

Handbook 6

Acitretin

1. Chemical and Physical Characteristics

1.1 Nomenclature

Acitretin is the free acid form of etretinate and belongs to the class of aromatic synthetic retinoids in which the lipophilic trimethylcyclohexenyl group of retinoic acid has been replaced by an aromatic ring (Figure 1). In the case of acitretin, the cyclohexenyl group has been replaced by a 4-methoxy-2,3,6-trimethylphenyl group, while the all-*trans*-tetraene structure of the retinoic acid side-chain has been retained. Acitretin, like retinoic acid, is a carboxylic acid and hence has direct biological activity and, unlike etretinate, does not require metabolic conversion for activity.

In this nomenclature, the side-chain of acitretin is numbered starting from the carboxylic acid

(Figure 1). Since acitretin is a synthetic derivative of retinoic acid, however, the retinoid numbering system is often used for acitretin and its derivatives. The common numbering system for retinoic acid and its application to the basic skeleton of acitretin are shown in Figure 2. Derivatives of acitretin are often given this common numbering system. For example, (2*Z*,4*E*, 6*E*,8*E*)-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4,6,8-tetraenoic acid, a geometric isomer of acitretin, is commonly referred to as 13-*cis*-acitretin (Figure 2), and the methyl groups attached to the tetraene side-chain are often referred to as the C-9 and C-13 methyls, in keeping with the retinoid nomenclature.

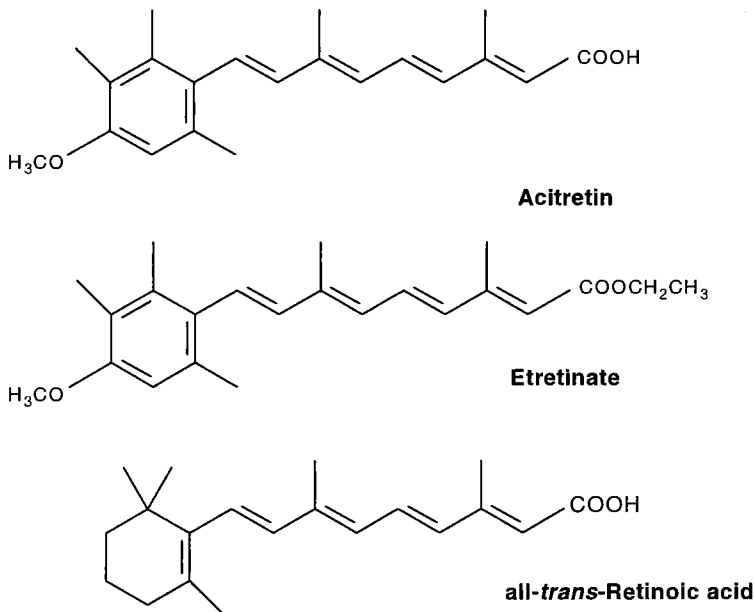


Figure 1. Structures of acitretin, etretinate and all-*trans*-retinoic acid

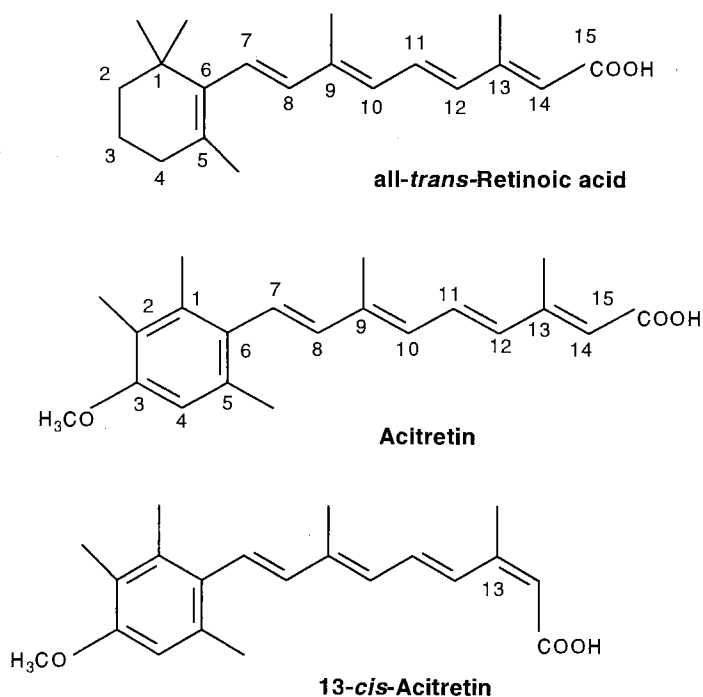


Figure 2. Common numbering scheme for retinoids

1.2 Name

Chemical Abstract Services Registry Number
160024-33-9

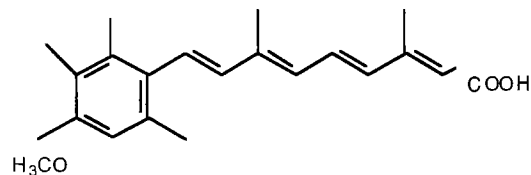
IUPAC Systematic name

all-trans-3,7-Dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4,6,8-tetraenoic acid

Synonyms

Acitretin, Etretin, Soriaten®, RO 10-9359

1.3 Structural formula



Composition: $\text{C}_{21}\text{H}_{26}\text{O}_3$

Relative molecular mass: 326

1.4 Physical and chemical properties

Melting-point

228–230 °C (Budavari *et al.*, 1989)

Spectroscopy

UV and visible spectrum: λ_{max} = 352 nm in methanol (Makin *et al.*, 1989)

$^1\text{H-NMR}$ (CDCl_3 , 270 MHz): δ 2.10 (3H, s), 2.28, 2.24 and 2.14 (9H, 3s), 2.37 (3H, s), 3.80 (3H, s), 5.80 (1H, s), 6.20 (1H, d, J = 11.4 Hz), 6.24 (1H, d, J = 16.3 Hz), 6.40 (1H, d, J = 15.04 Hz), 6.60 (1H, s), 6.70 (1H, d, J = 16.3 Hz), 7.09 (1H, dd, J = 15.02, 11.4 Hz) (Aurell *et al.*, 1995).

$^{13}\text{C-NMR}$ (CDCl_3): δ 11.80, 12.85, 13.85, 17.35, 21.36, 55.40, 110.25, 119.10, 122.85, 128.65, 130.00, 130.40, 130.55, 133.55, 133.85, 135.80, 135.85, 138.20, 138.95, 152.30, 156.25, 166.85 (Aurell *et al.*, 1995)

Infrared spectrum

ν_{\max} 3600–3300 (O-H), 1700 (C=O), 1600 (C=C)
 cm^{-1} (Aurell *et al.*, 1995)

Geometrical isomers

Sixteen possible isomers

Photochemical properties

Acitretin is a yellow to greenish-yellow powder with an absorption maximum (λ_{\max}) at 352 nm (methanol) in the UV-visible spectrum (Makin *et al.*, 1989). Because of its conjugated tetraene structure, acitretin can readily undergo photoisomerization reactions when exposed to light, particularly in solution.

