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PHENACETIN - Pharmaceuticals

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PHENACETIN

Phenacetin was considered by previous IARC Working Groups in 1976 and 1980 ([IARC, 1977](#), [1980](#)). Analgesic mixtures containing phenacetin were considered by a previous IARC Working Group in 1987 ([IARC, 1987a](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Go to: [▼](#)

1.1. Identification of the agent

Chem. Abstr. Serv. Reg. No.: 62-44-2

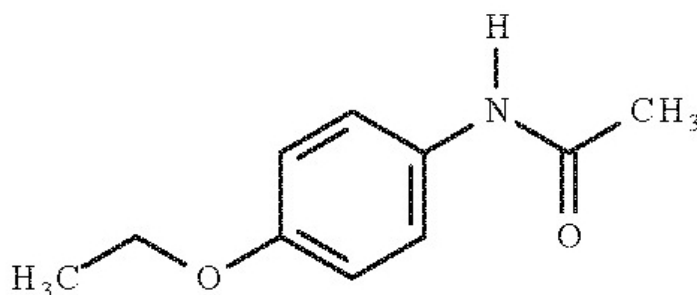
Chem. Abstr. Name: Acetamide, *N*-(4-ethoxyphenyl)-

IUPAC Systematic Name: *N*-(4-Ethoxyphenyl)acetamide

Synonyms: Aceto-4-phenetidine; acetophenetidin; acetophenetidine; acetophenetin; acetphenetidin; 4-(acetylamino)phenetole; *N*-acetyl-4-ethoxyaniline; *N*-acetyl-*p*-ethoxyaniline; *N*-acetyl-*p*-phenetidine; 4-ethoxyacetanilide; 4'-ethoxyacetanilide; *p*-ethoxyacetanilide; *N*-(4-ethoxyphenyl)acetamide; Mironal

Description: Slightly bitter, crystalline scales or powder ([O'Neil, 2006](#))

1.1.1. Structural and molecular formulae, and relative molecular mass



C₁₀H₁₃NO₂

Relative molecular mass: 179.22

1.2. Use of the agent

1.2.1 Indications

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. Phenacetin also was once used as a stabilizer for hydrogen peroxide in hair-bleaching preparations (IARC, 1980; Nugent & Hall, 2000).

1.2.2 Dosage

Analgesic mixtures containing phenacetin were previously marketed as tablets or capsules containing between 150 and 300 mg phenacetin. Common combinations were: 150 mg phenacetin, 230 mg aspirin, and 15 or 30 mg caffeine; or 150 mg phenacetin, 230 mg aspirin, 30 mg caffeine, and 8, 15, 30, or 60 mg codeine phosphate. Phenacetin alone was also available in 250 and 300 mg doses as tablets, and up to 500 mg doses as powder. The usual dose was 300 mg 4–6 times per day, and the daily dose was not to exceed 2 g (IARC, 1977, 1980).

1.2.3 Trends in use

Phenacetin was withdrawn from the market in Canada in 1978, in the United Kingdom in 1980 (IARC, 1980), and in the Unites States of America in 1983 (FDA, 1999). Over-the-counter sales of phenacetin-containing analgesics have been legally prohibited in most countries. For example, in Australia, analgesic mixtures containing phenacetin were legally banned in 1977 (Michielsen & de Schepper, 2001), in Belgium in 1987 (Michielsen & de Schepper, 2001), in Germany in 1986 (Schwarz et al., 1999), and in Denmark in 1985 (Nørgaard & Jensen, 1990). In the Czech Republic, analgesic mixtures containing phenacetin were recently removed from the market. They are still available in Hungary under the trade names Antineuralgica and Dolor (Sweetman, 2008). Phenacetin was withdrawn from many analgesic mixtures long before the legal ban in several countries.

2. Cancer in Humans

Go to: 

2.1. Case reports

Many case reports of renal pelvic and other urothelial tumours in patients who used large amounts of phenacetin-containing analgesics have been recorded (IARC, 1987a).

