loss are also observed. Major organs to be affected are the liver, blood forming organs and the reticulo-endothelial system. Progressive weight loss, the first clinical sign of toxicity in the monkey, may be accompanied by alopecia, facial edema and a dry, scaly dermatitis over the rest of the body.

The metabolism of TCDD in man is unknown, and for the present there is only limited information available on the metabolic pathways and metabolites that may occur in other mammals. TCDD is distributed equally among the fat and liver of mammals, to a lesser extent in the kidneys, and is eliminated via the feces. Samples of fat from beef cattle and samples of milk from cows that had grazed on 2,4,5-T-treated pasture or rangeland, in addition to human milk from an area where 2,4,5-T herbicides were used repeatedly over a period of twenty years, had small to undetectable (not more than 10 ppt) amounts of TCDD.

No clearly defined mutagenic effect has been observed in vitro with TCDD. TCDD does induce genetic changes by the Ames test with S typhimurium and E coli but not with repair-defective strains; there is no evidence (from dominant lethal and cytogenetic evaluations in rodents) that such changes occur in whole animals.

Of perhaps more relevance to man are the in vitro studies on mammalian cells – i.e., HeLa; Balb-3T3, normal mouse fibroblasts; SV101, virus (SV40) – transformed 3T3 mouse fibroblasts; human foreskin fibroblasts; and normal human lymphocytes. No significant growth inhibition in the cell cultures nor discernible ultrastructural changes have been observed by electron microscopy.

The teratogenicity and fetotoxicity of TCDD were discovered in 1969, in the course of a study on the biological activity of 2,4,5-T. The sample being used was later found to be contaminated with TCDD. The incidence of cleft palate was greater in two particular mouse strains (C57BL/6 and AKR), while the C57BL/6 mouse and the rat developed a higher incidence of cystic kidney. All doses given the rat led to gastrointestinal hemorrhage in the fetus. The increased ratio of fetal liver to body weight in the mouse suggested that TCDD was fetotoxic in this particular species.

A majority of studies using high doses of 2,4,5-T with 0.1 ppm of TCDD or less showed cleft palate in mice, but no other species, and embryotoxicity in the mouse, rat, hamster, sheep, monkey and rabbit. There is no scientific evidence that 2,4-D, 2,4,5-T or TCDD has caused reproductive difficulties or hazards in the human. No conclusive evidence is yet available that phenoxy herbicides or TCDD are mutagenic or teratogenic in man.

TCDD can induce cancer or serve as a cancer promoter in some strains of rats and mice. In contrast to some other chemical carcinogens, the carcinogenicity is always accompanied by considerable systemic toxicity.

From an environmental view, TCDD breaks down rapidly on leaves of plants, in water and on the surface of soil, especially through the action of sunlight. In soil it generally has a half-life of about 230 days; some soil microorganisms can degrade it, especially if other chlorinated hydrocarbons are present.

EXPERIENCE IN MAN

One of the most extensive human experiences with the adverse effects of TCDD in man involves the residents of Seveso, Italy. In July of 1976, TCDD was accidentally released from the ICMESA* trichlorophenol synthesis plant when a safety disk in a steam-heated reactor vessel ruptured. The plume of reactor contents, including TCDD, rose 160 feet above the factory and fell in a cone-shaped pattern about a mile long and a half-mile wide. This is the largest single population to have been exposed to the compound. Over 37,000 persons were potentially exposed to varying doses.

Two years after the incident occurred, the acute and mid-term health effects were assessed; the mild chloracne, which occurred mainly in a small group of children, healed quickly. Subclinical peripheral nerve impairment was reported; there was also some liver involvement, but without apparent functional disorder. Neither immunoresponse nor susceptibility to infectious diseases was altered.

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*Industrie Chimiche Meda Societa Anonima

The most recent progress report on the long-term epidemiologic survey of the residents of the Seveso area emphasizes the preliminary nature of their findings and reiterates the conclusions of prior investigators. Except for the skin, no organs or body functions were impaired. No derangement of gestation, no fetal lethality and loss, no gross malformations, no growth retardation at term and no cytogenetic abnormalities have yet occurred.

The first of several accidental releases of TCDD and other dioxins, attending the manufacture of 2,4,5-trichlorophenol (TCP) or 2,4,5-T occurred in 1949 in the United States. At least 11 other industrial accidents or exposure incidents have occurred since then, both here and abroad. To date, an estimated 579 workers are known to have been exposed, including 156 employees in the ICMESA plant at Seveso.

CURRENT STUDIES

There are now a number of studies underway by agencies of the U. S. government and industry, which may resolve questions on the kinds and extent of human damage from exposure to low levels of TCDD:

Through its Department of Environmental and Drug-Induced Pathology, the Armed Forces Institute of Pathology (AFIP) is examining biopsy and autopsy tissue of all Vietnam veterans. To date, only 152 cases have been assessed: the dominant diseases are epidermal inclusion cysts and chronic, non-specific dermatitis. If any malignancies were to have been induced by TCDD, they should be appearing by now, yet there have been no unusual morphological features nor clustering of tumors by diagnosis or site as to implicate Agent Orange.

A soft-tissue sarcoma study also has been proposed that will be conducted jointly by the Armed Forces Institute of Pathology and the National Cancer Institute.

The Air Force, through Project Ranch Hand, will administer and examine the 1,200 personnel who were involved in the actual handling and spraying of Agent Orange. They, and the control population of 20,000, are to be followed over the next twenty years.

The University of California, Los Angeles, was awarded a contract by the Veterans Administration for the design of an epidemiologic study of Vietnam veterans.

Approximately 45,000 Vietnam veterans who expressed concern about the hazards of Agent Orange have been examined by the VA; data on 25,000 of these men have been placed in a special Agent Orange Registry, which may serve later to identify them and to provide medical information as well as indications of health trends over the long term.

The Chloracne Task Force was established to sift out those cases of dermatitis that either resemble or are truly chloracne. Cases of the former type will be reexamined by dermatologists who have an expert knowledge of the disease. Thus far, there are only 700 cases of "skin conditions" out of the total of 3,500 filed claims for damage from Agent Orange.

RECOMMENDATIONS:

The Council on Scientific Affairs recommends that:

1. The above studies on exposed, or allegedly exposed, persons continue to be supported and, if feasible, enlarged to include the cooperative engagement of all internationally known exposure data, as recommended by the International Agency for Research on Cancer (IARC).

2. All physicians be alerted through AMA publications to the classical signs of chloracne and the possible signs and adverse effects of TCDD exposure. They should be encouraged to enlist in the present efforts to identify and treat those persons who have had serious exposures to TCDD, and to cooperate in the collection of vital information that is needed for the ongoing human epidemiologic studies.