Piroxicam

1. Chemical and Physical Characteristics

1.1 Name

Chemical Abstracts Services Registry Number
36322-90-4

Chemical Abstracts Primary Name
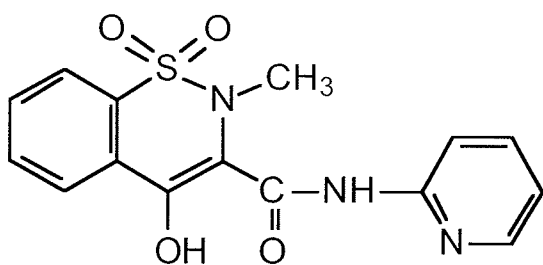Piroxicam

IUPAC Systematic Name
4-Hydroxy-2-methyl-N-2-pyridinyl-2H-1,2-benzo-thiazino-3-3-carboxamide-1,1-dioxide

Synonyms
3,4-Dihydro-2-methyl-4-oxo-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide

1.2 Structural and molecular formulae and relative molecular mass

$C_{15}H_{13}N_3O_4S$ Relative molecular mass: 331.35

1.3 Physical and chemical properties

From Budavari *et al.* (1996), unless otherwise specified

Description
Crystals

Melting-point
198–200 °C

Solubility
Piroxicam may be crystallized from methanol; has a pK_a of 6.3 in solution (2:1 dioxane:water)

Spectroscopy data
The ultraviolet, infrared, ^1H- and ^{13}C-nuclear magnetic resonance and mass spectra of the compound have been determined (Mihalic *et al.*, 1982).

Stability
Stable at 40 °C in the dark for up to 24 months (Mihalic *et al.*, 1982). The three main degradation products are 2-aminopyridine, 2-methyl-2H-1,2-benzothiazine-4-(3H)one 1,1-dioxide and N-methyl-N'-(2-pyridinyl)ethanediamide (Tománkova & Sabartová, 1989).

1.4 Technical products

2-Aminopyridine may be present as an impurity in the final product (Tománková & Sabartová, 1989).

2. Occurrence, Production, Use, Analysis and Human Exposure

2.1 Occurrence

Piroxicam is not known to occur in nature.

2.2 Production

The synthesis of piroxicam has been described (Lombardino & Wiseman, 1972; Lombardino *et al.*, 1973), but technical details of its current commercial production were not available to the Working Group.

2.3 Use

Piroxicam was introduced in 1980 as an analgesic, anti-inflammatory and antipyretic agent. It is generally taken in single or divided doses of 10–40 mg. In Sweden, a single daily dose of 20 mg accounted for 90% of piroxicam prescriptions (Wessling *et al.*, 1990). Piroxicam is used primarily for the treatment of rheumatoid arthritis and osteoarthritis. Other conditions for which it is used include juvenile rheumatoid arthritis, anklylosing spondylitis and acute gout. It has been administered for

musculoskeletal disorders, minor sports injuries and post-partum pain (Brogden *et al.*, 1981).

2.4 Analysis

Methods for the determination of piroxicam in pharmaceutical preparations and in biological fluids are refined continually, and the appropriate references should be consulted for the most recent developments. Most procedures are based on high-performance liquid chromatography (HPLC), but methods involving thin-layer chromatography and spectrophotometry have also been described. Piroxicam has been determined by HPLC in serum (Twomey *et al.*, 1980) and plasma (Edno *et al.*, 1995). A method for the determination of piroxicam and its major metabolites in human plasma, urine or bile by HPLC has been described (Milligan, 1992).

2.5 Human exposure

Piroxicam is one of the commoner NSAIDs in use (Guess *et al.*, 1988; Langman *et al.*, 1994). Usage has tended to decline as a consequence of the toxicity of piroxicam to the gastrointestinal tract (McManus *et al.*, 1996).

3. Metabolism, Kinetics and Genetic Variation

3.1 Humans
3.1.1 Metabolism

Piroxicam is extensively metabolized by the liver. The metabolic pathway in humans is shown in Figure 1. The primary route of biotransformation, however, involves hydroxylation to form the primary metabolite, 5'-hydroxypiroxicam (Hobbs, 1986; Verbeeck *et al.*, 1986a). The metabolites have little or no anti-inflammatory activity (Calin, 1988). A single cytochrome P450 monooxygenase enzyme, the CYP2C subfamily, is thought to catalyse hepatic oxidation and may be responsible for the considerable interindividual that has been observed. Polymorphism of the *CYP2C* gene family has been noted in humans (Zhao *et al.*, 1992; Leemann *et al.*, 1993).

3.1.2 Pharmacokinetics

The piroxicam molecule has four functional groups that significantly affect its pharma-

cokinetics: the enol group, the sulfate group, the *N*-methyl group and the hetrocyclic side-chain (Calin, 1988). The enol group has a low pK_a and is completely ionized, therefore prolonging the activity of the drug. The sulfate group is lipopholic, which enhances absorption in the gut. The *N*-methyl group increases absorption and slows hydroxylation, thereby prolonging the effect of the drug. Finally, the heterocyclic side-chain increases the effectiveness of the agent by strongly inhibiting prostaglandin synthesis. Overall, the pharmacokinetics of piroxicam are linear (Calin, 1988).

(a) Absorption

Piroxicam is well absorbed after oral administration (Hobbs, 1986). It is more completely absorbed after oral or rectal administration than after intravenous injection; rectal absorption was slower than oral absorption, however, with a peak at 5.6 h (Verbeeck *et al.*, 1986a). Food has been shown to slow the rate of oral absorption, increasing the mean time from 2.8 to 4.3 h. It does not, however, apparently affect the extent to which the drug is absorbed (Ishizaki *et al.*, 1979; Verbeeck *et al.*, 1986a).

After absorption, piroxicam, like other anti-inflammatory drugs is extensively bound to human serum albumin (Hobbs, 1986) and may displace other protein-bound agents. About 99% of all circulating piroxicam is protein bound (Richardson *et al.*, 1987; Calin, 1988). While the maximum plasma concentrations are generally reached within 2 h, this time can vary between 1 and 6 h (Hobbs, 1986; Calin, 1988). The plasma concentrations are generally within 20% of peak levels about 1 h after ingestion of a single oral dose. Multiple peaks are observed in the concentration–time profile of piroxicam in plasma 2–12 h after dosing, which may indicate enterohepatic recirculation (Verbeeck *et al.*, 1986a), as discussed below. As the mean plasma half-life is about 50 h, the drug can be administered once per day; however, there is considerable interindividual variability (> 36%) in the half-life (Hobbs, 1986).

After repeated daily oral doses of 20 mg, the plasma concentrations increase gradually and

