8-METHOXYPSORALEN (METHOXSALEN) PLUS ULTRAVIOLET RADIATION (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

The development of nonmelanocytic skin cancer (basal- and squamous-cell skin cancers) has been reported in patients treated with 8-methoxypsoralen and long-wave ultraviolet light (UVA) (PUVA) for psoriasis or mycosis fungoides[1-5]. Three cases of malignant melanoma of the skin have been reported in patients with psoriasis treated with PUVA[6,7]. The strongest evidence for a causal association between PUVA treatment and nonmelanocytic skin cancer comes from the follow-up of 1380 psoriatic patients treated in the USA. The standardized incidence ratio (SIR) for squamous-cell carcinoma increased from 4.1 (95% confidence interval, 2.3-6.8) at low doses to 22.3 (13.5-34.1) at medium doses and 56.8 (42.7-74.2) at high doses; this effect was independent of possible confounding effects of therapy with ionizing radiation and topical tar. The effect on basal-cell cancer incidence was much weaker (high doses: SIR, 4.5; 2.8-6.9)[8]. One cohort study of 525 psoriatic patients treated with PUVA did not suggest an increase in the incidence of skin cancer (mean follow-up period, 2.1 years)[9]. This 'negative' result could have been due to lack of statistical power and to the low doses used in the study. Another study with a five-year follow up showed no skin tumour in 94 patients treated with PUVA for psoriasis or mycosis fungoides[10].

8-Methoxypsoralen alone did not alter the incidence of new skin cancer over two years in two small controlled trials of its use as a prophylactic for skin cancer[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

8-Methoxypsoralen was tested by oral and intraperitoneal administration and by skin application in combination with ultraviolet A radiation in mice, producing epidermal and dermal tumours[1,11-15]. When it was tested alone in mice by intraperitoneal administration[13] or by skin application[12,13], it did not induce skin tumours. The studies were inadequate to evaluate the systemic carcinogenicity of 8-methoxypsoralen.

C. Other relevant data

In patients treated with PUVA, neither chromosomal aberrations (one study) nor sister chromatid exchanges were observed[16].

8-Methoxypsoralen in combination with ultraviolet A radiation induced sister chromatid exchanges in epithelial cells of cheek pouches of hamsters treated *in vivo*. In a large number of studies, it induced chromosomal aberrations, sister chromatid exchanges, mutation, DNA damage and DNA cross-links in human cells *in vitro*. It transformed mouse C3H 10T1/2 cells. In rodent cells in culture, it induced chromosomal aberrations, micronuclei, sister chromatid exchanges, mutation, unscheduled DNA synthesis and DNA cross-links. It induced mitotic recombination and mutation in fungi and mutation and DNA damage in bacteria[16].

8-Methoxypsoralen in the absence of ultraviolet A radiation induced mutation in bacteria, but inconclusive results were obtained with respect to chromosomal aberrations and sister chromatid exchanges in human cells *in vitro*, gene mutation and DNA damage in rodent cells *in vitro* and mutation in yeast[16].

References

[1]*IARC Monographs, 24*, 101-124, 1980

[2]Roenigk, H.H., Jr & Caro, W.A. (1981) Skin cancer in the PUVA-48 cooperative study. *J. Am. Acad. Dermatol., 4*, 319-324

[3]Stüttgen, G., Kentsch, V., Schalla, W. & Schneider, L. (1981) The risks of photochemotherapy (Ger.). *Z. Hautkr., 56*, 1379-1399

[4]Abel, E.A., Deneau, D.G., Farber, E.M., Price, N.M. & Hoppe, R.T. (1981) PUVA treatment of erythrodermic and plaque type mycosis fungoides. *J. Am. Acad. Dermatol., 4*, 423-429

[5]Stern, R., Zierler, S. & Parrish, J.A. (1982) Psoriasis and the risk of cancer. *J. invest. Dermatol., 78*, 147-149

[6]Frenk, E. (1983) Malignant melanoma in a patient with severe psoriasis treated by oral methoxsalen photochemotherapy. *Dermatologica, 167*, 152-154

[7]Marx, J.L., Auerbach, R., Possick, P., Myrow, R., Gladstein, A.H. & Kopf, A.W. (1983) Malignant melanoma *in situ* in two patients treated with psoralens and ultraviolet A. *J. Am. Acad. Dermatol., 9*, 904-911

[8]Stern, R.S., Laird, N., Melski, J., Parrish, J.A., Fitzpatrick, T.B. & Bleich, H.L. (1984) Cutaneous squamous-cell carcinoma in patients treated with PUVA. *New Engl. J. Med., 310*, 1156-1161

[9]Lassus, A., Reunala, T., Idänpää-Heikkilä, J., Juvakoski, T. & Salo, O. (1981) PUVA treatment and skin cancer: a follow-up study. *Acta dermatol. venereol., 61*, 141-145

[10]Fitzsimons, C.P., Long, J. & MacKie, R.M. (1983) Synergistic carcinogenic potential of methotrexate and PUVA in psoriasis. *Lancet, i*, 235-236

[11]Kripke, M.L., Morison, W.L. & Parrish, J.A. (1982) Induction and transplantation of murine skin cancers induced by methoxsalen plus ultraviolet (320-400 nm) radiation. *J. natl Cancer Inst., 68*, 685-690

[12]Nagayo, K., Way, B.H., Tran, R.M. & Song, P.S. (1983) Photocarcinogenicity of 8-methoxypsoralen and aflatoxin B_1 with longwave ultraviolet light. *Cancer Lett., 18*, 191-198

[13]Young, A.R., Magnus, I.A., Davies, A.C. & Smith, N.P. (1983) A comparison of the phototumorigenic potential of 8-MOP and 5-MOP in hairless albino mice exposed to solar simulated radiation. *Br. J. Dermatol., 108*, 507-518

[14]Gibbs, N.K., Young, A.R. & Magnus, I.A. (1985) A strain of hairless mouse susceptible to tumorigenesis by TPA alone: studies with 8-methoxypsoralen and solar simulated radiation. *Carcinogenesis, 6*, 797-799

[15]Hannuksela, M., Stenbäck, F. & Lahti, A. (1986) The carcinogenic properties of topical PUVA. A lifelong study in mice. *Arch. dermatol. Res., 278*, 347-351

[16]*IARC Monographs, Suppl. 6*, 380-385, 1987