2.2. Case–control studies

Case–control studies have been used almost exclusively to examine the association between consumption of analgesics and various cancers of the urinary tract. In all of the studies available to the Working Group, the cumulative use of groups of pharmaceuticals was assessed by asking study subjects about their retrospective use. In most epidemiological studies reviewed, it was rather difficult to estimate the effect of phenacetin separately from the effect of other analgesics, as various pain-relieving substances are often combined in the same pharmaceutical product.

See Table 2.1

Table 2.1 Case-control studies of cancer of the urinary tract									
Reference	Study	Characteristics	Exposures	Outcomes	Relative risk	95% CI	OR	95% CI	Comments
Cancer of the urinary tract and cancer									
Michielsen & de Schepper, 1987	Case-control	Belgium	Analgesic mixtures	Renal pelvic cancer	4.2	1.5–11.5	4.2	1.5–11.5	Analgesic mixtures containing phenacetin
Schwarz et al., 1999	Case-control	Germany	Analgesic mixtures	Renal pelvic cancer	4.2	1.5–11.5	4.2	1.5–11.5	Analgesic mixtures containing phenacetin
Nørgaard & Jensen, 1990	Case-control	Denmark	Analgesic mixtures	Renal pelvic cancer	4.2	1.5–11.5	4.2	1.5–11.5	Analgesic mixtures containing phenacetin

Table 2.1

Case–control studies of cancer of the urinary tract and consumption of analgesic mixtures containing phenacetin.

2.2.1 Cancer of the renal pelvis and ureter

Small-to-medium-sized case–control studies from Australia (McCredie et al., 1982, 1983a, b; McCredie & Stewart, 1988), Denmark (Jensen et al., 1989) and Germany (Pommer et al., 1999) all suggested a moderate-to-strong association between the regular use of analgesics containing phenacetin and tumours of the renal pelvis (relative risk, 4.2–6.0).

This relationship was also tested in three larger case–control studies, one from Australia (McCredie et al., 1993), and two from the USA (Ross et al., 1989; Linet et al., 1995), each of which included some 150–500 patients with cancers of the renal pelvis and ureter. The Australian study, which

included information on subjects' cumulative intake of phenacetin before 1987, showed a highly increased relative risk of cancers of the renal pelvis and ureter associated with regular use of phenacetin-containing preparations, and a strong, statistically significant dose–response relationship of increasing risk with increasing consumption of phenacetin ([McCredie et al., 1993](#)). In the study area (New South Wales), phenacetin was banned in 1979 from all preparations but was commonly used as an analgesic before that year. The Californian cancer-registry-based study ([Ross et al., 1989](#)), including 187 patients with tumours of the renal pelvis and ureter, found a non-significant increased risk for these tumour types associated with heavy use of phenacetin-containing preparations. In the second study from the USA, [Linnet et al., \(1995\)](#) did not find a positive association between the use of phenacetin and tumours of the renal pelvis and ureter, and no indication of a positive trend in risk estimates with increasing duration of use or increasing cumulative dose of phenacetin-containing preparations. This apparent lack of association was ascribed by the authors to the fact that phenacetin products had been off the US market for a decade or more when the patients were diagnosed during 1983–87, and that the study revealed a low prevalence of regular users (6–7%) with an apparent lack of any phenacetin abusers.

In the only study in which tumours of the ureter were analysed separately ([McCredie & Stewart, 1988](#)), the use of phenacetin was not associated with an increased incidence of tumours of the ureter. [The Working Group noted that the statistical power of the study was limited.]

2.2.2 Cancer of the kidney parenchyma

Two early case–control studies from the USA and Australia, which included kidney cancer patients diagnosed in the late 1970s and early 1980s, i.e. in the decade following the withdrawal of phenacetin from these markets, reported an increased risk of kidney cancer among regular users of phenacetin-containing preparations ([McLaughlin et al., 1984](#); [McCredie et al., 1988](#)). However, the US study findings were not statistically significant, and the Australian study did not show any positive trend in risk by increasing cumulative intake of phenacetin.