Solubility

Soluble in most organic solvents, fats and oils; low solubility in water probably similar to that of all-*trans*-retinoic acid, i.e. 0.21 $\mu\text{mol/L}$ (Szuts & Harosi, 1991)

Relationships between chemical structure and biological activity

The pharmacological activity of acitretin is likely to be due primarily to activation of the retinoic acid receptors (RARs). The physiological ligand for the RARs is all-*trans*-retinoic acid (Giguère *et al.*, 1987; Petkovich *et al.*, 1987), and extensive studies

of structure-activity relationships with retinoid analogues have established that a terminal carboxylic acid group and a lipophilic head group are required for interaction with the RARs (Gale, 1993). The lipophilic head group required for RAR activity is provided by the 4-methoxy-2,3,6-trimethylphenyl group of acitretin. The planar all-*trans* configuration and the terminal carboxylic acid group of the acitretin side-chain appear to be optimal for RAR activity, but 9-*cis*-retinoic acid, the putative physiological ligand for the retinoid X receptors, also activates RARs (Heyman *et al.*, 1992), and it is possible that the 9-*cis* isomer of acitretin can also activate RARs.

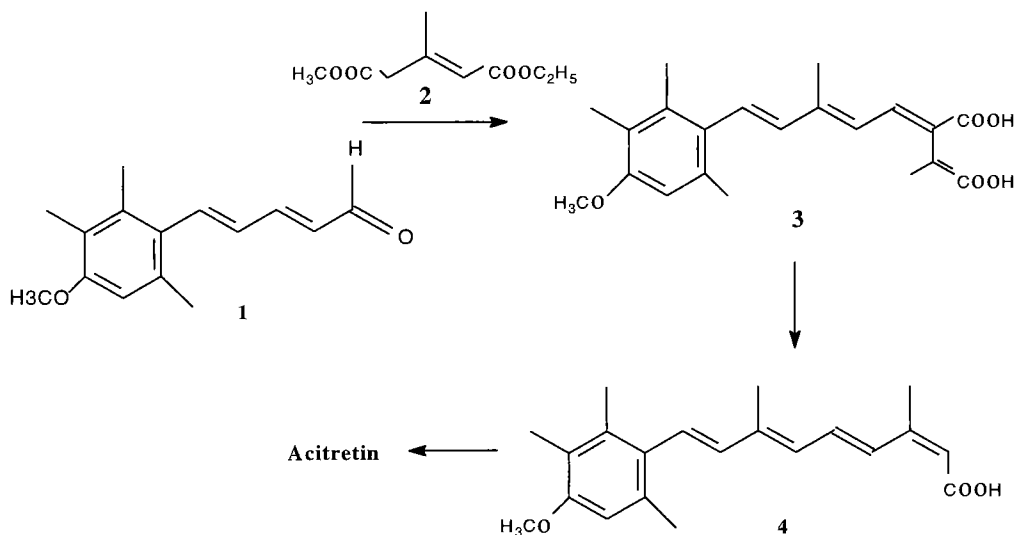
2. Occurrence, Production, Use, Human Exposure and Analysis

2.1 Occurrence

Acitretin is not a naturally occurring compound but can readily be synthesized by a variety of routes.

2.2 Production

In the synthesis of acitretin, outlined in Scheme 1, the aryl-substituted pentadienal, **1**, is used as the starting material (Makin *et al.*, 1989). Reaction of **1** with the diester **2** in the presence of ethanolic sodium hydroxide gave the dicarboxylic acid, **3**.



Scheme 1

Decarboxylation of **3** gave primarily the 13-*cis* isomer of acitretin, compound **4**. Isomerization of a benzene and ether solution of **4** in the presence of catalytic amounts of iodine followed by recrystallization afforded acitretin.

An alternative synthesis of acitretin is described in section 2.2 of Handbook 5 (scheme 3). Several other syntheses described for etretinate can be used for acitretin, since etretinate is readily hydrolysed to acitretin. Two of these syntheses are described in section 2.2 of Handbook 5 (schemes 1 and 2). Syntheses of etretinate, derivatives of etretinate and geometric isomers of these compounds have also been described by Bestmann and Ermann (1984). The large-scale synthesis of acitretin and various derivatives, including etretinate, has been described by Bollag *et al.* (1978).

2.3 Use

Acitretin has been approved by the appropriate regulatory authorities in many countries for the oral treatment of severe psoriasis, including erythrodermic and generalized pustular psoriasis (Goldfarb & Ellis, 1998; Paul & Dubertret, 1998). Several double-blind comparative clinical trials with acitretin and etretinate showed that the efficacy of the two drugs in psoriasis is essentially identical. Thus, acitretin is being used in the treatment of a variety of other skin diseases, cancers and premalignant conditions which respond to etretinate, including mycosis fungoides, basal-cell carcinoma, actinic keratoses, keratoacanthoma and epidermodysplasia verruciformis (Paul & Dubertret, 1998) and has largely replaced etretinate on the market. It is recommended that acitretin be administered with a meal.

2.4 Human exposure

Acitretin is marketed in 10-mg and 25-mg gelatin capsules for oral administration. The manufacturer recommends individualization of dosage in order to achieve an optimal therapeutic index. In general, it is recommended that acitretin therapy be initiated at an initial dose of 25 or 50 mg/day given as a single dose with the main meal. After an initial response to therapy, maintenance doses of 25–50 mg/day may be used. Goldfarb and Ellis (1998) recommended slightly lower doses of acitretin than of etretinate and that two-thirds of the dose of etretinate be used when switching from

etretinate to acitretin. A starting dose of 0.5 mg/kg bw per day is recommended for plaque psoriasis. Slightly higher initial doses are recommended for pustular psoriasis and slightly lower doses for erythrodermic psoriasis. Acitretin is contraindicated in women of childbearing potential, and negative results in a pregnancy test in serum prior to initiation of therapy and strict contraception during treatment and for at least two years after drug withdrawal are required (Bouvy *et al.*, 1992; Stricker *et al.*, 1992; for more details, see section 7.2.1).

2.5 Analysis

Numerous methods based on high-performance liquid chromatography (HPLC) have been described for the quantitative analysis in plasma of acitretin, etretinate and their geometric isomers. The limit of detection of a reversed-phase HPLC method for analysis of etretinate and acitretin in plasma was 10 ng/ml (Palmskog, 1980), while that of a normal-phase HPLC method for the same two compounds was 4 ng/ml (Paravicini & Busslinger, 1983). An alternative reversed-phase HPLC method for the simultaneous determination of etretinate and acitretin in rat blood required much smaller sample volumes and allowed for serial sampling (Thongnopnua & Zimmerman, 1988). Another normal-phase HPLC method which allowed for the determination of etretinate, acitretin and the 13-*cis* isomer of acitretin, with a detection limit of 3 ng/ml, was used to study the long-term pharmacokinetics of etretinate in patients with psoriasis who had been changed from etretinate to acitretin therapy (De Leenheer *et al.*, 1990). A reversed-phase HPLC method with shorter retention times was also used to detect these three compounds in human plasma (Jakobsen *et al.*, 1987). A programmed-gradient HPLC system for the analysis of etretinate, its metabolites and other retinoids in plasma allowed shortened analysis and better peak shapes (Annesley *et al.*, 1984). Problems of recovery arising from strong binding of retinoids to plasma proteins were addressed by column-switching techniques (Wyss & Bucheli, 1988; Wyss, 1990).

