Chloramine-T
[127-65-1]
and
Metabolite *p*-Toluenesulfonamide
[70-55-3]

Review of Toxicological Literature

February 2002

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Prepared for

Scott Masten, Ph.D.
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, North Carolina 27709
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Submitted by

Karen E. Haneke, M.S.
Integrated Laboratory Systems
P.O. Box 13501
Research Triangle Park, North Carolina 27709

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Executive Summary

Nomination
Chloramine-T was nominated by a small commercial organization for toxicology studies based on its current status as an Investigational New Animal Drug (INAD) for controlling proliferative gill disease and bacterial gill disease in aquaculture and the need for additional toxicology studies to support it's safe use. The metabolite *p*-Toluenesulfonamide (*p*-TSA) is of importance as the primary residue of chloramine-T in chloramine-T treated fish intended for human consumption.

Non-toxicological Information
Chloramine-T, as an anti-microbial agent, has had widespread use in a broad range of practices, including medical, dental, veterinary, food processing, and agricultural. As a disinfectant, it is used to disinfect surfaces and instruments. Chloramine-T has a low degree of cytotoxicity and has been used in direct contact with tissues. As such, it is used in the treatment of burns, in whirlpools for the treatment of wounds, and as an oral mouthwash. In agricultural practices, chloramine-T has been approved as a broad-spectrum biocide for foot-and-mouth disease, swine vesicular disease, diseases of poultry, and tuberculosis in the United Kingdom, and is used in numerous branches of industry such as intensive farming, slaughterhouses, and kitchens. Within the United States, use of chloramine-T is more restricted. EPA registration for eating establishment utensils, barbershop instruments and as an herbicide was withdrawn between 1983 and 1987.

Currently, there is interest in obtaining approval from the Food and Drug Administration (FDA) for the use of chloramine-T in aquaculture. In 1994 the International Association of Fish and Wildlife Agencies (IAFWA) agreed to support research on a priority list of chemicals, including chloramine-T, identified as being important to various state fisheries. The list included chemicals there were needed but not currently labeled for aquaculture use. Data regarding target animal safety, efficacy, analytical methods, residue analysis, and metabolism studies, and environmental assessment were either collected or generated to fill data gaps for the investigational new animal drug (INAD)/new animal drug application (NADA) submission. In addition, toxicology data on *p*-TSA, the major metabolite of chloramine-T, was needed for the development of tolerances. In March 2001, concern over the potential carcinogenicity of p-TSA was voiced. Although work continues to gain FDA approval for chloramine-T, only laboratory studies or studies in which fish will not be released or slaughtered for food will be approved.

Chloramine-T is used in several other industries. It is used to bleach products (textiles and in the conservation of books), to dye textiles, as the starting material for other compounds, and as a laboratory reagent.

p-TSA is used as an intermediate for pesticides and drugs and is used as an additive to outdoor paints in Sweden. Mixtures of *o*- and *p*-TSA are used as reactive plasticizers in hot-melt adhesives to improve flow properties of thermosetting resins. The mixture also adds flexibility to coatings based on some resins. The TSA mixture is used as a carrier in fluorescent pigments. Both *o*- and *p*-TSA were common, and quantitatively important, contaminants of saccharin produced by the Remsen and Fahlberg process, and therefore have been studied for their ability to cause mutations.

p-TSA is used in the formulation of toluenesulfonamide/formaldehyde resin (TSFR), which is used in fingernail polishes and enamels at concentrations up to 10%.

The United States aggregated production volumes for chloramine-T were reported to be between 10,000 and 500,000 lbs. in 1998. Total aggregated production of p-TSA was reported between one and ten million lbs. for the same year.

Based on the screening information data set (SIDS) initial assessment report (SIAR) developed by the OECD, *p*-TSA was considered to be "presently of low concern." The OECD SIAR concluded that "although 4-methylbenzenesulfonamide [*p*-TSA] is persistent and toxicological tests showed moderate toxicity, no further testing is needed at present considering its use pattern and exposure levels", and further recommended that "if this chemical is used largely in consumer products in the future, long-term repeated dose (e.g. 90 days) toxicity test may be needed, because histopathological changes of urinary bladder and thymus were observed in combined repeat/repro. toxicity test."

Human Data

Exposures to chloramine-T, *p*-TSA, and TSFR are likely to occur whenever they are used in the above-mentioned practices. Chloramine-T is typically purchased in solid form and is then made into solutions. Either the solid or the liquid forms may produce adverse reactions. There is a potential for oral exposures to chloramine-T based on residue carry-over from food industries where it may be used to disinfect surfaces. Occupational exposures to *p*-TSA are likely in the production of other chemicals derived from it or through its addition to paints. Restrictions have been made on the amount of total TSAs allowed as contaminants of saccharin. Exposures to TSFR are usually associated with the use of nail polishes.

Chloramine-T is considered harmful if swallowed, inhaled, or absorbed through the skin or eyes. Symptoms include burning sensation, coughing, wheezing, laryngitis, shortness of breath, sore throat, bronchitis, pneumonitis, and possible pulmonary edema. Chloramine-T dust is irritating to the eyes. Skin contact with chloramine-T produces redness, itching, and pain, with a potential for the development of an allergic skin reaction. A probable oral lethal dose of 0.5 to 5 g/kg (1.8 to 18 mmol/kg) for a 70 kg individual has been suggested.

Exposures to chloramine-T have the potential to result in hypersensitivity or occupational asthmatic reactions. Case reports discuss urticaria and respiratory problems associated with occupational exposures. This has been supported by positive results for chloramine-T in the guinea pig maximization test, local lymph node assay, and Buehler occluded patch test.

TSFR has also been associated with hypersensitivity reactions, typically in areas that come in frequent contact with fingernails. One case report described the development of onycholasis of the fingernails that resolved once the use of nail products was discontinued.

Animal Studies

Chemical Disposition, Metabolism, and Toxicokinetics

In fish studies, chloramine was poorly absorbed from water, and that which was absorbed was rapidly metabolized to the residue marker, *p*-TSA. A second, as of yet unidentified, metabolite may also exist.

In the rat, chloramine-T is rapidly distributed throughout the body. Plasma clearance is relatively rapid, with elimination primarily through the urine. *p*-TSA is rapidly eliminated from rats, also. The primary metabolite found in the urine is 4-sulphamoylbenzoic acid. The data suggest that that the methyl group of *p*-TSA is oxidized to primarily the benzoic acid derivative.

Chloramine-T, used as an udder wash, was poorly absorbed percutaneously, and rapidly metabolized to *p*-TSA.

Acute Toxicity

Acute toxicity values for chloramine-T reported in mice were 1100 mg/kg (3.9 mmol/kg) *per os* (p.o.) (LD_{50}) and 300 mg/kg (1.07 mmol/kg) intraperitoneally (i.p.) (LD_{50}). For rats, the values were 0.275 mg/L (0.976 µM) via inhalation (LC_{50}) and 935 mg/kg (3.32 mmol/kg) p.o. (LD_{50}). In Guinea pigs, the

LD_{Lo} was reported as 900 mg/kg (3.20 mmol) subcutaneously (s.c.), and in rabbits, the dermal LD_{50} was greater than 2000 mg/kg (7.1 mmol/kg), while the intravenous LD_{Lo} was 25 mg/kg (89 µmol/kg).

The LD_{50}s for *p*-TSA in mice were 400 mg/L (2.34 mM) p.o. and 250 mg/kg (1.46 mmol/kg) i.p. In rats, the oral LD_{50} was reported to be greater than 2000 mg/L (11.68 mM). In guinea pigs, the s.c. LD_{Lo} was 2 g/kg (0.01 mol/kg).

Chloramine-T is irritating to the skin, eyes, and gastrointestinal tract. In acute LD_{50} studies, gastric inflammation, apathy, gastric bleeding and intestinal hemorrhage was observed in the animals that died. *In vivo* and *in vitro* animal studies using chloramine-T indicate an ability to affect elastase inhibitory capacity (EIC) negatively. An age-dependent toxicity was observed in rabbits, with young rabbits more susceptible than adults.

TSFR was found to be relatively non-toxic in rats or rabbits when tested acutely through oral, ocular, or dermal exposures.

Short-Term and Subchronic Toxicity
In the rat, higher doses of chloramine-T over 28 to 90 days resulted in reduced weight gains and increased relative kidney and liver weights. Leukocyte counts were slightly elevated and livers were discolored in the 28-day study. Female rats demonstrated an increased severity and frequency of calcareous deposits in the kidneys. Similar results were observed in dogs. In addition, hematological and clinical chemistry changes were observed in some treatment groups. Histopathological examination showed a thickening of the urinary bladder epithelium. TSA (mixture of *ortho*- and *para*- isomers in the diet) resulted in a slight reduction in food consumption and weight gain in dogs. No significant treatment-related lesions were observed in dogs fed TSFR in their diets for 90 days.

Chronic Toxicity
Chronic exposure of dogs to chloramine-T resulted in a persistent mild or moderate anemia and a reduction in EIC in both serum and pulmonary lavage fluids.

Reproductive and Teratological Effects
Maternal toxicity expressed as decreased weight gain was observed in several teratology studies for *p*-TSA. One study reported difficult labors in two of the rats in the 750 mg/kg/d [4.38 mmol/kg/d] dose group along with 100% mortality of offspring by day three of lactation. Increased resorption rates and postimplantation losses ere observed at doses as low as 250 mg/kg/d [1.46 mmol/kg/d]. Fetal body weights were reduced at 50 mg/kg/d [0.29 mmol/kg/d]. Increased unossified sternebrae were observed at 500 mg/kg/d [2.92 mmol/kg/d]. A no observed adverse effect level and no observed effect level were estimated as 300 and 50 mg/kg/d [1.75 and 0.29 mmol/kg/d], respectively, by two different studies.

No differences in mating performance or fertility were observed in reproductive studies of *p*-TSA, nor were any differences in reproductive parameters found between treatment groups. Neonatal survival and body weights were significantly decreased at the 750 mg/kg/d treatment levels.

Genotoxicity
The genotoxic potential of chloramine-T has been studied in a variety of systems, with mostly negative results. A statistically significant dose-dependent increase in sister chromatid exchanges was observed in one study. The effect was reduced, but not abolished, with the addition of methionine.

p-TSA has undergone more extensive genotoxicity testing. A single study reported a weak mutagenic effect in a modified *Salmonella*/microsome assay. Positive results were also noted when tested in the

Drosophila assay. *p*-TSA was negative in Chinese hamster lung cells, Chinese hamster ovary cells, RSa cells, and in the micronucleus assay.

Other Data
Chloramine-T has the ability to bind to enzymes and alter their characteristics. Plasma-kallikrein treated with chloramine-T was not cleared from the liver. The spectral characteristic of serum albumin treated with chloramine-T was altered. Chloramine-T impacts a variety of serine protease inhibitors, decreasing their effectiveness. Methionine and tyrosine residues represent susceptible sites.

Several investigators have examined the potential for using chloramine-T to develop an animal model for chronic human α_1-protienase inhibitor deficiency, mostly without success, as the changes induced by chloramine-T are transient in nature.

In wound healing studies, chloramine-T was shown to be less irritating than hypochlorite solutions, though it was also less effective in cleaning the wound. Chloramine-T also significantly delayed the production of collagen and prolonged the acute inflammatory responses relative to saline.

Chloramine-T has been used as a surrogate chemical to study voltage-gated sodium channels and the effects of free radicals and activated oxygen compounds associated with brain ischemia and head trauma. One case study was identified that investigated the possible potentiation of formate-induced blindness by chloramine ingestion.

No studies were identified for synergistic/antagonistic effects, carcinogenicity, initiation/promotion, anticarcinogenicity, cogenotoxicity, antigenotoxicity, or immunotoxicity of chloramine or *p*-TSA.

Structure-Activity Relationships
o-Toluenesulfonamide (*o*-TSA) is the major contaminant in saccharin produced by the Remsen and Fahlberg process. Numerous studies have been conducted examining the toxicities of *o*-TSA. At low oral doses, humans excreted *o*-TSA more slowly than rats.

LD_{50}'s for *o*-TSA in rats ranged from 2 g/kg to 4,870 mg/kg [11.68 to 28.44 mmol/kg]. Applied to the eyes of rabbits, *o*-TSA was rated as a moderate irritant at the 24-hour endpoint. In long-term assays (two to six generations) low numbers of animals developed benign bladder tumors, including the control groups. Dose-related incidences in bladder calculi were found in the offspring of rats dosed throughout gestation and lactation. *o*-TSA predisposes neonatal animals to urolithiasis and/or bladder lesions.

When tested for the ability to cause morphological changes in the eye lens, *o*-TSA was almost inactive.

Results in mutagenicity studies of *o*-TSA have been somewhat equivocal. Mutation rates were doubled in TA98 at very high doses in the presence of an S9 fraction, but only on a special medium. Several *Drosophila* studies reported either negative or weakly positive results. One study demonstrated statistically significant doubling frequencies after three days' feeding of *o*-TSA. *o*-TSA was negative in mammalian systems.

In carcinogenicity studies, lymphosarcomas were observed in all dose groups exposed to *o*-TSA. Papillomas of the bladder were found in both low-dose and high-dose groups, with one carcinoma of the bladder observed. The incidence of malignant tumors was no different in the treated groups than in the control groups. In a separate study, no bladder tumors were observed though a mild diffuse urothelial hyperplasia was found in one rat.

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1.0 Basis for Nomination

Chloramine-T was nominated by a small commercial organization for toxicology studies based on its current status as an Investigational New Animal Drug (INAD) for controlling proliferative gill disease (PGD) and bacterial gill disease (BGD) in aquaculture and the need for additional toxicology studies to support it's safe use. The metabolite *p*-Toluenesulfonamide (*p*-TSA) is of importance as the primary residue of chloramine-T in chloramine-T treated fish intended for human consumption.

2.0 Introduction

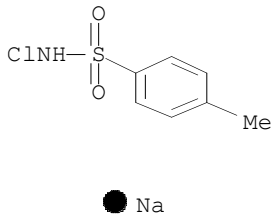
Chloramine-T has been used as a disinfectant since the early 1900s in a wide variety of industries that range from hospital to agricultural use. It is effective against a large number of bacteria and viruses without inducing drug resistance. The aquaculture industry has become very interested in developing Chloramine-T for use as a therapeutant against PGD and BGD. Investigational new animal drug applications (INADs) have been submitted to the U.S. Food and Drug Administration (FDA) to support the approval of chloramine-T for this use in the United States. In March 2001, the FDA announced a concern that the residue marker for chloramine-T, *p*-toluenesulfonamide, might be a carcinogen, and that no slaughter authorizations for fish treated with chloramine-T would be approved after the current INADs expired. The focus of this report is chloramine-T and its metabolite, p-toluenesulfonamide (*p*-TSA).

Chloramine-T should not be confused with the generic chloramine. In the municipal water treatment industry, chloramine refers to a combination of chlorine and ammonia used by some communities as an alternate to chlorination. Chloramination of drinking water is less effective than chlorine and may cause adverse health effects by both damaging and interfering with the repair of red blood cells. Where water is chloraminated, dialysis centers have had to treat their water with a combination of reverse osmosis and charcoal filtration systems to prevent anemia in hemodialysis patient (Tibbetts, 1995).

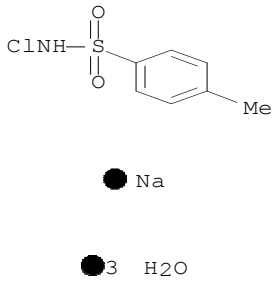
Chloramines may also be created endogenously through inflammatory processes. Myeloperoxidase, secreted by stimulated monocytes and neutrophilic polymorphonuclear leukocytes, catalyzes the oxidation of chloride by H_2O_2 to form hypochlorous acid (HOCl). Hypochlorous acid in turn reacts with ammonia and amines to form chloramines (*N*-Cl) (Thomas et al., 1987). Much of the scientific literature regarding chloramines uses chloramine-T as a surrogate for these endogenously formed chloramines to study the mechanisms by which they exert their activities.

The term chloramine-T has been used without distinction between the anhydrous form [CAS RN 127-65-1] and the trihydrate [7085-50-4] forms. As most of the Material Safety Data Sheets (MSDS) cited the molecular weight of the trihydrate while listing the anhydrous CAS RN, the assumption was made that the manufacturers were supplying the trihydrate. Therefore, the molecular weight of the trihydrate was used in converting doses in the toxicology sections.

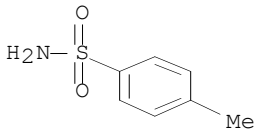
Chloramine-T
[127-65-1]



Chloramine-T Trihydrate
[7085-50-4]



p-Toluenesulfonamide
[70-55-3]



2.1 Chemical Identification and Analysis

Chloramine-T ([$C_7H_7ClNNaO_2S$]; mol. wt. = 227.65) is also called[1]:

Benzenesulfonamide, *N*-chloro-4-methyl, Sodium salt (CA Index Name)
p-Toluenesulfonamide, *N*-chloro-, sodium salt
Actamid
Acti-chlore
Aktivin
Anexol
Aseptoclean
Berkendyl
Chloralone
Chloramine-T
Chlorasan
Chloraseptine
Chlorazan
Chlorazene
Chlorazone
Chlorozone
Chlorseptol
Cloramine T
Clorina
Clorosan
Desinfect
Euclorina
Gansil
Gyneclorina
Halamid
Helogen
Kloramin
Kloramine-T
Mannolite
Mianine
Monochloramine T
Multichlor
N-Chloro-4-methylbenzylsulfonamide sodium salt
N-Chloro-*p*-toluenesulfonamide sodium
N-Chloro-*p*-toluenesulfonamide sodium salt
N-Chlorotoluenesulfonamide sodium salt
Sodium chloramine T
Sodium *N*-chloro-4-methylbenzenesulfonamide
Sodium *N*-chloro-*p*-toluenesulfonamide
Sodium *p*-toluenesulfochloramide
Sodium *p*-toluenesulfonchloramide
Sodium *p*-toluenesulfonylchloramide
Sodium tosylchloramide
Tampules
Tochlorine
Tolamine
Tosylchloramide sodium

[1] Budavari, 1996

Chloramine-T trihydrate ([$C_7H_7ClSO_2N$ NaCl ($3H_2O$)]; mol. wt. = 281.69) is also called[2]:

Benzenesulfonamide, *N*-chloro-4-methyl-, sodium salt, trihydrate
Sodium, (*N*-chloro-*p*-toluenesulfonamido)-, trihydrate
Tosylchlora

p-Toluenesulfonamide ([$C_7H_9NO_2S$]; mol. wt. = 171.23) (*p*-TSA) is also called:

Bensenesulfonamide, 4-methyl- (CA Index Name)
4-Methylbenzenesulfonamide
4-Methylphenylsulfonamide
PTSA
p-Toluenesulfamide
para-Toluenesulfamine
para-Toluenesulfonamide
4-Toluenesulfanamide
4-Tolylsulfonamide
p-Methylbenzenesulfonamide
4-MBSA
p-Tolylsulfonamide
p-Tosylamide
Plasticizer 15
Toluene-4-sulfonamide
Toluene-*p*-sulfonamide
4-Toluenesulfonic acid, amide
Tolylsulfonamide
p-Tolylsulfonamide
Tosylamide
p-Tosylamide
Uniplex 173

Synthesis and Analysis

Chloramine-T is synthesized from methylbenzene and four volumes of chlorosulfonic acid, which are allowed to react together at less than –5 °C. This reaction results in equal amounts of *ortho*- and *para*-toluenesulfonyl chloride. Pouring the mixture over ice separates the isomers. The *p*-toluenesulfonyl chloride crystallizes out of the mixture while the *o*-toluenesulfonyl chloride remains in solution. *p*-Toluenesulfonyl chloride is treated with ammonia, followed by sodium hypochlorite to form chloramine-T (Omikron-Online, 2000).

