CHLOROPHENOXY HERBICIDES (Group 2B)

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

In a Danish cohort study of chemical workers exposed to chlorophenoxy herbicides [particularly (4-chloro-2-methylphenoxy)acetic acid (MCPA), 2-(4-chloro-2-methylphenoxy)-propanoic acid (mecoprop), 2,4-dichlorophenoxyacetic acid (2,4-D) and 2-(2,4-dichloro-phenoxy)propanoic acid (dichlorprop)], as well as other chemicals, no overall increase in cancer incidence rate was observed, but there were significantly increased risks for soft-tissue sarcoma and lung cancer in some subcohorts, which were not necessarily those with the highest exposures to chlorophenoxy herbicide preparations[1].

A recently reported cohort of 5784 male employees in a UK company that manufactured, formulated and sprayed MCPA and other pesticides, but only small amounts of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), had no general excess mortality from cancer. Three potentially exposed workers died from nasal carcinoma, however. One death due to soft-tissue sarcoma approximately equalled the expected rate. No excess of lymphoma was seen[2].

A Finnish cohort study of brush control workers with short follow-up time showed no increased cancer risk. A small Swedish cohort study of railroad workers who sprayed herbicides showed an increased risk of cancers at all sites combined for those exposed to chlorophenoxy herbicide preparations and other herbicides. An excess incidence of all

cancers was also reported from a very small cohort of Swedish forestry foremen exposed to chlorophenoxy herbicide preparations and other herbicides. A study of long-term pesticide applicators in the German Democratic Republic, heavily exposed to a number of chemicals, including 2,4-D and MCPA, demonstrated an increased risk of bronchial carcinoma[1].

Two population-based case-control studies conducted in northern and southern Sweden, respectively, showed a statistically significant association between exposure to chlorophenoxy herbicides, especially in forestry and agriculture, and the occurrence of soft-tissue sarcomas. An increased risk of soft-tissue sarcoma was described among highly exposed Italian rice weeders in a population-based case-control study. However, a case-control study from New Zealand did not demonstrate any increased risk of soft-tissue sarcoma in people exposed to chlorophenoxy herbicides[1]. Nor did a recently reported population-based case-control study of soft-tissue sarcoma and lymphoma in Kansas, USA, find any association between soft-tissue sarcoma and exposure to 2,4-D[3].

A statistically significant association between malignant lymphoma (Hodgkin's and non-Hodgkin's) and exposure to chlorophenoxy herbicides was found in a Swedish case-control study[1]. The population-based case-control study of soft-tissue sarcoma and Hodgkin's and non-Hodgkin's lymphoma in Kansas showed that use of 2,4-D was associated with non-Hodgkin's lymphoma, especially among farmers who had been exposed for more than 20 days per year, among whom there was an approximately six-fold excess, and among those who had mixed or applied the herbicides themselves. Hodgkin's lymphoma was not, however, found to be associated with herbicide exposure[3]. No significant or consistent association was seen in a case-control study of these tumours from New Zealand, and in a Danish cohort of chemical workers exposed to chlorophenoxy herbicides there was also no significantly increased risk of malignant lymphoma[1,4]. Farmers and forestry workers in Washington State, USA, with exposure to phenoxy herbicides had a significantly increased risk of non-Hodgkin's lymphoma. People of Scandinavian descent in the area had an increased risk of soft-tissue sarcoma in connection with phenoxy herbicide exposure, but no increased risk of non-Hodgkin's lymphoma[5].

Three Swedish case-control studies of colon, liver, and nasal and nasopharyngeal cancer, which used the same study design and methods as in the studies on soft-tissue sarcoma and malignant lymphoma, did not demonstrate significantly increased risks, although a risk ratio of 2.1 was reached for nasal and nasopharyngeal cancer[1].

A record-linkage study using census data on occupation and cancer registry information in Sweden did not reveal any excess of soft-tissue sarcoma among agricultural and forestry workers[6,7]. However, on the basis of occupational titles, the elevated risks seen in Swedish case-control studies of soft-tissue sarcoma and lymphoma were reduced to 1.4 or less[8]. A UK study based on data from cancer registration showed a slightly but significantly increased risk of soft-tissue sarcoma among farmers, farm managers and market gardeners, but not in other subgroups in forestry and farming[9]. No association with soft-tissue sarcoma has been found with military service in Viet Nam, despite potential exposure to phenoxy herbicides[1,10], although there is a case report in this respect[1].

B. Evidence for carcinogenicity to animals (*inadequate* for 2,4-D and 2,4,5-T)

2,4-D and several of its esters were tested in rats and mice by oral administration and in mice by subcutaneous administration. All of these studies had limitations, due either to inadequate reporting or to the small number of animals used. Therefore, although increased incidences of tumours were observed in one study in which rats received 2,4-D orally and in another in which mice received its isooctyl ester by subcutaneous injection, no evaluation of the carcinogenicity of this compound could be made[11].

2,4,5-T was tested in mice by oral and subcutaneous administration. All of the studies had limitations due to the small numbers of animals used. Therefore, although an increased incidence of tumours at various sites was observed in one study in which 2,4,5-T (containing less than 0.05 mg/kg chlorinated dibenzodioxins) was given orally, no evaluation of the carcinogenicity of this compound could be made on the basis of the available data[12]. In rats fed diets containing three different concentrations of 2,4,5-T, the incidences of all tumour types were comparable to those in the control groups, with the exception that the incidence of interfollicular C-cell adenomas of the thyroid was increased significantly in female rats receiving the lowest dose. This increase was not considered to be related to treatment since it was not dose-related and the female control group had an unusually low incidence of thyroid adenomas[13].

