NATIONAL TOXICOLOGY PROGRAM

EXECUTIVE SUMMARY OF SAFETY AND TOXICITY INFORMATION

HALAZONE

CAS Number 80-13-7

October 4, 1991

Submitted to:

NATIONAL TOXICOLOGY PROGRAM

Submitted by:

Arthur D. Little, Inc.

Board of Scientific Counselors Draft Report

TABLE OF CONTENTS

OVERVIEW[1]

Nomination History: *Halazone was nominated for toxicity and carcinogenicity testing by the National Institute of Environmental Health Sciences (NIEHS) in 1987. The nomination was based on the lack of chronic toxicity data, positive mutagenicity data, and the potential for high consumer exposure to halazone from its use as a water disinfectant.*

Chemical and Physical Properties: *Halazone is a white powder or crystalline solid with a chlorine- or chloroform-like odor and a melting point of 213.0^{o}C (415.4^{o}F). This compound is slightly soluble in water and is soluble in alcohol, glacial acetic acid, alkali hydroxides and alkali carbonates. Halazone decomposes at ~195^{o}C , emitting chlorine and nitrous and sulfur oxides, and hydrolyzes to yield hypochlorous acid and chlorine gas.*

Production/Uses/Exposure: *Halazone is not listed in the United States International Trade Commission's Synthetic Organic Chemicals or in SRI's Chemical Economics Handbook. No production data were available in the public file of the EPA TSCA Inventory. Halazone is used for the extemporaneous disinfection of drinking water. In addition, halazone has been patented for use as an ingredient in contact lens cleaning solutions, as a disinfectant for solid biological wastes, and for determining the amount of iodine in fats and oils.*

No data concerning human exposure to halazone in the workplace were available from the National Occupational Exposure Survey (NOES). OSHA has not established a PEL, ACGIH has not recommended a TLV, and NIOSH has not established a REL for halazone .

Toxicological Effects:

Human: *Halazone caused dermatitis, rhinitis, conjunctivitis, and bronchitis as well as asthmatic symptoms and sensitization among workers exposed to this compound. No data were found on the prechronic, chronic, carcinogenic, reproductive, or teratogenic effects of halazone in humans.*

Animal: *Halazone was metabolized to p-sulphonamidobenzoic acid in rabbits. In an acute toxicity study, an oral LD_{LO} for halazone was found to be 1.0 g/kg in rats, and a dose of 3.5 g/kg caused death in 100% of the rats tested. Lesions of the gastric mucosa were observed at necropsy. Rats administered halazone by intravenous injection were observed to have dyspnea. Necropsy revealed pulmonary congestion and edema. In these rats, an intravenous LD_{LO} was found to be 300.0 mg/kg, and a dose of 800 mg/kg caused death in 100% of the animals studied. Halazone has been found to be a strong inhibitor of sodium currents in myelinated nerve fibers of the frog.*

Rabbits administered oral doses of halazone for 20-29 days exhibited decreased hemoglobin levels, urine albumin, and abnormal liver function. One animal had slight centrolobular atrophy and fatty degeneration. Prechronic halazone administration for 80 days in the feed of rats caused retarded growth, decreased food consumption, and premature death.

No studies were found on the chronic toxicity, carcinogenicity, or the reproductive and teratogenic effects of halazone in animals.

Genetic Toxicology: *Halazone has been found to be mutagenic in Salmonella typhimurium strain TA100 in the presence and absence of metabolic activation. No other data were found.*

Structure Activity Relationships: *Halazone, an aromatic N-chlorosulfonamide, is structurally related to chloramine-T and chloramine-B for which limited acute toxicity data, and no chronic/carcinogenicity data, were found.*

---

[1] The information contained in this Executive Summary of Safety and Toxicity Information (ESSTI) is based on data from current published literature. The summary represents information provided in selected sources and is not claimed to be exhaustive.

A. Nomination History

1. Source: National Institute of Environmental Health Sciences (NIEHS) [NIEHS, 1987]
2. Date: December 1987
3. Recommendations:
    - Toxicity
    - Carcinogenicity
4. Priority: --
5. Rationale/Remarks:

- Potential for high consumer exposure resulting from use as a water disinfectant
- Lack of chronic toxicity data
- Positive in *Salmonella typhimurium*
- Originally nominated by NIOSH for *Salmonella* testing

B. Chemical Evaluation Committee Review

1. Date of Review: August 8, 1991
2. Recommendations: No testing
3. Priority: -
4. NTP Chemical Selection Principle(s): -
5. Rationale/Remarks:
   - Limited exposure
   - Compound undergoes rapid hydrolysis
   - Lack of suspicion of toxicity

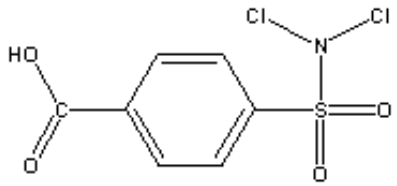
C. Board of Scientific Counselors Review