Many analytical methods have been developed to detect residues of both chloramine-T and its major metabolite (*p*-TSA) in a variety of foods (milk, ice cream, whole eggs, mechanically deboned poultry meat and croquettes (Beljaars et al., 1994; Steverink and Scholtyssek, 1977; Appel et al., 1988b). Most recently, isocratic reverse-phase liquid chromatography (absorbance detection set at 226 nm) has been used to measure chloramine-T's drug marker residue (*p*-TSA) in edible tissues of fish. Meinertz et al. (1999) reported mean recoveries of *p*-TSA ranging from 77 to 93.17% (method quantitation limits: 13 to 18 ng/g [0.076 to 0.11 nmol/g]; method detection limits: 3.8 to 5.2 ng/g [0.022 to 0.030 nmol/g]).

To detect chloramine-T or *p*-TSA in water, a reverse-phase liquid chromatographic method with ion suppression, using 0.01M phosphate buffer at pH 3, may be used (Dawson and Davis, 1990 abstr., 1997 abstr.). The mobile phase involves phosphate buffer-acetonitrile at one mL/min. Both chemicals can be detected with an UV spectrophotometer at 229 nm. Mean recoveries were about 95 or 96% for water samples fortified with 0.005 mg *p*-TSA/L [0.030 μmol/L] or

[2] ThermoNESLAB MSDS, 2000

0.03 mg chloramine-T/L [0.11 μmol/L], respectively. Limits of detection were 0.001 [0.006 μmol/L] and 0.01 mg/L [0.036μmol/L], respectively.

Van Gils et al. (1975) describe a method for the quantitative determination of traces of chloramine-T in dairy products. After removing proteins, the samples are extracted with ether. The solvent is removed and the residue oxidized with an alkaline potassium permanganate solution. This is extracted again with ether and the residue remaining after removal of solvent is subjected to reduction with Raney Nichol catalyst in a sodium hydroxide solution. The sulfonamide group is removed, leaving the benzoic acid, which is then analyzed by gas chromatography. Steverink and Scholtyssek (1977), describe a gas chromatographic determination of chloramine-T used in mechanically deboned chicken that is sensitive in the part per million (ppm) range with an average recovery of 80%.

Other methods used are specific for *p*-and/or *o*-TSA. The toluenesulfonamides are major impurities found in saccharine, one of the original non-nutritive sweeteners. Stavric et al. (1976) analyzed 13 saccharine samples used for cancer bioassay studies in a number of laboratories. The saccharine samples were dissolved in water and extracted with chloroform: methanol mixture (proportions not provided). The extract was concentrated and impurities were separated, underivatized, by gas liquid chromatography. Eleven major, well-separated peaks were collected, analyzed by mass spectroscopy, and compared with known standards. Quantitatively, *o*- and *p*-TSA were the most important impurities isolated and identified from saccharine.

Beginning around 1980, high performance liquid chromatography (HPLC) was used to isolate and quantify *p*-TSA. Duin and Nuijens (1981) analyzed dairy samples for *p*-TSA, first extracting the samples with acetone. The acetone extract was centrifuged and placed in a freezer for 30 minutes. The filtrate was analyzed by HPLC. In spiked ice cream samples, Duin and Nuijnes achieved, on average, 92.8% recoveries of *p*-TSA. Mooser (1984), using reverse phase HPLC, reported detection limits for *o*- and *p*-TSA of eight and sixteen ng, respectively. The mobile phase was water and tetrahydrofuran. Recovery and linearity were tested in the five to one hundred mg/kg range.

Beljaars et al. (1993) combined dialysis with chromatography to measure *p*-TSA in ice cream. Samples were extracted with water and then dialyzed in a continuous flow system. Dialysates (500 μL) were injected onto a reverse-phase octadecylsilane bonded-phase (C-18) column and exposed to a methanol-water (25 + 75, v/v) mobile phase. Quantification was through a fluorescence detector (230 nm excitation, 295 nm emission). Mean recoveries using this method were 76 to 79%, with a range of 63 to 101%. This method was adopted (first action) by the Association of Official Analytical Chemists (AOAC) International in 1994 (Beljaars et al., 1994).

A method for the detection of *p*-TSA in baby food was described by Abete et al. (1996). As in the method of Beljaars, the samples were extracted with water. However, in this method, concentration of the sample was achieved through an Extrelut Column, followed by purification on a SPE C-18 cartridge. Samples were analyzed by a gas chromatography equipped with a flame ionization detector. Mean recoveries of *p*-TSA using this method were 85%.

2.2 Physical-Chemical Properties Chloramine-T and *p*-Toluenesulfonamide

Property	Information	Reference(s)
Chloramine-T		
Physical State	White or slightly yellow crystals, crystalline powder, or prisms (trihydrate)	HSDB (2001b)
Odor	Weak chlorine odor (trihydrate)	HSDB (2001b)
Boiling Point (°C)	not applicable	Akzo Nobel (1998)
Melting Point (°C)	167 to 169; decomposes ca 174 (trihydrate)	H&S Chemical Co. Inc. (2000); (Akzo Nobel (1998); Physchem (1999)
Flash Point (°C)	192 (trihydrate)	Physchem (1999)
Density (kg/m^3)	1430	Akzo Nobel (1998)
Solubility (g/L) in: Water Benzene, chloroform, or ether	 150 practically insoluble (trihydrate)	 Akzo Nobel (1998) HSDB (2001b)
Specific Gravity	1.43 (trihydrate form)	Physchem (1999)
p-Toluenesulfonamide (p-TSA)		
Physical State	Solid (white leaflets) Solid (monoclinic plates) (dihydrate form)	HSDB (2001a)
Boiling Point (°C): at 1.33 kPa at 10 mm Hg	 214 221	 HSDB (2001a) OECD (1994)
Melting Point (°C)	137.5 138.5	OECD (1994) HSDB (2001a)
Flash Point (°C)	202	OECD (1994)
Solubility: In water (g/L at 25 °C) In alcohol	 3.16 Soluble	HSDB (2001a)
Octanol-water partition coefficient (log P_{ow}, 25 °C)	0.82	HSDB (2001a)

Chloramine-T trihydrate is a stable material, but is incompatible with oxidizing agents (Physchem, 1999). Chloramine-T trihydrate may decompose violently if heated above 130°C, and may decompose on exposure to air. On combustion, chloramine-T trihydrate forms toxic and irritating gases (e.g., hydrogen chloride, and nitrogen, sulfur, and carbon oxides) (ILO, 1997).

Chloramine-T has usually been classified as a slow hypochlorite-releasing agent (Axcentive, undated; Mavlab, undated). However, chloramine-T has several properties that do not fit the typical pattern of slow releasing agents, including stability in aqueous solutions, moderate pH dependency for biocidal efficacy, influence of organic matter on biocidal efficacy, minor skin irritation, and low chlorinating ability. Chloramine-T does not form chlorine or hypochlorous acids; therefore production of chlorinated organic compounds (AOX) is irrelevant (Axcentive, undated.

p-TSA is a non-volatile material, which is stable in neutral, acidic, or alkaline solutions (OECD, 1994).

2.3 Commercial Availability

Common vendors of chloramine-T are listed in **Table 1**. For the most part, chloramine-T is sold as a soluble concentrate (purity not provided). One source recommended a final concentration of 1% solution.

Chloramine-T trihydrate is available from many of the major chemical supply houses such as Fisher Scientific (Fairlawn, NJ [ThermoNESLAB MSDS, 2000] and Mallinckrodt Baker (Phillipburg, N.J. [Mallinckrodt Baker, 2000]). *p*-TSA was produced by Davos Chemical Corporation and RIT-Chem Company, Inc. in 1998 (U.S. EPA, 1999a, 2000), and by Unitex Chemical Co., Greensboro, NC (SRI, 1995; cited by HSDB, 2001a).

3.0 Production Processes

Chattaway (1905, cited by Budavari, 1996) reports the formation of chloramine-T through *p*-TSA. Chloramine-T is obtained from the reaction of *p*-TSA treated with sodium hypochlorite, chloramine B, $C_6H_5SO_2NClCa$, halazone, $HOOCC_6H_4SO_2NCl_2$, and *N*-chloro-*N*-methyl-*p*-toluenesulfonamide (Nelson, 1985).

Chloramine-T (trihydrate form) may also be formed by a reaction of ammonia and *p*-toluene-sulfochloride under pressure (Lewis, 1993). The latter is reacted with sodium hypochlorite in the presence of an alkali. Chloramine-T is produced from this reaction by crystallization.

p-TSA is formed by reaction of *p*-toluenesulfonyl chloride with ammonia (OECD, 1994). All processes are in a closed system except for drying and packaging. *p*-TSA is also formed by amination of *p*-toluene sulfonchloride (Lewis, 1993).

4.0 Production and Import Volumes

Production and import volumes for chloramine-T were not located. The United States aggregated production volumes for chloramine-T were reported to be between 10,000 and 500,000 lbs. in 1998. Total aggregated production of *p*-TSA was reported between one and ten million lbs. for the same year. Davos Chemical Corporation and RIT-Chemical Company, Inc. each produce greater than 10,000 lbs *p*-TSA/year (U.S. EPA, 2000). In Japan, production volumes of *p*-TSA were about 1700 and 1000 metric tons for 1985 and 1991, respectively (OECD, 1994).

Table 1. Vendors of Chloramine-T

Manufacturer	Address	Product Name	Reference
Akzo Nobel	Dobbs Ferry, NY	Halamid®	Akzo Nobel (undated-b)
Advanced Therapeutic Concepts	Spokane, WA	Chlorazene®	Advanced Therapeutic Concepts (2000)
H&S Chemical Co., Inc.	Covington, KY	Chloramine-T	H&S Chemical Co. Inc. (2000)
Maxim	1101-D West Melinda Phoenix, AZ	Pedi Redi Plus	Maxim LLC (undated)
OraTec Corporation	Manassas, VA	OraChlor	OraTec (2001)
Syndel International, Inc.	Vancouver, British Columbia, Canada	Halamid®	Syndel International Inc (2001)
Whirlpool Supplies Direct Nicholas Robert Corporation	912 W. Britain Road Oklahoma City, OK	Advantage Antimicrobial Whirlpool Additive	Nicholas Robert Corporation (undated)
Whitehall Manufacturing	City of Industry, CA	HydroChlor™	Whitehall Manufg. (undated)
Wisconsin Pharmacal, Inc.	1 Repel Road Jackson, WI	Chlorazene®	Ferno (undated)

According to IARC (1980), mixtures of *o*- and *p*-TSA have been produced commercially since 1939. In 1980, one U.S. company reported commercial production of the mixture in 1977, although the production amount was undisclosed. In 1979 and 1981, more than 2.27 thousand kg of the mixture were produced (HSDB, 2001a).

In 1973, U.S. imports of "*o*-, *p*-TSA" were 70.2 thousand kg and imports of "*o*-, *p*-TSA mixtures" were 77.1 thousand kg (IARC, 1980). In 1974, imports of "*o*-, *p*-TSA mixtures' were reported as 18.6 thousand kg. U.S. imports of the mixture were 82.2 thousand kg in 1979 and 450 kg in 1981 (HSDB, 2001a).

Telechemische, Inc. produces Ultralac®N (a toluenesulfonamide formaldehyde resin) in bulk quantities (Telechemische, 2000).

5.0 Uses

5.1 Chloramine-T

Use in cosmetics and in medical practices: Chloramine-T has been used in the cosmetics industry; typically it is added to a product as an anti-microbial agent (INCI, 1998).

First introduced as a disinfectant by Dakin in 1916, chloramine-T has been used as such in a number of different industries. Chloramine-T has been used to irrigate various parts of the body including the pleural cavity, urethra, urinary bladder, uterus, sinuses, mouth, and the eye (Martin and Cook, 1961; OraTec, 2001). However, in 1955, the FDA withdrew the approved uses of buccal and ophthalmic sprays and drops containing 0.13% chloramine-T; the compound had been used in combination with actilamide (concentration n.p.) and sulfanilamide (0.4%) (FDA,

2001b; FDA, 2001c; FDA, 2001d). In 1957, the FDA withdrew approval for use of chloramine-T (5 g) in Halo-San vaginal powder. In 2000, the FDA also withdrew the approval for Heliogen tablets (29.22 mg chloramine-T), Chloracidin topical paste (1.6% chloramine-T), Fawn topical soap (7% chloramine-T), and Xilor topical lotion (chloramine-T concentration n.p.) (FDA, 2001f; FDA, 2001e; FDA, 2001a). Reasons for discontinuation of approval were not provided.

Chloramine-T is easy to use and effective against many bacteria (both Gram-negative and -positive), viruses (enveloped and naked), fungi, algae, yeast, and parasites (Akzo Nobel, undated-a). During the Second World War, chloramine-T was used to prevent gangrene (OraTec, 2001). The mode of action of chloramine-T is thought to be through oxidative processes, quickly destroying cell material or disrupting essential cellular processes. Microorganisms do not develop resistances to chloramine-T as often happens with antibiotics. In addition, the chloramine-T ion is highly stable and remains active over an extended period of time. Because chloramine-T is effective at low concentrations (200 to 300 ppm [710 to 1070 μM]), it is an effective disinfectant without causing tissue cytotoxicity (Ferno, undated). It may be used as a disinfectant for both skin and for wounds.

In Europe, chloramine-T has been approved for many uses in medical, dental, and veterinary applications (ThermoElastic Technologies, 2001. It is used as a disinfectant and sterilizer for use on utensils, tools, equipment, and surfaces (Dellabianca et al. 1988; Keskinen et al., 1995; Mavlab, undated). In Germany, chloramine-T was used in the treatment of bacterial infections in premature and newborn infants and children (Handrick et al., 1981a, b).

Reports from Germany indicate that using chloramine-T as a prophylactic peritoneal lavage (0.1% solution [3.6 mM]) reduces the rate of wound-healing disorders substantially (from 9% to 2.6%). As a therapeutic peritoneal lavage, chloramine-T is superior to simple washing with physiological salt solution (reduction in wound healing disorders from 22.4% to 8.3%). In the case of perforations, the rate of healing disorders was reduced to 4.5% when chloramine-T was applied directly to the surgical wound (Effenberger et al., 1984; Effenberger and Kraas, 1987; Effenberger, 1988).

In the United States, chloramine-T has been used in the treatment of burns, specifically for wet-to-dry dressings used in preparing a graft recipient site or for minor debridement of the wound surface. The dressing is applied every four to six hours and is particularly effective during the 24 hours prior to a split thickness skin grafting (Figgie et al., 1982; University of Miami, undated). It has been used in other countries in the treatment of burns resulting from chemical and microbiological war gases (Mandl et al., 1984; Heyndrickx, 1989).

With low cytotoxicity, chloramine-T has been used by the dental industry as a whole-mouth wash, especially in the prevention and treatment of periodontal disease and as a subgingival irrigation system (Wolff, 1985; Herzog and Hodges, 1988). However, the status of subgingival irrigation is controversial in the treatment of periodontitis. The evidence suggests that although suspected pathogenic organisms were reduced, they were not eliminated, and the effects were transient in nature, with a rebound to baseline levels within weeks (Am. Acad. Periodont., 1995). When studied for effectiveness in preventing localized alveolitis and infections associated with the removal of the mandibular third molar, there seemed to be no apparent advantage to either

preoperative or postoperative use of chloramine-T in place of the normal saline solution (Sweet and Macynski, 1985). Chloramine-T has been used in Denmark for root canal therapy (Lambjerg-Hansen et al., 1982).

As an oral irrigation solution (1% [35 mM]), OraChlor® (active ingredient chloramine-T) is four times more bactericidal than sodium hypochlorite (bleach), but less irritating (OraTec, 2001). It also has a fair duration of activity, excellent clinical results, and is very economical (Hoverter, undated). In one scientific study, chloramine-T was classified as a product that exerted a sustained effect (reduction of at least one log colony-forming unit one hour after application) (Pitten and Kramer, 1999). In vitro studies, however, suggest that a 5% (178 mM) solution of chloramine-T causes severe cell and tissue reactions (Wennberg, 1980). Chloramine-T also has a very strong taste (chlorine) and results in a slight staining of teeth (Hoverter, undated; OraTec, 2001). In Europe, chloramine-T is an ingredient in dental creams (EC, 1983).

Use in whirlpool baths: One of the major marketing areas for chloramine-T is for use in whirlpool baths. It is marketed under the various names of Chlorazene Whirlpool Antiseptic (LifeTec Inc., undated), Advantage Antimicrobial Whirlpool Additive (Nicholas Robert Corp., undated), Chlorazene® (Advanced Therapeutic Concepts, 2000; Ferno, undated), and HydroChlor™ Whirlpool Antiseptic (Whitehall Manufg., undated). Most of these products are listed as 100% chloramine-T, though they are dissolved in water for use.

Maxim LLC (undated) has formulated an all-in-one product for whirlpool pedicure spas called Pedi Redi Plus. Containing chloramine-T, this product is marketed as a superior sanitizing formulation that replaces the need to further sanitize the whirlpool or run bleach or calgon through the system. According to the manufacturer, one of the advantages of chloramine-T use is that it does not cause skin irritation and actually assists in wound healing.

There is some controversy over the use of antiseptic agents in whirlpool baths. The scientific evidence suggests that the most commonly used agents are harmful to the cells responsible for tissue repair. Antiseptic agents may not be as effective if the bacterial load in the wound is high. Also, there is a risk of developing allergic responses to the chemical agents in patients with chronic wounds (Sussman, 1998). As a cautionary note, chloramine-T is considered an antiseptic and as such reduces the levels of microorganisms during the bath. However, chloramine-T is not a considered to be a disinfectant because it is not able kills 100% of microorganisms except spores; nor it is considered to be a sanitizer because it is not capable of killing 99.999% of the test organism. Although Maxim LLC has stated that Pedi Redi Plus replaces the need for other sanitizers, Sussman (1998) stated that all whirlpools should be disinfected at the start of the day, after each use, and at the end of the day with an appropriate disinfectant cleaner (Central Solutions, undated).

