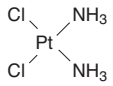
Cisplatin

CAS No. 15663-27-1

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as *cis*-dichlorodiammineplatinum(II)



Carcinogenicity

Cisplatin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Cisplatin caused tumors in two rodent species and at several different tissue sites. Repeated intraperitoneal injection of cisplatin caused leukemia in rats of both sexes in two studies and increased the incidence of benign lung tumors (adenoma) and number of tumors per animal in female mice. In a similar study in female mice, the incidence of benign skin tumors (papilloma) was increased when croton oil was applied to the skin as a tumor promoter (IARC 1981, 1987a).

Since cisplatin was listed in the *Fifth Annual Report on Carcinogens,* additional studies in rodents have been identified. Cisplatin administered by intraperitoneal injection caused benign lung tumors (adenoma) in female mice (Satoh *et al.* 1993), and a single intraperitoneal injection caused a dose-related increase in liver cancer (hepatocellular carcinoma) in metallothionein-I/II double-knockout mice (which lack a metal-binding protein thought to mitigate the toxicity of various metals) (Waalkes *et al.* 2006). In initiation-promotion studies in mice and rats, cisplatin acted as a tumor initiator following transplacental exposure via a single intraperitoneal injection late in gestation. In mice, transplacental exposure to cisplatin followed by dermal application of 12-*O*-tetradecanoylphorbol-13-acetate at 4 weeks of age initiated the development of benign skin tumors (papilloma). The offspring also developed thymic lymphoma and proliferative kidney lesions (renal-tubular dysplasia) in the presence or absence of the promoter (Diwan *et al.* 1993). In rats, transplacental exposure to cisplatin followed by administration of sodium barbital in the drinking water at 4 weeks of age initiated the development of benign kidney tumors (renal-cell adenoma) in males. Offspring of both sexes developed benign liver tumors (hepatocellular adenoma) in the presence or absence of the promoter (Diwan *et al.* 1995).

Cancer Studies in Humans

No epidemiological studies were available at the time cisplatin was listed in the *Fifth Annual Report on Carcinogens.* Since then, epidemiological studies have been identified, including several large case-control studies of secondary leukemia associated with cisplatin or carboplatin treatment. Excesses of leukemia were found in women treated for ovarian cancer (Kaldor *et al.* 1990, Travis *et al.* 1996) and men treated for testicular cancer (Pederson-Bjergaard *et al.* 1991, Travis *et al.* 1997, Howard *et al.* 2008). However, in most studies, the patients were also exposed to other potentially carcinogenic agents (including carboplatin and doxorubicin hydrochloride) or radiation. No studies to date have attempted to analyze the specific effects of cisplatin on the risk of secondary solid tumors. The studies on solid tumors were also limited by relatively short follow-up times. Cisplatin-based treatment without radiation was associated with a significant increase in the long-term risk of combined secondary solid tumors among five-year survivors of testicular cancer (van den Belt-Dusebout *et al.* 2007).

In a number of studies, cisplatin-induced platinum-DNA adducts were observed in tissue culture (IARC 1987b) and in patients receiving cisplatin-based chemotherapy (Reed *et al.* 1993).

Properties

Cisplatin is a metallic (platinum) coordination compound with a square planar geometry that is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in dimethylprimanide and *N*,*N*-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the *trans*-isomer (IARC 1981, Akron 2009). Physical and chemical properties of cisplatin are listed in the following table.

Property	Information
Molecular weight	300.0
Density	3.74 g/m^3
Melting point	270°C (decomposes)
Log K_{ow}	–2.19
Water solubility	2.53 g/L at 25°C

Source: HSDB 2009.

Use

Cisplatin is a cytostatic agent used for the treatment of various malignancies, often in combination with other antineoplastic agents (IARC 1981, HSDB 2009). Since the 1970s, cisplatin has been used in the treatment of many types of cancer, including soft-tissue and osteogenic sarcoma, Kaposi sarcoma, retinoblastoma, neuroblastoma, Wilms tumor, gestational trophoblastic tumors, and cancer of the ovary, uterus, endometrium, cervix, prostate, urinary bladder, anus, vulva, testis, adrenal gland, lymphatic system, head and neck, skin, esophagus, thyroid gland, lung (other than small-cell cancer), breast, liver (including hepatoblastoma), stomach, and bile duct (IARC 1981, MedlinePlus 2003).

Production

Preparation of cisplatin was reported in the 1840s (IARC 1981). In 2009, cisplatin was produced by eleven manufacturers worldwide, including four in India, three in Central and South America, two in Europe, one each in China and Mexico, and none in the United States (SRI 2009). It was available from 35 suppliers, including 23 U.S. suppliers (ChemSources 2009), and seven drug products with cisplatin as the active ingredient were produced by five pharmaceutical companies (FDA 2009).

Exposure

Cisplatin is used in human medicine to treat a variety of malignancies (IARC 1981). It is available as injectable solutions at a concentration of 1 mg/mL, in 10- or 50-mg vials. The usual intravenous dose of cisplatin is 20 mg/m^2 of body surface per day for five days or 100 mg/m^2 once every four weeks. Doses as high as 40 mg/m^2 daily for five consecutive days have been used (Chabner *et al.* 2001). Manufacturing and health-care workers, including housekeeping personnel, potentially are exposed to cisplatin during its production, preparation, or administration or during cleanup of medical waste, including excretions of patients treated with cisplatin. Occupational exposure to chemotherapeutic drugs was demonstrated in a study which found that urine of nurses who administer these agents was mutagenic in bacteria-based assays (Falck *et al.* 1979). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated

that 21,216 U.S. health-services workers, including 15,289 women, potentially were exposed to cisplatin (NIOSH 1990).

Environmental release of cisplatin may occur during its manufacture and through disposal of medical wastes (Zimmerman *et al.* 1981, NIOSH 2004, HSDB 2009). If released to water, cisplatin is likely to remain in solution and transform slowly to the trans form. If released to soil, it is likely to leach into the subsurface. Cisplatin has been shown to be nonbiodegradable (HSDB 2009).

Regulations

Food and Drug Administration (FDA)

Cisplatin is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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