Figure 1. Metabolism of piroxicam in humans
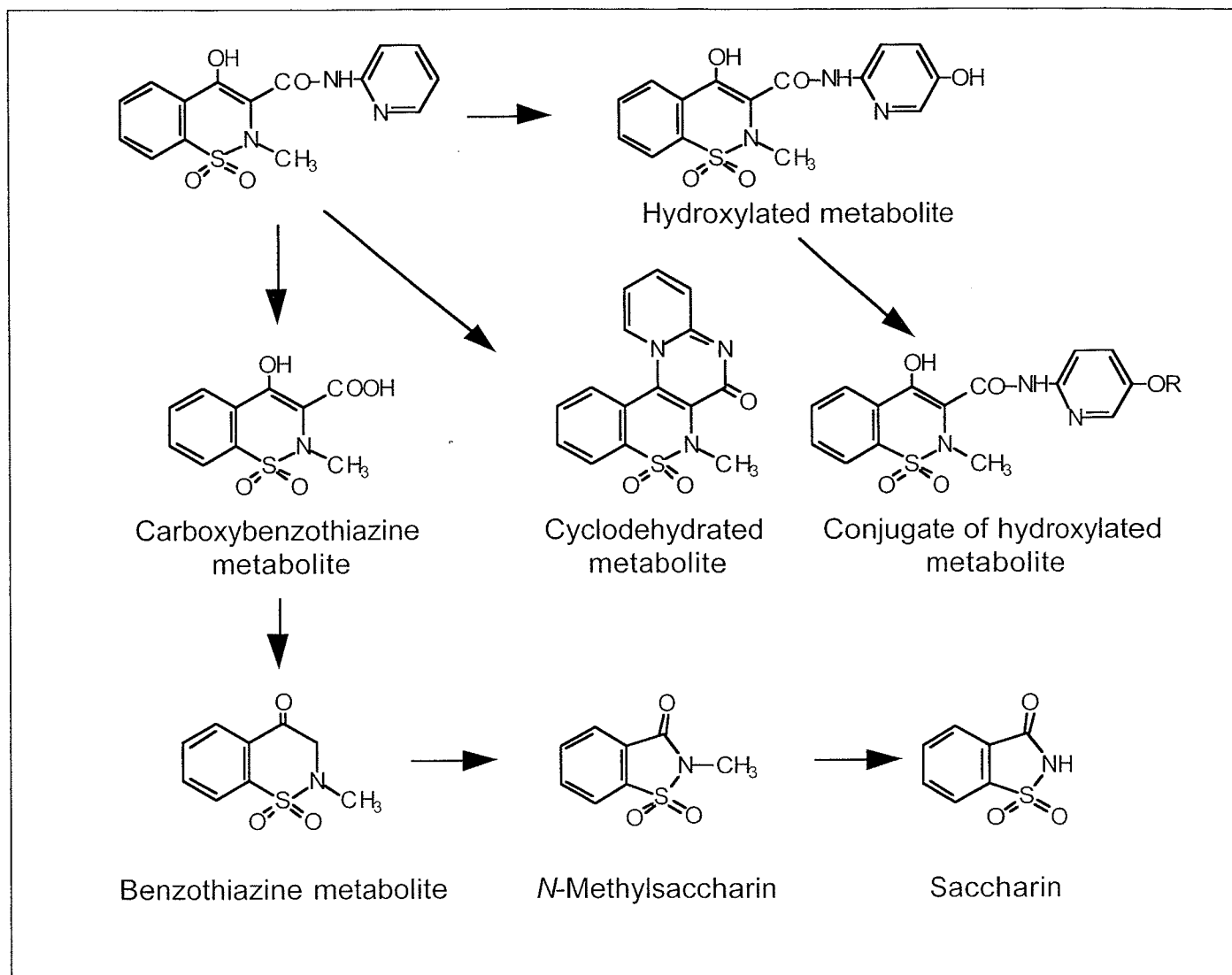
From Hobbs (1986)

reach a steady-state concentration of approximately 7 µg/ml (peak range, 4.5–7.2 µg/ml; trough range, 3.9–5.6 µg/ml) within 7–12 days (Hobbs, 1986; Calin, 1988). The volume of distribution is approximately 8 litres (Hobbs, 1986).

After administration of 20 mg/day to six healthy young volunteers for 15 days, the trough steady-state level of piroxicam was 5.5 mg/ml, and the half-life was 55 h. An average of 1% remained unbound. An average of 25% of the dose was recovered in urine as 5′-hydroxypiroxicam and 17% in the form of the glucuronide conjugate. The average steady-state level of piroxicam in plasma was 7.0 µg/ml (Richardson et al., 1987).

(b)   Distribution

Since about 99% of a dose of piroxicam is bound to protein, its distribution is limited primarily to the extracellular spaces. Nevertheless, it readily penetrates the synovial fluid and is found in concentrations that are approximately 40% (Verbeeck et al., 1986a; Calin, 1988) or 50% (Trnavska et al., 1984) of those in plasma. The extent of binding of piroxicam to protein in synovial fluid was approximately the same as that in plasma.

The apparent volume of distribution is reportedly small, 0.14 litre/kg, a value typical for most NSAIDs (Verbeeck et al., 1986a). The volume of distribution is 0.10–0.20 litre/kg (Olkkola et al., 1994).

In a study of four lactating women undergoing long-term treatment with piroxicam for arthritis, the concentrations in breast milk were 1–3% of those in plasma (Ostensen et al., 1988). No accumulation of piroxicam in milk relative to that in plasma was seen after 52 days of treatment. The investigators concluded that the daily dose ingested by breast-fed infants is only 3.5% (maximum 6.3%) of the weight-related maternal dose of piroxicam.

(c) Elimination

No more than 5% of a dose of piroxicam is excreted intact in the urine (Hobbs, 1986). At steady-state, 75% of a dose is excreted in approximately equal proportions in urine and faeces as 5'-hydroxypiroxicam and its glucuronide conjugate (Verbeeck et al., 1986a).

Since renal clearance is so low, the kinetics of piroxicam are usually not altered in patients with renal impairment (Table 1). Piroxicam could, however, accumulate in patients with pronounced renal impairment and/or in patients receiving longer courses of therapy (Whelton et al., 1990). Rudy et al. (1994) found that the time to reach the maximum concentration was shorter and unbound clearance was approximately 11% higher in elderly individuals with renal impairment than in younger individuals.

The total body clearance of piroxicam is extremely low (2–3 ml/min) (Verbeeck et al., 1986a). As a consequence, the plasma half-life is long, ranging from 30 to 60 h in healthy

subjects (Calin, 1988). Total plasma clearance has been determined to be 0.002–0.003 litre/kg bw per hour (Olkkola et al., 1994).

A summary of the pharmacokinetic parameters of piroxicam is provided in Table 2.

(d) Enterohepatic recirculation

Enterohepatic recirculation of NSAIDs has been proposed as a major factor in the development of intestinal lesions, such as ulceration of the duodenum and jejunum. To assess the extent of enteroheptic recirculation, the pharmacokinetics of piroxicam were compared in six healthy volunteers, with and without concomitant treatment with cholestyramine, in a randomized cross-over study. The participants were given either 20 mg piroxicam once daily, alone or with a dose of 24 g/day of cholestyramine, each for four days. Cholestyramine increased the elimination of piroxicam by about twofold (half-time, 50 vs 28 h). Simultaneous administration of piroxicam and cholestyramine increased the clearance of piroxicam by 58%. The investigators concluded that piroxicam is eliminated to a large extent in the bile (Benveniste et al., 1990). The effect of 12–16 g/day cholestyramine or 15–70 g/day activated charcoal on the binding of piroxicam in the intestine, thus preventing its enterohepatic circulation, has been studied further (Laufen & Leitold, 1986; Ferry et al., 1990). Significant reductions in the half-life of piroxicam were seen during treatment. Charcoal had a slightly smaller effect (control half-life of 53 h reduced

Table 1. Effect of renal impairment on the kinetics of piroxicam

No. of subjects	Age range (years)	Impairment	Conclusion	Reference
18 (26 controls)	30–80	Mild: elevated N-acetyl-β–glucosaminidase, urea or creatine level	No change in half-life, clearance or steady-state level	Darragh et al. (1985)
19	27–94	Mild to moderate: creatinine clearance, 22–88 ml/min	No correlation between creatinine clearance and kinetics	Woolf et al. (1983)
6 (6 controls)	23–72	Mild to moderate: creatinine clearance, 13–48 ml/min	Normal half-life (17–59 h)	Dupont et al. (1982)

Modified from Hobbs (1986)

Table 2. Principal pharmacokinetic parameters of piroxicam after oral administration

Study participants	Dose (mg)	C_{max} (mg/ml)	C_{av}^{ss} (g/ml)	T_{max} (h)	V_d (l/kg)	Protein binding (%)	$T_{1/2}\beta$ (h)	Reference
Young adult volunteers	20 sd	1.5–3		2–3	0.1–0.2	99	30–70	Darragh et al. (1985)
Young adult volunteers	30 sd	3–5						Hobbs & Twomey (1979)
Young adult volunteers	60 sd	6–8						Ishizaki et al. (1979)
Young adult volunteers	20 od md		5–8		0.1–0.2		30–70	Mäkelä et al. (1991); Richardson et al. (1985)
Elderly volunteers	20 sd	1.5–3		1.5–3	0.1–0.2		40–70	Rogers et al. (1981)
Children	0.4 mg/kg bw per day; md	5–10	3–8		0.12–0.25		21–40	Tilstone et al. (1981); Woolf et al. (1983)

Modified from Olkkola et al. (1994)

C_{max}, maximum plasma concentration; C_{av}^{ss} average steady-state plasma concentration; T_{max}, time to achieve maximum plasma concentration; V_d, volume of distribution; $T_{1/2}\beta$, half-life; sd, single dose; od, daily dose; md, multiple doses

to 40 h) than cholestyramine (control half-life of 47 h reduced to 28 h).