HPLC methods were used to isolate metabolites from the faeces and urine of persons treated with tritium-labelled acitretin. The structures of the metabolites were elucidated by mass spectrometry

and $^1\text{H-NMR}$ spectroscopy (Hänni *et al.*, 1977). Bile samples collected from patients treated with ^{14}C -labelled etretinate were analysed by HPLC after β -glucuronidase treatment, and the structures of the metabolites were determined by mass spectrometry and $^1\text{H-NMR}$ spectroscopy (Vane *et al.*, 1989a). Similarly, HPLC methods were used to isolate metabolites from the blood of persons with psoriasis treated with etretinate, and spectroscopic techniques were used to elucidate their structures (Vane *et al.*, 1989b). Another reversed-phase HPLC method has been developed for the simultaneous assay of etretinate, acitretin and their metabolites in whole perfusate, perfusate plasma, bile and hepatic tissue obtained in a perfused rat liver model, and was used to study the first-pass hepatic metabolism of etretinate and acitretin (Decker & Zimmerman, 1995). A reliable method has been reported involving normal-phase HPLC and ultraviolet detection which allows improved quantification of acitretin and 13-*cis*-acitretin in human plasma (Meyer *et al.*, 1991). A rapid HPLC method for the simultaneous, specific analysis of acitretin and its 13-*cis* isomer in blood, plasma and urine has been used to measure the concentrations of the compounds in patients receiving acitretin therapy (Al-Mallah *et al.*, 1987). A very sensitive method involving microbore liquid chromatography–negative chemical ionization mass spectrometry has been used to measure acitretin and its 13-*cis* metabolite in human plasma at a detection limit of 1 ng/ml (Fayer *et al.*, 1991). A highly sensitive HPLC method has been used to quantify acitretin and 13-*cis*-acitretin in the plasma and skin of patients being treated for psoriasis with acitretin (Laugier *et al.*, 1989).

3. Metabolism, Kinetics and Genetic Variation

Acitretin was developed clinically because the extreme lipophilicity of etretinate led to its storage in adipose tissue and hence to an extended half-life of elimination (Paravicini *et al.*, 1981). Acitretin, because of its free carboxyl group, is much less lipophilic than etretinate and as a consequence has a much shorter half-life: 50 h compared with approximately four months for etretinate (Brindley, 1989; Goldfarb & Ellis, 1998). In the circulation, more than 99.9% of acitretin is bound to plasma proteins, primarily albumin.

3.1 Humans

About 60% of an oral dose of acitretin is bioavailable, with a wide range of 36–95%. The pharmacokinetics of acitretin has been studied extensively, and the results have been summarized (Pilkington & Brogden, 1992; Larsen, 1994). Typically, the maximum plasma concentrations detected in healthy volunteers about 2–3.3 h after ingestion of a single oral dose of 50 mg of acitretin were 200–400 ng/ml, and the mean terminal elimination half-life was 2.5–6.7 h. In these studies, the maximum concentration of the metabolite 13-*cis*-acitretin was reached 4–22 h after administration, and its mean terminal elimination half-life was 50–60 h.

Most studies of the pharmacokinetics of multiple oral doses of acitretin have involved patients with psoriasis receiving 30–50 mg/day for up to six months (Larsen, 1994). [The Working Group noted that the half-life depends markedly on the dosing schedule, the tissue considered and when the measurements are made after dosing.] Under the conditions used by Larsen (1994), the maximum plasma concentrations of the drug were 230–400 ng/ml and were recorded 1–4 h after administration. In 11 patients with psoriasis, the time to the mean peak concentration was 3.5 h after 50 mg/day for two months (Larsen *et al.*, 1991; Koo *et al.*, 1997). The elimination half-life was 2 h after single oral doses and about 50 h after multiple dosing (Gollnick *et al.*, 1990). Within one month of treatment with an oral dose of acitretin at 30 mg/day, the steady-state concentration of acitretin in the epidermis of 12 patients with psoriasis was 17 ng/g, with a significant correlation to plasma levels. Acitretin is fairly well absorbed from the gastrointestinal tract, the average concentrations in the dermis being 177 ng/g after one month of treatment and 227 ng/g after six months. The concentration in adipose tissue (98 ng/g) exceeded that in skin (28 ng/g) within 5 h of consumption of a dose of 25 mg (Koo *et al.*, 1997).

The concentrations of acitretin in blood and epidermis after a therapeutic dose are generally one-fourth those of etretinate. Since acitretin contains a comparatively polar carboxylic acid (pK_a 3.7), it is less likely to be sequestered in adipose tissue (Larsen *et al.*, 1992). It is eliminated by excretion of its metabolites in the liver and

kidney. After a single 50-mg oral dose of ^{14}C -acitretin, 21% of the radiolabel in six healthy volunteers was found in urine and 63% in faeces. The immediate major metabolite of acitretin is its 13-*cis* isomer, isoacitretin (Koo *et al.*, 1997). After administration of acitretin to animals or humans, both acitretin and its 13-*cis* isomer are observed in plasma. Glutathione catalyses the interconversion of acitretin and its 13-*cis* isomer (Jewell & McNamara, 1990). all-*trans*-Acitretin and 13-*cis*-acitretin are demethylated and are subsequently eliminated in the bile as the acyl- β -glucuronide derivatives or through the kidney as soluble metabolites with shorter side-chains (Koo *et al.*, 1997). Acitretin and 13-*cis*-acitretin are transferred into breast milk, acitretin being distributed almost exclusively in the lipid fractions of the milk. The estimated amount of the drug consumed by suckling infants corresponded to about 1.5% of a single maternal dose of 40 mg (Rollman & Pihl-Lundin, 1990).

When 12 patients with psoriasis ceased taking acitretin, the terminal elimination half-life of the drug was 16–110 h, whereas that of the 13-*cis* metabolite was 36–250 h (Larsen *et al.*, 1991).

Etretinate is detectable in the plasma of patients taking acitretin, and the concentration is affected by alcohol consumption (Larsen *et al.*, 1993a; Maier & Hönigsmann, 1996). In human liver preparations, acitretin may be esterified to etretinate in a reaction requiring ethanol and coenzyme A (Schmitt-Hoffmann *et al.*, 1995). The recommended two-year period of contraception after etretinate therapy has been considered to be applicable to acitretin (Lambert *et al.*, 1994). The elimination half-life of acitretin is much shorter than that of etretinate in most patients.

3.2 Experimental models

Radiolabelled acitretin administered intravenously was ultimately distributed in the skin and in adipose tissue where its storage was moderate and short-lived. The metabolite 13-*cis*-acitretin was detected in all tissues but not in plasma. After 6 h, < 1% of the intravenously injected dose remained in rat plasma as acitretin (Eisenhardt & Bickel, 1994). In isolated perfused rat liver, acitretin undergoes α -oxidation, chain shortening, O-demethylation and glucuronidation; isoacitretin undergoes glucuronidation as the major route of metabolism (Cotler *et al.*, 1992).

