GEMFIBROZIL

1. Exposure Data

1.1 Chemical and physical data

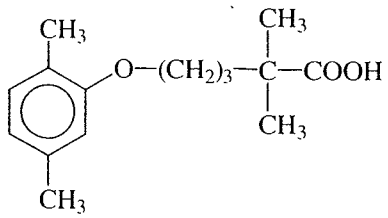
1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 25812-30-0

Chem. Abstr. Name: 5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoic acid

IUPAC Systematic Name: 2,2-Dimethyl-5-(2,5-xylyloxy)valeric acid

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{15}H_{22}O_3$ Relative molecular mass: 250.34

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White crystals (Gennaro, 1995)

(*b*) *Boiling-point*: 158–159 °C (at 0.02 mm Hg [2.7 Pa]) (Budavari, 1995)

(*c*) *Melting-point*: 61–63 °C (Budavari, 1995)

(*d*) *Solubility*: Practically insoluble in water (19 µg/mL); soluble in ethanol (100 mg/mL) (American Hospital Formulary Service, 1995); slightly soluble in dilute alkali (Gennaro, 1995)

(*e*) *Dissociation constant*: $pK_a = 4.7$ (Gennaro, 1995)

1.1.4 *Technical products and impurities*

Gemfibrozil is available as 300-mg capsules, 600- and 900-mg tablets and 900- and 1200-mg microencapsulated granular powders which also may contain calcium stearate, candelilla wax, colloidal silicon dioxide, gelatin, flavouring, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylparaben, microcrystalline cellulose, Opaspray white, polyethylene glycol, polysorbate 80, precipitated silica, pregelatinized starch, propylparaben, sodium carboxymethylstarch, sorbitol, talc or titanium

dioxide (Farmindustria, 1993; British Medical Association/Royal Pharmaceutical Society of Great Britain, 1994; Medical Economics, 1996).

Trade names and designations of the chemical and its pharmaceutical preparations include: Bolutol; CI-719; Decrelip; Elmogan; Fibrocit; GEM; Gemlipid; Genlip; Gevilon; Hipolixan; Ipolipid; Lipozid; Lipur; Lopid; Micolip; Trialmin.

1.1.5 *Analysis*

The United States Pharmacopeia specifies liquid chromatography as the assay for purity of gemfibrozil, and gas chromatography with flame ionization detection for determining impurities and decomposition products. Assays for water content and heavy metals are also specified. The assay for gemfibrozil in capsules and tablets also applies to liquid chromatography using standards (United States Pharmacopeial Convention, 1994).

Gemfibrozil and its metabolites can be analysed in biological fluids by gas chromatography (Randinitis *et al.*, 1984) and high-performance liquid chromatography (Hengy & Kölle, 1985; Randinitis *et al.*, 1986; Nakagawa *et al.*, 1991).

1.2 Production and use

1.2.1 *Production*

Gemfibrozil can be prepared by adding lithium to a solution of diisopropylamine in tetrahydrofuran/styrene, followed by addition of 2-methylpropyl 2,2-dimethylacetate and then 1-bromo-3-chloropropane to produce 2-methylpropyl 2,2-dimethyl-5-chloropentanoate. Reaction of this intermediate with a solution of 2,5-dimethylphenol and sodium hydroxide in toluene/dimethyl sulfoxide yields gemfibrozil (Kearney, 1987).

1.2.2 *Use*

Gemfibrozil was first marketed in the United States of America in 1982 (Wysowski *et al.*, 1990) and in France in 1985 (Vidal, 1994).

Gemfibrozil is used as a hypolipidaemic drug. Like clofibrate (see this volume), gemfibrozil is primarily a triglyceride-lowering agent. It lowers very low-density lipoprotein (VLDL) levels by promoting the lipolysis of VLDL-triglycerides through activation of lipoprotein lipase. Gemfibrozil also inhibits VLDL secretion (Vogt, 1991). It is more active than clofibrate in reducing plasma concentrations of total cholesterol (see IARC, 1983), VLDL-cholesterol and triglycerides (Larsen *et al.*, 1994). Gemfibrozil is recommended in the treatment of type IIa, type IIb, type III, type IV and type V hyperlipoproteinaemia (see Glossary, p. 448) at daily levels of 0.9–1.5 g given as two oral doses 30 min before morning and evening meals (Reynolds, 1993). Gemfibrozil substantially increases plasma concentrations of high-density lipoprotein (HDL)-cholesterol (Goodman Gilman *et al.*, 1990; Miller *et al.*, 1993). In trials in patients with hyperlipoproteinaemia (e.g., the Helsinki Heart Study), gemfibrozil has been shown to reduce coronary heart disease (Grundy, 1988; Manninen *et al.*, 1988).