(e) Effects of age and sex

The pharmacokinetics of piroxicam do not appear to be related to age or sex (Table 3). No significant difference was found in the mean elimination half-time for old and young subjects (Campbell et al., 1985); however, sig-nificant interindividual variation was seen, the measured steady-state levels being three times higher in subjects with slow clearance than in those with more rapid clearance. Furthermore, patients with slow drug clearance required three weeks to achieve steady-state. The slow clearance of these individuals may give cause for concern, since side-effects have been shown to be dose-related.

Plasma concentrations, elimination half-life, the concentration–time relationship and the volume of distribution were not influenced by age or sex (Woolf et al., 1983; Edwards et al., 1985; Hundal et al., 1993). Additionally, mild to moderate renal impairment had no observable effect (Darragh et al., 1985).

Some studies have shown differences between young and elderly individuals in the pharmacokinetics of piroxicam. In a study of 23 patients aged 27–79 years given a standard dose of 20 mg/day for six weeks, the clearance, half-life and steady-state concentrations of piroxicam were modestly correlated with the age of the patients. Thus, patients over 60 years eliminated piroxicam more slowly than younger patients, their clearance values were lower, and the steady-state concentrations were higher (Blocka et al., 1988). In a further series of patients, aged 57–71 years, a twofold increase in the concentration–time relationship and a 53% reduction in clearance were found (Caldwell, 1994).

Table 3. Effect of age on the kinetics of piroxicam

Study type	No. of subjects	Age range (years)	Influence of age	Reference
Single dose	25	20–75	Clearance significantly lower in elderly females only	Richardson et al. (1985)
	24	19–86	No significant effect	Campbell et al. (1985)
	44	20–80	No significant effect	Darragh et al. (1985)
Multiple doses	23	27–79	Significant effect	Verbeeck et al. (1986b)
	44	20–80	No significant effect	Darragh et al. (1985)
	19	27–94	No significant effect	Woolf et al. (1983)
Kinetic monitoring	254	21–83	No significant effect	Hobbs & Gordon (1984)
	635	24–90	Mean levels significantly higher in elderly females only; small effect	Rugstad et al. (1986)

Modified from Hobbs (1986)

In a study of 10 children with rheumatic disease, aged 7–16 years, the maximum concentration was 3.6–9.8, the volume of distribution was 0.12–0.25 litre/kg (mean, 0.16 litre/kg), and the total body clearance was 2.1–5.0 ml/kg bw per hour, with a mean of 3.4 ml/kg bw per hour. The clearance was higher and the half-life shorter than those reported in other studies (Mäkelä et al., 1991).

Healthy elderly women eliminate piroxicam more slowly than healthy young women (Richardson et al., 1985). Although plasma protein binding was not affected by age or sex, body clearance was 33% lower in elderly women than in young women, yielding higher steady-state plasma concentrations.

In patients with osteoarthritis, the plasma concentration increased significantly with increasing age, and women had higher concentrations than men (Rugstad et al., 1986).

3.2 Experimental models

The kinetics and metabolism of piroxicam in laboratory animals have been reviewed extensively (Wiseman & Hobbs, 1982; Ando & Lombardino, 1983; Brogden et al., 1981).

3.2.1 Metabolism

The biotransformation of piroxicam has been studied in rats, rabbits, dogs and rhesus monkeys. In Sprague–Dawley rats, rhesus monkeys and beagle dogs, hydroxylation of the pyridyl ring at the 5′ site was the primary route of metabolism. The metabolic pathways were qualitatively the same in all three species, but an additional hydroxylation of the benzothiazine ring was seen in rats (Hobbs & Twomey, 1981). The primary metabolite of piroxicam metabolism is the same in humans as in these three animal species.

3.2.2 Pharmacokinetics

(a) Absorption

The kinetics of piroxicam (at 3 and 10 mg/kg bw) in plasma of rabbits was similar after oral and rectal administration (Schianterelli et al., 1981). Half-lives of 2–9 h in rabbits, rats and rhesus monkeys and 45 h in beagle dogs have been measured (Wiseman et al., 1976; Hobbs & Twomey, 1979).

After intravenous administration of 10 mg/kg bw to fasted, male Wistar rats, the volume of distribution was lower than the physiological volume (232 ml/kg bw at steady-state and 234 ml/kg bw at the terminal phase) (Fernandez-Troconis et al. 1991). Plasma clearance was 22 ml/h per kg bw and blood clearance was 35 ml/h per kg bw. The extraction ratio was 0.0006, the intrinsic clearance 1140 ml/h per kg bw and the half-life 7.5 h.

Studies conducted with tritiated piroxicam in the beagle dog indicate that piroxicam is well absorbed after oral administration (Hobbs & Twomey, 1981). In three young male and three young female beagle dogs, piroxicam

showed a high level of bioavailability after oral administration (Galbraith & McKellar, 1991).

The elimination half-life in dogs is similar to that in humans (approximately 45 h), and the LD_{50} for piroxicam is 700 mg/kg bw. The half-life after intravenous injection of 0.3 mg/kg bw was 40 h; the volume of distribution was 0.29 litre/kg (± 0.018), and the clearance was 0.66 litre/h. After oral administration of 0.3 mg/kg bw, the maximum concentration was 1.35 μg/ml (± 0.12), and the time to achieve that concentration was 3.1 h (± 1.0) (Galbraith & McKellar, 1991). The plasma concentration showed successively lower peaks and troughs, strongly suggesting that the drug had undergone enterohepatic cycling, as has also been postulated in humans. If this is the case, piroxicam may accumulate when administered daily. Further studies are required to determine the extent to which the drug accumulates before steady-state levels are reached, to ensure that dogs tolerate repeated treatments. Different breeds of dogs may differ in measured pharmacokinetic parameters.

(b) Distribution
In two model systems, piroxicam was preferentially distributed in inflamed tissue: in urate-inflamed knee joints of dogs and in the region of carrageenan-induced paw oedema in mice (Noguchi *et al.*, 1984).

(c) Elimination
CD Sprague-Dawley rats given an oral dose of 20 mg/kg bw excreted 86% of the dose in the urine within 48 h. Beagle dogs given an oral dose of 20 mg/kg bw of piroxicam excreted 72% of the dose over 168 h, equally divided between the urine and faeces. This finding is consistent with the measured long half-life in this species. Rhesus monkeys given an oral dose of 20 mg/kg bw of piroxicam excreted 86% of the dose during the initial 72 h, equally divided between the urine and faeces (Hobbs & Twomey, 1981).

(d) Effects of age and sex
After intravenous doses of 0.50 and 5.0 mg/kg bw piroxicam to Sprague-Dawley rats, the half-life was 13 h in males and 41 h in females.