The percutaneous absorption of [^{14}C]acitretin from an isopropyl myristate formulation (160 μg acitretin per 2.5 cm^2) was approximately twice as high in hairless guinea-pigs as in rhesus monkeys after a 24-h exposure. Administration of up to 10 mg/kg bw per day to rats for six weeks altered the composition of liver microsomal phospholipid and induced cytochrome P450 enzyme activities (Tsambaos *et al.*, 1994). Pretreatment with acitretin orally at a dose of 10 mg/kg bw per day did not significantly alter the systemic clearance, volume of distribution or mean residence time of acitretin in male or female rats (Small & McNamara, 1994). The complex of microsomal UDP-glucuronosyl transferases in rat liver catalyses the formation of β -glucuronides from all-*trans*-retinoic acid and other retinoids, including acitretin (Genchi *et al.*, 1996).

4. Cancer-preventive Effects

4.1 Humans

4.1.1 Epidemiological studies

No data were available to the Working Group.

4.1.2 Intervention trials

Bavinck *et al.* (1995) evaluated the effect of acitretin on the development of squamous- and basal-cell carcinomas in a group of 44 renal transplant recipients with more than 10 keratotic skin lesions on the hands and forearms. Twenty-one patients were allocated to receive acitretin at 30 mg daily and 23 to placebo, for six months. Two patients allocated to acitretin and four to placebo withdrew before the first follow-up visit and were not included in the analysis. The pre-treatment characteristics of the remainder were similar. There was a significantly lower incidence of new skin tumours in the treated group ($p < 0.01$). During the six-month treatment period, two of the 19 patients given acitretin developed squamous-cell carcinomas, whereas nine of the 19 given placebo developed a total of 18 new skin cancers, of which 15 were squamous-cell carcinomas, two were basal-cell carcinomas and one was a case of Bowen disease. After cessation of treatment, the number of skin cancers appeared to increase.

4.1.3 Intermediate end-points

Bavinck *et al.* (1995; see above) also evaluated the effect of acitretin on the prevalence of keratotic skin lesions. A reduction was noted in the group receiving acitretin when compared with those given placebo during the six-month period of treatment. The treated patients showed a 13% reduction from baseline in the number of keratotic lesions, whereas the number of lesions in the placebo group increased by 28% ($p = 0.008$). The treated group had an increased incidence of lesions after cessation of treatment.

4.2 Experimental models

4.2.1 Cancer and preneoplastic lesions

These studies are summarized in Table 1.

Mouse: In a study of the effects of acitretin in C3H/HeNCrj mice, which are susceptible to spontaneous development of hepatomas, the control group was fed basal diet whereas the treatment group received 0.01% acitretin for 60 weeks, which was reduced from 0.01% to 0.005% at week 4 because of toxicity manifested as a reduction in body weight. Hepatomas [identified only macroscopically] developed in 12/13 control mice and 8/14 of those treated with acitretin ($p < 0.05$, Student's *t* test) (Muto & Moriwaki, 1984). [The Working Group noted the marked decrease in body weight in acitretin-treated mice.]

Rat: Groups of 40 male Fischer 344 rats were fed a diet containing 0.06% 3'-methyl-dimethylazobenzene for 20 weeks to induce hepatocellular carcinomas and were given acitretin at 10 mg/kg bw by gavage on five days per week for the entire period of 20 weeks. Acitretin reduced the incidence of hyperplastic nodules and hepatocellular carcinoma from 22/40 in controls to 13/40 in the treated group ($p < 0.01$, Student's *t* test) (Muto & Moriwaki, 1984). [The Working Group noted the marked decrease in body weight in acitretin-treated rats.]

4.2.2 Intermediate biomarkers

No data were available to the Working Group.

4.2.3 In-vitro models

4.2.3.1 Cellular studies

These studies are summarized in Table 2.

Acitretin, like its parent drug etretinate, is highly lipophilic and insoluble in water. In tests *in*

vitro it has therefore been dissolved in dimethylsulfoxide (DMSO) or ethanol. The cells were usually exposed to the drug for at least two days; when the exposure was for longer than four days, the medium was changed every two or three days.

(a) Effects on cell proliferation

The antiproliferative effects of acitretin have been assessed in transformed cells of various histotypes and in normal epidermal cells. In studies of the growth inhibitory activity of acitretin, it was always more effective than its parent drug etretinate, and it is considered to be the active metabolite. Acitretin reduces the proliferation of various tumour cell lines, including human breast cancer cells (T47D and MCF-7) (Wetherhall & Taylor, 1986; Frey *et al.*, 1991), acute myelocytic leukaemia (HL-60), squamous carcinoma (SCC4, SCC15 and A431) (Frey *et al.*, 1991) and 1/4 Kaposi sarcoma cells (Corbeil *et al.*, 1994). The combination of acitretin with tamoxifen and interferon- α enhanced the antiproliferative effect (Fontana, 1987; Frey *et al.*, 1991). In all these cells, acitretin was less active than all-*trans*-retinoic acid. Acitretin had no effect on cell proliferation in rat bladder carcinoma cells exposed for only 1 h, even at a concentration of 10^{-4} mol/L (Fujita & Yoshida, 1984). [The Working Group noted the very high concentration used.]

No correlation was found between the sensitivity of four murine sarcomas and four murine carcinomas to etretinate *in vivo* and their sensitivity to acitretin *in vitro*; acitretin inhibited the growth of two carcinomas. The antiproliferative effect of acitretin in transformed and nontransformed epidermal cells has been shown to depend on the culture conditions and cell proliferation (Eccles *et al.*, 1985). Acitretin inhibited the proliferation of normal human vaginal keratinocytes and of early-passage dysplastic epithelial cell lines derived from vaginal lesions. At late passages, the premalignant cell lines showed a more transformed phenotype and became less sensitive to acitretin. Like all-*trans*-retinoic acid and 13-*cis*-retinoic acid, acitretin was less effective in cells grown in a medium with a low concentration of Ca^{++} (Hietanen *et al.*, 1998). In neonatal murine epidermal keratinocytes with different rates of proliferation obtained by growing cells in media with high or low concentrations of Ca^{++} , etretinate caused

Table 1. Prevention or regression of liver tumours by acitretin

Species, sex, age at carcinogen treatment	No. of animals per group	Carcinogen, dose, route	Acitretin (dose, route)	Duration in relation to carcinogen	Hepatoma bearing animals (%)		Multiplicity		Efficacy
					Control	Treated	Control	Treated	
Mice C3H/HeNCrj [sex not specified]	13-14		0.01% in diet, 4 wks, 0.005%, 56 wks	Throughout life	92	57	1.9	0.7*	Effective**
Rats, Fischer 344, male	40	3'-MeDAB, 0.06% in diet for 20 wks	10 mg/kg bw by gavage 5 d/week	day 0 to end	55	33	0.9	0.4*	Effective**

From Muto & Moriwaki (1984). 3'-MeDAB, 3'-methyl-dimethylazobenzene; wk, week; d, day

*Statistically significant (see text)

** Associated with reductions in body weight

dose-dependent inhibition of DNA synthesis in rapidly growing cells cultured in a medium with a high concentration of Ca^{++} but stimulated DNA synthesis in slowly growing cells in a medium with a low concentration of Ca^{++} (Tong *et al.*, 1988).

