RESERPINE (Group 3)

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

Sixteen case-control and three cohort studies on the relationship between reserpine and breast cancer were available to the Working Group[1-6]. Between and within studies, estimates of relative risk for different degrees of reserpine use varied from 0.6 to over 3. Many of the positive findings were not coherent with one another; and the studies considered to be most satisfactory methodologically showed little or no evidence of increased risk. However, a recent, large case-control study of breast screening participants showed that, although use of rauwolfia (reserpine) was not significantly associated with an overall increase in risk (odds ratio, 1.2; 95% confidence interval, 0.9-1.8), users for ten years or more had a risk ratio of 4.5 [2.3-11.6][7]. A study of prolactin levels in 15 women who had taken reserpine for five years or longer showed only 50% greater elevation of levels than in 15 women taking non-reserpine-containing medications and in 15 women taking no

hypertensive medication. Elevated prolactin levels have been postulated as the mechanism for increased breast cancer risk following reserpine use, and the authors postulated that the increase in prolactin observed would probably cause only small increases in breast cancer risk[8].

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

Reserpine was tested for carcinogenicity in three experiments in mice by oral administration; in two experiments, it induced malignant mammary tumours in females, and in one experiment it induced carcinomas of the seminal vesicles in males[1,9]. It was tested in four experiments in rats by oral administration; in two, it increased the incidence of phaeochromocytomas[1,9]. An increase in tumour incidence was observed after repeated subcutaneous injections to mice and rats[9].

When reserpine was administered orally either prior to and concurrently with or following treatment with 3-methylcholanthrene, it had a protective effect against the induction of mammary tumours in rats[10]. Concurrent subcutaneous administration of reserpine reduced mammary tumour multiplicity and increased the percentage of well-differentiated tumours induced in rats by *N*-methyl-*N*-nitrosourea given intravenously[11]; its intravenous administration decreased skin tumour growth in 3-methylcholanthrene-treated mice[12].

C. Other relevant data

No data were available on the genetic and related effects of reserpine in humans.

Reserpine did not induce dominant lethal mutations in mice *in vivo*. In human cells *in vitro*, it did not induce chromosomal aberrations or sister chromatid exchanges. It did not induce chromosomal aberrations in cultured rodent cells or unscheduled DNA synthesis in rat hepatocytes. Reserpine was not mutagenic to bacteria[13].

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