Gemfibrozil can have a variable effect on low-density lipoprotein (LDL)-cholesterol, with a possible increase in patients with primary hypertriglyceridaemia or mixed hyper-

lipoproteinaemia (Vogt, 1991; Zimetbaum *et al.*, 1991). In persons with hypercholesterolaemia, however, gemfibrozil produces minor decreases in LDL-cholesterol (Smith *et al.*, 1987).

In patients at high risk for coronary heart disease, gemfibrozil reduces triglyceride levels, lowers production and fractional clearance of LDL and normalizes the composition of LDL. The LDL-cholesterol level usually rises but generally not to abnormally high levels (Vega & Grundy, 1985). Gemfibrozil is one of the drugs that is most effective in raising HDL-cholesterol levels (Miller *et al.*, 1993).

Gemfibrozil is also used, in conjunction with dietary modification (Reynolds, 1993), as a second drug, after nicotinic acid, in persons with high triglyceride levels and increased LDL-cholesterol or LDL-cholesterol : HDL-cholesterol ratio (Smith *et al.*, 1987). The addition of gemfibrozil to lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (Wysowski *et al.*, 1990), or nicotinic acid usually produces additional lowering of triglycerides, but the effect on the change in LDL-cholesterol levels is quite variable (East *et al.*, 1988; Expert Panel, 1988). For the treatment of combined hyperlipoproteinaemia, a combination of a resin (colestipol, a bile acid sequestant (Wysowski *et al.*, 1990)) with gemfibrozil can be used (Vogt, 1991).

In the United States, gemfibrozil represented 18.1% of prescriptions for cholesterol-lowering medications in 1983 and 29.4% in 1988 (Wysowski *et al.*, 1990).

1.3 Occurrence

Gemfibrozil is not known to occur as a natural product.

1.4 Regulations and guidelines

Gemfibrozil is listed in the French and United States pharmacopoeias (Reynolds, 1993; Vidal, 1995).

Gemfibrozil was originally approved by the United States Food and Drug Administration for lowering triglyceride levels. In 1989, the United States Food and Drug Administration also approved its use for the adjunctive treatment of type IIb hyperlipidaemia (see Glossary, pp. 447–448) patients with low HDL cholesterol levels who had an inadequate response to weight loss, diet, exercise and other pharmacological agents, such as bile acid sequestrants and nicotinic acid (Wysowski *et al.*, 1990).

2. Studies of Cancer in Humans

A randomized, double-blind trial was conducted in Finland to investigate the effect of gemfibrozil on the incidence of coronary heart disease in asymptomatic men, aged 40–55 years, with dyslipidaemia (non-HDL cholesterol level, ≥ 5.2 mmol/L) (Frick *et al.*, 1987). Of 4081 men, 2051 were randomized to receive 600 mg gemfibrozil twice daily for five years and 2030 to receive a placebo. A cholesterol-lowering diet, as well as an

increase in physical activity and a reduction in smoking and body weight, were recommended to all participants. A total of 2859 subjects (70%) participated in the trial until its completion; however, all 4081 men were followed for five years. Cancer mortality was identical in the two treatment groups (11 deaths among the treated group and 11 deaths in the placebo group). A borderline statistically significant difference was found in the numbers of basal-cell carcinomas of the skin: five in treated men and none in controls ($p = 0.062$, Fisher's exact test). The expected numbers of basal-cell carcinomas, based on the national cancer statistics of Finland, were 4.8 cases in the gemfibrozil group and 4.7 in the placebo group. No difference was found for other cancers (26 cases, 26 controls).

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 72 male and 72 female non-inbred albino CD-1 mice, eight weeks old, were given 0, 30 or 300 mg/kg of diet (ppm) pharmaceutical-grade gemfibrozil (96.1% pure; mixed with polysorbate 80 on silica) in the diet for 78 weeks, after which time all surviving animals were killed. From graphic presentations, approximately 80% of male mice and 70–80% of female mice survived. Body-weight gain was depressed in gemfibrozil-treated animals [details not given]. All tissues and visually apparent lesions were evaluated histologically. Absolute and relative liver weights in high-dose males and females were increased significantly. Slight hypertrophy and increased cytoplasmic eosinophilia of hepatocytes were observed in high-dose males. The incidence of hepatocellular adenomas in male mice was 10/72 control, 13/72 low-dose and 10/72 high-dose animals, that of hepatocellular carcinomas was 6/72 control, 14/72 low-dose ($p < 0.05$, Fisher's exact test) and 10/72 high-dose animals. The incidence of lung adenomas was decreased in males (19/72 control, 16/72 low-dose and 11/72 high-dose; $p < 0.01$, Fisher's exact test). No increase in tumour incidence was observed in female mice (Fitzgerald *et al.*, 1981) [The Working Group noted that the experiment was terminated at 78 weeks and the lack of a dose–response relationship for hepatocellular carcinomas in males.]