1. Date of Review:
2. Recommendations:
3. Priority:
4. Rationale/Remarks:

D. Executive Committee Review

1. Date of Review:
2. Decision:

A. Chemical Identifiers



HALAZONE

CAS No. 80-13-7
RTECS No. DG8050000

Molecular formula: $C_7H_5Cl_2NO_4S$ Molecular weight: 270.10

B. Synonyms and Trade Names

- Synonyms: benzoic acid, *p*-(dichlorosulfamoyl)- (8CI); benzoic acid, 4-((dichloroamino) sulfonyl)- (9CI); *p*-(N,N-dichlorosulfamoyl) benzoic acid; *p* carboxybenzenesulfondichloroamide; *p*-dichlorosulfamoylbenzoic acid; *p*-sulfondichloramidobenzoic acid
- Trade Names: Pantocid ®; Pantocide ®

C. Chemical and Physical Properties

- Description: White powder or crystals with a chlorine [Budavari, 1989; Reynolds, 1989] or a chloroform-like odor [Sax and Lewis, 1989].
- Melting Point: 213.0^{o}C (415.4^{o}F) [Weast, 1988] {decomposes @ ~195^{o}C [Budavari, 1989]}.
- Boiling Point: No data were found.
- Density/Specific Gravity: No data were found.
- Refractive Index: No data were found.
- Solubility in Water: Slightly soluble [Budavari, 1989];1 g in > 1000 mL water [Gennaro, 1985].
- Solubility in other Solvents: Slightly soluble in chloroform [Budavari, 1989] (1 g in >1000 mL) [Gennaro, 1985]). Soluble in alcohol (1 g in 140 mL), ether (1 g in >2000 mL) [Gennaro, 1985], glacial acetic acid [Weast, 1988; Budavari, 1989], solutions of alkali hydroxides, and alkali carbonates {with the formation of a salt} [Budavari, 1989; Gennaro, 1985].
- Log Octanol/Water Partition Coefficient: No data were found.
- Reactive Chemical Hazards: Decomposes at approximately 195_C [Budavari, 1989; Gennaro, 1985; Kirk-Othmer, 1979; Sax and Lewis, 1989] and emits chlorine, nitrous oxides, and sulfur oxides [Sax and Lewis, 1989]. Halazone is light-sensitive [Gennaro, 1985; Reynolds, 1985]. Solutions of halazone are unstable and rapidly lose chlorine [Reynolds, 1989]. Halazone hydrolyzes to yield hypochlorous acid [O'Connor and Kapoor, 1970; Gennaro, 1985] and chlorine gas [Gennaro, 1985].
- Flammability Hazards: No data were found.

A. Production

1. Manufacturing Process

Several methods have been used to prepare halazone. A common method involves the chlorination of *p*-sulfonamidobenzoic acid in an alkaline medium [Budavari, 1989; Saljoughian and Sadeghi, 1986]. In this process, *p*-sulfonamidobenzoic acid is chlorinated using either chlorine gas in dilute sodium hydroxide or sodium hypochlorite in sodium hydroxide resulting in a 93% and 78% halazone yield, respectively. It has also been reported that when *p*-sulfonamidobenzoic acid is treated with an excess of sodium hypochlorite, the addition of hydrochloric acid or acetic acid also results in the precipitation of halazone as the main reaction product [Saljoughian and Sadeghi, 1986]. Other sources report that halazone can be synthesized by oxidizing the methyl group of *p*-toluenesulfonamide to a carboxyl and treating the resultant compound [Kirk-Othmer, 1979], *p*-sulfonamidobenzoic acid [Hranilovic *et al*., 1977] with hypochlorite [Kirk-Othmer, 1979] to form halazone at a 60-80% yield [Hranilovic *et al*., 1977]. Halazone may also be prepared when *p*-toluenesulfonyl chloride (obtained by the reaction of toluene and chlorosulfonic acid) is converted to the amide, which is treated with hypochlorite to form *p*-toluenesulfondichloramide. The methyl group is then oxidized with dichromate or permanganate to form

halazone [Gennaro, 1985].

An additional method, which is reportedly both fast and efficient, involves the oxidation of dichloramine-T with potassium permanganate in a mildly alkaline medium containing sodium carbonate. In this procedure, the sodium salt of halazone is initially formed which, following hydrolysis with dilute acetic acid, results in a halazone yield of 95% [Saljoughian and Sadeghi, 1986]. As described in the abstract of a Japanese patent, halazone has been prepared by diaphragmic electrolysis using aqueous chlorides (*e.g.*, 25% sodium chloride solutions) as catholytes, and mixtures of *p*-sulfonamidobenzoic acid as anolytes. This process, which was carried out at 20°C for 1-6 hours using 0.5 amperes, resulted in a 93.2% halazone yield. The authors reported that 2.5% sodium chloride can be substituted with 40% calcium chloride, 33% magnesium chloride, or 23% potassium chloride [Miyazaki, 1975]. According to another paper by the same authors, halazone has also been prepared by electrolytic N-chlorination of *p*-sulfonamidobenzoic acid in aqueous solutions of sodium chloride at a platinized titanium anode under constant current conditions. The halazone yield varied from 81%-94%, decreasing at temperatures greater than 40°C, and increasing as the amount of electricity passed through the system increased [Mikazaki, 1976].

