Sulindac

1. Chemical and Physical Characteristics

1.1 Name

Chemical Abstracts Services Registry Number
38194-50-2

Chemical Abstracts Primary Name
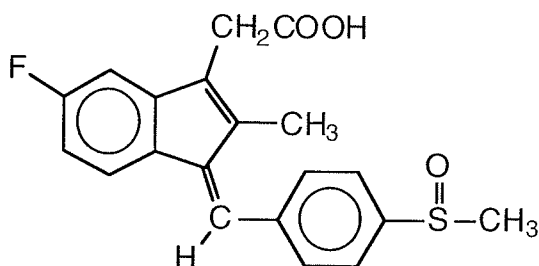Sulindac

IUPAC Systematic Name
1*H*-Indene-3-acetic acid, 5-fluoro-2-methyl-1-{[4-(methyl-sulfinyl)phenyl]methylene}

Synonyms
(Z)-5-Fluoro-2-methyl-1-{[4-(methyl-sulfinyl)-phenyl]methylene}-1*H*-indene-3-acetic acid; *cis*-5-fluoro-2-methyl-1-[*p*-(methylsulfinyl)-benzylidene]indene-3-acetic acid; MK-231

1.2 Structural and molecular formula and relative molecular mass

$C_{20}H_{17}FO_3S$ Relative molecular mass: 356.42

1.3 Physical and chemical properties

The data presented are for the pure substance and are taken from Budavari (1989) and Reynolds (1993), unless otherwise specified.

Description
Yellow, odourless crystals

Melting-point
182–185 °C

Solubility
A weak acid with a pK_a of 4.7 at 25 °C. Sparingly soluble in methanol and ethanol; slightly soluble in ethyl acetate; soluble in chloroform; practically insoluble in water at pH below 4.5. Solubility increases with rising pH to about 3.0 mg/ml at pH 7.

Spectroscopy data
Ultraviolet, infrared, nuclear magnetic resonance and mass spectra have been reported.

Stability
Stable in aquous solutions of acids and bases. In a solid state, stable for at least three days in air at 100 °C.

Stereoisomers
Sulindac is the Z isomer of 1*H*-indeno-3-acetic acid, 5-fluoro-2-methyl-1-{[4-(methyl-sulfinyl)-phenyl]methylene}.

1.4 Technical products
Trade names
Aflodac, Algocetil, Apo-Sulin, Arthrobid, Arthrocine, Artribid, Citireuma, Clinoril, Clisundac, Imbaral, Lyndak, Novosundac, Reumofil, Reumyl, Sudac, Sulartrene, Sulen, Sulic, Sulindal, Sulinol, Sulreuma.

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

2.1 Occurrence
Sulindac is not known to occur as a natural product.

2.2 Production
Sulindac is a synthetic product; it is manufactured in several countries. Accepted standard procedures for the synthesis of sulindac are described by Shen and Winter (1977). Technical details regarding its current commercial production were not available to the Working Group.

2.3 Use

Sulindac was introduced in the 1970s (Shen & Winter, 1977). It has analgesic, anti-inflammatory and antipyretic properties and is used in musculoskeletal and joint disorders, such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis, and also in the short-term management of conditions such as bursitis and tendinitis and acute gouty arthritis. The usual dose by mouth is 100–200 mg twice daily, taken with food (Reynolds, 1993).

Sulindac is a pro-drug, a pharmacologically inactive precursor that is converted *in vivo* to an active drug by metabolism or other physiological processes. Its sulfide metabolite inhibits cyclo-oxygenases. Some of its clinical properties may be attributable to the sulfone metabolite (Singh *et al.*, 1994).

2.4 Analysis

Sulindac has been measured in human plasma by high-performance liquid chromatography (Shimek *et al.*, 1981; Swanson & Boppana, 1981; Stubbs *et al.*, 1987), by combined isotope dilution radioimmunoassay (Hare *et al.*, 1977) and by differential pulse polarographic analysis (Zamboni *et al.*, 1983). Fluorescence detection combined with reversed-phase high-performance liquid chromatography has also been used to determine sulindac and its sulfone and sulfide metabolites in human serum (Siluveru & Stewart, 1995).

2.5 Human exposure

Estimates of the prevalence of sulindac use vary, but it is limited. Jones and Tait (1995) reported that sulindac accounted for less than 7% of NSAID prescriptions in 1014 cases identified in general practice in the United Kingdom.

Sulindac accounts for a minor proportion of NSAID use in the USA, as seen in the Tennessee Medicaid Programme (Griffin *et al.*, 1991).

3. Metabolism, Kinetics and Genetic Variation

3.1 Human studies

3.1.1 Metabolism

Sulindac is an anti-inflammatory pro-drug which, after absorption, undergoes two major biotransformations in humans: reversible reduction to the sulfide metabolite, the most potent inhibitor of prostaglandin production, and irreversible oxidation to the sulfone metabolite, which is inactive as an antiinflammatory agent. Figure 1 shows the proposed metabolic scheme for sulindac. Approximately 88% of sulindac is absorbed in humans after oral administration of a 200-mg dose (Duggan *et al.*, 1977). In normal subjects and patients with surgical ileostomies, as much as 50% of the total sulfide was formed by gut bacteria (Strong *et al.*, 1985), probably from sulindac excreted in bile. It appears to undergo extensive reabsorption and enterohepatic recycling. Incubation of sulindac and its derivatives with over 200 strains of bacteria isolated from human faeces *in vitro* showed extensive reduction by both aerobes and anaerobes (Strong *et al.*, 1987).

3.1.2 Pharmacokinetics

After a single 200-mg oral dose of sulindac, the peak plasma concentration was 4.7 µg/ml after 1.6 h in one study (Strong *et al.*, 1985) and 5.4 µg/ml after 1 h in another (Duggan *et al.*, 1977). Sulindac binds tightly to human serum albumin (Russeva *et al.*, 1994) and has a mean half-life of 97 h (Strong *et al.*, 1985). The peak plasma concentration of the sulfide metabolite was about 2.7 mg/ml and was reached after 3.1 h. The half-life was 14 h in normal subjects and 2.6 h in patients with an ileostomy (Strong *et al.*, 1985). Sustained plasma levels of the sulfide metabolite are consistent with a prolonged anti-inflammatory action. The peak plasma concentration of the sulfone metabolite was about 1.5 mg/ml and was reached after 2.9 h. The half-life was 20 h in normal subjects and 5.4 h in patients with an ileostomy (Strong *et al.*, 1985).

The primary route of excretion in humans is via the urine, as both sulindac and its sulfone metabolite (free and as glucuronide conjugates). About 50% of an administered dose is excreted in the urine, the conjugated sulfone metabolite accounting for the major portion. No significant level of free or conjugated sulfide was detected in urine About 25% is found in the faeces, primarily as the sulfone and sulfide

metabolites (Duggan *et al.,* 1977). The concentrations of these metabolites in the gut lumen and mucosa were not known to the Working Group.

Because sulindac is excreted in the urine primarily as biologically inactive forms, it may affect renal function to a lesser extent than other NSAIDs (Miller *et al.,* 1984); however, adverse renal effects have been reported (see section 7.1.1.(c)). Patients with end-stage renal failure had substantially lower total and free plasma concentrations of the active sulfide metabolite of sulindac (Ravis *et al.,* 1993). The apparent half-lives of sulindac and sulindac sulfide were similar in the two groups, but the half-life of the sulfone metabolite was longer in patients with renal failure.

