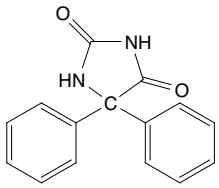
Phenytoin and Phenytoin Sodium

CAS Nos. 57-41-0 and 630-93-3

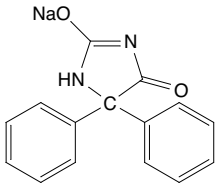
Reasonably anticipated to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as diphenylhydantoin, 5,5-diphenylhydantoin, or Dilantin (a registered trademark of Warner-Lambert Co., LLC)



Phenytoin



Phenytoin sodium

Carcinogenicity

Phenytoin and its sodium salt are *reasonably anticipated to be human carcinogens* based on sufficient evidence from studies in experimental animals.

Cancer Studies in Experimental Animals

Phenytoin as its sodium salt caused lymphoma and leukemia in mice by two different routes of exposure. Administration of phenytoin sodium in a liquid diet caused thymic and generalized lymphoma in females, and administration by intraperitoneal injection caused leukemia and thymic and mesenteric lymphoma in both sexes (IARC 1977).

Since phenytoin and phenytoin sodium were listed in the *First Annual Report on Carcinogens,* additional studies in rodents have been identified. The effects of phenytoin in mice and rats were evaluated following dietary exposure of adults, perinatal exposure (*in utero* and via lactation), or combined perinatal and adult exposure. In mice, phenytoin caused liver tumors in females after adult-only exposure or combined perinatal and adult exposure and in males after combined perinatal and adult exposure; liver-tumor incidence was not significantly increased in male mice after adult-only exposure. In rats, phenytoin marginally increased the incidence of liver tumors in males after adult-only exposure or combined perinatal and adult exposure; however, the effect was not enhanced by the combined exposure (NTP 1993).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to phenytoin. Several case reports and case series linked cancer outcomes to treatment with phenytoin, including reports of lymphoma among individuals undergoing phenytoin therapy, but no significant excess of lymphoma was reported in two small follow-up studies of lymphoma among epilepsy patients (IARC 1977).

Since phenytoin and phenytoin sodium were listed in the *First Annual Report on Carcinogens,* additional epidemiological studies have been identified. The International Agency for Research on Cancer concluded that there was inadequate evidence for the carcinogenicity of phenytoin in humans (IARC 1996). In studies of brain and central nervous system cancer in patients given phenytoin for epilepsy, significantly increased risks were observed in a cohort mortality study of patients treated with phenobarbital and phenytoin (White *et al.* 1979) and in two cohort incidence studies of patients treated with phenytoin (with or without phenobarbital) (Olsen *et al.* 1989, Selby *et al.* 1989). However, IARC noted that brain tumors could have been the cause of the seizure disorder and were unlikely to be drug related. Findings from case-control studies were inclusive (IARC 1996).

Properties

Phenytoin is a white, odorless powder at room temperature (Akron 2009). It is practically insoluble in water, but it is soluble in acetone, ethanol, and alkali hydroxides (IARC 1996). It is stable under normal temperatures and pressures (Akron 2009). The only physical property identified for phenytoin sodium (molecular weight = 274.2) was its solubility in water (1 g in ~66 mL) and its insolubility in ether and chloroform (HSDB 2009). Phenytoin sodium dissociates easily to regenerate phenytoin, even in weakly acidic solutions. Phenytoin may also be administered as the water-soluble prodrug fosphenytoin (molecular weight = 362.3) or its disodium salt (molecular weight = 406.2), which are converted to phenytoin by phosphatases in the liver (McNamara *et al.* 2001). Fosphenytoin solubility in water is estimated as 349 mg/L at 25°C, and fosphenytoin disodium salt is soluble at 142 mg/mL at 25°C (O'Neil *et al.* 2006). Physical and chemical properties of phenytoin are listed in the following table.

