSA, administered orally and by i.p. injection to mice, did not induce micronuclei in bone-marrow cells (Ref. 47).

o-TSA did not induce morphological transformation in BHK 21/Cl 13 cells (Ref. 47)

Both o-TSA and p-TSA were considered weakly positive in a sex-linked recessive lethal assay (SLR) in *Drosophila melanogaster*. However other SLR assays conducted on the isomers were negative (Refs. 8 and 9).

Table 12 summarizes mutagenicity/genotoxicity studies on o,p-TSA and isomers.

Based on a weight of evidence approach, o,p-TSA is not expected to be mutagenic or genotoxic.

Recommendation: No additional genotoxicity testing proposed.

Table 12. Mutagenicity/Genotoxicity Studies on o,p-TSA and Isomers

Test	Test Substance	Result	Reliability	Reference
Bacterial Reverse Mutation	o,p-TSA	Negative	2	40 and 41
Bacterial Reverse Mutation	p-TSA	Negative	4 (secondary reference)*	8
Bacterial Reverse Mutation	p-TSA	Negative	2	42
Bacterial Reverse Mutation	o-TSA	Six Negative/ One Weak Positive	4 (secondary reference)*	9
Mouse Lymphoma	p-TSA	Negative without activation/ Positive with activation	1	45
Chromosomal Aberrations	p-TSA	Negative	2	43
Chromosomal Aberrations	o-TSA	Negative	2	44
Micronucleus	p-TSA	Negative	2 and 1	42 and 46
Micronucleus	p-TSA	Negative	4 (secondary reference)**	47
Micronucleus	o-TSA	Negative	4 (secondary reference)**	47
Morphological transformation	o-TSA	Negative	4 (secondary reference)**	47
Ouabain Resistance	o-TSA	Negative	4 (secondary reference)*	9
SLR	p-TSA	Negative/Weak Positive	4 (secondary reference)*	8
SLR	o-TSA	Negative/Weak Positive	4 (secondary reference)*	9

*OECD/SIDS document

**IARC Monograph Vol. 22

Other Studies

In addition to the above studies, the OECD/SIDS document summaries several carcinogenicity studies and concludes that o-TSA is not carcinogenic (Ref. 9).

Therefore, based on a weight of evidence approach from repeat dose and lifetime studies, o,p-TSA is not expected to be carcinogenic.

3.0 USE AND EXPOSURE INFORMATION

o,p-TSA is used as an intermediate in the production of pigments and is totally consumed in the production of the end product. Therefore, both occupational and environmental exposure are expected to be minimal.

o,p-TSA environmental exposure and fate as well as occupational exposure are summarized in Appendix B of this submission.