Since many patients who take NSAIDs have rheumatoid arthritis and are also given methotrexate for their joint inflammation, a study was conducted to evaluate the potential interactions between methotrexate and sulindac. Sulindac had little effect on the disposition

of methotrexate but a minor effect on the 7-OH-methotrexate metabolite (Furst *et al.,* 1990).

Sulindac and its active sulfide metabolite undergo placental transfer; however, the reduction of sulindac to the metabolite is decreased in the human fetus, and the process seems to be independent of gestational age (Kramer *et al.,* 1995).

3.2   Experimental models

The half-life of sulindac in plasma was 10 h in Sprague-Dawley rats, 3 h in beagle dogs and 0.5 h in rhesus monkeys (Hucker *et al.,* 1973). Rats had by far the highest plasma concentration (44.0 μg/ml) 1 h after an oral dose of 10 mg/kg bw; the concentrations were 0.8 μg/ml in dogs at 1 h, not detectable in rhesus monkeys 1 h after a dose of 3 mg/kg bw and 1.3 μg/ml in humans 1 h after a 50-mg oral dose. Rats and dogs eliminated the drug almost exclusively in faeces, whereas urinary excretion is favoured in monkeys and humans. The tissue distribution in rats indicated that the drug was

Figure 1. Sulindac and its sulfide and sulfone metabolites
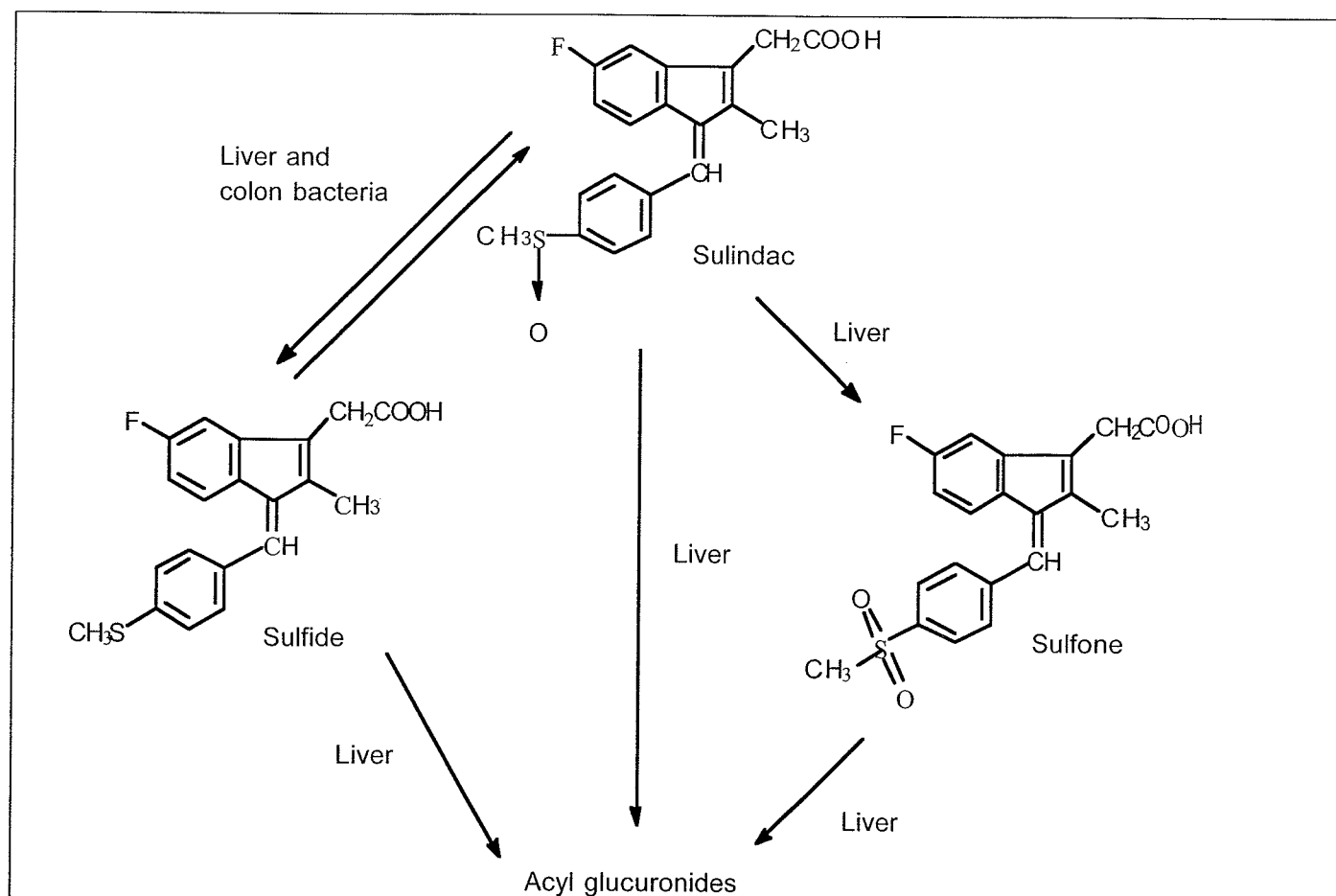
present at levels in the following order: plasma > liver > stomach > kidney > small intestine. The values increased after 4 h in stomach (37 µg/g), small intestine (17 µg/g) and large intestine (7.2 µg/g) but declined in all other tissues. In rats, 86% of the dose was recovered in bile 24 h after an intravenous dose of 10 mg/kg, whereas 53% was recovered after an equivalent oral dose. Bile collected from a dog given 10 mg/kg intravenously contained 93% of the dose. Administration of a large oral dose (100 mg/kg bw) to rats did not appreciably alter the excretion pattern. In rats, placental transfer is quite low. The concentrations of sulindac and the sulfide and sulfone metabolites found in rat milk were 10–20% of plasma levels.

Sulindac can be reduced to the sulfide by rat liver or kidney homogenates and by rat faecal contents (Lee & Renwick, 1995a,b).

3.3 Genetic variation

No data were available to the Working Group.

4. Cancer-preventive Effects

4.1 Human studies

4.1.1 Studies of adenomatous polyps in patients with familial adenomatous polyposis

The relationship between familial adenomatous polyposis (FAP) and colorectal cancer is discussed in the General Remarks.

(a) Non-randomized intervention studies

Thirteen non-randomized case series comprising a total of 128 patients with FAP have been studied to examine the efficacy of sulindac in preventing or inhibiting adenomatous polyps (Waddell & Loughry, 1983; Gonzaga et al., 1985; Waddell et al., 1989; Charneau et al., 1990; Friend, 1990; Rigau et al., 1991; Tonelli & Valanzano, 1993; Winde et al., 1993; Mäkelä & Laitinen, 1994; Spagnesi et al., 1994; Cerdán et al., 1995; Kadmon et al., 1995; Winde et al., 1995). Sulindac at doses of 100–400 mg daily, maintained for up to four years, results in a reduction in the number and size of colorectal polyps in comparison with those before treatment, regression of some adenomatous polpys on endoscopy and regression of some extra-

colonic desmoid tumours. (Desmoid tumours are histologically benign, extracolonic, connective tissue tumours that affect FAP patients.) When treatment with sulindac was stopped, the polyps reappeared; when treatment was resumed, the polyps regressed again (Charneau et al., 1990; Labayle et al., 1991; Rigau et al., 1991; Mäkelä & Laitinen, 1994). In studies to establish optimal doses, in which sulindac was administered in rectal suppositories, sustained treatment with doses as low as 50 mg/day maintained polyp suppression in many patients. The maintenance of treatment with sulindac appeared to be more important for polyp inhibition than did the amount taken daily (Winde et al., 1993, 1995, 1997). Carcinoma of the rectum was, however, reported in three patients with FAP during sulindac therapy in whom regression of polyps had been observed (Niv & Fraser, 1994; Thorson et al., 1994; Lynch et al., 1995).