It was concluded that the dose had no effect on the disposition of piroxicam, but the sex of the animals had a marked effect on the pharmacokinetics. The mean total clearance of 0.0062 litre/h per kg bw in females was more than three times greater than the value in males. Males thus had a larger free fraction, and females had a higher association constant for binding to serum proteins. The free piroxicam clearance differed twofold (0.76 litre/h per kg bw in males and 0.42 litre/h per kg bw in females). The steady-state volume of distribution, however, appeared to be unaffected by the sex of the animals. It is believed that protein binding explains some of the sex-dependent disposition of piroxicam and that sex-dependent metabolism may be a primary consideration (Roskos & Boudinot, 1990).

In a study of the effect of age on the pharmacokinetics of piroxicam in rats, male Fischer 344 rats, aged 5 and 24 months, were given 1 mg/kg bw piroxicam per day intravenously for five days. Statistically significant, age-related differences in pharmacokinetics were seen. For example, the half-life of piroxicam was 5.9 ± 0.7 h in young rats and 31 ± 9.9 h in older rats — nearly five times longer. Total clearance was faster in the young rats, with a value of 0.048 ± 0.012 litre/h per kg bw, while the older rats had a clearance rate of only 0.021 ± 0.003 litre/h per kg bw. The steady-state volume of distribution was 0.42 ± 0.05 litre/kg bw in the young rats and 0.56 ± 0.10 in the older rats (Boudinot *et al.*, 1993).

3.3 Genetic variation
No data were available to the Working Group.

4. Cancer-preventive Effects

4.1 Human studies
The only available data on the effects of piroxicam on cancer risk are derived from case series. One case report (Gowen, 1996) described a 73-year-old man with a history of rectal carcinoma who subsequently was found to have two villous adenomas of the caecum. Since the patient refused surgery, piroxicam was given, at 10 mg

three times per week and the patient was urged to reduce his alcohol intake and adhere to a bland diet. Both adenomas regressed within three months. In another study, two patients with three adenomas were followed by regular endoscopy. One polyp appeared to have shrunk from 12 to 8 mm in diameter after six months, and two others of 4 and 10 mm remained unchanged in size (Hixson *et al.*, 1993). [The Working Group noted that these limited data provide little information about the chemopreventive potential of piroxicam.]

Piroxicam at 20 mg/day had no effect on rectal mucosal proliferation in seven patients with a history of colorectal adenoma, a finding with limited statistical power. Piroxicam did, however, induce a dose-related decrease in mucosal prostaglandin E_2 levels; a modest decrease was seen at 5 mg/kg bw, which was not significantly different from the baseline value. A dose of 10 mg daily reduced the prostaglandin E_2 levels by about 30%, and 20 mg/day reduced the levels by more than 50% (Earnest *et al.*, 1990).

4.2 Experimental models
4.2.1 Experimental animals

(a) Colon
Short-term studies. Groups of five to eight Fischer 344 rats were given a diet containing 125 ppm piroxicam for 35 days. Azoxymethane was given at a dose of 30 mg/kg bw as a single subcutaneous injection seven days after the start of piroxicam treatment. All rats were killed 35 days after the end of the experimental period, and the numbers of aberrant crypt foci were counted under a microscope. The numbers of foci per colon were 25.8 ± 2.2 in controls and 15.7 ± 2.8 in those given piroxicam. Piroxicam also significantly reduced the numbers of aberrant crypts per focus (1.84 ± 0.10) as compared with those in the control group (2.04 ± 0.04) ($p < 0.05$) (Pereira *et al.*, 1994).

Groups of 5–10 male Fischer 344 rats, weighing 100–125 g, were given azoxymethane at a dose of 15 mg/kg bw by subcutaneous injection once a week for two weeks. Two weeks after the second injection of azoxymethane, rats were given AIN-76A diet containing 0, 200

or 400 ppm piroxicam (40% and 80% of the maximum tolerated dose (MTD) determined in an eight-week study) for four weeks and were then killed. No significant growth retardation was observed. Piroxicam reduced not only the total numbers of foci per colon but also those containing more than three crypts per focus, in a dose-dependent manner ($p < 0.05$) (Wargovich *et al.*, 1995).

Long-term studies. Seven randomized groups of eight weanling C57Bl/6J-Min/+ mice were fed AIN-93 diets containing 0, 50, 100 or 200 ppm piroxicam. All animals were killed after six weeks, and the intestinal adenomas were counted. Tumour multiplicity was decreased in a dose-dependent manner, from 17.3 ± 2.7 in the controls to 2.1 ± 1.1 in mice fed 200 ppm piroxicam ($p < 0.001$); the tumour multiplicity was 5.2 ± 1.2 in animals at 50 ppm and 4.5 ± 1.0 in those at 100 ppm ($p < 0.001$) (Jacoby *et al.*, 1996).

Groups of 9–10 Lobund inbred Sprague-Dawley weanling rats received intrarectal administrations of N-methyl-N-nitrosourea at a dose of 0.5 ml of a 0.8% solution, three times every two days (total dose, 12 mg/rat). One week after the last administration of carcinogen, rats were given 0 (control) or 130 mg/kg of diet [130 ppm] piroxicam [purity and source unspecified] in L-485 all-grain diet for 19 weeks and then killed. The experiment was repeated using the same protocol. The animals were examined for intestinal tumours macroscopically and histologically. Piroxicam did not retard the growth of the rats significantly during the experimental period, but the number of rats that died during this time was not given. The incidences of tumours of the small intestine and colon were 9/9 (100%) in the control groups in both the first and second experiments and 5/10 (50%) and 3/9 (33%) in piroxicam-treated groups in the two experiments. [The method used for deriving p values was not described.] Most of the tumours were adenocarcinomas. The numbers of small intestinal tumours were 33 in controls and three in piroxicam-treated animals in the first experiment and one in controls and none in piroxicam-treated animals in the second experiment;

the numbers of colon tumours were 28 in controls and six in piroxicam-treated animals in the first experiment and 33 in controls and three in piroxicam-treated animals in the second experiment. Piroxicam significantly decreased the total numbers of intestinal tumours per rat in both the first ($p < 0.0001$) and second ($p < 0.001$) experiments (Pollard & Luckert, 1984).

Groups of 21–25 male Sprague-Dawley rats, weighing 100–125 g each, were given azoxymethane subcutaneously at a dose of 8 mg/kg bw once a week for eight weeks and 0, 65 or 130 mg/kg of diet [65 and 130 ppm] piroxicam in the diet during and after carcinogen treatment for 26 weeks; they were then killed. The basal diet used in this experiment was a semisynthetic, dextrose- and casein-based diet. Intestinal tumours were counted macroscopically, and 10 tumours from each group were examined histologically. No significant growth retardation was observed. The incidences and numbers of tumours per rat in the small and large intestines were not significantly different in control and piroxicam-treated groups; however, the total numbers of intestinal tumours per rat were 3.4 ± 2.3 in controls, 3.2 ± 1.9 in those given 65 ppm piroxicam and 2.3 ± 1.6 in those given 130 ppm piroxicam, showing a significant reduction as compared with the control group ($p < 0.05$) (Nigro et al., 1986).

Groups of 36 male Fischer 344 rats, seven weeks of age, were given a single subcutaneous injection of azoxymethane at a dose of 29.6 mg/kg bw. Piroxicam was mixed with basal NIH-07 diet at concentrations of 0 (control), 25, 50, 75 or 150 mg/kg of diet [25, 50, 75 or 150 ppm] and was fed to the rats one, 13 and 23 weeks after carcinogen treatment; the stability of piroxicam in the diet for seven days was > 92%. All of the rats were killed 40 weeks after azoxymethane treatment, and intestinal tumours were examined macroscopically and histologically. No significant growth retardation was observed. The incidences of colon tumours (percentage of animals with tumours) were inhibited in a dose-dependent manner in rats fed diets containing piroxicam ($p < 0.001$) one or 13 weeks after carcinogen treatment, with incidences in animals fed diets containing

0, 25, 50, 75 and 150 ppm piroxicam of 89, 61, 58, 50 and 39%, respectively, when starting at one week (Table 4) and 89, 69, 69, 44 and 33% respectively, when starting at 13 weeks. The numbers of tumours per animal were also significantly inhibited in these animals ($p < 0.01$–0.0001). When the diets containing piroxicam were fed 23 weeks after carcinogen treatment, the colon tumour incidences were significantly inhibited ($p < 0.05$) in groups fed 25 or 150 ppm piroxicam (Reddy et al., 1987).

