PHENACETIN

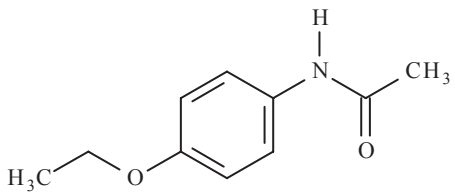
Phenacetin was considered by previous IARC Working Groups in 1976 and 1980 (IARC, 1977, 1980). Analgesic mixtures containing phenacetin were considered by a previous IARC Working Group in 1987 (IARC, 1987a). Since that time, new data have become available, these have been incorporated into the *Monograph*,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

1. Exposure Data

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



$C_{10}H_{13}NO_2$
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Phenacetin was withdrawn from the market in Canada in 1978, in the United Kingdom in 1980 (IARC, 1980), and in the Unites States of America in 1983 (FDA, 1999).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

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

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, showe a

Table 2.1 Case–control studies of cancer of the urinary tract and consumption of analgesic mixtures containing phenacetin

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Cancer of the renal pelvis and ureter									
McCredie et al. (1982) New South Wales, Australia, 1977–80	Renal pelvis (ICD-8: 189.1)	27 men, 40 women from the New South Wales Cancer Registry and from 3 Sydney hospitals; cases confirmed histologically	180 volunteers, friends and relatives	In-person structured interview undertaken at hospital or at home	*Lifetime consumption of phenacetin-containing analgesics (kg) in women* No latency: No use (< 0.1) ≥ 0.1 5-year latency: No use (< 0.1) ≥ 0.1	 NR NR NR NR	 1 (ref) 2.4 (1.0–6.0) 1 (ref) 4.1 (1.8–9.2)	Age and use of other types of analgesics. Not adjusted for smoking	Response rates not given, rates of renal pelvis cancer in men not given
McCredie et al. (1988) New South Wales, Australia, 1980–82	Renal pelvis (ICD-8: 189.1)	73 (31 men, 42 women) from the New South Wales Central Cancer Registry	688 (307 men, 381 women) population-based controls 50-yr-old or above selected at random from the New South Wales election rolls 1980–81; response rate 72%	Standardized questionnaire mailed to participants	*Lifetime consumption of phenacetin (kg)* No use ≥ 0.1 ≥ 1.0	 [37] NC [24]	 1 (ref) 5.7 (3.2–10.0) 7.9 (4.6–13.8)	Sex, paracetamol use, smoking	Response rate for cases not given. No use defined as lifetime consumption < 0.1 kg up till the date of diagnosis or the equivalent date for control. Phenacetin always in preparations containing aspirin and either caffeine or codeine

Table 2.1 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
McCredie et al. (1983a; 1983b) 1980–82	Ureter (ICD-8: 189.2)	36 males from the New South Wales Central Cancer Registry	307 male population-based controls 50-yr-old or above selected at random from the New South Wales election rolls 1980–81; response rate 72%		No use	NR	1 (ref)		Re-analysis of the original data
					≥ 0.1	NR	0.7 (0.3–2.2)		
					≥ 1.0	NR	1.2 (0.5–3.0)		
McLaughlin et al. (1983) Minneapolis-St. Paul metropolitan area, USA, 1974–79	Renal pelvis (ICD-8: 189.1)	74 (50 men, 24 women) from the Minneapolis-St. Paul metropolitan area 30–79-yr-old; cases confirmed histologically; 95% response rate	697 (428 men, 269 women) selected at random from telephone listings, from files of the Health Care Financing Administration and from death certificate listings; response rate 94%	In-person structured interview of participants or next-of-kin undertaken at home	*Use of phenacetin- or acetaminophen-containing analgesics*			Age and cigarette smoking	No use defined as: never used phenacetin- or paracetamol-containing drugs regularly for ≥ 1 mo. Of 7 cases who were long-term users, 1 used paracetamol compounds only
					Men:				
					No use	23	1 (ref)		
					Non-regular use	21	0.9 (0.4–1.8)		
					Regular use, ≤ 36 mo	2	0.7 (0.1–3.9)		
					Regular use, > 36 mo	4	3.9 (0.7–20.4)		
					Women:				
					No use	9	1 (ref)		
					Non-regular use	10	1.4 (0.5–4.2)		
					Regular use, ≤ 36 mo	2	2.3 (0.2–19.7)		
					Regular use, > 36 mo	3	3.7 (0.5–24.7)		