3.1.2 *Rat*

Groups of 50 male and 50 female non-inbred albino CD rats, eight weeks old, were given 0, 30 or 300 mg/kg of diet (ppm) pharmaceutical-grade gemfibrozil (96.1% pure; mixed with polysorbate 80 on silica) in the diet for 104 weeks, after which time all surviving animals were killed. Survival of exposed and control animals was comparable. From graphic presentations, it appeared that approximately 50–60% of rats survived. Body-weight gain was depressed in gemfibrozil-treated animals. All tissues and visually apparent lesions were evaluated histologically. Absolute and relative liver weights in high-dose males and females were increased. Hepatocyte hypertrophy with increased

cytoplasmic eosinophilia was observed in treated rats. The incidences of tumours in male rats were: hepatocellular adenomas (neoplastic nodules) — 1/50 control, 2/50 low-dose and 18/50 high-dose ($p < 0.01$; Fisher's exact test); hepatocellular carcinomas — 0/50 control, 4/50 low-dose and 5/50 high-dose; adrenal phaeochromocytomas [malignancy not specified] — 3/50 control, 13/50 low-dose ($p < 0.01$; Fisher's exact test) and 9/50 high-dose; pancreatic acinar adenomas — 0/50 control, 6/50 low-dose and 1/50 high-dose; interstitial-cell tumours of the testis — 1/50 control, 8/50 low-dose ($p < 0.05$; Fisher's exact test) and 17/50 high-dose ($p < 0.01$; Fisher's exact test). In female rats, the incidence of hepatocellular adenomas and carcinomas decreased: 9/50 control, 5/50 (2 carcinomas) low-dose and 3/50 high-dose animals (Fitzgerald *et al.*, 1981). [The Working Group noted the lack of a dose–response relationship for adrenal phaeochromocytomas and pancreatic acinar adenomas.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

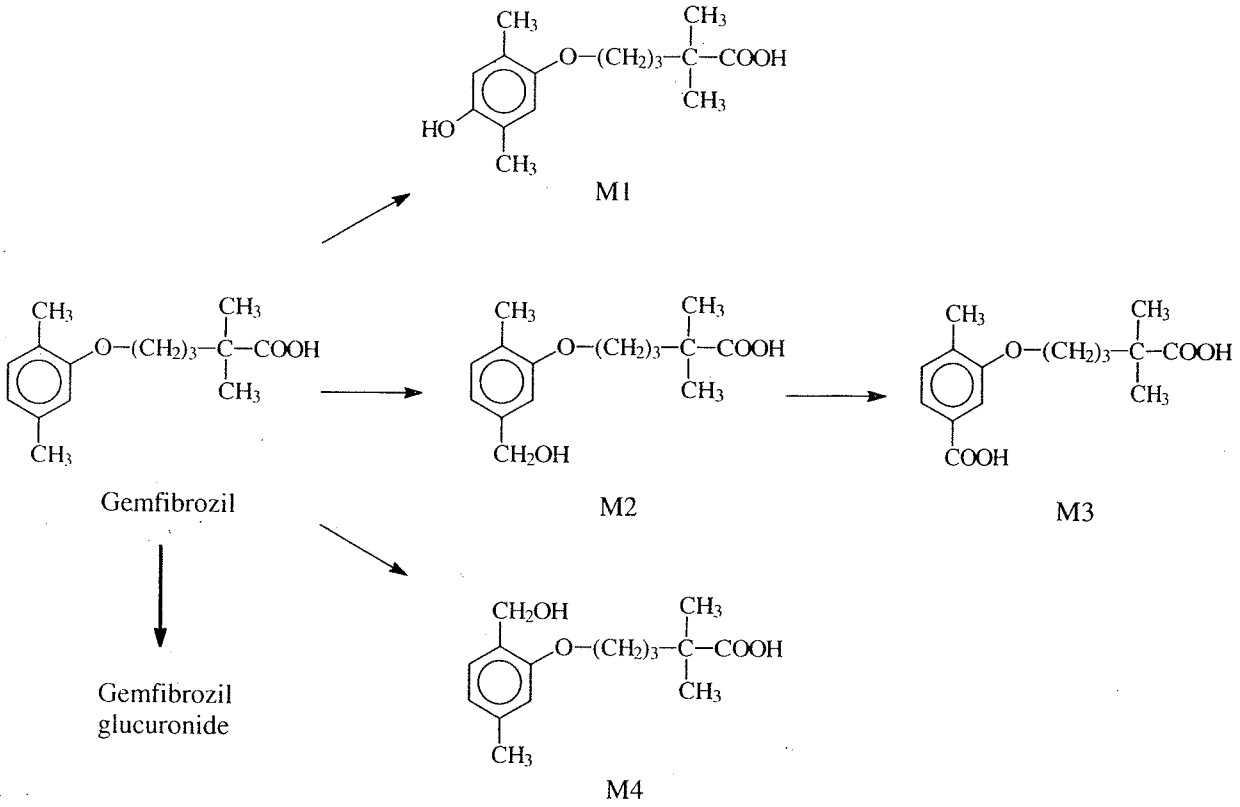
The absorption of gemfibrozil in humans following oral exposure has been examined. In six subjects (three men, three women), single oral administration of 900 mg [13 mg/kg bw est.] gemfibrozil resulted in maximal plasma concentrations of 46 ± 16 μg/mL observed between 1 and 4 h after administration (Knauf *et al.*, 1990). In another study, six healthy adult male subjects were given 600 mg [9 mg/kg bw est.] gemfibrozil twice daily for six days followed by an additional dose on day 7 of 600 mg [9 mg/kg bw est.] tritiated gemfibrozil (Okerholm *et al.*, 1976). A maximal plasma concentration of 36 μg gemfibrozil equivalents/mL was observed 1–2 h following administration.

