

# Safety Data Sheet

# Streptozocin

Division of Safety  
National Institutes  
of Health



## WARNING!

THIS COMPOUND IS TOXIC, CARCINOGENIC, TERATOGENIC, AND MUTAGENIC. IT IS READILY ABSORBED BY VARIOUS BODY TISSUES THROUGH THE INTESTINAL TRACT AND TRANSPLACENTALLY. IT MAY IRRITATE THE SKIN AND EYES. AVOID FORMATION AND BREATHING OF AEROSOLS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND COLD WATER. AVOID WASHING WITH SOLVENTS. AVOID RUBBING OF SKIN OR INCREASING ITS TEMPERATURE.

IN CASE OF FIRE, USE WATER-BASED OR DRY CHEMICAL EXTINGUISHER.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, DRINK MILK OR WATER. REFER FOR GASTRIC LAVAGE. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. SEE CASTEGNARO ET AL. (1985) FOR DETAILS. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

### A. Background

Streptozocin (STR), a compound of glucose and N-methyl-nitroso-urea (NMNU), is a pale-yellow crystalline compound, stable in dry form and in solution at slightly acid pH, unstable in strong acid and alkali, and soluble in water and lower molecular weight alcohols. It is a natural product, first isolated from Streptomyces achromogenes var. streptozoticus fermentation broth, but is now produced synthetically. It is toxic in all mammalian species

Issued: 8/86

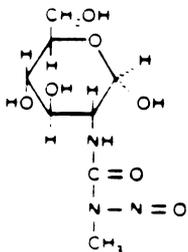
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tested, carcinogenic, mutagenic, and teratogenic. STR has a specific toxic action on the  $\beta$  cells of the pancreas, resulting in diabetes in some, but not all, animal species. Because of this action it has been used clinically in the treatment of tumors of these cells as well as of other tumors (Hodgkin's, lymphomas, lymphocytic leukemias), usually in combination with 5-fluorouracil, and as a research tool in diabetogenesis. Toxic side effects are mainly confined to the liver and kidney with little or no effect on the hematopoietic system except at high doses. Its mechanism of toxic action is thought to be similar to that of its aglucone NMNU, the glucose moiety acting as a carrier into the pancreatic  $\beta$  cells.

General reviews include: Rudas (1972); IARC (1978); Wiley (1980); Agarwal (1981); Mitchell and Schein (1986).

## B. Chemical and Physical Data

1. Chemical Abstract No.: general, 18883-66-4;  $\alpha$  anomer: 66395-18-4;  $\beta$  anomer: 66395-17-3 (see B5).
2. Synonyms: Glucopyranose, 2-deoxy-2(3-methyl-3-nitrosoureido) D-; <sup>A</sup> D-glucose, 2-deoxy-2[[[(methylnitrosoamino) carbonyl]amino] N-D-glucosyl-(2)-N'-nitrosomethylurea; NCI-CO3167; NSC-85998; streptozotocin; STN; STRZ; SZ; U-9889; Zanosar.
3. Chemical structure and molecular weight:



$C_8H_{15}N_3O_7$ ; 265.22

4. Density: No data.

**Optical activity:** STR as normally isolated by crystallization from various solvents varies widely in optical rotation ( $[\alpha]_D^{25}$  between  $+15^\circ$  and  $+68^\circ$ ). This is due to variation in content of the two ( $\alpha$  and  $\beta$ ) anomers involving carbon atom 1 of the glucose ring. In aqueous solution mutarotation occurs with final  $[\alpha]_D^{25} = +39^\circ$  (Herr et al., 1967) and an approximately equimolar mixture of  $\alpha$  and  $\beta$  anomers (Wiley, 1981). Chromatographic separation of the anomers has been described (Oles, 1978).

**Absorption spectroscopy:** STR has a strong ultraviolet band with  $\lambda_{\max} = 228$  nm ( $\epsilon = 6360$ ) with weaker maxima at 380, 394, and 412 nm. Infrared absorption data have been published (Herr et al., 1959-60; Herr et al., 1967). There is a weak fluorescence with  $\lambda_{\text{ex}} = 320$  and  $\lambda_{\text{em}} = 395$  nm (Pavlik et al., 1983).

**Volatility:** No data; may be regarded as essentially non-volatile.

**Solubility:** STR is very soluble in water, slightly soluble in polar organic solvents, and insoluble in nonpolar solvents.