Table 2.1 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Jensen et al. (1989) Copenhagen, Denmark, 1979–82	Renal pelvis and ureter	96 (60 men, 36 women) notified directly from 27 hospital units of Eastern Denmark; response rate 99%	288 (180 men, 108 women) selected at random from medical or surgical wards matched for hospital, sex and age in 5-yr age groups; patients with urinary-tract- and smoking-related diseases were not eligible; response rate 99%	In-person structured interview undertaken at hospital	*Lifetime consumption of phenacetin (g)*			Age	Use of analgesics measured up until 5 yr before interview. The 'no use' level not clearly defined. The influence of phenacetin and aspirin could not be separated in the analysis. Incomplete adjustment for smoking habits (< 10 vs ≥ 10 pack-yr)
					Men				
					Never used analgesics	31	1 (ref)		
					Ever used phenacetin	13	3.9 (1.7–9.1)		
					1–749	6	3.1 (1.0–9.6)		
					≥750	5	9.1 (2.2–38)		
					Women				
					Never use of analgesics	9	1 (ref)		
					Ever used phenacetin	17	6.9 (2.7–18)		
					1–749	4	6.1 (1.5–26)		
					≥750	7	6.1 (1.9–20)		
					Ever used phenacetin			Age, tobacco smoking, 'high risk' occupations and aspirin	
					Men	12	2.4 (0.9–6.8)		
					Women	15	4.2 (1.5–12)		
Pommer et al. (1999) Berlin Germany 1990–94	Renal pelvis and ureter (ICD-9: 189.1–2)	76 (37 men, 39 women) diagnosed in 1 of 8 urological departments; response rate 85%	76 subjects selected at random from the central inhabitant registry of the former West Berlin area individually matched to case subject by sex and age (± 2 yr); response rate 70%	In-person structured interview undertaken at hospital (cases) or at participants' home (controls)	No or rare intake of analgesics	31	1 (ref)	Current smoking, former smoking, socioeconomic status, laxative intake	Rare intake defined as intake of less than 1 analgesic dose/mo
					Lifetime consumption of phenacetin (kg)				
					≥ 1	7	1.8 (0.2–14)		

Table 2.1 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
McCredie et al. (1993) New South Wales Australia, 1989–90	Renal pelvis (ICD-9: 189.1)	147 (58 men, 89 women) in age range 20–79-yr at diagnosis from a rapid-ascertainment system and the New South Wales Central Cancer Registry; patients had to be listed in telephone directory and able to speak English to be included; response rate 89%	523 (231 men, 292 women) frequency-match to cases on age and sex and selected at random from the New South Wales electoral rolls; controls had to be listed in telephone directory and able to speak English to be selected; response rate 74%	Structured interview undertaken at participants' home or conducted over the telephone	*Phenacetin-containing analgesics* Non-consumers Any *Total use pre-1987 (kg)* ≤ 2.04 2.04–6.87 ≥ 6.88	 76 70 12 16 42	 1 (ref) 12.2 (6.8–22) 5.2 (2.2–12) 8.3 (3.4–21) 18.5 (8.7–39) Test for trend: $P = 0.019$	Age, sex, cigarette smoking, education level, method of interview Age, sex, cigarette smoking, education level, method of interview, paracetamol in any form	The non-consumer category defined as persons reporting taking analgesics less than 20 times in their lifetime. Intake of analgesics included in analysis up till end of 1986. Phenacetin always in preparations containing aspirin plus either caffeine or codeine
Ross et al. (1989) Los Angeles County USA, 1978–82	Renal pelvis and ureter	187 (127 men, 60 women) selected from the Los Angeles County Cancer Registry, diagnosed under age 75; response rate 80%	187 neighbourhood controls selected at random and matched individually to cases by sex, date of birth (± 5 yr), and race	Structured interview over the telephone	*Phenacetin-containing analgesics* > 30 d/yr > 30 consecutive d	 11 7	 1.1 ($P = 0.83$) 1.4 ($P = 0.56$)	Age, sex, race	Response rate not given for control subjects. Use of analgesic measured up until date of diagnosis or equivalent date for control. Reference category defined as 'no use or use fewer than 30 times in a yr'. Non-prescription compounds in focus of the study

