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to the class of aromatic synthetic retinoids in which the lipophilic trimethylcyclohexenyl group of retinoic acid has been replaced by an aromatic ring (Figure 1). In the case of acitretin, the cyclohexenyl group has been replaced by a 4-methoxy-2,3,6-trimethylphenyl group, while the all-trans-tetraene structure of the retinoic acid side-chain has been retained.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, (2Z,4E,6E,8E)-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: C_{21}H_{26}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)

$^{1}$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, $J$ = 15.0 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).

$^{13}$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
\( \nu_{\text{max}}: 3600-3300 \text{ (O-H), 1700 (C=O), 1600 (C=C)} \text{ cm}^{-1} \) (Aurell et al., 1995)

Geometrical isomers
Sixteen possible isomers

Photochemical properties
Acitretin is a yellow to greenish-yellow powder with an absorption maximum (\( \lambda_{\text{max}} \)) 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 µmol/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 hydrolyzed 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 1H-NMR spectroscopy (Hänni et al., 1977). Bile samples collected from patients treated with 14C-labelled etretinate were analysed by HPLC after β-glucuronidase treatment, and the structures of the metabolites were determined by mass spectrometry and 1H-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 liquidchromatography–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 (pKₐ 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 14C-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 (Uewell & 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 & Höningmann, 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 [14C]acitretin from an isopropyl myristate formulation (160 μg acitretin per 2.5 cm²) 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 pretreatment 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 \( (p < 0.05, \text{ Student's } t \text{ test}) \) (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'-methyldimethylazo- benzene 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 \( (p < 0.01, \text{ Student's } t \text{ test}) \) (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-\( \alpha \) 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

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

From Muto & Moriwaki (1984). 3'-MeDAB, 3'-methylidimethylazobenzene; 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 \( \text{Ca}^{++} \) but stimulated DNA synthesis in slowly growing cells in a medium with a low concentration of \( \text{Ca}^{++} \) (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, acetretin 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 steryl 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).

