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Effect of Polychlorinated Biphenyls on the Elimination Rate of Antipyrine from Plasma of Rats and Man

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The ability of polychlorinated biphenyls /PCBs/ to induce the activity of hepatic microsomal enzymes that catalyze the metabolism of drugs and other xenobiotics has been well documented /VILLANEUVE et al.1971, BENTHE et al.1972, BICKERS et al.1972, LITTEREST et al.1972, CHEN and DU BOIS 1973, JOHNSTONE et al.1974, SCHMOLDT et al.1974, ECOBICHON and COMEAU 1974, GOLDSTEIN et al.1975, SANDERS and KIRKPATRICK 1975/. This phenomenon has been paralleled by an enlargment of the liver and proliferation of the endoplasmatic reticulum /NISHIZUMI 1970, ALLEN et al. 1973, BRUCKNER et al.1974, ALLEN 1975, KASZA et al. 1976/.

While these studies have provided information on the ability of PCBs to cause enzyme induction in various animals no data are available on the effect of exposure to PCBs on enzyme induction in man. Therefore the main objective of our investigation was to study whether occupational exposure to PCBs changes the half-life of antipyrine in plasma of workers in production of these important industrial chemicals. It has been shown /KOLMODIN et al.1968, VESELL and PAGE 1968/ that the measurement of plasma antipyrine half-life is a good indicator for assessing the activity of liver microsomal enzymes.

Present paper reports that a single dose as well as the short-term administration of Delor 103, a polychlorinated biphenyl, increased markedly the elimination of antipyrine from plasma of rats and that plasma half-life of antipyrine in workers occupationally exposed to a commercial mixture of PCBs was significantly shorter than in control subjects.

Materials and Methods

A n i m a l s. Male Wistar rats, 140 - 155 g

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maintained on Larsen diet were used in these experiments and were fasted overnight prior to killing.

There were two experimental groups. A group for subacute treatment received 5 mg/kg body weight of polychlorinated biphenyl Delor 103 /a commercial product that contains 42 % chlorine by weight/ daily for a period of 5 weeks. Rats in the so called acute group obtained 100 mg/kg body weight of Delor 103 in a single dose. Doses were administered in pure vegetable oil by means of oral tube. Control animals received only oil.

Antipyrine was administered orally, as an aqueous solution, in a single dose of 50 mg/kg body weight 72 hours after the last treatment.

S u b j e c t s. Three groups of subjects were investigated. A group of 26 workers-men, ranging in age from 18 to 54 years, who have been exposed to a mixture of commercial products PCBs /Delor 103, Delor 104 and Delor 106/ in the production these compounds for a period from 2 months to 19 years.

A control group of 18 not exposed men from the same factory, mainly research workers and office personnel in the age from 19 to 50 years. They have worked in the factory for a period 1 to 22 years. All subjects have been from the same geographical area.

A control group of 27 not exposed student volunteers from different geographical areas. All the volunteers were men between 20 and 27 years of age. No subject investigated received medication during or for one month preceding the investigation.

M e t h o d s. Antipyrine was given orally in a single dose of 1 g. Venous blood was collected in heparinized tube 3,6,9 and 12 hours after ingestion. Plasma concentrations of antipyrine were assayed by precipitation procedure according to method of BRODIE et al./1949/. The half-life of antipyrine in each subject was determined from the linear portion of a plot of the plasma values on semilogarithm paper.

Results

Animal model was used to find out whether PCBs alter the rate of disappearence of antipyrine from plasma. The elimination rate of antipyrine from plasma of rats treated with Delor 103 was significantly increased. The plasma concentrations of antipyrine in rats treated with Delor 103 in both acute and subacute groups were significantly lower /$P \leq 0.05 - 0.001$/ than those in controls at each time interval with the