Three further case–control studies from the USA, Canada and the People's Republic of China with recruitment of patients with renal cell cancer diagnosed in the late 1980s did not report significant associations with use of phenacetin, even in cumulative doses of more than 1 kg ([McLaughlin et al., 1992](#); [Kreiger et al., 1993](#); [Chow et al., 1994](#)). Similarly, a large international multicentre case–control study from six well defined geographic areas in Australia, Denmark, Germany, Sweden, and the USA did not link renal cell cancer with consumption of phenacetin-containing preparations ([McCredie et al., 1995](#)).

In a large case–control study from California, a statistically significant elevation in risk of renal cell cancer was associated with use of each of four chemical classes of analgesics included in the analysis ([Gago-Dominguez et al., 1999](#)). However, no clear increase in risk was observed even with an increase in maximum weekly intake doses of phenacetin.

2.2.3 Cancer of the urinary bladder

Two small case–control studies from Australia ([McCredie et al., 1988](#)) and one study from the USA ([Piper et al., 1986](#)), with recruitment of bladder cancer patients during the late 1970s and early 1980s, reported a positive association with use of phenacetin-containing analgesics. In the US study, heavy use, defined as daily use of phenacetin-containing analgesics, was associated with a non-significant increased risk of bladder cancer; in the Australian study, lifetime use of phenacetin of 0.1 kg or more was associated with a significant 2-fold increased risk.

In a large study from California ([Castelao et al., 2000](#)), any use of phenacetin-containing analgesics was related to a non-significant increase in bladder cancer risk, however, it was associated with a significant increase in relative risk estimates by an increasing cumulative lifetime consumption of phenacetin. Furthermore, in a cancer-registry-based case–control study from the USA, risks of bladder cancer were evaluated in association with use of analgesics and anti-inflammatory drugs ([Fortuny et al., 2007](#)). Based on information obtained through an in-person interview, the investigators found a significantly increased risk of bladder cancer in association with use of phenacetin-containing analgesics. A positive, statistically significant trend was observed with reported increasing duration of use.

These findings were not corroborated in a medium-sized German case–control study, in which no elevation of the relative risk estimate for bladder cancer was found in subjects with a lifetime consumption of phenacetin of 1 kg or more ([Pommer et al., 1999](#)). [The Working Group noted that phenacetin was banned in 1986 from the pharmaceutical market of the Federal Republic of Germany

phenacetin was banned in 1989 from the pharmaceutical market of the Federal Republic of Germany before reunification, and patients included in the study were diagnosed during 1990–94, i.e. less than 10 years after the ban.]

In another large case–control study from Spain (Fortuny et al., 2006), ever use of phenacetin was slightly, but non-significantly, more prevalent among cases than among controls. [The Working Group noted that in this study, most cases and controls were interviewed more than 10 years after phenacetin-containing preparations were withdrawn from the Spanish market, and few participants only reported use of this compound.]

3. Cancer in Experimental Animals

Go to: 

3.1. Analgesic mixtures containing phenacetin

Phenacetin has been tested in mice and rats by oral administration, alone and in combination with aspirin, caffeine, and/or phenazone. In a study in male and female mice and rats, 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 observed increase in tumour incidence in mice. There was a significant increase in pituitary adenomas and carcinomas, and adrenal pheochromocytomas in treated males, and a small increase (not statistically significant) in the incidence of urinary tract tumours in female rats (NCI, 1978; IARC, 1980, 1987b). Male rats treated with phenacetin, phenazone, and caffeine combined developed liver tumours (hepatomas), while phenacetin-alone or in combination with phenazone with or without caffeine slightly increased the incidence of renal cell and renal pelvic tumours combined (Johansson, 1981; IARC, 1987b).

Phenacetin-alone given orally at doses ranging from 0.5–2.5% in the diet caused benign and malignant tumours of the urinary tract in mice and rats of both sexes (Isaka et al. 1979; Nakanishi et al., 1982; Muradian, 1986; IARC, 1987b), and of the nasal cavity in rats of both sexes (Isaka et al. 1979; IARC, 1980, 1987b). In male rats, phenacetin at doses of 2.5% also enhanced the incidence of urinary bladder tumours induced by *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine (IARC 1980, 1987b).

