Phenacetin and Analgesic Mixtures Containing Phenacetin

Introduction

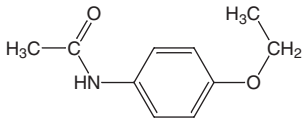
Phenacetin was first listed in the *First Annual Report on Carcinogens* (1980), and analgesic mixtures containing phenacetin were first listed in the *Fourth Annual Report on Carcinogens* (1985). The evidence for carcinogenicity of these two compounds is discussed separately; however, information on properties, use, production, exposure, and regulation is common to both and is combined into one section.

The listings for phenacetin and analgesic mixtures containing phenacetin are as follows:

- Phenacetin is *reasonably anticipated to be a human carcinogen*
- Analgesic mixtures containing phenacetin are *known to be human carcinogens*

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 in experimental animals. When administered in the diet, phenacetin caused benign and malignant tumors of the urinary tract in mice and rats of both sexes and of the nasal cavity in rats of both sexes (IARC 1982, 1987).

There is limited evidence for the carcinogenicity of phenacetin in humans because this medication was usually taken mixed with other drugs. Many case reports provide evidence that abuse of analgesic mixtures containing phenacetin results in kidney cancer (renal pelvic cancer) (IARC 1977, 1980).

Analgesic Mixtures Containing Phenacetin*

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 in humans. Many cases of kidney and urinary tract cancer have been reported in patients using large amounts of analgesic mixtures containing phenacetin. Case-control studies have been consistent in showing a relationship between cancers of the renal pelvis and bladder and use of phenacetin-containing analgesics, which is not explained by confounding from other causes of cancer. A dose-response relationship has been observed in some studies (IARC 1982, 1987).

When a mixture of aspirin (50%), phenacetin (46%), and caffeine (4%) was administered in the diet (0.7% or 1.4%) for up to 78 weeks, there was no association with tumor incidence in mice. There was a low incidence (not statistically significant) of urinary tract tumors in female rats (NCI 1978). A mixture of phenacetin and caffeine or phenacetin alone induced a slight increase in the incidence of kidney tumors in rats. Rats treated with phenacetin, phenazone, and caffeine in combination developed liver tumors (hepatomas). Based on these data, IARC (1982, 1987) concluded that there is limited evidence of carcinogenicity of analgesic mixtures containing phenacetin in experimental animals.

Phenacetin and Analgestic Mixtures Containing Phenacetin

Properties

Phenacetin occurs as white, odorless crystals or as a powder with a molecular weight of 179.2 and a melting point of 134°C to 135°C. It is slightly soluble in water and benzene, soluble in acetone, and very soluble in pyrimidine. The log octanol-water partition coefficient is 1.58, and the vapor pressure is 3.16×10^{-3} mm Hg at 25°C (HSDB 2003).

Analgesic mixtures containing phenacetin are no longer available in the United States. They previously were marketed as tablets or capsules containing either 150 mg of phenacetin, 230 mg of aspirin, and 15 or 30 mg of caffeine or 150 mg of phenacetin, 230 mg of aspirin, 30 mg of caffeine, and 8, 15, 30, or 60 mg of codeine phosphate (IARC 1977, 1980). The variety of mixtures precludes a specific discussion of properties.

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). Phenacetin was withdrawn from the U.S. market in 1983 (Ronco and Flahault 1994, FDA 1998, 1999). Phenacetin was available in tablet or capsule form in the formulations described above in "Properties" (IARC 1977, 1980). Phenacetin also was once used as a stabilizer for hydrogen peroxide in hair-bleaching preparations (IARC 1980, HSDB 2003).

Production

No information on current U.S. production of phenacetin was located, but 15 U.S. suppliers were identified in 2003 (ChemSources 2003). Phenacetin was first produced in the United States in the 1920s and production continued until it was banned in the early 1980s (IARC 1977, FDA 1999). Total sales of phenacetin for use in human medicine were estimated to be less than 640,000 kg/year (1.4 million pounds/year) by the late 1970s. Phenacetin was produced by one U.S. company in 1974 and two U.S. companies in 1978. 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 2003).

Analgesic mixtures containing phenacetin were produced until phenacetin was removed from the market in the early 1980s. No specific data on historical production, imports, or exports of the analgesic mixtures were located.

Exposure

Phenacetin and analgesic mixtures containing phenacetin were administered in tablet 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. In the past, potential occupational exposure may have occurred through

inhalation or dermal contact for workers involved in the manufacture, formulation, packaging, or administration of phenacetin. The National Occupational Exposure Survey (1981-1983) estimated that 18,808 workers potentially were exposed to phenacetin, and 869 workers were potentially exposed to phenacetin powder (NIOSH 1984). The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 4,191 workers potentially were exposed to phenacetin in the workplace in 1970 (HSDB 2003). However, the number of potentially exposed workers may be higher because these estimates did not include exposure to trade-name products that contained phenacetin (including analgesic mixtures containing phenacetin).

Regulations

EPA

Comprehensive Environmental Response, Compensation, and Liability Act
- Reportable Quantity (RQ) = 100 lb

Resource Conservation and Recovery Act
- Listed as a Hazardous Constituent of Waste
- Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - U187

FDA

Phenacetin may not be used in over the counter drugs for digestive aid, 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

*No separate CAS registry number assigned to analgesic mixtures containing phenacetin.

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