

SUMMARY OF DATA FOR CHEMICAL SELECTION

BENZOTHIAZOLE

CAS NO. 95-16-9

BASIS OF NOMINATION TO THE CSWG

The nomination of benzothiazole is based on the potential for human exposure through its presence in foods and as an environmental contaminant, and a lack of chronic toxicity data.

Benzothiazole came to the attention of the Chemical Selection Planning Group (CSPG) because of its ability to leach from rubber stoppers into parenteral solutions. Although benzothiazole is a chemical intermediate of moderate production volume, widespread exposure of consumers occurs through its presence in foods and beverages. Through weathering of an antioxidant from tires, road dust and street runoff contribute additional potential for human exposure to benzothiazole.

SELECTION STATUS

ACTION BY CSWG: 7/16/97

Studies requested Carcinogenicity

Priority: High

Rationale/Remarks:

Potential for human exposure based on its presence in foods and as an environmental contaminant
Lack of chronic toxicity data
Lack of information about the benzothiazole moiety, which is present in many common products

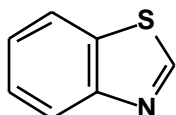
INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), provided information on the annual production range of benzothiazole. Ms. Joellen Putnam, Scientific Project Manager, Flavor and Extract Manufacturers' Association (FEMA) provided a copy of the FEMA monograph on benzothiazole.

CHEMICAL IDENTIFICATION

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| <u>CAS Registry Number:</u> | 95-16-9 |
| <u>Chemical Abstracts Service Name:</u> | Benzothiazole (8CI, 9CI) |
| <u>Synonyms and Trade Name:</u> | Benzosulfonazole; 1-thia-3-azaindene; Vanguard BT |
| <u>Structural Class:</u> | Benzothiazole |

Structure, Molecular Formula and Molecular Weight:



C_7H_5NS

Mol. wt.: 135.19

Chemical and Physical Properties:

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|--------------------------|---|
| <u>Description:</u> | Yellow liquid with unpleasant odor (Lewis, 1993) |
| <u>Boiling Point:</u> | 231°C (Lide, 1996) |
| <u>Melting Point:</u> | 2°C (Lide, 1996) |
| <u>Flash Point:</u> | >110°C (Aldrich Chemical Co., Inc., 1996) |
| <u>Density:</u> | 1.2460 g/cm ³ at 20°C (Lide, 1996) |
| <u>Solubility:</u> | Slightly soluble in water; very soluble in ethanol, diethyl ether and carbon disulfide; soluble in acetone (Budavari, 1996; Lide, 1996) |
| <u>Refractive Index:</u> | 1.6379 at 20°C (Lide, 1996) |
| <u>Vapor Pressure:</u> | 0.07 mm Hg at 20°C (Fisher Scientific, 1997) |
| <u>Reactivity:</u> | Reacts with aldehydes or ketones to generate hydroxy carbonyl compounds (Aldrich Chemical Co., Inc., 1996) |
| <u>Log P:</u> | 2.01 (Hansch <i>et al.</i> , 1995) |

Technical Products and Impurities: Benzothiazole is available at purities ranging from 96 to >99% from Aldrich Chemical Co., Acros Organics, and Fisher Scientific (Aldrich Chemical Co., Inc., 1996; Acros Organics, 1997; Fisher Scientific, 1997).

EXPOSURE INFORMATION

Production and Producers: Benzothiazole can be prepared from N,N-dimethylaniline and sulfur (Budavari, 1996). It can also be prepared by refluxing a mixture of zinc *o*-aminophenylsulfide and formic acid followed by steam distillation of the alkaliized reaction mixture; by oxidation of 2-mercaptobenzothiazole or of the corresponding disulfide; and by heating formanilide or dimethylaniline with sulfur (NLM, 1997a). Benzothiazole is manufactured and/or distributed by Fisher Chemicals, Penta Manufacturing Co., Acros Organics, Allchem Industries, Inc., Aldrich Chemical Co., Chugai Boyeki (America) Corp., Cytec Industries, Inc., Pyrazine Specialties, Inc. and Miki Sangyo (USA), Inc. (Van, 1995; Aldrich Chemical Co., Inc., 1996; Hunter, 1996; Acros Organics, 1997; Fisher Scientific, 1997).

