The Chronic Toxicity of Hexamethylphosphoramide in Rats

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Several years ago we studied the acute and subacute toxicity of hexamethylphosphoramide (HMPA) (Kimbrough and Gaines 1966). HMPA had been suggested as a chemosterilant for houseflies (Chang et al. 1964). In our studies atrophy of the testes was observed in adult male rats fed 750 ppm (80-40 mg/kg/day) in the diet for 61-103 days. A high incidence of pneumonia was also found in the poisoned animals. This finding was further investigated (Kimbrough, R.D. and Sedlak, V.A., 1968). Corresponding observations were made by Jackson et al. (1966, 1969). Shott et al. (1971) reported a reproduction study where 2 and 10 mg/kg HMPA were given to male and female rats daily for 169 days. Reproduction was not affected but a high incidence of murine pneumonia was observed. Following our preliminary study (Kimbrough and Gaines 1966) we investigated the toxicity of HMPA in a long term study in rats with lower dietary levels. It is the purpose of this communication to report very briefly the main findings of that study.

In the study groups of 15 male conventional 6-week-old Sherman strain rats were fed HMPA in their diet at the rate of 6.25, 3.12, 1.56 and 0.78 mg/kg/day for 2 years. The diets were adjusted to give these dosage levels by frequent measurements of the food consumption. The controls consisted of two groups of 15 animals which were fed plain chow. The study was done in two parts. Each part consisted of two groups of treated animals and a group of controls as indicated in Table 1. The incidence of the leading abnormal findings made by microscopic examination are given in Table 1. Autopsy tissues were fixed in 10% buffered formalin and stained with hematoxylin and eosin.

After our Sherman strain rats were more than a year old they began to show evidence of periarteritis in different organs. The incidence of this abnormality was similar in the treated and in the control animals and was therefore not listed in the table. The incidence of lung disease primarily related to an inflammatory process was generally higher in the exposed animals than in the controls Table 1). Animals were considered to have lung disease when microscopic examination showed evidence of bronchitis, peri-bronchitis, bronchietases, bronchopheumonia, abcess formation or fibrosis. Several of these changes were usually observed in the same lung. Occasionally tumors were encountered which were not included in the tabulation of the lung disease. The tumor incidence was low and the same in all groups studied. Most of the tumors encountered were either reticulum cell or lymphosarcoma of the lungs. The incidence of kidney disease which consisted predominantly of chronic pyelone-

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phritis varied in the different groups but did not follow any particular pattern.

The rats receiving 6.25 mg/kg and a group of 15 controls were also tested for their ability to reproduce. Our results indicated that reproduction was not affected at these low dietary levels which is in agreement with the results reported by Shott et al. (1971). The rats were mated 6 and 12 months after onset of exposure to the HMPA containing diets, when they were 7 and 13 months old. The testicular atrophy observed microscopically occurred late in life and was the result of age and debilitating disease. In this study conventional rats were used and the high incidence of pneumonia in the treated groups is probably due to a potentiating effect of HMPA on Mycoplasma pulmonis infection (Overcash et al. 1972).

TABLE 1

Death Rate and Organopathology of Male Rats Fed HMPA for 2 years

No. of Rats Studied Microscopically	Dosage Level HMPA mg/kg	No. Rats to die	Malignant tumors	Lung Disease	Chronic Kidney Disease	Testicular Atrophy
14	6.25	9	2	12	12	6
15	3.12	12	-	12	11	2
15	0	9	2	8	9	4
15	1.56	10	2	11	12	10
15	0.78	7	1	8	14	4
15	0	10	2	4	13	3

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