RATIONALE FOR CONSIDERING PCB MIXTURE AS A CARCINOGENIN RISK ASSESSMENT

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ABSTRACT. According to a weight-of-evidence classification epidemiologic data are inadequate to prove the carcinogenic activity of PCBs in humans. Thus, it is essential to use chronic animal bioassay data to estimate risk from exposure to PCBs. Data from a few bioassays on PCB mixtures viz., Aroclor 1260, Aroclor 1254, Kanechlor 500, Clophen A-60 and Clophen A-30, suggest their carcinogenicity in animals. Only the data on Aroclor 1260 are suitable for utilization in cancer risk estimation. Two strains of rats had statistically significant incidence of hepatocellular carcinoma in chronic feeding studies with Aroclor 1260. Kanechlor 500 exposure in the diet also produced liver tumors in mice. Although Aroclor 1254 in the diet induced dose response incidences of liver tumors in mice and rats, these increases were not statistically significant. Clophen A-30 and Clophen A-60 have also been found to induce liver tumors in rats in feeding studies. Carcinogenic response data from bioassays with these PCB mixtures provide sufficient evidence for the carcinogenic activities of PCBs in animals. Accordingly, PCB mixtures are classified as probable human carcinogens. The bioassay data on Aroclor 1260 have been used for cancer risk assessment. Recognizing their variety and variability, and the lack of adequate chronic long-term bioassay data for most of the PCB mixtures, the carcinogenic potency of other PCB mixtures is considered to be equal to that of Aroclor 1260.

HAZARD ASSESSMENT. Human exposure to PCBs may occur from contact with industrial products, contamination of foodstuffs or from association with contaminated environmental components. Chloracne is the most commonly encountered dermatologic symptom. Other reported dermatologic symptoms include rash, burning sensation, pigmentation (darkening), thickening, and discoloration of the fingernails. It is not clear whether PCB mixtures are solely responsible for chloracne or other adverse health effects and whether PCDF contaminats result. In the Yusho and Yu-cheng poisoning incidents, the toxic effects correlated to the PCDFs, not PCB exposure dose for the liver and other tissues of the victims. Hepatic effects associated with PCB exposure include hepatomegaly, hepatic enzyme induction with accelerated rate of metabolism of drugs and hormones, and hepatic dysfunction indicated by increases in serum hepatic enzyme activities. A decrease in pulmonary function associated with cough, wheezing, tightness in chest, and upper respiratory and eye irritation were also reported in PCB-exposed capacitor manufacturing workers.

In evaluating the toxicity of PCBs in animals, it is important to consider the isomer specific composition of the PCBs and potential impurities, the length of exposure, and the species under investigation. In general, PCB mixtures have low to moderate acute toxicity in mammalian species. Single dose oral LD50s of commercial PCB mixtures in rats range from 1.0-11.3 g/kg bw. Limited data also suggest that the acute toxic potency of PCB mixtures is similar in other species following oral, dermal or i.p.

exposure. Data on purified PCB isomers have established that the toxic, metabolic and toxicokinetic behavior of the different component molecules varies not only with the degree of chlorination but also with the position of the chlorine atoms. The relative toxicity and persistency of four pure 3,4,5-sym-hexa-CB was found to be the most acutely toxic (LD50=19mg/kg bw/day) and persistent (levels in liver and adipose tissue) isomer, followed by 2,4,6-sym-hexa-CB; 2,4,5-sym-hexa-CB; and 2,3,6-sym-hexa-CB (McConnell and McKinney, 1978). Although structure-activity relationships are most interesting for this class of compounds, it is also important to note that highly toxic, coplanar PCB isomers, such as 3,4,5-symhex-CB, have only been detected as very minor constituents of commercial PCB formulations. PCB rapidly bioaccumulates to toxic levels following longterm, low-level exposure. A major target organ for PCBs is the liver; an increase in the liver-to-body weight ratio is one of the most sensitive indicators of PCB exposure. Hepatomegaly has been observed in rats ingesting diets containing PCB's. Hepatomegaly results from liver cell hypertrophy, which is caused by fatty infiltration and proliferation of the smooth endoplasmic reticulum. The latter response is associated with the induction of hepatic enzymes, particularly the microsomal mixed function oxidases. Hepatic fluorescence, which is suggestive of porphyria has also been reported after exposure of rats for 16 weeks to 10 ppm of Aroclor 1254 (0.5 mg/kg bw/day). Focal necrosis and iron-containing deposits in Kupffer cells have been observed at higher levels of exposure. PCBs have also been shown to produce immunosuppression, which may be associated with thymic atrophy, lymphocytopenia and splenomegaly. Other PCB-related toxic effects include reduction in food and water intake, wasting syndrome (though this has also been associated with PCDF toxicity), and decreased body temperature. Another sensitive indicator of PCB exposure is an enlarged thyroid. Ultrastructural evidence suggestive of increased thyroid gland activity has been reported in rats maintained on diets containing as little as 5 ppm Aroclor 1254 (0.25 mg/kg bw/day) for 4 weeks.