Groups of 20–23 male Lobund Sprague-Dawley rats, six weeks of age, were given a single subcutaneous injection of methylazoxymethanol acetate at a dose of 30 mg/kg bw, followed by an L-485 diet containing 0 or 130 mg/kg of diet [130 ppm] piroxicam [purity unspecified] starting one or 20 weeks after carcinogen treatment. Control animals were killed after 20 and 40 weeks, and those given piroxicam were killed after 40 weeks of carcinogen treatment. Intestinal tumours were examined macroscopically and histologically. No significant growth retardation was observed. The combined incidences of tumours of the small and large intestine were 19/21 (90%) in control rats killed at 20 weeks, 19/20 (95%) in controls killed at 40 weeks, 9/21 (43%) in animals given piroxicam one week after carcinogen treatment and 17/23 (74%) in rats started at 20 weeks. The numbers of intestinal tumours were 2.8/rat in controls at 20 weeks, 2.7/rat in those killed at 40 weeks, 0.6/rat in animals given piroxicam starting at one week and 1.4/rat in those started at 20 weeks (Pollard & Luckert, 1989).

Groups of 30 male Fischer 344 rats, seven weeks of age, were given a single subcutaneous injection of azoxymethane at a dose of 29.6 mg/kg bw, followed one week later by piroxicam mixed with AIN-76A basal diet at concentrations of 0 (control), 25, 75 or 150 ppm. All rats were sacrificed 56 weeks after azoxymethane treatment, and intestinal tumours were examined macroscopically and histologically. None of the rats died during the experimental period, and no significant growth retardation was observed. The incidences and numbers of colon adenocarcinomas, but not colon adenomas or small intestinal tumours, were reduced in rats receiving piroxicam at

Table 4. Effects of piroxicam on azoxymethane (AOM)-induced colon tumourigenesis when given one week after carcinogen treatment for 39 weeks to groups of 36 male Fischer 344 rats

Treatment (dose, ppm)	Incidence (%)			No. of tumours/rat (mean ± SD)		
	Total	Adenoma	Adeno-carcinoma	Total	Adenoma	Adeno-carcinoma
AOM alone	89	69	56	2.4 ± 1.4	1.3 ± 1.0	1.1 ± 0.9
AOM + piroxicam (25)	61*	61*	28*	1.3 ± 1.4*	1.0 ± 1.3	0.3 ± 0.6*
AOM + piroxicam (5)	58*	44*	25*	0.9 ± 1.1*	0.6 ± 0.7*	0.3 ± 0.6*
AOM + piroxicam (75)	50*	31*	25*	0.8 ± 1.1*	0.4 ± 0.7*	0.4 ± 0.7*
AOM + piroxicam (150)	39*	25*	22*	0.5 ± 0.6*	0.3 ± 0.4*	0.2 ± 0.4*

From Reddy et al. (1987)
*Significantly different from group receiving AOM alone ($p < 0.05$–0.001)

25 or 75 ppm ($p < 0.05$). The incidences of adenocarcinomas were 17/30 (57%) in controls, 10/30 (33.3%) in those receiving 25 ppm piroxicam, 6/30 (20%) in rats receiving 75 ppm piroxicam and 7/30 (23%) in those given 150 ppm piroxicam. The numbers of tumours/rat (mean ± SD) were 0.73 ± 0.14, 0.37 ± 0.10, 0.20 ± 0.09 and 0.30 ± 0.11 in the four groups, respectively (Reddy et al., 1990).

Groups of 36 male Fischer 344 rats, five weeks of age, were given a modified AIN-76A diet containing piroxicam at concentrations of 0 (control), 200 or 400 ppm (40 and 80% of the MTD, determined in a six-week study) throughout the experimental period. Two weeks after the diets were begun, azoxymethane was given by subcutaneous injection at a dose of 15 mg/kg bw once a week for two weeks. All rats were killed 52 weeks after the azoxymethane treatment, and intestinal tumours were examined macroscopically and histologically. No significant growth retardation was observed. The incidences and numbers of both small intestinal and colon adenocarcinomas, but not those of adenomas, were dose-dependently reduced. The incidences of colon adenocarcinomas were 72% in controls, 31% in rats at 200 ppm piroxicam and 22% in those given 400 ppm piroxicam ($p < 0.001$). The numbers of tumours per rat were 1.14 ± 0.18, 0.31 ± 0.07 and 0.29 ± 0.09 in the three groups, respectively ($p < 0.001$) (Rao et al., 1991).

Groups of 36 male Fischer 344 rats, six weeks of age, were given diets containing 0, 200 or 400 ppm piroxicam (40 and 80% of the MTD, determined in a six-week study) throughout the experimental period. Azoxymethane was given by subcutaneous injection at a dose of 15 mg/kg bw once a week for two weeks, starting one week after the beginning of the diet. All rats were killed 50 weeks after the second azoxymethane injection, and colon tumours were examined macroscopically and histologically. No significant growth retardation was observed. The numbers of colon adenocarcinomas, but not of adenomas, were reduced in the groups given piroxicam ($p < 0.05$–0.01). The reduction in incidence was dose-related: by 45% at 200 ppm piroxicam ($p < 0.05$) and by 64% at 400 ppm ($p < 0.01$) (Table 5; Reddy et al., 1992).

Groups of 20–32 male Fischer 344 rats, weighing 90–130 g were given an AIN-76 diet containing 75 ppm piroxicam throughout the experimental period. Azoxymethane was given by subcutaneous injection at a dose of 15 mg/kg bw once a week for two weeks starting two weeks after the diet was begun. All of the rats were killed 28 weeks after the first carcinogen treatment, and colon tumours were examined macroscopically and histologically. No significant growth retardation was observed. The incidences of colon tumours were 10/20 (50%) in controls and 9/32 (28%) in those given piroxicam ($p < 0.05$). The

Table 5. Effects of piroxicam on azoxymethane (AOM)-induced colon tumourigenesis when given before, during and after carcinogen treatment for 52 weeks to groups of 36 male Fischer 344 rats

Treatment (dose ppm)	Incidence (%)			No. of tumours (mean ± SD)		
	Total	Adenoma	Adeno-carcinoma	Total	Adenoma	Adeno-carcinoma
AOM alone	61	5.6	58	1.03 ± 1.14	0.05 ± 0.22	0.98 ± 1.1
AOM + piroxicam (200)	33*	8.3	33*	0.47 ± 0.68*	0.08 ± 0.2	0.39 ± 0.59*
AOM + piroxicam (400)	22*	2.8	19*	0.38 ± 0.72*	0.09 ± 0.36	0.29 ± 0.50*

From Reddy et al. (1992)
* Significantly different from group receiving AOM alone ($p < 0.05-0.001$)

numbers of tumours per tumour-bearing rat were not significantly reduced (Earnest et al., 1994).

(b)   Liver

Groups of 19 male inbred ACI/N rats, six weeks of age, were given a diet containing 0 or 130 ppm piroxicam for 18 weeks, followed by basal diet for a further 19 weeks. 2-Acetylamino-fluorene was added to the diet at a dose of 200 ppm starting one week after the diet containing piroxicam had been started, for 16 weeks. Rats were killed serially 17 (three rats), 21 (three rats), 25 (three rats) and 37 weeks (10 rats) after the beginning of the experiment, and the livers were examined macroscopically. No significant growth regardation was observed. The numbers of iron-excluding altered liver cell foci were significantly decreased by piroxicam at all times. By 37 weeks, the numbers of altered liver-cell foci (mean ± SD) were 42.6 ± 6.7 in controls and 24.2 ± 5.2 in rats given piroxicam. The incidences of hepatocellular adenomas and carcinomas were 10/10 (100%) in controls and 1/10 (10%) in rats given piroxicam, and the numbers of tumours per rat were 4.0 ± 2.4 in controls and 0.10 ± 0.30 with piroxicam. Piroxicam significantly decreased the numbers of foci ($p < 0.05$) and the incidences ($p < 0.0001$) and numbers ($p < 0.001$) of hepatic tumours (Tanaka et al., 1993).

