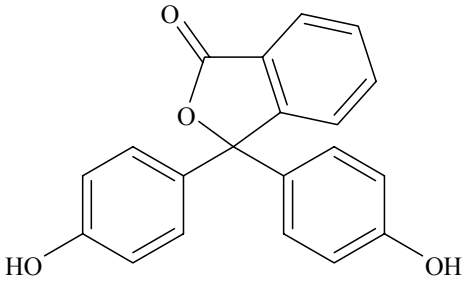
PHENOLPHTHALEIN
CAS No. 77-09-8
First Listed in the *Ninth Report on Carcinogens*



CARCINOGENICITY

Phenolphthalein is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of increased incidence of malignant and/or combination of malignant and benign tumors in multiple tissue sites and in multiple species (IARC 2000). In a two-year $B6C3F_1$ mouse carcinogenicity study, NTP (1996) concluded that phenolphthalein, administered in feed, induced significant increases in the incidence of histiocytic sarcoma and lymphomas of thymic origin in males and females and malignant lymphoma (all types) and benign ovarian sex cord stromal tumors in females. In the corresponding Fischer 344 rat dietary carcinogenicity study, phenolphthalein induced significant increases in the incidence of benign pheochromocytoma of the adrenal medulla in males and females and renal tubule adenoma in males (NTP 1996). In a 6-month dietary study with female heterozygous p53-deficient transgenic mice, phenolphthalein induced a significant increase in the incidence of malignant lymphoma of thymic origin (Dunnick *et al.* 1997).

A few epidemiological studies have investigated the association between the use of phenolphthalein-containing laxatives and colon cancer or adenomatous colorectal polyps. No consistent association was found. Cancers at other sites have not been investigated in humans (IARC 2000).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

The malignant thymic lymphomas induced by phenolphthalein in female heterozygous p53-deficient transgenic mice exhibited a loss of the normal p53 allele, suggesting the involvement of a mutagenic mechanism in tumor induction and/or progression (Dunnick *et al*. 1997).

Phenolphthalein causes enhanced oxygen radical production in *in vitro* systems. *In vivo*, reduction of phenoxyl radicals could allow reformation of phenolphthalein, establishing a futile cycle of oxidation and reduction, thereby generating more free radical species. Thus, phenolphthalein may be a significant source of oxidative stress in physiological systems.

Although negative for mutagenicity and DNA damage in bacteria, phenolphthalein exhibits genetic activity in several *in vitro* and *in vivo* mammalian assays. Phenolphthalein was positive for the induction of chromosomal aberrations in cultured Chinese hamster ovary cells in

the presence of metabolic activation and induced *hprt* gene mutations, chromosomal aberrations, and morphological transformation in Syrian hamster embryo cells. Phenolphthalein was also positive for the induction of micronucleated erythrocytes in mice following multiple, but not single, treatments administered by gavage or dosed feed. Phenolphthalein also induced micronuclei in female heterozygous p53-deficient transgenic mice exposed via dosed feed for 26 weeks. Abnormal sperm were induced in male mice, but not male rats, treated with phenolphthalein via dosed feed for 13 weeks. Phenolphthalein was negative for Na/K ATPase gene mutations and aneuploidy in Syrian hamster embryo cells.

No data were available that would suggest that the mechanisms thought to account for tumor induction by phenolphthalein in experimental animals would not also operate in humans. Phenolphthalein causes oxidative stress and also demonstrates the capability to alter tumor suppressor gene pathways, which are both mechanisms believed to be involved in human cancer.

PROPERTIES

Phenolphthalein is an odorless, white or faintly yellow-white powder comprising minute, triclinic crystals (Budavari 1996, NTP 1996, HSDB 2001). It has a melting point of 258 to 262°C. It is almost insoluble in water, very slightly soluble in chloroform, and soluble in alcohol, diethyl ether, dilute solutions of alkali hydroxides, and hot solutions of alkali carbonates. Phenolphthalein-titrated solutions are colorless at pH <8.5 and pink to deep red at pH >9 (Budavari 1996).

USE

Phenolphthalein in 1% alcoholic solution is used as a visual indicator in titrations of mineral and organic acids and most alkalies (Budavari 1996). It is also used in a variety of ingested products as well as in some scientific applications. Because phenolphthalein is odorless and tasteless, it can be incorporated easily in tablets, powder, and liquid. It has been commonly used as a laxative, available worldwide as an over-the-counter chocolate or gum laxative product. The typical oral dose is 30 to 200 mg for adults and children ≥12 years of age. A dose of 270 mg should not be exceeded. The dosages for children aged 6 to 11 years or 2 to 5 years are 30 to 60 mg and 15 to 30 mg, respectively (IARC 2000). Bedridden patients require 500 mg doses (Sollman 1957).