Use in agriculture and aquaculture: In the United Kingdom, chloramine-T has been approved by the Ministry of Agriculture, Fisheries & Food, the Secretary of State for Wales, and the Secretary of State for Scotland as a broad spectrum biocide for foot-and-mouth disease, swine vesicular disease, diseases of poultry, and tuberculosis (Vetrepharm, undated). Akzo Nobel (1997b) lists their product (Halamid® Pharma Grade) as an all-purpose disinfectant used in numerous branches of industry, including intensive farming, veterinary practice, slaughterhouses, kitchens,

food industry including canning, ice cream industry, and aquaculture. As a general disinfectant and fungicide, chloramine-T is used on working surfaces, in foot dips, as a vehicle for disinfection, as an aerial fogger, and for disinfecting water systems for poultry (Dijkman et al., 1981; cited by Reybrouck, 1982; Vetrepharm, undated). In Australia, chloramine-T is approved for use on cats, cattle, dogs, domestic birds, goats, horses, pigs, poultry, and sheep, and may be used to treat superficial wounds or skin infections by swab, douche, or irrigation with a 0.3% [10.6 mM]solution (Mavlab, undated). In dairy farming, chloramine-T is applied directly to the cow in cleaning the udder prior to milking and in dipping the teats after milking.

Although Halamid® has been used for a number of decades as a disinfectant in the farming of cattle, pigs, and poultry, it is receiving increased attention as a disinfectant in the farming of trout, salmon, sea bass, sea bream, and turbot, especially in Europe. In aquaculture, Halamid® may be used to disinfect both surfaces and water. Akzo Nobel provides information regarding the use of Halamid® in the fish hatchery, the nursery, the grow-out farm, and the processing plant (Akzo Nobel, 1997a).

Chloramine-T is effective for the control of BGD, PGD, and flexibacteriosis. BGD is caused by a variety of Gram-negative bacteria (myxobacteria, aeromonads, and pseudomonads (Snieszko, 1981; cited by Bills et al., undated). The disease is highly contagious among cultured salmonids and can lead to substantial fish losses. An approved therapeutant to control BGD is needed to enable the production of salmonids for restoration of fish stocks and for sport and commercial fisheries (Bills et al., undated). Flexibacteriosis is a generic term that includes columnaris disease, saddleback disease, bacterial cold water disease, tail rot, peduncle disease, and related infections caused by the disease organisms *Flexibacter columnaris* (*Cytophaga columnaris*) and *F. psychrophilus* in freshwater and *F. maritimus* in marine fish. There is no FDA-approved therapeutant that will control or prevent external flexibacteriosis on cultured fish (Upper Midwest Environmental Sciences Center [UMESC] 2000).

Although chloramine-T is not licensed in the United States for use with fish intended for human consumption, as a therapeutic agent, it is used as an effective treatment of BGD in freshwater or marine aquaria, garden ponds, or other aquatic systems (Fancy Koi Outlet, 2000) at concentrations ranging from 6.5 to 10.0 mg/L [23.1 to 35.5 μM] (Bullock et al., 1991; cited by Powell and Perry, 1996) and as a preventative, prophylactic, and disinfectant treatment in many fresh water hatcheries (Thorburn and Moccia, 1993; Smith et al., 1993; both cited by Powell and Perry, 1996).

Use of chloramine-T as a therapeutant in fish culture in the U.S. depends on approval by the FDA.

<u>Use in the bookbinding and book conservation industry</u>: Chloramine-T is used in the bookbinding and conservation industry to remove “fox marks” and stains (Etherington and Roberts, 2001) and also for general bleaching purposes (Etherington and Roberts, 2001).

<u>Use in the textile industry</u>: Uses in the textile and clothing industry include both bleaching and dying of fabrics (Akzo Nobel, 1997b).

Use in laboratory research: As a reagent in analytical chemistry, chloramine-T is used in assays to determine cyanide in either human tissues (blood) (Cardeal et al., 1995) or agricultural products (FDA, 1990). Analyses of collagen in meat and meat products (Kolar, 1990), proline in biological samples (Wu, 1993), and lactose in milk products (Stds. Assoc. Australia, 1988) all rely on reactions with chloramine-T. Other laboratory uses include the production of dipolar reagents in the construction of 5-member heterocycles (Padmavathi et al., 1999), radioiodination of proteins, preparation of α-aminoaldehydes from enamines, and in the determination of sulfa drugs (Christopher et al., 1978; Dyong and Lam-Chi, 1979; Verma and Gupta, 1982; all cited by Serva, undated), bromates, and halogens (Welcher 1948; cited in Budavari, 1996). Chloramine-T is used in an ^{125}I-postlabeling assay that measures the induction of DNA-protein crosslinks in cultured Chinese hamster ovary cells (Zhuang and Costa, 1994).

Other uses: Finally, chloramine-T is used as a deodorizer (both gas and wastewater) (Akzo Nobel, 1997b) and for emergency sanitation of drinking water (Axcentive, undated). In the past, chloramine-T was used in the U.S. as an anti-microbial to disinfect eating establishment utensils and barbershop instruments, and as an herbicide. EPA registration for these applications was withdrawn between 1983 and 1987 (Orme and Kegley, 2000).

5.2 *p*-TSA and Mixtures or Resins Containing TSA

p-TSA is used mainly as an intermediate for pesticides and drugs in a closed system, but is also used as an additive to outdoor paints in Sweden (OECD, 1994).

The *o*- and *p*-TSA mixture is used as a reactive plasticizer in hot-melt adhesives to improve the flow properties of thermosetting resins (e.g., melamine, urea, and phenolic resins) (IARC, 1980). The mixture is also used to add flexibility to coatings based on these resins. The *o*- and *p*-TSA mixture is also used as a carrier in fluorescent pigments.

A toluenesulfonamide formaldehyde resin sold under the name Ultralac® N is used as a plasticizer in nitrocellulose (Telechemische, 2000). The toluenesulfonamide formaldehyde resin is used in color lacquers and paints, and in fingernail varnishes (Draelos, 2001).

6.0 Environmental Occurrence and Persistence

Chloramine-T does not bind to soil or sludge and is readily biodegradable if it is in sufficiently low concentrations in water. There is no evidence to indicate that chloramine-T bioaccumulates. Although reported to be hazardous to the environment, especially to fish and crustaceans (IPCS, 1993), no other references were retrieved to support this data. Chloramine-T is used as a therapeutant at 10 mg/L for up to one hour without adverse effects. Akzo Nobel, (1998) lists *p*-TSA as readily biodegradable. Other studies do not agree. *p*-TSA is classified as not readily biodegradable under aerobic conditions (Unpublished report on Biodegradation Test of *p*-TSA Conducted by MITI; cited by OECD, 1994). Limited biodegradation was found in anoxic methanogenic conditions. However, the disappearance of *p*-TSA did not correlate with production of methane in this study (Kuhn and Suflita, 1989).

Commercially produced *p*-TSA may be released into the environment through various waste streams (HSDB, 2001a). It has been detected in drinking water, surface water, ground water, and in the effluents from nonferrous metals (22 ng/μL [0.18nmol/μL] extract) and the printing and

publishing industries (19,841 ng/μL [115.87 nmol/μL] extract) (Bursey and Pellizzari, 1982; cited by HSDB, 2001a). Environmental concentrations of *p*-TSA have been calculated using several models (OECD, 1994). The calculated concentrations ranged from 4.22 to 5.88 x 10^{-8} μg/L [6.03 to 8.40 x10^{-9} ppm] in air, 0.0202 to 0.0203 μg/L [0.118 to 0.119 nmol/L] in water, 5.93 x 10^{-8} to 3.63 x 10^{-2} μg/kg [3.46 x 10^{-10} to 2.12 umol/kg] in soil, and 0.0113 to 0.104 μg/kg [6.60 to 60.7 x 10^{-5} μmol/kg] in sediment.

p-TSA has high mobility if released into soil, and volatilization should not be important from moist or dry soil surfaces (HSDB, 2001a). *p*-TSA is not susceptible to direct photolysis on soil surfaces based on its lack of absorption of light at wavelengths >290 nm. Anaerobic degradation in soil and water is not expected to be an important fate process according to a biodegradation study conducted in anaerobic aquifer slurries. The importance of aerobic degradation is not known. However, lack of biodegradation in a test of the *ortho* isomer suggests that aerobic biodegradation of *p*-TSA may be slow. If released into water, *p*-TSA should not adsorb to suspended solids or sediment. *p*-TSA will be essentially non-volatile from water surfaces. An estimated bioconcentration factor (BCF) of 2.5 suggests that *p*-TSA will not bioaccumulate in aquatic organisms. If released into the atmosphere, *p*-TSA will exist as both a vapor and particulate in the ambient atmosphere. Vapor-phase *p*-TSA is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals with an estimated half-life of about 13 days. Particulate-phase *p*-TSA may be physically removed from the air by wet and dry deposition.

p-TSA is slightly toxic to algae, but is non-toxic to fish and daphnids, which implies that its environmental risk is low (OECD, 1994).

7.0 Human Exposure

Humans are potentially exposed to chloramine-T and *p*-TSA from the uses summarized in Section 5.0.

Oral: Exposure to chloramine-T via ingestion also occurs from its presence as a residue in foods, such as milk (Steverink and Steunenberg, 1979), ice cream (Beljaars and Rondags, 1978; Beljaars and Rondags, 1979), whipped cream (Beljaars and Rondags, 1978), whole egg (Steverink and Steunenberg, 1979), minced meat (Beljaars and Rondags, 1979), mechanically de-boned poultry meat (Steverink and Steunenberg, 1979; cited by HSDB, 2001a), shrimp (Beljaars and Rondags, 1979), and croquettes (Steverink and Steunenberg, 1979; cited by HSDB, 2001a). Exposure to *p*-TSA may occur due to its presence as an impurity in saccharin (IARC, 1980). Reported levels of *p*-TSA in saccharin are less than or equal to 5 mg/kg [0.02 mmol/kg], based on information provided to IARC by the National Research Council/National Academy of Sciences.

Dermal and/or Inhalation: Exposures are likely in the production of chloramine-T, and in the textile industry and possibly in bookbinding and conservation industries. Nurses, medical, and veterinary professionals are exposed to chloramine-T via dermal and inhalation routes in the operating room, and where it is used for other medicinal practices (Montanaro, 1992). Anywhere that chloramine-T is used as a disinfectant, dermal and inhalation exposures of either the powder or aerosols are possible. In Europe, these industries include food processing,

breweries and beverage production, butchering and meat processing plants along with farms (ThermoElastic Technologies, 2001). In addition, exposures will be likely in those industries that use chloramine-T as a starting product for other chemicals. Evaporation of chloramine-T trihydrate at 20 °C is negligible; however, a harmful concentration of airborne particles can be reached quickly (ILO, 2000). Exposure to *p*-TSA occurs from the use of nail polish; nail polish that has completely dried on the fingernails contains water-soluble *p*-TSA that may be absorbed into the skin as it leaches from the polish (Hausen, 1995).

Although probably a smaller population overall, individuals exposed through the treatment of wounds may have higher exposures, based on dermal absorption of chloramine-T as a topical wetting agent for wound dressings or through wound sites treated in whirlpools using chloramine-T as an antiseptic.

Based on a 1981-1983 survey of U.S. workers (NOES Survey, 1981 - 1983), the National Institute for Occupational Safety and Health (NIOSH) statistically estimated that 757 workers (727 male; 30 female) were potentially exposed to *p*-TSA in the workplace (HSDB, 2001a). Dermal or inhalation exposure to *p*-TSA may occur in Sweden through its use as a preservative in all types of outdoor paints (<100 kg) (OECD, 1994). However, consumer exposure as a whole appears to be low because this chemical is used mainly as a raw material for synthesis of pesticides, drugs, and fluorescent colorants in a closed system.

8.0 Regulatory Status

8.1 Chloramine-T

There is a great deal of interest in obtaining approval from the FDA for the use of chloramine-T in aquaculture. Few chemicals have been approved for the use in aquaculture, primarily because the market potential for the sale of the product is not large enough to warrant the investment needed to get FDA approval. In 1994 the International Association of Fish and Wildlife Agencies (IAFWA) agreed to support research on a priority list of chemicals identified as being important to various state fisheries. The list, compiled in 1993, included chemicals needed but not currently labeled for aquaculture use, such as chloramine-T. Most of the project oversight is conducted by the Upper Mississippi Science Center in Lacrosse, WI, and the Stuttgart National Aquaculture Research Center in Stuttgart, AR, under the coordination of Rosalie Schnick (National Coordinator for Aquaculture New Animal Drug Applications) (Griffith, 1999). Work on the project began in 1994 and is anticipated to continue until 2002.

The overall goal of this project is to obtain FDA approval of a group of chemicals for use in aquaculture. Intermediate goals are to identify sponsors for individual chemicals; to identify existing data and remaining data requirements for new animal drug application (NADA) approval; to review, record, and provide information on the status of INADs and NADAs; to provide liaison and coordination among all the federal agencies involved in the INAD/NADA process; and provide public education related to training and guidance in obtaining INAD exemptions and pursuing NADA approval (Schnick, 1997).

Through this project, data regarding target animal safety, efficacy, analytical methods, residue analysis and metabolism studies and an environmental assessment were either collected from past research or generated to fill data gaps for the INAD/NADA submission. The original

sponsor for chloramine-T, Akzo Nobel forwarded a letter of intent commitment to develop Halamid® to control or prevent external flavobacterial infection in fresh water fish in 1997. In July 1997, Akzo Nobel forwarded to the Center of Veterinary Medicine (CVM), FDA, a letter of intent to pursue an INAD exemption. It was their intent at that time to develop a new Animal Drug Application for chloramine-T under their existing INAD. In October 1998, a draft proposal was submitted to the CVM, proposing to use chloramine-T exclusively for use on early life stages of fish. At this time, acceptable mammalian toxicology studies were lacking that were necessary to estimate the tolerance of *p*-TSA, the major metabolite of chloramine-T and the chemical for which tolerances would be developed. If fish were only exposed in their early life stages, then all residues should have been eliminated by harvest time (Schnick, 1998).

The Coordinator for Aquaculture New Animal Drug Applications was informed in April 2000, that Akzo Nobel had sold Halamid® to Axcentive bv. Axcentive bv agreed to continue the sponsorship of chloramine-T. During the May to November 2000 timeframe, both the genetic toxicology studies and the environmental assessment for chloramine-T were submitted to INAD #8086. Total residue depletion and metabolism studies in rainbow trout were accepted by CVM. The validation of the analytical methods for *p*-TSA in edible tissue of cold-water fish (rainbow trout) was completed. Method accuracy and precision data were within the range of acceptance for the FDA (Schnick, 2000).

In March 2001, CVM called a meeting of all Investigational New Animal Drug (INAD) holders based on a concern that *p*-TSA may be a potential carcinogen. At that time, it was announced that no slaughter authorizations for fish treated with chloramine-T would be approved after the current INADs expire. Only laboratory studies or studies in which fish will not be released or slaughtered for food will be approved in the future.

Work continues to gain FDA approval for chloramine-T. Marker residue depletion studies in rainbow trout are ongoing. UMESC has committed to complete an evaluation of the accuracy and precision of *p*-TSA analysis in channel catfish and walleye before working on marker residue depletion studies in these species. The sponsor, Axcentive bv, is addressing product chemistry and mammalian safety. The CVM accepted two residue chemical studies performed by the Upper Midwest Environmental Science Center for total residue depletion and metabolism of chloramine-T in rainbow trout. Toxicity testing is being expanded to include several additional fish species in support of an all fish label claim. Efficacy data requirements were met for the control of mortality associated with flavobacteria infection in gill salmonids reared in fresh water (12 to 20 mg/L [42 to 71 μM], for one hour) (Schnick, 2001).

In 1999, the Pharmacy Compounding Advisory Committee of the FDA met to review drug substances considered for use in pharmacy compounding, but that did not have a U.S. Pharmacopeia or National Formulary Monograph, and were not components of FDA-approved drugs (Peterson and Juhl, 1999). The Committee concluded that chloramine-T should not appear on the Bulk Drug Substances list because its uses appeared to be limited or restricted to very few limited sites.

8.2 *p*-TSA

In the United Kingdom, *p*-TSA (0.2% [11.7 mM]) is listed as a substance that may not be present in cosmetic products (U.K. SI, 2000).

The U.S. FDA has classified the mixture of *o*- and *p*-TSA as a safe component of adhesives used in articles intended for packaging, transporting, or holding food if used in quantities not exceeding the limits of good manufacturing practice (21 CFR 175.105 [4/1/93]; cited by (HSDB, 2001a; IARC, 1980).

Uniplex 171 (a mixture containing 70% *p*-TSA and 30% *o*-TSA) is regulated under the Toxic Substances Control Act (TSCA). TSCA was enacted in 1976 to give the EPA the ability to track industrial chemicals currently produced or imported into the United States. EPA can require reporting or testing of those chemicals that may pose a threat to the environment or human health, or even ban the manufacture and importation of chemicals that pose an unreasonable risk (U.S. EPA, 1999b). Uniplex 171 is not considered to be a hazardous substance as defined by OSHA (29 CFR 1910.1200) (Unitex Chemical, undated). The mixture is considered as nonhazardous for transport purposes, and is not regulated by the U.S. Department of Transportation (US DOT).

FDA regulations (21 CFR 177.2260) state that resin-bonded filters that contain *p*-TSA-formaldehyde resin may be used to filter milk or potable water at operating temperatures not to exceed 100 ^{o}F, provided that the finished filter when exposed to distilled water at 100 ^{o}F for two hours yields total extracts not to exceed one percent by weight of the filter. The filter may also be used to filter milk or potable water at operating temperatures not to exceed 145 ^{o}F, provided that the finished filter when exposed to distilled water at 145 ^{o}F for two hours yields total extracts not to exceed 1.2 percent by weight of the filter.

FDA regulations (21 CFR 176.170) state that toluenesulfonamide-formaldehyde resins may be safely used as components of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods.

p-TSA was included in the Organization for Economic Co-operation and Development (OECD) investigation of high production volume (HPV) chemicals to identify possible data gaps for assessing potential risks to human health and the environment. Based on the screening information data set (SIDS) initial assessment report (SIAR) developed by the OECD, *p*-TSA was considered to be "presently of low concern" (OECD, 1994). The OECD SIAR concluded that "although 4-methylbenzenesulfonamide [*p*-TSA] is persistent and toxicological tests showed moderate toxicity, no further testing is needed at present considering its use pattern and exposure levels", and further recommended that "if this chemical is used largely in consumer products in the future, long-term repeated dose (e.g. 90 days) toxicity test may be needed, because histopathological changes of urinary bladder and thymus were observed in combined repeat/repro. toxicity test."