Table 2.1 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Linet et al. (1995) Multicentre study USA, 1983–86	Renal pelvis and ureter	502 (331 men, 171 women) Caucasians in age range 20–79-yr-old at diagnosis selected from population-based cancer registries in New Jersey, Iowa and Los Angeles; response rate 72%; cases confirmed histologically	496 (315 men, 115 women) frequency-matched to cases by sex and 5-yr age groups and selected using random-digit dialling (under age 65) or taken from the files of Health Care Financing Administration (65-yr-old or above); response rate 66%	In-person structured interview in subjects' home	None or no regular use of analgesics	385	1 (ref)	Age, sex, geographic area, cigarette smoking	Regular use defined as at least 2 or more times/wk for at least 1 mo. Use of analgesics measured up until 5 yr before interview. Non-prescriptive as well as prescriptive analgesics included. Low proportion of regular analgesic users and lack of "phenacetin abusers." Phenacetin rarely available as a single agent
					Regular use of phenacetin-containing analgesics	30	0.8 (0.5–1.4)		
					Duration of use of phenacetin-containing analgesics (yr)				
					≤ 4	12	0.7 (0.3–1.6)		
					5–9	6	0.8 (0.3–2.7)		
					≥ 10	11	0.9 (0.4–2.2)		
					Lifetime consumption of phenacetin (kg)				
					≤ 1.0	21	0.8 (0.4–1.6)		
					> 1.0	9	0.8 (0.3–2.1)		
Cancer of the kidney									
Mc Laughlin et al. (1992) Shanghai, China, 1987–89	Renal cell carcinoma (ICD-9: 189.0)	154 (90 men, 64 women) in age range 35–74-yr-old from a population-based cancer registry covering urban Shanghai; response rate 87%; cases confirmed histologically	157 (91 men, 66 women) selected at random from the Shanghai Resident Registry and frequency matched on sex and age; response rate 100%	In-person structured interview of participants at home	No or non-regular use of analgesics	NR	1 (ref)	Age, sex, education, BMI, smoking	Regular consumption of analgesics defined as at least twice/wk for 2 wk or longer; use of analgesics uncommon in study area
					Use of phenacetin-containing analgesics				
					Regular use	NR	2.3 (0.7–7.0)		