(c)   Urinary bladder

Groups of 50–72 male B6D2F$_1$ mice, seven to eight weeks of age, were given a diet containing 0, 15 or 30 ppm piroxicam (40 and 80% of

the MTD, determined in 6–8-week studies) throughout the experimental period. The experiments with the low and high doses of piroxicam were performed separately. One week after the start of the diet containing piroxicam, mice were given doses of 7.5 mg N-nitrosobutyl(4-hydroxybutyl)amine in 20% ethanol once a week for eight weeks and were killed six months after the first treatment. Urinary bladder carcinomas were examined histologically. No significant growth retardation was observed, and the survival rate was more than 80%. The incidences of transitional-cell carcinomas were 25/63 (40%) in controls and 5/69 (7%) at the low dose of piroxicam, and 28/65 (43%) in controls and 7/56 (13%) at the high dose. Both doses of piroxicam inhibited urinary bladder carcinogenesis ($p < 0.0001$ and $p < 0.001$, respectively) (Moon et al., 1993).

(d)   Mammary gland

Groups of 18–22 female Sprague-Dawley rats, 40 days old, were given a single intragastric intubation of 5 mg 7,12-dimethylbenz[a]-anthracene [solvent unspecified]. One week later, high- or low-fat diets containing 0 or 100 ppm piroxicam were given for 19 weeks. All rats were killed 20 weeks after carcinogen treatment, and the mammary carcinomas were examined macroscopically and histologically. Significant growth retardation was seen with the high-fat diet containing piroxicam. Piroxicam did not significantly affect the incidences or numbers of mammary adenocarcinomas (Kitagawa & Noguchi, 1994).

(e) Lung

Two groups of 25 female A/Jg mice, six to seven weeks old, were given a total dose of 9.1 mg per animal of 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) in drinking-water between weeks 0 and 7. One group received AIN-76 diet without piroxicam and the other received piroxicam at 25 mg/kg diet. All mice were killed 16 weeks after the end of NNK treatment, and lung adenomas larger than 1 mm were counted under a dissecting microscope. The numbers of lung tumours were 8.44 ± 1.01 in controls and 5.88 ± 0.82 in those given piroxicam ($p < 0.05$) (Jalbert & Castonguay, 1992).

4.2.2 In-vitro models

(a) Canine tumour cells

Four canine tumour cell lines, established from spontaneously arising canine tumours, were used to evaluate the effects of piroxicam and other NSAIDs against transitional-cell carcinoma, squamous-cell carcinoma, melanoma and soft-tissue sarcoma (Knapp et al., 1995). Piroxicam was tested at concentrations of 0, 3, 30, 100, 250, 500, 750 and 1000 μmol/litre. The 50% inhibitory concentration, measured in short-term assays for growth rate, was 530 μmol/litre, a concentration more than 10 times the serum concentration that could be achieved safely in vivo. When piroxicam was combined with zileuton, a lipoxygenase inhibitor, the 50% inhibitory concentration was not significantly different from that of zileuton alone; combinations with the chemotherapeutic agents cisplatin (1.5 μmol/litre) and carboplatin (6.1 μmol/litre) had similar effects as when administered without piroxicam. Piroxicam is therefore not cytotoxic at concentrations that can be achieved safely in vivo, and the authors concluded that the antitumour activity of piroxicam is unlikely to be attributable to direct cytotoxicity against the tumour.

(b) HT-29 colon adenocarcinoma cells

Shiff and colleagues (1996) evaluated the effects of piroxicam and other NSAIDs on cell proliferation, cell cycle phase distribution and the development of apoptosis in HT-29 colon adenocarcinoma cells in vitro. To evaluate the effect of piroxicam on cell proliferation, a monolayer of HT-29 cells was grown for 72 h in culture medium supplemented with 0, 100, 300, 600 or 900 μmol/litre piroxicam. The cells treated with piroxicam showed a significant, apparently concentration-dependent reduction in the rate of proliferation: at 100 μmol/litre, piroxicam had no significant effect but at 300 and 600 mmol/litre proliferation was reduced by 4.3–4.5-fold at 72 h; at 900 μmol/litre, cell proliferation was reduced by 18-fold.

A nonlinear, concentration-dependent effect was seen on the distribution of cells in different stages of the cell cycle. After 48 h of treatment with piroxicam, the number of cells in G_0/G_1 phase was increased and the proportion of those in the S phase was consequently decreased, indicating that piroxicam either inhibits the progression of cells through the G_1 phase or from G_1 into the S phase. Piroxicam, unlike other NSAIDs tested, did not reduce the proportion of cells in the G_2/M phase of the cell cycle.

Although the anti-proliferative effect of piroxicam can be partially accounted for by the observed effects on the cell cyle, the investigators also evaluated the effect of piroxicam on the rate of cell death, by studying the DNA content of HT-29 cells treated with piroxicam. Chromatin condensation was observed after treatment with 900 μmol/litre piroxicam for 72 h, and a rough correlation was seen between apoptosis reduction and the ability of piroxicam to suppress cell proliferation.

Piroxicam also induced distinctive morphological changes in the HT-29 colon adenocarcinoma cell line. After growth at a plate density of 0.5×10^6 for 72 h, untreated cells grew in aggregates, with individual cells assuming polygonal or rectangular shapes. After treatment with piroxicam at a concentration of 1500 μmol/litre, however, the cells grew in small groups, with individual cells assuming irregular shapes. These morphological changes were seen at 24 h and reached a maximum at 72 h.

The effects observed on cell proliferation, cell growth cycle distribution, rate of apoptosis

and cell morphology are in agreement with results obtained in studies of the effects of sulindac sulfide on colon cancer cells (Shiff et al., 1995) and of other NSAIDs on the proliferation of non-intestinal cultured cells (Neupert & Muller, 1975; Hial et al., 1977; Bayer et al., 1979).

(c) Human breast cancer line

The effect of piroxicam, with or without linoleic acid, on a human breast cancer cell line, MDA-MS-231, was evaluated by Noguchi et al. (1995). Linoleic acid was included because, theoretically, it can be converted to arachidonic acid, which can in turn be converted into prostaglandins. The addition of linoleic acid alone to the cell culture at a concentration of 625 ng/ml promoted prostaglandin synthesis and thymidine incorporation. In the absence of linoleic acid, piroxicam suppressed cell growth and thymidine incorporation. Although piroxicam reduced the secretion of prostaglandin in the absence of linoleic acid, concentrations in excess of 100 μmol/litre were required to suppress prostaglandin secretion in the presence of linoleic acid. These results suggest that cyclooxygenase (COX[1]) inhibition, and therefore piroxicam administration, could play an active role in the suppression of cell growth.

(d) Antimutagenicity in short-term tests

In addition to being important mediators of the inflammatory response, reactive oxygen species have been shown to induce mutations, malignant transformation and sister chromatid exchange in cultured mammalian cells (Weitzman & Stossel, 1981; Weitzman et al., 1985). In addition, there is evidence that the intermediate formation of reactive oxygen species plays a role in the mechanism of action of several tumour promoters (Kenzler & Trush, 1984). For example, receptor binding by 12-O-tetradecanoylphorbol 13-acetate (TPA) results in activation of phospholipase A_2 and stimulation of the arachidonic acid cascade (Emerit & Cerutti, 1982), which progresses in part through COX to form oxygen-centred free radicals and malondialdehyde as well as

prostaglandins. TPA-induced chromosomal breakage can be prevented by inhibitors of arachidonic acid metabolism (Emerit et al., 1983). Weitberg (1988) showed that piroxicam, which inhibits arachidonic acid metabolism by COX, prevents generation of sister chromatid exchange in Chinese hamster ovary cells when incubated with TPA-stimulated human blood leukocytes as the source of COX and the resulting reactive oxygen species and lipid peroxidation. The results support the concept that intermediates of lipid peroxidation play a role in DNA damage induced by free radicals and that NSAIDs like piroxicam and indomethacin may exert a protective or anticancer effect by decreasing the amount of free radical and toxic lipid peroxidation products resulting from COX metabolism of arachidonic acid.