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

Chloramine-T is considered harmful if swallowed, inhaled, or absorbed through skin or eyes (H&S Chemical Co., undated). Inhalation results in irritation of the mucous membranes and upper respiratory tract. Symptoms include burning sensation, coughing, wheezing, laryngitis, and shortness of breath, sore throat, bronchitis, pneumonitis, and possible pulmonary edema. Inhalation exposures may result in pulmonary sensitization or allergic asthma (U.S. EPA, 1994; Mallinckrodt Baker, 2000). Asthmatic symptoms may not become obvious for several hours, and are aggravated by physical effort. Exposures through ingestion are irritating to the gastrointestinal tract and produces nausea, vomiting, and diarrhea (U.S. EPA, 1994; Mallinckrodt Baker, 2000). Chloramine-T dust in the air is irritating to the eyes, resulting in pain and produces conjunctivitis without any serious damage (Grant 1974; cited by HSDB, 2001b; Mallinckrodt Baker, 2000). Skin contact with chloramine-T produces redness, itching, and pain, with a potential for the development of an allergic skin reaction (Mallinckrodt Baker, 2000). Chloramine-T is considered to be moderately toxic with a probable oral lethal dose of 0.5 to 5 g/kg [1.8 to 18 mmol/kg] (approximately one ounce to one pint) for a 70 kg individual (150 lbs) (Gosselin et al., 1976; cited by HSDB, 2001b).

Rest and medical attention are important to anyone who has demonstrated asthmatic reactions in response to chloramine-T exposures (IPCS, 1993). In a patch test study of 501 consecutive patients suspected of contact dermatitis, only one (0.2%) showed a positive reaction to chloramine-T (Halamid®, 0.5% [17.8 mM] aqueous solution) (De Groot et al., 1986). Individuals with impaired respiratory function may be more susceptible to the effects of chloramine-T (Mallinckrodt Baker, 2000).

Few available studies specifically addressing effects in humans were located. Most of the studies identified addressed either hypersensitivity or occupational asthmatic reactions. Occupational exposures to chloramine-T have been associated with hypersensitivity resulting in eczema (Dooms Goossens et al., 1983; Rudzki et al., 1988). Case reports discuss urticaria as a result of exposure of hospital and dental personnel to chloramine-T (Rudzki et al., 1988; Kanerva et al., 1997). A single retrospective study of hairdressers with hand eczema found the role of chloramine-T questionable in the etiology of eczema in this population (Ozkaya-Bayazit, 1997).

Chloramine-T tested positive in the guinea pig maximization test (GPMT), local lymph node assay (LLNA), and the Buehler occluded test when tested for its potential to cause contact dermatitis (Basketter and Scholes, 1992; Kimber et al., 1994). The ability of chloramine-T to react with lysine-containing peptides was positive; suggesting that chloramine-T had the potential to act as a hapten (Wass and Berlin, 1990). Use of chloramine-T has also been associated with occupational asthma, bronchoconstriction, and rhinitis, either through handling the powder concentrate or as an aerosol formed from diluted solutions. Disinfectant use was identified as a risk factor for both atopic sensitization and symptoms associated with asthma in pig farmers of the Netherlands; the association was strongest for quaternary ammonia products (Rosenberg, 1991; Blasco et al., 1992; Malo and Bernstein, 1993; Preller et al., 1996; Anonymous, 1997).

Case studies of small groups of patients can be found in the literature describing both hypersensitivity and occupational asthma induced by chloramine-T. Patients are derived from a large number of industries, including pharmaceutical, hospital, kitchen, hospital, beverage, and agricultural backgrounds (Feinberg and Watson, 1945 [cited by Malo and Bernstein, 1993]; Bourne et al., 1979; Flindt, 1980 [both; cited by HSDB, 2001a]; Dijkman et al., 1981 [cited by Reybrouck, 1982]). In most of these industries, chloramine-T is use as a disinfectant or sterilizer. Symptoms include nasal irritation and/or wheezing, usually within minutes of dissolving the chloramine-T in water, though in one case, the response was delayed several hours and was accompanied by fever and sputum production (Dijkman et al., 1981; cited by Reybrouck, 1982).

Chloramine-induced symptoms in several hospital workers have been described. A 28-year-old nurse developed a severe angioneurotic edema when exposed to a 2 % [71 mM] chloramine-T solution to treat a dental abscess. She had previously come in contact with chloramine-T as an antiseptic for the treatment of infected ulcers (Beck, 1983; cited by U.S. EPA, 1994). Chloramine-T exposure, from its use as an antiseptic in cleaning burns, was thought to be the cause of a case of subacute eczema in a 38-year-old nurse (Lombardi et al., 1989; cited by U.S. EPA, 1994). One hospital worker's reaction was characterized as a stage three contact urticaria syndrome with an immunological mechanism; she suffered from both cutaneous and extracutaneous symptoms (Dooms Goossens et al., 1983).

Although toluene sulfonamide/formaldehyde resin (TSFR), (10% w/v solution in dimethyl phthalate), was not found to act as an irritant, fatiguing agent, or sensitizer in the Shelanski Repeated Insult Patch Test (Monsanto Co. Company, 1983; Industrial Biology Research and Testing Laboratories, 1985b; both cited by Elder, 1986), it has been associated with hypersensitivity reactions, typically in areas that come in contact with polished nails (face, especially eyelids, sides of the neck, retroauricular zone, shoulders, upper chest, and vulva) (Fisher, 1981; cited by Elder, 1986). Three women with contact dermatitis of the neck, face, and/or eyelids and using nail lacquers containing TSFR had positive patch tests for TSFR (Fisher, 1981; cited by Elder, 1986). Sixteen of 8093 patients identified as contact dermatitis cases tested positive to TSFR in patch tests (Eiermann et al., 1982; cited by Elder, 1986). In one case study, when a patient mistakenly assumed that she had a nickel sensitivity, dermatitis was induced when the back of a watch was painted with nail lacquer to prevent contact with nickel. When tested, the patient demonstrated a positive reaction to TSFR (Kanerva, 1995). Two women, who had developed onycholasis of the fingernails, tested positive for TSFR and 2% formaldehyde in petrolatum. Two months after discontinuance of the nail products, the nails had grown back and looked almost normal (Paltzik and Enscoe, 1980; cited by Elder, 1986).

p-TSA is not currently included on the standard patch test series approved by the FDA/AAD (American Academy of Dermatology) (Fisher, 1998).

The mechanism of chloramine-T-induced occupational asthma was shown to be mediated through immunoglobulin E (IgE) (Kramps et al., 1981; cited by Malo and Bernstein, 1993). Skin tests of four of five patients in various industries produced immediate type wheal and flare reactions followed by late-type infiltrative reactions. Three of these patients were given inhalation performance tests. One patient demonstrated asthmatic bronchial obstruction

immediately after inhalation of 0.5 mg/mL [1.8 mM] chloramine-T (total volume not provided). Three patients exhibited late-type asthmatic reactions with dyspnea accompanied by wheezing four to eight hours post-challenge and lasting 24 to 72 hours (Dijkman et al., 1981; cited by Reybrouck, 1982). Seven brewery workers occupationally exposed to chloramine-T responded to skin prick tests with a positive wheal and flare reaction (Bourne et al., 1979; cited by HSDB, 2001b). Kramps et al. (1981) and Flindt (1980; cited by HSDB, 2001b) both demonstrated that chloramine-T-induced occupational asthma coincided with the occurrence of specific IgE antibodies (both cited by (HSDB, 2001b). The antigenic determinant is thought to be the *p*-toluene sulfonyl group (Kramps et al., 1981; cited by Malo and Bernstein, 1993).

In one controlled study, changes in cytogram, protein content, eosinophil cationic protein (ECP), and tryptase levels were evaluated through nasal washings collected before and 30 minutes and 4 and 24 hours after challenge with chloramine-T in patients with a history of chloramine-T-induced asthma. A significant increase was reported in eosinophil and basophil number and percentage, albumin, tryptase, and ECP level in the chloramine-T challenged individuals versus the control group (Wittczak et al., 2001 abstr.).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

The details of selected studies are presented in **Table 2**. Note: Information on fish is provided since chloramine-T is being considered in the treatment of BGD/PGD in fish raised for human consumption.

Fish (trout) were immersed for up to one hour in radiolabeled chloramine-T (20 mg/L [71 μM], or twice the recommended therapeutic dose) as part of residue analyses. In adult trout, analysis of muscle fillet, residual carcass tissue, and gall bladder bile were negative for chloramine-T. Chloramine-T had been rapidly reduced to *p*-TSA (not quantitated) (EMEA, 1999). Obeale (2000) reports the presence of 4010 ng *p*-TSA/g fillet tissue [23.42 nmol/g] in a similarly treated fish. Two additional fish fillet samples were spiked with 333.33 ng *p*-TSA/g tissue [1.9467 nmol/g tissue], giving final values of 4268 and 4911 ng/g tissue [24.93 and 28.68 nmol/g]. The untreated control sample contained 32.5 ng *p*-TSA ng/g fillet tissue [0.190 nmol/g]. In a field trial, a 1/10-acre pond containing approximately 700 fish with signs of mixed infection of ESC (enteric septicemia of catfish), Columnaris, and PGD were treated with chloramine-T (2 ppm [7 μM]). Residue analysis of a small sample of fish demonstrated a range of *p*-TSA (46.13 to 60.54 ng/g tissue [0.2694 to 0.3536 nmol/g]). Control fish analysis had 47.68 ng *p*-TSA/g tissue [0.2785 nmol/g]. This background level was thought to be interference with another substance and not *p*-TSA (Mitchell, 2000). The conclusion made from these experiments were that chloramine-T was poorly absorbed from water (fingerlings and juveniles); *p*-TSA does not appear to accumulate in fish (EMEA, 1999; Mitchell, 2000).

Whole body homogenates of fingerling and juvenile trout were used to assess the half-life of *p*-TSA. Fish were immersed in water containing 20 mg/L [71 μM] of radiolabeled chloramine-T for one hour. Half lives for *p*-TSA after exposures to chloramine-T were 27.3 and 36.3 hours for the fingerling, estimated through radiometric data and HPLC analyses, respectively, and 32.6 and 40.3 hours for the juveniles (EMEA, 1999).

Table 2. Chemical Disposition, Metabolism, and Toxicokinetics of Chloramine-T and *p*-Toluene Sulfonamide

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Trout, fingerlings and juveniles, strain, number and sex n.p.	[Ring UL-^{14}C]Chloramine-T; purity 93.7%; specific activity, 1.2 µCi/µM,	Fish were placed into water containing 20 mg/L [71µM] radiolabeled chloramine-T for up to 1 h and then transferred to freshwater. Water temperature was 11.6° to 12.2°C.	$t_{1/2}$ for *p*-TSA equivalents was calculated through two methods (radiometric versus HPLC analyses) Estimates for $t_{1/2}$ from radiometric analysis were 27.3 and 32.6 h for the fingerlings and juveniles, respectively. HPLC whole body analyses provided t_ estimates of 36.3 and 40.3 h in the fingerlings and in the juveniles, respectively. Elimination was significantly more rapid in the fingerlings than the juveniles.	EMEA (1999)
Trout, rainbow, adult, 15, sex n.p.	[Ring UL-^{14}C]Chloramine-T; purity 93.7%; specific activity, 1.2 µCi/uM)	Fish were placed into water containing 20 mg/L [71µM] radiolabeled chloramine-T for up to 1 h and then transferred to freshwater. Water temperature was 11° to 13°C.	Muscle fillet, residual carcass tissue, and gall bladder bile were collected and frozen until analyzed. No chloramine-T residues were observed. Chloramine-T was rapidly reduced to *p*-TSA. *p*-TSA equivalents in whole body homogenates were 980 and 570 µg/kg [5.72 and 3.33 µmol/kg] for fingerlings and juveniles, respectively, representing 5% and 3% of the concentration in the exposure bath.	EMEA (1999)
Trout, rainbow (*Oncorhynchus mykiss*), 1-yr-old, 15, M and F	[Ring UL-^{14}C]Chloramine-T; radiochemical purity >94%; specific activity of 0.955 mCi/mmol	Fish were exposed to 20 mg/L [71µM] radiolabeled chloramine-T (for approximately 60 min. Fish were rinsed in well water and euthanized.	Tissues (fillet, gall bladder bile, and residual carcass) were frozen for further analysis. Analysis failed to detect chloramine-T residues in any tissues, nor was there any evidence of any residues other than *p*-TSA.	Dawson et al. (1994)
Rat, Wistar, age and number n.p. , M	Chloramine-T (purity n.p.)	Animals were dosed with 30 mg/kg [0.11 mmol/kg] i.v. or 100 mg/kg [0.355 mmol/kg]orally.	Serial blood samples were collected; plasma concentrations of chloramine-T were determined. Chloramine-T was characterized by a rapid distribution and elimination phases ($t_{1/2}\alpha$=0.12 and 0.42 and $t_{1/2}\beta$=1.41 and 1.98 h after i.v. and oral dosing, respectively). Plasma clearance was relatively high (0.147 and 0.149 L/h, respectively) with a volume of distribution at steady state of 0.24 L.	Martinez-Larrañaga and Fernandez-Cruz (1996 abstr.)

Table 2. Chemical Disposition, Metabolism, and Toxicokinetics of Chloramine-T and Metabolite *p*-Toluene Sulfonamide (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rat, Wistar, 200 to 300 g, number n.p. , M	Chloramine-T (purity n.p.)	Group 1 animals were dosed orally with chloramine-T (100 mg/kg [355 µmol/kg]); animals in Group 2 were dosed (5 mg/kg [18 µmol/kg]) i.p. for four consecutive days. Group 3 was given 0.5 mL of distilled water i.p.	Serial blood collections and brains were taken from Group 1. Tissues were assayed for chloramine-T concentrations. For groups 2 and 3, brains were removed and hypothalamus, striatum, and frontal cortex dissected out. Tissues were analyzed for 5-HT and 5-HIAA. The analysis suggested that chloramine-T is rapidly absorbed and enters the CNS. The ratio of AUC_{brain}/AUC_{blood} indicated a potential for chloramine-T storage in the brain. Chloramine-T exposure resulted in a decrease in levels of 5-HT in the striatum and frontal cortex (13% and 17%, $p<0.05$ and $p<0.01$, respectively). No changes in the levels of 5-HIAA were found.	Anadón et al. (1997)
Rat, Wistar, 200-250 g, , 3F	*p*-TSA, purity n.p.; [Methyl-^{14}C]-TSA was obtained as by-products in the synthesis of [3-^{14}C]-saccharin.	Animals received either 29 mg/kg [0.17 mmol/kg] containing 8 µCi/rat or 200 mg/kg [1.17 mmol/kg] *p*-TSA containing 15 µCi/rat, in 1 mL 20% ethanol or 1 mL 50% aqueous propylene glycol, respectively, p.o	*p*-TSA was rapidly eliminated from the rats, primarily through the urine. At the end of 24 h, 78.1% and 63.4% of the radioactivity was accounted for in the urine from low and high dose treatments, respectively. The cumulative urinary totals were 80.6 and 70.4% of the low and high doses on days 5 and 4, respectively. In the low-dose group, unchanged parent compound, 4-sulphamoylbenzyl alcohol, and 4-sulphamoylbenzoic acid were identified in the 0 – 24-h urine of all the rats. In addition, 4-sulphamoylbenzaldehyde was identified in the urine of a single animal. Metabolites identified in the 0 – 24-h urine of the high-dose rats were 4-sulphamoylbenzoic acid, 4-sulphamoylbenzyl alcohol, parental TSA, and *N*-acetyltoluene-4-sulphonamide in the urine.	Ball et al. (1978)
Cow (lactating), strain n.p. adult, , 5F	Chloramine-T, purity n.p.	Dermal exposure to 0.5% [17.8 mM] chloramine-T 2x/d, 8d. Blood samples were taken (*vena jugularis*) immediately before the last treatment and 30 min, 1, 2, 4, 8, 16, and 24 h after the last treatment.	Teats were cleaned before milking with udder tissues dipped in 0.5% [17.8 mM] chloramine–T. Blood was analyzed by HPLC. No residues of *p*-TSA could be detected in any blood sample (method detection limit for *p*-TSA = 5 µg/kg [0.03 µmol/kg] and for chloramine-T = 8 µg/kg [0.03 µmol/kg]). The results suggested that percutaneous absorption of chloramine-T in blood was negligible.	EMEA (2001)

Table 2. Chemical Disposition, Metabolism, and Toxicokinetics of Chloramine-T and Metabolite *p*-Toluene Sulfonamide (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Cow (lactating), strain n.p., adult;, 12 - 28 F/group	Chloramine-T sodium, purity n.p.	Dermal exposure 1x/d, 5 consecutive days, concentration n.p.	Teats were dipped immediately after milking. Milk samples were collected from the measuring can containing individual milk for 5 cows; 20 bulk milk samples were taken from 5 farms. No residues of *p*-TSA were found in bulk milk, in the control sample, or in 16 out of 25 individual milk samples. In the remaining 9 samples, 5 - 9 µg *p*-TSA /kg milk [0.03 – 0.05 µmol *p*-TSA /kg milk] was found.	EMEA (2001)

Abbreviations: 5-HT = 5-hydroxytryptamine; 5-HIAA = 5-hydroxyindoleacetic acid; AUCχ = area under the curve for the indicated tissue; CNS = central nervous system; F = female; HPLC = high performance liquid chromatography; h = hour(ly)(s); i.p. = intraperitoneal (ly); M = males; n.p. = not provided; p.o. = *per os*; $t_{1/2}$ = half life

Dawson et al. (1994) conducted a follow-up study to isolate and characterize major residues in tissues sampled from trout exposed to chloramine-T. Adult rainbow trout were exposed to 20 mg/L [71 μM] radiolabeled chloramine-T for one hour prior to sacrifice. Analysis of tissues (fillet, gall bladder, and residue carcass) failed to detect any residue other than *p*-TSA. In their previous study (Dawson and Gingerich, 1991; cited by Dawson et al., 1994), *p*-TSA residues did not account for the entire radioactivity in sampled tissues.

Archived samples from the previous study were extracted and reanalyzed. It was concluded that the test article from the earlier study contained a radiolabeled contaminant accounting for approximately 5% of the total radioactivity. The contaminant was not found in the 1994 study. However Dawson (1994 abstr.) reports that chloramine-T is metabolized to a second, as yet unidentified, metabolite other than *p*-TSA. This second metabolite elutes earlier than *p*-TSA on a gel permeation chromatography column, suggesting a higher molecular weight than *p*-TSA, but elutes later than *p*-TSA during HPLC analysis on a reverse-phase column, indicating that the second metabolite is less polar than *p*-TSA.

Martinez-Larrañaga et al. (1996 abstr.) investigated pharmacokinetics of chloramine-T in the rat. Chloramine-T was found to be rapidly distributed ($t_{1/2}\alpha$ = 0.12 and 0.42 hour for intravenous and oral administration, respectively) throughout the body with an elimination half-life of 1.41 and 1.98 hours (intravenous and oral administration, respectively). Plasma clearance was considered relatively rapid (0.147 and 0.149 hours after intravenous and oral dosing, respectively) with a volume of distribution at steady state of 0.24 L.