PRODUCTION

As reported in 1997, only one company produced phenolphthalein in the United States, with an annual production of 250 tons (197 metric tons) (SRI 1997a). Twenty manufacturers of phenolphthalein-containing laxatives were identified in 1997 (FDA 1997). There are 39 current suppliers of phenolphthalein in the U.S. (Chem Sources 2001). Combined sales of the top three phenolphthalein-containing drugs, Correctol®, Phillips®, and Ex-Lax®, totaled 16.4% of the laxative market in 1989 (Drug Store News 1990), 23.9% in 1992 (Advertising Age 1993), and 19.9% in the period July 1993 to July 2, 1994 (DeNitto 1994). The three drugs were still among the top-selling laxatives in 1995 (SRI 1997b). Ex-Lax®, which continued to hold a top-three position in 1996, accounted for approximately 7% of the brand-name sales (Suplee 1997, Drug Topics 1997). The use of phenolphthalein in laxatives has decreased since the FDA proposed the reclassification of its use in over-the-counter laxative products (FDA 1997). Producers of Correctol® and Feen-a-Mint® brand products replaced phenolphthalein with bisacodyl in January

1996. Bayer's Phillips' GelCaps was voluntarily removed from the market in mid 1997. Novartis AG, the marketer of Ex-Lax®, announced in late August 1997 that its product would be reformulated, substituting senna for phenolphthalein (Suplee 1997, Drug Topics 1997).

EXPOSURE

The major routes of human exposure to phenolphthalein are ingestion, dermal contact, and inhalation of contaminated air originating from process units manufacturing the compound. The general population is exposed to phenolphthalein through its common application as an over-the-counter drug, particularly as a laxative. Many studies show that the use of laxatives to relieve constipation and to maintain regularity in bowel habits is widespread in the United States; however, few studies report on the prevalence of phenolphthalein laxative use.

From studies of four U.S. populations (Harari *et al*. 1996, Everhart *et al.* 1989), it would appear that no more than 10% of the U.S. population has used phenolphthalein-containing laxatives as often as once per month, but up to 5% may have used them weekly or more often. In one study of 424 cases of invasive adenocarcinoma of the colon and 414 controls in Washington state, ages 30 to 62 years, it was found that 13.6% of the subjects reported constipation requiring treatment (use of a laxative, enema, or prunes), 4.7% reported ever using phenolphthalein laxatives, and 3.5% reported use of phenolphthalein laxatives at least 350 times in their lifetimes (Jacobs and White, 1998). In three U.S. populations of 268 to 813 persons comprising approximately equal numbers of cases of adenomatous colorectal polyps and controls, 0.97 to 5.1% of the subjects used phenolphthalein laxatives at least once per week. The two North Carolina groups included subjects aged 30 to 89 years, 58% and 53% of which were female; the group in Los Angeles, California, included subjects aged 50 to 74 years of which 34% were female. Mean ages of the three groups were comparable (59 to 62 years). The frequent phenolphthalein laxative users represented 8% to 30% of all frequent laxative users. The overuse of phenolphthalein laxatives in the two North Carolina groups was 17.5% and 25%, with 10% and 7% using them at least once per month (Longnecker *at al.* 1997).

Potential occupational exposure could occur through inhalation or dermal contact for workers involved in the manufacturing, formulating, packaging, or administering of drugs containing phenolphthalein. The National Occupational Exposure Survey (NOES), conducted by NIOSH between 1981 to 1983, listed 75,243 workers (26% female) as being potentially exposed to phenolphthalein. The number of Health Services employees potentially exposed to the compound was 20,122 (65% female) (NIOSH 1990).

REGULATIONS

Phenolphthalein is regulated by EPA under the Clean Air Act (CAA). Emission standards are given for organic hazardous air pollutants for chemical manufacturing process units that produce phenolphthalein.

FDA, under the Food, Drug, and Cosmetic Act (FD&CA), regulates phenolphthalein-containing drug products as new drugs. In the *Federal Register* notice, which affects 21 CFR Part 310 and 334, FDA proposed to reclassify phenolphthalein from Category I (generally recognized as safe and effective and not misbranded) to Category II (not generally recognized as safe and effective and misbranded) and added it to a list of non-monograph active ingredients. Phenolphthalein would be added to 21 CFR Section 310.545(a)(12)(iv), the list of stimulant laxatives.

OSHA regulates phenolphthalein under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 145.

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