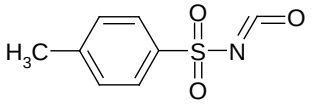
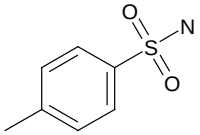
SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL
p-Toluenesulfonyl isocyanate CASRN 4083-64-1

SUPPORTING CHEMICAL
p-Toluenesulfonamide CASRN 70-55-3

Chemical Abstract Service Registry Number (CASRN)	**Sponsored Chemical** **4083-64-1** **Supporting Chemical** **70-55-3**
Chemical Abstract Index Name	**Sponsored Chemical** **Benzenesulfonyl isocyanate, 4-methyl-** **Supporting Chemical** **Benzenesulfonamide, 4-methyl-**
Structural Formula	**Sponsored Chemical**  SMILES: O=C=NS(=O)(=O)c(ccc(c1)C)c1 **Supporting Chemical** 

Summary

p-Toluenesulfonyl isocyanate is a liquid with moderate vapor pressure that reacts rapidly with water to form the corresponding carbamic acid, which in turn undergoes immediate decomposition to carbon dioxide and p-toluenesulfonamide. Mobility in soil, volatilization, and biodegradation are not important environmental fate properties due to the rapid rate of hydrolysis: the supporting chemical p-toluenesulfonamide is not readily biodegradable. The rate of atmospheric photooxidation is slow; however, this substance will likely react with moisture in the atmosphere. p-Toluenesulfonyl isocyanate is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Acute oral toxicity of p-toluenesulfonyl isocyanate is low. In a combined oral gavage repeated-dose/reproductive/developmental toxicity study in rats with the supporting chemical p-toluenesulfonamide, dose-related hypersalivation was noted in all treatment groups. Decreased

body weight gain, thymic atrophy and hematological and clinical biochemistry changes at 300 and 750 mg/kg-day; the NOAEL for systemic toxicity is 120 mg/kg-day. Reproductive and developmental effects from this study included pup mortality in a limited number of dams, decreased pup survival and decreased pup body weight at 750 mg/kg-day; the NOAEL for reproductive/developmental toxicity is 300 mg/kg-day. The supporting chemical, p-toluenesulfonamide, was not mutagenic in bacteria and did not induce chromosomal aberrations in mammalian cells *in vitro*.

No ecotoxicity data are available for the sponsored substance. For the supporting chemical, p-toluenesulfonamide, the 96-h LC_{50} to fish is 435 mg/L, the 24-h EC_{50} to aquatic invertebrates is 150 mg/L and the 72-h EC_{50} to aquatic plants is 23 mg/L based on biomass. The 60-d LOEC to fish is 9 mg/L.

No data gaps were identified under the HPV Challenge Program.

The sponsor, ISOCHEM Inc., submitted a Test Plan and Robust Summaries to EPA for p-toluenesulfonyl isocyanate (CASRN 4083-64-1; CA Index name: benzenesulfonyl isocyanate, 4-methyl-) on June 12, 2004. EPA posted the submission on the ChemRTK HPV Challenge website on June 21, 2004 (http://www.epa.gov/chemrtk/pubs/summaries/ptoluene/c15409tc.htm). EPA comments on the original submission were posted to the website on February 6, 2006. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on April 24, 2006 and January 3, 2007, which were posted to the ChemRTK website on July 21, 2006 and March 30, 2007, respectively.

Justification for Supporting Chemical

The sponsor provided data for the hydrolysis product p-toluenesulfonamide (CASRN 70-55-3) as a supporting chemical for p-toluenesulfonyl isocyanate based on likely rapid hydrolysis of the sponsored substance to the supporting chemical. EPA accepts this substance as a supporting chemical for all SIDS endpoints.

p-Toluenesulfonamide has been assessed in the OECD HPV program (SIAM 1; 1993) and the assessment can be viewed at: http://www.chem.unep.ch/irptc/sids/OECDSIDS/70553.pdf

1. Chemical Identity

1.1 Identification and Purity

p-Toluenesulfonyl isocyanate is a liquid with moderate vapor pressure that reacts rapidly with water to form the corresponding carbamic acid, which in turn undergoes immediate decomposition to carbon dioxide and p-toluenesulfonamide.

1.2 Physical-Chemical Properties

The physical-chemical properties of p-toluenesulfonyl isocyanate are summarized in Table 1.

