PHENACETIN and
ANALGESIC MIXTURES CONTAINING PHENACETIN

INTRODUCTION

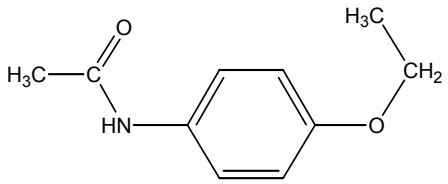
Phenacetin was listed in the First Annual Report on Carcinogens (RoC) in 1980. Analgesic mixtures containing phenacetin were listed in the Fourth Annual RoC in 1985. The profiles for phenacetin and analgesic mixtures containing phenacetin follow this introduction.

The listings for phenacetin and analgesic mixtures containing phenacetin in the Tenth Edition of the RoC are as follows:

Phenacetin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1982, 1987).

Analgesic mixtures containing phenacetin are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans (IARC 1977, 1980, 1982, 1987).

PHENACETIN
CAS No. 62-44-2
First listed in *the First Annual Report on Carcinogens*



CARCINOGENICITY

Phenacetin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1982, 1987). When administered in the diet, phenacetin induced benign and malignant tumors of the urinary tract of mice and rats of both sexes and of the nasal cavity in rats of both sexes.

There is limited evidence for the carcinogenicity of phenacetin in humans (IARC 1982, 1987). There are many case reports of renal pelvic cancer associated with abuse of analgesic mixtures containing phenacetin (IARC 1977, 1980). Analgesic mixtures containing phenacetin are discussed in the following profile.

PROPERTIES

Phenacetin occurs as white, odorless crystals or as a powder. It is slightly soluble in water, ethanol, chloroform, benzene, and glycerol, but is soluble in diethyl ether, pyrimidine, chloroform, and acetone. Phenacetin reacts with oxidizing agents, iodine, and nitrating agents. When heated to decomposition, phenacetin emits toxic fumes (HSDB 2000, NTP 2001).

USE

Phenacetin was used as an analgesic and antipyretic 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 analgesic-abuse nephropathy (Flower *et al.* 1985). Consequently, phenacetin was withdrawn from the market in 1983 (Ronco and Flahault 1994, FDA 1998, 1999). Phenacetin was available in tablet or capsule form in combination with aspirin and caffeine in formulations containing 150 mg phenacetin, 230 mg aspirin, and 15 or 30 mg caffeine or in combination with aspirin, caffeine, and codeine in formulations containing 230 mg aspirin, 30 mg caffeine, and 8, 15, 30, or 60 mg codeine phosphate (IARC 1977, 1980). Phenacetin was also once used as a stabilizer for hydrogen peroxide in hair-bleaching preparations (IARC 1980, HSDB 2000).

PRODUCTION

No current U.S. production information for phenacetin was located; however, 20 U.S. suppliers were identified (Chem Sources 2001). Phenacetin was first produced domestically in the 1920s (IARC 1977). The 1979 TSCA Inventory reported two companies producing 550,000 lb of phenacetin and five firms importing 55,000 lb in 1977 (TSCA 1979). There was at least one domestic firm producing undisclosed quantities of phenacetin in 1979 and 1980 (USITC 1980, 1981). U.S. imports of phenacetin increased from approximately 147,000 lb in 1972 to more than 620,000 lb a year in 1978 (IARC 1977, 1980); these import values subsequently declined to approximately 58,000 and 82,000 lb in 1985 and 1987, respectively (USDOC Imports 1986, 1988).

EXPOSURE

The primary routes of potential human exposure to phenacetin include ingestion, inhalation, and dermal contact. Phenacetin was previously formulated with other pharmaceutical agents and used in over-the-counter remedies for pain and fever; however, it is no longer used in drug products in the United States. The usual dosage was 300 mg 4 to 6 times per day, and the dose was not to exceed 2 g (IARC 1977). Potential occupational exposure may occur through inhalation and dermal contact for workers involved in the manufacture, formulation, packaging, or administration of phenacetin. The National Occupational Exposure Survey (1981-1983) indicated that 868 workers were potentially exposed to phenacetin. The actual number of potentially exposed workers was probably higher because this estimate did not include exposure to trade name compounds that contained phenacetin. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 4,191 workers were potentially exposed to phenacetin in the workplace in 1970 (HSDB 2000).

REGULATIONS

EPA regulates phenacetin under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA). A reportable quantity (RQ) of 100 lb has been proposed for phenacetin under CERCLA. This compound is regulated as a hazardous waste and is subject to reporting and record-keeping requirements under RCRA.

