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Letter to the editor

Tumour induction in mice following exposure to aristolochic acid*

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Abstract. After treatment for 3 weeks with aristolochic acid (AA) in daily doses of 5.0 mg/kg mice were kept under observation for approximately 1 year. During this period papillomatous changes occurred in the forestomach. At a later stage, squamous cell carcinomas were observed in all the animals. In one case, an adenocarcinoma was found in the glandular stomach. In addition, malignant lymphomas were found, as well as adenomas of the kidneys, carcinomas of the lungs, and haemangiomas of the uteri.

Key words: Aristolochic acid – Toxicity – Experimental carcinogenesis – Mouse

Previous studies have demonstrated the carcinogenic action of aristolochic acid (AA) in rats (Mengs et al. 1982; Mengs 1983). In these studies AA was orally administered over a period of 3–6 months in doses ranging from 0.1 to 10.0 mg/kg. As a result of this treatment, the rats developed metastasizing squamous cell carcinomas of the forestomach as well as benign and malignant tumours of the kidneys and of the urinary tract. In view of these findings, it was of interest whether AA could also induce tumours in other species.

As far as the study design is concerned, the experiment described here does not claim to be one of the long-term carcinogenesis studies which are routinely performed in toxicology. Instead, its aim was simply to gather evidence of any possible carcinogenic effect, caused by AA in mice, by means of a toxicological screening involving fewer animals. For this purpose 39 female mice (strain: NMRI) were given AA by gavage in daily doses of 5.0 mg/kg for 3 weeks. The mice were kept under conventional laboratory conditions and remained under observation until the 56th week of the experiment. A further 11 animals served as controls; they were given the solvent only. The mice were dissected at various stages (Table 1) and histological examinations made of all the organs, and of all the tumours which had been diagnosed macroscopically.

The results of the study are shown in Table 1. Following oral administration of 5.0 mg AA/kg for a period of 3 weeks, histological examinations of the forestomach revealed low-grade regenerative hyperplasia of squamous epithelium with hyperkeratosis. The changes observed, however, receded during the following 6 weeks; no AA was administered during this period. At the 18 and 26 week stages low to middle-grade papillomatosis, showing no signs of malignancy, was observed in the forestomach of all the mice. Investigations conducted at 37 and 48 weeks revealed squamous cell carcinoma in one in every five mice and by the end of the experiment, after 56 weeks, carcinomas had formed in all of the mice. In addition to

Table 1. Tumour incidence within 56 weeks in female mice following oral administration of 5.0 mg AA/kg over a period of 3 weeks

Time of sacrifice (weeks after beginning of treatment)	*n*	Forestomach		Gl. stomach Carcinoma	Kidneys Adenoma	Lungs Carcinoma	Uteri Haemangioma	Malignant lymphoma
		Papilloma	Carcinoma					
3[a]	10[b]	0[c]	0	0	0	0	0	0
9	4	0	0	0	0	0	0	0
18	4	4	0	0	0	0	0	0
26	3	3	0	0	1	0	0	1
37	5	4	1	1	1	2	0	2
48	5	4	1	0	3	3	0	3
56	8	0	8	0	6	8	3	4

No tumours were detected in the control mice ($n = 11$) after 56 weeks
[a] End of treatment period
[b] Total number of mice
[c] Number of mice with tumours

* This is a short report on the experiments conducted. All results are available from the author on request

the papillomatosis of the forestomach, an adenocarcinoma of the glandular stomach was observed after 37 weeks in one mouse. Further neoplastic changes were manifested progressively from the 26th week onwards: these consisted of cystic papillary adenomas in the renal cortex, malignant lymphomas, alveologenic carcinomas in the lungs and haemangiomas in the uteri. No neoplastic changes were detected in the 11 control animals in either histological or macroscopic examinations.

The results justify the conclusion that AA exerts a carcinogenic effect of similar strength in two species, mice and rats.

References

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