2. Producers and Importers

U.S. Producers:

Producers	Reference
American Tokyo Kasei, Inc. Portland, Oregon	American Tokyo Kasei, Inc, 1991 Fine Chemicals, 1991
Chemical Systems Lab Commander/ Director[2] Aberdeen Proving Ground, Maryland	USEPA,1991
Sigma Chemical Co. St. Louis, Missouri	Sigma Chemical Co., 1991 Fine Chemicals, 1991

Importers:

No information was found on importers of halazone from the public file of the EPA Toxic Substances Control Act (TSCA) Inventory [USEPA, 1991].

3. Volume

One company is listed as a processor of halazone in the public file of the EPA Toxic Substances Control Act (TSCA) Inventory, but no information was provided on volume [USEPA, 1991]. Halazone is not listed in the United States International Trade Commission's publication, Synthetic Organic Chemicals for the years 1985-1989 [USITC, 1986-1990]. This compound is not listed in SRI's Chemical Economics Handbook [SRI, 1991].

4. Technical Product Composition

The commercially available product is a mixture of mono- and di-chloroamides; the dichloro compound predominates [Budavari, 1989]. Halazone contains not less than 91.5% and not more than 100.5% pure halazone {calculated on a dried basis}[USPC, 1990].

B. Use

Halazone is used for the extemporaneous disinfection of drinking water [Reynolds, 1989; Gennaro, 1985; Olin, 1989; Budavari, 1989, Grant, 1974], primarily on a small-scale and under adverse conditions when populations or individuals must depend on sources of water that are potentially contaminated. This compound has been used for this purpose since World War II [O'Connor and Kapoor, 1970]. Halazone tablets are used to disinfect water when boiling is not feasible. The use of halazone for this purpose has been recommended for individuals traveling

abroad, especially to developing nations [Newsday, 1991], and for backpackers and hunters who cannot conveniently boil water [Newsday, 1991].

Following reports in September, 1988 that hurricane Gilbert was approaching, Halazone was recommended by the International Bottled Water Association (IBWA) for consumer use to prepare for potential damage to public water supply systems. For consumers who were unable to buy bottled water because of its limited supply, the IBWA recommended that consumers add halazone tablets to boiled tap water before storing to further reduce the risk of contamination [PR Newswire, 1991]. In addition, in its publication, Will Your Drinking Water Be Safe When?, concerning what the public can do to prepare for emergencies (including earthquakes, droughts, and hurricanes) that may affect the availability of the drinking water supply, the IBWA recommends the use of halazone tablets for tap water disinfection [IBWA, 1991].

Halazone is used at a concentration of 2 to 10 ppm for water disinfection [Gennaro, 1985]. Halazone tablets employed for this purpose have the following composition: 5.3 mg halazone, 5.18 mg soda ash, 11.92 mg boric acid and 114.0 mg sodium chloride [O'Connor and Kapoor, 1970]. One halazone tablet per quart of water is generally used to treat contaminated water (one tablet dissolved in one quart of water liberates 2.3 ppm chlorine and 1.1 ppm hypochlorous acid {as chlorine gas}). Halazone is available to consumers in drug stores and camping supply stores [Magazine ASAP, 1991].

Halazone has also been patented for the following uses:

Disinfection of biological solid wastes (hospitals and biological laboratories) before incineration [Gasparotti, 1988].

Ingredient of a disinfectant for contact lenses [Hopkinson and Cannell, 1986].

Determination of iodine numbers of fats and oils [Budavari, 1989].

---

[2]Chemical Systems Lab is listed in the EPA TSCA Inventory as a processor of halazone.

A. Consumer Exposure

No data were found on consumer exposure to halazone. However, because this compound is used as a water disinfectant, there is potential for high consumer exposure [NIEHS, 1987].

B. Occupational Exposure

No data were found on halazone from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983 [NIOSH, 1991]. It was reported in 1947 that workers in the pharmaceutical industry had been exposed to halazone [Watrous, 1947; Grant, 1974].

C. Environmental Occurrence

No data were found.

D. Regulatory Status

OSHA has not established a permissible exposure limit (PEL) for halazone.

Halazone is not regulated by the Food and Drug Administration. (On March 12, 1980, Abbott Laboratories in North Chicago, Illinois, withdrew its 1976 petition to the Food and Drug Administration (GRASP 5G0050) proposing that halazone is generally recognized as safe (GRAS) for use in emergency situations only, as a microcidal chemical for the treatment of potable water of unknown biological quality and where other treatments are not feasible [Federal Register, 1980].)

E. Exposure Recommendations

ACGIH has not recommended a threshold limit value (TLV) for halazone.