REFERENCES

1. EPISuite v3.120 2000-2007 U.S. EPA
2. ECOSAR v0.99 U.S. EPA
3. Klimisch, H.J. et al (1997) Reg. Toxicol. And Pharmacol. 25: 1-5
4. Axcentive SARL, (1991). Determination of Melting and Crystallization Points of O/P-AMID. Akzo Nobel Research Study Number 4841.
5. Axcentive SARL, (1962). Boiling Point. TNO Report Number 62/795.
6. Monsanto (1983). Determination of Ambient Vapor Pressure of Santicizer® 9. ABC Laboratories, Report Number 30483.
7. Monsanto (1983). Determination of Aqueous Solubility of Santicizer® 9. ABC Laboratories Report Number 30482.
8. OECD/SIDS p-Toluenesulfonamide
9. OECD/SIDS o-Toluenesulfonamide
10. Monsanto (1981). Unpublished Report. Ultimate Biodegradation Screening of Santicizer® 8 and 9. MIC Environmental Sciences Report Number ES-81-SS-47.
11. Monsanto (1983). Unpublished Report. Semi-continuous Activated Sludge (SCAS) Biodegradation of Santicizer® 8 and Santicizer® 9 (Analytical methodology and Test Results). ABC Laboratory Report Number 30429.
12. van Haperen, A.M. (2001) *Biodegradation of p-toluenesulphonamide by a Pseudomonas sp.* Microbiology Letters 204: 299-304.
13. Blok, J. (1981) Bilogische afbreekbaarheid van afzonderlijke afvalwatercomponenten van Akzo Chemie, Lokatie Amserdam-Noord. [Ready biodegradability of separate waste water components from Akzo Chemie, location Amsterdam-Noord]; Akzo Research, Corporate Research Department, Arnhem, The Netherlands Report No.: D81/111, September 23, 1981.
14. Monsanto (1983). Acute Toxicity of Santicizer® 9 Plasticizer to Rainbow Trout (*Salmo gairdneri*). ABC Laboratories Report Number 29981.
15. Monsanto (1983). Acute Toxicity of p-Toluenesulfonamide to Rainbow Trout (*Salmo gairdneri*). ABC Laboratories Report Number 30007.
16. Monsanto (1983). Acute Toxicity of Santicizer® 9 Plasticizer To Bluegill Sunfish (*Lepomis macrochirus*). ABC Laboratory Report Number 29980.
17. Monsanto (1983). Acute Toxicity of p-Toluenesulfonamide To Bluegill Sunfish (*Lepomis macrochirus*). ABC Laboratory Report Number 30006.
18. Monsanto (1981). Acute Toxicity of Santicizer® 8 and Santicizer® 9 to *Daphnia Magna*. MIC Environmental Sciences Report Number ES-81-SS-32.
19. Akzo Nobel (1981) Unpublished Report. Ecotoxicological Aspects of Halamid (para-toulene-chloramide-sodium). Akzo Research, Corporate Research Department, Arnhem, The Netherlands Report No.: D81/124, November 11, 1981.
20. Akzo Chemie (1986). Evaluation of the Acute Oral Toxicity of Ketjenflex®-9 in the Rat. NOTOX Report Number 0292/367

21. Akzo NV (1978). Determination of the Acute Oral Toxicity of Ketjenflex® 9R in Rats. TNO Report.
22. Monsanto (1957). Toxicological Investigation of Santicizer® 9-Oral LD50 in Rats. Younger Laboratories Report Number Y-57-26
23. Monsanto (1957). Toxicological Investigation of Santicizer® 9-Toxicity by Skin Absorption in Rabbits. Younger Laboratories Report Number Y-57-26.
24. Akzo NV (1978). Primary Skin and Eye Irritation Tests with Four Chemical Products. TNO Report Number 5794.
25. Akzo NV (1978) Unpublished Report. Determination of the acute oral toxicity of para-toluene sulphonamide in rats. TNO Report.
26. Akzo NV (1978) Unpublished Report. Determination of the acute oral toxicity of ortho-toluene sulphonamide in rats. TNO Report.
27. Monsanto (1974). Toxicological Investigation of ortho-toluene sulfonamide. Younger Laboratories Report Number Y-74-111.
28. Monsanto Unpublished Report (1974). 90-Day Subacute Oral Toxicity Study with Santicizer® 9 in Albino Rats. Industrial Bio-Test Laboratories Inc Report Number 622-04497.
29. Monsanto Unpublished Report (1974). 90-Day Subacute Oral Toxicity Study with Santicizer® 9 in Beagle Dogs. Industrial Bio-Test Laboratories Inc Report Number 651-04496.
30. TSCA 8(e) 90-day oral OECD 408 with p-toluenesulfonamide. 8EHQ-0607-16877A
31. Ministry of Health and Welfare (1994). Combined Repeat Dose and Reproductive/Developmental Toxicity on p-TSA. Hantano Research Institute.
32. p-TSA NTP 2-week study, http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm
33. Ministry of Health and Welfare (1994). Combined Repeat Dose and Reproductive/Developmental Toxicity on o-TSA. Hantano Research Institute.
34. Arnold et al., Lifetime Feeding study with o-TSA. Tox & Applied Pharm. 52: 113-152, 1980.
35. TSCA 8(e) Two-generation Oral OECD 416 with p-toluenesulfonamide. 8EHQ-0308-1711A
36. Monsanto (1985). Teratology Study in Rats. International Research and Development Corporation Report Number IR-84-238.
37. Monsanto (1985). Range-Finding Teratology Study in Rats. International Research and Development Corporation Report Number IR-84-173.
38. TSCA 8(e) Dietary developmental study with p-toluenesulfonamide in rabbits. 8EHQ-408-16908B
39. Arnold et al., The Effect of ortho-Toluenesulfonamide and Sodium Saccharin on the Urinary Tract of Neonatal Rats. Tox & Applied Pharm. 51: 455-463, 1979.
40. Akzo (1978). Mutagenicity Evaluation of Ketjenflex® 9R in the Ames Salmonella/Microsome Plate Test. Litton Bionetics Report Number 20838