In a chronic study that defined a NOAEL, BALB/CJ mice were maintained for 9 months on diets containing 0, 3.75, 37.5 or 375 ppm of the Aroclors 1221, 1242 or 1254 (0.45, 4.57 or 45.7 mg/kg bw/day). The Aroclor with the lowest chlorine content (Aroclor 1221) produced no liver lesions, while exposure to Aroclor 1242 resulted in increased liver weight in the high-dose group. Mice exposed to Aroclor 1254 showed increased mortality in the high-dose group, mild hepatopathology in the median-dose group, and no liver lesions in the low-dose group. The NOEL observed in the study, using mice of 0.45 mg/kg bw/day, is nearly identical to the LOELs of 0.5 mg/kg bw/day associated with porphyria in rats and 0.25 mg/kg bw/day associated with enlarged thyroid. Monkeys have been found to be highly sensitive to the toxic effects of PCBs. Signs of toxicity with chronic exposure to Aroclor 1248 include severe facial and subcutaneous edema, comedones and cysts of the meibomian glands, gastric lesions, body weight loss and reduced hemoglobin and leukocytes. The lesions are unique to the monkey and resemble chloracne in man. In the monkey, chronic exposure to as low as 0.1 mg/kg bw/day of Aroclor 1248 produce frank toxic effects; no studies have been conducted from which a NOAEL can be derived or to indicate how close 0.1 mg/kg bw/day is to the NOAEL for monkeys. There are reports of a slight increase in the incidence of cleft palate in the progeny of mice exposed to PCBs during gestation. PCB's can result in fetal toxicity including resorptions, abortions, reduced birth weight, and decreased postnatal survival in several species. The mink and monkey are the most sensitive species tested

relative to reproductive toxicity of PCBs. Complete reproductive failure was observed in mink maintained on a diet containing 5 ppm Aroclor 1242 (0.75 mg/kg bw/day) for 18 months. Rhesus monkeys maintained on diets containing 2.5 or 5 ppm Aroclor 1248 (0.1 or 0.3 mg/kg bw/day) for 18 months had increased abortions at the low dose and maternal toxicity with no live births at the high dose.

HIGH RISK POPULATIONS. Two separate groups of high-risk subpopulations for exposure to PCB's include those persons with the potential for frequent or high exposure, namely, occupationally-exposed workers and breast-fed infants, as PCBs are excreted in the breast milk or lactating humans and individuals with a limited ability to metabolize and excrete PCBs, such as fetuses and neonates (2-3 months old). Infants born to women exposed to PCB during pregnancy (Yusho incident) have been found to be generally small for gestational age and exhibited dark brown pigmentation on the skin and mucous membranes, gingival hyperplasia, or early eruption of teeth, and facial edema. In Yusho and Yu-cheng incidence, the PCDF impurities and their components may also determine the severity of these effects (Nagayama et al., 1976; Chen et al., 1985; Hayabuchi et al., 1979; Masuda and Kuroki, 1982).

RISK ASSESSMENT. PCBs (Aroclor 1260, Kanechlor 500, Aroclor 1254, Clophen A-30 and Clophen A-60) have been evaluated for carcinogenicity in several animal bioassays. Aroclor 1260 induced a statistically significant increase of hepatocellular carcinomas in two rat (Sherman, Sprague-Dawley) feeding studies. Kanechlor 500 produced a statistically significant liver tumor response in dd mice when given in the diet for 32 weeks. Aroclor 1254 fed in the diet to mice (Balb/cj) and rats (Fischer 344) induced liver tumors that were dose-related but not statistically significant. Clophen A-30 and A-60 induced hepatocellular carcinomas in rats after 832 days of feeding 100 ppm in the diet. This level of carcinogenic evidence in rats and mice for some commercial PCBs (Aroclor 1260, Kanechlor 500 and Aroclor 1254, Clophen A-30 and Clophen A60) constitute sufficient evidence for carcinogenicity of these commercial PCBs in animals.

Only one recent epidemiologic study reports significant risk of liver cancer among victims of the Yusho accident in Japan, which involved injestion of contaminated rice oil. There is some uncertainty regarding concurrent exposure to other possibly carcinogenic substances. No conclusion can be derived regarding the relationship of exposure to PCB-contaminated rice oil and increased cancer risk. At present, the human epidemiologic evidence is suggestive, but from a weight-of-evidence classification this observation is regarded as inadequate because of the tentative nature of the data.

The positive evidence in rats and mice, together with inadequate evidence in humans, places Aroclor 1254 and 1260, Kanechlor 500, and Clophen A-30 and A-60 in the weight-of-evidence category B2, as a probable human carcinogen. PCB mixtures containing significant amounts of components present in Aroclor 1254 and 1260, Kanechlor 500, and Clophen A-30 and A-60 are likely to present a carcinogenic hazard to the human population. Recognizing the variety and variability to PCB mixtures, all PCB mixtures is currently considered to have a carcinogenic potential (category B2) similar to that of Aroclor 1260 (EPA 1988). The human carcinogenic potency of Aroclor 1260 are estimated to be 7.7/mg/kg/day using the multistage model with hepatocellular carcinoma data from a Sprague-Dawley rat chronic Aroclor

1260 feeding study by Norback and Weltman (1985). This position is required because of a lack of adequate information about which constituents of Aroclor 1260 or any other PCB mixture are carcinogenic. This is thought to be a prudent public health judgment for which changes could be made if additional statistically significant evidence is forthcoming.

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