Hamberger et al. (1986) reported that over a clinically relevant range of concentrations (48–504 μM), gemfibrozil was bound approximately 99% to serum protein. In the study of Okerholm *et al.* (1976), the major route of elimination was urinary, this accounting for 66% of the dose in 5 days. Faecal excretion accounted for an additional 6%.

Gemfibrozil is biotransformed extensively following oral administration (Figure 1). A major pathway of gemfibrozil metabolism is via glucuronidation. Following a single oral administration of 450 mg [6 mg/kg bw est.] gemfibrozil to six male subjects, gemfibrozil glucuronide represented approximately 50% of the total urinary metabolites (32% of the dose) recovered within 24 h (Nakagawa *et al.*, 1991). Very similar results had been obtained in the Okerholm *et al.* (1976) study (see above), in which 31% of the dose was recovered as urinary gemfibrozil glucuronide over 0–48 h. Among metabolites resulting from phase I biotransformation, 5-(5-carboxy-2-methylphenoxy)-2,2-dimethyl pentanoic acid (M3) was the major metabolite recovered. In the study of Nakagawa *et al.* (1991), a 24-h urine collection contained both free and conjugated M3 at approximately 15% and

5% of the total dose, respectively, while, in the study of Okerholm *et al.* (1986), free and conjugated M3 represented approximately 7% and 5% of the recovered radiactivity, respectively. Other minor metabolites identified were the 5-hydroxymethyl derivative (M2, an intermediate in the pathway to M3), a 4-hydroxy derivative (M1) and a 2-hydroxymethyl derivative (M4). In aggregate, urinary and faecal excretion of radioactivity accounted for 66% and 6%, respectively, of the elimination of orally administered gemfibrozil over five days.

Figure 1. Postulated metabolic pathways of gemfibrozil



Based upon Nakagawa *et al.* (1991)

4.1.2 *Experimental systems*

Information on absorption, distribution, metabolism and excretion of gemfibrozil in animals is extremely limited. In male Fischer 344 rats given 6000–20 000 mg/kg diet (ppm) gemfibrozil in the diet for 42 days, maximal mean serum levels of 19.6–21.2 μg/mL were associated with daily exposure in the range of 522–964 mg/kg, indicating that a plateau in circulating levels of gemfibrozil was achieved (Sausen *et al.*, 1995). In male rats [strain not specified] given 50 mg/kg bw tritiated gemfibrozil as a single oral administration, 47% of the dose was eliminated by the faecal route, while 25% of the dose was recovered in the urine over seven days (Okerholm *et al.*, 1976). The lack of an intravenous formulation of gemfibrozil precludes total plasma clearance determinations in laboratory studies (Knauf *et al.*, 1990).

Okerholm *et al.* (1976) also studied gemfibrozil metabolism in two beagle dogs and two rhesus monkeys. In dogs given a single oral 25 mg/kg bw dose of tritiated gemfibrozil, 62% was recovered in the faeces in five days, with an additional 7% appearing in the urine. A bile-fistula experiment with one dog indicated that 75% of the dose was excreted in the bile, only 2% and 12% being found in the faeces and urine, respectively. In the monkeys, 62% of the dose was recovered in the urine in 4 days and only 2% was found in the faeces. A bile-fistula experiment with a rhesus monkey demonstrated 41% of the dose was excreted in bile, 7% in faeces and 36% in urine.