Benzothiazole is listed in the EPA's TSCA Inventory (NLM, 1997b). U.S. production of benzothiazole in 1993 was reported to be in the range of 10,000-1,000,000 lbs. based on non-confidential data received by the EPA (Walker, 1997). Benzothiazole is listed as a chemical of commerce in the U.S. International Trade Commission (USITC) publication *Synthetic Organic Chemicals, US Production and Sales*, for the years 1987 and 1990. The reporting companies were Reichhold Chemicals, Inc. and Ciba-Geigy Corp.; but no production or sales quantities were included (USITC, 1988, 1991). According to the USITC, separate statistics were not published to avoid disclosure of individual company operations; however, the USITC reporting guidelines specify that each company's report of a chemical represents production $\geq 4,500$ kg [10,000 lbs] or sales \geq \$10,000.

The Port Import/Export Reporting Service (PIERS) reported benzothiazole imports of 449,455 lbs. over the 14-month period from August 1995 to October 1996 (Dialog Information Services, 1997).

Use Pattern: Benzothiazole is used as a chemical intermediate in organic synthesis. It is a precursor of rubber accelerators and a component of cyanine dyes. It is also used as a flavoring substance [FEMA #3256]. Its reported uses in foods at levels up to 0.5 ppm include non-alcoholic and alcoholic beverages, soft and hard candy, baked goods, meat products, gravies, soups, milk products, and cheese. It has been used as an antimicrobial agent in athletic shoe insoles (FEMA, 1997; NLM, 1997a).

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Human Exposure: No reports of occupational exposures to benzothiazole during its production or processing were found in the available literature. No listing was found for benzothiazole in the National Occupational Exposure Survey (NOES).

There is potential for widespread, low-level exposures to benzothiazole in general and consumer populations resulting from its natural presence in foods and its use as a flavoring substance. Food products containing benzothiazole and the lower limit reported (ppm) include: papaya (0.004), cooked asparagus (0.02), malt whiskey (0.006), and cocoa (trace) (FEMA, 1997). Benzothiazole is formed by the Maillard reaction in heat-processed chocolate, peanuts, filberts, beef, popcorn, and coffee. It has been isolated from boiled potatoes, sesame seed oil (22.5 ppb), and beer (Shimoda *et al.*, 1996; NLM, 1997a). Benzothiazole has been identified in the leachate from rubber stoppers, in large-volume parenteral solutions of sodium bicarbonate (27-32 &g/500 ml) and sodium chloride (Danielson, 1992). There is also potential human exposure to benzothiazole through its occurrence as an environmental pollutant. Benzothiazole has been identified as one of the anthropogenic chemicals in human thrombogenic coronary plaques (Ferrario *et al.*, 1985).

Environmental Occurrence: Benzothiazole has been identified in drinking water, lake water, river water, rainwater, and wastewater (Junk & Stanley, 1975; Jungclaus *et al.*, 1976; Brownlee *et al.*, 1981; Ellis *et al.*, 1982; Scott *et al.*, 1996). Benzothiazoles have been identified in estuarine sediments and they have been proposed as possible indicators of the contribution of street runoff to the contaminants in sediments of urban coastal areas. Benzothiazole can occur in street runoff from the weathering of an antioxidant used in rubber manufacture (Spies *et al.*, 1987). Rogge and coworkers (1993) identified benzothiazole in tire wear particles and in road dust. It has also been detected in the floor dust in office buildings and in the emissions from textile floor coverings (Wilkins *et al.*, 1993; Sollinger *et al.*, 1994).

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of benzothiazole. The American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended a threshold limit value (TLV) or biological exposure index (BEI) for benzothiazole. Benzothiazole is a “generally recognized as safe” (GRAS) substance approved by the Flavor and Extract Manufacturers Association (FEMA) as a flavor ingredient (FEMA, 1997).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to benzothiazole and cancer risk in humans were identified in the available literature. Skin irritation and sensitization from benzothiazole have been reported (Bogert & Husted, 1932).

Animal Data: No 2-year carcinogenicity studies of benzothiazole in animals were identified in the available literature. Toxicity information identified was limited to acute studies. Acute toxicity values are shown in Table 1.