A study of the incidence of small-intestinal adenocarcinoma in groups of sheep from different farms showed an association with use of phenoxy herbicides, as elicited by farmers' responses to a questionnaire. However, other herbicides were in use, and there was no documentation of exposures[14].

No adequate data were available on the carcinogenicity of MCPA[15].

C. Other relevant data

In single studies, lymphocytes of persons occupationally exposed to chlorophenoxy herbicides, including 2,4-D, did not show increased frequencies of sister chromatid exchanges or chromosomal aberrations. Other studies could not be assessed since workers were also exposed to other formulations. A single study of herbicide and pesticide sprayers exposed to 2,4,5-T, in which a small increase in the incidence of sister chromatid exchanges was reported, could not be assessed since workers were also exposed to other formulations. Persons occupationally exposed to MCPA did not have increased frequencies of sister chromatid exchanges (one study) or chromosomal aberrations in their lymphocytes[16].

2,4-D did not induce dominant lethal mutations, micronuclei or sister chromatid exchanges in rodents treated *in vivo*. Pure 2,4-D did not induce chromosomal aberrations in human lymphocytes *in vitro*, whereas a commercial formulation did. 2,4-D induced sister chromatid exchanges and unscheduled DNA synthesis in human cells *in vitro*. It did not induce sister chromatid exchanges but did induce mutation and inhibited intercellular communication in Chinese hamster cells *in vitro*. 2,4-D induced somatic mutation in *Drosophila*, but conflicting results were obtained for induction of sex-linked recessive lethal mutations; it did not induce aneuploidy. 2,4-D caused chromosomal aberrations and was

mutagenic in plants. It induced mutation, gene conversion and mitotic recombination in yeast. It was not mutagenic to bacteria or bacteriophage. The n-butyl and iso-octyl esters of 2,4-D were also not mutagenic to bacteria[16].

2,4,5-T induced chromosomal aberrations in bone-marrow cells of Mongolian gerbils, but not in spermatogonia of Chinese hamsters, and aneuploidy in oocytes of rats treated in vivo. It did not induce micronuclei in mice or dominant lethal mutations in mice or rats in vivo. 2,4,5-T inhibited intercellular communication in Chinese hamster V79 cells in vitro. There was weak evidence for the induction of sex-linked recessive lethal mutations in Drosophila; it did not induce aneuploidy or somatic mutation. It induced chromosomal aberrations in plants. It was mutagenic to yeast, but neither 2,4,5-T nor the n-butyl-, iso-butyl or iso-octyl ester of 2,4,5-T was mutagenic to bacteria[16].

MCPA did not induce structural chromosomal aberrations or micronuclei in mice treated in vivo; weakly positive results were obtained for sister chromatid exchanges in cells of Chinese hamsters treated in vivo and in vitro. It was weakly active in inducing sex-linked recessive lethal mutations but did not induce aneuploidy in Drosophila. MCPA and its methyl ester were mutagenic to yeast but not to bacteria[16].

References

[1]IARC Monographs, 41, 357-406, 1986

[2]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

[3]Hoar, S.K., Blair, A., Holmes, F.F., Boysen, C.D., Robel, R.J., Hoover, R. & Fraumeni, J.F., Jr (1986) Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. J. Am. med. Assoc., 256, 1141-1147

[4]Pearce, N.E., Sheppard, R.A., Smith, A.H. & Teague, C.A. (1987) Non-Hodgkin's lymphoma and farming: an expanded case-control study. Int. J. Cancer, 39, 155-161

[5]Woods, J.S., Polissar, L., Severson, R.K., Heuser, L.S. & Kulander, B.G. (1987) Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxy herbicide and chlorinated phenol exposure in western Washington. J. natl Cancer Inst., 78, 899-910

[6]Wirklund, K. & Holm, L.-E. (1986) Soft tissue sarcoma risk in Swedish agricultural and forestry workers. J. natl Cancer Inst., 76, 229-234

[7]Wirklung, K., Holm, L.-E. & Dich, J. (1987) Soft tissue sarcoma risk among agricultural and forestry workers in Sweden. Chemosphere (in press)

[8]Hardell, L. & Axelson, O. (1986) Phenoxyherbicides and other pesticides in the etiology of cancer: some comments on Swedish experiences. In: Becker, C.E. & Coye, M.J., eds, Cancer Prevention. Strategies in the Workplace, Washington DC, Hemisphere, pp. 107-119

[9]Balarajan, R. & Acheson, E.D. (1984) Soft tissue sarcomas in agriculture and forestry workers. J. Epidemiol. Commun. Health, 38, 113-116

[10]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

[11]IARC Monographs, 15, 111-138, 1977

[12]IARC Monographs, 15, 273-299, 1977

[13]Kociba, R.J., Keyes, D.G., Lisowe, R.W., Kalnins, R.P., Dittenber, D.D., Wade, C.E., Gorzinski, S.J., Mahle, N.H. & Schwetz, B.A. (1979) Results of a two-year chronic toxicity and oncogenic study of rats ingesting diets containing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). *Food Cosmet. Toxicol.*, *17*, 205-221

[14]Newell, K.W., Ross, A.D. & Renner, R.M. (1984) Phenoxy and picolinic acid herbicides and small intestinal adenocarcinoma in sheep. *Lancet*, *ii*, 1301-1305

[15]*IARC Monographs*, *30*, 255-269, 1983

[16]*IARC Monographs*, *Suppl. 6*, 161-163, 233-236, 538-540, 1987