Table 1. Physical-Chemical Properties of p-Toluenesulfonyl isocyanate[1]	
Property	**Value**
CASRN	4083-64-1
Molecular Weight	197.21
Physical State	Liquid
Melting Point	-2°C (measured freezing point)
Boiling Point	144°C at 10 mm Hg (measured) 279°C (estimated)[2]
Vapor Pressure	0.011 mm Hg at 25°C (measured)
Dissociation Constant (pK_a)	Not applicable
Henry's Law Constant	Not applicable[3]
Water Solubility	Not applicable[3]
Log K_{ow}	Not applicable[3]

[1]ISOCHEM Inc. 2007. Test Plan and Robust Summary for p-Toluenesulfonyl Isocyanate. Available online at http://www.epa.gov/chemrtk/pubs/summaries/ptoluene/c15409tc.htm as of July 6, 2012.
[2]NOMO5. 1987. Programs to Enhance PC-Gems Estimates of Physical Properties for Organic Compounds. The Mitre Corp.
[3]p-Toluenesulfonyl isocyanatehydrolyzes rapidly in water to yield the corresponding carbamic acid, which in turn undergoes immediate decomposition to carbon dioxide and p-toluenesulfonamide. The values for these data points have minimal utility due to the rapid hydrolysis of this substance in aqueous systems.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

p-Toluenesulfonyl isocyanate had an aggregated production and/or import volume in the United States between 1 to 10 million pounds during calendar year 2005 (U.S. EPA, 2010).

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include adhesive manufacturing, paint and coating manufacturing, and printing ink manufacturing as intermediates. No commercial and consumer uses were reported for the chemical.

2.2 Environmental Exposure and Fate

Due to the rapid rate of hydrolysis, volatilization, mobility in soil, biodegradation and bioaccumulation will not be important environmental fate processes for p-toluenesulfonyl isocyanate. Its hydrolysis product, p-toluenesulfonamide (CASRN 70-55-3) achieved 3% of its theoretical biochemical oxygen demand (BOD) over the course of a 28-day incubation period using an activated sludge inoculum during the modified MITI (OECD TG 301C) test and is considered not readily biodegradable. The rate of atmospheric photooxidation is slow; however,

this substance will likely react with moisture in the atmosphere. p-Toluenesulfonyl isocyanate is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The environmental fate of p-toluenesulfonyl isocyanate is summarized in Table 2.

Table 2. Environmental Fate Characteristics of p-Toluenesulfonyl isocyanate[1]

Property	Value
CASRN	4083-64-1
Photodegradation Half-life	8.7 days (estimated)[2]
Hydrolysis Half-life	<10 minutes at 25°C (estimated)
Biodegradation	3% after 28 days (not readily biodegradable, OECD TG 301C)[3]
Bioaccumulation Factor	Not applicable due to hydrolysis
Log K_{oc}	Not applicable due to hydrolysis
Fugacity (Level III Model)[2,4]	
Air (%)	99.5
Water (%)	0.3
Soil (%)	0.2
Sediment (%)	<0.1
Persistence[5]	P1 (low)
Bioaccumulation[5]	B1 (low)

[1]ISOCHEM Inc. 2007. Test Plan and Robust Summary for p-Toluenesulfonyl Isocyanate. Available online at http://www.epa.gov/chemrtk/pubs/summaries/ptoluene/c15409tc.htm as of July 6, 2012.
[2]U.S. EPA. 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of July 6, 2012.
[3] Data for hydrolysis product p-toluenesulfonamide CASRN 70-55-3.
[4]Half-lives of 0.1 hours were used for the water, soil, and sediment compartments while a half-life of 105 hours was used for the atmosphere compartment.
[5]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: p-Toluenesulfonyl isocyanate is a liquid with moderate vapor pressure that reacts rapidly with water to form the corresponding carbamic acid, which in turn undergoes immediate decomposition to carbon dioxide and p-toluenesulfonamide. Mobility in soil, volatilization, and biodegradation are not important environmental fate properties due to the rapid rate of hydrolysis: the supporting chemical p-toluenesulfonamide is not readily biodegradable. The rate of atmospheric photooxidation is slow; however, this substance will likely react with moisture in the atmosphere. p-Toluenesulfonyl isocyanate is expected to have low persistence (P1) and low bioaccumulation potential (B1).

3. Human Health Hazard

A summary of health effects data for SIDS endpoints is provided in Table 3. The table also indicates where data for the supporting chemical is read-across (RA) to the sponsored chemical.