**Description:** Pale-yellow platelets or prisms from 95% ethanol.

**Boiling point:** No data; **melting point:** about  $115^\circ\text{C}$  with decomposition (gas evolution).

**Stability:** The dry powder, consisting either of pure STR in the form usually distributed for investigational use (which contains 1 g STR and 220 mg anhydrous citric acid + sodium hydroxide in 20 ml vials) is stable for at least one year at room temperature and for at least 3 years at refrigerator temperatures. Solutions of this material in water or saline are stable for at least 48 and 96 hours at room temperature or in the refrigerator, respectively (Trissel et al., 1978). STR in solution has highest stability at pH 4 and is rapidly inactivated at lower pH, and in alkali with liberation of diazomethane (Herr et al., 1959-60; White, 1963).

**Chemical reactivity:** This has been reviewed (Wiley et al., 1979). The glucose moiety is converted to the tetraacetyl derivative with acetic anhydride and presumably undergoes other reactions characteristic for glucose. In dimethylsulfate there is a rapid exothermic decomposition with evolution of gas, probably nitrogen. Alkaline decomposition, resulting in diazomethane production, has been mentioned above.

13. Flash point: No data.
14. Autoignition temperature: No data.
15. Explosive limits in air: No data.

#### Fire, Explosion, and Reactivity Hazard Data

1. STR is likely to be inactivated under conditions of fire. Fire-fighting personnel should wear protective clothing and face masks. Use water to extinguish fires.
2. Flammability is likely to be low.
3. Conditions contributing to instability are acid, alkali, and elevated temperatures.
4. Hazardous decomposition products under conditions of fire are likely to include diazomethane and nitrogen oxides.

#### Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The NIH Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving STR.

It should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

1. Chemical inactivation: Validated methods have been reported (Castegnaro et al., 1985).
2. Decontamination: Turn off equipment that could be affected by STR or the materials used for cleanup. If there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Consult Castegnaro et al. (1985) for details concerning decontamination of surfaces, glassware, and animal cages.

3. Disposal: It may be possible to decontaminate waste streams containing STR before disposal. For details, see Castegnaro et al. (1985). No waste streams containing STR shall be disposed of in sinks or general refuse. Surplus STR or chemical waste streams contaminated with STR shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing STR shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing STR shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with STR shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing STR shall be handled in accordance with the NIH radioactive waste disposal system.
4. Storage: Store solid STR in unopened vials. Avoid exposure to light and moisture. Store working quantities of STR and its solutions in an explosion-safe refrigerator in the work area. See B11 for further information.

#### Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling: Tissue (and probably also plasma) samples should be stored in ice after preparation or dilution with buffer (Bhuyan et al., 1974).
2. Analysis: A disk plate bioassay has been described (Sokolski et al., 1959-60), without indication of sensitivity or specificity. The most commonly used method is the colorimetric analysis, based on acid cleavage, diazotization, and coupling to yield a compound which is read at 550 nm (Forist, 1964). The useful range is 3-30  $\mu\text{g/ml}$  of sample. This method is positive for other nitrosoureas also; nitrite ion is a positive interference, and therefore results of stability and metabolic studies, using this method, must be interpreted with caution. A polarographic procedure (calibration curve linear to 0.2  $\text{mg/ml}$ ) (Garett, 1960) and high pressure liquid chromatography (Oles, 1978) have been used in the study of behavior of STR in solution but have not been applied to biological materials.

## Biological Effects (Animal and Human)

1. Absorption: STR is readily absorbed after parenteral (intravenous intraperitoneal) injection. Absorption from the gastrointestinal tract occurs readily in mice but is poor in monkeys and negligible in dogs (White, 1963). It is also transmitted through the placenta in the rat (Deuchar, 1977) and monkey (Reynolds et al., 1974).
2. Distribution and pharmacokinetics: Note: Information discussed in this and the subsequent section on metabolism and excretion must be treated critically. Much of this information is based on studies with STR labeled in one of three positions which will be designated as follows: a: C<sub>1</sub> of the glucose moiety; b: the carbonyl group; and c: the aminomethyl group. Differences in results of studies, using these three labels, on distribution and metabolism indicate extensive breakup of the STR molecule in the animal body and afford no indication of retention or excretion of intact STR. Other studies which employ bioassay or colorimetric analysis may provide a truer picture in this regard but attention must be paid to interferences (false positives) due to metabolites (see Section E).