NIOSH has not recommended an exposure limit (REL) for halazone.

A. Chemical Disposition

1. Human Data

No data were found.

2. Animal Data

oral, rabbits:

The metabolism of halazone was studied in 1917 using rabbits (unspecified sex, strain, and number) given daily doses of halazone in an unspecified vehicle. The rabbits were administered (via stomach tube) halazone at 100-200 mg/day for "many" (unspecified number) weeks, or received repeated (unspecified number) doses of 500 mg. Urine was collected and examined. Urinalyses indicated that no "unchanged" halazone was present, and that all active chlorine had disappeared. The urine was acidified and extracted with ether, producing a crystalline acid. *p*-Sulphonamido-benzoic acid was identified following purification and analysis of the acid at a concentration equal to 60% of the halazone administered. No other compounds were identified. The authors concluded that it is probable that halazone is quantitatively converted into *p*-sulphonamidobenzoic acid in the rabbit, with the loss of two atoms of chlorine [Dunham and Dakin, 1917].

No other data were found.

B. Acute

1. Human Data

In a study describing the health hazards related to employment in the pharmaceutical industry, halazone was reported to be a local irritant and a sensitizer. Contamination of the working environment from halazone dust caused dermatitis, rhinitis, conjunctivitis, and bronchitis. Exposure to high concentrations resulted in asthmatic symptoms with subsequent sensitization [Watrous, 1947].

No other data were found.

2. Animal Data

oral, rats:

The acute oral toxicity of halazone was studied using an unspecified strain of rats. The rats were administered a single dose of halazone at a concentration of 1.0 (n=9), 1.5 (n=9), 2.0 (n=11), 3.0 (n=15), or 3.5 (n=11) g/kg. The mortality rates and signs of toxicity were recorded. Mortality rates were observed to be dose related: 22% (1.0 g/kg), 33% (1.5 g/kg), 27% (2.0 g/kg), 60% (3.0 g/kg), and 100% (3.5 g/kg). Although the lowest lethal dose [LD_{LO}] observed was 1.0 g/kg (22% mortality), the authors reported that the minimum lethal dose was 3.5 g/kg. (An LD_{50} value was not reported). Necropsies performed on an unspecified number of animals revealed lesions of the gastric mucosa. No other necropsy findings were reported [Stohlman and Smith, 1944].

oral, rabbits:

In the chemical disposition study described in Section VA.2., halazone did not induce toxic effects following oral administration via stomach tube at concentrations of 100-200 mg/day for an unspecified number of weeks, or after repeated doses of 500 mg halazone [Dunham and Dakin, 1917]. No other data concerning the acute toxicity of this compound were reported.

intravenous, rats:

The acute toxicity of halazone was studied in rats of unspecified strain and sex. Rats were administered halazone

in an unspecified solvent via intravenous infusion at concentrations of 300.0 (n=12), 400.0 (n=15), 500.0 (n=9), 600.0 (n=13), or 800.0 (n=8) mg/kg, and were observed for signs of toxicity. The rats exposed to halazone exhibited dyspnea, labored respiration, and death within 30 minutes to 18 hours. The observed mortality rates were: 25% (300.0 mg/kg), 40% (400.0 mg/kg), 22% (500.0 mg/kg), 39% (600.0 mg/kg), and 100% (800.0 mg/kg). Although 300.0 g/kg was the lowest lethal dose [LD_{LO}] observed (25% mortality), Stohlman and Smith reported that the minimum lethal dose was 800 mg/kg. (An LD_{50} value was not reported). Necropsies performed on an unspecified number of animals revealed pulmonary congestion and edema [Stohlman and Smith, 1944].

intravenous, cats:

The pharmacodynamic action of continuous intravenous infusion of halazone in physiologic saline among cats of unspecified number and species under amytal anesthesia has been studied. In two experiments, a total of 200 mg/kg halazone was infused, and in a third experiment, cats received a total of 300 mg/kg halazone. Halazone was found to be mildly depressing to the circulation and respiration. Halazone did not exhibit primary stimulating action on respiration [Stohlman and Smith, 1944].

C. Prechronic

1. Human Data

No data were found.

2. Animal Data

oral, rats:

Rats of unspecified strain were used to determine the prechronic effects of halazone following administration in the diet for 80 days, or until death. The rats were given halazone at concentrations of 0.1, 0.5, or 1.0% in a semisynthetic diet. Although the total number of rats in each test group was unreported, results concerning growth inhibition (see below) were reported for 6 females, 6 males, and 5 females in the 0.1, 0.5 and 1.0% dose groups, respectively. In addition, results were reported for 5 male and 7 female control rats. The control group received the same semisynthetic diet without the test compound. The animals were allowed to feed freely over the 80-day test period and the amount of food consumed by each animal was recorded. The retention of intravenously injected rose bengal dye (25 mg/kg) was determined as a measure of liver function at 1 hour for an unspecified number of rats in unspecified dose groups. All animals were weighed weekly throughout the duration of the experiment. At the end of the dosing period, hemoglobin was measured, and necropsies were performed to determine the presence of gross parenchymatous lesions.