Acute Oral Toxicity

p-Toluenesulfonyl isocyanate (CASRN 4083-64-1)
No study details were provided for this study.
LD_{50} = 2600 mg/kg

Repeated-Dose Toxicity

p-Toluenesulfonamide (CASRN 70-55-3, supporting chemical)
In a combined oral gavage repeated-dose/reproductive/developmental toxicity screening test, Crj:CD(SD) rats (13/sex/dose) were administered 0, 120, 300 or 750 mg/kg-day. Males were dosed 42 days prior to mating and females were dosed 14 days before mating through day 3 of lactation. Dose-related hypersalivation was noted in all treatment groups. Body weights of high-dose males were significantly lower than controls throughout the dosing period. Decreased body weight gain was noted in females in the mid- and high-dose groups during gestation and lactation. Relative kidney and liver weights were increased in high-dose animals and dark colored livers were noted in six high-dose males. Thymic atrophy was noted in eight mid- and high-dose females. Four animals from the high-dose group displayed hematuria within the first 3 days of dosing. Hematological examinations indicated a dose-dependent increase in white blood cell counts in the mid- and high-dose males and increased neutrophils in high-dose males. Clinical biochemistry parameters (elevated BUN, GOT and chloride) were also altered in mid- and high-dose males.
LOAEL = 300 mg/kg-day (based on decreased body weight gain, thymic atrophy and hematological and clinical biochemistry changes)
NOAEL = 120 mg/kg-day

Reproductive/Developmental Toxicity

p-Toluenesulfonamide (CASRN 70-55-3, supporting chemical)
In the combined repeated-dose toxicity study with reproductive/developmental toxicity screening described previously, newborns showed significant decreased body weight and survival in the high-dose group. Two of the high-dose female rats showed signs of difficult labor and all offspring died by day 3 of lactation. Otherwise, no effects were noted on mating performance and fertility at any dose level. Other reproductive parameters were comparable among all three dose groups and controls. Morphological observations of offspring revealed no teratogenic effect of the test substance.
LOAEL (parental systemic toxicity) = 300 mg/kg-day (based on decreased body weight gain, thymic atrophy and hematological and clinical biochemistry changes)

NOAEL (parental systemic toxicity) = 120 mg/kg-day
LOAEL (reproductive/developmental toxicity) = 750 mg/kg-day (based on pup mortality in a limited number of dams, decreased survival and decreased body weight of F1 pups)
NOAEL (reproductive/developmental toxicity) = 300 mg/kg-day

Genetic Toxicity – Gene Mutations

In vitro

p-Toluenesulfonamide (CASRN 70-55-3, supporting chemical)
Salmonella typhimurium (TA 98, TA 100, TA 1535 and TA 1537) and *Escherichia coli* (WP2*uvrA*) were exposed to concentrations of 0, 312.5, 625, 1250, 2500 or 5000 µg/plate in the presence or absence of S9 metabolic activation. Three plates were tested at each concentration and the results were confirmed in a second replicate of experiments. The cytotoxic concentration was 5000 µg/plate. Positive controls were tested concurrently, but results were not provided.
p-Toluenesulfonamide was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

p-Toluenesulfonamide (CASRN 70-55-3, supporting chemical)
CHL cells were exposed to concentrations of 0, 0.33, 0.65 or 1.30 mg/mL in the absence of metabolic activation or 0, 0.43, 0.85 or 1.70 mg/mL in the presence of S9 metabolic activation. Positive controls were tested concurrently, but results were not provided. Two replicates were conducted for each dose level. The cytotoxic concentration was > 2.0 mg/mL with metabolic activation and 2.0 mg/mL without metabolic activation; above the test conditions of the assay.
p-Toluenesulfonamide did not induce chromosomal aberrations in this assay.

Conclusion: Acute oral toxicity of p-toluenesulfonyl isocyanate is low. In a combined oral gavage repeated-dose/reproductive/developmental toxicity study in rats with the supporting chemical p-toluenesulfonamide, dose-related hypersalivation was noted in all treatment groups. Decreased body weight gain, thymic atrophy and hematological and clinical biochemistry changes at 300 and 750 mg/kg-day; the NOAEL for systemic toxicity is 120 mg/kg-day. Reproductive and developmental effects from this study included pup mortality in a limited number of dams, decreased pup survival and decreased pup body weight at 750 mg/kg-day; the NOAEL for reproductive/developmental toxicity is 300 mg/kg-day. The supporting chemical, p-toluenesulfonamide, was not mutagenic in bacteria and did not induce chromosomal aberrations in mammalian cells *in vitro*.

