SUMMARY OF DATA FOR CHEMICAL SELECTION

GLYCOLURIL
CAS NO. 496-46-8

BASIS OF NOMINATION TO THE CSWG

Glycoluril is presented to the CSWG for review because of its potential for human exposures in the workplace and in the general population. Glycoluril or its derivatives have several uses, primarily in paint and coating formulations. No information on the potential toxicity of this compound was found.

SELECTION STATUS

ACTION BY CSWG: 7/16/97

Studies requested:
- Metabolism studies
- *In vitro* cytogenetics
- *In vivo* micronucleus assay
- Carcinogenicity

Priority: High

Rationale/Remarks:
- Potential for exposure
- Lack of any toxicity data
- Suspicion of carcinogenicity based on potential for nitrosation

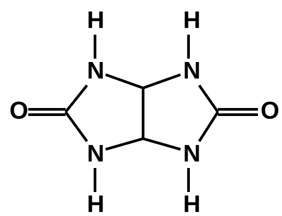
INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), provided information on the annual production range of glycoluril (Walker, 1997).

CHEMICAL IDENTIFICATION

CAS Registry Number:	496-46-8
Chemical Abstracts Service Name:	Imidazo[4,5-d]imidazole-2,5(1H,3H)-dione, tetrahydro- (9CI)
Synonyms:	Acetylene carbamide; acetylenediurea; acetylenedi- ureine; acetyleneurea; diurea glyoxalate; glyoxalbi-uret; glyoxaldiureine
Structural Class:	Bicyclic bis-urea

Structure, Molecular Formula and Molecular Weight:



$C_4H_6N_4O_2$ Mol. wt.: 142.12

Chemical and Physical Properties:

Description:	Odorless white power (Hoechst Celanese Corp., 1997)
Melting Point:	Decomposes at ~300%C (Budavari, 1996)
Density:	800 kg/m^3 (Hoechst Celanese Corp., 1997)
Solubility:	Slightly soluble in cold water (<2 g/l at 20%C), more soluble in hot water (15 g/l at 100%C); soluble in ammonium hydroxide, diethylether, and hydrochloric acid; insoluble in ethanol and acetic acid (Lide, 1995; Budavari, 1996; Hoechst Celanese Corp., 1997)
Stability:	Stable; thermal decomposition may generate carbon monoxide, carbon dioxide, and oxides of nitrogen (Budavari 1996; Hoechst Celanese Corp., 1997)
Reactivity:	Emits toxic fumes under fire conditions (Hoechst Celanese Corp., 1997)

Technical Products and Impurities: Glycoluril is available from Hoechst Celanese Corp. in commercial quantities and from Aldrich Chemical Co., Inc., and Spectrum Chemical Manufacturing Corp. (98+% purity) in research quantities (Janssen Chimica, 1992; Van, 1995; Aldrich Chemical Co., Inc. 1996).

EXPOSURE INFORMATION

Production and Producers: Glycoluril can be prepared by the sodium amalgam reduction of allantoin (Budavari, 1996). It can also be obtained in yields as high as 90% from the reaction of urea with glyoxal (Shimizu, 1987). Glycoluril is manufactured in France by Hoechst Celanese and exported to the US (Pound, 1997).

Glycoluril is listed in the EPA's TSCA Inventory (Hoechst Celanese Corp., 1997). No data were reported for glycoluril by the USITC in the most recent ten volumes of *Synthetic Organic Chemicals, US Production and Sales.* However, the annual production and importation of glycoluril 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). No other quantitative information on annual production was found in the available literature.

Use Pattern: Glycoluril or the related compounds, tetrachloroglycoluril and tetrabromoglycoluril, have been used for water treatment, as swimming pool disinfectants, and as a slimicide enhancer in pulp and paper processing (Nelson, 1979; Jones *et al.*, 1995; Sweeny, 1996). Glycoluril is a slow-release nitrogen fertilizer that may have limited use because of cost (Huffman, 1980; Shimizu, 1987). Glycoluril resins (2-50%) have been used in paint and coating formulations (Anon., 1985, 1989).

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

There is potential for widespread, low level exposures to glycoluril in general and in consumer populations from its use in water treatment, agricultural, and coating formulations. Glycoluril has also been identified as the main impurity in technical grade allantoin, a chemical used in biochemical research and medicine (Baloniak & Blaszczak, 1983; Lewis, 1993).

Environmental Occurrence: No information on the natural or environmental occurrence of glycoluril was identified in the available literature.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of glycoluril. The American

Conference of Governmental Industrial Hygienists (ACGIH) has not recommended a threshold limit value (TLV) or biological exposure index (BEI) for glycoluril. Glycoluril has been reviewed for SARA Title III (Hoechst Celanese Corp., 1997).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

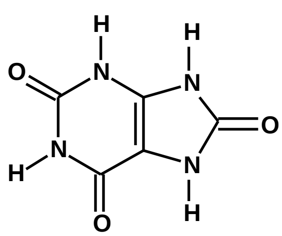
Human Data: No epidemiological studies or case reports investigating the association of exposure to glycoluril and cancer risk in humans were identified in the available literature.

Animal Data: No 2-year carcinogenicity studies of glycoluril in animals were identified in the available literature.

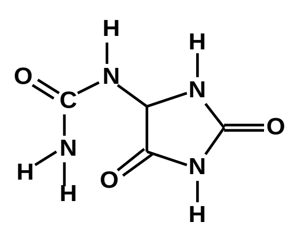
Short-Term Tests: No *in vitro* or *in vivo* studies evaluating glycoluril for mutagenic effects were found in the available literature.

Metabolism: No studies on the metabolism of glycoluril were identified in the available literature. The structurally-related compound, allantoin, is the end product of purine metabolism in mammals other than human and nonhuman primates; it results from the oxidation of uric acid (Lewis, 1993). It is generally accepted that all of the allantoin-degrading enzymes (allantoinase, allantoicase, ureidoglycollate lyase, and urease) used in purine degradation were lost during mammalian evolution. However, a recent study identified ureidoglycollate lyase in various rat tissues. High-level activity was detected in adrenal gland, kidney, liver, brain, submandibular gland and pancreas; moderate-level activity in heart and lung; and low-level activity in intestine, spleen, and skeletal muscle. The researchers suggested that ureidoglycollate lyase might play a role in metabolism other than the degradation of purines in mammals, perhaps in creatine synthesis as its structure is similar to guanidinoacetate (Fujiwara & Noguchi, 1995).

Uric acid structure



Allantoin structure



Structure/Activity Relationships: No compounds providing good structural analogues for the potential carcinogenicity or mutagenicity of glycoluril were found. The most relevant information found in the published literature was for uric acid which is also a fused ring structure, one half being identical to the two halves of glycoluril. Allantoin, the oxidation product of uric acid, was administered at 0.2% in the food to 24 male and 24 female F344 rats for 106 weeks. Afterwards they were placed on untreated feed and tap-water until 127-130 weeks. Allantoin did not induce an increase in the incidence of any tumor compared with untreated control groups. There was a significant increase in the incidence of papillomas of the forestomach in the male rats given allantoin plus nitrite (P=0.047) (Lijinsky, 1984).

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