Percutaneous absorption of chloramine-T was investigated for use in bovine applications. There was interest in using chloramine-T as a teat and udder disinfection to prevent udder disease in lactating cows. Two studies were identified investigating the potential for absorption of the parent compound or the excretion of *p*-TSA in the milk. Analysis of blood samples failed to detect either chloramine-T or *p*-TSA. Small amounts of *p*-TSA (five to nine μg/kg [0.03 to 0.05 μmol/kg] milk) were found in about one-third of the individual milk samples. Sampling from the bulk tank failed to detect any *p*-TSA. These studies suggest the percutaneous absorption and transfer of chloramine-T to the blood stream was negligible (EMEA, 2001).

There appears to be less transfer of either chloramine-T or iodine to the milk if chloramine-T is used as the udder wash prior to milking and iodophor used for the teat dip after milking (43.2 ± 40.9 ppb [153.4 ± 145.0 μM] chloramine-T alone versus 16.1 ± 9.8 ppb [57.2 ± 34 μM] combined with iodophor post-milking treatment (Appel et al., 1988a, 1988b; Appel, 1989).

Administered *p*-TSA is rapidly eliminated from rats, with 78.1% and 63.4% of the radioactivity recovered in the urine within 24 hours in rats dosed with 29 or 200 mg/kg [0.17 or 1.17 mmol/kg] *p*-TSA (Ball et al., 1978). Metabolites isolated from the 24-hour urine of the low dose group included 4-sulphamoylbenzyl alcohol (3.3 to 4.9% urinary radioactivity) and 4-sulphamoylbenzoic acid (93.9 to 95.7% urinary radioactivity), along with unchanged parent compound. One rat in the low-dose group also produced sulfamoyl-benzaldehyde (1.5% urinary radioactivity). In the high-dose group, 4-sulphamoylbenzoic acid (92.7 to 94.5% urinary radioactivity), 4-sulphamoylbenzyl alcohol (2.0 to 2.7 % urinary radioactivity), and *N*-acetyl toluene-4-sulfonamide (2.1 to 2.3% urinary radioactivity) were found in the 24-hour urine in

addition to the parent compound. The relative amounts of the metabolites suggested that the methyl group of *p*-TSA is oxidized to produce primarily the benzoic acid derivative. The alcohol and aldehyde, found in trace amounts, represent intermediate steps in metabolism (Ball et al.,1978). Minegishi (1972; cited by HSDB, 2001a) found that 80% of administered *p*-TSA was found in the urine; 50% of that had been metabolized to 4-sulphamoylbenzoic acid.

Early experiments in dogs suggest a similar metabolic pathway. Flaschentrager et al. (1934; cited by Ball et al., 1978) reported that *p*-TSA was oxidized to 4-sulphamoylbenzoic acid and excreted in the urine in the dog. Sammons et al. (1941; cited by Ball et al., 1978) presented evidence that metabolism in the rabbit does not undergo ring oxidation as they failed to find any increase in the production of ethereal sulfate after dosing rabbits with *p*-TSA.

9.1.3 Acute Exposure

Acute toxicity values for chloramine-T and *p*-TSA are presented in **Tables 3 and 4,** respectively, except where note**.** Details of acute studies discussed in this section are presented in **Table 5.**

As with humans, chloramine-T is irritating to the skin, eyes, and gastrointestinal tract. In acute LD_{50} studies in the rat and mouse, gastric inflammation, apathy, and gastric bleeding, as well as intestinal hemorrhage, were observed in animals that died (study details not provided) (EMEA, 1999).

Impacts of chloramine-T have been assessed in a variety of freshwater and marine life. In spotted sea trout eggs and larvae, 48-hour medium tolerance limits were 14.14, 0.57 and 5.75 ppm [50.20, 2.0, and 20.4 μM] for two-hour- and ten-hour-old eggs, and one-hour post-hatch larvae, respectively (Johnson et al., 1977b; cited by HSDB, 2001b). Exposure of larval lobsters to 1.0 mg/L [3.6 μM] chloramine-T resulted in a reduction in dry weight increase, standard respiration rate, growth, and metabolic activity (Capuzzo, 1977; cited by HSDB, 2001b).

In intermittent exposures of rainbow trout to chloramine-T at the therapeutic concentration (10 mg/L [36 μM]), the fish exhibited behaviors that were consistent with respiratory distress (i.e., fish crowing at the surface and appeared to hyperventilate (study details not provided) (Powell et al., 1994; cited by Powell and Perry, 1996). Additional studies were performed to investigate the impact of a single exposure to chloramine-T. One-hour exposures of rainbow trout to chloramine-T (9 or 2 mg/L [30 or 7 μM]) or *p*-TSA (9 mg/L [50 μM]) through catheterized dorsal aorta resulted in a significant increase in both ventilation rates and P_{CO2} levels. Both parameters returned to baseline levels within 90 minutes of removal from chloramine-T.

Chloramine-T also caused a reduction in arterial pH. *p*-TSA had no significant effect on ventilation rates, P_{CO2}, or P_{O2} levels. A gradual decrease in pH was noted during the exposure period that persisted throughout the recovery period. No effects were found for either hematological parameters or serum catecholamine levels with any of the treatments (Powell and Perry, 1996). Despite the increased ventilation rate in the chloramine-T treated fish, P_{CO2} remained elevated. This suggested that a difference in the diffusive conductance of the gills, impairing CO_2 excretion, possibly by the secretion of mucous by the gills, increasing the blood to

Table 3. Acute Toxicity Values for Chloramine-T

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference(s)
Imm.	Guppy (*Poecilia reticulata*)	LC_{50} = 31 mg/L (110 μM) (96 h)	Akzo Nobel (1997b. 1998)
	Rainbow trout	LC_{50} = 2.80 mg/L (9.94 μM) (96 h)[a]	Bills et al. (undated)
	Fathead minnow	LC_{50} = 7.30 mg/L (25.9 μM) (96 h)[a]	
	Channel catfish	LC_{50} = 3.75 mg/L (13.3 μM) (96 h)[a]	
	Dero digitata	LC_{50} = 29.5 mg/L (105 μM) (24 h, Halamid)[b]	Mischke et al. (undated-a, b)
		LC_{50} = 28.1 mg/L (99.8 μM) (48 h, Halamid)[b]	
		LC_{50} = 27.4 mg/L (97.3 μM) (24 h, Actamide)[b]	
		LC_{50} = 26.1 mg/L (92.7 μM) (48 h, Actamide)[b]	
Inh.	Rat (sex and strain n.p.)	LC_{50} > 0.275 mg/L (0.976 μM) (4 hrs) (max. attainable concentration)	Akzo Nobel (1998)
p.o.	Mouse (sex and strain n.p.)	LD_{50} = 1100 mg/kg bw (3.905 mmol/kg bw)	EMEA (1999)
	Rat (sex and strain n.p.)	LD_{50} = 935 mg/kg bw (3.32 mmol/kg bw)	
	Rat and/or mouse (sex and strain n.p.)	LD_{50} ~ 1000 mg/kg (3.550 mmol/kg)	Akzo Nobel (1997b, 1998)
	Rat (sex and strain n.p.)	LD_{100}~1.4 g/kg (5.0 mmol/kg) (in 15% aqueous solution)	Monsanto Co. (1947)
	Rat (sex and strain n.p.)	LD_{100}~2.1 g/kg (7.5mmol/kg) (in 15% olive oil solution)	
	Rabbit (sex and strain n.p.)	LD_{100}~0.68 g/kg (2.41 mmol/kg) (in 15% aqueous solution)	
	Rabbit (sex and strain n.p.)	LD_{100}~1.4 g/kg (5.0 mmol/kg) (in 15% olive oil solution)	
Derm.	Rabbits (sex and strain n.p.)	LD_{50} > 2000 mg/kg (7.100 mmol/kg)	Akzo Nobel (1997b)
s.c.	Guinea pig	LD_{Lo} = 900 mg/kg (3.20 mmol/kg)	RTECS (1998b)
i.p.	Frog (sex and strain n.p.)	LD_{Lo} = 200 mg/kg (0.710 μmol/kg)	
	Mouse (sex and strain n.p.)	LD_{Lo} = 300 mg/kg (1.07 mmol/kg)	
i.v.	Rabbit (sex and strain n.p.)	LD_{Lo} = 25 mg/kg (89 μmol/kg)	

Abbreviations: Derm. = dermal; h = hour(s); Imm. = immersion; Inh. = inhalation; i.p. = intraperitoneal (ly); i.v. = intravenous(ly); LC (D)χ = concentration (dose) lethal to χ% of test animals; LD_{Lo} = lowest lethal dose tested; n.p. = not provided; p.o. = *per os*.

[a] Fish maintained in soft water at 12°C.

[b] Pond water had an alkalinity = 185 mg/L-$CaCo_3$, hardness = 171 mg/L-$CaCO_3$. Laboratory cultured *Dero digitata* were used in the tests.

water diffusion distance and/or unstirred boundary layer of the gills. This effect could be a result of the release of hypochlorite from chloramine-T. Single exposures of therapeutic concentrations of chloramine-T appear to have little pathophysical impact on the health of rainbow trout (Powell and Perry, 1996). Maximum tolerated levels for rainbow trout ranged

from 325 mg/L [1150 μM] for 0.1-hour one-hour exposures to 20 mg/L [71 μM] for 12-hour exposures (From, 1980).

Table 4. Acute Toxicity Values for *p*-Toluenesulfonamide

Route	Species (sex and strain)	LD_{50}/LC_{50}	Reference(s)
Imm.	Orange–red Killifish (*Oryzias latipes*)	LC_0 = 324 mg/L (1.89 mM) (24, 48, 72, and 96 hrs)	Unpublished Report on Toxicity to Fish-HPV/SIDS test conducted by the EA (cited by OECD, 1994)
		LC_{50} = 435 mg/L (2.54 mM) (24, 48, 72, and 96 hrs)	
		LC_{100} = 538 mg/L (3.14 mM) (24, 48, 72, and 96 hrs)	
p.o.	Mouse (sex and strain n.p.)	LD_{50} = 400 mg/kg (2.34 mmol/kg)	Sax and Lewis (undated, cited by OECD, 1994)
	Rat and/or rabbit (sex and strain n.p.)	LD_{100} ~ 4.7 g/kg (27.4 mmol/kg) (in 15% suspension of 2% aqueous solution of methyl cellulose)	Monsanto Co. (1947)
	Rat (sex and strain n.p.)	LD_{100} ~ 3.2 g/kg (18.7 mmol/kg) (in 15% olive oil)	
	Rat (sex n.p.; Sprague Dawley Crj:CD(SD)	LD_{50} >2000 mg/kg (11.68 mmol/kg)	Unpublished Report on Acute Toxicity Screening Test of p-Toluenesulfonamide-HPV/SIDS test, conducted by MHW (cited by OECD, 1994)
	Rat (sex and strain n.p.)	LD_{50} = 2330 mg/kg bw (13.61 mmol/kg bw)	EMEA (1999)
	Rat (sex and strain n.p.)	LD_{50} = 2400 mg/kg bw (14.02 mmol/kg bw) (41% *o*-TSA; 51% *p*-TSA)	
	Rat (M and F, Sprague Dawley)	LD_{50} = 3.8 g/kg bw ( ) (25% suspension in corn oil)	Monsanto Co. (1957)[a]
	Wild bird species (sex and strain n.p.)	LD_{50} = 75 mg/kg (0.44 mmol/kg)	Schafer (1972; cited by OECD, 1994); RTECS (2000)
	Rabbit (sex and strain n.p.)	LD_{100} ~ 1.4 g/kg (8.2 mmol/kg) (in 15% olive oil)	Monsanto Co. (1947)
	Rabbit (M and F, New Zealand white)	LD_{Lo} = 1.25 – 1.50 g/kg ( ) (25% suspension in corn oil)	Monsanto Co. (1957)[a]
s.c.	Guinea pig (sex and strain n.p.)	LD_{Lo} = 2 g/kg (0.01 mol/kg)	RTECS (2000)
i.p.	Mouse (sex and strain n.p.)	LD_{50} = 250 mg/kg (1.46 mmol/kg)	

Abbreviations: bw = body weight; F = female; LC(D)χ = concentration (dose) lethal to χ% of test animals; h = hour(s)(ly); imm. = immersion; i.p. = intraperitoneal; M = male; n.p. = not provided; p.o. = *per os*; s.c. = subcutaneous(ly)

[a] represents a mixture of o- and p-TSA

Table 5. Acute Exposure to Chloramine-T and Toluenesulfonamide

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Lobster, larval, strain, number, and sex n.p.	Chloramine-T (purity n.p.)	Larval lobsters were maintained in chloramine-T (1.0 mg/L [3.6 μM]), 60 min, at 25 °C	Reduction in increase in dry weight, growth, metabolic activity, and standard respiratory rate was observed when compared to controls.	Capuzzo (1977; cited by HSDB, 2001b)
Spotted Sea trout, eggs and larvae, numbers and sex n.p.	Chloramine-T (purity n.p.)	Animals were exposed by immersion; 48-h medium tolerance limits were determined.	2-h-old eggs 14.14 ±1.13 ppm [50.20 ± 4.01 μM] 10-h-old eggs 0.57 ±0.28 ppm [2.02 ± 0.99 μM] 1-h-post-hatch larvae 5.75 ±3.01 ppm [20.4 ± 10.69 μM]	Johnson et al. (1977a; cited by HSDB, 2001b)
Rainbow trout (*Oncorhynchus mykiss*), age n.p., 20, sex n.p.	Chloramine-T (analytical grade); *p*-TSA (purity n.p.)	Catheterized fish (dorsal aorta) were exposed to a 60-minute pulse of chloramine-T, 9 or 2 mg/L [30 and 7 μM], n = 7), *p*-TSA, 9 mg/L [53 μM] in 0.0012% DMSO (n = 6); or sodium hypochlorite, 0.45 mg/L (n = 7). Fish were monitored for an additional 90-min prior to termination of experiment.	Fish exposed to chloramine-T were compared to other treatment groups (*p*-TSA, 9 mg/L [53 μM], n = 6); and sodium hypochlorite solution (0.45 mg/L)] and untreated fish (n = 7). Arterial P_{O2}, P_{CO2}, and pH were measured continuously. Both concentrations of chloramine-T resulted in a significant increase in both the ventilation frequency and P_{CO2}. For the high dose, both returned to baseline levels within 90 min of removal of exposure. Ventilation rates reached baseline within 15 min of removal from the 2 mg/L [7 μM] concentration, while P_{CO2} levels remained significantly elevated upon withdrawal. Although P_{CO2} returned to baseline levels with the 9 mg/L group [30 μM] , the 2 mg/L [7 μM] group remained elevated to the end of the recovery period. Chloramine-T (either concentration) caused a decrease in arterial pH (non-significant). There was no significant effect of chloramine-T on P_{O2}. *p*-TSA had no significant effect on ventilation rate, P_{CO2} levels, or P_{O2} levels. There was a gradual decline in arterial pH during exposure, which was pronounced throughout the recovery period. There was no significant effect of treatment on any blood parameter (hematocrit, hemoglobin, and total oxygen content). Similarly there was no significant increase in plasma catecholamine levels in any of the treatments.	Powell and Perry (1996)

Table 5. Acute Exposure to Chloramine-T and Toluenesulfonamide (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rat, , strain, age, and number n.p., M	Chloramine-T (purity n.p.)	Single injection; dose and observation period n.p.	Serum elastase inhibitory capacity was reduced to about 28 to 35 % of the initial levels within 1 to 3 h of injections; however, levels returned to control values within 9 h. This is consistent with a rapid synthesis of the protein molecule, resulting in a rapid recovery.	Lungarella et al. (1983)
Hamster, Syrian, age n.p., 5 – 10 M	Chloramine-T (Purity n.p.)	.Animals were injected i.p. with chloramine-T (0.5 mmol/kg [0.1 g/kg]. Blood samples were taken from anesthetized animals at intervals ranging from 0.5 to 20 hours post-treatment. Serum was assayed for HLE and PPE inhibitory activity	Although obviously irritated at the site of injection within 30 sec, all animals were outwardly normal at 15 to 30 min post-treatment. Serum from these animals showed an increased ability to inhibit PPE from 0.5 to 6 h post-treatment, with the increase being significant at the 1 and 2 h time-points. The same serum showed a slight decrease in ability to inhibit HLE, becoming significantly depressed from 3 to 5 h post-treatment. The effects of chloramine-T were transient in nature. HLE and PPE returned to control levels by 8 and 20 h post-treatment, respectively.	Williams et al. (1986)
Rabbit, < 3-wk-old and adult number and sex n.p.	Chloramine-T, purity n.p.	Route, dose, and observation period n.p.	Lethal dose for rabbits under 3 wk of age was in the range of 40-50 mg/kg [140 - 180 μmol/kg]. Edema typical in the adult animals was only found with the administration of high (200-250 mg/kg [710 - 890 μmol/kg]) doses to the young animals. Hemorrhage was present, possibly due to the direct effect of chloramine-T excreted through the lungs on the walls of the arterioles and capillaries of the vascular system. Lethal doses for adult rabbits were in the range of 60 – 70 mg/kg [210 - 250 μmol/kg]. Death was associated with acute edema of the lungs.	Arshavskaya (1975)

Abbreviations: 5-HIAA = 5-hydroxyindoleacetic acid; 5-HT = 5-hydroxytryptamine; DMSO = dimethyl sulfoxide; h = hour(s)(ly); HLE = human leukocyte elastase; PPE = porcine pancreatic elastase; i.p. = intraperitoneal; M = male; min = minute(s); n.p. = not provided; P_{CO2} = arterial carbon dioxide concentration; P_{O2} = arterial oxygen concentration; wk = week(s)(ly)

In early LD_{50} studies, rabbits succumbing to chloramine-T toxicity showed signs of general weakness, opisthotonos, severe clonic, and mild tonic convulsions. Toxicity progressed to increased weakness and respiratory difficulties, eventually resulting in coma and death. Rats treated under the same conditions demonstrated no signs of central nervous system involvement, but rather demonstrated increasing degrees of anesthesia. Animals passed into a coma prior to death. Cyanosis was noted for some rats (Monsanto Co., 1985).

Pathological examination of both rats and rabbits showed evidence of generalized vascular and organic parenchymal damage, with severe damage to the stomach and duodenum, probably due to localized irritation and corrosive action of chloramine-T. Acute congestive changes were noted throughout the viscera. Histological examination demonstrated evidence of edema and congestion of the brain and leptomeninges. Three of five rabbits presented with pyknosis and chromatolysis in the cerebral cortex and midbrain. Although the rats failed to present with CNS effects similar to that observed in the rabbits, neurons of the pons and medulla were severely damaged, with complete destruction of the Nissl substance, rupture of cell membranes, and swollen and fragmented nuclei (Monsanto Co., 1985). LD_{50} studies of *p*-TSA resulted in very similar types of intoxication and pathology in the corresponding animals as observed with chloramine (Monsanto Co., 1985).