In a model of a skin equivalent, acitretin inhibited the growth of epidermal cells, but when dermal fibroblasts were present in the culture, reflecting the situation *in vivo*, acitretin had no effect on cell proliferation (Sanquer *et al.*, 1993). The effects of acitretin contrasted with those of all-*trans*-retinoic acid and 13-*cis*-retinoic acid, which stimulated the epidermis alone but inhibited epidermal growth in the presence of viable dermal fibroblasts. In pig epidermis, acitretin significantly decreased thymidine incorporation even after a short (24-h) exposure (Hashimoto *et al.*, 1990). In fibroblast lines from normal and psoriatic skin, acitretin was cytostatic in psoriatic cells but had no effect on normal skin fibroblasts (Priestley, 1987). In primary cultures of human sebocytes, acitretin at a high concentration (10^{-5} mol/L) had minimal effects on cell proliferation and decreased lipogenesis. Acitretin markedly decreased the synthesis of triglycerides, wax or stearyl esters and free fatty acids, whereas all-*trans*-retinoic acid and 13-*cis*-retinoic acid were potent inhibitors of both cell proliferation and lipid synthesis (Zouboulis *et al.*, 1991). Acitretin inhibited endothelial cell proliferation in a dose- and time-dependent manner in endothelial cells obtained from small vessels and capillaries of human skin (Imcke *et al.*, 1991).

(b) *Effects on cell differentiation*

Explants of trachea from vitamin A-deficient hamsters have been used to measure the effects of retinoids on the squamous metaplasia that usually results when this tissue is cultured in the absence of vitamin A. Acitretin dissolved in DMSO reversed the metaplasia, with a median effective dose of 5×10^{-9} mol/L when applied over 10 days. The median effective dose of all-*trans*-retinoic acid under these conditions was 3×10^{-11} mol/L, indicating that acitretin was significantly less potent. Over 90% of the control cultures showed metaplasia (Newton *et al.*, 1980).

In the human myelomonocytic cell lines HL-60 and U937, often used to test the efficacy of differentiating agents, all-*trans*-retinoic acid and 13-*cis*-

retinoic acid induced differentiation but acitretin was completely inactive (Chomienne *et al.*, 1986). Acitretin at a higher dose induced a moderate increase in the differentiation of HL-60 cells but not U937 cells, but it was much less effective than all-*trans*-retinoic acid and 13-*cis*-retinoic acid. Differentiation induced by acitretin, but not by these two retinoids, was potentiated by interferon- β but not by interleukin-4 (Peck & Bollag, 1991). The addition of acitretin at a high concentration (10^{-5} mol/L) for five days strongly reduced keratin formation in cultured explants of pig skin (Aoyagi *et al.*, 1981a). In the same experimental system, acitretin was much more effective than etretinate in stimulating epidermal outgrowth, and this stimulation resulted in reduced keratin formation (Aoyagi *et al.*, 1981b). In human epidermal cells isolated from skin biopsy samples and cultured on a 3T3 cell feeder layer, addition of acitretin decreased the relative amount of keratin 16, thus markedly increasing the ratio of keratin 14 to keratin 16 (West *et al.*, 1992).

(c) *Effects on immune function*

The ability of acitretin to interfere with lymphocyte proliferation has been examined in few studies. Exposure for three days to acitretin at a concentration much higher than those achievable *in vivo* (7×10^{-5} mol/L) inhibited the stimulation of human lymphocytes induced by various lectins (Bauer & Orfanos, 1981). It reduced proliferation induced by the mixed epidermal cell-lymphocyte reaction by 20–30% but only when the epidermal cells had been exposed to acitretin. In the mixed lymphocyte reaction, a decrease of 10–15% was found only at a concentration of 10^{-5} mol/L (Dupuy *et al.*, 1989). At an extremely high concentration (10^{-4} mol/L), acitretin inhibited human peripheral blood mononuclear cells and phytohaemagglutinin-stimulated proliferation (Chaidaroglou *et al.*, 1998). [The Working Group noted the very high concentration used.] In stimulated polymorphonuclear leukocytes, acitretin, unlike etretinate, suppressed generation of hydroxy radicals (Yoshioka *et al.*, 1986).

4.2.3.2 *Antimutagenicity in short-term tests*

No data were available to the Working Group.

Table 2. Effect of acitretin on cell proliferation, differentiation, tumour promotion and immune function

Cell line; end-point	Vehicle	Concentration (mol/L)	Response	Comments	Reference
Cell proliferation					
Human breast cancer cell line (T47D); proliferation	DMSO	10 ⁻⁹ to 10 ⁻⁵ for 7 days	Decreased proliferation	Less potent than ATRA	Wetherall & Taylor (1986)
Human breast cancer cell line (MCF7); proliferation	Ethanol	10 ⁻⁸ for 6 days	Decreased proliferation	Additive interaction with tamoxifen	Fontana (1987)
Human cancer cell lines (MFC-7, HL-60, SCC ₄ , SCC ₁₅ , A431); proliferation	DMSO	3 x 10 ⁻⁸ to 3 x 10 ⁻⁵ for 7 days	Decreased proliferation at the highest dose in all 5 cell lines	Less potent than ATRA; enhanced effect with IFN α	Frey <i>et al.</i> (1991)
Human Kaposi sarcoma cell lines; TdR incorporation	DMSO	10 ⁻⁸ to 10 ⁻⁵ for 2 days	Decreased TdR incorporation in 1/4 lines	Less potent than ATRA	Corbeil <i>et al.</i> (1994)
Murine sarcomas (4) and carcinomas (4); proliferation	Ethanol	10 ⁻⁸ to 10 ⁻⁶ for 7, 9 days	Decreased proliferation in 2 carcinomas		Eccles <i>et al.</i> (1985)
Human keratinocyte cell lines derived from vaginal intraepithelial neoplasia, normal vaginal keratinocytes and fibroblasts; proliferation	DMSO	10 ⁻⁹ to 10 ⁻⁵ for 4 days	Decreased proliferation of early-passage cell lines and of normal keratinocytes; reduced inhibition in late-passages and in low Ca ⁺⁺ medium	IFN α -2A potentiates the antiproliferative effect	Hietanen <i>et al.</i> (1998)
Normal murine epidermal cells; DNA synthesis	DMSO	10 ⁻⁸ to 10 ⁻⁴ for 4 days	Decreased proliferation in fast-growing (high Ca ⁺⁺) cells; increased proliferation in slow-growing (low Ca ⁺⁺) cells	More potent than etretinate	Tong <i>et al.</i> (1988)
Normal human epidermal cells; TdR incorporation,	DMSO	10 ⁻⁷ to 10 ⁻⁶ for 2 weeks	Decreased proliferation in epidermal cells. No effect in epidermis when grown with dermis fibroblasts	Effects opposite to those of ATRA and 13- <i>cis</i> -RA	Sanquer <i>et al.</i> (1993)
Normal pig epidermis	DMSO	10 ⁻⁷ to 10 ⁻⁴ for 24 h	Decreased TdR incorporation	More potent than etretinate	Hashimoto <i>et al.</i> (1990)
Normal and psoriatic skin fibroblasts; proliferation	DMSO	10 ⁻⁷ to 10 ⁻⁴ for 3 days	Cytostatic in psoriatic cells; no effect in normal skin		Priestley (1987)
Normal human sebocytes; TdR incorporation, lipid lipogenesis	DMSO	10 ⁻⁸ to 10 ⁻⁵ for 7-14 days	No effect on proliferation; decreased lipid synthesis	Less potent than ATRA and 13- <i>cis</i> -RA	Zouboulis <i>et al.</i> (1991)

