s-Trioxane
[110-88-3]

Review of Toxicological Literature

Prepared for

Errol Zeiger, Ph.D.
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, North Carolina 27709
Contract No. N01-ES-65402

Submitted by

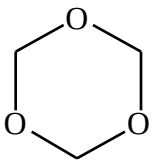
Raymond Tice, Ph.D. (Principal Investigator)
Brigette Brevard, M.A. (Co-Principal Investigator)
Integrated Laboratory Systems
P.O. Box 13501
Research Triangle Park, North Carolina 27709

March 1999

BASIS FOR NOMINATION

s-Trioxane was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicity and carcinogenicity testing based on its high U.S. production volume and potentially high human exposure.

Chemical Identification: s-Trioxane (CASRN: 110-88-3; $C_3H_6O_3$; mol. wt. = 90.08) is also called formaldehyde, trimer; metaformaldehyde; sym-trioxane; 1,3,5-trioxacyclohexane; 1,3,5-trioxane; and trioxymethylene (Lewis, 1993; Budavari, 1996).



Physical-Chemical Properties:

Property	Information	Reference
Physical State	White, crystalline solid	Budavari (1996); Radian (1991)
Odor	Chloroform-like	Budavari (1996)
Boiling Point (°C @ 759 mm Hg)	114.5	Budavari (1996); Lide and Milne (1994)
Melting Point (°C)	64	Budavari (1996); Radian (1991)
Specific Gravity (@ 65°C/20 °C)	1.17	Budavari (1996); Lide and Milne (1994)
Vapor Pressure (mm Hg @ 25 °C)	13	Radian (1991)
Flash Point (°C/ °F)	45/113	Budavari (1996); Radian (1991)
Soluble in:	Water, alcohol, ether, ketones, dimethyl-sulfoxide, and chlorinated and aromatic hydrocarbons	Budavari (1996); Lide and Milne (1994)

s-Trioxane is converted to formaldehyde in the presence of a strong acid in non-aqueous systems (Budavari, 1996). It is slowly depolymerized in strong acids, and is unreactive in basic solutions. When heated, it gives off formaldehyde vapors.

Production: s-Trioxane is produced by Hoechst-Celanese (Performance Products and Fine Chemicals Division) by distillation of formaldehyde with an acid catalyst, with solvent extraction (Lewis, 1993; Kuney, 1994). Annual production is estimated to be 92 to 181 million pounds

(42-82 million kg) (U.S. EPA, 1998).

Use: s-Trioxane is used as an intermediate in organic synthesis, mainly in the production of acetal resins (Gerberich and Seaman, 1992; Starr, 1991), as a medical disinfectant (Ligocka et al., 1998), and as a non-luminous, odorless fuel (Lewis, 1993). It is an active ingredient in some contraceptive creams (Ligocka et al., 1998). It is also used as an intermediate in the manufacture of artificial horns and ivory, and synthetic resins (Ligocka et al., 1998). Additionally, s-trioxane is used to produce CELCON□, a highly crystalline thermoplastic (Kitchens et al., 1976).

Environmental: s-Trioxane may enter the environment via waste streams as a result of its production and use. s-Trioxane has been detected at levels of 0.020-0.022 ppm (0.07-0.08 mg/m^3; 0.78-0.89 $\mu mol/m^3$) in air samples taken above preserved tissues under a canopy hood in a histology laboratory (Trocha and Samimi, 1993). In the atmosphere, depolymerization of s-trioxane would not be expected because of its stability under neutral or basic conditions. However, under slightly acidic conditions, slow depolymerization to formaldehyde is expected (Kitchens et al., 1976).

Human Exposure: Inhalation of vapors is the primary route of exposure. An estimated 5,829 employees were potentially exposed to s-trioxane in 1974 (RTECS, 1998). Dental students (male and female) exposed to allergy-producing substances, such as s-trioxane, had a higher incidence of latent allergies (65%) at the end of their fourth year of dental school than at the end of their second year (14%) (Dzhemileva et al.,1976; cited by HSDB, 1998).

Regulatory: Polyoxymethylene copolymers (used as an article or article component intended for food contact) containing s-trioxane are regulated by the Food and Drug Administration as indirect food additives (FDA) at 21 CFR §177.2470.

Chemical Disposition, Metabolism, and Toxicokinetics: s-Trioxane is metabolized to

formaldehyde (Ligocka et al., 1998). In an investigation of its distribution, excretion, and metabolism, s-trioxane was excreted mainly as exhaled CO_2 (Ligocka et al., 1998). It was distributed mainly to the liver and to a lesser extent to the fat and brain tissues. Because it is eliminated rapidly, s-trioxane is not expected to bioaccumulate significantly.

Toxicological Data: In rats, the oral LD_{50} is 5,000 mg/kg (55.5 mmol/kg) and the inhalation LC_{50} is <26 g/m^3 (7,057 ppm; 288 mol/m^3) (Czajkowska et al., 1980; cited by Ligocka et al., 1998). In rabbits, the dermal LD_{50} is 10,000 mg/kg (111 mmol/kg) (Radian, 1991). s-Trioxane was strongly irritating to the eyes and skin of rabbits (Radian, 1991). In rats, chronic inhalation exposures (concentration n.p.) to s-trioxane caused pulmonary irritation and central nervous system impairment (Jedlinska et al., 1982; Czajkowska et al., 1983; both cited by Ligocka et al., 1998).

s-Trioxane retarded fetal development and caused significant congenital malformations and maternal toxicity in rats orally administered 1.55 or 3.87 g/kg (17.2 or 43.0 mmol/kg) every other day on days 8-20 of gestation (Sitarek et al., 1988; cited by Ligocka et al., 1998).

s-Trioxane was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1538 in the presence or absence of metabolic activation (Kowalski et al., 1984; Zeiger et al., 1988). It did not induce a significant increase in micronucleated mouse erythrocytes following intraperitoneal (i.p.) administration of 2,125-4,250 mg/kg (23.59-47.18 mmol/kg) (Przybojewska et al., 1984).