Table 2.1 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Kreiger et al. (1993) Province of Ontario, Canada, 1986–87	Renal cell carcinoma (ICD-9: 189.0)	513 (312 men, 201 women) in age range 25–69-yr-old from the Ontario Cancer Registry; response rate 81%; cases confirmed histologically	1381 (664 men, 705 women) selected at random from the 1986 and 1987 Enumeration Records of Ontario and frequency-matched to case group on age, sex and geographic region of residence	Standardized questionnaire mailed to participants	*Use of phenacetin or phenacetin-containing analgesics* Men No phenacetin or paracetamol Phenacetin only Any phenacetin Women No phenacetin or paracetamol Phenacetin only Any phenacetin	 265 2 5 166 3 3	 1 (ref) 2.5 (0.3–18.5) 1.7 (0.5–5.9) 1 (ref) 1.8 (0.5–7.3) 0.8 (0.2–2.7)	Age, smoking, BMI	Exposure to analgesics was defined as use at least every other day for one month or more before 1980; very few individuals were classified as analgesic users; only 5 male cases and 3 female cases ever exposed
Chow et al. (1994) Minnesota USA, 1988–90	Renal cell carcinoma (ICD-9: 189.0)	440 in age range 20–79-yr-old from the Minnesota state cancer surveillance system; response rate 87%; cases confirmed histologically	707 frequency-matched to cases by sex and 5-yr age groups and selected using random-digit dialling (under age 65) or the files of Health Care Financing Administration (65-yr-old or above); response rate ≈85%	In-person structured interview of participants or next-of-kin (for deceased patients) at their homes	*Lifetime consumption of phenacetin (kg)* No or non-regular use of analgesics Men < 0.1 0.1–1 > 1 No or non-regular use of analgesics Women < 0.1 0.1–1 > 1	195 2 1 3 101 2 2 2	1 (ref) 0.4 (0.1–1.9) 0.1 (0.0–0.8) 0.6 (0.2–2.6) 1 (ref) 0.9 (0.1–5.8) 0.6 (0.1–3.5) 0.4 (0.1–2.3)	Age, smoking, quartile of BMI	Regular use of analgesics were defined as at least 2 or more times/wk for 1 mo before 1987. Overlapping at least in part with the international study described below

Table 2.1 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
McCredie et al. (1995) International multicentre study: Australia, Denmark, Germany, Sweden and USA, 1989–91	Renal cell carcinoma	1732 in age range 20–79-yr-old (20–75 in German centre) recruited through a nationally modified rapid ascertainment system (all study centres) in combination with the files of population-based cancer registries (in Australia, Denmark, Sweden and the USA); overall response rate (including non-response due to death) 72.3%; cases confirmed histologically	2309 frequency-matched to cases by age and sex and selected by centre-specific methods from the same study base as the case group; response rate 74.7%	In-person structured interview at participants' home	*Lifetime consumption of phenacetin (kg)*			Centre, age, sex (where appropriate), BMI, pack-yr of tobacco	Reference group was composed of subjects who – before 1987 – never took analgesics, were not regular takers (less than twice/wk), or took a lifetime total of < 0.1 kg of all types of analgesics combined; lack of association not altered by restricting analgesic use to that which occurred 5 or 10 yr before cutoff data (1987)
					Men and women				
					Reference group	1313	1 (ref)		
					< 0.1	31	0.8 (0.5–1.3)		
					≥ 0.1	97	1.1 (0.8–1.4)		
					0.1–1.0	51	0.9 (0.6–1.3)		
					1.1–5.0	36	1.6 (0.9–2.6)		
					> 5.0	10	0.9 (0.4–2.1)		
					Men				
					< 0.1	14	0.6 (0.3–1.2)		
					≥ 0.1	46	0.9 (0.6–1.4)		
					0.1–1.0	25	0.7 (0.4–1.2)		
					1.1–5.0	16	1.3 (0.6–2.7)		
					> 5.0	5	2.6 (0.5–14.2)		
					Women				
					< 0.1	17	1.1 (0.6–2.3)		
					≥ 0.1	51	1.4 (0.9–2.1)		
					0.1–1.0	26	1.3 (0.7–2.3)		
					1.1–5.0	20	2.1 (1.0–4.4)		
					> 5.0	5	0.6 (0.2–1.8)		