4.2 Toxic effects

4.2.1 *Humans*

Several studies have documented the pharmacological reduction in circulating triglycerides and cholesterol in humans treated with gemfibrozil. Larsen *et al.* (1994) reported the effects of 600 mg [9 mg/kg bw est.] oral gemfibrozil twice daily for eight weeks in patients with hyperlipoproteinaemia type III. Reductions in circulating total cholesterol, VLDL-cholesterol and triglycerides were observed, as was an increase in circulating HDL-cholesterol. In patients with primary familial endogenous hypertriglyceridaemia treated orally with 600 mg [9 mg/kg bw est.] gemfibrozil twice daily for eight weeks, reduction in circulating triglycerides was observed, as was an increase in HDL-cholesterol (Saku *et al.*, 1985). In patients with hyperlipoproteinaemia type IIB treated with 900 mg [13 mg/kg bw est.] gemfibrozil once a day for six weeks gave statistically significant reductions in levels of triglycerides, and cholesterol localized to LDL and VLDL fractions, while HDL-cholesterol content was increased; in patients with hyperlipoproteinaemia type IV, there was a reduction in levels of triglycerides and cholesterol localized to VLDL fractions (but an increase in LDL as well as HDL-cholesterol (Klosiewicz-Latoszek & Szostak, 1991). These pharmacological effects of gemfibrozil in patients with various disorders of lipid metabolism may have several mechanisms of activity, including stimulation of apolipoprotein synthesis (Saku *et al.*, 1985) and stimulation of lipoprotein lipase activities in plasma and adipose tissue (Schwandt, 1991).

Leiss *et al.* (1985) studied the effect of gemfibrozil on biliary lipid metabolism in eight male volunteers treated for three months with gemfibrozil. The dose was 600 mg per day 12 times over 3 months. Despite the absence of any hyperlipidaemic disease in these volunteers, gemfibrozil reduced plasma concentrations of cholesterol and triglycerides and also increased the HDL-cholesterol levels. Significant increases in biliary output of cholesterol and reduction of bile acid output were observed. The authors suggested that administration of gemfibrozil would enhance the risk of gallstone formation in human subjects, although clear evidence for this was not presented.

Male patients receiving 600 mg [9 mg/kg bw est.] gemfibrozil (twice daily for two months) were examined with respect to effects on the coagulation system (Wilkes *et al.*, 1992). Levels of plasma prothrombin fragment F_{1+2}, a marker of the in-vivo rate of thrombin generation, were reduced by gemfibrozil therapy. A significant reduction in factor VII_c was observed in subjects with elevated cholesterol levels in the circulation.

The authors suggested that the beneficial reduction in the incidence of coronary heart disease associated with gemfibrozil therapy might arise in part through a reduction in procoagulant activity.

A variety of case reports have documented unusual side-effects of gemfibrozil therapy. These include exacerbation of psoriasis (Fisher *et al.*, 1988; Frick, 1989), myopathy (Magarian *et al.*, 1991) and impotence (Bain *et al.*, 1990; Pizzaro *et al.*, 1990) (see Section 4.3.1).

The potential for gemfibrozil to induce structural changes in human liver was examined by percutaneous liver biopsy (de la Iglesia *et al.*, 1982). The subjects included six men and three women with hyperlipoproteinaemia (types IIa, IIb or IV) treated with gemfibrozil for 17–27 months. The dose rate was not defined but may be presumed to approximate therapeutic recommendations (1.2 g per day) [17 mg/kg bw est.]. Light microscopic findings were considered to show no abnormality. The peroxisomes were mostly of normal shape with uniform matrix, but a few were of polyhedral shape on account of marginal plate development. Subjective estimation of the peroxisome population indicated no significant increase in number. The authors concluded that, under the conditions of this study, the lack of a drug-related increase in peroxisomes in humans comparable to that described in rats constituted a real species difference. Results of quantitative ultrastructural analysis of peroxisomes in livers of hyperlipoproteinaemic patients receiving gemfibrozil therapy were described separately (de la Igelsia *et al.*, 1981). Numbers of peroxisomes per hepatocyte ranged from 656 to 1452, with a mean of 850, and the size of peroxisomes varied from 0.059 to 0.129 μm^3. In comparison with normal values reported in the literature, these results show no apparent difference in the gemfibrozil-treated patients.