After an advisory panel determined that phenacetin could not be considered "safe" for over-the-counter (OTC) use, FDA held hearings to remove it from OTC and prescription products. FDA has withdrawn approval of all drugs containing phenacetin and has required manufacturers to reformulate them to omit phenacetin.

OSHA regulates phenacetin under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 143.

REFERENCES

Chem Sources. Chemical Sources International, Inc. http://www.chemsources.com/, 2001.

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USITC. U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales, 1979. USITC Publication No. 1099. Washington, DC: U.S. Government Printing Office, 1980.

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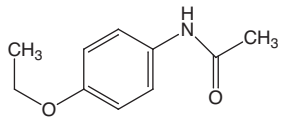
ANALGESIC MIXTURES CONTAINING PHENACETIN

First listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Analgesic mixtures containing phenacetin are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans (IARC 1977, 1980, 1982, 1987). Many case reports have indicated that abuse of analgesic mixtures containing phenacetin induces increased incidences of papillary necrosis, adenocarcinomas of the renal parenchyma, transitional cell carcinomas or papillomas of the renal pelvis, and urinary bladder carcinomas.

An IARC Working Group reported that there is limited evidence of carcinogenicity of analgesic mixtures containing phenacetin in experimental animals (NCI 1978, IARC 1982, 1987). When administered orally, a mixture of aspirin, phenacetin, and caffeine induced increased incidences of benign and malignant carcinomas of the urinary tract in mice and rats (IARC 1987). A mixture of phenacetin and caffeine or phenacetin alone induced renal pelvic tumors and urinary bladder tumors in male rats. Half of the rats treated with phenacetin, phenazone, and caffeine in combination developed hepatomas (IARC 1982, 1987).

PROPERTIES

Analgesic mixtures containing phenacetin are no longer available in the U.S., but they were previously marketed in tablet formulations containing either 150 mg phenacetin, 230 mg aspirin, and 15 or 30 mg caffeine or 230 mg aspirin, 30 mg caffeine, and 8, 15, 30, or 60 mg codeine phosphate (IARC 1977, 1980).

USE

Analgesic mixtures containing phenacetin were previously used as prescription and over-the-counter drugs for mild-to-moderate pain associated with the musculoskeletal system. Such mixtures were used for more than 80 years (IARC 1977). Phenacetin was introduced into therapy in 1887 and was extensively used in analgesic mixtures until it was implicated in analgesic-abuse nephropathy (Flower *et al*. 1985). Consequently, phenacetin was withdrawn from the U.S. market in 1983 (Ronco and Flahault 1994, FDA 1999).

PRODUCTION

Analgesic mixtures containing phenacetin are no longer manufactured or imported into the United States. No specific data on historical production, imports, or exports of the analgesic mixtures were available. However, total sales of phenacetin for use in human medicine were estimated to be less than 1.4 million lb/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 147,000 lb, 207,000 lb, 422,000 lb, 511,000 lb, 620,000 lb, and 83,000 lb in 1972, 1973, 1974, 1976, 1978, and 1984, respectively (IARC 1977, 1980, HSDB 2001).

EXPOSURE

The primary routes of potential human exposure to analgesic mixtures containing phenacetin are ingestion, inhalation, and dermal contact. No information was found regarding the number of people who used analgesic mixtures containing phenacetin prior to its removal from the U.S. market. Tablets or capsules of analgesic mixtures usually contained 150 to 200 mg phenacetin (IARC 1977). Potential occupational exposure could have occurred through inhalation and dermal contact for workers involved in manufacturing, formulating, packaging, or administering the pharmaceuticals. The National Occupational Exposure Survey (1981-1983) indicated that 868 workers were potentially exposed to phenacetin. The actual number of potentially exposed workers was probably higher because this estimate did not include exposure to trade name compounds that contained phenacetin. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 4,191 workers were potentially exposed to phenacetin in the workplace in 1970 (HSDB 2001).

REGULATIONS

Analgesic mixtures containing phenacetin are not regulated by EPA because they are used as pharmaceuticals and in low quantities relative to other chemicals. However, there may be a small pollution problem relative to hospital wastes.

FDA regulates these mixtures under the Food, Drug, and Cosmetic Act (FD&CA) and the Public Health Service Act as over-the-counter (OTC) drugs. FDA also regulates the labeling of all drugs containing phenacetin under FD&CA.

OSHA regulates analgesic mixtures containing phenacetin under the Hazard Communication Standard and as chemical hazards in laboratories. It is listed as a medication that a physician and employer may wish to review. Regulations are summarized in Volume II, Table 143.

REFERENCES

FDA. Food and Drug Administration. List of Drug Products that have been Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness. Federal Register, Vol. 64, pp. 10944-10947. Final Rule, March 8, 1999.

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