41. Monsanto (1976) Mutagenicity Evaluation of Bio76-111 Santicizer® 9E. Litton Bionetics Report Number 2547.
42. National Toxicology Program http://ntp-apps.niehs.nih.gov/ntp_tox
43. Ministry of Health and Welfare (1994). Non-Bacterial in vitro (Chromosomal aberration). Hantano Research Institute.
44. Ministry of Health and Welfare (1994). Non-Bacterial in vitro (Chromosomal aberration). Research Institute for Animal Science in Biochemistry and Toxicology.
45. PNP Holding B.V. (2000). L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay with a Confirmatory Assay with p-Toluenesulfonamide. Covance Report Number 21198-0-431- ICH.
46. PNP Holding B.V. (2000). *In Vivo* Mouse Micronucleus Assay with p-Toluenesulfonamide. Covance Report Number 21198-0-455OECD.
47. World Health Organization (1980). IARC Monographs on the Evaluation of the Carcinogenic Risk to Chemicals to Humans. Vol. 22.

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APPENDIX A

O,P-TSA HPV ROBUST SUMMARIES

o,p-TSA

**HPV Robust Summaries
Day-Glo Color Corp.**

July, 2008

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1. Substance Information

<i>CAS Number:</i>	1333-07-9
<i>Chemical Name:</i>	Benzenesulfonamide, ar-methyl-
<i>Structural Formula:</i>	C ₇ H ₉ NO ₂ S
<i>Other Names:</i>	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
<i>Exposure Limits:</i>	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.

4

Additional
References for
Melting Point
Studies:

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).

4

Additional
References for
Boiling Point
Studies:

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: None
 References for
Density Studies:

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	Log Kow = 0.85 from experimental database match in EPI
References for	Suite from Hansch, C et al, 1995
Partition	
Coefficient Studies:	

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	5 g/l at 25 deg C
temperature°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	None
References for Flash Point Studies:	

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	None
References for Flammability Studies:	

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	No data available
Products:	
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	None
References for	
Photodegradation	
Studies:	

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	Not applicable
Products:	
Conclusions:	Rate constants can not be estimated for this structure based on the EPISuite model
Reliability:	Not applicable
Reference:	4

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

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 Not available
 Products:
 Concentration Of 25.3 mg/l
 Test Chemical:
 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:

$$\text{Mg CO}_2 \text{ Evolved} = (\text{Titer} - \text{Mean Control Titer}) \times 2.200$$

$$\text{CO}_2 \text{ Evolution (\% of Theory)} = \frac{\sum \text{Mg Co}_2 \text{ Evolved}}{\text{Mg of Test Compd} \times \%C \times 3.664} \times 100$$

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	Not available
Products:	
Concentration Of	56.9 ppm
Test Chemical:	
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 2.1×10^6 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 or below the 70 ppm level.

