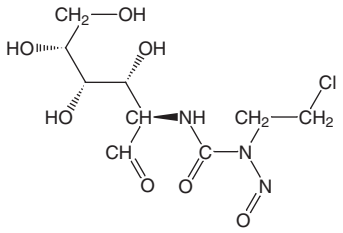
Chlorozotocin
CAS No. 54749-90-5

Reasonably anticipated to be a human carcinogen
First Listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

Chlorozotocin (CZT) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1990), and because it is a member of a well-defined, structurally related class of substances listed in a previous NTP Report on Carcinogens as either *known to be human carcinogens* or *reasonably anticipated to be human carcinogens* (NTP 1994).

When administered intraperitoneally to male and female rats, chlorozotocin induced an increase in the combined incidence of sarcoma and mesothelioma in the peritoneal cavity. When administered intravenously to male rats, chlorozotocin induced increases in the formation of malignant tumors of the nervous system, lungs, and forestomach. Chlorozotocin is an alkylating agent and is structurally related to other chloroethyl nitrosoureas, one of which, 1-(2-chloro)-3-(4-methylcyclohexyl)-1-nitrosourea (methyl-CCNU), is listed in the Report on Carcinogens as a *known human carcinogen* and two of which, *N,N*-bis(2-chloroethyl)-*N*-nitrosourea (BCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) are listed in the Report on Carcinogens as *reasonably anticipated to be human carcinogens*.

No adequate data were available to evaluate the carcinogenicity of chlorozotocin in humans.

Additional Information Relevant to Carcinogenicity

Chlorozotocin exhibits genetic activity in a wide variety of bacteria and mammalian cellular assays, inducing mutations in bacteria, yeast, insects, and cultured mammalian cells, and DNA damage in human, mouse, and Chinese hamster cells *in vitro*, and in bone-marrow cells in rats *in vivo*. Chlorozotocin exerts its adverse effects through the formation of mono- and bi-functional alkylating agents.

No data were available that would suggest that the mechanisms thought to account for tumor induction by chlorozotocin in experimental animals would not also operate in humans.

Properties

Chlorozotocin occurs as ivory crystals that are soluble in water. The melting point of chlorozotocin is 147 to 148°C. Chlorozotocin is stable in solution at room temperature (22 to 25°C) for 3 hours and at 2 to 8°C for 24 hours; the powder is stable for 24 months under refrigeration (IARC 1990).

Use

Chlorozotocin is a cytostatic agent that is used in the investigational treatment of cancers of the stomach, large intestine, pancreas, and lung, melanoma, and multiple myeloma. It has been given intravenously at doses of 100 to 225 mg/m^2 (IARC 1990).

Production

Chlorozotocin is reported to be produced in the United States (IARC 1990), but no production data were found. Data on imports or exports of chlorozotocin were also not available. No U.S. suppliers could be identified.

Synthesis of chlorozotocin occurs by nitrosation of the urea derivative prepared from D-glucosamine and 2-chloroethyl isocyanate (Johnston *et al.* 1975, cited by IARC 1990).

Exposure

The primary route of potential human exposure to chlorozotocin is intravenous administration. It has been given intravenously at doses of 100 to 225 mg/m^2 (IARC 1990). Potential exposure of health professionals may occur during the preparation and administration of the compound. Potential occupational exposure may also occur for workers involved in the formulation and packaging of the pharmaceutical. The National Occupational Exposure Survey (1981-1983) indicated that 267 workers, including 223 women, potentially were exposed to chlorozotocin (NIOSH 1990). This estimate was derived from observations of the use of the actual compound (100% of total observations). Chlorozotocin is not a naturally occurring substance, but it can be synthesized by nitrosation of the urea derivative prepared from D-glucosamine and 2-chloroethyl isocyanate (IARC 1990).

Regulations and Guidelines

No specific regulations or guidelines relevant to reduction of exposure to chlorozotocin were identified.

REFERENCES

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