STR (assayed biologically or colorimetrically), after intraperitoneal injection, disappears rapidly from plasma with  $t_{1/2} = 10-15$  min (Bhuyan et al., 1974). In possible contrast to these findings in animals, Adolphe et al. (1975) could demonstrate STR colorimetrically in plasma of cancer patients 3 hours after administration. Highest tissue concentrations are found in liver and kidney, with little or no distribution to brain (Bhuyan et al., 1974). Liver accumulation of the three labels in mice and rats is about the same; the pancreas shows little or no accumulation of labels a and b but considerable accumulation of label c (Karananayake et al., 1974). Autoradiography of mice and rats injected with c also indicates high accumulation in the pancreas, particularly in the  $\beta$  cells (Johansson and Tjalve, 1978), and the time course for this accumulation roughly parallels that of  $\beta$  cell necrosis (Karananayake et al., 1976a). In patients, plasma disappearance analysis indicates that the time course of STR in the body fits a two-compartment model (Adolphe et al., 1977). Strangely, no pancreatic accumulation of c or glucose-labeled STR was demonstrated in the dog (Ryo et al., 1974), although this species shows diabetogenic effects.

3. Metabolism and excretion: In the rat after intravenous injection, 70-80% of a and b derived label is excreted in the urine, mostly during the first 6 hours, but only 42% of c

(Karunanayake et al., 1974, 1976b). Excretion in bile and feces is minimal. Several urinary metabolites, not as yet identified, derived from a and b have been found whereas only unchanged c - STR is excreted in the urine (Karunanayake et al., 1976b). The same metabolites are also found in vitro with rat liver supernatants and on liver perfusion, indicating that the liver is the organ for metabolic conversion. These results indicate that the major path of metabolism involves cleavage of the molecule between the carbonyl and the N-methyl group.

4. Toxic effects: Acute LD50 values are: 264, 275, 360 (mouse oral, iv, ip, respectively); 138 (rat, iv); 50 (dog, iv) mg/kg.<sup>A</sup> Toxic side effects have been reviewed (Weiss, 1982); in addition to those involving the pancreas, which will be discussed below, they include nausea, vomiting, emesis [STR is the most emetogenic nitrosourea (Mitchell and Schein, 1986)], and effects on liver and kidney. There is little or no effect on the hematopoietic system except at high dosages. In patients the most common additional effect is hepatic and renal toxicity (proteinuria, decreased creatinine clearance, tubular acidosis) but this is mild and usually reversible in 2-4 weeks after discontinuance of administration; nevertheless, renal toxicity has been implicated as a contributing cause of death (Schein et al., 1974). Ocular changes (cataract, changes in the caliber of retinal vessels) have been noted in the hamster (Sibay et al., 1971), and reversible neurological effects in the cat (Weinstein and Gertner, 1971). Local necrosis may occur due to extravasation at the site of parenteral injection (Dunagin, 1984).

STR exerts a specific toxic effect on the  $\beta$  cells of the pancreas. This effect is highly species dependent: susceptible species include the mouse, rat, dog, and monkey, while the cat and man appear to be resistant. In the hamster, diabetogenic symptoms are induced but there is no evidence of  $\beta$  cell damage (Sibay et al., 1971; Berman et al., 1973). In susceptible species the result of STR administration is the typical onset and progression of diabetes and is paralleled by necrosis and destruction of the  $\beta$  cells. This appears to be the result of a drastic reduction in the level of the coenzyme nicotinamide adenine dinucleotide (NAD) and is prevented by administration of nicotinamide (Schein et al., 1973; Anderson et al., 1974). It is generally assumed that the mechanism of this action is transport of STR into the

<sup>A</sup>These figures are presumably for pure STR. Evans et al. (1965) state that early investigations were carried out with crystalline lots of STR which contained 15% of an impurity (zeldalan) which had variable effects on the toxic and diabetogenic properties of STR.

β cells aided by its glucose moiety, and intracellular liberation of its aglycone N-methylnitrosourea, which methylates cellular DNA.

5. Carcinogenic effects: These have been reviewed (IARC, 1978). STR in mice, rats, and hamsters, in single or multiple intravenous or intraperitoneal doses produces benign or malignant tumors of liver, kidney, and pancreas, often with metastasis. Concomitant administration of nicotinamide reduces the incidence of renal tumors (Rakieten et al., 1976) but increases that of pancreatic tumors (Rakieten et al., 1971).
6. Mutagenic and teratogenic effects: STR is highly mutagenic in the Ames test (Franza et al., 1980) and in Chinese hamster cells (Bradley et al., 1980). The activity is greatly enhanced in the presence of activation mixture, indicating metabolic transformation of STR. The mechanism is not understood: STR is at least 250 times more mutagenic than N-methylnitrosourea or chlorozotocin but has only 7% of the alkylating activity of the latter. In rats, teratogenicity has been observed (Deuchar, 1977).

### Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents. Avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes. Obtain ophthalmological evaluation.
2. Ingestion: Drink plenty of water or milk. Refer for gastric lavage.
3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.
4. Refer to physician. Consider treatment for symptoms of diabetes and liver or kidney involvement.

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