The animals receiving 1.0 and 5.0% halazone exhibited marked signs of test-compound induced toxicity, including growth inhibition (see Figure 1, next page) decreased food consumption (see Figure 2, next page) and mortality (rate not reported). Evidence of retarded growth and reduced food intake was evident in the 0.1% halazone dose group. (P values were not specified for any results reported.) Hemoglobin levels and rose bengal clearance were reported to be within the normal range. Necropsies of test animals did not reveal any abnormalities [Stohlman and Smith, 1944].

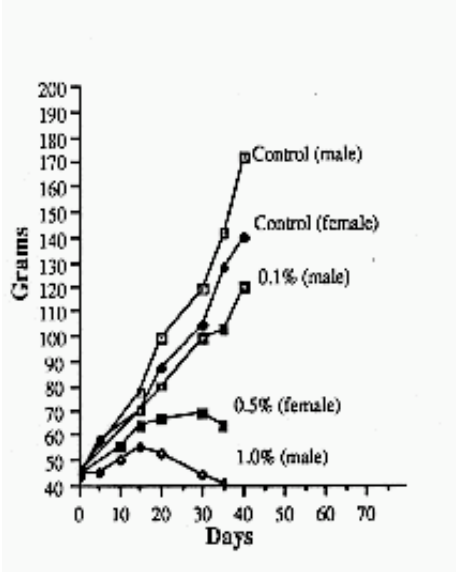


Figure 1: Growth (in grams) of Rabbits Fed 0.1, 0.5, or 1.0% Halazone

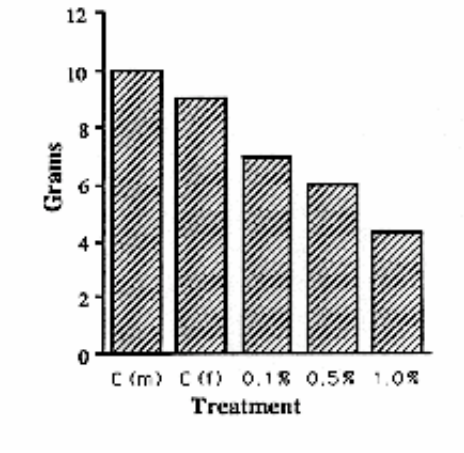


Figure 2: Amount of Food (in grams) Consumed by Test Animals and Control Animals [C (m) = control males, C (f) = control females]

_____

Reference: Stohlman and Smith, 1944

oral, rabbits:

The toxicity of halazone was studied using 5 rabbits of an unspecified species. The test animals were administered oral doses of 0.2 g/kg in an unspecified vehicle by stomach tube daily, 6 days per week, for a total of 20-29 doses. No information on control animals was reported. At the end of the dosing period, the animals were injected with 5.0 mg/kg of rose bengal dye.The extent of dye retention at 30 minutes was determined as a measure of liver function. In addition, final body weights were recorded, hemoglobin determinations were made, and urine was tested for albumin. Animals were sacrificed, gross post-mortem findings were noted, and microscopic examination was conducted on the stomach tissue.

The following signs of toxicity were observed in the test animals: a "marked" reduction in hemoglobin in 2/5 animals; abnormal dye retention in 5/5 animals (0.7-1.3 mg% in test animals versus a "normal" level of 0.3-0.6

mg%)[3]; and the presence of urine albumin in 2/5 animals. Body weights remained relatively constant during the dosing period, and no body weight decreases were noted. Gross and microscopic examination of the animals' stomachs showed no abnormalities. Slight centrolobular atrophy and fatty degeneration of the liver was observed in the animal exhibiting the greatest dye retention (1.3 mg%). All other animals with elevated rose bengal retention had varying degrees of coccidiosis. P values were not reported for the results presented [Stohlman and Smith, 1944].

D. Chronic/Carcinogenicity

1. Human Data

   No data were found.

2. Animal Data

   No data were found.

E. Reproductive Effects and Teratogenicity

1. Human Data

   No data were found.

2. Animal Data

   No data were found.

F. Genetic Toxicology

1. Prokaryotic Data

   Salmonella typhimurium:

   Halazone was tested in a preincubation modification of the standard Ames test in *Salmonella typhimurium* strains TA98, TA100, TA1537, and TA1535 with and without aroclor 1254-induced metabolic activation. This compound was tested at concentrations of 0.0 (DMSO control), 100.0, 333.0, 666.0, 1000.0, 1666.0, 3333.0, and 6666.0 µg/ plate. Halazone was found to be positive in strain TA100 with and without activation, and negative in the other strains tested [Mortelmans *et al.,* 1986].

2. Eukaryotic Data:

   No data were found.

G. Other Toxicological Effects

1. Immunotoxicity

   No data were found.