(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 \times 10^{-5} \text{ 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} \text{ mol/L} (Dupuy et al., 1989). At an extremely high concentration (10^{-4} \text{ 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>
<thead>
<tr>
<th>Cell line; end-point</th>
<th>Vehicle</th>
<th>Concentration (mol/L)</th>
<th>Response</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell proliferation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human breast cancer cell line (T47D); proliferation</td>
<td>DMSO</td>
<td>$10^{-6}$ to $10^{-5}$ for 7 days</td>
<td>Decreased proliferation</td>
<td>Less potent than ATRA</td>
<td>Wetherali &amp; Taylor (1986)</td>
</tr>
<tr>
<td>Human breast cancer cell line (MCF7); proliferation</td>
<td>Ethanol</td>
<td>$10^{-6}$ for 6 days</td>
<td>Decreased proliferation</td>
<td>Additive interaction with tamoxifen</td>
<td>Fontana (1987)</td>
</tr>
<tr>
<td>Human cancer cell lines (MFC-7, HL-60, SCC4, SCC15, A431); proliferation</td>
<td>DMSO</td>
<td>$3 \times 10^{-8}$ to $3 \times 10^{-6}$ for 7 days</td>
<td>Decreased proliferation at the highest dose in all 5 cell lines</td>
<td>Less potent than ATRA; enhanced effect with IFNα</td>
<td>Frey et al. (1991)</td>
</tr>
<tr>
<td>Human Kaposi sarcoma cell lines; TdR incorporation</td>
<td>DMSO</td>
<td>$10^{-9}$ to $10^{-5}$ for 2 days</td>
<td>Decreased TdR incorporation in 1/4 lines</td>
<td>Less potent than ATRA</td>
<td>Corbeil et al. (1994)</td>
</tr>
<tr>
<td>Murine sarcomas (4) and carcinomas (4); proliferation</td>
<td>Ethanol</td>
<td>$10^{-8}$ to $10^{-6}$ for 7, 9 days</td>
<td>Decreased proliferation in 2 carcinomas</td>
<td></td>
<td>Eccles et al. (1985)</td>
</tr>
<tr>
<td>Human keratinocyte cell lines derived from vaginal intraepithelial neoplasia, normal vaginal keratinocytes and fibroblasts; proliferation</td>
<td>DMSO</td>
<td>$10^{-9}$ to $10^{-5}$ for 4 days</td>
<td>Decreased proliferation</td>
<td>IFNα-2A potentiates the antiproliferative effect</td>
<td>Hietanen et al. (1998)</td>
</tr>
<tr>
<td>Normal murine epidermal cells; DNA synthesis</td>
<td>DMSO</td>
<td>$10^{-8}$ to $10^{-4}$ for 4 days</td>
<td>Decreased proliferation</td>
<td>More potent than etretinate</td>
<td>Tong et al. (1988)</td>
</tr>
<tr>
<td>Normal human epidermal cells; TdR incorporation</td>
<td>DMSO</td>
<td>$10^{-7}$ to $10^{-6}$ for 2 weeks</td>
<td>Decreased proliferation</td>
<td>Effects opposite to those of ATRA and 13-cis-RA</td>
<td>Sanquer et al. (1993)</td>
</tr>
<tr>
<td>Normal pig epidermis</td>
<td>DMSO</td>
<td>$10^{-7}$ to $10^{-4}$ for 24 h</td>
<td>Decreased TdR incorporation</td>
<td>More potent than etretinate</td>
<td>Hashimoto et al. (1990)</td>
</tr>
<tr>
<td>Normal and psoriatic skin fibroblasts; proliferation</td>
<td>DMSO</td>
<td>$10^{-7}$ to $10^{-4}$ for 3 days</td>
<td>Cytostatic in psoriatic cells; no effect in normal skin</td>
<td></td>
<td>Priestley (1987)</td>
</tr>
<tr>
<td>Normal human sebocytes; TdR incorporation, lipid lipogenesis</td>
<td>DMSO</td>
<td>$10^{-8}$ to $10^{-6}$ for 7–14 days</td>
<td>No effect on proliferation; decreased lipid synthesis</td>
<td>Less potent than ATRA and 13-cis-RA</td>
<td>Zouboulis et al. (1991)</td>
</tr>
<tr>
<td>Cell-line; end-point</td>
<td>Vehicle</td>
<td>Concentration (mol/L)</td>
<td>Response</td>
<td>Comments</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
<td>------------------------</td>
<td>----------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Normal human endothelial cells from skin vessels; proliferation and differentiation</td>
<td>DMSO</td>
<td>$10^{-8}$ to $10^{-6}$ for 6 days</td>
<td>Decreased proliferation; no effect on HLA-DR or ICAM-1</td>
<td>More potent than etretinate</td>
<td>Imcke et al. (1991)</td>
</tr>
<tr>
<td>Cell differentiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human myelomonocytic cell lines (HL-60, U937) and fresh human leukaemic blast cells; cell viability and differentiation (NBT reduction)</td>
<td>DMSO</td>
<td>$10^{-7}$ to $10^{-6}$ for 4 or 6 days</td>
<td>No effect on viability; No effect on differentiation</td>
<td>ATRA is active</td>
<td>Chomienne et al. (1986)</td>
</tr>
<tr>
<td>Human myelomonocytic cell lines (HL-60, U937); differentiation (NBT reduction)</td>
<td>DMSO</td>
<td>$10^{-5}$ for 2 days</td>
<td>Moderate increase in differentiation of HL-69 cells; potentiation of differentiation by IFNβ and not by IL-4</td>
<td>Less potent than ATRA and 13-cis-RA</td>
<td>Peck &amp; Boillag (1991)</td>
</tr>
<tr>
<td>Normal pig skin explant cultures; keratin formation</td>
<td>Not reported</td>
<td>$10^{-6}$ for 5 days</td>
<td>Modified keratin formation</td>
<td>High concentration</td>
<td>Aoyagi et al. (1981a)</td>
</tr>
<tr>
<td>Normal pig skin explant cultures; growth and keratin formation</td>
<td>DMSO</td>
<td>$10^{-7}$ to $10^{-6}$ for 4 days</td>
<td>Stimulated growth and reduced keratin formation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal human epidermal cells; keratin expression and envelope formation</td>
<td>Not reported</td>
<td>$10^{-6}$ to $10^{-5}$ for 9 days</td>
<td>Increased keratin 14:16 ratio; decreased envelope formation</td>
<td>More potent than etretinate but less poten than ATRA</td>
<td>West et al. (1992)</td>
</tr>
<tr>
<td>Immune function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human lymphocytes; response to lectins</td>
<td>DMSO</td>
<td>$7 \times 10^{-8}$ to 7 $x 10^{-6}$ for 3 days</td>
<td>Inhibition of PHA- and Con A-induced stimulation</td>
<td>Effective</td>
<td>Bauer &amp; Orfanos (1981)</td>
</tr>
<tr>
<td>Human lymphocytes; mitogenic response to PHA, MLR and MECLR; cell viability</td>
<td>DMSO</td>
<td>$10^{-6}$ to $10^{-5}$ for 4–6 days</td>
<td>Inhibition (20–30%) of MECLR-induced proliferation; no consistent inhibition of PHA mitogenic response</td>
<td></td>
<td>Dupuy et al. (1989)</td>
</tr>
<tr>
<td>Zymosan-stimulated polymorphonuclear lymphocytes; reactive oxygen species generation</td>
<td>50% DMSO</td>
<td>$2 \times 10^{-6}$ to $2 \times 10^{-4}$ during stimulation</td>
<td>Inhibition of OH• generation</td>
<td></td>
<td>Yoshioka et al. (1986)</td>
</tr>
</tbody>
</table>

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)B1-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 kerato-hyaline-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 intradermal 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 acetretin 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 ≤ 0.008; χ² 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 antiovulatory actions of these combined oral contraceptives (Berbis et al., 1988).

7.2.1.2 Developmental effects
Acitretin is contraindicated in women of childbearing 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, oligodacyly, absence of nails, microstomia, micrognathia, bilateral low-set microtia with preauricular skin tags, imperforate auditory meatus and atroventricular septal defect (de Diesmulders 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 & Höngßmann, 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). Eretinate 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, hydrenephrosis 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposed during pregnancy</th>
<th>Exposed before pregnancy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• normal</td>
<td>1</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>• with typical jaw, ear and cardiac malformations</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>• with other malformations</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>4</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Late fetal death</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Induced abortion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• no information</td>
<td>1</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>• normal fetus</td>
<td>–</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>• with typical jaw, ear and cardiac malformations</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>• with other malformations</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>67</td>
<td>75</td>
</tr>
</tbody>
</table>

Modified from Geiger et al. (1994)

* 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 \textit{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 \textit{in vitro}. In normal epidermal cells, it decreased envelope formation and modified the pattern of keratin. In studies of lymphocyte proliferation \textit{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 \textit{in vitro} and \textit{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 cerebi. 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 levonorgestrel and ethinylestradiol 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.

11. References


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