Measurements of the test article during the biodegradation phase indicated that 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. 14 th 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 (<i>Salmo gairdneri</i>)
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 (CaCO₃) 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 3.9×10^{-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: Method:	o,p-TSA (CAS# 1333-07-9) 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 (CaCO₃) 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 6.2×10^{-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 <i>Daphnia magna</i> . 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 <i>Daphnia magna</i> -Static Test
GLP:	Yes
Year:	1981
Species/Strain/:	<i>Daphnia magna</i>
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	32, 36
References for	Data from additional sources support the study results
Acute Toxicity to	summarized above. These studies were not chosen for
Invertebrates	detailed summarization because the data were not
Studies:	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/	Green algae
Supplier:	
Analytical	Not applicable
Monitoring:	
Exposure Period:	96 hours
Nominal/Measured	Not applicable
Concentrations:	
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	16, 32, 36
References for	Data from additional sources support the study results
Acute Toxicity to	summarized above. These studies were not chosen for
Aquatic Plants	detailed summarization because the data were not
Studies:	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	5
Sex Per Dose:	
Vehicle:	Corn Oil
Route Of	Oral gavage
Administration:	
Time Of	14 days
Observation	
Period:	
Doses	1800, 2100 and 2400 mg/kg
Administered:	
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.
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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	1
Sex Per Dose:	
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	6
Sex Per Dose:	
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.
Reference:	Apparently well conducted study.
Remarks:	22 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.
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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	Not available
Sex Per Dose:	
Vehicle:	Not available
Route Of	Not available
Administration:	
Time Of	Not available
Observation	
Period:	
Concentration Of	Not available
Test Material:	
Results:	Not available
Conclusions:	Not available
Reliability:	Not available
Reference:	Not available
Remarks:	Not available
Additional	None
References for Acute Dermal Sensitization Studies:	

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	6
Sex Per Dose:	
Vehicle:	None
Route Of	100 mg of the test article were instilled into the everted
Administration:	lower lid of one eye of each rabbit. Eyes were washed 24 hours after instillation.
Time Of	7 days post instillation
Observation	
Period:	
Concentration Of	Applied as received
Test Material:	
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	25
References for	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.
Acute Eye Irritation	
Studies:	

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 15
 Sex Per Dose:
 Vehicle:
 Route of Administration: Oral dietary
 Time of Observation: 90 days
 Period:
 Doses: 300, 1000 and 3000 ppm
 Administered:
 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: NO
 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	13
Sex Per Dose:	
Vehicle:	5% CMC Na
Route of	Gavage
Administration:	
Time of	Clinical signs: daily; Body weight and Food consumption:
Observation	weekly; Clinical Laboratory: prior to scheduled sacrifice;
Period:	Macroscopic and Microscopic: scheduled sacrifice.
Doses	0 (vehicle), 20, 100, and 500 mg/kg/day
Administered:	
Frequency of	Males were dosed daily for 42 days. Males were sacrificed
Treatment:	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	Mortality: three females in the high dose group, and two
Dose Level:	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 32

References for These studies were not chosen for detailed summarization

Repeated Dose because the data were not substantially additive to the

Toxicity Studies: 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 50 males and 50 females per dose group

Sex Per Dose:

Vehicle: Appropriate amount of the test article was premixed with 500 g of ground rat chow.

Route of Dietary

Administration:

Time of Clinical signs: daily; Body weight and Food consumption:

Observation 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 0 (control), 2.5, 25, 250 mg/kg/day

Administered:

Frequency of Rats were exposed to the chemical from 90 days before

Treatment: 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 Growth rates decreased in the 250 mg/kg dose group. Food

Dose Level: 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	32
References for	Data from additional sources support the study results summarized above. These studies were not chosen for
Repeated Dose	detailed summarization because the data were not
Toxicity Studies:	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	13
Sex Per Dose:	
Vehicle:	5% gum Arabic solution
Route Of	gavage
Administration:	
Time Of	Mating: checked daily during cohabitation (from mating
Observation	results mating rate, conception rate were calculated);
Period:	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

Additional References for Reproductive Toxicity Studies:	report was translated from Japanese. 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.
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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	13
Sex Per Dose:	
Vehicle:	0.5% CMC Na
Route Of	gavage
Administration:	
Time Of	Mating: checked daily during cohabitation (from mating
Observation	results mating rate, conception rate were calculated);
Period:	Pregnancy periods: day 0 to delivery; Pup data: from
	delivery to day 4 lactation; Autopsy: day 4 of lactation
Doses	0 (vehicle), 20, 100 or 500 mg/kg/day
Administered:	
Frequency Of	Males were dosed daily for 42 days. Males were sacrificed
Treatment:	day 43. Females from 14 days before mating to day 3 of
	lactation. Females were sacrificed day 4 of lactation.
Premating	14 days
Exposure For	
Males:	
Premating	14 days
Exposure For	
Females:	
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.
Conclusions:	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.
Reliability:	The NOEL for reproductive and developmental toxicity was 250 mg/kg/day and 25 mg/kg/day, respectively.
Reference:	4 (not assignable) Details of reproductive parameters such as ovulation, implantation, delivery and lactation analyses were not provided.
Remarks:	30 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
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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:	<i>in vitro</i> 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:	<i>in vitro</i> 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

Rat liver induced with Phenobarbital and 5,6-benzoflavone

Activation

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

2250 ug/ml for continuous treatment. No cytotoxicity for short-term treatment with or without activation.

