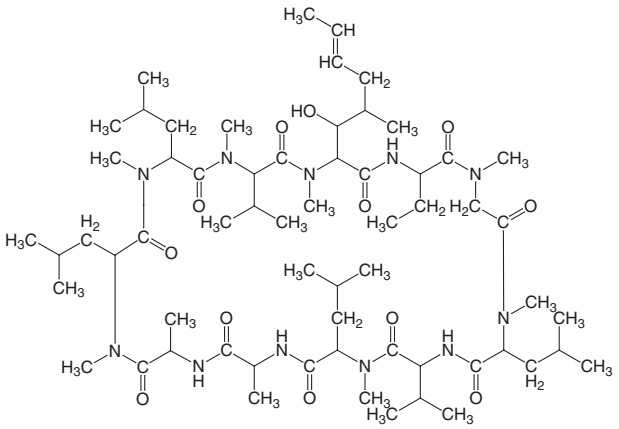
Cyclosporin A
CAS No. 59865-13-3

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



Carcinogenicity

Cyclosporin A is *known to be a human carcinogen* based on studies in humans indicating a causal relationship between exposure to cyclosporin A and human cancer. Numerous case reports describe cancer (mainly lymphoma or skin cancer) developing in organ transplant recipients, psoriasis patients, and rheumatoid arthritis patients treated with cyclosporin A as an immunosuppressive agent (IARC 1990). 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 treatment initiation and tumor development ranged from 1 month to 10 years. In some cases, tumors regressed after discontinuation of treatment with cyclosporin A. Several cohort studies also indicate that cyclosporin A is carcinogenic in humans, inducing a tumor incidence of less than 5% in the patient population (IARC 1990).

Cyclosporin A was tested by oral administration, alone and in combination with other treatments, in rats and mice and by intramuscular injection in monkeys (macaques) that had received heart or heart-lung transplants (allografts). Mice fed diets containing up to 16 mg/kg cyclosporin A for 78 weeks and rats fed diets containing up to 8 mg/kg for 95 to 105 weeks did not develop an increased incidence of tumors. However, an increased incidence of thymic lymphoma was observed in male mice administered 150 mg/kg cyclosporin A in the diet for 20 to 34 weeks (IARC 1990), and renal tumors were detected in more than 50% of streptozotocin-induced diabetic animals administered 10 mg of cyclosporin A. The incidence of lymphoma (a rare neoplasm in macaques) was significantly increased in groups of grafted macaques receiving cyclosporin A alone or in combination with other immunosuppressive agents compared to immunosuppressive regimens excluding cyclosporin A. Lymphoma was not observed in groups that were not treated with cyclosporin A. In dietary studies, an increased incidence of thymic lymphoma was observed in male mice administered 150 ppm cyclosporin A for 20 to 34 weeks; however, no increase in the incidence of tumors in any organ was found in male mice administered 1, 4, or 16 ppm cyclosporin A for 78 weeks (IARC 1990). In rats, in a study in which there was no mention of control tumor incidence, renal tumors were detected in more than 50% of streptozotocin-induced diabetic animals administered 10 mg cyclosporin A/kg b.w. orally for 20 weeks (Reddi *et al.* 1991). However, no increase in the incidence of tumors of any organ was observed in rats administered 0.5, 2, or 8 mg cyclosporin A/kg b.w. orally for 95 (males) or 105 (females) weeks (IARC 1990).

Additional Information Relevant to Carcinogenicity

In initiation-promotion studies, cyclosporin A increased the incidence of lymphoid tumors in male mice either irradiated or treated with *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). Treatment with cyclosporin A also increased the incidence of cervical lymph node metastasis in Syrian golden hamsters treated with 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 adenomas detected in male mice treated with urethane, in male rats initiated with 3-methylcholanthrene, or in rats treated with *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (IARC 1990, Bussiere *et al.* 1991).

Cyclosporin A did not induce genetic damage in a number of test systems (e.g., gene mutations in prokaryotes, gene mutations and chromosomal aberrations in cultured mammalian cells, chromosomal aberrations and micronuclei in rodent bone marrow cells, DNA repair in mouse testicular cells, and dominant lethal mutations in male mice) (IARC 1990, Zwanenburg and Cordier 1994). However, cyclosporin A did cause sister chromatid exchanges 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 (cyclosporine or ciclosporine) is the major component of the cyclosporins, a group of nonpolar cyclic oligopeptides possessing immunosuppressive activity, and it is the only member of this group used clinically (Budavari *et al.* 1996). It consists of 11 amino acids with a molecular weight of 1202.6 and occurs as a white solid with a melting point of 148°C to 151°C (natural) and 149°C to 150°C (synthetic) (IARC 1990). Cyclosporin A is slightly soluble in water and soluble in organic solvents (Budavari *et al.* 1996). It is stable in solution at temperatures below 30°C but is sensitive to light, cold, and oxidization (IARC 1990). Cyclosporin A is incompatible with alkali metals, aluminum, and heat. Hazardous combustion or decomposition products include carbon monoxide, carbon dioxide, nitrogen oxides, hydrogen chloride gas and phosgene (Sigma 2000).

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 for the prevention of rejection of kidney, heart, and liver transplants. It also has been tested for the therapy of a large variety of other diseases in which immunological factors may have a pathogenetic role, including Graves' disease, uveitis, Crohn's 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 and/or phototherapy (e.g., PUVA, UVB). Cyclosporin A is administered orally or intravenously (i.v.). Oral preparations may contain corn,

castor, or olive oil in ethanol; i.v. preparations contain 33% alcohol and a castor oil vehicle. In July 1995, a microemulsion oral formula of cyclosporin A was approved by the FDA (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 2003). Chem Sources (2003) listed 12 U.S. suppliers, and eight U.S. pharmaceutical companies were identified as having drug products approved by the U.S. Food and Drug Administration (FDA) containing cyclosporin A as the active ingredient (FDA 2003). No data on imports or exports of cyclosporin A were available.

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 (25-, 50-, or 100-mg) oral capsules, 100 mg/mL oral solutions, 0.05% ophthalmic emulsions, and 50 mg/mL injectable vials (FDA 2003). In 2002, sales of one brand-name product with cyclosporine as the active ingredient totaled $142 million while sales of generics were $34 million (DrugTopics 2003). A typical oral dose of cyclosporin A is 18 mg/kg daily, beginning 12 hours before transplantation and continuing for one to two weeks. The dosage may subsequently be reduced to 5 to 10 mg/kg or less. Cyclosporin A also may be given by intravenous administration at one-third the oral dose. This drug is often given for several months to transplant recipients (IARC 1990). Potential occupational exposure may occur for workers formulating or packaging the solutions and for health care professionals administering the drug.

Regulations

CPSC

Any orally-administered, prescription drug for human use requires child-resistant packaging

FDA

Cyclosporin A is a prescription drug subject to specific labeling requirements

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