SUMMARY OF DATA FOR CHEMICAL SELECTION

1,3,5-Triazine-1,3,5(2H,4H,6H)-triethanol
4719-04-4

BASIS OF NOMINATION TO THE CSWG

1,3,5-Triazine-1,3,5(2H,4H,6H)-triethanol (TZT) is presented to the CSWG for review because of its high production volume, 789,118-1,200,195 pounds a year, and its potential for exposure to large numbers of workers, approximately 225,000.

TZT was selected as a member of a Biocides Class Study but was rejected for nomination in 1979 because of lack of suspicion of toxicity. Since that time, concerns have been raised that the toxicity of biocides, including TZT, has not been adequately tested, that there is the possibility of the release of formaldehyde from TZT-like biocides, and that inhalation of oil mists, themselves, may be toxic. Positive in the Ames *Salmonella* assay, orally administered TZT also produced evidence of adverse effects in the lungs and stomachs of rats exposed for 90 days.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), provided "tox oneliners" from the Office of Pesticide Programs.

SELECTION STATUS

ACTION BY CSWG: 12/14/98

Studies requested:

- Carcinogenicity study

Priority: Moderate

Rationale/Remarks:

Industrial biocide with very high production volume and worker exposure potential
No structural counterpart among formaldehyde-releasing biocides
Dermal absorption and inhalation are characteristic routes of human exposure

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CHEMICAL IDENTIFICATION

CAS Registry Number: 4719-04-4

Chemical Abstract Service Names: *s*-Triazine-1,3,5(2H,4H,6H)-triethanol (8CI)

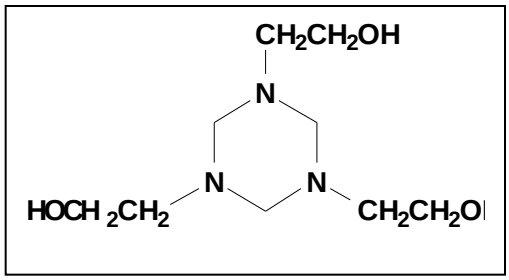
1,3,5-Triazine-1,3,5(2H,4H,6H)-triethanol (9CI);

Synonyms and Trade Names:

Hexahydro-1,3-5-triazine-1,3,5-triethanol; hexahydro-1,3,5-tris(2-hydroxyethyl)triazine; 1,3,5-tris(2-hydroxyethyl)hexahydro-1,3,5-triazine; 1,3,5-tris-(2-hydroxyethyl)hexahydro-s-triazine; Actane; Bioban GK; Busan 1060; Grotan B; Grotan BK; Kalpur TE; KM 200; Onyxide 200; Roksol T 1-7; Triadine 3; Triadine 174

Structural Class: Triazine

Structure, Molecular Formula and Molecular Weight:



$C_9H_{21}N_3O_3$ Mol. wt.: 219.3

Chemical and Physical Properties:

Description: Clear amber-colored liquid (Angus Chemical Co., 1997)

Boiling Point: 106°C (Olin Corp., 1998)

Freezing Point: -24°C (Angus Chemical Co., 1997)

Flash Point: >100°C, CC (Angus Chemical Co., 1997)

Vapor Pressure: 19 mm Hg @ 20°C (Angus Chemical Co., 1997)

Solubility: Soluble in water, ethylene glycol, acetone, and the lower alcohols; insoluble in most hydrocarbons,

toluene, and methyl ethyl ketone (Angus Chemical Co., 1997)

Density: 1.15 @ 20°C (Angus Chemical Co., 1997)

Octanol/water partition coefficient (P): log P, 0.0713 (Agnus Chemical Co., 1997)

Technical Products and Impurities: Bioban GK, a 78 percent solution of 1,3,5-triazine-1,3,5(2H,4H,6H)-triethanol (TZT) in water, is available from Angus Chemical Company in 55-gal. drums and 5-gal. pails (Angus Chemical Co., 1997; Rodnan, 1998). Olin Corporation supplies the following TZT products: Triadine 3 and Triadine 174 bactericides, 78.5 percent active solutions; Triadine 10 microbiostat, 63.6 percent solution with 6.4 percent sodium pyrithione; and Triadine 20, a 71.4 percent solution with 3.6 percent sodium pyrithione; they are available in 10-pound bottles and 60- and 500-pound drums (Olin Corp., 1998; Rodnan, 1998).

