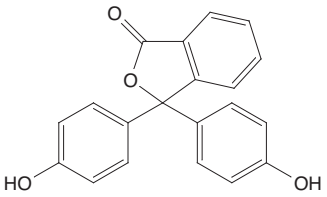
Phenolphthalein

CAS No. 77-09-8

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)



Carcinogenicity

Phenolphthalein is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to phenolphthalein caused tumors at several different tissue sites in mice and rats. Dietary administration of phenolphthalein caused thymic lymphoma and connective-tissue tumors (histiocytic sarcoma at various tissue sites) in mice of both sexes. It also increased the combined incidence of all types of malignant lymphoma in female mice and caused benign tumors of the ovary (sex-cord-stromal tumors) in female mice, the adrenal gland (pheochromocytoma of the adrenal medulla) in rats of both sexes, and the kidney (renal-cell adenoma) in male rats (NTP 1996).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to phenolphthalein. In several case-control studies of the risk of colon cancer or adenomatous colorectal polyps and the use of phenolphthalein-containing laxatives, the results were inconsistent. Most of the studies had limited statistical power (IARC 2000). Since phenolphthalein was listed in *Ninth Report on Carcinogens,* additional epidemiological studies have been identified. Two small case-control studies found no significant association between epithelial ovarian cancer and the use of phenolphthalein as a laxative (Cooper *et al.* 2000, 2004). A case-control study of cancer at several tissue sites reported a statistically nonsignficant twofold increase in the risk of colon cancer among heavy users of phenolphthalein; however, the study was limited by small numbers of cases for most tumor sites in subjects with higher exposure (Coogan *et al.* 2000).

Studies on Mechanisms of Carcinogenesis

Phenolphthalein caused genetic damage in several *in vitro* and *in vivo* mammalian test systems. It caused *hprt* gene mutations, chromosomal aberrations, and morphological transformation in Syrian hamster embryo cells with or without mammalian metabolic activation, and it caused chromosomal aberrations in Chinese hamster ovary cells with metabolic activation. *In vivo,* phenolphthalein caused micronucleus formation in mouse erythrocytes after repeated, but not single, exposure by gavage or in the diet, and dietary administration for 13 weeks caused abnormal sperm in male mice (NTP 1999, IARC 2000). Dietary administration of phenolphthalein to female heterozygous *p53*-deficient transgenic mice for 26 weeks caused micronucleus formation and malignant thymic lymphoma. In the tumors, the normal allele of the *p53* tumor-suppressor gene had been lost, suggesting the involvement of a mutagenic mechanism in tumor induction and/or progression (Dunnick *et al.* 1997).

Phenolphthalein is absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the intestinal epithelium and liver, resulting in almost complete conversion to its glucuronide, which is eliminated in the bile (NTP 1999). Phenolphthalein enhances the production of oxygen radicals in *in vitro* systems (IARC 2000). *In vivo*, reduction of phenoxyl radicals could allow re-formation 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 (Sipe *et al.* 1997).

No evidence is available to suggest that mechanisms by which phenolphthalein causes tumors in experimental animals would not also operate in humans. In rodents, phenolphthalein caused oxidative stress and altered tumor-suppressor gene pathways, both of which are mechanisms believed to be involved in human cancer.

Since phenolphthalein was listed in the *Ninth Report on Carcinogens,* an additional study relevant to mechanisms of carcinogenesis has been identified. Dietary administration of phenolphthalein to transgenic mice with the human c-*Ha-ras* proto-oncogene promoted the development of lung cancer (adenocarcinoma) induced by a single intraperitoneal injection of *N*-ethyl-*N*-nitrosourea (*N*-nitroso-*N*-ethylurea, which is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*) (Imaoka *et al.* 2002).

Properties

Phenolphthalein is a benzofuran derivative that exists as an odorless white or yellowish white triclinic crystal at room temperature (NTP 1996, Akron 2009). It is practically insoluble in water, but is soluble in dilute solutions of alkali hydroxides, ether, acetone, pyrene, chloroform, toluene, and ethanol. It is insoluble in benzene and petroleum ether (NTP 1996, HSDB 2009). Phenolphthalein is not flammable (Akron 2009). Phenolphthalein-titrated solutions are colorless at pH less than 8.5 and pink to deep red at pH greater than 9 (NTP 1996). Physical and chemical properties of phenolphthalein are listed in the following table.

