Cyclosporin A

CAS No. 59865-13-3

Known to be a human carcinogen
Also known as ciclosporin or cyclosporine

![Chemical structure of Cyclosporin A](image)

**Carcinogenicity**

Cyclosporin A is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

**Cancer Studies in Humans**

Numerous case reports describe cancer (mainly lymphoma, Kaposi sarcoma, or skin cancer) developing in organ-transplant recipients, psoriasis patients, and rheumatoid arthritis patients treated with cyclosporin A as an immunosuppressive agent. Some of these patients were treated with cyclosporin A alone, whereas others were treated with other immunosuppressive agents in combination with cyclosporin A. The time between the start of treatment and development of tumors ranged from 1 month to 10 years. In some cases, tumors regressed after treatment with cyclosporin A was discontinued. Several epidemiological studies (cohort studies) also indicate that cyclosporin A is carcinogenic in humans, causing tumors at an incidence of less than 5% in the patient population (IARC 1990).

**Cancer Studies in Experimental Animals**

Cyclosporin A administered in the diet of mice for 78 days (at doses of up to 16 ppm) or in the diet of rats for 95 to 105 weeks (at doses of up to 8 mg/kg of body weight) did not cause tumors at any tissue site. However, when male mice of a strain with a high spontaneous rate of thymus cancer (thymic lymphoma) were fed a diet containing a high dose of cyclosporin A (150 ppm) for 20 to 34 weeks, the incidence of this cancer was increased (IARC 1990). When rats with streptozotocin-induced diabetes were administered cyclosporin A in the diet at 10 mg/kg of body weight for 20 weeks, more than half developed kidney tumors; however, the incidence of these tumors in control animals was not reported (Reddi et al. 1991). Macaque monkeys that had received heart or heart-lung transplants (allografts) were administered cyclosporin A alone or in combination with other immunosuppressive agents, by intramuscular injection. The incidence of lymphoma (a rare neoplasm in macaques) was increased in these monkeys, but not in grafted monkeys treated with immunosuppressive regimens that did not include cyclosporin A (IARC 1990).

**Studies on Mechanisms of Carcinogenesis**

In tumor initiation-promotion studies, cyclosporin A increased the incidence of lymphoid tumors in male mice exposed either to radiation or N-methyl-N-nitrosourea (MNU), hepatocellular carcinoma in male rats initiated with diethylnitrosamine, and intestinal adenocarcinoma in male rats administered MNU (IARC 1990, Masuhara et al. 1993). Cyclosporin A also increased the incidence of cervical lymph node metastasis in hamsters exposed to dimethylbenz[a]anthracene (Yamada et al. 1992) and metastasis of tumors to the liver in male mice inoculated via the portal vein with MCA 38 colon tumor cells (Yokoyama et al. 1994) or colon-26 tumor cells (Suzaki et al. 1995). In contrast, cyclosporin A did not increase the incidence of adenoma in male mice exposed to urethane, in male rats initiated with 3-methylcholanthrene, or in rats exposed to N-methyl-N-nitro-N-nitrosoguanidine (IARC 1990, Bussiere et al. 1991).

Cyclosporin A did not cause genetic damage in a number of test systems, including gene mutation in prokaryotes, gene mutation or chromosomal aberrations in cultured mammalian cells, chromosomal aberrations or micronucleus formation in rodent bone-marrow cells, DNA repair in mouse testicular cells, or dominant lethal mutation in male mice (IARC 1990, Zwanenburg and Cordier 1994). However, cyclosporin A did cause sister chromatid exchange in human lymphocytes *in vitro* and unscheduled DNA synthesis and chromosomal aberrations in the peripheral blood lymphocytes of kidney-transplant patients treated with cyclosporin A and prednisolone (IARC 1990).

The most likely explanation for the increased incidence of tumors in patients treated with cyclosporin A is immune suppression (Ryffel 1992).

**Properties**

Cyclosporin A is an immunosuppressive agent that is a cyclic non-polar oligopeptide composed of 11 amino acid residues. It is a white crystalline solid at room temperature and is slightly soluble in water and saturated hydrocarbons, very soluble in acetone, diethyl ether, and methanol, and soluble in chloroform. It is sensitive to light, cold, and oxidation (IARC 1990). Physical and chemical properties of cyclosporin A are listed in the following table.

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
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</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>1203&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Melting point</td>
<td>148°C to 151°C&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Log $K_{ow}$</td>
<td>2.92&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Sources: <sup>a</sup>HSDB 2009, <sup>b</sup>ChemIDplus 2009.

**Use**

Cyclosporin A has been used as an immunosuppressive agent since the mid 1980s. It is used extensively in the prevention and treatment of graft-versus-host reactions in bone-marrow transplantation and to prevent rejection of kidney, heart, and liver transplants. It is also used as an ophthalmic emulsion for the topical treatment of dry eye syndrome. In addition, it has been tested for use as therapy for a large variety of other diseases in which immunological factors may have a pathogenetic role, including Graves disease, uveitis, Crohn disease, ulcerative colitis, chronic active hepatitis, primary biliary cirrhosis, diabetes mellitus, myasthenia gravis, sarcoidosis, dermatomyositis, systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and certain nephropathies (IARC 1990, Reents 1996). Cyclosporin A is used alone or in combination with azathioprine, prednisolone, prednisone, antilymphocyte globulin, actinomycin, cyclophosphamide, methylprednisolone, or phototherapy (e.g., PUVA, UVB). Cyclosporin A is administered orally, intravenously, or topically. Oral preparations may contain corn, castor, or olive oil in ethanol; intravenous
preparations contain 33% alcohol and a castor-oil vehicle; and topical preparations may contain glycerin, castor oil, polysorbate 80, carbomer 1342, and sodium hydroxide. A microemulsion oral formula of cyclosporin A was approved by the U.S. Food and Drug Administration in 1995 (Reents 1996).

Production
Cyclosporin A may be biosynthesized by the fungus *Tolypocladium inflatum* or may be produced synthetically. It is manufactured commercially in Europe and East Asia (SRI 2009). In 2009, 20 U.S. suppliers of cyclosporin A were identified (Chem Sources 2009), and FDA-approved drug products containing cyclosporin A as the active ingredient were produced by 11 U.S. pharmaceutical companies (FDA 2009). No data on U.S. imports or exports of cyclosporin A were found.

Exposure
The primary routes of potential human exposure to cyclosporin A are intravenous and oral administration. Patients receiving immunosuppressive therapy for organ transplants, rheumatoid arthritis, and other diseases may be exposed to cyclosporin A. Cyclosporin A is available in oral capsules (25, 50, or 100 mg), 100-mg/mL oral solutions, 0.05% ophthalmic emulsions, and 50-mg/mL injectable vials (FDA 2009). In 2008, sales of one brand-name product with cyclosporin A as the active ingredient totaled over $339 million, with over 2 million prescriptions filled, and sales of generic cyclosporin A totaled $56 million (DrugTopics 2009a,b,c). A typical oral dosage of cyclosporin A is 18 mg/kg of body weight daily, beginning 12 hours before transplantation and continuing for one to two weeks, followed by reduction of the dosage to 5 to 10 mg/kg or less. Cyclosporin A may also be given intravenously at one third the oral dose. This drug often is given to transplant recipients for several months (IARC 1990). Occupational exposure potentially may occur among workers formulating or packaging the solutions and health-care professionals administering the drug.

Regulations

Consumer Product Safety Commission (CPSC)
Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)
Cyclosporin A is a prescription drug subject to specific labeling 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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References