2,3,7,8-TETRACHLORODIBENZO-*para*-DIOXIN (TCDD) (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

The epidemiological studies and case reports considered with regard to producers and users of 2,4,5-trichlorophenol and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (see also summaries on chlorophenols and chlorophenoxy herbicides, pp. 154 and 156) also relate to TCDD exposure, since those products may contain TCDD as an impurity. Only studies of particular relevance to TCDD exposure are considered here.

Aggregation of six relatively small cohorts[1-6] shows 37 deaths from cancer, with 33.3 expected, among 956 men likely to have been exposed to TCDD during the manufacture or use of 2,4,5-trichlorophenol and/or 2,4,5-T. The total number of deaths was 135, with 157.3 expected. Two of the deaths were from Hodgkin's lymphoma and two from soft-tissue sarcoma. Five more cases of soft-tissue sarcoma have been reported in men with potential exposure to TCDD during the manufacture of 2,4,5-trichlorophenol or 2,4,5-T[7-9]. A histological review and a reassessment of the exposure in seven of the cases in these various reports indicated that only five were actually soft-tissue sarcomas, and that only two of the cases had had definite exposure to 2,4,5-trichlorophenol or 2,4,5-T; the population background for these two cases was assumed to be fewer than 1000 workers[10].

Three other small cohorts with potential exposure to TCDD have been studied. In one, there were two non-Hodgkin's lymphomas, with 0.3 expected, in 158 individuals with chloracne[11], whereas another, similar group of 79 individuals with chloracne had no cancer[12]. In the third group of 55 individuals with chloracne, there were two lung cancers[13]. A cohort study of 2189 men involved in the manufacture of 2,4,5-trichlorophenol and 2,4,5-T showed no excess of deaths from all cancers (61 observed, 63.5 expected; standardized mortality ratio [SMR], 96), but five non-Hodgkin's lymphomas were seen (SMR, 238; 95% confidence interval, 77-556), although there was no dose-response relationship with TCDD exposure[14]. In the USA, 14 cases of soft-tissue sarcoma among the

employees of a large chemical company showed no association with potential TCDD exposure in reference to nine controls per case from the same company[15].

In Seveso, Italy, 15 cases of soft-tissue sarcoma were observed in polluted and 44 cases in unpolluted areas, resulting in rates of 5.7 and 3.2 per 100 000 inhabitants, respectively. However, the rate in the polluted area was high even before the accident, possibly reflecting earlier emissions[16]. Three cases of soft-tissue sarcoma have been reported in Viet Nam veterans who had been in contact with TCDD-containing defoliants[17].

In view of these findings and with regard to chlorophenoxy herbicides, it may be noted that some excesses of soft-tissue sarcoma, nasal cancer and non-Hodgkin's lymphoma, respectively, have been observed in two cohort and one case-control studies, in which no substantial TCDD exposure was likely to have occurred[18-20]. No association between soft-tissue sarcoma and military service in Viet Nam could be demonstrated in the published studies in this respect, despite potential exposure to the heavily TCDD-contaminated chlorophenoxy herbicides that were used[21,22].

B. Evidence for carcinogenicity to animals (*sufficient*)

TCDD was tested in several studies in mice and rats by oral administration and in mice by skin application, but no evaluation of its carcinogenicity could be made[23]. In subsequent, more complete reports and in other studies in mice, oral administration of TCDD alone or, in one study, in combination with 2,4,5-trichlorophenoxyethanol increased the incidence of liver tumours[24-26] and, in one study, produced thyroid tumours in female mice[26]. In rats, oral administration of TCDD increased the incidences of a variety of tumours, including hepatocellular carcinomas, squamous-cell carcinomas of the lung and tumours of the hard palate/nasal turbinates, tongue and thyroid[26-29]. Application of TCDD to the skin of mice was associated with an increased incidence of fibrosarcomas in the integument in females[30].

Intraperitoneal administration of TCDD to infant mice induced thymic lymphomas and liver tumours. Oral administration of TCDD to infant mice increased the incidence of liver tumours[31].

In female rats, TCDD given subcutaneously enhanced the incidences of foci of altered hepatocytes and of hepatocellular carcinomas induced by *N*-nitrosodiethylamine[32]. TCDD did not increase skin carcinogenesis when applied to the skin of mice before administration of polycyclic aromatic hydrocarbons[33,34] or after administration of 7,12-dimethylbenz[*a*]-anthracene[35], but it enhanced the incidence of subcutaneous tumours induced by 3-methyl-cholanthrene[36].