2. Neurotoxicity

   in vitro, frog:

The effect of halazone on sodium current inactivation in myelinated nerve fibers of the frog *Rana esculenta* has been investigated. A node of Ranvier was voltage clamped and the fiber was cut on both sides of the node. The node was superfused continuously with Ringer's solution with or without 5 mM halazone. The potential at which 30% of the sodium channels were inactivated was taken as the normal resting potential and defined as E=-70 mV. The fibers were held at E=-70 mV. Command voltage pulses were generated by a 12-bit converter. To measure the curve relating the steady state inactivation parameter to the conditioning potential, 40-ms conditioning pulses to varying potentials followed by a constant test pulse to +10 mV were used. Normalized test pulse current was plotted against membrane potential during the conditioning pulse. The curve relating the steady state inactivation parameter to the conditioning potential became nonmonotonic after treatment with halazone. The authors concluded that halazone is a strong inhibitor of sodium currents [Rack *et al*., 1986].

3. Biochemical Toxicology

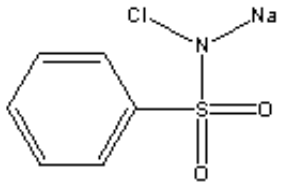
   No data were found.

---

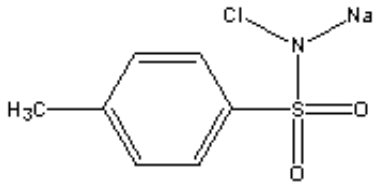
[3] The authors reported that 4/5 animals exhibited abnormal dye retention, however Table 3 on page 544 of the Stohlman and Smith study indicates that all of the animals given halazone had dye retention values that fell outside of the normal range (0.3-0.6mg%).

Halazone has been reported to be structurally related to other aromatic N-chloro-sulfonamides including chloramine-B [Kirk Othmer, 1979] and chloramine-T [Kirk Othmer, 1979; Rack *et al*., 1986] (see Figure 3). Chloramine-T has been found to cause respiratory abnormalities, cyanosis, hypotension, subnormal temperature, abdominal pain and convulsion following acute exposure to high concentrations [Arena, 1986]. Chloramine-T is reportedly irritating to the eyes and has caused conjunctivitis, but not serious eye injury. Occupational asthma has resulted from the inhalation of this compound. Chloramine-T has been found to be non-mutagenic in *Salmonella typhimurium* [HSDB, 1991]. However, this compound induced chromosomal aberrations in cultured human lymphocytes [RTECS, 1991]. No data were found on the chronic toxicity or carcinogenicity of chloramine-T [HSDB, 1991; RTECS, 1991; Cancerlit, 1991; Toxline 1991; CCRIS, 1991]. No acute of chronic toxicity data were found for chloramine-B [RTECS, 1991, Cancerlit, 1991; CCRIS, 1991].

Figure 3. Structurally Related Compounds



Chloramine-B



Chloramine-T

American Tokyo Kasei, Incorporated (Portland, Oregon), Telephone Communication with Sales Representative, May 23, 1991.

Arena, J.M., ed., Poisoning: Toxicolgy, Symptoms and Treatments, Fifth Edition. Springfield, Illinois: Charles C. Thomas, 1986, p.653.

Budavari, S., ed., The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, Eleventh Edition. Rahway, New Jersey: Merck, 1989. pp. 723-724.

Dunham, E.K. and Dakin, H.D., "Note on the Fate of Halazone in the Animal Body and on the Stability of Tablets Containing It." British Medical Journal, Vol.2 (1917), pp. 790-791.

Federal Register, "Abbott Laboratories; Withdrawl of Petition for Affirmation of GRAS Status." Federal Register, Vol.45, No.57 (1980), pp. 18479-18480.

Fine Chemicals, on-line Dialog database, January, 1991.

Gasparotti, F.A., Method for Sterilizing Solid Refuse by Active Chlorine Released by the Reaction of Halazone with Water, European Patent Application, Patent Number 88118123.4, October, 1988.

Gennaro, A.R., ed., Remington's Pharmaceutical Sciences, Seventh Edition. Easton, Pennsylvania: Mack Publishing Company, 1985. p. 1160.

Grant, W.M., Toxicology of the Eye, Second Edition. Springfield, Illinois: C.C. Thomas, 1974. p. 538.

Hopkinson, A. and Cannell, J.S., Disinfection of Contact Lenses, European Patent Application, Patent Number 86300537.7, January, 1986.

Hranilovic, J., Lukic, M. and Dostal, K., "Electrochemical Preparation of *p*-Sulphonamidobenzoic Acid." Acta Pharmaceutica Jugoslavica, Vol. 27 (1977), pp. 93-95.

International Bottled Water Association (IBWA), Will Your Drinking Water Be Safe When? International Bottled Water Association, Alexandria Virginia, 1991.

Kirk-Othmer, Encyclopedia of Chemical Technology. Third Edition, Volume 5. New York: Wiley-Interscience, (1979), p. 575.

Magazine ASAP, on-line Dialog database, January, 1991.