(b) Randomized trials

Three small randomized clinical trials have confirmed that sulindac reduces the number and size of colorectal polyps in patients with FAP (Table 1).

Labayle et al. (1991) conducted a randomized, placebo-controlled, double-blind cross-over study of 10 patients with FAP and rectal polyps, previously treated by colectomy and ileorectal anastamosis. One patient was excluded from treatment because of noncompliance. Nine patients received either sulindac, 300 mg/day (100 mg three times per day), or placebo during two four-month periods separated by one month. During sulindac treatment, the rectal polyps regressed completely in six patients and almost completely in three. During placebo treatment, the polyps increased in size in five patients, remained unchanged in two and decreased in two. The difference between the groups given sulindac and placebo was statistically significant ($p < 0.01$).

Giardiello et al. (1993) conducted a randomized, double-blind, placebo-controlled trial of 22 patients with FAP, including 18 who had not undergone colectomy. The patients received either sulindac at 300 mg/day (150 mg twice a day) or placebo for nine months and were

evaluated by flexible sigmoidoscopy for the number and size of polyps every three months for one year. When sulindac treatment was stopped at nine months, the mean number of polyps had decreased to 44% of the original number ($p = 0.014$) and the diameter of the polyps to 35% of the original value ($p < 0.001$). No patient had complete resolution of polyps. Three months after treatment with sulindac was stopped, both the number and the size of the polyps in the sulindac-treated patients had increased, but the values remained significantly lower than the original ones.

Nugent et al. (1993) described a randomized, placebo-controlled trial of 24 patients with FAP, all of whom had duodenal polyps, and 14 with rectal polyps. Patients were randomized to sulindac at 400 mg/day (200 mg twice daily) or placebo for six months. Treatment was associated with a reduction in epithelial-cell proliferation, as measured by 5-bromo-2-deoxyuridine in the duodenum (median labelling index, 15.8 or 14.4%; $p = 0.003$) and some regression of duodenal polyps ($p = 0.12$). In the rectum, a larger reduction in cell proliferation (median labelling index, 8.5 vs. 7.4; $p = 0.018$) and a greater reduction in rectal polyps were seen. Debinski et al. (1995) later clarified that this trial showed a significant reduction in small (< 2 mm) duodenal polyps in the group given sulindac (9/11) versus the placebo group (4/12) but no reduction in

polyps ≥ 3 mm. [The Working Group noted that duodenal polyps in FAP patients may not be relevant to the situation of sporadic polyps and colon cancer, that cell proliferation in the duodenum may be less relevant to cancer than is proliferation in the colon or rectum and that the number of patients was not clearly stated for all end-points.]

(c) Studies of biomarkers

Spagnesi et al. (1994) studied 20 FAP patients (six with ileorectal anastomoses and 14 with an intact colon) and examined three end-points: cell proliferation (by thymidine labelling), labelled cell distribution along the crypts and number of polyps. While administration of sulindac (100 mg twice a day for two months) induced a significant reduction in the number of polyps, there were no changes in the proliferation indices.

Winde et al. (1997) measured genetic biomarkers of epithelial proliferation in a non-randomized, dose-finding, intervention study of 38 patients with FAP. All of the patients had had a colectomy and ileoanastomosis. Twenty-eight were given sulindac by intrarectal suppository at an initial dose of 150 mg twice daily, which was reduced to a mean dose of 64 mg/day for up to four years. Ten control patients with FAP received no sulindac. The treated patients had a marked reduction in the number of rectal polyps (386 polyps in

Table 1. Published randomized clinical trials of sulindac and adenomatous polyps

Authors	Patients	Dosage	Design	Results
Labayle et al. (1991)	10 patients with FAP, colectomy and rectal polyps, France	300 mg/day or placebo, 4-month regimens, alternating	Randomized double-blind, cross-over	Polyps regressed completely in 6 patients, partly in 3 during sulindac treatment
Giardiello et al. (1993)	22 patients with FAP (18 without colectomy), USA	300 mg/day or placebo x 9 months	Randomized double-blind	Sulindac decreased number of polys by 56% ($p = 0.014$) and size by 65% ($p < 0.001$), in comparison with baseline
Nugent et al. (1993); Debinski et al. (1995)	24 patients with FAP and duodenal polyps, USA	400 mg/day or placebo x 6 months	Randomized double-blind	Duodenal polys < 2 mm regressed in 9 of 11 patients on sulindac vs 4 of 12 on placebo. No change in larger (≥ 3 mm) polyps

FAP, familial adenomatous polyposis

28 people originally; no polyps in 24 people treated for 11 months or longer). Mutant *ras* oncogene expression became undetectable after sulindac treatment for ≥ 6 months. The proliferative index was significantly (20%) lower in patients treated with sulindac for one year than at baseline. A significant decrease in the frequency of wild and mutant *p53* was seen only when antibodies with broad specificity were used but not with those more specific to mutant *p53*. Immunohistochemical overexpression of the apoptosis-blocking protein BCL-2 was correlated inversely to mutant p53 staining in adenomatous tissue.

4.1.2 Randomized clinical trial of sporadic adenomatous polyps

Ladenheim *et al.* (1995) randomized 44 adults to either sulindac (150 mg twice a day for four months) or placebo to assess the effect on regression of sporadic polyps that were originally < 1 cm. The patients were selected from 162 asymptomatic people aged ≥ 50, who were screened by flexible sigmoidoscopy at three hospitals. People with adenomatous polyps > 1 cm or contraindications to taking NSAIDs were excluded. Treatment of four of the 22 patients given sulindac was stopped because of side-effects (anaemia in two patients, heartburn in one) or complications (urogenital sepsis in one patient), thought to be unrelated to treatment. No significant difference in the number or the mean size of polyps was seen among the sulindac-treated patients. Five polyps in patients given sulindac had disappeared in comparison with three in the group given placebo; nine adenomas remained in the group given sulindac and 12 in controls. [The Working Group noted the low statistical power of the study.]

4.1.3 Case studies of treatment for desmoid tumours

Regression of desmoid tumours during treatment with sulindac has been reported in some studies (Belliveau & Graham, 1984; Waddell & Kirsch, 1991; Kadmon *et al.*, 1995; Izes *et al.*, 1996) but not in all (Klein *et al.*, 1987).