C. Other relevant data

Conflicting results have been reported from studies of chromosomal aberrations in peripheral blood lymphocytes of individuals exposed to TCDD occupationally or as a result of industrial accidents. No convincing evidence for the induction of chromosomal aberrations was obtained in a study of abortuses of women accidentally exposed to TCDD[37].

TCDD did not induce dominant lethal mutations, chromosomal aberrations, micronuclei or sister chromatid exchanges in rodents treated *in vivo*. It did not induce transformation of mouse C3H 10T1/2 cells *in vitro* but did enhance transformation induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. In another study using the same cell type, it did not inhibit intercellular communication. It was mutagenic to mouse lymphoma cells but did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro*. TCDD was not mutagenic to bacteria[37].

References

[1]Axelson, O., Sundell, L., Andersson, K., Edling, C., Hogstedt, C. & Kling, H. (1980) Herbicide exposure and tumor mortality. An updated epidemiologic investigation on Swedish railroad workers. *Scand. J. Work Environ. Health, 6*, 73-79

[2]Cook, R.R., Townsend, J.C., Ott, M.G. & Silverstein, L.G. (1980) Mortality experience of employees exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). *J. occup. Med., 22*, 530-532

[3]Hogstedt, C. & Westerlund, B. (1980) Cohort studies of cause of death of forest workers with and without exposure to phenoxy acid preparations (Swed.). *Läkartidningen, 77*, 1828-1831

[4]Ott, M.G., Holder, B.B. & Olson, R.D. (1980) A mortality analysis of employees engaged in the manufacture of 2,4,5-trichlorophenoxyacetic acid. *J. occup. Med., 22*, 47-50

[5]Thiess, A.M., Frentzel-Beyme, R. & Link, R. (1982) Mortality study of persons exposed to dioxin in a trichlorophenol-process accident that occurred in the BASF AG on November 17, 1953. *Am. J. ind. Med., 3*, 179-189

[6]Zack, J.A. & Suskind, R.R. (1980) The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident. *J. occup. Med., 22*, 11-14

[7]Cook, R.R. (1981) Dioxin, chloracne, and soft-tissue sarcoma. *Lancet, i*, 618-619

[8]Moses, M. & Selikoff, I.J. (1981) Soft tissue sarcomas, phenoxy herbicides, and chlorinated phenols. *Lancet, i*, 1370

[9]Johnson, F.E., Kugler, M.A. & Brown, S.M. (1981) Soft tissue sarcomas and chlorinated phenols. *Lancet, ii*, 40

[10]Fingerhut, M.A., Halperin, W.E., Honchar, P.A., Smith, A.B., Groth, D.H. & Russell, W.O. (1984) An evaluation of reports of dioxin exposure and soft tissue sarcoma pathology among chemical workers in the United States. *Scand. J. Work Environ. Health, 10*, 299-303

[11]Bishop, C.M. & Jones, A.H. (1981) Non-Hodgkin's lymphoma of the scalp in workers exposed to dioxins. *Lancet, ii*, 369

[12]May, G. (1982) Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure. *Br. J. ind. Med., 39*, 128-135

[13]Pazderova-Vejlupková, J., Némcova, M., Pícková, J., Jirásek, L. & Lukáš, E. (1981) The development and prognosis of chronic intoxication by tetrachlorodibenzo-*p*-dioxin in men. *Arch. environ. Health, 36*, 5-11

[14]Cook, R.R., Bond, G.G., Olson, R.A., Ott, M.G. & Gondek, M.R. (1986) Evaluation of the mortality experience of workers exposed to the chlorinated dioxins. *Chemosphere, 15*, 1769-1776

[15]Sobel, W., Bond, G.G., Skowronski, B.J., Brownson, P.J. & Cook, R.R. (1986) Soft-tissue sarcoma: case-control study. *J. occup. Med., 28*, 804, 806, 808

[16]Puntoni, R., Merlo, F., Fini, A., Meazza, L. & Santi, L. (1986) Soft tissue sarcomas in Seveso. *Lancet, ii*, 525

[17]Sarma, P.R. & Jacobs, J. (1982) Thoracic soft-tissue sarcoma in Vietnam veterans exposed to Agent Orange. *New Engl. J. Med., 306*, 1109

[18]Lynge, E. (1985) A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. *Br. J. Cancer, 52*, 259-270

[19]Coggon, D., Pannett, B., Winter, P.D., Acheson, E.D. & Bonsall, J. (1986) Mortality of workers exposed to 2 methyl-4 chlorophenoxyacetic acid. *Scand. J. Work Environ. Health, 12*, 448-454