4.2.2 *Experimental systems*

Many of the pharmacological effects of gemfibrozil observed in animals are similar to those reported in humans. Treatment of male CDS rats with gemfibrozil (100 mg/kg bw per day by gastric instillation for four weeks) significantly reduced plasma cholesterol and triglyceride levels, with decreases in cholesterol content in the LDL fraction and increased cholesterol content in the HDL fraction (McGuire *et al.*, 1991). Male Sprague-Dawley rats fed diets containing 20% olive oil and 2% cholesterol were treated for two weeks with 50 mg/kg bw per day gemfibrozil by gastric instillation. Gemfibrozil reduced total cholesterol and triglyceride levels, with reduction of LDL-cholesterol and increased HDL-cholesterol (Krause & Newton, 1986). In these rats, circulating levels of apolipoproteins (Apo) were measured. Apo B was decreased, while Apo A-I and Apo E were increased. Male Dahl S rats treated for 12 days with 30 mg/kg bw per day gemfibrozil by gastric instillation also had reduced plasma triglyceride concentrations (Donnelly *et al.*, 1994). In female Swiss OF1 strain mice, treatment with 300 mg/kg bw per day gemfibrozil by gastric instillation for two weeks reduced plasma concentrations of triglycerides but increased HDL-cholesterol (Olivier *et al.*, 1988).

Hepatic peroxisome proliferation, potentially relevant to the mechanism of carcinogenic activity of a variety of agents, has been observed in gemfibrozil-treated animals.

Gray and de la Iglesia (1984) described ultrastructural changes in the livers of male and female CD rats receiving gemfibrozil (300 mg/kg per day) in the diet for one year. Increases in the number of peroxisomes per cell (7-fold) and peroxisomal volume (males only) and in total peroxisomal volume fraction per cell (20-fold) were observed by quantitative analysis. In male CDS albino rats given 100 mg/kg bw per day gemfibrozil by gastric instillation for four weeks, increases in the number of peroxisomes per hepatocyte and number of peroxisomes per gram of tissue were observed. This effect was associated with an increase in the relative liver weights following administration of gemfibrozil (McGuire *et al.*, 1991). Gorgas and Krisans (1989) evaluated the zonal heterogeneity of peroxisomal changes in livers of male Sprague-Dawley rats given 2000 mg/kg diet (ppm) gemfibrozil [120 mg/kg bw est.] in the diet for two weeks. The greatest increases in numbers of peroxisomes were observed in centrilobular hepatocytes. Several studies have documented increases in peroxisomal enzyme activities. In male Fischer 344 rats given gemfibrozil in the diet for 21 days, 20 ppm [150 μg/kg bw est.] was the no-effect level and 50 ppm [375 μg/kg bw est.] was the lowest-effect level. Maximal induction of peroxisomal acyl coenzyme A (CoA) oxidase activity (16–18 fold) was observed in male Fischer 344 rats given 9000–20 000 ppm (522–1179 mg/kg bw per day) gemfibrozil for 42 days. These exposures were associated with a plateau in serum gemfibrozil levels (see Section 4.1.2) (Sausen *et al.*, 1995). In male Fischer 344 rats given 2000 ppm gemfibrozil in the diet for four weeks, activity of two peroxisomal enzyme, palmitoyl-CoA oxidase and enoyl-CoA hydratase, was increased in liver homogenates (Lalwani *et al.*, 1983). Male Wistar rats given 2000 ppm gemfibrozil in the diet for two weeks had increased peroxisomal activities for fatty acyl-CoA β-oxidation and catalase in liver homogenates (Hashimoto *et al.*, 1995). Similar studies in laboratory mice have not been reported. Furthermore, the potential for gemfibrozil to modulate hepatocellular replication in laboratory animals has not been evaluated. While peroxisome proliferation has been hypothesized to contribute to the mechanism of action of gemfibrozil and other agents, no data are available on the induction of oxidative damage to cytoplasmic or nuclear constituents.

Kähönen and Ylikahri (1979) analysed hepatic responses in male Wistar rats rendered hypertriglyceridaemic by adding 10% fructose to the drinking-water. Gemfibrozil was injected subcutaneously at doses of 15–100 mg/kg bw per day for 14 days. Increases in relative liver weights were observed at doses of 15 mg/kg per day or more. Mild but statistically significant increases in mitochondrial activities of carnitine acyltransferases were detected at doses of 15 mg/kg per day or more.

In primary cultures of rat hepatocytes, incubation with 100–500 μM gemfibrozil for up to 72 h resulted in induction of peroxisomal β-oxidation (Foxworthy & Eacho, 1986). This response is probably mediated by the peroxisome proliferator-activated receptor α (PPARα), a member of the nuclear steroid hormone receptor superfamily. In the presence of gemfibrozil, PPARα and retinoid X receptor-α form a heterodimer which binds to response elements located in the promoter regions of several peroxisomal genes, such as that of the rat acyl CoA oxidase gene, and facilitates transcriptional activity (Issemann *et al.*, 1993). The critical role of PPARα in mediating responses to peroxi-

some proliferating agents has been demonstrated with knockout mice that do not express the receptor (Lee *et al.*, 1995).

No attempt to induce peroxisome proliferation in human cells *in vitro*, such as primary cultures of human hepatocytes or human hepatoma cell lines, has been reported.