Miyazaki, H., "Electrosynthesis of Organic N-Halogen Compounds (1): Synthesis of Halazone." Denki Kagaku Oyobi Kogyo Butsuri, Vol. 44, No. 6 (1976), pp. 409-412.

Miyazaki, H., Halazone, Japan Patent, Patent Number 50069043, June 1975. (abstract obtained from Chemical Abstracts database, 1991.)

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B. and Zeiger, E., "*Salmonella* Mutagenicity Tests: II. Results from the Testing of 270 Chemicals." Environmental Mutagenesis, Vol. 8, Supplement 7 (1986), pp. 1-4, 7, 12-27, 33, 39, 78.

National Institute of Environmental Health Sciences, 1987, Memo from Dr. T. Damstra, Assistant to the Director for International Programs, to Dr. D. Canter, Assistant to the Director, NTP. December 22,1987.

Newsday, on-line Dialog database, January, 1991.

NIOSH, National Institute for Occupational Safety and Health, National Occupational Exposure Survey (NOES), data communicated by Joseph A.Seta, Acting Section Chief, Division of Surveillance, Hazard Evaluations and Field Studies. January 1991.

O'Connor, J., T. and Kapoor, S., K., "Small Quantity Field Disinfection." Journal of the American Water Works Association, Vol. 62, No. 2 (1970), pp.80-84.

Olin, B.R., Drug Facts and Comparisons, 1990 Edition. St. Louis, Missouri: J.B. Lippincott Company, 1989. p. 2288.

PR Newswire, on-line Dialog database, January, 1991.

Rack, M., Rubly, N. and Waschow, C., "Effects of Some Chemical Reagents on Sodium Current Inactivation in Myelinated Nerve Fibers of the Frog." Biophysical Journal, Vol. 50 (1986), pp. 557-564.

Reynolds, J.E.F., ed., Martindale: The Extra Pharmacopoeia, Twenty-ninth Edition. London: The Pharmaceutical Press, 1989. pp. 949, 963.

Saljoughian, M. and Sadeghi, M.T., "An Improved Procedure for the Synthesis of p-(Dichlorosulfamoyl)benzoic Acid (Halazone)." Monatshefte für Chemie, Vol. 117 (1986), pp. 553-555.

Sax, N.I. and Lewis, R.J., Dangerous Properties of Industrial Materials, Volume III. Seventh Edition. New York:Van Nostrand Reinhold, 1989, p. 1834.

Sigma Chemical Company (St. Louis, Missouri), Telephone Communication with Sales Representative, May 22, 1991.

SRI, Chemical Economics Handbook Online. Database available from SRI, Menlo Park, California, March, 1991.

Stohlman, E.F. and Smith, M.I., "Experiments on the Pharmacologic Action of Succinchlorimide." Public Health Reports, Vol. 59, No. 17 (1944), pp. 541-546.

United States Environmental Protection Agency (USEPA), 1991 U.S. Environmental Protection Agency, Computer Printout (TSCAPP): 1977 Production Statistics for Chemicals in the Nonconfidential Initial TSCA Chemical Substances Inventory. Washington, D.C.: Office of Pesticides and Toxic Substances.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1985. U.S, Government Printing Office. Publication No. 1892. Washington, D. C., 1986.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1986. U.S, Government Printing Office. Publication No. 2009. Washington, D. C., 1987.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1987. U.S, Government Printing Office. Publication No. 2118. Washington, D. C., 1988.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1988. U.S, Government Printing Office. Publication No. 2219. Washington, D. C., 1989.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1989. U.S, Government Printing Office. Publication No. 2219. Washington, D. C., 1990.

The United States Pharmacopeial Convention (USPC), The United States Pharmacopeia The National Formulary, Twenty-Second Revision. Rockville, Maryland: The United States Pharmacopoeial Convention, Inc., 1990. pp. 625-626.

Watrous, R.M., "Health Hazards of the Pharmaceutical Industry." British Journal of Industrial Medicine, Vol.4 (1947), pp.111-125.

Weast, R.C., ed., 1988-1989 CRC Handbook of Chemistry and Physics, Sixty Ninth Edition. Boca Raton, Florida: CRC Press, Inc., 1988, p. C-130.

	DATE OF SEARCH	TIME PERIOD
BRS:		
HZDB	January, 1991	
DIALOG:		
Agricola	January, 1991	1970-1990
Agris International	January, 1991	1974-1990
Aquatic Sciences Abstracts	January, 1991	1974-1990
Biosis Previews	January, 1991	1969-1990