Property	Information
Molecular weight	318.3[a]
Specific gravity	1.277 at 32°C[a]
Melting point	262.5°C[a]
Log K_{ow}	2.41[a]
Water solubility	0.4 g/L at room temperature[a]
Vapor pressure	6.7×10^{-13} mm Hg at 25°C[b]
Vapor density relative to air	11[c]
Dissociation constant (pK_a)	9.7 at 25°C[a]

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

Use

Phenolphthalein in 1% alcoholic solution is used as a visual indicator in titrations of mineral and organic acids and most alkalis (IARC 2000). One of the indicator uses of phenolphthalein is to determine the depth of concrete carbonation (Chang and Chen 2006), which is an indicator of the start of corrosion. Phenolphthalein has also been used in a variety of ingested products and in some scientific applications (NTP 1996). It is odorless and tasteless, and has been incorporated in tablets, powders, and liquids for use as a laxative. Over-the-counter chocolate or gum laxative products containing phenolphthalein formerly were available worldwide. However, in 1999, phenolphthalein was removed from the U.S. Food and Drug Administration's list of products generally recognized as safe and effective for use in over-the-counter stimulant laxatives (FDA 1999). Phenol-

phthalein has also been used to test for dilute blood in forensic applications. Phenolphthalein was as sensitive as other common indicators of blood, but was not as specific as other reagents for blood in a variety of substrates, and it reduced the amount of DNA in the sample that could be used for further identification (Tobe *et al.* 2007).

Production

In 1997, the year the FDA proposed reclassification of the use of phenolphthalein in over-the-counter laxative products, 20 manufacturers produced phenolphthalein-containing laxatives (FDA 1997). In 2009, phenolphthalein was produced by eight manufacturers worldwide, including one each in the United States and China and six in India (SRI 2009), and was available from 57 suppliers, including 34 U.S. suppliers (ChemSources 2009).

Exposure

The routes of human exposure to phenolphthalein are ingestion, dermal contact, and inhalation of contaminated air originating from process units manufacturing the compound (HSDB 2009). The general population has been exposed to phenolphthalein through its common use as an over-the-counter drug, particularly as a laxative. The typical oral dose of phenolphthalein as an over-the-counter laxative was 30 to 200 mg for adults and children aged 12 years or older; the recommended dose was not to exceed 270 mg. Children's doses were 15 to 30 mg for children aged 2 to 5 years and 30 to 60 mg for children aged 6 to 11 years (IARC 2000). Phenolphthalein also has been found as an undeclared drug in several weight-loss products that are marketed as dietary supplements (FDA 2009).

Many studies have shown that the use of laxatives to relieve constipation and to maintain regularity in bowel habits is widespread in the United States; however, few studies reported on the prevalence of phenolphthalein laxative use. From studies of four U.S. populations, it would appear that no more than 10% of the U.S. population used phenolphthalein-containing laxatives as often as once per month, but up to 5% may have used them weekly or more often (Everhart *et al.* 1989, Harari *et al.* 1996). In one case-control study of invasive adenocarcinoma in the state of Washington, with 424 cases and 414 control subjects aged 30 to 62 years, 13.6% of the subjects (cases plus controls) reported constipation requiring treatment (use of a laxative, enema, or prunes) 12 or more times per year, 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 case-control studies of adenomatous colorectal polyps in U.S. populations (two groups in North Carolina and one in California, each with a mean age between 59 and 62 years and 268 to 813 subjects, about equally divided between cases and controls), 0.97% to 5.1% of the subjects reported using phenolphthalein laxatives at least once a week. The frequent phenolphthalein laxative users accounted for 8% to 30% of all frequent laxative users; in the two North Carolina groups, the figures were 17.5% and 25%, with 10% and 7% using phenolphthalein laxatives at least once a month (Longnecker *et al.* 1997).

Occupational exposure could occur through inhalation or dermal contact during the manufacture, formulation, packaging, or administration of drugs containing phenolphthalein (HSDB 2009). Other exposures occur from the use of phenolphthalein in the laboratory setting. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 75,243 workers (26% female) potentially were exposed to phenolphthalein (NIOSH 1990); of these, 20,122 (65% female) were employed in the Health Services industry. Occupational exposure also occurs during the use of phenolphthalein in forensic applications and in determining the depth of carbonation of concrete in paved surfaces (Chang and Chen 2006).

Regulations

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)

Over-the-counter drug products containing phenolphthalein for use as a stimulant laxative are no longer generally recognized as safe and effective.

When used in laxatives, a warning must be provided that the product should not be used when abdominal pain, nausea, or vomiting are present and that frequent or prolonged use may result in dependence on laxatives. Additionally, the following cautionary statement must be provided: "If skin rash appears, do not use this or any other preparation containing phenolphthalein."

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)

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