[20]Riihimäki, V., Asp, S. Pukkala, E. & Hernberg, S. (1983) Mortality and cancer morbidity among chlorinated phenoxyacid applicators in Finland. *Chemosphere, 12*, 779-784

[21]Greenwald, P., Kovasznay, B., Collins, D.N. & Therriault, G. (1984) Sarcomas of soft tissues after Vietnam service. *J. natl Cancer Inst., 73*, 1107-1109

[22]Kang, H.K., Weatherbee, L., Breslin, P.P., Lee, Y. & Shepard, B.M. (1986) Soft tissue sarcomas and military service in Vietnam: a case comparison group analysis of hospital patients. *J. occup. Med., 28*, 1215-1218

[23]*IARC Monographs, 15*, 41-102, 1977

[24]Tóth, K., Sugár, J., Somfai-Relle, S. & Bence, J. (1978) Carcinogenic bioassay of the herbicide, 2,4,5-trichlorophenoxyethanol (TCPE) with different 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin) content in Swiss mice. *Progr. Biochem. Pharmacol., 14*, 82-93

[25]Tóth, K., Somfai-Relle, S., Sugár, J. & Bence, J. (1979) Carcinogenicity testing of herbicide 2,4,5-trichlorophenoxyethanol containing dioxin and of pure dioxin in Swiss mice. *Nature, 278*, 548-549

[26]National Toxicology Program (1982) *Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Osborne-Mendel Rats and B6C3F$_1$ Mice (Gavage Study) (Tech. Rep. Ser. No. 209; NIH Publ. No. 82-1765)*, Bethesda, MD

[27]Van Miller, J.P., Lalich, J.J. & Allen, J.R. (1977) Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Chemosphere, 6*, 537-544

[28]Kociba, R.J., Keyes, D.G., Beyer, J.E., Carreon, R.M., Wade, C.E., Dittenber, D.A., Kalnins, R.P., Frauson, L.E., Park, C.N., Barnard, S.D., Hummel, R.A. & Humiston, C.G. (1978) Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in rats. *Toxicol. appl. Pharmacol., 46*, 279-303

[29]Kociba, R.J., Keyes, D.G., Beyer, J.E. & Carreon, R.M. (1979) *Toxicologic studies of 2,3,7,8-tetrachlorobenzo-p-dioxin (TCDD) in rats.* In: Deichmann, W.B., ed., *Toxicology and Occupational Medicine*, New York, Elsevier/North-Holland, pp. 281-287

[30]National Toxicology Program (1982) *Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Swiss-Webster Mice (Dermal Study) (Tech. Rep. Ser. No. 201; NIH Publ. No. 82-1757)*, Bethesda, MD

[31]Della Porta, G., Dragani, T.A. & Sozzi, G. (1987) Carcinogenic effects of infantile and long-term 2,3,7,8-tetrachlorodibenzo-*p*-dioxin treatment in the mouse. *Tumori* (in press)

[32]Pitot, H.C., Goldsworthy, T., Campbell, H.A. & Poland, A. (1980) Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin of hepatocarcinogenesis from diethylnitrosamine. *Cancer Res.*, *40*, 3616-3620

[33]DiGiovanni, J., Berry, D.L., Gleason, G.L., Kishore, G.S. & Slaga, T.J. (1980) Time-dependent inhibition by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin of skin tumorigenesis with polycyclic hydrocarbons. *Cancer Res.*, *40*, 1580-1587

[34]DiGiovanni, J., Decina, P.C. & Diamond, L. (1983) Tumor initiating activity of 9- and 10-fluoro-7,12-dimethylbenz[*a*]anthracene (DMBA) and the effect of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on tumor initiation by monofluoro derivatives of DMBA in SENCAR mice. *Carcinogenesis*, *4*, 1045-1049

[35]Berry, D.L., DiGiovanni, J., Juchau, M.R., Bracken, W.M., Gleason, G.L. & Slaga, T.J. (1978) Lack of tumor-promoting ability of certain environmental chemicals in a two-stage mouse skin tumorigenesis assay. *Res. Commun. chem. Pathol. Pharmacol.*, *20*, 101-108

[36]Kouri, R.E., Rude, T.H., Joglekar, R., Dansette, P.M., Jerina, D.M., Atlas, S.A., Owens, I.S. & Nebert, D.W. (1978) 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin as cocarcinogen causing 3-methylcholanthrene-initiated subcutaneous tumors in mice genetically 'nonresponsive' at *Ah* locus. *Cancer Res.*, *38*, 2777-2783

[37]*IARC Monographs, Suppl. 6*, 508-510, 1987