Toxicity of 2,3,7,8-Tetrachlorodibenzo-p-diozin for Rhesus Monkeys: Brief Report[1]

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ALLEN and CARSTENS (1967) described pathologic changes in rhesus monkeys fed "toxic fat," a poultry feed component which was later found to contain chlorinated dibenzo-p-dioxins, 64% of which were the tetrachloro homolog (NORBACK and ALLEN 1973). The amount of dioxins ingested by the monkeys was not estimated, and the crude industrial fat could have contained other unidentified toxic chemicals.

This is a report of pilot experiments with two rhesus monkeys, in which the same pathologic changes found by ALLEN resulted from dietary intake of pure 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Furthermore, the lethal dose of TCDD for these animals was found to be only a few μg/kg.

METHODS

Individually caged one-year-old male rhesus monkeys, weighing 1.8 kg each, were fed ad libitum cubes of a moist diet cake made from ground Purina monkey chow, vitamin and mineral supplements, bananas and water, modified by the addition of TCDD (courtesy of Dow Chemical Company) in acetone-corn oil to a final concentration of 2 or 20 μg/kg (2 or 20 ppb). Complete autopsies were performed immediately after spontaneous death.

RESULTS AND DISCUSSION

The monkey fed the 20 ppb diet was active and eating well for two days. On the third day, its activity and appetite decreased and on the fifth day it stopped eating altogether. Vomit was found in the cage pan on the eighth to tenth days. Regular monkey chow was offered on the tenth day, but the animal became progressively more lethargic and died on the twelfth day, with a 30% weight loss.

Activity of the monkey given the 2 ppb diet decreased after ten days, and by 28 days the eyelids were red. The monkey continued to eat normally. At 58 days the eyelids were swollen and the face was edematous. Neither acne nor hair loss was apparent. At 61 days, a full thickness biopsy of the fundus of the stomach was obtained at laparotomy, and a soft postoperative diet (no TCDD) was provided thereafter. The monkey seemed to recover uneventfully from the surgery, but died suddenly 15 days later. Total weight

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loss was 33%.

Paraffin sections of the stomach biopsy showed complete mucous metaplasia of the fundic mucosa with high mitotic activity and extension of glands into the submucosa. The principal autopsy findings in both animals were cachexia, mucous metaplasia, hyperplasia and ulceration of the gastric mucosa, squamous metaplasia of sebaceous glands, and atrophy of the thymus. These changes were obvious after only 12 days at the higher dose level.

These pathologic findings are the same as those reported by ALLEN and CARSTENS (1967) in monkeys fed toxic fat and corroborate their conclusion that the disease in these monkeys was indeed caused by the contaminating TCDD. The same gastric lesions have also been seen in monkeys poisoned with polychlorinated biphenyls (PCBs) (ALLEN and NORBACK 1972), but not in other laboratory animals given either TCDD or PCBs.

An upper limit for the cumulative dose of TCDD may be computed from the normal daily intake of 50 gm diet/kg for young rhesus monkeys. At the higher dose level, this would be 10 μg TCDD/kg over 10 days, although the actual amount was considerably less because of the profound anorexia. The second animal ate at most a total of 6 μg TCDD/kg in 61 days.

The acute oral LD_{50}'s for TCDD differ widely among species: 0.6 μg/kg for male guinea pigs, 45 μg/kg for rats and over 100 μg/kg for rabbits and dogs (SCHWETZ et al. 1973). The effects of chronic oral intake are cumulative. KOCIBA et al. (1976) found a 30% mortality in rats of both sexes, given 1 μg/kg daily, five days a week, for 13 weeks; no deaths occurred at 0.1 μg/kg on the same schedule. VOS et al. (1974) reported a mortality of 18% in mice given 25 μg/kg orally once a week for six weeks; there was no mortality at 5 μg/kg on this schedule.

Observations on two monkeys scarcely permit statistical calculation, but in view of the increasingly limited availability and escalating expense of rhesus monkeys, the destruction of enough animals to provide an accurate numerical estimate of toxicity is probably unwarranted. Nevertheless, these pilot tests do indicate that young male rhesus monkeys are among the most susceptible of laboratory animals; daily oral intake of less than 1 μg/kg is lethal.

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