The central role of PPARα in mediating the hepatic effects of fibrate drugs in rodents indicates that characterization of human PPARα could be important for the extrapolation of effects in rodents to humans. Tugwood *et al.* (1996) found generally low (but variable) expression of PPARα mRNA in 10 human liver samples compared with rodent liver samples. They characterized the function of human PPARα cDNA clones isolated from two livers. One had a deleted segment leading to a C-terminal truncation of the receptor; the other had non-conservative codon substitutions at amino acid positions 71 and 123. Both clones failed to activate transcription under conditions in which the mouse wild-type PPARα clone is active, indicating a non-functional human receptor. Thus, the insensitivity of human liver to the adaptive effects of peroxisome proliferators may be attributable to low expression of PPARα and/or genetic variations in the PPARα gene that result in lack of response to peroxisome proliferators.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

A number of cases of reversible impotence in men being treated with gemfibrozil have been reported (Bain *et al.*, 1990; Pizarro *et al.*, 1990; Bharani, 1992; Figueras *et al.*, 1993).

4.3.2 *Experimental systems*

Groups of pregnant CD rats were given 0, 81 or 281 mg/kg bw gemfibrozil in the diet on gestation days 6–15 (Fitzgerald *et al.*, 1987). Although food intake and body-weight gain were markedly reduced in the high-dose group, no adverse affect on postimplantation loss, litter size or fetal weight was observed. The incidence of fetal malformations and variations was similar between the three groups. Dutch belted rabbits were treated by gastric instillation with 60 or 200 mg/kg bw gemfibrozil or with the vehicle on gestation days 6–18. No significant effect on weight gain, litter size, postimplantation loss, fetal sex ratio, fetal weight or incidence of fetal anomalies occurred. In fertility studies, groups of sexually mature male CD rats were given 93 or 326 mg/kg bw gemfibrozil for 61 days and females were given 94 or 318 mg/kg bw gemfibrozil for 15 days before mating within the treatment groups. Administration of the drug to females continued throughout gestation and weaning of the F_1 offspring. In subsequent fertility experiments, treated male rats were mated with untreated females, while treated females were placed with untreated males. The only apparent drug-related effect was reduced pup weights during the neonatal and weaning periods in the female fertility study. When similar doses of gemfibrozil were given to female rats from gestation day 15 through to weaning, the only apparent drug-related effect was reduced pup weight during the neonatal weaning period.

4.4 Genetic and related effects (see also Table 1 for references and Appendices 1 and 2)

Gemfibrozil was not mutagenic towards five strains of *Salmonella typhimurium* in the presence of rat liver S9 fraction.

Five metabolites were also tested under the same conditions as gemfibrozil, except that the highest dose was 300 µg/plate (approx. 150 µg/mL of soft agar). No mutagenicity was observed with the metabolites that were structures (MI-MIV) (Figure 1) and 2-(2-carboxy-5-hydroxymethylphenoxy)-2,2-dimethyl pentanoic acid (Fitzgerald *et al.*, 1981).

Table 1. Genetic and related effects of gemfibrozil

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1250	Fitzgerald *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1250	Fitzgerald *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1250	Fitzgerald *et al.* (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1250	Fitzgerald *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1250	Fitzgerald *et al.* (1981)

[a] +, positive; (+), weak positive; –, negative; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day

4.5 Mechanistic considerations

The role of data on peroxisome proliferation in evaluating carcinogenicity in humans has been discussed. When data support the conclusion that a tumour response in mice or rats is secondary only to peroxisome proliferation, this should be considered in addressing the potential carcinogenicity of an agent in humans. The report of the Working Group on Peroxisome Proliferation and its Role in Carcinogenesis (IARC, 1995) indicates that the following issues should be considered:

"(*a*) Information is available to exclude mechanisms of carcinogenesis other than those related to peroxisome proliferation.

(*b*) Peroxisome proliferation (increases in peroxisome volume density or fatty acid β-oxidation activity) and hepatocellular proliferation have been demonstrated under the conditions of the bioassay.

(*c*) Such effects have not been found in adequately designed and conducted investigations of human groups and systems."

The weight of evidence, including structural similarities to other fibrates, indicates that gemfibrozil, and peroxisome proliferators in general, do not act as direct DNA-damaging agents and that their mechanism of tumour initiation is indirect. Two responses have been proposed to account for liver carcinogenesis by peroxisome proliferators in rodents. These include (i) induction of peroxisome proliferation and (ii) increased hepatocellular proliferation. These responses are not mutually exclusive with respect to tumour formation.