Table 2.1 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Gago-Dominguez et al. (1999), Los Angeles, USA, 1986–94	Renal cell cancer	1204 (781 men, 423 women) non-Asians in age range 25–74-yr-old from the Los Angeles County Cancer Registry; response rate (including non-response due to death) 74%; cases confirmed histologically	1204 non-Asians neighbourhood controls selected at random and matched individually to cases by sex, date of birth (± 5 yr), race; response rate not given	In-person structured interview at participants' home	No or irregular use of analgesics	616	1 (ref)	Level of education, obesity, history of hypertension, smoking (yes/no), regular use of amfetamines	Exposure information requested up to 2 yr before the date of diagnosis for cases and at the equivalent date for the matched control. No use was defined as an intake less than 20 times in a lifetime; irregular use was defined as intake of analgesics less than twice/wk. Equally increased risks were seen for other types of analgesics, i.e. aspirin, non-aspirin NSAIDs, and paracetamol
					Regular use of phenacetin	86	1.9 (1.3–2.7)		
					Maximum weekly dose (g)				
					< 2	41	1.3 (0.8–2.2)		
					2– < 4	22	4.1 (1.5–10.8)		
					4– < 8	20	2.3 (1.0–5.0)		

BMI, body mass index; d, day or days; mo, month or months; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; ref., reference; vs, versus; wk, week or weeks; yr, year or years

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, Linet *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 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

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 or analgesic mixtures containing phenacetin

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 94 wk NCI (1978)	Feed 0, 0.7 or 1.4% of a mixture of aspirin, phenacetin and caffeine (50:46:4) for up to 78 wk, observed for an additional 16 wk 50/group	**Males:**		
		Lung (alveolar/bronchiolar adenomas or carcinomas)– 6/48 in controls, 9/46 fed 0.7%, 12/47 fed 1.4%	NS	
		Haematopoietic system (leukaemias or malignant lymphomas)– 4/48 in controls, 7/48 fed 0.7%, 4/48 fed 1.4%	NS	
		Liver (hepatocellular carcinomas)– 7/48 in controls, 11/46 fed 0.7%, 6/47 fed 1.4%	NS	
		Females:		
		Lung (alveolar/bronchiolar adenomas or carcinomas)– 4/46 in controls, 7/45 fed 0.7%, 4/47 fed 1.4%	NS	
		Haematopoietic system (leukaemia or malignant lymphoma)– 5/48 in controls, 6/45 fed 0.7%, 5/47 fed 1.4%	NS	
		Liver (hepatocellular carcinomas)– 1/47 in controls, 2/45 fed 0.7%; 3/47 fed 1.4%	NS	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C57BL/6 (M, F) 75–80 wk Macklin & Szot (1980)	Feed Diets containing aspirin, phenacetin and caffeine, single or in combination, for 75–80 wk. Group 1: 696 mg/kg bw/d aspirin-phenacetin-caffeine Group 2: 693 mg/kg bw/d aspirin-phenacetin Group 3: 321 mg/kg bw/d phenacetin-caffeine Group 4: 754 mg/kg bw/d phenacetin Group 5: 268 mg/kg bw/d phenacetin Group 6: none (controls) 40 males and 40 females/group	No tumours related to treatment reported		The study was limited by the limited extent of histological examination. Ratio of the components of the combinations was: aspirin, 7; phenacetin, 5; caffeine, 1
Rat, F344 (M, F) 113 wk NCI (1978)	Feed 0, 0.7 or 1.4% of a mixture of aspirin, phenacetin and caffeine (50:46:4) for up to 78 wk, observed for an additional 34–35 wk 50/group	**Males:** Pituitary gland (adenomas or carcinomas)–8/47 in controls, 18/47 fed 0.7%, 12/44 fed 1.4% Adrenal gland (pheochromocytomas)–7/47 in controls, 17/49 fed 0.7%, 9/48 fed 1.4% **Females:** One transitional cell carcinoma of the urinary bladder (low dose) One transitional cell carcinoma of the urinary bladder (high dose) One transitional cell papilloma of the urinary bladder (high dose) One tubular cell adenocarcinoma of the kidney (low dose) [also one in low-dose males] No urinary system tumours in control females	 $P = 0.018$ for low dose $P = 0.022$ for low dose NS NS NS NS	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours		Significance	Comments
Rat, Sprague-Dawley (M) 117 wk Johansson (1981)	Feed Group 1: 0.5% phenacetin Group 2: 0.5% phenazone Group 3: 0.1% caffeine Group 4: 0.5% phenacetin+ 0.5% phenazone+ 0.1% caffeine Group 5: 0.5% phenacetin+ 0.5% phenazone Group 6: 0.5% phenacetin 0.1% caffeine Group 7: acetaminophen Group 8: none (controls) 30/group	**Kidney**			
		Renal cell	*Renal pelvis*		
		Group 1: 4/29	1/29	[$P = 0.024$][a]	
		Group 2: 0/29	4/29		
		Group 3: 0/28	0/28		
		Group 4: 2/30	4/30	[$P = 0.012$][a]	
		Group 5: 7/29	3/29	[$P = 0.003$][a]	
		Group 6: 2/29	1/29		
		Group 7: 0/30	0/30		
		Group 8: 0/30	0/30		
		Urinary bladder			
		Group 1: 5/29			
		Group 2: 5/29			
		Group 3: 0/29			
		Group 4: 1/30			
		Group 5: 4/29			
		Group 6: 4/29			
		Group 7: 4/30			
		Group 8: 2/30			
		Liver (hepatomas)			
		Group 1: 0/29			
		Group 2: 0/29			
		Group 3: 0/29			
		Group 4: 14/30		[$P < 0.001$]	
		Group 5: 0/29			
		Group 6: 0/29			
		Group 7: 0/29			
		Group 8: 0/29			