Property	Information
Molecular weight	252.3[a]
Density	1.29 g/cm^3[b]
Melting point	286°C[b]
Log K_{ow}	2.47[b]
Water solubility	0.032 g/L at 22°C[b]
Vapor pressure	1.2×10^{-10} mm Hg at 25°C[b]
Dissociation constant (pK_a)	8.33[c]

Sources: [a]Akron 2009, [b]ChemIDplus 2009, [c]HSDB 2009.

Use

Phenytoin is an anticonvulsant drug used alone or in combination with phenobarbital or other anticonvulsant drugs to treat patients with tonic-clonic (grand mal), focal, and psychomotor seizures (IARC 1977, 1996). It can be used to control seizures occurring during neurosurgery and to reverse digitalis-induced arrhythmia. Phenytoin is also used in a 10% ointment formulation to promote healing of ulcers in patients with diabetes (Younes *et al.* 2006). Phenytoin has been used in the treatment of chorea or Parkinson's syndrome to control involuntary movements (IARC 1977, HSDB 2009). In the past, phenytoin was used to treat acute alcoholism, migraine, polyneuritis, pregnancy disorders, certain psychoses, and trigeminal neuralgia. Phenytoin is also used to control seizures in dogs (IARC 1977, 1996, NTP 1993).

Production

Commercial production of phenytoin was first reported in the United States in 1946 (IARC 1977). U.S. sales totaled 1,093,250 standard dosage units in 1990 and 984,527 in 1995 (IARC 1996). In 2009, phenytoin was produced by four manufacturers in Europe, three in South or Central America, and one in India and (SRI 2009); it was available from 14 U.S. suppliers (ChemSources 2009), and 35 pharmaceutical products contained phenytoin as an active ingredient (FDA 2009a).

Exposure

The routes of potential human exposure to phenytoin are injection, ingestion, inhalation, and dermal contact (NTP 1993, HSDB 2009). Statistics on the number of patients using phenytoin were not available, but the drug is widely used by individuals suffering from epilepsy (Epilepsy.com 2007). Phenytoin is the active ingredient in seven oral pharmaceutical products, and sodium phenytoin in nine oral products and four injectable formulations (Drugs.com 2009b). Fosphenytoin, which is a phosphate ester prodrug converted

to phenytoin (Browne *et al.* 1996), is available in one short-term injectable formulation used to administer phenytoin to individuals who cannot take an oral medication (e.g., during status epilepticus) (Drugs.com 2009a). The initial oral dosage of phenytoin for adults and children over 6 years of age is 100 mg 3 times per day; the dosage may be gradually increased by 100 mg every two to four weeks until the desired therapeutic response is obtained. Daily maintenance dosages usually range from 300 to 600 mg for adults and 3 to 10 mg/kg of body weight for children under 6 years of age (NTP 1993). As a cardiac depressant, phenytoin is usually administered in an oral dose of 100 mg two to four times per day or by intravenous injection of 50 to 100 mg every 10 to 15 minutes up to a maximum dose of 10 to 15 mg/kg of body weight (IARC 1977). Patients with large diabetic ulcers may receive dermal applications of an ointment containing 10% phenytoin to promote healing (Younes 2006). Phenytoin is also given for pain associated with peripheral neropathy, for bipolar disorder, and for localized scleroderma; usual therapeutic levels are 10 to 20 µg/mL in blood (SF 2008, MedlinePlus 2009). In 2009, 48 clinical trials involving phenytoin were in progress or recently completed, including 22 that were recruiting patients in the United States (ClinicalTrials 2009). Phenytoin was also found as an undeclared drug in several weight-loss products marketed as dietary supplements (FDA 2009b).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of phenytoin before 2007 ranged from 8,000 to 20,000 lb except in 2002, when no releases were reported, and in 2003, when 41,000 lb was released. In 2007, one facility released 40 lb of phenytoin to air (TRI 2009).

Occupational exposure to phenytoin may occur among workers involved in formulation and packaging of the pharmaceutical products and health professionals involved in its preparation and administration. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 23,400 workers, including 16,795 women, potentially were exposed to phenytoin (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

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

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Food and Drug Administration (FDA)

Phenytoin 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.

Occupational Safety and Health Administration (OSHA)

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

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