Concentration:

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 <i>In Vitro</i> 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	25
Sex Per Dose:	
Vehicle:	Corn Oil
Route Of	Gavage
Administration:	
Time Of	Twice daily for mortality and once daily for clinical signs of
Observation	toxicity on gestation days 6-15. Body weights were
Period:	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	0 (vehicle), 50, 250, and 500 mg/kg/day. Doses were
Administered:	prepared daily. The dosage volume was 10 ml/kg.
Frequency Of	Daily on gestation days 6-15
Treatment:	
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	There were no maternal mortalities. Body weights were
Response By Dose	recorded on gestation days 0, 6, 9, 12, 16 and 20. There was
Level:	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	Fetal body weight was statistically significantly less than
Response By Dose	control in the mid and high dose groups and slight in the low
Level:	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. Embryo lethality (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 40, 41

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

6.0 References

1. Axcentive SARL, (1991). Determination of Melting and Crystallization Points of O/P-AMID. Akzo Nobel Research Study Number 4841.
2. Axcentive SARL, (1962). Boiling Point. TNO Report Number 62/795.
3. Monsanto (1983). Determination of Ambient Vapor Pressure of Santicizer® 9. ABC Laboratories, Report Number 30483.
4. EPI Suite v3.20 U.S. Environmental Protection Agency 2000-2007
5. Monsanto (1983). Determination of Aqueous Solubility of Santicizer® 9. ABC Laboratories Report Number 30482.
6. Monsanto (1981). Ultimate Biodegradation Screening of Santicizer® 8 and 9. MIC Environmental Sciences Report Number ES-81-SS-47.
7. Monsanto (1983). Semi-continuous Activated Sludge (SCAS) Biodegradation of Santicizer® 8 and Santicizer® 9 (Analytical methodology and Test Results). ABC Laboratory Report Number 30429.
8. van Haperen, A.M. (2001) *Biodegradation of p-toluenesulphonamide by a Pseudomonas sp.* Microbiology Letters 204: 299-304.
9. Blok, J. (1981) Bilogische afbreekbaarheid van afzonderlijke afvalwatercomponenten van Akzo Chemie, Lokatie Amserdam-Noord. [Ready biodegradability of separate waste water components from Akzo Chemie, location Amsterdam-Noord]; Akzo Research, Corporate Research Department, Arnhem, The Netherlands Report No.: D81/111, September 23, 1981.
10. Monsanto (1983). Acute Toxicity of Santicizer® 9 Plasticizer to Rainbow Trout (*Salmo gairdneri*). ABC Laboratories Report Number 29981.
11. Monsanto (1983). Acute Toxicity of p-Toluenesulfonamide to Rainbow Trout (*Salmo gairdneri*). ABC Laboratories Report Number 30007.
12. Monsanto (1983). Acute Toxicity of Santicizer® 9 Plasticizer to Bluegill Sunfish (*Lepomis macrochirus*). ABC Laboratory Report Number 29980.
13. Monsanto (1983). Acute Toxicity of p-Toluenesulfonamide To Bluegill Sunfish (*Lepomis macrochirus*). ABC Laboratory Report Number 30006.
14. Monsanto (1981). Acute Toxicity of Santicizer® 8 and Santicizer® 9 to Daphnia Magna. MIC Environmental Sciences Report Number ES-81-SS-32
15. ECOSAR v0.99 U.S. Environmental Protection Agency 2001
16. Akzo Nobel (1981) Unpublished Report. Ecotoxicological Aspects of Halamid (para-toulene-chloramide-sodium). Akzo Research, Corporate Research Department, Arnhem, The Netherlands Report No.: D81/124, November 11, 1981.
17. Akzo Chemie (1986). Evaluation of the Acute Oral Toxicity of Ketjenflex®-9 in the Rat. NOTOX Report Number 0292/367
18. Akzo NV (1978). Determination of the Acute Oral Toxicity of Ketjenflex® 9R in Rats
19. Monsanto (1957). Toxicological Investigation of Santicizer 9-Oral LD50 in Rats. Younger Laboratories Report Number Y-57-26
20. Monsanto (1957). Toxicological Investigation of Santicizer® 9-Minimum Lethal Oral Dose in Rabbits. Younger Laboratories Report Number Y-57-26.