4.2 Experimental models
4.2.1 Experimental animals

(a) Colon
Short-term studies. Groups of 14 male Fischer 344 rats, seven weeks of age, were fed AIN-76A diets containing sulindac at concentrations of 0, 200 or 400 µg/g diet [0, 200 or 400 ppm]. After seven days of feeding sulindac, all rats were given weekly subcutaneous injections of 15 mg/kg bw azoxymethane for two weeks. Formation of aberrant colonic foci was determined eight weeks after the second weekly treatment. The numbers of foci per colon were 181 in controls, 118 in rats at 200 ppm (7.7% inhibition) and 81 in those at 400 ppm (37% inhibition; $p < 0.05$) (Pereira *et al.*, 1994). In a similar study, dietary administration of sulindac at 320 ppm in the diet suppressed the number of foci per colon by 59% ($p < 0.05$) (Reddy *et al.*, 1996).

Long-term studies. These studies are summarized in Table 2.

Two groups of 48 female Balb/c mice, six to eight weeks of age, were injected subcutaneously with 25 mg/kg bw 1,2-dimethylhydrazine dissolved in 0.4% ethylenediamine tetraacetic acid in normal saline, pH 6.5, once weekly with or without sulindac for up to 25 weeks. Sulindac [purity unspecified] was administered in drinking-water at a concentration [unspecified] such that each animal received about 5 mg/kg bw per day. In a second experiment, 48 female Balb/c mice were treated with 1,2-dimethylhydrazine for 17 weeks and then randomized to control (22 rats) or sulindac (23 rats). The control group received water. Those given sulindac received a solution in drinking-water for up to 11 weeks, as described above. Body weights were not given.

In the first study, which was designed to investigate the efficacy of sulindac administered simultaneously with 1,2-dimethylhydrazine, 38 animals in each group survived until the end of the study. Of the tumours observed macroscopically, 96% were adenomas and the rest were adenocarcinomas. Microadenomas developed in 92% of control animals and 47% of those given sulindac

($p < 0.0001$), and colon tumours developed in 89% (34/38) of control animals and 42% (16/38) treated with sulindac (odds ratio, 12; 95% CI, 3.5–40). The overall colon tumour burden, the number of tumours per mouse and the number of tumours per tumour-bearing mouse were significantly reduced in the group given sulindac as compared with the control group ($p < 0.022$–0.0001). In the second study, in which sulindac was administered after the carcinogen, it did not inhibit colon carcinogenesis (numbers of animals with tumours, 17/18 and 18/18) (Moorghen *et al.*, 1988).

A group of 18 male Sprague-Dawley rats, weighing 400–500 g (age unspecified), was given 1,2-dimethylhydrazine dihydrochloride subcutaneously at a dose of 20 mg/kg bw once weekly (equivalent to 10 mg/kg bw 1,2-dimethylhydrazine) for 20 weeks. The site and diameter of each colon tumour were determined by laporotomy and colonoscopy. The rats were then randomized into two groups, receiving either 10 mg/kg bw sulindac (eight rats) or the vehicle, 0.5% methylcellulose (10 rats), twice daily by intragastric administration for four weeks. The animals given sulindac developed no additional tumours, whereas the controls had 13 additional colon tumours. Furthermore, the mean size of the 14 tumours in animals treated with sulindac was significantly smaller (9.3 mm) than that of the 39 tumours in the controls (57 mm; $p = 0.026$). In this model system, predominantly carcinomas were induced (Skinner *et al.*, 1991).

Groups of 30 male Fischer 344 rats (age unspecified) were given subcutaneous injections of 15 mg/kg bw azoxymethane once weekly for two weeks. Two weeks after the second injection, 30 animals were fed AIN-76A diet containing 0.04% [400 ppm] sulindac for 31 weeks. These animals showed a 27% reduction in the number of colon tumours per rat in comparison with controls (Alberts *et al.*, 1995). [The Working Group noted that the actual numbers of colon tumours were not given and statistical significance was not reported.]

In a preliminary study, the MTD of sulindac in male Fischer 344 rats was shown to be about 400 ppm. In a preclinical efficacy study, groups of 36 male Fischer 344 rats, five weeks of age,

were fed AIN-76A diet containing 0, 160 or 320 ppm sulindac (purity, > 98%). At seven weeks of age, all animals were given two weekly subcutaneous injections of 15 mg/kg bw azoxymethane per week. Animals intended for studying the post-initiation effects of sulindac were given the compound in the diet at 320 ppm, starting 14 weeks after the second azoxymethane injection. Treatment was continued in all groups until termination of the study 52 weeks after azoxymethane treatment. All of the colonic tumours were evaluated histopathologically. No differences in body weight were seen among the groups. Inhibition of the incidence (percentage of animals with tumours) and multiplicity (tumours per animal) of invasive and non-invasive adenocarcinomas of the colon in rats during the initiation and post-initiation phases was seen to be dose-dependent ($p < 0.001$–0.0001). Furthermore, administration of sulindac post-initiation significantly suppressed the incidence ($p < 0.0001$) and multiplicity ($p < 0.0001$) of colon adenocarcinomas (see Table 2). Oral administration of sulindac also reduced the colon tumour volume by more than 52% ($p < 0.01$) (Rao *et al.*, 1995).

Genetically altered mice. Sulindac has been tested in the Min/+ mouse model, which is described in the General Remarks. These studies are summarized in Table 2.

Groups of 10 female C57Bl/6J-Min/+ mice, five to six weeks of age, were fed AIN-76A diet and given sulindac at 160 mg/ml [160 ppm] in the drinking-water (estimated to provide 0.5 mg/animal per day). Control animals were given the diet alone. No differences in body weights or food intake were seen among the study groups. All animals were killed at 110 days of age. Multiple intestinal tumours were seen in all control animals, whereas only one mouse treated with sulindac had an adenoma of the colon. The control Min/+ mice had 12 intestinal tumours per mouse, and those given sulindac had 0.1 tumour/mouse ($p < 0.001$). Ninety percent of the tumours were located in the ileum and jejunum (Boolbol *et al.*, 1996).

In another study, groups of 32–36 male and female Min/+ mice, 28 days of age, were given

Table 2. Chemopreventive activity of sulindac against tumourigenesis in the colon and small intestine of experimental animals

Site	Strain, species, sex and basal diet	Carcinogen, doses, route of administration	Sulindac dose, route and duration of administration	Tumour incidence (% animals with tumours)		Tumour multiplicity (tumours/animals)		Reference
				Control	Sulindac	Control	Sulindac	
Colon	Mice, Balb/c, female, standard chow	DMH, s.c., 25 mg/kg bw once weekly for 25 weeks	5 mg/kg bw, daily in drinking-water during and after carcinogen treatment	89 $p < 0.05$	42	NR	NR	Moorghen et al. (1988)
Colon	Mice, Balb/c, female, standard chow	DMH, s.c., 25 mg/kg bw, once weekly for 17 weeks	5 mg/kg bw, daily in drinking-water during and after carcinogen treatment	94 $p > 0.05$	100	NR	NR	Moorghen et al. (1988)
Colon	Rats, Sprague-Dawley, male, standard chow	DMH, s.c., 10 mg/kg bw, once weekly for 20 weeks	10 mg/kg bw, daily by gavage for 4 weeks after carcinogen treatment	100 $p > 0.05$	100	39 $p < 0.012$	14	Skinner et al. (1991)
Colon	Rats, F344, male, AIN-76A diet	AOM, 15 mg/kg bw, once weekly for 2 weeks	0.4 mg/g diet, daily two weeks after carcinogen treatment	Reduced to 39% of control		Reduced to 27% of control		Alberts et al. (1995)
Colon	Rats, F344, male, AIN-76A diet	AOM, 15 mg/kg bw, once weekly for 2 weeks	0.16 mg/g diet, daily one week before, during and after carcinogen treatment	81 $p < 0.01$	42	1.5 $p < 0.001$	0.68	Rao et al. (1995)
Colon	Rats, F344, male, AIN-76A diet	AOM, 15 mg/kg bw, once weekly for 2 weeks	0.16 mg/g diet, daily one week before, during and after carcinogen treatment	81 $p < 0.001$	55	1.5 $p < 0.001$	0.44	Rao et al. (1995)
Colon	Rats, F344, male, AIN-76A diet	AOM, 15 mg/kg bw, once weekly for 2 weeks	0.32 mg/g diet, beginning 14 weeks after carcinogen treatment	81 $p < 0.0001$	68	1.5 $p < 0.0001$	0.29	Rao et al.(1995)