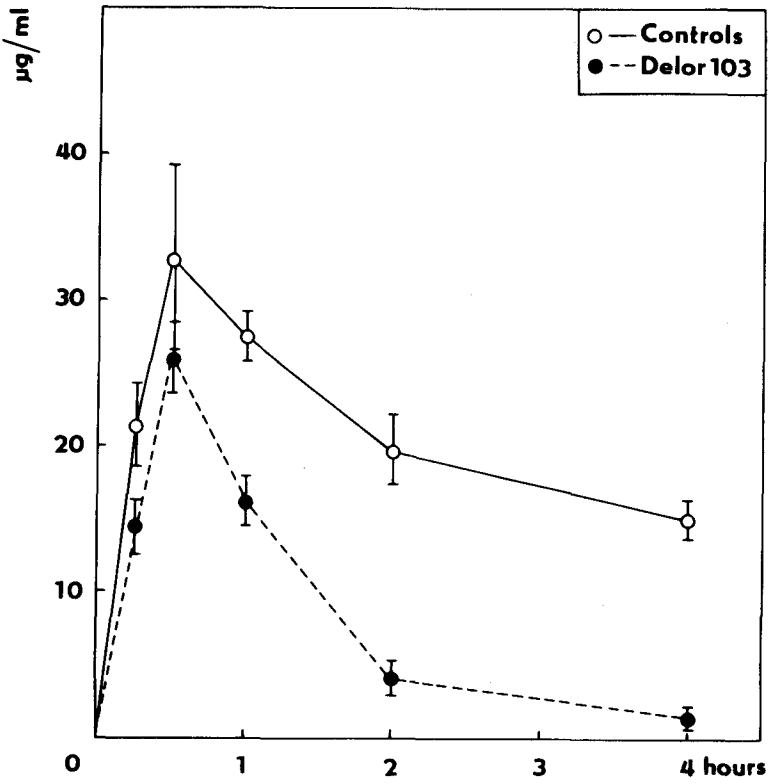

Figure 1. The rate of elimination of antipyrine from plasma of rats treated with a single dose /100 mg/kg B.W./ of Delor 103 and in control group. Antipyrine was administered orally 72 hours after treatment. Each point represents the mean value and S.D. of 6 animals.

exception of concentration at half an hour after ingestion of antipyrine in rats of subacute group. This concentration was not significantly higher than that in control rats. See Figures 1 and 2.

The plasma half-lives of antipyrine in workers occupationally exposed to PCBs and nonexposed control subjects are depicted in Figure 3.

For the exposed group the mean of antipyrine half-life was 10.2 hours, with a standard deviation of 4.1, and a range of 4.7 to 19.8 hours. In the nonexposed group of subjects from the same factory,

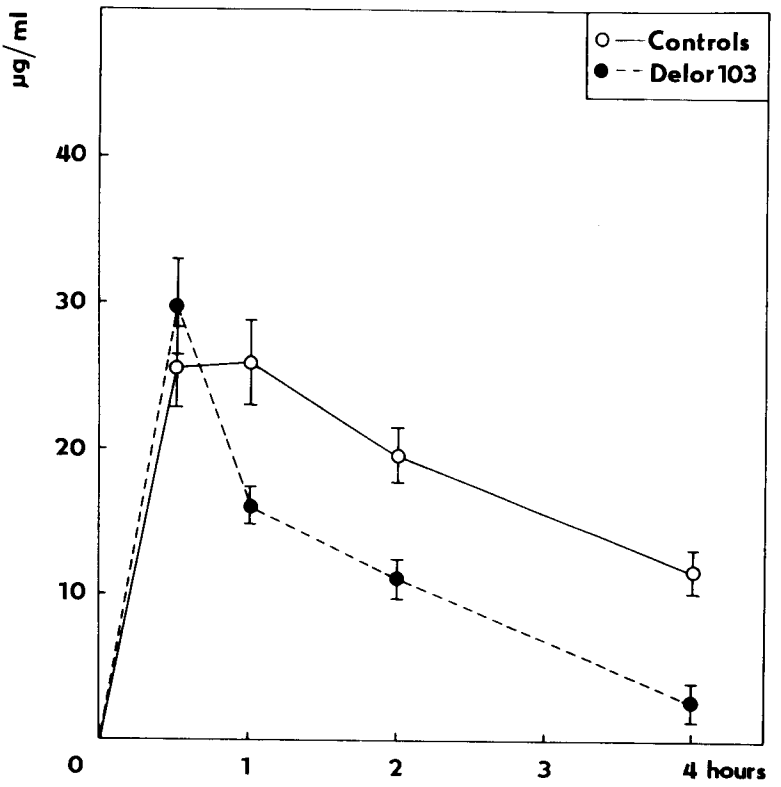

Figure 2. The rate of elimination of antipyrine from plasma of rats treated with the repeated daily doses /5 mg/kg B.W./ of Delor 103 and in control group. Antipyrine was administered orally in a single dose of 50 mg/kg B.W. 72 hours after treatment. Each point represents the mean value and S.D. of 6 animals.

there was a mean of 14.6 hours, with a standard deviation 1.7, and a range of 10.2 to 20.8 hours. For control group of student volunteers the mean of antipyrine half-life was 18.2 hours, with a standard deviation of 5.3 and a range of 9.4 to 29.1 hours.

