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MONSANTO BIOHAZARDS COMMITTEE

Minutes of a Meeting

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Dr. Timothy Long, a new toxicology staff member, then reviewed the data on the toxicology of dioxins. He pointing out that the dioxin ring system can take up one to eight chlorine-atoms/molecule which can result in seventy-five positional isomers. These isomers are of widely varying toxicity in different animal species. The most potent is 2,3,7,8-tetrachlorodibenzo-p-dioxin, sometimes designated as TCDD, even though there are sixteen isomers of the tetrachloro derivative. The toxicity of this family of compounds depends upon the dose, the degree of chlorination, the positional isomer, the length of time of exposure and the species. Species vary greatly in sensitivity to acute toxicity of dioxins. For example, a guinea pig has a LD₅₀ of 0.6 microgram per kilogram whereas the hamster requires 10,000 times more for its LD₅₀ or 6,000 microgram per kilogram. Other common rodents like rats and rabbits have LD₅₀'s in the range of 10-100 microgram per kilogram. No one is sure where man stands in this spectrum of animal sensitivity. Acute exposure to dioxins in some animals, including man, causes chloracne to appear within a few weeks. It has been reported in man, without direct evidence of cause and effect, that neuromuscular changes, porphyria and hypertriglyceridemia follow acute exposure to dioxins. It is generally believed that dioxins, like other halogenated hydrocarbons produce a hyperplasia of hepatocytes, hepatomegaly, and, in some animals, hepatic necrosis. The cause of death from the acute toxicity of dioxins, however, is not known.

In chronic toxicity studies at lower doses of TCDD failure of reproduction and carcinogenesis have been observed. TCDD at doses of the order of 0.1 microgram per kilogram per day is a teratogen in female mice and rats. Dioxins, including 2,3,7,8-tetrachlorodibenzo-p-dioxin, are probably not mutagens. In general the short-term genotoxic tests (like the Ames test) are negative, the in vivo dominant lethal test is negative and tests of chromosomal alteration are equivocal. Carcinogenicity tests in two-year lifetime studies in rats and mice have shown that tumors of the lung, liver, tongue and nasal passages can occur with doses of about 0.1 microgram per kilogram per day with a no effect level at 1 nanogram per kilogram per day. Mixtures of hexachlorodibenzo-p-dioxins are also carcinogenic in male and female mice and in female rats. Studies by Pitot and his colleagues (Cancer Research 40, 3616-3620, 1980) have shown that the tetrachlorodibenzo-p-dioxin has promoter activity for dimethyl-nitrosamine induced hepatomas in rats. TCDD might be a particularly effective promoter because it appears to react with the estrogen receptor and thus be targeted to the nucleus where it can exert its "chlorinated hydrocarbon" effect at a specific locus.