Table 2 (contd)

Site	Strain, species, sex, and basal diet	Carcinogen, doses, route of administration	Sulindac dose, route and duration of administration	Tumour incidence (% animals with tumours)		Tumour multiplicity (tumours/animals)		Reference
				Control	Sulindac	Control	Sulindac	
Small intestine	Mice, C57Bl/6J-Min, female, AIN-76A diet	No treatment	0.5 mg/mouse per day in drinking-water daily	100	10 NR	12 $p < 0.001$	0.1	Boolbol et al. (1996)
Small intestine	Mice, C57Bl/6J-Min, male, AIN-76A diet	No treatment	21 mg/l in drinking-water daily	100	100	49 $p < 0.05$	52	Beazer-Barclay et al. (1996)
Small intestine	Mice, C57Bl/6J-Min, male, AIN-76A diet	No treatment	84 mg/l in drinking-water daily	100	100	49 $p < 0.001$	30	Beazer-Barclay et al. (1996)
Small intestine	Mice, C57Bl/6J-Min, male, AIN-76A diet	No treatment	0.17 mg/g diet daily	100	100	33 $p < 0.0001$	12	Beazer-Barclay et al. (1996)
Small intestine	Mice, C57Bl/6J-Min, male, AIN-76A diet	No treatment	0.33 mg/g diet daily	100	100	33 $p < 0.00001$	9.8	Beazer-Barclay et al. (1996)

DMH, 1,2-dimethylhydrazine; s.c., subcutaneous; bw, body weight; NR, not reported; AOM, azoxymethane

sulindac in the drinking-water at 21 or 84 mg/litre [5 and 20 mg/kg bw per day] or in AIN-76A diet at 167 or 334 µg/g [40 and 80 mg/kg bw per day] for about 50 days. Administration of sulindac had no effect on body-weight gains, but the numbers of intestinal tumours were significantly suppressed by treatment with sulindac in drinking-water at 84 mg/litre or in the diet at either dose (Beazer-Barclay et al., 1996).

(b)   Mammary gland

These studies are summarized in Table 3.

Groups of 30 female Sprague-Dawley rats, 50 days old, were given a single intraperitoneal injection of N-methyl-N-nitrosourea at 50 mg/kg bw and fed AIN-76A diet containing 0 or 0.06% [600 ppm] sulindac [purity unspecified] beginning seven days after the carcinogen treatment. Sulindac had no effect on body-weight gain. After 24 weeks of treatment with sulindac, all mammary tumours were examined histopathologically. The tumour incidence was not significantly different in the controls (93%; 28/30) and those treated with sulindac (87%; 26/30) groups; however, the tumour multiplicity and burden were significantly inhibited in animals fed sulindac as compared with those fed the control diet ($p < 0.05$). The mean numbers of mammary tumours ($\pm$ SE) were 4.2 $\pm$ 0.5 in the control group and 2.7 $\pm$ 0.4 in the sulindac-treated group; the tumour burdens in grams $\pm$ SE were 15.8 $\pm$ 2.5 in the control group and 5.7 $\pm$ 1.8 in the sulindac-treated group. Mammary tumour latency was longer in the rats given sulindac than in controls ($p < 0.02$) (Thompson et al., 1995).

Female Sprague-Dawley rats, 50 days of age, were injected with either 12.5 or 37.5 mg/kg bw N-methyl-N-nitrosourea to induce mammary tumours. Seven days later, the metabolite of sulindac, sulindac sulfone, was incorporated into AIN-76A diet at a concentration of 0.03 or 0.06% (w/w) [300 or 600 ppm]. Thirty rats were assigned to each dietary group treated with the high dose of carcinogen and 44 rats to each group treated with the low dose. Sulindac sulfone significantly reduced the incidence and the number of tumours per rat, irrespective of the dose of carcinogen injected. Its preven-

tive activity was comparable to that of sulindac. Tumour latency was prolonged significantly by sulindac sulfone, particularly at the low dose of carcinogen, when it was prolonged by more than eight weeks (Thompson et al., 1997).

(c)   Oesophagus

This study is summarized in Table 3. Groups of 15 male Fischer 344 rats [age unspecified] received three subcutaneous injections of 1 mg/kg bw N-nitrosomethylbenzylamine per week for five weeks. Two weeks before the start of this treatment, 15 rats received sulindac (purity, > 99%) in the diet at a concentration of 125 mg/g [125 ppm]; another group received sulindac one week after completion of carcinogen treatment, up to 25 weeks. There were no differences in mean body weights among the groups. The oesophageal tumours observed in this study were primarily exophytic, pedunculated lesions which proved to be squamous-cell papillomas. Neither the tumour incidence (100, 93 and 93%) nor the tumour multiplicity (2.9, 2.3 and 2.3 tumours/rat) was significantly inhibited when sulindac was administered before and during or after carcinogen treatment, respectively (Siglin et al., 1995). [The Working Group noted that the tumour yield induced by N-nitrosomethylbenzylamine was high and that the dose of sulindac may have been insufficient to inhibit these oesophageal tumours.]

(d)   Urinary bladder

This study is summarized in Table 3. Groups of 75 male B6D2F1 mice, five to six weeks of age, received sulindac in the diet a doses of 200 or 400 mg/g [200 and 400 ppm] one week before the first of eight weekly oral doses of 7.5 mg N-nitroso(4-hydroxybutyl)amine in ethanol:water. The study was terminated 24 weeks after administration of the carcinogen. The survival of animals at termination ranged from 93 to 100% in both groups, and administration of sulindac had a minimal effect on terminal body weights. Sulindac induced a dose-related decrease in the incidence of nitrosamine-induced urinary bladder cancer: control, 20/74 (27%); 200 ppm sulindac, 6/73 (8.2%); and 400 ppm sulindac, 2/75 (2.7%). There was no significant difference

Table 3. Chemopreventive activity of sulindac against carcinogenesis in other organs of experimental animals