See [Table 3.1](#)

Table 3.1. Studies of cancer in experimental animals exposed to phenacetin			
Species	Dose	Number of animals	Findings
Mice	0.7% or 1.4% diet	100	No increase in tumour incidence
Rats	0.7% or 1.4% diet	100	Significant increase in pituitary adenomas and carcinomas, and adrenal pheochromocytomas in treated males, and a small increase in the incidence of urinary tract tumours in female rats
Mice	0.5–2.5% diet	100	Benign and malignant tumours of the urinary tract
Rats	0.5–2.5% diet	100	Benign and malignant tumours of the urinary tract, and of the nasal cavity

Table 3.1

Studies of cancer in experimental animals exposed to phenacetin or analgesic mixtures containing phenacetin.

4. Other Relevant Data

Go to: 

4.1. Absorption, distribution, excretion, and metabolism

4.1.1. Humans

After oral administration of phenacetin, *N*-acetyl-*p*-aminophenol, either conjugated or free, is the major metabolite found in urine. Small amounts of 2-hydroxyphenacetin, 3-[(5-acetamido-2-hydroxyphenyl)thio]alanine, *S*-(1-acetamido-4-hydroxyphenyl)cysteine, 3-methyl-thio-4-hydroxyacetanilide, and *N*-hydroxyphenacetin are also detected.

Urinary excretion of 2-hydroxyphenacetin, *N*-acetyl-*p*-aminophenol and their conjugates is decreased when phenacetin is administered in combination with aspirin, caffeine, and codeine (Gault et al., 1972)

4.1.2. Experimental systems

Metabolic pathways for phenacetin involve de-ethylation, *N*-deacetylation, and ring hydroxylation. The main route, as shown in rats, is oxidative de-ethylation, forming *N*-acetyl-*p*-aminophenol, which is excreted in the urine as the sulfate or as the glucuronide (Dubach & Raaflaub, 1969). Metabolism by the second pathway, *N*-deacetylation, is greatest in rats (21% of the dose), and least in guinea-pigs and rabbits (7 and 4% of the dose, respectively) (Smith & Timbrell, 1974). *p*-Phenetidine, resulting from *N*-deacetylation, can be converted to 2-hydroxy-*para*-phenetidine, which in rats is excreted as the sulfate in increasing amounts with increasing doses of phenacetin (Dubach & Raaflaub, 1969).

Other metabolites identified in the urine of experimental animals are 2-hydroxyphenacetin, 3-[(5-acetamido-2-hydroxyphenyl)thio]alanine, 3-methylthio-4-hydroxyacetanilide, 2-hydroxyacetophenetidine glucuronide, 4-acetaminophenoxyacetic acid, 4-hydroxy-3-

methylthioacetanilide, and *N*-hydroxy-phenacetin (IARC, 1980). Intestinal microflora in rats have been shown to deconjugate the metabolite *N*-acetyl-*p*-aminophenyl glucuronide, excreted partly in bile, to *N*-acetyl-*p*-aminophenol (Smith & Griffiths, 1976).

Evidence that phenacetin is *N*-hydroxylated by a cytochrome P-450 mono-oxygenase-catalysed reaction has been demonstrated *in vitro* with hamster and rabbit liver microsomes (Hinson & Mitchell, 1976; Fischbach et al., 1977).

Using rat liver preparations, Mulder et al. (1977) demonstrated the formation of *N*-*O*-glucuronide and *N*-*O*-sulfate conjugates of *N*-hydroxyphenacetin.

In rats treated with 3-methylcholanthrene or benzo[*a*]pyrene or exposed to cigarette smoke, an increased rate of *O*-de-ethylation of phenacetin to *N*-acetyl-*p*-aminophenol in the lung and intestine was observed (Welch et al., 1972; Kuntzman et al., 1977).