4.3 Mechanisms of chemoprevention
(see also General Remarks)

4.3.1 Preneoplastic lesions

Inhibition of colon cancer by piroxicam is directly related to the ingested dose and occurs regardless of whether the drug is given one week or 23 or more weeks after the carcinogen in a 40-week tumour development protocol (Reddy et al., 1987). In this model, the earliest phenotypic changes in colonic mucosa that correlate with ultimate cancer formation are aberrant crypt foci (McLellan et al., 1991). These microscopic clusters of abnormal crypts have been shown to contain mutations similar to those occurring in human adenomatous polys and tumours and to grow over time after carcinogen administration (McLellan et al., 1991; Pretlow et al., 1993). Piroxicam administered in the diet of azoxymethane-treated rats both decreased the formation of aberrant crypt foci and caused them to regress (Pereira et al. 1996). Thus, piroxicam appears to suppress cancer development at both early and later stages after carcinogen exposure.

4.3.2 Inhibition of carcinogen activation

Piroxicam and other NSAIDs decrease activation of procarcinogens in colonic mucosa and reduce production of reactive oxygen species

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[1] COX is used as a synonym for prostaglandin endoperoxide synthase (PGH synthase)

and malondialdehyde. Peroxyl free radicals and malondialdehyde are produced as by-products of the COX reaction and may directly contribute to tumour initiation and promotion (Mukai & Goldstein, 1976; Marnett, 1990). The peroxidase activity of COX can also result in oxidation and activation of environmental carcinogens, including dietary mutagens, which potentially play a role in causing colon cancer (Petry et al., 1989; Smith et al., 1991). Thus, piroxicam and other NSAIDs may decrease the risk for colon cancer by suppressing non-prostaglandin effects of COX.

4.3.3 Effects on cell proliferation and apoptosis

An important question raised by the results of the study of Shiff et al. (1996; (see p. 138) is whether the antiproliferative and apoptotic effects of piroxicam on tumour cells are due to inhibition of prostaglandin synthesis via an effect on COX. Some evidence which suggests that the effect is independent of prostaglandin synthesis is provided by results of a study by Hanif et al. (1996). Two human colon cancer cell lines were studied: HT-29 which produces prostaglandins and HCT-15 which does not. Culture medium from the HCT-15 cells was thus devoid of prostaglandins, while that from HT-29 contained prostaglandins E_2, $F_{2\alpha}$ and I_2. When the culture medium was supplemented with serum, the HCT-15 cell medium had prostaglandins only at the levels found in the serum, but the HT-29 cells had an additional amount owing to synthesis by these cells. Stimulation of prostaglandin synthesis by A23187, arachidonic acid and mellitin could not increase prostaglandin production by the HCT-15 cells but resulted in three- to fivefold increases in prostaglandin production by the HT-29 cells. COX-1 and COX-2 mRNA could not be demonstrated by reverse transcriptase–polymerase chain reaction in HCT-15 cells, while the messages for both were clearly present in HT-29 cells. Proliferation of HCT-15 cells was only modestly affected by addition of prostaglandin E_2 or $F_{2\alpha}$ (25% increase) but was severely reduced by incubation with piroxicam or sulindac and also severely reduced by addition of exogenous prostaglandin, sulindac

or piroxicam. Thus, both piroxicam and sulindac exerted their antiproliferative and pro-apoptotic effects independently of prostaglandin synthesis (Hanif et al., 1996). It should be noted that the concentrations of NSAIDs used in these studies were significantly higher than those that could be achieved in vivo.

A variety of other factors potentially related to the development of colon cancer have also been shown to be affected by piroxicam. The cause for most is unclear. For example, colon tumour-suppressing doses of piroxicam in azoxymethane-treated rats exert a significant inhibitory effect on the expression of certain cancer-promoting oncogenes, such as ras p21 (Singh et al., 1994). Components of cellular signal transduction pathways may also be altered by NSAID treatment (Kantor & Hampton, 1978): pirixocam affects the cellular distribution of protein kinase C isoforms in colon tumour epithelial cells harvested from azoxymethane-treated rats (Roy et al., 1995). A similar change in protein kinase C isoform distribution was observed after oral treatment with ursodeoxycholic acid, a colon cancer-preventive agent in rats that is structurally unrelated to piroxicam (Wali et al., 1995). This observation suggests an effect of piroxicam on protein kinase C-related signalling pathways that may modify cell growth and differentiation. Further evaluation of this effect would be of interest.

4.3.4 Immune surveillance

Suppression of colon cancer in rats by piroxicam is accompanied by a reduction in prostaglandin concentrations in the colon mucosa (Kulkarni et al., 1992). Piroxicam and other NSAIDs may modify cancer development and progression by reducing the concentrations of prostaglandin E_2 in tissue, resulting from the up-regulation of COX-2. For example, immune cell surveillance and killing of malignant cells can be suppressed by high tissue levels of prostaglandin E_2, whereas immune cell responses are generally enhanced by drugs that decrease prostaglandin E_2 synthesis (Goodwin, 1984).

NSAIDs, and piroxicam in particular, have also been found to modify neutrophil activa-

tion and affect other inflammatory and immunological events (Calin, 1988). Abramson et al. (1991) postulated that the anti-inflammatory effects of piroxicam and other NSAIDs may be due to inhibition of neutrophil activation, possibly due to their effects on a guanosine-5′-triphosphate-binding protein within the plasma membrane of the neutrophil. In fact, Rosenstein et al. (1994) demonstrated that piroxicam modulates the production of various cytokines, causing elevated levels of interleukin-2, decreased levels of interleukins 1 and 6, tumour necrosis factor α and interferon-γ, but no effect on interleukin-4.

5.   Other beneficial effects

No data were available to the Working Group.

6.   Carcinogenicity

6.1   Humans
No data were available to the Working Group.

6.2   Experimental animals
No study of adequate duration to evaluate carcinogenicity was available to the Working Group.

7.   Other Toxic Effects

7.1   Adverse effects
7.1.1   Humans

(a)   Gastrointestinal tract toxicity
In a meta-analysis, the risks for serious upper gastrointestinal complications after use of piroxicam were statistically indistinguishable from those of most other NSAIDs. Within individual studies, however, piroxicam was consistently associated with higher risks for such complications, and in a ranking analysis it ranked 4 (1 being most and 12 least toxic) of 12 NSAIDs analysed. The pooled relative risk estimates for piroxicam users were 2.7–5.2 in comparison with ibuprofen users (Henry et al., 1996). Given the baseline risk of ulcer disease, which ranges from 0.5 per 1000 per year in young adults (Garcia Rodriguez et al., 1992) to 4 per 1000 in older

adults (Smalley et al., 1996), the rates of serious ulcer complications among piroxicam users can be estimated to be about 2 per 1000 in younger adults and 15 per 1000 in those 65 years and older.

Case reports indicate that piroxicam can exacerbate reflux disease and occasionally lead to oesophageal ulceration and stricture (Kikendale, 1991). Piroxicam may also have deleterious effects on the small intestine, including stricture (Matsuhashi et al., 1992), ulceration, perforation and diarrhoea (Kwo & Tremaine, 1995).