Table 2 (contd)

Cell-line; end-point	Vehicle	Concentration (mol/L)	Response	Comments	Reference
Normal human endothelial cells from skin vessels; proliferation and differentiation	DMSO	10 ⁻⁸ to 10 ⁻⁵ for 6 days	Decreased proliferation; no effect on HLA-DR or ICAM-1	More potent than etretinate	Imcke <i>et al.</i> (1991)
Cell differentiation					
Human myelomonocytic cell lines (HL-60, U937) and fresh human leukaemic blast cells; cell viability and differentiation (NBT reduction)	DMSO	10 ⁻⁷ to 10 ⁻⁶ for 4 or 6 days	No effect on viability; No effect on differentiation	ATRA is active	Chomienne <i>et al.</i> (1986)
Human myelomonocytic cell lines (HL-60, U937); differentiation (NBT reduction)	DMSO	10 ⁻⁵ for 2 days	Moderate increase in differentiation of HL-69 cells; potentiation of differentiation by IFN β and not by IL-4	Less potent than ATRA and 13- <i>cis</i> -RA	Peck & Bollag (1991)
Normal pig skin explant cultures; keratin formation	Not reported	10 ⁻⁵ for 5 days	Modified keratin formation	High concentration	Aoyagi <i>et al.</i> (1981a)
Normal pig skin explant cultures; growth and keratin formation	DMSO	10 ⁻⁷ to 10 ⁻⁵ for 4 days	Stimulated growth and reduced keratin formation		Aoyagi <i>et al.</i> (1981b)
Normal human epidermal cells; keratin expression and envelope formation	Not reported	10 ⁻⁸ to 10 ⁻⁵ for 9 days	Increased keratin 14:16 ratio; decreased envelope formation	More potent than etretinate but less potent than ATRA	West <i>et al.</i> (1992)
Immune function					
Human lymphocytes; response to lectins	DMSO	7 x 10 ⁻⁸ to 7 x 10 ⁻⁵ for 3 days	Inhibition of PHA- and Con A-induced stimulation	Effective	Bauer & Orfanos (1981)
Human lymphocytes; mitogenic response to PHA, MLR and MECLR; cell viability	DMSO	10 ⁻⁸ to 10 ⁻⁵ for 4-6 days	Inhibition (20-30%) of MECLR-induced proliferation; no consistent inhibition of PHA mitogenic response		Dupuy <i>et al.</i> (1989)
Zymosan-stimulated polymorphonuclear lymphocytes; reactive oxygen species generation	50% DMSO 50% ethanol	2 x 10 ⁻⁶ to 2 x 10 ⁻⁴ during stimulation	Inhibition of OH [•] generation		Yoshioka <i>et al.</i> (1986)

DMSO, dimethylsulfoxide; ATRA, all-*trans*-retinoic acid; IFN, interferon; TdR, ³H-thymidine; 13-*cis*-RA, 13-*cis*-retinoic acid; NBT, nitroblue tetrazolium test; IL, interleukin; PHA, phytohaemagglutinin; MLR, mixed lymphocyte reaction; MECLR, mixed epidermal cell-lymphocyte reaction; ConA, concanavalin A

4.3 Mechanisms of cancer prevention

Information on the biological action of acitretin was obtained from studies of patients with skin disease.

4.3.1 Effects on cell differentiation

Acitretin modifies cell membrane glycosylation. In primary cultures of epidermal and dermal cells, acitretin stimulated the biosynthesis of cell and matrix glycosaminoglycans (Shapiro & Mott, 1981), and this occurred at a low concentration (10^{-7} mol/L) and declined as the concentration increased (Priestley, 1987). Acitretin, like etretinate, inhibited tumour necrosis factor (TGF) β 1-stimulated type 1 collagen production by normal human lung fibroblasts. The pattern of keratinocyte proteins in cells removed from the dermal layer and grown in culture was modified by acitretin (Redlich *et al.*, 1995). Acitretin, like etretinate, inhibited non-disulfide, disulfide and envelope proteins, whereas it stimulated keratohyaline-associated proteins (Stadler *et al.*, 1987). Acitretin was twice as active as etretinate in decreasing the relative amount of keratin 16 and consequently in causing a marked increase in the ratio of keratin 14:16 (West *et al.*, 1992). In primary human sebocyte cultures, acitretin decreased lipogenesis at concentrations that did not affect cell proliferation (Zouboulis *et al.*, 1991).

4.3.2 Inhibition of cell proliferation

The only suggestion for a mechanism by which acitretin inhibits cell proliferation is that it inhibits the activity of ornithine decarboxylase (Xue *et al.*, 1996).

4.3.3 Effects on immune function and cytokine production

Few studies have addressed the effects of acitretin on immune function. It was more active than etretinate in decreasing the migration of neutrophils from the bloodstream to human skin when applied locally (Dubertret *et al.*, 1982). A two- to threefold increase in epidermal interleukin-1 was found in acitretin-treated hairless rats when compared with control rats (Schmitt *et al.*, 1987). Acitretin also increased interleukin-1 production in keratinocytes grown *in vitro* (Tokura *et al.*, 1992).

4.3.4 Effects on angiogenesis

Acitretin inhibited angiogenesis evoked by intra-dermal injection of human epidermoid cancer cell lines in mice and was more effective than etretinate at an equivalent dose (Rudnicka *et al.*, 1991).

5. Other Beneficial Effects

Acitretin has been shown in clinical trials to be of benefit in the treatment of severe psoriasis, including erythrodermic and generalized pustular psoriasis. Relevant references are given in the General Remarks.

6. Carcinogenicity

6.1 Humans

No data were available to the Working Group.

6.2 Experimental models

No data were available to the Working Group.

7. Other Toxic Effects

7.1 Adverse effects

7.1.1 Humans

Pilkington and Brogden (1992) and Gollnick (1996) summarized the multicentre clinical trials in which acitretin was compared with etretinate. Acitretin has a lower therapeutic index than etretinate, and while the total incidence of adverse effects is higher with etretinate, the symptoms were more severe with acitretin. Clinical experience with these drugs has demonstrated that the hazards posed are very similar. Because acitretin is less lipophilic and has a much shorter elimination half-life than etretinate, it has replaced etretinate in 34 countries (Lacour *et al.*, 1996). The doses used in the treatment of moderate-to-severe psoriasis are 10–75 mg/day (Pilkington & Brogden, 1992).

Most of the information about the toxicity of acitretin is derived from dermatological studies, which indicate that the incidence of idiosyncratic hepatitis, musculoskeletal problems and hyperlipidaemia is comparable to that seen with etretinate (Halioua & Saurat, 1990). Rare effects that may be associated with acitretin treatment include pancreatitis, pseudotumour cerebri,

keratoconus (Larsen *et al.*, 1993b), myopathy (Lister *et al.*, 1996) and vulvo-vaginal candidiasis (Sturkenboom *et al.*, 1995). A unique contraindication to the use of acitretin is the ingestion of alcohol (see section 3.1).