21. Monsanto (1957). Toxicological Investigation of Santicizer® 9-Toxicity by Skin Absorption in Rabbits. Younger Laboratories Report Number Y-57-26.
22. Akzo NV (1978). Primary Skin and Eye Irritation Tests with Four Chemical Products. TNO Report Number 5794
23. Monsanto (1957). Toxicological Investigation of Santicizer® 9-Skin Irritation in Rabbits. Younger Laboratories Report Number Y-57-26.
24. Akzo NV (1978). Primary Skin and Eye Irritation Tests with Four Chemical Products. TNO Report Number 5794
25. Monsanto (1957). Toxicological Investigation of Santicizer® 9-Eye Irritation in Rabbits. Younger Laboratories Report Number Y-57-26.
26. Monsanto (1974). 90-Day Subacute Oral Toxicity Study with Santicizer® 9 in Albino Rats. Industrial Bio-Test Laboratories, Inc. Report Number 622-04497.
27. Monsanto (1974). 90-Day Subacute Oral Toxicity Study with Santicizer® 9 in Beagle Dogs. Industrial Bio-Test Laboratories, Inc. Report Number 622-04496.
28. Ministry of Health and Welfare (1994). Combined Repeat Dose and Reproductive/Developmental Toxicity on p-TSA. Hantano Research Institute.
29. Ministry of Health and Welfare (1994). Combined Repeat Dose and Reproductive/Developmental Toxicity on o-TSA. Hantano Research Institute.
30. Arnold et al., Lifetime Feeding study with o-TSA. Tox & Applied Pharm. 52: 113-152, 1980.
31. TSCA 8(e) 90-day oral OECD 408 with p-toluenesulfonamide. 8EHQ-0607-16877A
32. OECD/SIDS o-Toluenesulfonamide
33. TSCA 8(e) Two-generation Oral OECD 416 with p-toluenesulfonamide. 8EHQ-08-17112
34. Akzo (1978). Mutagenicity Evaluation of Ketjenflex® 9R in the Ames Salmonella/Microsome Plate Test. Litton Bionetics Report Number 20838
35. Monsanto (1976) Mutagenicity Evaluation of Bio76-111 Santicizer® 9E. Litton Bionetics Report Number 2547.
36. OECD SIDS p-TSA
37. Ministry of Health and Welfare (1994). Non-Bacterial in vitro (Chromosomal aberration) with p-TSA. Hantano Research Institute.
38. Ministry of Health and Welfare (1994). Non-Bacterial in vitro (Chromosomal aberration) with o-TSA. Research Institute for Animal Science in Biochemistry and Toxicology.
39. Monsanto (1985). Teratology Study in Rats. International Research and Development Corporation Report Number IR-84-238.
40. TSCA 8(e) dietary developmental study with p-toluenesulfonamide in rabbits OECD 414 8EHQ-
41. Arnold et al., The Effect of ortho-Toluenesulfonamide and Sodium Saccharin on the Urinary Tract of Neonatal Rats. Tox & Applied Pharm. 51: 455-463, 1979.
42. National Toxicology Program http://ntp-apps.niehs.nih.gov/ntp_tox
43. PNP Holding B.V. (2000). L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay with a confirmatory Assay with p-Toluenesulfonamide. Covance Report Number 21198-0-431- ICH.
44. PNP Holding B.V. (2000). *In Vivo* Mouse Micronucleus assay with p-Toluenesulfonamide. Covance Report Number 21198-0-455OECD.

45. World Health Organization (1980). IARC Monographs on the Evaluation of the Carcinogenic Risk to Chemicals to Humans. Vol. 22.

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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:

<u>Task</u>	<u>Number of Workers</u>
• 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.