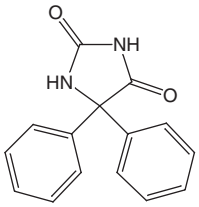
Phenytoin
CAS No. 57-41-0

Reasonably anticipated to be a human carcinogen
First Listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Phenytoin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence in experimental animals. When administered in the diet, phenytoin induced increased incidences of thymic and generalized lymphomas in female mice. Hepatocellular tumors increased in a dose-dependent manner in female mice (adult exposure), in male and female mice (perinatal and adult exposure), and male rats (perinatal and adult exposure). Intraperitoneal injection induced increased incidences of thymic and mesenteric lymphomas and leukemias in mice of both sexes (IARC 1977, 1996, NTP 1993). An IARC Working Group reported that there is inadequate evidence for the carcinogenicity of phenytoin in humans (IARC 1996). Cancer, mostly neuroblastoma and tumors of neural crest origin, has been reported in six children aged 3 years or less who had been diagnosed as having congenital abnormalities thought to be induced by prenatal exposure to phenytoin. Although the number of patients is small, the concordance of rare events suggests that phenytoin may be a transplacental carcinogen in humans. There is also one report of malignant mesenchymoma in a patient with phenytoin malformations (IARC 1982). There have been several case reports of lymphomas among individuals under phenytoin therapy. However, no significant excess of lymphoma was reported in two follow-up studies of epilepsy patients. An increased incidence of brain and other neurological tumors was reported among people prescribed phenytoin. This incidence is similar to that reported among epileptics and may reflect the underlying disease, rather than use of the drug *per se* (IARC 1977, 1979, 1982, 1996).

Properties

Phenytoin is a white crystalline powder that is practically insoluble in water, but soluble in ethanol, acetone, acetic acid, and alkali hydroxides. Phenytoin is available in the United States as a grade containing 98.5% to 100.5% active ingredient on a dried basis (NTP 1993, IARC 1996, 1977).

Use

Phenytoin is an anticonvulsant drug used alone, or in combination with phenobarbital or other anticonvulsants to treat grand mal epileptic patients with focal and psychomotor seizures (NTP 1993). Phenytoin can also be used to control seizures occurring during neurosurgery, to reverse digitalis-induced arrhythmias (particularly ventricular arrhythmias), and to prevent postcountershock arrhythmias in digitalized patients (Kirk-Othmer 1978, 1981, IARC 1996). Phenytoin has been used in the treatment of chorea or Parkinson's syndrome to control involuntary movements. It has been investigated for the treatment of trigeminal neuralgia, migraine, polyneuritis of pregnancy, acute alcoholism, and certain psychoses, but these uses have not been approved by FDA. Phenytoin is also used to control epileptic-like convulsions in dogs (IARC 1977).

Production

The USITC identified one manufacturer of phenytoin and sodium phenytoin from 1980 to 1986, but no production volumes were reported (USITC 1987). The Chem Sources International directory lists 13 current suppliers of phenytoin in the United States (Chem Sources 2001). In 1983, U.S. imports of phenytoin were 551 lb, and imports of its sodium salt were close to 15,000 lb (USITC 1984). In 1977, total estimated U.S. sales of phenytoin for use in human medicine were less than 172,000 lb annually. In 1974, imports exceeded 5,000 lb. Commercial production of phenytoin was first reported in the United States in 1946 (IARC 1977). Sales in the United States for 1990 and 1995 were 1,093,290 and 984,527 standard dosage units, respectively (IARC 1996).

Exposure

The primary routes of potential human exposure to phenytoin are injection, ingestion, inhalation, and dermal contact. Statistics on the number of patients using phenytoin were not available, but the drug is given to a major segment of individuals suffering from epilepsy. The oral dosage for adults and children over 6 years of age is initially 100 mg 3 times per day; the dosage may be gradually increased by 100 mg every 2 to 4 weeks until the desired therapeutic response is obtained. Maintenance dosages usually range from 300 to 600 mg daily for adults, and 3 to 10 mg/kg body weight daily for children under 6 years of age (NTP 1993). As a cardiac depressant, phenytoin is usually administered in an oral dose of 100 mg 2 to 4 times per day. Sodium phenytoin is typically administered by intravenous or intramuscular injection (IARC 1977). 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 pharmaceuticals. The NIOSH (unpublished data) estimated that 23,400 males and 16,795 females may have been exposed to phenytoin between 1981 and 1983 (NTP 1993).

EPA's Toxic Chemical Release Inventory (TRI99 2001) listed one industrial facility that reported releases of phenytoin in 1999. These reported releases of phenytoin to the environment were estimated to total 27,052 lb (9,401 lb total on- and off-site releases, 152 lb treated on-site, and 17,500 lb treated off-site).

Regulations

CPSC

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

EPA

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements

FDA

Phenytoin is a prescription drug subject to labeling and other requirements

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