7.1.1.1 Skeletal toxicity

Like other retinoids, acitretin can be toxic to the bone in children (reviewed by Orfanos *et al.*, 1997). When the dose of acitretin given to 29 paediatric patients was limited to < 0.4 mg/kg bw per day, only one child experienced osteo-articular symptoms (transient knee pain), and no remarkable effects were found on physical examination or X-ray of this patient (Lacour *et al.*, 1996). Nevertheless, maintenance doses of 0.5–0.75 mg/kg bw per day have been used successfully (Salleras *et al.*, 1995). Although skeletal changes are seen in adults given 0.5 mg/kg bw per day for two years (Mork *et al.*, 1992), acitretin can be given to children over long periods with no such complications if all four limbs and the lateral spine are screened radiologically before treatment, the dose is maintained at 0.49 ± 0.12 mg/kg bw per day and the patients are observed carefully for musculoskeletal complaints (Lacour *et al.*, 1996).

7.1.1.2 Effects during chemotherapy

Acitretin has been evaluated in combination with interferon α -2a for the treatment of cutaneous T-cell lymphomas. The combination increased the number of flu-like symptoms, skin dryness, hair loss, increased triglyceride concentrations and neurological or psychiatric symptoms when compared with interferon α -2a plus psoralen-ultraviolet A therapy. The rate of complete response in 98 patients was no greater with acitretin plus interferon α -2a at 25–50 mg/week for 48 weeks than with the interferon α -2a plus phototherapy (38% vs 70%; $p \leq 0.008$; χ^2 test) (Stadler *et al.*, 1998).

7.1.2 Experimental models

Short- and long-term studies in rats and dogs showed dose-related, reversible toxic effects typical of the retinoids. In rats, these included decreased body-weight gain and increased serum cholesterol, triglyceride and lipoprotein concentrations and alkaline phosphatase activity. Fractures and evidence of healed fractures were observed. The doses

that produced these effects were one to two times the recommended human therapeutic dose. In dogs at doses up to 10 times the human dose, the signs of intolerance included erythema, skin hypertrophy and hyperplasia. Most of these side-effects were readily reversed upon cessation of treatment (Arky, 1998).

7.2 Reproductive and developmental effects

7.2.1 Humans

7.2.1.1 Reproductive effects

Sperm concentration, sperm morphology, total sperm motility and ejaculate volume were unchanged in four patients with psoriasis and six healthy volunteers aged 21–61 years who were given acitretin at 50 mg/day for six weeks, with individual dose adjustment to 25–50 mg/day for the next six weeks (Sigg *et al.*, 1987; Parsch *et al.*, 1990). No significant alterations from pretreatment values occurred during or after treatment in follicle-stimulating hormone, luteinizing hormone or testosterone, and there was no evidence of alterations in male reproductive function up to three months after discontinuation of treatment (Parsch *et al.*, 1990).

In nine fertile women aged 17–40 who were given acitretin at 25–40 mg/day (0.2–0.8 mg/kg bw per day) and maintained on laevonorgestrel or ethinyloestradiol, acitretin did not interfere with the antioviulatory actions of these combined oral contraceptives (Berbis *et al.*, 1988).

7.2.1.2 Developmental effects

Acitretin is contraindicated in women of child-bearing potential, and negative results in pregnancy test before initiation of therapy and strict contraception during treatment and for at least two years after drug withdrawal are required (Bouvy *et al.*, 1992; Stricker *et al.*, 1992). The prolonged elimination half-time of its ethyl ester metabolite—more than one year in some patients (Lambert *et al.*, 1990, 1992)—indicates the need for prolonged contraception in potentially fertile women.

Of 75 women whose exposure during pregnancy had been reported before December 1993, 67 had been exposed for a median of 15 months before the pregnancy. Thirty-seven of these women had normal infants (Table 3). The remaining pregnancies were terminated after elective

abortion or by spontaneous embryonic or fetal death *in utero* or ended with the birth of a malformed infant (Geiger *et al.*, 1994).

Exposure to acitretin at 1 mg/kg bw per day from 10 days after conception through week 10 was embryolethal. Autopsy revealed symmetrical short limbs, oligodactyly, absence of nails, microstomia, micrognathia, bilateral low-set microtia with preauricular skin tags, imperforate auditory meatus and atrioventricular septal defect (de Die-Smulders *et al.*, 1995). In another case, in which the mother received 50 mg/day during the first 19 weeks of pregnancy, autopsy of the fetus showed microtia and malformations of the face and limbs. In a third example, the infant of a mother who received 20 mg/day during the first eight months of her pregnancy was born with impaired hearing (Geiger *et al.*, 1994).

Because of the initial reports that the efficacy of acitretin, the main pharmacologically active metabolite of etretinate, was equivalent to that of etretinate in the therapy of psoriasis (Bjerke & Geiger, 1989) and because of its shorter terminal elimination half-time (2.4 vs 120 days) (Paravicini *et al.*, 1985; Larsen *et al.*, 1988), acitretin was thought to be more suitable than etretinate for use in women of child-bearing potential (O'Brien, 1990). Identification of the acitretin esterification pathway in humans (Chou *et al.*, 1992; Larsen, 1994; Laugier *et al.*, 1994; Maier & Hönigsmann, 1996), however, has reduced the potential value of acitretin as a substitute for etretinate. Although etretinate and acitretin are comparable in terms of efficacy, etretinate tends to be better tolerated (reviewed by Gollnick, 1996). Etretinate given at a dose of 25–50 mg/day for 5–24 months was still present in the circulation 500 days later (Lambert *et al.*, 1990).

7.2.2 Experimental models

7.2.2.1 Reproductive effects

No data were available to the Working Group.

7.2.2.2 Developmental effects

In mice given acitretin at 200 mg/kg bw on day 11 of gestation, typical retinoid-related effects were induced, including cleft palate and shortening of the long bones of the limbs (Kochhar *et al.*, 1988; Reiners *et al.*, 1988). In mice given 100 mg/kg bw

on day 11, cleft palate and limb bone shortening were also seen, but the 13-*cis* isomer was not teratogenic at this dose (Löfberg *et al.*, 1990). Acitretin was considerably less potent than etretinate in these studies, but when tested *in vitro* for inhibition of chondrogenesis, acitretin was as potent as all-*trans*-retinoic acid (Kistler, 1987; Kochhar *et al.*, 1988; Reiners *et al.*, 1988). The lowest teratogenic dose for mice was found to be 3 mg/kg bw given not as a single large dose on one day but as daily doses on days 7–17 of gestation. In these experiments, the 13-*cis* metabolite of acitretin was also considerably less active than the parent all-*trans* isomer (Kistler & Hummler, 1985; Kistler, 1987).