In a separate series of acute toxicity tests, Monsanto Co. (1957) found that Santicizer 9 (a mixture of *o*- and *p*-TSA) resulted in labored breathing and some nervous twitching in rats (Sprague Dawley). Animals were comatose within a couple of hours of oral dosing of a 25% suspension in corn oil. Marked pulmonary hyperemia and moderate kidney congestion were noted on necropsy. In rabbits, unsteadiness was noted within a few hours of oral dosing, progressing to coma and paralysis. The loss of muscular control was more pronounced in the hindquarters. On necropsy, liver and kidney congestion were noted, along with moderate inflammation of the gastrointestinal mucosa. Santicizer 9 was demonstrated to be relatively non-toxic and non-irritating when applied to the closely clipped skin of the rabbits. When applied to the eye, Santicizer was classified as a mild eye irritant.

Most animal studies have been performed to investigate the impact of *in vivo* exposures to chloramine-T on protease inhibitors, specifically on the α_1-protease inhibitor (α_1-PI). Serum derived from rats receiving a single dose of chloramine-T demonstrated a 28 to 35% reduction in elastase inhibitory capacity (EIC) within one to three hours of injection (Lungarella et al., 1983). Similarly, Williams et al. (1986) found that intraperitoneal injections of chloramine-T reduced the ability of hamster serum to inhibit human leukocyte elastase, significantly at three to five hours post-treatment. In hamsters only there was an increased ability to inhibit porcine pancreatic elastase (PPE). In both the rat and hamster, EIC returned to normal in eight to twenty hours post-treatment, consistent with rapid protein synthesis.

Age-dependent toxicity was observed in rabbits. Rabbits under three weeks of age were more susceptible to the effects of chloramine-T, with lethal doses in the range of 40 to 50 mg/kg [140 to 180 μmol/kg], as opposed to lethal doses in adult rabbits (60 to 70 mg/kg [210 to 250 μmol/kg]). Death in adult rabbits was associated with acute edema of the lungs, which was absent from the young rabbits until doses of 200 to 250 mg/kg [710 to 890 μmol/kg].

Hemorrhage was present in the young animals possibly due to direct effects of chloramine-T on the walls of the vascular system (Arshavskaya, 1975).

Acute toxicity of TSFR has been investigated. TSFR was found to be relatively non-toxic in rats (Sprague-Dawley) or rabbits (New Zealand) dosed orally with 7.94 g/kg in a 70% acetone solution or dermally with up to 7.94 g/kg in a 40 % corn oil suspension, respectively. Reductions in activity and appetite were observed for two to four days post-treatment in both species. Gross examination at fourteen days was unremarkable. One hundred mg of finely ground TSFR was instilled in the eyes of six New Zealand rabbits, without rinsing. Slight erythema of conjunctivae was observed up to 48 hours after treatment, but had been cleared by 72 hours. Based on these results, TSFR was considered to be only a slight ocular irritant. TSFR failed to induce any skin irritation in an occlusive patch to intact and abraded skin in the New Zealand rabbits (Younger Laboratories, 1974; cited by Elder 1986).

9.1.4 Short-term and Subchronic Exposure

The details of the following studies, except where noted, are presented in **Table 6**.

Rats were exposed to chloramine-T through feeding studies for either 28 days or 90 days. The target tissue doses for the 28- and 90-day exposures ranged from 150 to 1500 mg/kg [0.533 to 5.325 mmol/kg/d] and 5 to 150 mg/kg per day [18 to 533 μmol/kg/d], respectively. Reduced weight gains were observed (slight in females, 90-day study; significantly in the 500 and 1500 mg/kg/d [1.78 and 5.325 mmol/kg per day] groups in the 28-day study). Relative kidney weights were increased in all dose groups in the 28-day study and in the two high dose groups in the 90-day study. Relative liver weights were increased in all of the dose groups in the 90-day study. A slight increase in leukocytes and pale, discolored livers were observed in the highest two dose groups in the 28-day study. An increased severity and frequency of calcareous deposits occurred in the kidneys of female rats receiving 50 and 150 mg/kg per day [180 and 533 μmol/kg per day] in the 90-day study (EMEA, 1999).

In another rat study, the target dose ranged from 15 mg/kg/d to 750 mg/kg/d [0.088 to 4.38 mmol/kg/d]. The animals were dosed with 120 to 750 mg/kg/d [0.701 to 4.38 mmol/kg/d] for up to 42 days before mating (males) or for 14 days before mating to day three of lactation (females), resulting in numerous endpoints. Reductions in body weight gains were observed in the high-dose males (significant) and mid- and high-dose females. This was accompanied by a slight increase in relative liver and kidney weights in the high-dose groups. High-dose groups had dark colored liver on gross observation. Hematological changes included a dose-dependant increase in white blood cells (mid- and high-dose animals) and neutrophils (high-dose males). Blood urea nitrogen (BUN), serum glutamic-oxalacetic transaminase (SGOT), and chloride were significantly elevated in the two highest dose groups (males); serum glutamic-pyruvic transaminase (SGPT) was significantly elevated in the high-dose male group only. Potassium levels were reduced in the high-dose male rats. Several animals in the female mid- and high-dose groups demonstrated an involution of the thymus. Histopathological examination showed a thickening of the urinary bladder epithelium (OECD, 1994; EMEA, 1999).

Table 6. Short-term and Subchronic Exposure to Chloramine-T or *p*-Toluenesulfonamide

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rat, strain, age, number, and sex n.p.	Chloramine-T, (purity n.p.)	Feeding study resulting in approximate doses of 150, 500, or 1500 mg/kg bw/d [0.533, 1.78, 5.325 mmol/kg bw/d], for 28 d	The mid- and high-dose groups demonstrated a significant decreased weight gain, slightly increased leukocyte count, and pale discoloration of the liver. Increased relative kidney and liver weight were observed in all dose groups. There were no significant treatment-related histologic alterations.	EMEA (1999)
Rat, Wistar, age n.p., 10 M and 10 F/dose	Chloramine-T (purity n.p.)	Feeding study resulting in approximate doses of 5, 15, 50, or 150 mg/kg bw/d [18, 53, 180, or 533 µmol/kg bw/d], for 90 d.	The highest dose resulted in a slight reduction in weight gain in F. Increased relative kidney weights were observed in the top 2 dose groups in both sexes. Increased severity and frequency of calcareous deposits were observed in the kidneys of the 50 and 150 mg/kg [178 and 533 µmol/kg] groups for F only. No hematologic or histopathologic analyses were performed for animals in the mid and high dose treatment groups. A NOEL of approximately 15 mg/kg bw [53 µmol/kg bw] was established. Noted: 300 mg/kg feed, equivalent to ~ 15 mg/kg bw.	EMEA (1999)
Rat, Crj:CD(SD), adult, age n.p., 13 M and 13 F/dose	*p*-TSA in 5% gum Arabic solution, >99.9% pure	Animals dosed orally (0,120, 300, and 750 mg/kg [0, 0.701, 1.75, and 4.38 mmol/kg]) for 42 d prior to mating (M) or 14 d before mating through d 3 lactation (F)	Dose-related hypersalivation was observed in all treatment groups. Significant decrease in body weight gains in the high-dose M relative to controls persisted throughout the dosing period. Relative kidney and liver weights were slightly increased in high-dose animals. A dose-dependent increase in white blood cells counts was observed in mid- and high-dose M and some F (1 low-, 12 mid-, and 7 high-dose groups). An increased number of neutrophils were observed in high-dose M. BUN, GOT, and chloride were significantly elevated in the two highest dose groups (M). GPT levels were significantly elevated and potassium levels decreased in the high-dose M. Four animals from the high-dose groups displayed hematuria within the first 3 d of dosing. There was an involution of the thymus in 8 high- and mid-dosed F.	Unpublished report on Combined Repeat Dose and Reproductive Developmental Toxicity Screening Test of (Specific chemical)-HPV/SIDS test conducted by MHW; cited by OECD (1994); EMEA (1999)
Rat strain, age, number, and sex n.p.	TSA (68% *p*-TSA; 32% *o*-TSA), purity n.p.	Feeding study resulting in approximate doses of 15, 50, or 150 mg/kg/d [88, 290, or 876 µmol/kg] for 90 d	The only treatment-related effect observed was a slight reduction of food consumption and weight gain at the high dose.	EMEA (1999)

Table 6. Short-term and Subchronic Exposure to Chloramine-T or *p*-Toluenesulfonamide

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Dog, strain, age, number, and sex n.p.	TSA (68% *p*-TSA; 32% *o*-TSA), purity n.p.	Feeding study of doses up to approximately 75 mg/kg/d [0.44 mmol/kg], for 90 d.	No treatment-related effects were observed. No hematologic or histopathologic analyses were performed for animals in the mid and high dose treatment groups.	EMEA (1999)

Abbreviations: BUN = blood urea nitrogen; bw = body weight; d = day(s); F = female(s); GOT = serum glutamic-oxalacetic transaminase (serum aspartate aminotransferase); GMPT = guinea-pig maximization test; GPT = serum glutamic-pyruvic transaminase (serum alanine aminotransferase); h = hour(s)(ly); ^{3}HTdR = [$_{3}$H] methyl thymidine; i.v. = intravenous(ly); LLNA = local lymph node assay; M = male(s); NOEL = no effect level; wk = week(s)(ly)

In 90-day feeding studies in rats (5, 15, 50, or 150 mg/kg/day [18, 53, 180, or 533 μmol/kg/d] and dogs (75 mg/kg/d [0.44 mmol/kg/d]) using a mixture of *o*- and *p*-TSA, the only treatment-related effect was a slight reduction in food consumption and weight gain in the rat only (EMEA, 1999). No hematologic or histopathologic analyses were performed for animals in the mid and high dose treatment groups.

Purebred beagle dogs were exposed to TSFR (1000 to 10,000 ppm) in their diets for 90 days with no treatment-related lesions found (study is not included in the table). Slight to moderate body weight gain was suppressed in females at the highest dose level. A slightly elevated liver to body weight ratio was observed in all animals in the high-dose exposure levels, but was considered minimal (Industrial Biology Research and Testing Laboratories, 1985; cited by Elder, 1986).

9.1.5 Chronic Exposure

The details of two chronic studies associated with chloramine-T are presented in **Table 7**. Both studies were conducted in dogs. Animals were dosed orally or intravenously, or through a combination of the two, with doses ranging from approximately 12.8 to 640 mg/kg [45.4 to 2270 μmol/kg] per day for up to six months. In the study by King et al. (1983 abstr.), 50% of the animals were sacrificed at 17 weeks. At that time, persistent mild or moderate anemia was observed. Both King et al. (1983 abstr.) and Abrams et al. (1981) found a reduction in EIC of serum collected from the animals. Furthermore, a reduction in EIC was found for the pulmonary lavage fluid (King et al., 1983 abstr.). Abrams et al. (1981) demonstrated that levels of immunologically determined protease inhibitor did not change with treatment. Therefore, the enzyme must have been inactivated by chloramine-T. The reaction was specific for the protease inhibitor, as the ability to inhibit trypsin was less affected. Emphysema-like alterations in lung morphology were found in both studies.

9.1.6 Synergistic/Antagonistic Effects

No information was found regarding the synergistic/antagonistic effects of chloramine-T or *p*-TSA.

9.2 Reproductive and Teratological Effects

Four teratology and two reproductive studies were identified, all for *p*-TSA; these are presented in **Table 8**. For most of the developmental studies, pregnant rats were dosed by oral gavage with *p*-TSA (50 to 1500 mg/kg [0.29 to 8.760 mmol/kg]) per day on gestation days six through fifteen (Monsanto Co., 1985; U.S. EPA, 1990; EMEA, 1999). Maternal toxicity, expressed as decreased weight gain, was observed at 250 mg/kg [1.46 mmol/kg] per day and higher doses (OECD, 1994; Monsanto Co., 1985; U.S. EPA, 1990; EMEA, 1999). In one study, 750 mg/kg [4.38 mmol/kg] per day resulted in difficult labors in two animals, with 100% mortality of offspring by day three of lactation (OECD, 1994). Developmental toxicity in the form of increased resorption rates and postimplantation losses were observed at doses as low as 250 mg/kg [1.46 mmol/kg] per day (U.S. EPA, 1990). Fetal body weights were reduced at the lowest doses (50 mg/kg [0.29 mmol/kg] per day). In one study, increased unossified sternebrae were observed at 500 mg/kg [2.92 mmol/kg] per day (Monsanto Co., 1985). No observed adverse effect levels (NOAEL) and no observed effect levels (NOEL) for the F_1 generation and

Table 7. Chronic Exposure to Chloramine-T

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Dogs, beagles, age n.p., 12 M (8 test, 4 control)	Chloramine-T, purity n.p.	Infusion: 300 mg (1.07 mmol) in 200mL saline delivered slowly for 1h [sequential adm: infusion of methylene blue, sodium chloride (saline), chloramine-T, methylene blue i.v., and DL-α-tocopherol i.m.] at a rate of 3 infusions/wk for 5 wk for 2 dogs. Other 2 were observed for an additional 6 wk (not intubated during 1.v. procedure). Oral; 300 mg (1.07 mmol) in gelatin capsules 10 min before a.m. and p.m. feedings for 4 mo. In 1 dog, 1200 mg/d was given for an additional 2 mo.	Immunologically determined levels of protease inhibitor did not change. There was a treatment-related reduction in ability of serum to inhibit elastase in *in vitro* assays, suggesting an inactivation of the enzyme. Ability to inhibit trypsin was less affected. Emphysema-like alterations in lung morphology were observable. This model parallels emphysema associated with genetic α-1-proteinase inhibitor deficiency in man. Effects were transient with EIC returning to normal concentrations at 14 d.	Abrams et al. (1981)
Dog, strain and age n.p., 12 (8 test, 4 controls),sex n.p.	Chloramine-T (Purity n.p.)	Animals dosed with chloramine-T, 15 or 60 mg/kg [53 or 210 μmol/kg], i.v. 2x/wk for 17 wk50% of animals were sacrificed after 17 wk	Persistent mild or moderate anemia was observed after 17 wk. of treatment. Fibrosis at catheterized blood vessels was observed. A reduction in EIC was found in both serum and pulmonary lavage fluid. Gross pathological lung changes typical for emphysema were observed.	King et al. (1983 abstr.)

Abbreviations: a. m. = morning; d = day; EIC = elastase inhibitory capacity; i.m. = intramuscular(ly); i.v. = intravenous(ly); n.p. = not provided; p.m. = evening; wk = week(s)(ly)

Table 8. Reproductive Toxicity and Teratology of Chloramine-T and *p*-Toluenesulfonamide

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rat, Crj:CD(SD), fetus, age and number n.p., F	*p*-TSA, ,99.9% pure)	Maternal doses: 0, 120, 300, 750 mg/kg/d [0, 0.701, 1.75, and 4.38 mmol/kg/d] (dose and route n.p.)	In the high-dose group, newborns showed significant decrease in body weight and survival rate. Two of the high-dose female rats showed signs of difficult labor; all their offspring died by d 3 of lactation. Morphological observations for offspring revealed no teratogenic effect of the test substance. NOAEL for F_1 generation was 300 mg/kg [1.75 mmol/kg] under the test conditions.	Unpublished Report of Combined Repeat Dose and Reproductive Developmental Toxicity Screening Test of (specific chemical)-HPV/SIDS test conducted by MHW, cited by OECD (1994)
Rat, Charles River CD, adult,25F/dose	Santicizer 9 (mix of *o*- and *p*-TSA, percent n.p.), purity n.p.	Animals gavaged with 0, 50, 250, or 500 mg/kg/d [0, 0.29, 1.46, and 2.92 mmol/kg/d] in corn oil on GD 6 through 15	Maternal toxicity, expressed as reduced weight gain, was noted in the mid- and high-dose groups. Fetotoxicity, in terms of increased postimplantation loss, was also apparent. Treatment-related fetal body weight inhibition was noted in all treatment groups, significantly in the mid- and high-dose offspring. High-dose offspring exhibited unossified sternebrae, which correlated with fetal body weight reduction.	Monsanto Co. (1985)
Rat, strain n.p., adult, number n. p., F	Santicizer 9 (mix of *o*- and *p*-TSA, percent n.p.), purity n.p.	Animals gavaged with 0, 100, 500, 1000, 1500, or 2000 mg *p*-TSA/kg/d [0, 0.584, 2.92, 5.840, and 11.68 mmol/kg/d] on GD 6 through 15	Maternal toxicity was apparent in all but the lowest treatment groups. Developmental toxicity expressed as increased resorption rates and post-implantation losses were found in the two highest dose groups. Developmental toxicity was observed only at doses that resulted in maternal toxicity.	U.S. EPA (1990)
Rat, strain n.p., , adult, number n.p., F	TSA (68% *p*-TSA; 32% *o*-TSA)	Pregnant F dosed (oral gavage) with 0, 50, 250, or 500 mg/kg bw [0, 0.29, 1.46, or 2.92 mmol/kg bw] GD 6 to 15	Maternal weight gain was significantly reduced during the treatment period at the 250 and 500 mg/kg bw [1.46 and 2.92 mmol/kg bw] groups. There was also a dose-related increase in postimplantation loss and reduction in fetal body weight at the same doses. No teratogenic effects were observed. The NOEL established for maternal and embryotoxicity/fetotoxicity from this study was 50 mg/kg bw [0.29 mmol/kg bw].	EMEA (1999)

Table 8. Reproductive Toxicity and Teratology of Chloramine-T and *p*-Toluenesulfonamide (Continued)

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference
Rat, strain n.p., age and number n.p., M and F	*p*-TSA, purity n.p.	M exposed (oral gavage) to 0, 120, 300, or 750 mg/kg bw [0, 0.701, 1.75, 4.38 mmol/kg bw] *p*-TSA for 42 d prior to mating. F exposed at same levels, same route, from 14 d before breeding through d 3 of lactation.	A dose-related hypersalivation was observed in all treatment groups. Blood chemistry revealed increased levels of blood urea nitrogen, serum aspartate aminotransferase, and chloride in both sexes in the two highest dose groups. Increased serum alanine aminotransferase was observed at 750 mg/kg bw [4.38 mmol/kg bw]. Reduced weight gain and food consumption was observed in the highest 2 dose groups. No teratogenic effects or impaired fertility were observed. Significantly reduced neonatal survival and body weight were observed at the 750 mg/kg [4.38 mmol/kg] level.	EMEA (1999)
Rat, Crj:CD(SD), adult, 13M and 13F/group	*p*-TSA, 99.9% purity, in 5% gum Arabic solution	M exposed (oral gavage) to 0, 120, 300, or 750 mg/kg/d [0, 0.701, 1.75, 4.38 mmol/kg/d] *p*-TSA for 42 d; F exposed at same levels, same route, from 14 d prior to mating throughout gestation and d 3 lactation	The test compound affected neither mating performance nor fertility. No differences in reproductive parameters between groups, including controls, were observed. Food consumption was reduced in the mid- and high-level dose groups (F). A difficult labor was observed in two of the high-dose females. A decrease of lactation index and in litter weight was observed in the high-dose female group. The estimated dose of low concern for reproduction was calculated as 0.6 mg/kg/d [3.50 μmol/kg/d].	Unpublished Report on Acute Toxicity Screening Test of (specific chemical)-HPV/SIDS, test conducted by MHW, cited by OECD (1994)

Abbreviations: d = day(s); F = females; GD = gestation day; M = males; NOAEL = no observed adverse effect level; NOEL = no observed effect level; n.p. = not provided

maternal/embryotoxicity/fetotoxicity were estimated at 300 and 50 mg/kg [1.75 and 0.29 mmol/kg] per day, respectively (OECD, 1994; EMEA, 1999).

