COMMUNICATION

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FORESTOMACH TUMORS INDUCED BY ORALLY ADMINISTERED EPICHLOROHYDRIN IN MALE WISTAR RATS*1

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Epichlorohydrin is an epoxide compound which is widely used in various industrial fields. The mutagenic action of this compound was first demonstrated in fruit flies, and it has since been studied by several investigators. The carcinogenic activity of epichlorohydrin was tested in mice, but the findings were inconclusive. In the present experiment, the carcinogenic activity of epichlorohydrin was tested in rats, and the chemical was found to induce forestomach hyperplasias, papillomas, and carcinomas.

Seventy-two, 6-week-old male outbred Wistar rats (Kiwa Animal Farm, Wakayama), weighing approximately 160 g each, were used. Epichlorohydrin (Nakarai Chemicals, Ltd., Kyoto) was dissolved in drinking water freshly every day and placed in a bottle covered with black tape to protect it from the light. Four groups of rats were treated: Group 1 received 0 ppm (control group); group 2, 375 ppm; group 3, 750 ppm; and group 4, 1500 ppm. However, epichlorohydrin administration had to be stopped intermittently due to the poor condition of rats, as shown in Fig. 1. The rats were housed in wire cages in an air-conditioned room at 24° and were given Oriental MF diet (Oriental Yeast Ind., Tokyo) and water containing epichlorohydrin ad libitum. The rats were weighed once a week and the daily intake

![Experimental period (weeks)]

Fig. 1. Experimental design

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<th>Group No.</th>
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Water without epichlorohydrin
375 ppm epichlorohydrin in drinking water
750 ppm epichlorohydrin in drinking water
1500 ppm epichlorohydrin in drinking water

Table I. Number of Forestomach Tumors and Tumor Incidence in Rats Given Epichlorohydrin

| Group No. | No. of rats Initial Effective | No. of tumors in forestomach per rat Tumor size (mm) Total 5< 5<2< 2> | Histological findings on squamous epithelium (%) Hyperplasia Papilloma Carcinoma |
|-----------|-------------------------------|---------------------------------------------------------------|---------------------------------|---------------------------------|------------------|-----------------|
| 1         | 18                            | 10                                                             | 0                               | 0                               | 0                | 0               | 0               |
| 2         | 18                            | 9                                                              | 5.6±8.4                         | 0                               | 0.1±0.3           | 5.4±8.2         | 7 (77.8)        |
| 3         | 18                            | 10                                                             | 9.9±12.8                        | 0.4±0.5                         | 1.2±1.2           | 8.3±12.0        | 9 (90.0) 1 (10.0) |
| 4         | 18                            | 12                                                             | 3.2±24.0                        | 0.8±1.0                         | 4.4±3.6           | 27.6±21.3       | 12 (100.0) 7 (58.3) 2 (16.7) |

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CARCINOGENICITY OF EPICHLOROHYDRIN

of water containing epichlorohydrin was measured. The initial and effective numbers of rats in each group are shown in Table I. All rats were fasted for 17 hr and killed with ether at 81 weeks after the beginning of the experiment, and a complete autopsy was performed. The tumors which had developed in the forestomach were counted after they had been fixed by instillation of 10% buffered formalin into the lumen of the stomach. Other tissues were also fixed in 10% buffered formalin. All tissues were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Although the rats which died during the experimental period were examined histologically, the findings were excluded from the present results because of postmortem changes.

The total intakes of epichlorohydrin per rat throughout the experimental period were 0, 5.0, 8.9, and 15.1 g in groups 1 to 4, respectively. The final body weights were approximately 7.7, 22.4, and 44.9% less in rats from groups 2, 3, and 4, respectively, than in rats from group 1. Macroscopically, multiple forestomach tumors appeared as whitish lesions from the serosal side and as elevated lesions from the mucosal side, occasionally with papillary structure. The number of forestomach tumors and their incidence are shown in Table I. The total number of tumors increased dose-dependently, and tumors measuring more than 5 mm in diameter were observed in rats from groups 3 and 4. All tumors counted were confirmed microscopically to be squamous and basal hyperplasias, squamous cell papillomas, or carcinomas. The hyperplasias were induced dose-dependently and their incidence reached 100% in rats from group 4. Squamous cell papillomas and carcinomas were seen in rats from groups 3 and 4. The carcinomas were seen in 1 of 10 (10.0%) rats from group 3 and in 2 of 12 (16.7%) rats from group 4. However, no distant metastases were found in those rats. At other sites, interstitial cell tumors of the testis were seen in 2 rats from group 1, 2 from group 2, 1 from group 3, and 3 from group 4, and squamous cell carcinomas of the oral cavity were seen in 2 of 12 (16.7%) rats from group 4.

The carcinogenic activity of epichlorohydrin was tested in mice by skin application, and by subcutaneous and intraperitoneal administrations, but no studies have been undertaken on oral administration. Sarcomas were induced at the injection site in 2 of 50 female ICR/Ha strain mice given a subcutaneous injection of 1 mg of epichlorohydrin 300 days after the beginning of the experiment, but no carcinogenic activity was observed following skin application or intraperitoneal injection. A further study by Van Durren et al. indicated that this compound, while not a carcinogen for mouse skin, was active as an initiator. In the present experiment, hyperplasias and papillomas were induced dose-dependently. The low incidence of carcinomas may be due to the experimental period selected. Testis tumors may have been spontaneous but oral cavity tumors may have been induced. The present results suggest that orally administered epichlorohydrin is directly carcinogenic in rats. However, further tests are required in different species of laboratory animals.

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REFERENCES