4.2. Genetic and related effects

4.2.1. Humans

In 29 *TP53* mutations found in 89 renal pelvic carcinomas, the incidence and type of mutations did not differ significantly between patients with a history of phenacetin abuse, smoking or neither of these habits, and thus do not reflect a mutagenic effect of exposure to phenacetin and/or smoking in the renal pelvis (Bringuier et al., 1998). No other data were available to the Working Group on the genetic and related effects of phenacetin in humans.

4.2.2. Experimental systems

The previous IARC Monograph states that the results of studies on the induction of chromosomal aberrations, sister chromatid exchange and micronuclei in rodents treated with phenacetin *in vivo* were equivocal (IARC, 1987a). More recently, several studies have provided additional evidence that phenacetin can induce chromosomal alterations or DNA damage in both target and non-target tissues. Treatment of mice either orally or via intraperitoneal injection with high doses of phenacetin results in increases in micronuclei in the bone-marrow erythrocytes (Hayashi et al., 1989; Sutou et al., 1990). Similarly in rats, daily oral phenacetin treatment for 2 or 14 days increases the frequency of micronuclei in bone-marrow cells, and in peripheral blood (Asanami et al., 1995). In rodents treated with phenacetin, increased DNA damage is detected in the kidney of mice 2–3 hours after treatment, and in the urinary bladder of rats after 20 hours of exposure (Sasaki et al., 1997; Sekihashi et al., 2001; Robbiano et al., 2002). Phenacetin induces cell proliferation in the urothelium of the kidney, the bladder, the renal pelvis (Johansson et al., 1989), and DNA synthesis in the nasal respiratory and olfactory mucosa of rats (Bogdanffy et al., 1989). Phenacetin also induces chromosomal aberrations in Chinese hamster cells *in vitro* and DNA strand breaks in rat and human cells from the urinary bladder *in vitro* but not in rat hepatocytes after exposure *in vivo* (IARC, 1987a; Robbiano et al., 2002). In rat kidney cells, a mixture of aspirin, phenacetin and caffeine as well as phenacetin-alone did not induce micronuclei, but the metabolite *N*-hydroxyphenacetin was found to induce micronuclei (Dunn et al., 1987). Phenacetin does not induce sex-linked recessive lethal mutations in *Drosophila*, and is not mutagenic in mouse embryo cells, but was found to induce a small number of transformed foci (IARC, 1987a; Patierno et al., 1989).

Phenacetin is mutagenic to bacteria when tested in the presence of a metabolic system derived from hamster or rat liver but not mouse (IARC, 1987a; Nohmi et al., 1987). The urine from phenacetin-treated Chinese hamsters, but not that from rats, is mutagenic to bacteria (IARC, 1987a). Administration of phenacetin (0.75%) mixed in the feed of mice deficient in nucleotide-excision repair results in an observed increased mutation frequency in a *Lac Z* reporter gene in the kidney (Luijten et al., 2006).

While there is evidence of genetic damage caused by phenacetin in various experimental systems, similar data are not available in humans.

5. Evaluation

Go to: 

There is *sufficient evidence* in humans for the carcinogenicity of analgesic mixtures containing phenacetin. Analgesic mixtures containing phenacetin cause cancer of the renal pelvis, and of the ureter.

There is *limited evidence* in experimental animals for the carcinogenicity of analgesic mixtures containing phenacetin.

There is *sufficient evidence* in humans for the carcinogenicity of phenacetin. Phenacetin causes cancer of the renal pelvis, and of the ureter.

There is *sufficient evidence* in experimental animals for the carcinogenicity of phenacetin.

Analgesic mixtures containing phenacetin are *carcinogenic to humans (Group 1)*.

Phenacetin is *carcinogenic to humans (Group 1)*.

For the overall evaluation of phenacetin, the Working Group took into consideration that tumours of the renal pelvis and ureter are not known to result from the other components of the analgesic mixtures used in most countries; namely, aspirin, codeine phosphate, and caffeine.

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Go to: 

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