Table 1. Acute toxicity data for benzothiazole

| Route | Species | Toxicity Value | Reference |
|-----------------|---------|------------------------------------|-----------------------------|
| Oral | Rat | LD ₅₀ = 478.6 mg/kg | Reddy & Mayhew, 1992 |
| Oral | Rat | LD ₅₀ = 380 mg/kg | Monsanto Co., 1991 |
| Oral | Mouse | LD ₅₀ = 900 mg/kg | Moran & Easterday, 1980 |
| Oral | Fish | LC ₅₀ = 63 mg/L @ 96 hr | Yoshioka & Ose, 1993 |
| Intraperitoneal | Mouse | LD ₅₀ = 100-200 mg/kg | Doull <i>et al.</i> , 1962 |
| Intravenous | Mouse | LD ₅₀ = 96 mg/kg | Domino <i>et al.</i> , 1952 |
| Dermal | Rabbit | LD ₅₀ = 126-200 mg/kg | Monsanto Co., 1991 |

Exposure of rats to benzothiazole saturated vapor in a glass desiccator for 6 hours was mildly toxic. All animals survived and no respiratory complications were noted during a 10-day recovery period (Monsanto Co., 1992).

Short-Term Tests: Kinae and coworkers (1981) reported that benzothiazole exhibited mutagenic activity in *Salmonella typhimurium* strain TA1537 in the presence of S9.

Metabolism: The metabolic fate of benzothiazole was determined in male guinea pigs following intraperitoneal administration of 30 mg/kg a day for 4 days. Five ring-cleavage products were identified in urinary extracts. The three major metabolites were 2-methyl-mercaptoaniline, 2-methylsulfinylaniline, and 2-methylsulfonylaniline; these were present in conjugated and unconjugated forms. The remaining two metabolites were postulated to be 2-methylsulfinylphenylhydroxylamine and 2-methylsulfonylphenylhydroxylamine; these were identified only after hydrolysis with

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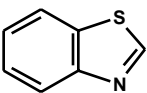
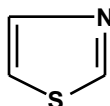
sulfatase (Wilson *et al.*, 1991). Formation of these five metabolites implied cleavage of the thiazole ring probably involving initial nucleophilic attack at the electron-deficient C-2 position (Fowler *et al.*, 1995).

To investigate the possible role of aldehyde oxidase in the ring cleavage of benzothiazole, partially purified guinea pig aldehyde oxidase was incubated with benzothiazole (0.125-2 mM). The products from the oxidation of [³H]benzothiazole by aldehyde oxidase were identified as benzothiazole and 2-hydroxybenzothiazole.

The *in vivo* metabolism of 2-hydroxybenzothiazole in guinea pigs was determined following intraperitoneal injection of 5 mg of radiolabeled compound. 2-Hydroxybenzothiazole was completely metabolized in 24 hours, producing the same major metabolites as benzothiazole. The authors stated that aldehyde oxidase may have a key role in the *in vivo* metabolism of benzothiazole and that the enzyme may play a more significant role in the *in vivo* metabolism of nitrogen heterocycles than had been previously thought (Fowler *et al.* 1995). A previous *in vitro* study with rabbit liver aldehyde oxidase found that benzothiazole was not a substrate for the enzyme. However, benzothiazole did inhibit the oxidation of quinazoline by rabbit aldehyde oxidase (Gristwood & Wilson, 1988).

Structure Activity Relationships: The parent compound, thiazole [288-47-1] was screened for relevant information associating it with mutagenic or carcinogenic activity. A summary of the information is presented in Table 2.

Table 2. Summary of information on benzothiazole and structurally related compounds

| Chemical Name | Carcinogenicity Data | Mutagenicity Data |
|---|----------------------|---|
| Benzothiazole [95-16-9]  | NDF | positive in <i>S. typhimurium</i> TA1537 with S9 (Kinae <i>et al.</i> , 1981) |
| Thiazole [288-47-1]  | NDF | negative at doses up to 10,000 &g/plate in <i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, and TA1538 with and without S9 (NCI, 1984) positive when tested at 4-100 &mol/plate in <i>S. typhimurium</i> TA98 without but not with S9 and TA100 with and without S9 (Lee <i>et al.</i> , 1994) |

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| | | negative in <i>S. typhimurium</i> TA100 at 11.7 mmol/l (Voogd <i>et al.</i> , 1983) negative in mouse L5178Y(Tk ⁺ /Tk ⁻) lymphoma cells with and without S9 (NCI, 1984) |
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NDF = no data found

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