No data on carcinogenicity, immunotoxicity or structure-activity relationships were located.

REFERENCES

Budavari, S. 1996. The Merck Index. 12th ed. Whitehouse Station, NJ: Merck & Co., Inc., p. 1658.

Czajkowska, T., E. Popinska, and B. Krysiak. 1980. Assessment of toxicity of trioxane and dioxolane. Final report BR-C. Institute of Occupational Medicine, Lodz (Polish). (Cited by Ligocka et al., 1998)

Czajkowska, T., B. Krysiak, and J. Sokol. 1983. Long-term inhalation toxicity of 1,3,5-trioxane. Final report C.J.01.P.02.04. Institute of Occupational Medicine, Lodz (Polish). (Cited by Ligocka et al., 1998)

Dzhemileva et al. 1976. Probl. Stomatol. 4. (Cited by HSDB, 1998)

Gerberich, H. R., and G. C. Seaman. 1992. Formaldehyde. In: Kroschwitz, J. I. (ed.). Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Vol. 11. New York, NY: John Wiley & Sons, Inc., p. 946.

HSDB (Hazardous Substances Data Bank). 1998. 1,3,5-Trioxane. HSN 3416. Bethesda, MD: National Library of Medicine (NLM). (Accessed 12/2/98)

Jedlinska, U., J. Stetkiewicz, and T. Czajkowska. 1982. Acute and subacute toxicity of trioxane and dioxolane: Pathomorphological examinations. Toczniki Naukowe IMP Lodz 3:79-89 (Polish). (Cited by Ligocka et al., 1998)

Kitchens, J. F., R. E. Casner, W. E. Harward, B. J. Macri, and G. S. Edwards. 1976. Investigation of selected potential environmental contaminants: Formaldehyde. Final Technical Report. Performed by Atlantic Research Corporation, Alexandria, VA, for the U. S. Environmental Protection Agency, Office of Toxic Substances (Washington, D. C.). Report No. EPA-560/2-76-009.

Kowalski, Z., E. Spiechowicz, and B. Baranski. 1984. Absence of mutagenicity of trioxane and dioxolane in *Salmonella typhimurium*. Mutat. Res. 136(3):169-171.

Kuney, J. H. (ed.). 1994. Chemcyclopedia. Vol. 12. Washington, D.C.: American Chemical Society, p. 305.

Lewis, R. J. (ed.). 1993. Hawley's Condensed Chemical Dictionary. 12th ed. New York, NY: Van Nostrand Reinhold, p. 1186.

Lide, D. R., and G. W. A. Milne (eds.). 1994. CRC Handbook of Data on Organic Compounds. 3rd edition. Ann Arbor, MI: CRC Press, p. 5151.

Ligocka, D., A. Sapota, and M. Jakubowski. 1998. The disposition and metabolism of 1,3,5-[U-^{14}C]trioxane in male Wistar albino rats. Arch. Toxicol. 72:303-308.

Przybojewska, B., E. Dziubatowska, and Z. Kowalski. 1984. Genotoxic effects of dioxolane and trioxane in mice evaluated by the micronucleus test. Toxicol. Lett. 21:349-352.

Radian Corporation. 1991. 1,3,5-Trioxane. NTP Chemical Repository. Website: http://ntp-server.niehs.nih.gov/htdocs/CHEM_H&S/NTP_Chem1/Radian110-88-3.html. (Accessed 1/17/99)

RTECS (Registry of Toxic Effects of Chemical Substances). 1998. s-Trioxane. RTECS No. 86627. Bethesda, MD: National Library of Medicine (NLM). (Accessed 12/2/98)

Sitarek, K., B. Baranski, J. Stetkiewicz, and I. Stetkiewicz. 1988. Teratogenicity, fetal and placental toxicity of 1,3,5-trioxane administered to pregnant female rats. Pol. J. Occup. Med. 1:51-61. (Cited by Ligocka et al., 1998)

Sitarek, K., B. Baranski, and A. Sapota. 1990. Distribution and binding of 1,3,5-[U-^{14}C]trioxane in maternal and fetal rats. Pol. J. Occup. Med. 3:83-94. (Cited by Ligocka et al., 1998)

Starr, J. B. 1992. Acetal Resins. In: Kroschwitz, J. I. (ed.). Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Vol. 1. New York, NY: John Wiley & Sons, Inc., p. 109.

Trocha, P. J., and B. S. Samimi. 1993. Analysis of volatile chemicals in the workplace by Fourier transform infrared spectroscopy. Appl. Occup. Environ. Hyg. 8(6):571-579.

U.S. EPA. 1998. OPPT High Production Volume Chemicals. Washington, D.C.: U. S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/opptintr/chemtest/hpv.htm. (11/20/97).

Zeiger, E., B. Anderson, S. Haworth, T. Lawlor, and K. Mortelmans. 1988. Salmonella mutagenicity tests IV: Results from the testing of 300 chemicals. Environ. Mol. Mut. 11(Suppl. 12):1-158.

ACKNOWLEDGEMENTS

Support to the National Toxicology Program for the preparation of s-Trioxane—Review of Toxicological Literature was provided by Integrated Laboratory Systems, Inc., through NIEHS Contract Number N01-ES-65402. Contributors included: Raymond R. Tice, Ph.D. (Principal Investigator); Brigette D. Brevard, M.A. (Co-Principal Investigator); and Esther M. Morris, M.S.