(b)   Blood pressure
In a meta-analysis of 50 randomized, placebo-controlled trials, treatment with NSAIDs raised supine mean blood pressure by 5 mm Hg (1.2–8.7) (Johnson et al., 1994). Most NSAIDs appeared to have this effect, but the most marked increases were observed with piroxicam. Nonetheless, the numbers were too small to demonstrate statistically significant differences between different NSAIDs.

(c)   Reproductive and developmental effects
No data specifically related to the reproductive or developmental effects of piroxicam were available to the Working Group.

(d)   Other toxic manifestations
Piroxicam users report skin rashes and pruritus more often than users of other NSAIDs (Fries et al., 1991).

7.1.2   Experimental animals

(a)   Gastrointestinal tract toxicity
The ulcerogenic dose or LD_{50} of orally administered piroxicam in starved rats was reportedly one-third to one-half that of indomethacin and fourfold greater than that of phenylbutazone. After rectal administration to rats, piroxicam had about one-half the ulcerogenic activity of that observed after oral administration (Schiantarelli & Cadel, 1981).

When piroxicam was given orally to fasted rats, the dose that induced gastric ulcers in 50% of rats was 6.2 mg/kg bw. The mean lesion score (a measure of ulceration intensity) was

9.5 ± 6.4 and 24.7 ± 10.5 for doses of 16 and 32 mg/kg bw piroxicam. No ulceration was seen at 2 mg/kg bw (Al-Ghamdi *et al.*, 1991).

In a study in which 62 dogs were given oral doses of 0.5–1.5 mg/kg bw piroxicam every 48 h, those receiving doses > 1 mg/kg bw had gastrointestinal irritation and ulceration after 7–120 days (median, 35 days) of treatment (Knapp *et al.*, 1992).

(b)　Effect on platelet function
Piroxicam inhibited collagen-induced platelet aggregation in dogs (Gaynor & Constantine, 1979).

(c)　Effect on articular cartilage and bone
Piroxicam administered to dogs at a dose of 0.3 mg/kg for eight weeks had no effect on articular cartilage structure (Mohr *et al.*, 1984). In a study of 12 rabbits given an oral dose of 10 mg/kg bw piroxicam per day for 12 weeks, a 3% decrease in tibial mineral content was seen, with 9% in controls, indicating that piroxicam may reduce the osteopenia caused by external fixation (Adolphson *et al.*, 1991).

(d)　Reproductive and developmental effects
Piroxicam has reportedly no dysmorphogenic, embryotoxic or teratogenic effects in rat or rabbit models when administered at concentrations of 2, 5 or 10 mg/kg bw (Perraud *et al.*, 1984). Also, no deleterious effect on mating or reproductive performance was observed when these doses were administered to animals before copulation.

Piroxicam does, however, affect parturition. Pregnant rats given piroxicam at 5 or 10 mg/kg bw on days 15–21 after insemination usually died. In surviving rats, labour was often prolonged, generally in relation to the dose and duration of piroxicam administered.

The numbers of live pups were reduced in rats treated with 5 or 10 mg/kg bw of piroxicam for at least five days, and the proportion of pups that were alive 24 h after birth was decreased as treatment was prolonged. Furthermore, lactation was impaired. Considerable maternal toxicity occurred 7–13 days after parturition in lactating female rats given 10 mg/kg bw of piroxicam (Perraud *et al.*, 1984).

These results cannot be extrapolated to pregnant or lactating women, since the standard daily dose of 20 mg piroxicam (equivalent to only about 0.3 mg/kg bw) is well below the threshold of 2 mg/kg bw at which any effect on gestation, labour or lactation was observed in rats (Brogden *et al.*, 1984).

(e)　Other toxic manifestations
Dogs given 1–1.5 mg/kg bw piroxicam orally every 48 h developed subclinical renal papillary necrosis (Knapp *et al.*, 1992). Intravenously administered piroxicam at cumulative doses up to 15 mg/kg bw had no significant effect on blood pressure or heart rate in experimental animals (Wiseman, 1978).

7.2　Genetic and related effects
7.2.1　Humans
Treatment with piroxicam at 20 mg/day for 14 days did not increase the frequency of sister chromatid exchange in peripheral blood lymphocytes (Kullich & Klein, 1986).

7.2.2　Experimental models
Piroxicam at 72 μg/ml increased the frequency of sister chromatid exchange in peripheral blood lymphocytes *in vitro* (Kullich *et al.*, 1990). It also enhanced the transformation of cultured rat tracheal cells (Steele *et al.*, 1990).

8. Summary of Data

8.1 Chemistry, occurrence and human exposure

Piroxicam, introduced in 1980, is a drug that has analgesic, anti-inflammatory and anti-pyretic properties. It has been widely and commonly used for the treatment of rheumatoid arthritis and osteoarthritis. Its use is in decline because of its gastrointestinal toxicity.

8.2 Metabolism and kinetics

Piroxicam is well absorbed after oral administration. Absorption is somewhat slower when the drug is administered rectally or with food. After initiation of therapy with the standard clinical dose of 20 mg/day, the plasma concentrations of piroxicam increase gradually and reach a steady state. This drug has a much longer half-life than other non-steroidal anti-inflammatory drugs.

Piroxicam is biotransformed in the liver to several metabolites. It is extensively bound to protein. It crosses the placenta and can be found in human milk.

8.3 Cancer-preventive effects
8.3.1 Humans

The only available data on the possible chemopreventive effects of piroxicam are from case series.

8.3.2 Experimental animals

The chemopreventive effects of piroxicam were studied in models of urinary bladder and lung carcinogenesis in mice and in models of colon, liver and mammary cancer in rats. In single studies in mice, piroxicam was preventive against urinary bladder and lung carcinogenesis. The preventive activity of piroxicam against adenomas in the intestine was demonstrated in mice predisposed to intestinal malignancy by a germ-line mutation in the *Apc* gene. Eight studies on colon cancer in rats indicate that piroxicam administered during the initiation and post-initiation phases of carcinogenesis reduces the incidence of both adenomas and adenocarcinomas. In rat models, piroxicam prevented liver carcinogenesis but had no preventive effect against mammary carcinogenesis.

8.3.3 Mechanism of action

The molecular mechanisms by which piroxicam exerts cancer preventive effects remain unclear; however, there is evidence that both prostaglandin-dependent and -independent events are involved, which result in suppression of cancer, regardless of whether piroxicam is administered early or many weeks after exposure to carcinogens.

8.4 Other beneficial effects

No data were available to the Working Group.

8.5 Carcinogenicity

No data were available to the Working Group.

8.6 Toxic effects
8.6.1 Humans

The spectrum of toxicity of piroxicam is similar to that of other aspirin-like non-steroidal anti-inflammatory agents, including gastrointestinal ulceration and bleeding, effects on blood pressure and skin rash.

8.6.2 Experimental animals

The most commonly observed toxic or adverse effect of piroxicam in experimental animals is ulceration and bleeding of the gastric and intestinal mucosa.

9. Recommendations for research

A central issue in relation to use of piroxicam as a cancer-preventive agent in humans is its toxic effects. Research on mitigating the toxicity of the drug while maintaining its cancer-preventive activity is recognized as a priority.

10.   Evaluation[1]

10.1   Cancer-preventive activity

10.1.1 Humans

There is *inadequate evidence* in humans for the cancer-preventive activity of piroxicam.

10.1.2 Experimental animals

There is *sufficient evidence* for the cancer-preventive activity of piroxicam in experimental animals. This evaluation is based on models of cancers of the colon, urinary bladder, lung and liver.

10.2   Overall evaluation

Epidemiological studies in humans provide *inadequate evidence* for the cancer-preventive activity of piroxicam. In experimental animals, there is *sufficient evidence* that piroxicam prevents cancers at several sites. Because of the toxicity of piroxicam, however, it will probably have only limited use as a cancer-preventive agent in humans.

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[1] For definition of the italicized terms, see Preamble pp. 12–13

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