Site	Strain, species, sex and basal diet	Carcinogen, doses, route of administration	Sulindac, dose, route and duration of administration	Tumour incidence (% animals with tumours)		Tumour multiplicity (tumours/animal)		Reference
				Control	Sulindac	Control	Sulindac	
Mammary gland	Rats, Sprague-Dawley, female, AIN076A diet	MNU, i.p., 50 mg/kg bw, single dose	600 ppm in diet for 24 weeks	93	87	4.2	2.7 $p < 0.05$	Thompson et al. (1995)
Mammary gland	Rats, Sprague-Dawley, female, AIN 76A diet	MNU, i.p., 12.5 mg/kg bw, single dose	Sulindac sulfone, 300 ppm diet 1 week after carcinogen treatment	100	39 $p < 0.05$	16	9 $p < 0.05$	Thompson et al. (1997)
			600 ppm in diet 1 week after carcinogen treatment	100	55 $p < 0.05$	16	8 $p < 0.05$	Thompson et al. (1997)
Mammary gland	Rats, Sprague-Dawley, female, AIN 76A diet	MNU, i.p., 37.5 mg/kg bw, single dose	300 ppm diet, 1 week after carcinogen treatment	100	100	126	103	Thompson et al. (1997)
			600 ppm in diet, 1 week after carcinogen treatment	100	100	126	68 $p < 0.005$	
Oesophagus	Rats, F344, male, AIN-76A diet	NMBzA, s.c., 1.0 mg/kg bw, 3 doses/week for 5 weeks	125 ppm diet before, during and after carcinogen for 25 weeks	100	93	2.9	2.3	Siglin et al. (1995)
Urinary bladder	Mice, B6D2F$_1$, AIN-76A diet	OH-BBN, oral, 7.5 mg/week for 8 weeks	200 ppm diet for 24 weeks	27	8.2 $p < 0.01$	NR	NR	Rao et al. (1996)
			400 ppm diet for 24 weeks	27	2.7 $p < 0.01$	NR	NR	
Lung	Mice, A/J AIN-76A diet	NNK, 9.1 mg/mouse, in drinking-water for 7 weeks	130 ppm diet for 2 weeks before carcinogen and until termination at 16 weeks	100	92	15.7	7.4 $p < 0.01$	Castonguay et al. (1991); Pepin et al. (1992)
Lung	Mice, A/J, AIN-76A diet	NNK, 9.1 mg/animal in drinking-water for 7 weeks	123 ppm diet −2 → 23 weeks	100	100	8.44	4.12 $p < 0.001$	Jalbert & Castonguay (1992)
			−2 → 7 weeks	100	100	8.44	6.04 $p < 0.05$	
			+7 → 23 weeks	100	100	8.44	7.41 $p > 0.05$	

MNU, N-methyl-N-nitrosourea; i.p., intraperitoneal; bw, body weight; NMBzA, N-nitrosomethylbenzylamine; s.c., subcutaneously; OH-BBN, N-nitrosobutyl(4-hydroxybutyl)amine; NR, not reported; NNK, 4-N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

in the histopathology of the lesions, including the degree of malignancy (Rao et al., 1996).

(e)   Lung

These studies are summarized in Table 3.

Groups of 23–28 female A/J mice, six to seven weeks of age, were fed sulindac (purity, 99%) at 0 or 130 mg/g diet [130 ppm]. Two weeks later, 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) (purity, 98.5%), which is present in tobacco smoke, was administered in the drinking-water for seven weeks (total dose, 9.0–9.2 mg/mouse). All animals were necropsied 16 weeks after the end of carcinogen treatment. Dietary administration of sulindac had no effect on body-weight gain or food consumption. The incidence of lung adenomas in the carcinogen-treated group was 90%, and the multiplicity was 15.7 tumours per mouse. Administration of sulindac reduced the tumour multiplicity to 7.4 tumours per mouse (53% inhibition; $p < 0.001$), without affecting tumour incidence (Castonguay et al., 1991; Pepin et al., 1992).

In a further study, NNK was administered by the same protocol as described above, but three groups of mice were given sulindac (123 ppm) on weeks –2 to +23, –2 to +7 or +7 to +23. Treatment with NNK alone induced 8.4 lung adenomas per mouse; the treatments with sulindac reduced the multiplicity (± SE) of lung adenomas to 4.12 ± 0.44 ($p < 0.001$), 6.04 ± 0.43 ($p < 0.05$) and 7.41 ± 0.82 ($p > 0.05$), respectively. The authors concluded that the efficacy of sulindac given during and after initiation was additive (Jalbert & Castonguay, 1992).

4.2.2 In-vitro models

No data were available to the Working Group.

4.3   Mechanisms of chemoprevention

Sulindac was the first NSAID reported to be useful for the treatment of FAP (Waddell & Loughry, 1983). Administration of sulindac to affected individuals induced polyp regression, which was reversed on cessation of treatment. These findings have been confirmed in several subsequent studies (Belliveau & Graham, 1984;

Waddell et al., 1989; Labayle et al., 1991; Rigau et al., 1991; Giardiello et al., 1993). The efficacy of sulindac may be related to its unique pharmacokinetic properties, which lead to high concentrations of its active metabolite, sulindac sulfide, in the colonic lumen (Hucker et al., 1973; Duggan et al., 1977; Shen & Winter, 1977).

4.3.1 Effects on cell proliferation and apoptosis

Numerous studies of the human colon cancer line HT-29 have shown that sulindac sulfide and sulfone can inhibit cell growth and stimulate apoptosis (Piazza et al., 1995; Shiff et al., 1995; Hanif et al., 1996; Shiff et al., 1996). In these studies, the cultured HT-29 cells were exposed to various concentrations of the sulindac metabolites, and several indices of growth regulation and/or apoptosis were evaluated. Both compounds inhibited cell growth and stimulated apoptosis, but in many of the studies only at concentrations in the range 0.5–1.2 mmol/litre. Therefore, the biological significance of these findings is uncertain.

Sulindac sulfone, when administered at pharmacological doses rather than the doses that result from the metabolism of sulindac, has no effect on cyclooxygenase (COX)[1] activity but inhibits cell proliferation and stimulates apoptosis (Thompson et al., 1995), indicating that these effects are not related to COX activity (Shiff et al., 1995; Hanif et al., 1996; Schnitzler et al., 1996). Another non-prostaglandin-related effect of sulindac sulfide and sulfone is to reduce the levels of cell-cycle regulatory proteins such as cdc2 (Shiff et al., 1996), which may be related to the ability of these metabolites to inhibit cell proliferation.

A study of another colon cancer cell line, LIM 1215, with very sensitive polymerase chain reaction assay techniques, demonstrated that both sulindac sulfide and sulfone at doses of about 10 mmol/litre can induce the expression of APC mRNA (Schnitzler et al., 1996). Since the APC gene has been shown to play a key role in colorectal carcinogenesis in both humans and

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[1] Used as a synonym for prostaglandin endoperoxide synthase (PGH synthase)

animal models, this could have some significance; however, the investigators did not determine whether the increase in *APC* mRNA resulted in an increase in the amount of the functional APC protein. A question raised by this study is that, if the *APC* gene has already been inactivated by a mutation leading to premature chain termination, which occurs in 50% of spontaneous human colorectal adenocarcinomas, what benefit would there be in increasing the mRNA levels of this detective tumour suppressor gene?

Some NSAIDs cause apoptosis when applied to *v-src*-transformed chicken embryo fibroblasts (Lu *et al.*, 1995); however, sulindac had no effect on morphological inhibition of transformation. This study was the first to indicate that cells which overexpress *COX-2* may be somewhat resistant to programmed cell death, and that this can be reversed by addition of an NSAID.