In rats, acitretin at 25 or 50 mg/kg bw increased the rate of embryo resorption; at the higher dose, almost all of the surviving embryos were abnormal. The malformations of the central nervous system included exencephaly, hydrocephaly and spina bifida; those in the craniofacial region were micrognathia, agnathia, clefting, ear deformities, anophthalmia and exophthalmia; those of the urogenital system were genital agenesis, undescended testes, hydronephrosis and dilated ureter; and those at the caudal end were imperforate anus and hindlimb and tail defects. No cardiac abnormalities were observed (Turton *et al.*, 1992). The lowest teratogenic dose for rat embryos was 15 mg/kg bw, and, in contrast to the effect in mice embryos, 13-*cis*-acitretin was slightly more teratogenic than the all-*trans* isomer (Kistler & Hummler, 1985; Kistler, 1987). When mid-gestation rat embryos were cultured for 48 h in the presence of acitretin, a concentration of 1 µg/ml caused embryonic abnormalities, measured as retarded growth and differentiation, a reduction in the number of pharyngeal arches and delayed closure of the anterior neuropore. At this concentration, acitretin was as potent as 13-*cis*-retinoic acid but only half as potent as all-*trans*-retinoic acid (Steele *et al.*, 1987).

Rabbit embryos were more sensitive to acitretin than mice or rats, the lowest teratogenic dose being 0.6 mg/kg bw (Kistler & Hummler, 1985; Kistler, 1987).

7.3 Genetic and related effects

No data were available to the Working Group.

Table 3. Exposure to acitretin and pregnancy outcome

Outcome	Exposed during pregnancy	Exposed before pregnancy ^a	Total
Newborns			
• normal	1	36	37
• with typical jaw, ear and cardiac malformations	–	–	0
• with other malformations	1	4	5
Spontaneous abortion	4	9	13
Late fetal death	–	–	0
Induced abortion			
• no information	1	15	16
• normal fetus	–	3	3
• with typical jaw, ear and cardiac malformations	1	–	1
• with other malformations	–	–	0
Total	8	67	75

Modified from Geiger *et al.* (1994)

^a Range: 6 weeks to 23 months, median: 5 months

8. Summary of Data

8.1 Chemistry, occurrence and human exposure

Acitretin [all-*trans*-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4,6,8-tetraenoic acid] is a synthetic retinoid of the aromatic class which is structurally related to all-*trans*-retinoic acid. Because of its conjugated tetraene structure, acitretin has a characteristic absorption in the ultraviolet and visible spectrum and is readily photoisomerized in solution to multiple geometric isomers. Acitretin has a free carboxylic acid and as a consequence is much less lipophilic than its ethyl ester derivative, etretinate; however, like other acidic retinoids, it is lipophilic and is partitioned into hydrophobic compartments.

Acitretin can be prepared by various routes from readily available starting materials. Human exposure is due entirely to treatment with oral formulations, primarily for dermatological indications.

The recommended doses of acitretin are 25–50 mg/day.

Various normal-phase and reversed-phase high-performance liquid chromatographic methods are available for the detection and quantification of acitretin and its geometric isomers.

8.2 Metabolism and kinetics

The pharmacokinetics of acitretin has been extensively studied, particularly in patients with psoriasis. Acitretin is eliminated from the body more rapidly than etretinate, and less is sequestered in adipose tissue. Its metabolites are eliminated via the hepatic and renal routes, but acitretin can be esterified to etretinate *in vivo*.

8.3 Cancer-preventive effects

8.3.1 Humans

In one trial with 44 renal transplant patients, acitretin reduced the frequency of occurrence of

squamous-cell cancers of the skin when compared with placebo. In the same trial, the prevalence of keratotic skin lesions was also reduced by acitretin. When treatment was stopped, the numbers of cancers and keratotic skin lesions increased.

8.3.2 Experimental models

In single studies, acitretin reduced the incidence of spontaneous and chemically induced liver tumours in mice and rats in conjunction with reductions in body weight.

Acitretin was evaluated for its ability to inhibit proliferation or to induce differentiation of tumour and normal cells *in vitro*. Acitretin was more active than etretinate, and both were less active than all-*trans*-retinoic acid and 13-*cis*-retinoic acid. Acitretin reversed squamous metaplasia in hamster trachea resulting from vitamin A deficiency. It had an anti-proliferative effect on some but not all tumour cell lines that were tested. Several studies with epidermal cells showed that the effects of acitretin depended on the culture conditions and/or the proliferation rate. It did not induce differentiation of leukaemic cells *in vitro*. In normal epidermal cells, it decreased envelope formation and modified the pattern of keratin. In studies of lymphocyte proliferation *in vitro*, the effects depended on the concentration of acitretin and on the mitogen used to induce proliferation.

8.3.3 Mechanisms of cancer prevention

The differentiating effect of acitretin on epidermal cells may be associated with modifications in the pattern of keratin expression and membrane glycosylation; however, the effect seems to depend on the concentration of the drug. The only mechanism that can be associated with the anti-proliferative activity of acitretin is inhibition of ornithine decarboxylase activity, which is increased in hyperproliferative states. The effects of acitretin on immune function have not been studied extensively. It stimulated the production of interleukin-1 both *in vitro* and *in vivo*, which might result in activation of lymphoid cells. In one study, acitretin inhibited angiogenesis, an effect that might contribute to its cancer-preventive activity.

8.4 Other beneficial effects

Acitretin is of benefit to patients suffering from psoriasis, including erythrodermic and generalized pustular forms.

8.5 Carcinogenic effects

No data were available to the Working Group.

8.6 Other toxic effects

8.6.1 Humans

At therapeutic doses, acitretin may produce hepatotoxicity, pancreatitis and pseudotumour cerebri. Ophthalmic toxicity, hyperostosis and lipid abnormalities have also been reported. These side-effects are readily reversible upon cessation of treatment in all but a small proportion of patients. Since acitretin is the active metabolite of etretinate and in view of case reports of malformations, acitretin is considered to be a human teratogen and is contraindicated in women of child-bearing potential. The recommended post-medication period during which pregnancy should be avoided is two years. No effects of acitretin were observed on spermatogenesis in humans in two studies. The efficacy of the oral contraceptives laevonorgestrel and ethinyloestradiol was not affected by treatment with acitretin in one study.

8.6.2 Experimental models

No published studies on the toxic effects of acitretin were available to the Working Group. In studies of cancer-preventive effects in experimental animals (see section 8.3.2), weight loss was associated with administration of acitretin.

Reproductive toxicity has not been reported in male animals. Acitretin is a potent teratogen in experimental animals, inducing the classical embryopathy seen with retinoids, with effects on the central nervous system, craniofacial region, urogenital system, limbs and tail in a range of animal models. Acitretin is slightly less potent as a teratogen than all-*trans*-retinoic acid.

9. Recommendations for Research

9.1 General recommendations for acitretin and other retinoids

See section 9 of the Handbook on all-*trans*-retinoic acid.

9.2 Recommendations specific to acitretin

None.

10. Evaluation

10.1 Cancer-preventive activity

10.1.1 Humans

There is *inadequate evidence* that acitretin has cancer-preventive activity in humans.

10.1.2. Experimental animals

There is *inadequate evidence* that acitretin has cancer-preventive activity in experimental animals.

10.2 Overall evaluation

There is inadequate evidence in humans and in experimental animals for the cancer-preventive activity of acitretin. Since acitretin is a derivative of etretinate, however, it probably has cancer-preventive efficacy similar to that of etretinate. Furthermore, it is less toxic than etretinate, although it is a potent teratogen in experimental animals and is considered to be a teratogen in humans.

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