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EXPOSURE INFORMATION

Production and Producers: TZT is a formaldehyde condensate product. These products are produced by reacting formaldehyde with one or more substituted alkylamines. The result is a cyclic, saturated, symmetrical triazine (Rossmoore, 1981).

According to recent chemical catalogs and directories, TZT is manufactured and/or distributed by Angus Chemical Company and Olin Corporation (Hunter, 1997; McCoy, 1997; Rodnan, 1998).

The annual production volume of TZT has been estimated to range from 789,118 to 1,200,195 pounds (USEPA, 1998). TZT is listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (NLM, 1998a).

TZT is listed as a chemical of commerce in the U.S. International Trade Commission (USITC) publication *Synthetic Organic Chemicals, US Production and Sales, 1983-1993* (USITC, 1984-1994). The reporting companies were Angus Chemical Company and an unidentified company, but no production or sales quantities were included. According to the USITC, separate statistics were not published to avoid disclosure of individual operations; however the USITC reporting guidelines specify that each company's report of a chemical represents production of ≥ 4,500 kg [10,000 lbs] or sales ≥ $10,000.

Use Pattern: TZT is widely used as an antimicrobial agent in metal working fluids. It is marketed for addition to water-miscible fluids of the oil-in-water emulsion (soluble oil) and synthetic types. Water-miscible fluids provide cooling and lubrication for metal-working processes such as cutting and grinding. Bacterial growth in these fluids can cause odor and metal corrosion problems as well as emulsion breakdown (Rycroft, 1978; Angus Chemical Co., 1997). TZT biocides are also recommended for use in aqueous-based paint, coating, and latex emulsion products and in oilfield water systems, drilling muds, and in workover and completion fluids (Angus Chemical Co., 1997; Olin Corp., 1998). TZT has been evaluated for use in water-compensated fuel tanks by the US Naval Research Laboratory (Hill, 1995).

TZT is effective against both Gram-positive and Gram-negative bacteria. At higher concentrations, it is also effective against fungi or it may be combined and used

effectively with a number of commonly used fungicides for broad spectrum control (Angus Chemical Co., 1997; Olin Corp., 1998).

Recommended levels of use for TZT by application include: metalworking fluids, 400-1,500 ppm (2,000 ppm may be required to control fungal growth or to inhibit bacterial growth in heavily contaminated fluids); oilfield water systems, 5-150 ppm; drilling muds and workover and completion fluids, 500-1000 ppm; and water-compensated fuel tanks, 100-1000 ppm (Hill, 1995; Angus Chemical Co., 1997; Olin Corp., 1998).

Human Exposure: There is potential for widespread human exposure to TZT in occupational settings related to its use as an industrial biocide. The formaldehyde condensate products, which include TZT, represent 60 percent of the total sales of metalworking biocides. It is estimated that over 10 million US workers are exposed to machining or metalworking fluids. This figure includes employees of many industries who are involved in drilling, grinding, cutting, textile production, mist lubrication, and printing (Rossmoore, 1981; Krystofiak & Schaper, 1996). The metalworking fluids are directed at the working surface in a spray or stream and are generally collected and reused. Workers may be exposed through skin contact as well as by inhaling and swallowing the oil mist that is produced when metalworking fluids are used (Occupational Disease Panel, 1996).

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 225,251 workers, including 28,071 female workers, were potentially exposed to TZT in the workplace. The NOES database does not contain information on the frequency, level or duration of exposure to workers of any chemical listed therein (NLM, 1998a).

Environmental Occurrence: No information was found in the available literature identifying TZT in environmental media. Preliminary biodegradation data indicate that TZT at 50 mg/L concentration or less should readily biodegrade (Angus Chemical Co., 1997).