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Phenacetin alone				
Mouse, $B6C3F_1$ (M, F) 110 wk Nakanishi et al. (1982)	Feed 1.25% or 0.6% phenacetin for 102 wk, observed for additional 8 wk 52/group 50/sex as untreated controls	**Kidney tumours:** *Adenomas*– M 32/48 (1.25% dose), 11/48 (0.6% dose), 0/48 (controls) F 0/48, 0/48, 0/48 *Carcinomas*– M 14/48, 1/48, 0/48 F 1/48, 0/48, 0/48 **Urinary bladder:** *Hyperplasia*– M 7/48, 1/48, 0/48 F 7/48, 0/48, 0/48 *Carcinomas*– M 0/48, 0/48, 0/48 F 2/48, 0/48, 0/48	 $P < 0.01$ (low and high dose) $P < 0.01$ (high dose) $P < 0.05$ (high dose) $P < 0.05$ (high dose)	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, BDI and BDIII 31 mo Schmähl & Reiter (1954)	Feed 40–50 mg phenacetin for at least 770 d 30/treatment group	No tumours related to treatment observed		Information for controls and other experimental details lacking; sex NR
Rats, Sprague-Dawley (M, F), 9 wk Isaka et al. (1979)	Feed 2.5% or 1.25% phenacetin for 18 mo, observed for an additional 6 mo 50/sex/group 65/sex as untreated controls	**Nasal cavity tumours:** M–16/27 (high dose), 16/22 (low dose), 0/19 (controls) F–7/27, 6/25, 0/25 **Urinary tract tumours:** M–13/27, 1/22, 0/19 F–4/27, 0/25, 0/25	 [$P < 0.01$; $P < 0.01$] [$P < 0.01$; $P < 0.01$] [$P < 0.01$; NS] [NS; NS]	Tumours observed in the high dose groups were mainly malignant
Rats, Sprague-Dawley (F), 9 wk 110 wk Johansson & Angervall (1976)	Feed 0% or 0.6% phenacetin for 110 wk 30/group	Breast (adenocarcinomas): 5/30 in treated group, 1/30 in controls Ear duct (squamous cell carcinomas): 4/30 in treated group, 0/30 in controls	NS NS	

[a] whe n kidney tumours were combined

bw, body weight; d, day or days; F, female; mo, month or months; M, male; NR, not reported; NS, not significant; wk, week or weeks; yr, year or years

4. Other Relevant Data

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-hydroxy-acetanilide, 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*-hydroxyphenacetin (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

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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