Few nontransformed intestinal epithelial cell lines are available for in-vitro studies. Several groups have evaluated the mechanisms of growth control of a rat intestinal epithelial-1 (RIE-1) cell line in culture (DuBois *et al.*, 1995). Sulindac sulfide can inhibit mitogenesis of these cells (DuBois *et al.*, 1994a). Additionally, the cells express the inducible COX-2 enzyme after treatment with cytokines and growth factors (DuBois *et al.*, 1994b), and the increased expression of *COX-2* in these cells makes them resistant to apoptosis (Tsujii & DuBois, 1995). Treatment of the cells with relatively low doses of sulindac sulfide (5–10 mmol/litre), however, reversed these phenotypic changes, indicating that a potential mechanism for the chemopreventive effect of sulindac may be its ability to inhibit COX-2.

4.3.2 Effects on oncogene expression
See the General Remarks for a discussion of the role of the *ras* oncogene in colon cancer.

Groups of six male Fischer 344 rats were fed a diet containing 320 ppm sulindac and were given azoxymethane dissolved in normal saline subcutaneously at a dose of 15 mg/kg bw per week for two weeks. Vehicle control groups received an equal volume of normal saline. The animals were sacrificed 52 weeks after

treatment and their colonic mucosa and tumours were analysed for mutations in codons 12 and 13 of *K-ras* and for expression of *ras p21*. Azoxymethane-induced G to A transitions were observed at the second nucleotide of codon 12 of *K-ras*, in which the amino acid aspartic acid replaced wild-type glycine. Sulindac not only suppressed the selective amplification of initiated cells with azoxymethane-induced mutated *K-ras* codon 12, but significantly inhibited the azoxymethane-induced expression of total and mutant *ras p21* (Singh & Reddy, 1995). The important finding of this study is that sulindac, which has been reported to induce polyp regression in patients with FAP and to inhibit carcinogen-induced colon carcinogenesis in experimental animals, significantly suppressed *ras* activation at both the DNA and protein level.

5. Other Beneficial Effects

No data were available to the Working Group.

6. Carcinogenicity

6.1 Humans
The Working Group was not aware of any epidemiological studies of the carcinogenicity of sulindac or its metabolites

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
See also the General Remarks and the chapter on sulindac. Relatively few studies refer specifically to the toxicity of sulindac. In many studies of the possible toxicity of NSAIDs, distinction was made only between aspirin and NSAIDs of other types. In common with other non-aspirin NSAIDs, sulindac is used at anti-inflammatory doses and inhibits COX-1 and COX-2; therefore, data on the toxicity of non-aspirin NSAIDs are relevant to the assessment of the toxicity of sulindac.

(a) Gastrointestinal tract toxicity

NSAIDs can damage the oesophagus and can exacerbate gastro-oesophageal reflux disease (Heller *et al.*, 1982; Kikendale, 1991). Gastrointestinal bleeding and ulceration are potentially serious side-effects of all NSAIDs, as discussed in the chapter on aspirin. In the meta-analysis of Henry *et al.* (1996), described in the General Remarks, the risks for serious complications in the upper gastrointestinal tract after use of sulindac were similar to those of most other NSAIDs. In a ranking analysis, sulindac ranked 7 (1 being the most and 12 the least toxic) of 12 NSAIDs analysed. The pooled estimated RRs for NSAID users in comparison with ibuprofen users were between 1.6 and 2.7. Given the baseline risk for 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.*, 1995), the rates of serious ulcer complications among sulindac users can be estimated to be about 2 per 1000 in young adults and 15 per 1000 in people over the age of 65.

NSAIDs other than aspirin have also been associated with other deleterious effects on the small intestine, including inflammation resulting in blood and protein loss (Bjarnasson *et al.*, 1987), stricture (Matsuhashi *et al.*, 1992), perforation and diarrhoea (Kwo & Tremaine, 1995). Large-bowel perforation and haemorrhage are also associated with use of non-aspirin NSAIDs (Langman *et al.*, 1985).

(b) Hepatotoxicity

Acute hepatotoxicity due to NSAIDs other than aspirin is an uncommon complication (Friis & Andreasen, 1992; Tarazi *et al.*, 1993; Rodriguez *et al.*, 1994). The incidence of acute liver injury was 3.7 per 100 000 NSAID users, or 1.1 per 100 000 NSAID prescriptions, among 625 307 persons who were prescribed any of 12 NSAIDs by a defined group of general practitioners in England between 1987 and 1991 (Rodriguez *et al.*, 1994).

(c) Nephrotoxicity

Acute renal toxicity due to NSAIDs can result from allergic interstitial nephritis, concurrent exposure to phenacetin, urate obstruction or

haemodynamic alterations in patients with underlying kidney disease (Murray & Brater, 1993; Murray *et al.*, 1995).

In a study of patients with chronic glomerular disease who were treated with therapeutic doses of sulindac, no effect was found on renal blood flow, glomerular filtration rate or urinary excretion of prostaglandins (Eriksson *et al.*, 1991); however, in a study of healthy volunteers and patients with liver disease (Laffi *et al.*, 1986), sulindac was found to blunt the renal responses to intravenous furosemide (Patrono, 1986).

Many experimental studies have shown that a large proportion of patients with conditions such as congestive heart failure, dehydration and cirrhosis, which result in a dependence on prostaglandins to maintain renal perfusion, suffer a decline in renal function when exposed to specific NSAIDs (Murray & Brater, 1990; Whelton *et al.*, 1990). There is some debate over whether all NSAIDs have a similar deleterious effect and, specifically, whether sulindac is less likely to cause a deterioration in renal function (Whelton & Hamilton, 1991). It is clear, however, that all such drugs, including sulindac, can both decrease renal prostaglandin production and cause a deterioration in renal function under conditions of decreased effective circulating volume (Brater *et al.*, 1985, 1986; Kleinknecht *et al.*, 1986; Stillman & Schlesinger, 1990).

The decline in renal function is usually reversible with discontinuation of the drugs. The frequency of the effect varies with the population studied, but may reach 13% in frail, elderly patients in nursing homes (Gurwitz *et al.*, 1990) and is much less frequent in healthier populations. In the general population, hospitalizations for acute renal failure are rare. Use of non-aspirin NSAIDs increases the risk by about fourfold, from a rate among non-users of about 2 per 100 000 yearly. The increase in risk is dose-dependent and highest during the first month of use (Perez-Gutthann *et al.*, 1996).

The data on NSAIDs and chronic renal failure are sparse. Typical analgesic nephropathy is widely accepted to be caused by phenacetin (Dubach *et al.*, 1991), but there is

also evidence that acetaminophen (Sandler et al., 1989; Pernerger et al., 1994) and NSAIDs (Adams et al., 1986; Pernerger et al., 1994) produce a similar type of kidney damage and/or other types of chronic renal failure.

(d) Blood pressure

Non-aspirin NSAIDs as a group interfere with the efficacy of antihypertensive drugs (Wong et al.,1986; Radack & Deck, 1987; Chrischilles & Wallace, 1993; Johnson et al.,1994), raise blood pressure in hypertensive subjects (Radack & Deck, 1987; Pope et al.,1993) and may result in the initiation of antihypersensitive treatment in older persons (Gurwitz et al.,1994).

In a meta-analysis of 50 randomized, placebo-controlled trials, use of NSAIDs for periods of weeks raised supine mean blood pressure by 5 mm Hg (range 1.2–8.7) (Johnson et al., 1994). All NSAIDs appeared to have this effect, but the most marked increases in blood pressure were observed with piroxicam, indomethacin and ibuprofen; however, the numbers were too small to demonstrate statistically significant differences.