9.3 Carcinogenicity

No carcinogenicity studies were identified for either chloramine-T or *p*-TSA.

9.4 Initiation/Promotion Studies

No initiation/promotion studies were identified for either chloramine-T or *p*-TSA.

9.5 Anticarcinogenicity

No anticarcinogenicity studies were identified for either chloramine-T or *p*-TSA.

9.6 Genotoxicity

The impetus to perform genotoxicity testing on chloramine-T and *p*-TSA derive from several concerns. Chloramine-T is used in the cosmetic industry as an anti-microbial agent and was included in tests on 31 chemicals selected from the cosmetic guidelines of the Council of European Communities (Gocke et al., 1981). Chloramine-T has been used as a model agent for endogenously produced chloramines (*N*-Cl) produced as a result of the inflammatory process. The *N*-Cl derivatives are a class of long-lived oxidants produced by stimulated phagocytes. Other phagocyte-generated oxidants have been shown to cause genetic damage in cultured mammalian cells. The *N*-Cl derivatives may exist long enough to reach target sites and cause damage (Weitberg, 1987). Chloramine-T has been uses as surrogate for these endogenously produced chloramines.

The details of the following studies, except where noted, are presented in **Table 9**.

Several studies have been identified that investigated the potential of chloramine-T to cause mutations in prokaryotic, eukaryotic, and *in vitro* mammalian systems. Most of the assay test systems have resulted in negative results (failure to produce mutations). Anderson and Styles (1978) and Gocke et al. (1981) tested chloramine-T in the *Salmonella*/microsome assay, using strains TA98, TA100, TA1535, TA1537, and TA1538, with and without the addition of an S9 (activating) fraction. Doses per bacterial plate ranged from 4 to 3600 μg [0.01 to 12.78 μmol]. Neither study detected an increase in mutation rate in the *Salmonella* system. Chloramine-T, tested in *Drosophila melanogaster* (sex-linked recessive lethal mutation), was also negative. *Drosophila* were exposed to chloramine-T (25 mM [7.0 mg/mL]) through feeding in 5% sucrose. Chloramine-T (70 or 35 mg/kg [0.25 or 0.12 mmol/kg]) also failed to produce an increase in micronucleated polychromatic erythrocytes when tested in the micronucleus test (Gocke et al., 1981).

Weitberg (1987) examined the potential for chloramine-T to produce sister chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells. Unlike the other *in vitro* assays, a statistically significant dose-dependent increase in SCE over a dose range of 10^{-8} M to 10^{-5} M [0.003 to 2.8 μg/mL] chloramine-T was observed. Addition of methionine (10^{-5} M) to the incubation mixture reduced, but did not abolish, the increase in SCE, probably by reducing chloramine-T.

Table 9. Genotoxicity Studies of Chloramine-T and *p*-Toluenesulfonamide

Test System or Species, Strain, Age, Number, and Sex of Animals	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Comments	Reference
Prokaryotic Systems						
Salmonella. typhimurium strains TA1535 (2 different strains, TA100, TA1538; TA98, and TA 1537	Increase in revertants due to mutations	+/-	Chloramine-T, purity n.p.	At least 5 doses, usually up to 3600 µg/plate [12.78 µmol/plate] were assayed, though the specific doses are n.p.	No increase in revertants was observed for any of the doses of chloramine-T tested.	Gocke et al. (1981)
S. typhimurium strains TA1535, TA1538, TA98, TA100	Increase in revertants due to mutations	+	Chloramine-T, purity n.p.	4, 20, 100, 500, or 2500 µg/plate [0.01, 0.071, 0.355, 1.78, or 8.875 µmol/plate]	Chloramine-T was negative (failed to significantly increase revertants) with all tested strains.	Anderson and Styles (1978)
S. typhimurium strains TA98, TA100, TA1535, TA1537; *Escherichia coli* WP2 ultra violet radiation A	Increase in revertants due to mutations	+/-	*p*-TSA in DMSO, purity n.p.	0, 312.5, 625, 1250, 2500, 5000 µg/plate [1.825, 3.65, 7.300, 14.60, and 29.20 µmol/plate]	Mutagenic effects were not observed under the test conditions. Minimum toxic concentration observed for bacteria was 5000 µg/plate [29.20 µmol/plate] with and without activation.	Unpublished report on Mutagenicity Test conducted by Ministry of Health and Welfare, Japan; cited by OECD (1994)
S. typhimurium strains TA1530, TA1535, TA1538, TA98, and TA100	Increase in revertants due to mutations	+	*p*-TSA, purest grade commercially available	Doses n.p.	Plate incorporation tests were performed in triplicate, mixing dilutions of test material (0.1 mL) with bacterial cultures (1 – 8 x10^7 cells) with broth and S9 mix. No direct mutagenic effects were observed. *p*-TSA was cytotoxic to TA1538 and TA98.	Poncelet et al. (1980)
S. typhimurium strains TA1535, TA100, TA1537	Increase in revertants due to mutations	+/-	*p*-TSA (form, source, and purity n.p.)	No less than 2500 µg/plate [14.60 µmol/plate]	No mutagenic activity was observed.	Herbold (1981)
S. typhimurium – TA98, TA100, TA1535, TA1537 and TA1538.	Increase in revertants due to mutations	+/-	*p*-TSA, purity n.p.	Doses of up to 70 µmol/plate [12 mg/plate] were used.	*p*-TSA induced revertants in tester strain TA98 only, and only with S9 activation. The action of *p*-TSA was considered weak but significant and reproducible.	Wild et al. (1980)

Table 9. Genotoxicity Studies of Chloramine-T and *p*-Toluenesulfonamide

Test System or Species, Strain, Age, Number, and Sex of Animals	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Comments	Reference
Lower Eukaryotic Systems						
Drosophila melanogaster (Berlin K [wild-type] and Basc strains)	Sex-linked recessive lethal mutations	-	Chloramine-T, purity n.p.	25 mM [7.0 mg/mL] chloramine-T was applied by the adult feeding method in 5% saccharose.	Approximately 1200 X-chromosomes were tested/experiment in each of 3 successive broods (3-3-4 d). F_2 progeny cultures with 2 or fewer wild-type males were routinely retested in the F_3 generation for confirmation of X-linked recessive lethal mutations. Mosaics were not counted, but "clusters" of 2 were included. Chloramine-T did not produce an increase in sex-linked recessive lethals relative to control groups.	Gocke et al. (1981)
D. melanogaster	Sex-linked recessive lethal mutations	-	*p*-TSA purity n.p.	n.p.	Positive mutagenic effects were observed under the test conditions.	Eckhardt et al. (1980)
D. melanogaster (Oregon-K [wild type] and Basc strains)	Sex-linked recessive lethal test	-	*p*-TSA, purity n.p.	Adult flies injected abdominal with about 0.2 µL of a 5 mM [860µg/mL] solution (~0.170 µg)	There were no positive effects observed under the test conditions.	Kramers (1977)
D. melanogaster (Berlin K [wild-type] and Basc strains)	Sex-linked recessive lethal test	-	*p*-TSA, purity n.p.	Adult flies through the diet at 2.5 mM [430 µg/mL].	A significant increase in the frequency of recessive lethal mutations in brood 1, corresponding to mature sperm, was observed.	Wild et al. (1980)

Table 9. Genotoxicity Studies of Chloramine-T and *p*-Toluenesulfonamide (Continued)

Test System or Species, Strain, Age, Number, and Sex of Animals	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Comments	Reference
Mammalian Systems *In Vitro*						
CHO cells	SCE	-	Chloramine-T, purity n.p.	Cell cultures were exposed to Chloramine-T (10^{-8} to 10^{-5} M [0.003 to $2.9X10^{-6}$ µg/mL]) for 30 h.	Statistically significant ($p<0.0005$) dose-dependant increase in SCEs was observed. Combined exposure to chloramine-T and methionine (10^{-5} M) diminished but did not abolish the effect by reducing the chloramine-T to the parent amine.	Weitberg (1987)
CHL cells	Cell or cellular change	+/-	*p*-TSA in DMSO, purity 99.9%	Without S9: 0, 0.33, 0.65, 1.30 mg/mL [0, 1.93, 3.80, 7.59 mM]; with S9: 0, 0.43, 0.85, 1.70 mg/mL [0, 2.5, 5.0, 9.9 mM].	The test material was classified as "negative" for chromosomal aberrations, under the test conditions. The lowest concentration producing cell toxicity was >2.0 mg/mL [11.68 mM] with metabolic activation and 2.0 mg/mL [11.68 mM] without metabolic activation.	Unpublished report on mutagenicity Test conducted by the Ministry of Health and Welfare (MHW), Japan; cited by OECD (1994)
CHO-K1 cells	CA induction	-	*p*-TSA, purity n.p.	Cells were treated with 14, 200, and 400 µg/mL [0.082, 1.17, 1.34 mM] *p*-TSA for 24 h.	Untreated cells were used as a negative control; sodium saccharine treated cells were the positive controls. There was no significant difference in the frequency of aberrant cells between treatment groups and controls. The sodium saccharine gave a positive response.	Masubuchi (1978a abstr)
RSa human cell line	Development of ouabain resistance	-	*p*-TSA , purity n.p.	900 and 1800 µg/mL [5.26 and 10.51 mM], for 24 h	$8x10^5$ cells were treated to *p-TSA* in serum-free medium for 24 h. Cells were allowed 48 h for mutant expression. The fraction of mutant cells was assayed by seeding $5X10^4$ cells/100-mm culture dish (6 dishes per time point) in ouabain-containing medium. Plating efficiency was also determined. Mutant frequency was calculated and expressed as mutants/10^5 colony-forming cells. No increase in ouabain resistance was observed in *p-TSA* treated cells, relative to controls, and UV- and sodium saccharin-treated cells.	Suzuki and Suzuki (1988)

Table 9. Genotoxicity Studies of Chloramine-T and *p*-Toluenesulfonamide (Continued)

Test System or Species, Strain, Age, Number, and Sex of Animals	Biological Endpoint	S9 Metabolic Activation	Chemical Form and Purity	Dose	Comments	Reference
Mammalian Systems *In Vivo*						
Mouse, NMRI, age n.p., 4-8 mice/group, M and F	PCE induction	na	Chloramine-T, purity n.p.	Animals dosed (i.p.) with chloramine-T (35 or 70 mg/kg [0.12 or 0.25 mmol/kg] at 0 and 24 h	Bone marrow smears were prepared at 30 h. 1000 polychromatic erythrocytes were scored per mouse. Chloramine-T treatment failed to result in an increase in micronucleated polychromatic erythrocytes (1.8% and 2.0% for 70 and 35 mg/kg [0.25 and 0.12 mmol/kg], respectively, compared to 1.5% in the control group).	Gocke et al. (1981)
Mouse, NMRI, adult, number n.p., M and F	MN induction	na	*p*-TSA, (purity n.p.	n.p.	There were no effects observed under the test conditions.	Eckhardt et al. (1980)
Mouse, strain, age, number, and sex n.p.	MN induction	na	*p*-TSA, (purity n.p.	*p*-TSA administered both orally and i.p. (doses n.p.)	*p*-TSA was negative in this assay.	Wild et al. (1980)

Abbreviations: CA = chromosomal aberrations; CHL = Chinese hamster lung; CHO = Chinese hamster ovary; d = day; F = female(s); h = hour(s)(ly); M = male(s); MN = micronucleus; na = not applicable; n.p. = not provided; PCE = polychromatic erythrocyte; SCE = sister chromatid exchange; UV = ultraviolet

p-TSA has undergone more extensive genotoxicity testing (studies not included in table), as it was found as a contaminant of sodium saccharin produced by the Remsen and Fahlberg process (Eckhardt et al., 1980; IARC, 1999). Genotoxicity studies using saccharin have shown increased SCE in CHO cells (Masubuchi et al., 1977a, b), weak mutagenic response in mouse lymphoma (L5178Y) cells (Clive et al., 1979), and an induction of unscheduled DNA synthesis (UDS) (Ochi and Tonomura, 1978; all cited by Suzuki and Suzuki, 1988). Masubuchi et al. (1977a, b) found that the impurities in saccharin were ineffective in producing mutations (cited by Suzuki and Suzuki, 1988).

As with chloramine-T, *p*-TSA has been assayed in a variety of genotoxicity studies, with the majority producing negative results. *p*-TSA was tested in the Ames test with and without the addition of an S9 activating system. In all the studies identified, *p*-TSA, alone or with an activating system, failed to produce revertants (mutations). *Salmonella* tester strains used included TA98, TA100, TA1530, TA1535, TA1537, and TA1538. A single *Escherichia coli (*strain WPZuvrA) was included in one study (Poncelet et al., 1980; Herbold and Lorke, 1980; Herbold, 1981; OECD, 1994). Wild et al. (1980) reports weak mutagenic effects for *p*-TSA in a modified *Salmonella*/microsome assay (additional details not provided).

p-TSA also failed to induce mutations in the two mammalian systems identified. A single assay testing *p*-TSA (0.33 to 2.70 mg/mL [1.9 to 15 mM]) with and without an S9 fraction in Chinese hamster lung CHL cells was classified as negative for chromosomal aberrations under the conditions tested (OECD, 1994). Masubuchi (1978a abstr.) showed a lack of mutagenicity in CHO-K1 cells treated with 14 to 400 μg/mL [82 μM to 1.34 mM] *p*-TSA. *p*-TSA was tested in a second cell line, RSa. This cell line is derived from embryonic cells and is sensitive to UV-induced mutagenesis. RSa cells exposed to *p-TSA* (900 or 1800 μg/mL [5.26 or 10.51 mM]) failed to demonstrate an increase in mutagenic response, as demonstrated by increased resistance to ouabain toxicity (Suzuki and Suzuki, 1988). *In vivo* genotoxicity studies (micronucleus assay) with *p*-TSA, negative results were also obtained. This study was also negative (Eckhardt et al., 1980).

Studies identified testing *p*-TSA in the *Drosophila* sex-linked recessive assay had equivocal results. Eckhardt et al. (1980) and Wild et al. (1980) report positive mutagenic effects for *p*-TSA in the *Drosophila assay*. A significant increase in the frequency of recessive lethal mutations was seen in mature sperm given 2.5 mM [430 μg/mL]. Kramers (1977) indicated that *p*-TSA failed to produce mutations when dosed either by abdominal injection (0.2 μL of a 2% solution [116mM] or 4 μg [0.02 μmol] in saline).

When tested in the Ames assay (tester strains TA98, TA100, TA1535, TA1537, and TA1538), TSFR failed to induce mutations (study details not provide) (Elder, 1986).

9.7 Cogenotoxicity

No cogenotoxicity studies were identified for either chloramine-T or *p*-TSA.

9.8 Antigenotoxicity

No antigenotoxicity studies were identified for either chloramine-T or *p*-TSA.

9.9 Immunotoxicity

No immunotoxicity studies were identified for either chloramine-T or *p*-TSA.

9.10 Other Data

Effects on Enzymes: The effects of *in vitro* treatment of various biological components with chloramine-T have been studied. After observing that ^{125}I-labeled rat serum albumin moved more easily from the intravascular to intraperitoneal compartments than ^{125}I-labeled human serum albumin, Gamble et al. (1982 abstr.) discovered that plasma clearance was directly related to the chloramine-T albumin ratio used during the iodination process. It was hypothesized that the change in mobility was due to changes in the physical characteristics of the molecules. The investigators examined spectrophotometric absorption at 280 nm and the viscosity of the solutions after clearing them of additional chloramine-T through dialysis. Although no effect was found on viscosity, there was a significant change in the spectral characteristics of the serum albumin. Human serum albumin was capable of binding appreciable amounts of chloramine-T, which apparently altered its physical properties.

Borges and Kouyoumdjian (1992) found that treatment of rat plasma-kallikrein with chloramine-T resulted in a dose-dependent impairment of hepatic clearance. Perfusion of the liver with chloramine-T prior to administration of plasma-kallikrein had similar results. The authors speculate that chloramine-T impairs receptor mediated endocytosis of plasma-kallikrein by the liver. Neither the amidolytic activity nor the molecular weight of the plasma-kallikrein was affected by the chloramine-T treatment.

Activated polymorphonuclear leukocytes (PMNs) release lysosomal proteinases (elastase, collagenase, prothrombinase, and urokinase) into inflamed tissues. These enzymes, in concert with thrombin and plasmin, break down connective tissues in the zone of inflammation. Leukocytes also secrete oxygen radicals and myeloperoxidase creating a zone of uncontrolled oxidation in the microenvironment of the leukocyte. This oxidation zone can be artificially created with combinations of chemicals, including *N*-chlorosuccinimide and chloramine-T. This combination also results in the production of HOCl. Stief and Heimburger (1988) have shown that serine α_1-PI and plasminogen-activator inhibitor (PAI-1) both lose their inhibitory action toward their target enzymes under these conditions. Other serine protease inhibitors impacted by chloramine-T include antithrombin III (AT III), α_2-plasmin inhibitor (α_2-PI), and α_1-PI. The reaction with chloramine-T is specific, as elastase, plasmin, thrombin, and C1-esterase is unaffected.

The major circulating elastase inhibitor, α_1-PI has been shown to susceptible to inactivation by oxidation of methionine residues to methionine sulfoxide at active sites. Modification of tyrosine residues of α_1-PI also results in a decrease in EIC *in vitro*. A variety of oxidizing systems, such as myeloperoxidase, hydrogen peroxide, and superoxide, and chloramine-T have been found effective in oxidizing α_1-PI (Williams et al. 1986). Mihajlovic et al. (1993) examined the reactivity of methionine residues in equine growth hormone towards chloramine-T. At 20-fold molar excess of chloramine-T over methionine residues, full oxidation of the four available residues was achieved. However, neither protein conformation nor binding capacity to specific receptors was affected, even at full oxidation. The reactivity of chloramine-T towards

triosephosphate isomerase from rabbit and yeast was also compared (Zubillaga et al. 1994). The rabbit isomerase has five cysteine (Cys) and two methionine (Met) residues, while the yeast isomerase has only two Cys residues. The rabbit isomerase was more sensitive to chloramine-T oxidation than the yeast isomerase. Conditions resulting in 100% inactivity of rabbit isomerase only produced a 50% inactivation of yeast isomerase. Chloramine-T caused the oxidation of the Cys residues and formation of catalytically active acidic isoform. Oxidation of Cys 126 (yeast) did not abolish catalysis. Ratios of 50 chloramine-T/monomer resulted in extensive alterations in both tertiary and secondary structures, along with formation of stable dimers in the rabbit, but not the yeast, isomerase.