CAB Abstracts	January, 1991	1972-1990
Cancerlit	January, 1991	1963-1990
Chem Bus Newsbase	January, 1991	1984-1990
Chemical Exposure	January, 1991	1974-1987
Compendex Plus	January, 1991	1970-1990
CRIS USDA	January, 1991	
Embase	January, 1991	1974-1990
Enviroline	January, 1991	1970-1990
Environmental Bibliography	January, 1991	1974-1990
Federal Register	January, 1991	1977-1990
Foods Adlibra	January, 1991	1974-1990
FSTA	January, 1991	1969-1990
Life Sciences Collection	January, 1991	1978-1990
Medline	January, 1991	1966-1990
NTIS	January, 1991	1964-1990
Occupational Safety and Health	January, 1991	1973-1990
PTS Newsletter	January, 1991	1987-1990
PTS Prompt	January, 1991	1972-1990
Pollution Abstracts	January, 1991	1970-1990
Trade and Industry ASAP	January, 1991	1983-1990
MEAD:		
Nexis/Lexis-BNA ENV	January, 1991	
NLM:		
Chemline	January, 1991	
HSDB	January, 1991	
RTECS	January, 1991	
Toxline 65	January, 1991	1965-1980
Toxline	January, 1991	1981-1990
Toxlit	January, 1991	1981-1990
Toxlit 65	January, 1991	1965-1980
STN:		
CA	January, 1991	1967-1990
Chemlist	January, 1991	

APPENDIX II. SAFETY INFORMATION

- HANDLING AND STORAGE

  Halazone is stable under normal laboratory conditions. It has been found to be stable indefinitely at room temperature. At 50°C, not more than 1 percent decomposition was noted within 60 days [Dunham and Dakin, 1917]. This compound is light-sensitive [Gennaro, 1985; Reynolds, 1985].

- EMERGENCY FIRST AID PROCEDURES

  Eye: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. Immediately transport the victim to a hospital even if no symptoms (such as redness or irritation) develop.

Skin: IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently was affected skin areas thoroughly with soap and water. If symptoms such as inflammation or irritation develop, IMMEDIATELY call a physician or go to a hospital for treatment.

Inhalation: IMMEDIATELY leave the contaminated area and take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital.

Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used.

Ingestion: If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control center. Be prepared to transport the victim to a hospital if advised by a physician.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY TRANSPORT THE VICTIM TO A HOSPITAL.

- PROTECTIVE EQUIPMENT

  Eye: Safety glasses

  Gloves: Two pairs of dissimilar protective gloves shall be worn when handling the neat chemical, otherwise one pair. When contact with this chemical has been known to occur, change gloves immediately.

  Clothing: Minimally, a disposable laboratory suit (e.g. Tyvek ®) shall be worn, as specified in the most current NTP Statement of Work or the NTP Health and Safety Minimum Requirements.

  Respiratory Protection: A NIOSH-approved chemical cartridge respirator with an organic vapor and high-efficiency particulate filter cartridge.

- EXTINGUISHANT

  Dry chemical, carbon dioxide or halon extinguisher.

- MONITORING PROCEDURES

  There is no NIOSH analytical method reported in the NIOSH Manual of Analytical Methods for Halazone.

- SPILLS AND LEAKAGE

  Persons not wearing the appropriate protective equipment and clothing shall be restricted from areas of spills until cleanup has been completed. When exposure to unknown concentrations may occur, air-purifying respirators may not be used. Chemical cartridge respirators with organic vapor cartridges may not be used when airborne concentrations exceed 1000 ppm.

  If halazone is spilled the following steps shall be taken:

  1. In order to prevent dust formation, use moistened paper towels to clean up a solid spill. Avoid dry sweeping.
  2. If a liquid solution is spilled, use vermiculite, sodium bicarbonate, sand, or paper towels to contain and absorb the spill.
  3. Clean the spill area with dilute alcohol (approximately 60-70%) followed by a strong soap and warm water washing.
  4. Dispose of all absorbed material as hazardous waste.

- DECONTAMINATION OF LABORATORY EQUIPMENT

TDMS Terminal:	Whenever feasible, a protective covering (e.g.,plastic wrap) shall be placed over the keyboard when in use.
General Equipment:	Before removing general laboratory equipment (e.g., lab carts, portable hoods and balances) from animal dosing rooms and/or chemical preparation areas, a decontamination process shall be conducted in addition to routine housekeeping procedures.

- WASTE MANAGEMENT AND DISPOSAL PROCEDURES

Waste Management:	If an inhalation study is to be conducted, all exhaust air from the inhalation chamber must be cleaned with appropriate air cleaning devices unless the laboratory has informed local and state air pollution regulatory agencies of both the laboratory's operating practices and the potential hazards of the chemical's in use. Compliance with all federal, state and local air pollution laws and regulations is required. A specific air cleaning system design must consider the specific conditions of the laboratory (eg., air flow rates and volumes, mixing of exhaust streams, size of inhalation chamber, etc.) and the dosing regimen selected. Air cleaning systems designs must be described by the laboratory and approved by the NTP Office of Laboratory Health and Safety.
Waste Disposal:	Securely package and label, in double bags, all waste material. All potentially contaminated material (i.e., carcasses, bedding, disposable cages, labware) shall be disposed of by incineration in a manner consistent with federal (EPA), state, and local regulations or disposed of in a licensed hazardous waste landfill.