(e) Reproductive and developmental effects

The reported adverse effects of NSAID treatment during pregnancy and labour include: (i) prolongation of pregnancy and labour, (ii) increased maternal blood loss associated with delivery and (iii) anaemia. Use of sulindac during the third trimester of pregnancy is contraindicated because of potential premature closure of the ductus arteriosus, pulmonary hypertension and haemostatic abnormalities causing bleeding. Reductions in fetal urine output and in the volume of amniotic fluid are other possible adverse effects of NSAID therapy (Ostensen, 1994). At least one case report has indicated that ingestion of sulindac during pregnancy can lead to toxic epidermal necrolysis in newborns (Roupe et al., 1986).

7.1.2 Experimental animals

The values for the short-term TD_{50} (a comparative measure of toxicity) for intestinal ulceration and perforation in rats are 27 and 71 mg/kg bw (0.08 and 0.2 mmol/kg bw), respectively (Shen & Winter, 1977). Rats given split daily doses of 0.28 mmol/kg bw per day sulindac intragastrically for four days (17.5 times the maximum human daily dose) developed medium and severe gastrointestinal ulceration with some evidence of perforation (Venuti et al.,1989). In 90-day studies, rats given a dose of 40 mg/kg bw per day had ulcerative enteritis (reviewed by Shen & Winter, 1977). Dogs showed hepatic changes at 20 mg/kg bw per day, without concomitant gastrointestinal ulceration. Microscopic examination revealed portal fibrosis, bile-duct proliferation and inflammatory cell infiltration. Monkeys also showed no gastointestinal ulceration, but they had hepatic effects similar to those seen in dogs.

Sulindac increases intestinal permeability in rats about five times less than indomethacin (Davies et al., 1994), indicating that it may cause less small intestinal ulceration than indomethacin. Although the clinical literature suggests that the sulfone metabolite does not cause gastric ulcer formation, it exacerbated ulcer formation due to stress in rodents (Glavin & Sitar, 1986).

Long-term administration of sulindac at a dose of 40 mg/kg bw per day resulted in one death related to ulcer in 30 animals. No occult blood was detected in faeces at any dose, but at autopsy, on termination of the experiment, ulcerative enteritis was detected in about one-third of the rats at the highest dose. Only minor effects on liver and kidney function have been reported in rats, mice, dogs and monkeys, and only at a maximum dose of 40 mg/kg bw per day (Shen & Winter, 1977).

7.2 Genetic and related effects

No data were available to the Working Group.

8. Summary of data

8.1 Chemistry, occurrence and human exposure

Sulindac, a non-steroidal anti-inflammatory drug introduced in the 1970s, has analgesic, anti-inflammatory and anti-pyretic properties. It has limited use. The usual dose for musculoskeletal and joint disorders is 100–200 mg twice daily.

8.2   Metabolism and kinetics

Therapeutic doses of sulindac are almost totally absorbed by humans after oral administration. The peak plasma concentrations of sulindac and its sulfide metabolite are achieved within a few hours. Sulindac undergoes extensive enterohepatic recyling. The primary route of excretion in humans is via the urine as both sulindac and its sulfone metabolite.

8.3   Cancer-preventive effects
8.3.1   Humans

Randomized trials have shown conclusively that daily doses of 300–400 mg sulindac reduce the number and size of adenomatous colorectal polyps in patients with familial adenomatous polyposis. One observational study suggested that suppression of adenomas can be maintained with a daily intrarectal dose of 60 mg. Tumour inhibition may be incomplete: Three patients in whom polyps were suppressed by treatment with sulindac developed carcinoma of the rectum despite continuing therapy.

One small randomized trial of sulindac with low statistical power showed no regression of small (< 1 cm) adenomatous polyps in patients without familial adenomatous polyposis. Thus, the efficacy of sulindac against sporadic polyps remains to be established.

No adequate data were available to address the effect of sulindac on the risk for colorectal cancer.

8.3.2   Experimental animals

In seven studies in mouse and rat models, sulindac administered with or subsequent to carcinogens inhibited the development of pre-neoplastic and neoplastic lesions in the colon. In mice predisposed to intestinal malignancy by a germ-line mutation in the Apc gene, sulindac reduced the incidence of spontaneous intestinal tumours.

In single studies on the effects of sulindac on urinary bladder and lung carcinogenesis in mouse models, sulindac administered during and after the carcinogen inhibited tumour development. In two studies on mammary carcinogenesis in rats, sulindac and its metabolite sulindac sulfone, given one week after carcinogen treatment, inhibited tumour development.

8.3.3   Mechanism of action

The precise mechanism for the chemopreventive action of sulindac is currently unknown. In human transformed intestinal epithelial cells in culture, doses of sulindac sulfide and sulindac sulfone higher than those that could be achieved pharmacologically inhibited cell growth and stimulated programmed cell death. In cells that overexpress the Cox-2 gene, sulindac can reverse the tumorigenic phenotype by inhibiting Cox-2. Sulindac suppresses ras activation in colon mucosal cells of azoxymethane-treated rats.

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

In common with other NSAIDs, sulindac increases the risk for gastrointestinal toxicity, including complications of ulcer, in a dose-dependent manner and increases the risks for toxic effects on the liver and kidney.

8.6.2   Experimental animals

Sulindac is well tolerated at high doses in rats, mice, dogs and rhesus monkeys. Minor effects occur in liver and kidney. Ulcerative enteritis is seen at very high doses in rats. The toxicity of the major human metabolites in these experimental models has not been reported.

9.   Recommendations for research

Research to define the relative importance of the two metabolites, sulindac sulfide and sulindac sulfone, in the prevention of tumorigenesis in given human organs is of high priority. Better understanding of the chemopreventive action of sulindac in humans would require long-term studies of patients with familial adenomatous polyposis or large epidemiological studies in the general population.

10. Evaluation[1]

10.1 Cancer-preventive activity

10.1.1 Humans

There is *limited evidence* that sulindac has cancer-preventive activity in patients with familial adenomatous polyposis. This evaluation is based on clear demonstration of the inhibition and regression of adenomatous polyps.

There is *inadequate evidence* that sulindac has cancer-preventive activity in people without familial adenomatous polyposis.

10.1.2 Experimental animals

There is *sufficient evidence* that sulindac has cancer-preventive activity in experimental animals. This evaluation is based on models of cancers of the colon, urinary bladder, lung and mammary gland.

10.2 Overall evaluation

Randomized controlled trials in humans provide *limited evidence* that sulindac prevents colorectal cancer by suppressing adenomatous polyps in patients with familial adenomatous polyposis. There is no evidence for the prevention of cancers at other sites. Experimental animal models provide *sufficient evidence* that sulindac prevents cancers of the colon, mammary gland, lung and urinary bladder. These findings indicate the need for further evaluation of the cancer-preventive activity of sulindac against colorectal cancer in persons at high risk for the disease but are not applicable to the general population. The adverse effects of sulindac in humans comprise dose-dependent upper gastrointestinal bleeding and ulceration and hepatic and renal toxicity. If sulindac were to be used as a chemopreventive agent in large populations, the evidence of benefit would have to be clear and the benefits themselves significant.

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

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