Williams et al. (1986) investigated the effect of chloramine-T on the catalytic activity of porcine pancreatic elastase (PPE) and human leukocyte elastase (HLE). They also examined the impact of chloramine-T treatment on EIC of hamster, rat and human serums and purified α_1-PI. Both PPE and HLE were inhibited in a concentration-dependent fashion, by chloramine-T at concentrations ranging from $4X10^{-5}$ to $4X10^{-2}$ M [11.27 μg/mL to 11.3 mg/mL]. The specificity of this reaction was demonstrated by the lack of an inhibitory effect of trypsin at chloramine-T concentrations ranging from $4X10^{-7}$ to $4X10^{-2}$ M [0.11 ng/mL to 11.3 mg/mL]. Rat and human serum behaved similarly, with the exception that human serum was somewhat more resistant to the inhibitory effects of chloramine-T on PPE than on HLE. The ability of chloramine-T treated rat serum to inhibit elastases diminished equally for PPE and HLE with oxidant pretreatment. Only in the hamster serum was the ability to inhibit the elastases specific. The ability of oxidized hamster serum to inhibit HLE was diminished in a concentration-dependent fashion, while the ability to inhibit PPE was unaffected. When the hamster and human serums were fractionated, it was found that almost all elastase inhibitory activity was found in a single peak for human plasma; in the hamster plasma, activity was found in two peaks. The first peak, eluting near the void volume, had a slight preferential inhibition of PPE, and the second peak inhibited predominantly HLE.

Another enzyme studied for potential interactions with endogenous N-chloramines, using chloramine-T as a surrogate, was poly-$(ADP\text{-}ribose)_n$ transferase (ADPRT). This as a nuclear enzyme, which is activated by DNA strand breaks and participates in DNA repair. ADPRT contains two zinc fingers with three Cys residues each in each finger. Because of the presence of the Cys residues, ADPRT, and therefore DNA repair involving ADPRT, is sensitive to reduction/oxidation balance in the cell. Pero et al. (1996) investigated the effect of physiologically relevant doses chloramine-T on DNA excision repair and found that both DNA repair (60% to 80% inhibition at 50 to 100 μM chloramine) and immune cell responsiveness (86% to 95% inhibition at 100 to 200 μM chloramine-T) were compromised by treatment with chloramine-T

<u>Animal Model for Human α_1-Proteinase Inhibitor:</u> Chloramine-T has been used in the development of an animal model for chronic human α_1-PI deficiency. α_1-PI plays a critical role in modulating the activity of elastase in lung tissue seen in emphysema (Lungarella et al., 1983). It has been hypothesized that the pathogenesis of emphysema involves both the release of endogenous proteases from PMN or leukocytes into the alveolar spaces or interstitium, and

reduced regulation by proteinase inhibitors of these proteases. Hence, excess in the available proteases relative to their proteinase inhibitors would lead to lung damage seen in pulmonary emphysema. Abrams et al. (1980) noted that dog serum treated with chloramine-T rapidly and selectively depleted its ability to inhibit PPE or dog-neutrophil elastase. Trypsin inhibitory capacity was not affected by chloramine-T treatment. Furthermore, reversal of oxidative inhibition was achieved through treatment with dithiothreitol.

Abrams et al. (1981) examined the possibility of developing an animal model for chronic human α_1-PI deficiency by dosing beagles with chloramine-T for extended periods of time (see Section 9.1.5). Chronic exposure to chloramine-T decreased the EIC to a level that, functionally, resembled the human disease state. Lungarella et al. (1983) and Williams et al. (1986) both attempted to develop functional animal model for human α_1-PI deficiency associated with emphysema. Lungarella et al. (1983) found that *in vivo* treatment of rats reduced the serum EIC 28 to 35% of initial values within one to three hours of treatment. EIC returned to normal within nine hours, demonstrating a relatively short half-life (1.45 hours) for serum elastase inhibition, consistent with rapid synthesis of protein. Similar effects were observed in hamsters (Williams et al., 1986), see Section 9.1.3), where chloramine-T treatment (i.p.) resulted in serum with a reduced the ability to inhibit HLE, significantly three to four hours post-treatment, with a return to control values within eight hours. The ability to inhibit PPE was enhanced, relative to control serum. Both authors concluded that the transient nature of the *in vivo* effects precluded the usefulness of these as animal models.

<u>Effects on Sodium Channels:</u> Studies of voltage-gated sodium channels showed that chloramine-T abolishes fast inactivation while continuing to accelerate slow inactivation in both mutant (I-S6 segment of mu1 Na^+ channel, N434A) and wild-type channels, demonstrating that N434 of mu1 Na^+ channel is also critical for slow inactivation, possibly analogous to the "C-type" inactivation in Shaker K^+ channels (Wang and Wang, 1997).

<u>Wound Healing:</u> Several studies were identified that investigated the effects of chloramine-T on wound healing. Brennan et al. (1986) compared the effects of chloramine-T and chlorhexidine with saline on 10 mm skin defects in Sprague-Dawley rats. Chloramine-T significantly delayed the production of collagen and prolonged the acute inflammatory response relative to saline. It was concluded that antiseptics might affect wound healing by secondary intention. Goetz et al. (undated abstr.) exposed rats with identical full thickness wounds by immersing in 150 and 250 ppm [533 and 888 μM] chloramine -T baths in an attempt to mimic the effects chloramine-T whirl pool treatments on wound healing. In a similar study using guinea pigs with full thickness wounds infected with *Pseudomonas aeruginosa.* The authors found that chloramines-T was an effective disinfectant in water, though it did not affect the rate of wound healing (Henderson et al., 1989). In an early rabbit study, it was concluded that chloramine-T (2% solution [71 mM]), while less irritating to skin than hypochlorite, it was also less effective in cleansing of necrotic tissue (Austin and Taylor, 1918). More recently Niedner (1997) indicated that chloramine-T does not have as strong an inhibitory effect as the triphenylmethane dyes. Specifically, chloramine-T showed only a minor inhibitory effect on the granulation layer, as measured by thickness, when compared to brilliant green, chlorhexidine, and gentian violet B. In an *in vitro* study comparing the cytotoxicity of 8-quinolinol and natamycin with chloramine-T treatment on

pig hepatocytes, chloramine-T was less cytotoxic than either of the other two chemicals (Martinez-Larranaga et al., 2000).

Neurotoxicity: Chloramine-T was used to mimic the effects of free radicals and active oxygen compounds implicated in brain ischemia and head trauma. Previous studies have shown that free radicals produce both synaptic and postsynaptic damage in guinea pig hippocampal brain slices. Chloramine-T (25 to 500 μM [7.0 to 140.8 μg/mL]) decreased both the population spike and population postsynaptic potential. However, the ability of the population postsynaptic potential was not impaired by the treatment. These studies suggest that oxidation reactions account for the synaptic component of free radical-induced damage in the nervous system but not the postsynaptic effects (Pellmar and Neel, 1989).

Interactions: A single case study was identified discussing the potential mechanism of chloramine (ammonia chloramine) generated by the combination of hydrochloric acid with sodium hypochlorite. The patient ingested this compound while cleaning a sewage tank. The eventual outcome of this exposure was blindness, caused by methyl chloride potentiated by the co-generated chloramine. The authors hypothesized that the ammonium chloramine exacerbated the toxic symptoms after exposure to methyl chloride by reducing formate oxidation by N^{10}-formyl-tetrahydrofolate dehydrogenase. Increased levels of formate may be responsible for the blindness reported in this study (Minami et al., 1993).

10.0 Structure-Activity Relationships - *o*-Toluenesulfonamide [CAS No. 88-19-7]

o-Toluenesulfonamide (*o*-TSA) is the major contaminant in saccharin produced by the Remsen-Fahlberg process, but not the Maumee process (Stavri_ and Klassen, 1975; cited by Wild et al., 1980). Not more than 0.0025% (25 mg/kg [0.146 mmol/kg]) of total toluenesulfonamides are allowable in saccharin to meet the requirements of the Food Chemicals Codex (NAS, 1996; cited by IARC, 1999). Numerous studies have been conducted examining the toxicities of *o*-TSA.

ADME: Renwick et al. (1978; cited by IARC, 1999) studied the excretion rates of radiolabeled *o*-TSA in both Wistar rats (females) and humans. Rats were dosed with 20, 125, and 200 mg/kg [0.12, 0.730, and 1.17 mmol/kg] radiolabeled *o*-TSA, and urine samples were collected for 48 hours. Excretion of radioactivity was dose-dependent with 79% of the low dose recovered within the first 24 hours. As doses increased, however, less radioactivity was recovered at 24 hours (58% and 36% for 125 and 200 mg/kg [0.730 and 1.17 mmol/kg], respectively). Cumulative recovery in the urine at 48 hours was 86%, 72%, and 69% for the low-, mid-, and high-dose groups, respectively. The major urinary metabolites were 2-sulfamoylbenzyl alcohol and its sulfate or glucuronic acid conjugates (80%), *N*-acetyltoluene-2-sulfonamide (6%), saccharine (3%), and 2-sulfamoylbenzoic acid (2%) (cited by IARC, 1999). *o*-TSA was metabolized predominantly by aromatic ring hydroxylation, producing a phenol (both free and as a glucuronic acid conjugate) as the major metabolite (60-70 % of administered dose). Less than 3% was oxidized to 2-sulphamoylbenzoic acid (Ball et al., 1977 abstr.)

At low oral doses (0.2 to 0.4 mg/kg bw [1.2 to 2.3 μmol/kg bw]), humans excreted *o*-TSA more slowly than the rats. On average, 56% of the radioactivity was recovered in the 24-hour urine. At 48 hours, cumulative recovery was at 90%. The primary human urinary metabolites were 2-sulfamoylbenzoyl alcohol (unconjugated, 7%; conjugated with glucuronic acid, 11%; conjugated

with sulfate, 20%), saccharin (35%), 2-sulfamoylbenzoic acid (4%), and *N*-acetyltoluene-2-sulfonamide (2%) (Ball et al., 1978; cited by IARC, 1999). In a similar study, it was demonstrated that 50% of an administered dose of *o*-TSA was excreted in the urine as *o*-sulfamoylbenzoic acids (Minegishi et al., 1972; cited by HSDB, 2001c; cited by IARC, 1999).

Acute Toxicity: Reported LD_{50}'s for *o*-TSA in rats ranged from about 2 g/kg [11.68 mmol/kg] (Schmähl, 1978; cited by IARC 1980) to 4870 mg/kg [28.44 mmol/kg] (RTECS 1998). *o*-TSA (100 mg [0.584 mmol]) applied to the eyes of rabbits was rated as a moderate irritant at the 24 hour endpoint (RTECS, 1998).

Reproductive and Developmental Toxicity: In a two-generation study of male and female CD rats exposed to dietary *o*-TSA (2.5 to 250 mg/kg bw [14.6 to 1460 μmol/kg bw] daily), no treatment-related effects were observed on longevity. Of the 378 total rats included in the study, six developed benign bladder tumors, one in a F_0 control male and one each in the F0 2.5 and 250 mg/kg bw [1460 μmol/kg bw] dose groups. One F_0 female in the 2.5 mg/kg bw [14.6 μmol/kg bw] group, developed a bladder tumor. The remainders of the bladder tumors were in the 2.5 mg/kg bw [14.6 μmol/kg bw] F_1 female dose group (Arnold et al. 1980; cited by IARC, 1999).

A six-generation study was performed in Swiss mice, dosed at 0.2 or 0.5 saccharin (containing 0.5% *o*-TSA) in the diets. No effects were observed on weight gain or histopathological alterations that could be related to the treatments (Kroes et al., 1977; cited by IARC, 1980). Saccharin (0.3 and 3% in the diet) produced morphological changes in the eye lens and increased embryonic mortality in offspring of pregnant Wistar rats. It was hypothesized that the anomalies were due to the impurities found in saccharin produced by the Remsen-Fahlberg process. When the contaminants were tested separately, many produced the ocular changes. *o*-Sulphobenzoic acid was the most active. *o*-TSA was almost inactive in producing the anomaly. In addition, a few of the ocular abnormalities occurred in the control group (Lederer, 1977; cited by IARC, 1980).

Dose-related incidences in bladder calculi were found in the offspring of rats dosed with up to 250 mg/kg/d [1460 μmol/kg/d] *o*-TSA throughout gestation and lactation. Sacrifice time-points were 8, 21, and 105 days. Eight-day old pups also had bladder lesions. *o*-TSA predisposed neonatal animals to urolithiasis and/or bladder lesions (Arnold et al., 1980; cited by IARC, 1999). The lowest toxic dose that resulted in reductions in growth parameters in newborn rats was 4300 mg/kg/d [28.44 mmol/kg/d], dosed throughout gestation and through weaning at 21 days postpartum. In the mouse, 1g/kg [6 mmol/kg] orally was sufficient to have an effect on fertility (RTECS, 1998a).

Mutagenesis: *o*-TSA has been tested in numerous predictive tests for mutagenicity. The results have been somewhat equivocal. In the *Salmonella*/microsome assay, several studies report negative results (Stoltz et al., 1977; Ashby et al., 1978; Jagannath and Brusick, 1978; all cited by IARC, 1980; Poncelet, 1979), with and without a metabolic activating system, while two studies indicate positive responses. Eckhardt et al. (1980) found that a modified *Salmonella* assay gave weak mutagenic effects. Mutation rates were doubled in TA98 at very high doses (up to 12 mg/plate [70 μmol/plate]) in the presence of an S9 fraction. Gene conversion did not occur, with

or without an activating system, in *Saccharomyces cerevisiae* (D4 strain) (Jagannath and Brusick, 1978; cited by IARC, 1980).

Results in *Drosophila* are also equivocal. *o*-TSA (0.2 µL or feeding 5 mol [856 mg/mL]) did not increase the incidence of sex-linked recessive lethal mutations (IARC, 1980). Kramers (1977) reported that *o*-TSA did not show a mutagenic response, or if it did, it was only marginal. However, in a larger study, statistically significant doubling of frequencies occurred after three days' feeding of 0.05% [2.9 mM] solution of *o*-TSA (IARC, 1980). Weak mutagenic effects were reported by Eckhardt et al. (1980), while Wild et al. (1980) reported significant increases in the frequency of recessive lethal mutations in brood one, corresponding to the mature sperm.

In mammalian systems, *o*-TSA was found negative in the micronucleus test (Wild et al., 1980), in CHO-K1 (Masubuchi, 1977a abstr.; Masubuchi, 1978b; both cited by IARC, 1980), and in BHK 21/CL 13 cells (Ashby et al., 1978; cited by IARC, 1980). *o*-TSA was found to produce specific locus mutations in embryonal prepigment cells in the mammalian spot test (Fahrig, 1978; cited by Wild et al., 1980).

Carcinogenicity: Sprague-Dawley rats were given diets containing 0, 20, or 200 mg/kg bw [0, 0.12, or 1.17 mmol/kg bw] *o*-TSA per day over a lifetime. The average survival rates were 700 days (controls), 770 days (low-dose group), and 840 days (high-dose group). Lymphosarcomas were observed in all dose groups. In the high dose group, one of 76 animals had carcinomas of the bladder and four of 76 animals had papillomas of the bladder papillomas. In the low-dose group, three of 75 animals developed papillomas of the bladder after 539, 766, and 873 days. However, the incidence of malignant tumors was no different in the treated groups than in the control groups (Schmähl, 1978; cited by IARC, 1999). Rats receiving 0.1% [5.8 mM] *o*-TSA in their drinking water or 90 mg/kg [0.53 mmol/kg] in their diets for two years showed no difference in overall tumor incidence between the control and test groups. No bladder tumors were observed in any group, though a mild diffuse urothelial hyperplasia was found in one of 50 rats. RTECS (1998a) classified *o*-TSA as an equivocal tumorigenic agent, based on a 96-week oral dosing study in rats resulting in both leukemia and kidney tumors at 13g/kg [76 mmol/kg] (details not provided). In a single initiation/promotion study, rats were dosed with MNU (0.15 mL saturated solution, intravesicular) two weeks prior to exposure to pure *o*-TSA (0.08 mg/kg [0.47 µmol/kg] in the diet or 0.1% [5.8 mM] in the drinking water) for two years with no differences in survival rates or overall tumor incidence. MNU alone resulted in 27 and 35% incidence of neoplasia and hyperplasia of the bladder, respectively (Hooson et al., 1980; cited by IARC, 1999).

11.0 Online Databases and Secondary References

11.1 Online Databases

Chemical Information System Files
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files
DIOGENES (Chemical Economics Handbook

STN International Files

AGRICOLA	CANCERLIT	IPA	Registry
BIOSIS	EMBASE	LIFESCI	RTECS
BIOTECHNO	ESBIOBASE	MEDLINE	TOXLINE
CABA	HSDB	NIOSHTIC	

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

In-House Databases
CPI Electronic Publishing Federal Databases on CD
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

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Units and Abbreviations

°C = degrees Celsius

μg/L = microgram(s) per liter

μg/m^3 = microgram(s) per cubic meter

μg/mL = microgram(s) per milliliter

μM = micromolar

ACGIH = American Conference of Governmental Industrial Hygienists

bw = body weight

CNS = central nervous system

EPA = Environmental Protection Agency

F = female(s)

g = gram(s)

g/mL = gram(s) per milliliter

h = hour(s)

HD = high dose

HSDB = Hazardous Substances Data Bank

i.p. = intraperitoneal(ly)

kg = kilogram(s)

L = liter(s)

lb = pound(s)

LC = liquid chromatography

LC_{50} = lethal concentration for 50% of test animals

LD_{50} = lethal dose for 50% of test animals

LD = low dose

LOD = limit of detection

M = male(s)

MD = mid dose

mg/kg = milligram(s) per kilogram

mg/m^3 = milligram(s) per cubic meter

mg/mL = milligram(s) per milliliter

min = minute(s)

mL/kg = milliliter(s) per kilogram

mm = millimeter(s)

mM = millimolar

mmol = millimole(s)

mmol/kg = millimoles per kilogram

mo = month(s)

mol = mole(s)

mol. wt. = molecular weight

NIEHS = National Institute of Environmental Health Sciences

NIOSH = National Institute for Occupational Safety and Health

NOEL = no observable effect level

nm = nanometer(s)

n.p. = not provided

OSHA = Occupational Safety and Health Administration

PEL = permissible exposure limit

ppb = parts per billion

ppm = parts per million

p.o. = peroral(ly), *per os*

REL = relative exposure limit

s = second(s)

s.c. = subcutaneous(ly)

STEL = short-term exposure limit

TSCA = Toxic Substances Control Act

TWA = time-weighted average

USEPA = U.S. Environmental Protection Agency

wk = week(s)

yr = year(s)