

ADDITIONAL CHEMICALS WITH EVIDENCE FROM HUMAN STUDIES

A. *ortho*- AND *para*-DICHLOROBENZENE

No adequate data on the carcinogenicity of *ortho*- or *para*-dichlorobenzene in experimental animals were available².

There is one report of four cases of leukaemia and one case of "myeloproliferative syndrome" occurring in subjects exposed to *ortho*- or *para*-dichlorobenzene as a solvent for other chemicals or in chlorinated benzene mixtures. The authors state that there was no evidence of exposure to benzene².

B. 3,3'-DICHLOROBENZIDINE

3,3'-Dichlorobenzidine is carcinogenic in rats, hamsters and dogs. In rats it produced tumours of the skin, mammary gland, zymbal gland and haematopoietic tissues following oral or subcutaneous administration^{3,4}. In dogs and hamsters, it produced malignant tumours of the liver and bladder following oral administration^{3,5}.

¹ IARC Monographs, 19: 377-437, 1979.

² IARC Monographs, 7: 231-244, 1974.

³ IARC Monographs, 4: 49-55, 1974.

⁴ Stula, E.F., Sherman, H., Zapp, J.A., Jr. & Wesley Clayton, J., Jr. (1975) Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis(2-chloroaniline) and 4,4'-methylene-bis(2-methylaniline). Toxicol. appl. Pharmacol., 31: 159-176.

⁵ Stula, E.F., Barnes, J.R., Sherman, H., Reinhardt, C.F. & Zapp, J.A., Jr. (1978) Liver and urinary bladder tumours in dogs from 3,3'-dichlorobenzidine. J. Environm. Path. Tox., 1: 475-490.

In three epidemiological studies^{1,2,3}, no bladder tumours were reported in men occupationally exposed to dichlorobenzidine; however, the numbers of exposed workers followed up in each study was small (35, 175 and 87), and few of the workers had been observed for more than 15 years after first exposure (most had been observed for 10 years or less). None of these investigations used a study design or method of statistical analysis which was adequate to rule out a carcinogenic effect.

C. PHENYLBUTAZONE

No adequate data on the carcinogenicity of phenylbutazone in experimental animals were available⁴.

There are at least 23 case reports of leukaemia occurring in patients after treatment with phenylbutazone. In a follow-up study of 25 patients who developed bone marrow depression following phenylbutazone treatment, one died of myeloproliferative disease (probably leukaemia)⁴.

D. 2,3,7,8-TETRACHLORODIBENZO-*para*-DIOXIN (TCDD)

Rats fed 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin developed a variety of malignant tumours, mainly of the respiratory tract, sebaceous glands, liver and bile ducts^{5,6,7}.

¹ Gadian, T. (1975) Carcinogens in industry, with special reference to dichlorobenzidine. *Chemistry and Industry*, 821-831.

² Gerarde, H.W., Gerarde, D.F. (1974) Industrial experience with 3,3'-Dichlorobenzidine: An epidemiological study of a chemical manufacturing plant. *J. Occ. Med.*, 16: 322-344.

³ MacIntyre, I. (1975) Experience of tumours in a British plant handling 3,3'-Dichlorobenzidine. *J. Occ. Med.*, 17: 23-26.

⁴ IARC Monographs, 13: 183-199, 1977.

⁵ IARC Monographs, 15: 41-102, 1977.

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

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

Two bronchogenic carcinomas were reported (*versus* 0.12 expected, calculated by the Monograph Working Group) in a study of workers exposed to TCDD; however smoking habits were not reported, only 55 of the 78 workers were traced, and they were only followed for five or six years. A study in Viet-Nam showed an increase in the proportion of liver cancer patients admitted to Hanoi hospitals during 1962 to 1968 - a period during the war in which herbicides (some containing TCDD) were being used^{1,2}.

E. *ortho*-TOLUIDINE

ortho-Toluidine is carcinogenic in mice and rats following its oral administration as the hydrochloride. It produced a variety of malignant tumours in rats including sarcomas of the spleen, fibromas of the subcutaneous and mammary tissues, mesotheliomas of the abdominal cavity and carcinomas of the urinary bladder. In mice it produced haemangiosarcomas at various sites and liver tumours^{3,4}.

Four epidemiological studies were available for review. Three of them deal with bladder tumours in workers who had exposures to many substances (including known bladder carcinogens) as well as to *ortho*-toluidine, and the results of these studies are equivocal. Another study appeared to involve occupational exposure to toluidines specifically; it was suggestive of a carcinogenic effect, but the information presented in the paper was insufficient to allow evaluation³.

F. VINYLIDENE CHLORIDE

Vinylidene chloride induced malignant tumours, including angiosarcomas, after inhalation in rats and mice. However, the results were not statistically significant. The preliminary results of another inhalation study in mice indicate the induction of kidney tumours in male animals, although the study had not been completed at the time of reporting. Other inhalation studies in rats and hamsters, as well as an oral study in rats is still in progress and cannot be evaluated⁵.

¹ IARC Monographs, 15: 41-102, 1977.

² International Agency for Research on Cancer (1978) Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. IARC Intern. Tech. Rep. No. 78/001, Lyon, France.

³ IARC Monographs, 16: 349-366, 1978.

⁴ National Cancer Institute (1979) Bioassay of *o*-toluidine hydrochloride for possible carcinogenicity. Tech. Rep. Ser. No. 153, DHEW Publication, No. (NIH) 79-1709.

⁵ IARC Monographs, 19: 452-453, 1979.

One epidemiological study of 138 workers exposed to vinylidene chloride showed no excess of cancer deaths, however only five deaths in all had occurred in the group. Another study of 629 workers (who were exposed to vinyl chloride and acrylonitrile as well as to vinylidene chloride) showed seven deaths due to malignant neoplasms (4.4 expected). Among workers aged 35-39 two bronchial carcinomas were reported (0.08 expected). However, no information on the smoking habits of these men was presented¹

¹ IARC Monographs, 19: 452-453, 1979.