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace maximum allowable levels of TZT. The American Conference of Governmental Industrial Hygienists (ACGIH) has not

recommended a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) for this compound.

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to TZT and cancer risk in humans were identified in the available literature.

TZT has been found to be sensitizing in some individuals (Angus Chemical Co., 1997). In early studies reviewed by Rycroft (1978), patch testing in occupational groups exposed to TZT (as Grotan BK) resulted in sensitization rates ranging from 0 to 8 percent; tested concentrations ranged from 0.1 to 1 percent TZT. Pre-existing eczematous dermatitis may have increased the likelihood of sensitization in some test subjects. In a more recent study, a 1 percent concentration of TZT (as Grotan BK) produced positive sensitization reactions in 1 percent of 1772 patients with suspected allergic contact dermatitis (Schnuch *et al*., 1998).

Animal Data: *Acute Studies.* LD_{50} values have been reported for the following TZT products: Grotan BK (78% TZT), rat oral LD_{50} = 580 mg/kg; Onyxide 200 (78% TZT), rat oral LD_{50} = 860 mg/kg, rabbit dermal LD_{50} > 3.5 g/kg; Triadine 10 (63.6% TZT and 6.4% sodium 2-pyridinethiol-1-oxide), rat oral LD_{50} = 734 mg/kg, rabbit dermal LD_{50} = 854 mg/kg (Rossmore, 1981).

The respiratory effects of two synthetic metalworking fluids and their components were evaluated in two inhalation studies; TZT was identified as an irritating component in both fluids. Male Swiss-Webster mice exposed to TZT at 112-351 mg/m^3 exhibited signs of both sensory and pulmonary irritation during the 3-hour exposure. In both studies, TZT resulted in delayed deaths of mice at 24 to 72 hours post exposure. The concentrations of TZT capable of evoking a 50 percent decrease in mean respiratory frequency based on pulmonary irritation ($RD_{50}P$) were calculated as 137 mg/m^3 in the study by Krystofiak and Schaper (1996) and as 190 mg/m^3 in the study by Detwiler-Okabayashi and Schaper (1996). From these RD_{50} P values the authors proposed respective occupational exposure limits of 2.3 and 3.2 mg/m^3.

In maximization tests performed by two separate laboratories, Grotan BK (80% TZT) sensitized 20 and 74% of the guinea pigs, respectively (Anderson *et al.*, 1984). Bioban GK (78% TZT) was judged to be nonsensitizing in guinea pigs; it is a primary eye irritant in rabbits (Angus Chemical Co., 1997; Walker, 1998).

Subchronic Studies. There were no mortalities and no systemic or adverse pathological effects noted in male and female rats dosed dermally with Bioban GK (78% TZT) at 0, 5, 50, and 250 mg/kg/day for 90 days. Skin irritation was noted in animals dosed at 50 mg/kg and higher (no further study details were provided) (Angus Chemical Co., 1997).

Male and female rats (strain not stated) were administered Bioban GK (78% TZT) doses of 0, 10, 50, 100, and 250 mg/kg/day by gavage for 90 days. At 250 mg/kg, there was increased mortality in females; microscopic changes in the lungs indicated that the test material had entered the lungs. Dose levels greater than 100 mg/kg were associated with increased erosion and lymphocytic infiltration in the stomach. The NOEL for female rats was 50 mg/kg/day; for male rats the NOEL was 10 mg/kg/day (Angus Chemical Co., 1998).

Reproductive/Teratogenicity Studies. No teratogenic or embryotoxic effects were observed in a study with pregnant rats dosed at 0, 250, 500, or 750 mg/kg/day from gestation day 6 to 15. Maternal toxicity was evident only in the high dose group as reduced maternal body weight and the necessity to sacrifice one animal due to poor clinical condition (no further study details were provided) (Angus Chemical Co., 1997). A developmental toxicity study in Sprague-Dawley rats administered TZT at 0, 250, 500, or 750 mg/kg/day by gavage noted decreased body weight gain and ulceration and/or scarring of the stomach mucosa (no further details were provided) (Walker, 1998).

