

Phenacetin and Analgesic Mixtures Containing Phenacetin

Introduction

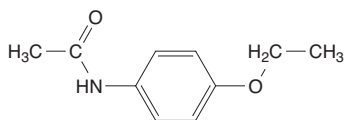
Phenacetin was first listed in the *First Annual Report on Carcinogens* (1980), as *reasonably anticipated to be a human carcinogen*, and analgesic mixtures containing phenacetin were first listed in the *Fourth Annual Report on Carcinogens* (1985), as *known to be human carcinogens*. The evidence for the carcinogenicity of these two substances is discussed separately; however, information on properties, use, production, exposure, and regulations is common to both and is combined into one section following the discussion of carcinogenicity.

Phenacetin

CAS No. 62-44-2

Reasonably anticipated to be a human carcinogen

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



Carcinogenicity

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

Cancer Studies in Experimental Animals

Dietary administration of phenacetin caused benign and malignant tumors of the urinary tract in mice and rats of both sexes and of the nasal cavity (adenocarcinoma, squamous-cell carcinoma, and transitional-cell carcinoma) in rats of both sexes (Isaka *et al.* 1979, IARC 1980).

Cancer Studies in Humans

There is limited evidence for the carcinogenicity of phenacetin in humans. There are numerous case reports of kidney cancer (transitional-cell carcinoma of the renal pelvis) among patients who had consumed large amounts of analgesic mixtures containing phenacetin; however, it is not possible to specify which component(s) of the mixture is carcinogenic (IARC 1977, 1980).

Analgesic Mixtures Containing Phenacetin

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Carcinogenicity

Analgesic mixtures containing phenacetin are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Many cases of kidney and urinary-tract cancer have been reported in patients who had consumed large amounts of analgesic mixtures containing phenacetin. Case-control studies have consistently shown a relationship between cancer of the renal pelvis and urinary bladder

and use of phenacetin-containing analgesics that is not explained by confounding by other causes of cancer. A dose-response relationship was observed in some studies (IARC 1977, 1982, 1987).

Cancer Studies in Experimental Animals

There is limited evidence for the carcinogenicity of analgesic mixtures containing phenacetin from studies in experimental animals. In male rats, oral exposure to a mixture of phenacetin, phenazone, and caffeine caused liver cancer (hepatocellular carcinoma), and phenacetin alone or in combination with phenazone slightly increased the incidence of kidney tumors (renal-cell and renal-pelvis tumors) (Johansson 1981, IARC 1982).

Phenacetin and Analgesic Mixtures Containing Phenacetin

Properties

Phenacetin occurs at room temperature as white, odorless monoclinic prisms. It is soluble in water (more so in hot than cold water), alcohol, glycerol, and acetone and is slightly soluble in benzene. It is unstable to oxidizing agents, iodine, and nitrating agents (IARC 1977). Physical and chemical properties of phenacetin are listed in the following table.

Property	Information
Molecular weight	179.2
Melting point	134°C to 135°C
Log K_{ow}	1.58
Water solubility	30 mg/L at 25°C
Vapor pressure	0.00316 mm Hg at 25°C

Source: HSDB 2009.

Use

Phenacetin was used as an analgesic and fever-reducing drug in both human and veterinary medicine for many years. It was introduced into therapy in 1887 and was extensively used in analgesic mixtures until it was implicated in kidney disease (nephropathy) due to abuse of analgesics (Flower *et al.* 1985) and was withdrawn from the U.S. market in 1983 (Ronco and Flahault 1994, FDA 1998, 1999). Phenacetin also was previously used as a stabilizer for hydrogen peroxide in hair-bleaching preparations (IARC 1980, HSDB 2009).

Production

Phenacetin was first produced in the United States in the 1920s and was used in human medicine until it was banned in the early 1980s (IARC 1977, FDA 1999). Total annual sales of phenacetin for medical use were estimated to be less than 640,000 kg (1.4 million pounds) by the late 1970s. Phenacetin was produced by one U.S. company in 1974 and two U.S. companies in 1978. In 2009, phenacetin was available from 32 suppliers, including 21 U.S. suppliers (ChemSources 2009). U.S. imports of phenacetin were 67,000 kg (148,000 lb) in 1972, 94,000 kg (207,000 lb) in 1973, 192,000 kg (423,000 lb) in 1974, 232,000 kg (511,000 lb) in 1976, 282,000 kg (620,000 lb) in 1978, and 37,500 kg (83,000 lb) in 1984 (IARC 1977, 1980, HSDB 2009). Reports filed in 1994, 1998, and 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of phenacetin totaled less than 10,000 lb (EPA 2004). No more recent data on U.S. production, imports, or exports of phenacetin were found.

Analgesic mixtures containing phenacetin were produced until phenacetin was removed from the market in the early 1980s. No spe-

cific U.S. historical production, import, or export data were found for the analgesic mixtures.

Exposure

Phenacetin and analgesic mixtures containing phenacetin were administered in tablet and capsule form. Until 1983, phenacetin was used in over-the-counter remedies for pain and fever; however, it no longer is used in drug products in the United States. The usual dosage was 300 mg four to six times per day, and the daily dose was not to exceed 2 g (IARC 1977). No information was found regarding the number of people who used phenacetin or analgesic mixtures containing phenacetin before it was withdrawn from the U.S. market, and no estimate of current exposure was found. In the past, occupational exposure may have occurred through inhalation or dermal contact by workers involved in the manufacture, formulation, packaging, or administration of phenacetin. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 18,808 workers potentially were exposed to phenacetin and 869 workers potentially were exposed to phenacetin powder (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of phenacetin = U187.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA, an HHS agency)

Phenacetin may not be used in over-the-counter drugs for digestive aid, for weight control, as an orally administered menstrual drug product, or as an internal analgesic.

Phenacetin has been withdrawn from the market because it was found to be unsafe or not effective, and it may not be compounded.

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