Table 3. Summary Table of the Screening Information Data Set under the U.S. HPV Challenge Program – Human Health Data		
Endpoint	**SPONSORED CHEMICAL p-Toluenesulfonyl isocyanate (4083-64-1)**	**SUPPORTING CHEMICAL p-Toluenesulfonamide (70-55-3)**
Acute Oral Toxicity LD_{50} (mg/kg)	**2600**	–
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-day)	No Data NOAEL = 120 LOAEL = 300 (RA)	**NOAEL = 120** **LOAEL = 300**
Reproductive Toxicity - NOAEL/LOAEL Oral (mg/kg-day) Reproductive Toxicity	No Data NOAEL = 300 LOAEL = 750 (RA)	**NOAEL =300** **LOAEL = 750**
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-day) Maternal/Developmental Toxicity	No Data NOAEL =300 LOAEL = 750 (RA)	**NOAEL =300** **LOAEL = 750**
Genetic Toxicity – Gene Mutation ***In vitro***	No Data Negative (RA)	**Negative**
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	No Data Negative (RA)	**Negative**

Measured data in BOLD; − indicates endpoint not addressed for this chemical; (RA) = read across

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for the supporting chemical is read-across (RA) to the sponsored chemical.

Acute Toxicity to Fish

p-Toluenesulfonamide (CASRN 70-55-3, supporting chemical)
(1) A 96-hour, semistatic acute toxicity test was conducted in Japanese medaka (*Oryzias latipes*). No other details were provided.
96-h LC_{50} = 435 mg/L

(2) An estimated 96-h toxicity value for fish was calculated using the ECOSAR program.
96-h LC_{50} = 1314 mg/L

Acute Toxicity to Aquatic Invertebrates

p-Toluenesulfonamide (CASRN 70-55-3, supporting chemical)
(1) A 24-hour acute toxicity study was conducted in *Daphnia magna*. No other details were provided.
24-h EC_{50} = 150 mg/L

(2) An estimated 48-h toxicity value for daphnia was calculated using the ECOSAR program.
48-h LC_{50} = 1307.201 mg/L

Toxicity to Aquatic Plants

p-Toluenesulfonamide (CASRN 70-55-3, supporting chemical)
(1) A 72-hour toxicity study was conducted in green algae (*Pseudokirchneriella subcapitata*). No other details were provided.
72-h EC_{50} (biomass) = 23 mg/L

(2) An estimated 96-h toxicity value for green algae was calculated using the ECOSAR program.
96-h EC_{50} = 767.966 mg/L

Chronic Toxicity to Fish

p-Toluenesulfonamide (CASRN 70-55-3, supporting chemical)
A 60-day, flow through toxicity study was conducted in rainbow trout (*Oncorhynchus mykiss*). Physiological changes were noted in the blood.
60-d LOEC = 9 mg/L

Conclusion: No ecotoxicity data are available for the sponsored substance. For the supporting chemical, p-toluenesulfonamide, the 96-h LC_{50} to fish is 435 mg/L, the 24-h EC_{50} to aquatic invertebrates is 150 mg/L and the 72-h EC_{50} to aquatic plants is 23 mg/L based on biomass. The 60-d LOEC to fish is 9 mg/L.

5. References

U.S. Environmental Protection Agency (2010) Non-confidential 2006 IUR Records by Chemical, including Manufacturing, Processing and Use Information for CASRN 4083-64-1. Inventory Update Reporting (IUR); Version 6: Updated May 12, 2010. Available online at http://www.epa.gov/cdr/tools/previouslycollected.html

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program - Aquatic Toxicity Data		
Endpoint	**SPONSORED CHEMICAL p-Toluenesulfonyl isocyanate (4083-64-1)**	**SUPPORTING CHEMICAL p-Toluenesulfonamide (70-55-3)**
Fish 96-h LC_{50} (mg/L)	No Data 435 (RA)	**435**
Aquatic Invertebrates 48-h EC_{50} (mg/L)	No Data 150 (RA)	**150**
Aquatic Plants 96-h EC_{50} (mg/L) (biomass)	No Data 23 (RA)	**23**
Chronic Fish (60-d) LOEC (mg/L)	No Data 9 (RA)	**9**

Bold = experimental data (i.e. derived from testing); (RA) = read-across