Chronic/Carcinogenicity Studies: TZT did not induce papillomas in NMRI female mice (9-11 per group) following dermal application of 0.15, 1.5 or 15% (w/v) 3/week for 31 weeks. Slight dysplasia was reported in two high-dose animals; hyperplasia occurred in one mid-dose and seven high-dose mice (Jepsen *et al.*, 1977).

No 2-year carcinogenicity studies of TZT in animals were identified in the available literature.

Short-Term Tests: TZT was mutagenic in *Salmonella typhimurium* strain TA100 when tested at 10-100 µg/plate with activation; it was negative in TA100 when tested without activation. TZT did not induce mutations in strains TA98, TA1535, or TA1537 when tested both with and without activation (Mortelmans *et al.*, 1986).

Bioban GK (78% TZT) was negative in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 when tested both with and without activation (Angus Chemical Co., 1997).

The results were inconclusive when Bioban GK (78% TZT) was tested in two separate studies for the induction of unscheduled DNA synthesis in rat hepatocytes. In the first assay, results were considered equivocal due to a lack of dose response when Bioban GK was tested at doses of 0.001 to 0.1 mg/ml. In the second study, Bioban GK doses of 0.01 to 0.3 mg/ml did not induce a significant increase in response; however, there was a slight dose-related response in terms of the mean net nuclear count and percentage of cells demonstrating DNA repair (Angus Chemical Co., 1997).

TZT (Grotan BK) did not increase the incidence of micronucleated erythrocytes in rat bone marrow when total doses of 15, 60, 240 or 969 mg/kg were administered by any of three routes (dermal, oral, or subcutaneous); bone marrow was screened 30 hours after the first of two Grotan doses (Urwin *et al.*, 1976). Based on this study, a report of the USEPA GeneTox Program classified Grotan BK as an "unconfirmed negative" for the induction of micronuclei because the test did not conform to the recommended protocol (Heddle *et al.*, 1983). TZT (Bioban GK) was also negative in an *in vivo* mouse micronucleus assay; doses of 200, 400, and 800 mg/kg were administered by an unspecified route and animals were sacrificed at 24, 48, and 72 hours (Angus Chemical Co., 1997).

Metabolism: No studies on the metabolism of TZT was identified in the published literature.

Other Biological Effects: The mode of action of formaldehyde-releasing biocides has not been fully explained; formaldehyde release during use by hydrolysis of the original compound has been suggested as one possibility although this is not likely to occur in the alkaline conditions of metalworking fluids. The supposition is that hydrolysis with formaldehyde release occurs at the cell boundary where the pH is more favorable. Formaldehyde-releasers do not produce nascent formaldehyde in metalworking fluid environments (Rossmoore, 1981; Anderson *et al.*, 1984; Occupational Disease Panel, 1996).

In a report to the Worker's Compensation Board on the health effects of occupational exposure to metalworking fluids, the Canadian Occupational Disease Panel (1996)

found that “there is a probable connection between cancer of the esophagus and occupational exposure to metalworking fluids.” A report prepared for the panel on the toxicology of metalworking fluids cited the potential risk associated with the biocides used in these fluids as follows: many of the biocides are themselves toxic and have not been adequately tested; some biocides e.g., bioban (not necessarily TZT) might be nitrosating agents, which can give rise to nitrosodiethanolamine and other nitrosamines by reaction with amines in the fluids; some bacteriocides are formaldyhyde releasers and formaldehyde facilitates the formation of nitrosamines, particularly in alkaline solution and participates in the formation of nitrosooxazolidines; and formaldehyde itself is carcinogenic to rats by inhalation, but has not caused tumors when ingested or applied in solution to the skin. The report does go on to note that since little or no free formaldehyde exists in metalworking fluids containing formaldehyde-releasing biocides, it is unlikely that the risk to workers from inhaling formaldehyde would be significant.

Structure Activity Relationships: No close structurally related compounds were found for TZT.

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