Chronic administration of peroxisome proliferators produces a sustained oxidative stress in rodent hepatocytes due to overproduction of hydrogen peroxide. This can theoretically generate reactive oxygen species which can attack DNA or may affect cells in other ways. There is also evidence from in vitro experiments that fatty acid metabolism in peroxisomal fractions can result in hydroxyl radical formation and DNA damage. In-vivo observations in support of this hypothesis include increased lipid peroxidation, increased lipofuscin deposition, the effects on levels of hepatic antioxidants and inhibition of tumour formation by antioxidants (Lake, 1995). However, some of the evidence suggests that the level of oxidative damage *in vivo* may be too low to account entirely for the carcinogenicity of peroxisome proliferators.

During the first few days of administration, peroxisome proliferators induce cell division in rodent hepatocytes; in some, but not all, studies, sustained stimulation of replicative DNA synthesis has also been observed (Lake, 1995). An enhanced rate of cell proliferation can be a critical effect in both tumour initiation, by increasing the frequency of spontaneous mutations and the rate of conversion of DNA adducts into mutations before they are repaired, and in tumour promotion by facilitating clonal expansion of initiated cells.

There are clear species differences in the responses of mammalian cells to peroxisome proliferators (Lake, 1995). Biopsy studies have clearly indicated that the responsiveness of human livers to the peroxisome proliferation produced by fibrate drugs is lacking or is much lower than that seen in the livers of treated rodents, although similar levels of drug are achieved in the circulation. The striking hepatomegalic effect of peroxisome proliferation is similarly not observed in patients receiving fibrate drugs. In cultures of hepatocytes, peroxisome proliferation and cell proliferation occur with rodent but not human hepatocytes. In rodent liver, hepatomegaly and peroxisome proliferation require expression of functional PPARα, a member of the steroid hormone receptor superfamily. Gemfibrozil activates rodent PPARα *in vitro*. The insensitivity of human liver to the effects of peroxisome proliferators is consistent with the low level of PPARα in human livers, as well as observations of genetic variations that render the human PPARα receptor inactive compared with PPARα expressed in rodent liver (Tugwood *et al.*,

1996). In non-human primates, administration of peroxisome proliferators has also failed to elicit the hepatomegaly and peroxisome proliferation induced in rodent liver.

Gemfibrozil-induced peroxisome proliferation has been demonstrated under bioassay conditions. An indirect measure of cell proliferation, liver weight, is also increased under bioassay conditions. Peroxisomal proliferation has not been found in studies of human groups and systems using gemfibrozil. Taken together, these findings indicate that the increased incidence of liver tumours in rodents treated with gemfibrozil results from a mechanism that would not be operative in humans.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Gemfibrozil has been used since the early 1980s to lower serum triglycerides and raise high-density lipoprotein-cholesterol in patients at high risk for coronary heart disease.

5.2 Human carcinogenicity data

In a Finnish trial that aimed to reduce cholesterol concentration with gemfibrozil, no difference was found in cancer incidence or mortality between the treated and control groups.

5.3 Animal carcinogenicity data

Gemfibrozil was tested for carcinogenicity by oral administration in the diet in one experiment in mice and one experiment in rats. There was a slight, not dose-related increase in the incidence of hepatocellular carcinomas in male mice and the incidence of lung adenomas was decreased. In male rats, increases were observed in the incidence of hepatocellular tumours, interstitial-cell tumours of the testis and adrenal phaeochromocytomas; the latter was not dose-related.

5.4 Other relevant data

Gemfibrozil exerts similar pharmacological responses in humans and laboratory rodents. It is readily absorbed, metabolized and eliminated in human subjects. Data are not available to characterize adequately its pharmacokinetic behaviour in animals, although maximal serum levels of gemfibrozil in rats are similar to those in humans receiving therapeutic doses of gemfibrozil.

Gemfibrozil-induced peroxisome proliferation has been demonstrated in rats. An indirect measure of cell proliferation, liver weight, is also increased in rats. Peroxisome proliferation has not been observed in studies of human livers with gemfibrozil.

There are a number of case reports of reversible impotence in men treated with gemfibrozil. No noteworthy effects on the fetus have been observed in studies in rats or rabbits.

Neither gemfibrozil nor its metabolites were mutagenic in bacteria in a single study.

Mechanistic considerations

The data on gemfibrozil are too limited to allow mechanistic assessment. In particular, genotoxicity has not been excluded. Upon exposure to gemfibrozil, proliferation of peroxisomes occurs in rat liver, whereas proliferation of peroxisomes does not occur in human liver. These observations suggest that the mechanism of liver carcinogenesis in gemfibrozil-treated rats would not be operative in humans.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of gemfibrozil.

There is *limited evidence* in experimental animals for the carcinogenicity of gemfibrozil.

Overall evaluation

Gemfibrozil is *not classifiable as to its carcinogenicity in humans (Group 3).*

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[1]For definition of the italicized terms, see Preamble, pp. 22–25.

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