NITROGEN MUSTARD (Group 2A)

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

No epidemiological study of nitrogen mustard as a single agent was available to the Working Group. However, it is the principal alkylating agent in leukaemogenic combination chemotherapy given for Hodgkin's disease, and other alkylating agents are clearly

leukaemogenic (see p. 254). The many case reports of cancer following topical application of nitrogen mustard cannot be interpreted with certainty because concurrent treatment with radiation and other potent drugs has been the rule rather than the exception, and occasionally such associations would be expected by chance.

Squamous-cell carcinomas of the skin following long-term topical application of nitrogen mustard alone or in combination with systemic therapy for mycosis fungoides[1-4] and psoriasis[5-7] have been observed to appear on skin surfaces not exposed to the sun.

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

Nitrogen mustard, administered mainly as the hydrochloride, has been tested for carcinogenicity in mice and rats by subcutaneous, intravenous and intraperitoneal administration and by skin painting. It produced mainly lung tumours and lymphomas in mice after subcutaneous, intravenous and intraperitoneal administration. Intravenous injection of nitrogen mustard to rats induced tumours in different organs[8]. Application by skin painting produced local tumours in mice in a dose-dependent manner[9,10].

C. Other relevant data

Nitrogen mustard is a bifunctional alkylating agent. In one study, it induced chromosomal aberrations in lymphocytes of treated patients[11].

Nitrogen mustard induced dominant lethal mutations and induced micronuclei in bone-marrow cells of mice exposed *in vivo* and alkylated DNA of ascites cells in experimental animals treated *in vivo*. It induced chromosomal aberrations, sister chromatid exchanges and unscheduled DNA synthesis in human cells *in vitro*. In rodent cells *in vitro*, it induced sister chromatid exchanges, chromosomal aberrations and DNA damage; studies on the induction of mutation were inconclusive. It transformed mouse C3H 10T1/2 cells. Nitrogen mustard induced aneuploidy and somatic mutation and recombination in *Drosophila*, chromosomal aberrations in plants, mitotic recombination and mutation in fungi, and mutation and DNA damage in bacteria[11].

References

[1]Du Vivier, A., Vonderheid, E.C., Van Scott, E.J. & Urbach, F. (1978) Mycosis fungoides, nitrogen mustard and skin cancer. *Br. J. Dermatol.*, *99*, 61-63

[2]Kravitz, P.H. & McDonald, C.J. (1978) Topical nitrogen mustard induced carcinogenesis. *Acta dermatol. venereol.*, *58*, 421-425

[3]Lee, L.A., Fritz, K.A., Golitz, L., Fritz, T.J. & Weston, W.L. (1982) Second cutaneous malignancies in patients with mycosis fungoides treated with topical nitrogen mustard. *J. Am. Acad. Dermatol.*, *7*, 590-598

[4]Abel, E.A., Sendagorta, E. & Hoppe, R.T. (1986) Cutaneous malignancies and metastatic squamous cell carcinoma following topical therapies for mycosis fungoides. *J. Am. Acad. Dermatol.*, *14*, 1029-1038

[5]Halprin, K.M., Comerford, M. & Taylor, J.R. (1982) Cancer in patients with psoriasis. *J. Am. Acad. Dermatol*, *7*, 633-638

[6]Ganor, S. (1983) Skin cancer in psoriatics treated with nitrogen mustard. *J. Am. Acad. Dermatol.*, *9*, 164

[7]Halprin, K.M., Comerford, M. & Taylor, J.R. (1982) Skin cancer in psoriatics treated with nitrogen mustard. *J. Am. Acad. Dermatol.*, *8*, 164-165

[8]*IARC Monographs*, *9*, 193-207, 1975

[9]Zackheim, H.S. & Smuckler, E.A. (1980) Tumorigenic effect of topical mechlorethamine, BCNU and CCNU in mice. *Experientia*, *36*, 1211-1212

[10]Epstein, J.H. (1984) Nitrogen mustard (mechlorethamine) and UVB photocarcinogenesis: a dose response effect. *J. invest. Dermatol.*, *83*, 320-322

[11]*IARC Monographs*, *Suppl. 6*, 421-424, 1987