POLYCHLORINATED BIPHENYLS (Group 2A)

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

Information on the possible carcinogenic risk of human exposure to polychlorinated biphenyls (PCBs) comes from studies of occupational populations and of populations

exposed to the compounds accidentally. PCB mixtures may be contaminated with polychlorinated dibenzofurans and polychlorinated dibenzodioxins (see, e.g., p. 350).

A slight increase in the incidence of cancer, particularly melanoma of the skin, was reported in a small group of men exposed to Aroclor 1254, a mixture of PCBs[1]. In a study of over 2500 US workers exposed to a similar mixture of PCBs during the manufacture of electrical capacitors, five deaths due to cancer of the liver and biliary passages were observed, whereas 1.9 would have been expected. This increase was sustained mainly by female workers in one of the two plants in the study (four of the five deaths), and all five workers had first been employed before the early 1950s[2,3]. Another study of workers in a capacitor plant was conducted in Italy. Exposure in the early years of production (until 1964) was to PCB mixtures containing 54% chlorine (mainly Aroclor 1254 and Pyralene 1476), which were later replaced by mixtures containing 42% chlorine (mainly Pyralene 3010 and 3011). Early results showed a significant excess of all cancers among male workers, which was due mainly to cancers of the digestive system and of the lymphatic and haematopoietic tissues. Among female workers, a slight increase in mortality from cancer of the lymphatic and haematopoietic tissues was reported[4]. The study was later enlarged and extended to include 2100 workers and to cover the period 1946-1982. Both male and female workers exhibited significantly increased cancer mortality in comparison with rates for the local population (14 observed, 7.6 expected; and 12 and 5.3, respectively, for men and women). Among male workers, cancers of the gastrointestinal tract (two stomach, two pancreas, one liver and one biliary passages) taken together were significantly increased (6 observed, 2.2 expected). Female workers showed a significant increase in deaths from haematological neoplasms (4 observed, 1.1 expected)[5]. In Sweden, among 142 male workers employed between 1965 and 1978 in a capacitor manufacturing plant when PCB mixtures containing up to 42% chlorine had been used, no significant excess of cancer deaths was noted. Cancer incidence was also examined: the number of cases observed corresponded well to that expected. One individual in a subgroup with higher exposure developed two relatively rare tumours, both of which occurred ten years after the start of exposure: a slow-growing mesenchymal tumour (desmoid) and a malignant lymphoma[6].

After contamination of cooking oil with a mixture of PCBs (Kanechlor 400) in Japan in 1968, a large population was intoxicated ('Yusho' disease). An early report on mortality from 1963-1983 showed a significantly increased risk of all cancers, and an almost five-fold significantly elevated risk of primary liver cancer. The edible rice oil had also been contaminated by polychlorinated quaterphenyls and polychlorinated dibenzofurans. Dose-response relationships were not clarified[7]. A further comprehensive study of 887 male 'Yusho' patients showed statistically significantly increased mortality from all malignancies (33 observed, 15.5 expected), from liver cancer (9 observed, 1.6 expected) and from lung cancer (8 observed, 2.5 expected). Use of local rather than national rates in calculating expected number of deaths decreased the observed:expected ratio for liver cancer from 5.6 to 3.9, which was still statistically significant. A closer look at the geographical distribution of liver cancer cases did not allow exclusion of factors other than PCB poisoning as a possible explanation for this finding. For the 874 female patients examined, none of the noted observed:expected ratios was significant[8]. In a series of ten autopsies of 'Yusho'

patients, two adenocarcinomas of the liver were found, with no indication of a direct association with exposure to PCBs[9]. Ultrasonic and tumour marker examination of two series of 79 and 125 patients with 'Yusho' disease in 1983 and 1984, respectively, did not reveal any case of hepatic-cell carcinoma[10]. Two studies of the PCB content of fat tissues and cancer occurrence were available. An association was suggested between PCB concentrations in subcutaneous abdominal adipose tissue and the occurrence of cancers of the stomach, colon, pancreas, ovaries and prostate[11]. No indication emerged of a relationship between PCB content in extractable breast fat tissue and the occurrence of breast cancer[12].

The available studies suggest an association between cancer and exposure to PCBs. The increased risk from hepatobiliary cancer emerged consistently in different studies. Since, however, the numbers were small, dose-response relationships could not be evaluated, and the role of compounds other than PCBs could not be excluded, the evidence was considered to be limited.

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

Certain PCBs (particularly with greater than 50% chlorination) produced benign and malignant liver neoplasms in mice and rats after their oral administration[1,13,14]. Oral administration of Aroclor 1254 to rats yielded hepatocellular adenomas and carcinomas as well as intestinal metaplasia and a low, statistically nonsignificant incidence of stomach adenocarcinomas[15]. PCBs were inadequately tested in mice for induction of skin tumours[16,17]. In several studies, oral or intraperitoneal administration of PCBs enhanced the incidences of preneoplastic lesions[18-20] and of neoplasms[21,22] of the liver induced in rats by *N*-nitrosodiethylamine or 2-acetylaminofluorene. In one study, intragastric administration of PCBs to mice increased the incidence of lung tumours induced by intraperitoneal administration of *N*-nitrosodimethylamine[23].

C. Other relevant data

No data were available on the genetic and related effects of PCBs in humans.

Dominant lethal effects were not induced in rats administered PCBs orally, but were produced in rats nursed by females that had received PCBs orally. PCBs did not induce chromosomal aberrations in bone-marrow cells or spermatagonia of rats treated *in vivo*; micronuclei were not induced in bone-marrow cells of mice in one study, while equivocal results were obtained in a second study in which the PCBs were administered in corn oil. They did not transform Syrian hamster embryo cells *in vitro*. PCBs induced DNA strand breaks and unscheduled DNA synthesis in rat hepatocytes *in vitro*. Neither chromosomal breakage nor aneuploidy was induced in *Drosophila*. PCB mixtures did not induce SOS repair and were not mutagenic to bacteria[24].

2,2′,5,5′-Tetrachlorobiphenyl induced DNA strand breaks in mouse cells *in vitro*. 2,4,5,2′,4′,5′-Hexachlorobiphenyl but not 3,4,5,3′,4′,5′-hexachlorobiphenyl inhibited intercellular communication in Chinese hamster V79 cells. Purified 2,4,2′,4′-, 2,5,2′,5′- and

3,4,3′,4′-tetrachloro- and 2,4,6,2′,4′,6′-hexachlorobiphenyl were not mutagenic to bacteria[24].

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