The plasma half-life of antipyrine in workers exposed to PCBs was significantly lower than that in both control groups represented by subjects from the same factory /$P \leq 0.001$/ and the student volunteers /$P \leq 0.001$/, respectively. The difference in the values of antipyrine half-lives between control

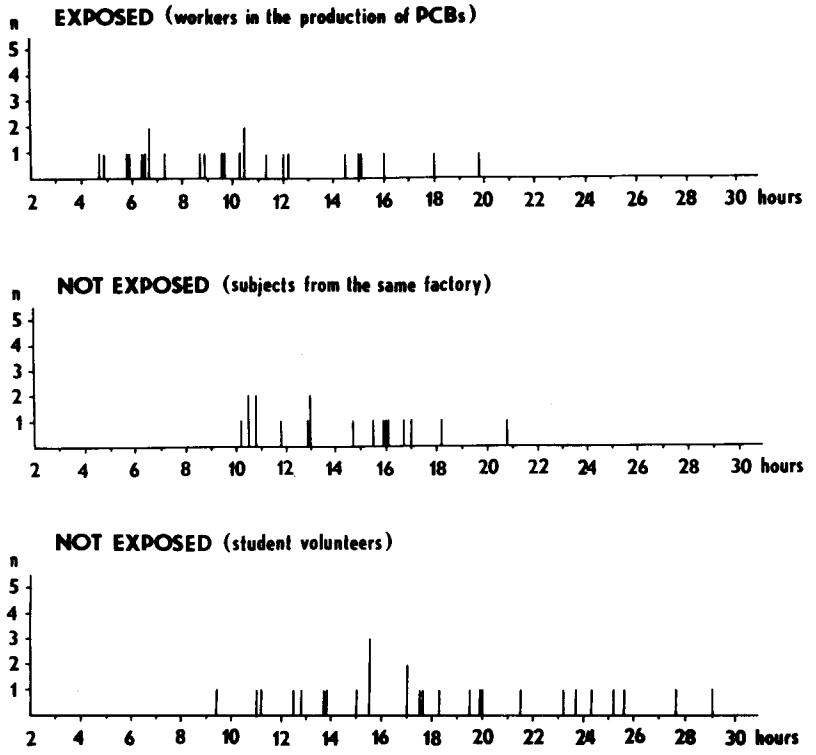

Figure 3. The plasma half-life of antipyrine in workers occupationally exposed to a mixture of commercial products of PCBs and in control subjects.

groups was statistically significant /$P < 0.02$/. In workers occupationally exposed to PCBs, no significant correlations was observed between duration of exposure and the plasma half-life of antipyrine.

Discussion

Our data from animal experiment indicate that Delor 103 increased markedly the elimination of antipyrine from plasma of rats following the acute as well as subacute treatment. These results confirm our previous unpublished observations demonstrating that

Delor 103 is a potent enzyme inducer. Since the elimination of antipyrine is totally dependent on its rate metabolism by liver microsomal enzymes we decided to study liver enzyme induction in workers occupationally exposed to PCBs by measuring of plasma half-life of antipyrine.

Plasma antipyrine half-life appears to be more sensitive indicator of liver enzyme induction than other methods proposed for examination of the drug metabolizing capacity of the liver in man. Thus, MORGAN and ROAN /1974/ have found no evidence that high tissue stores of DDT, DDE and dieldrin stimulate the hepatic synthesis of D-glucaric acid in exposed workers despite reports that the estimation of urinary excretion D-glucaric acid is a sensitive and reliable measure of hepatic-enzyme activity /HUNTER et al.1971, DAVIDSON et al.1974/.

KOLMODIN et al./1969/ have reported that workers occupationally exposed to various chlorinated hydrocarbon insecticides, mainly lindane and DDT, had a significantly shorter plasma half-life of antipyrine than control subjects from the same factory. In the present study it has been shown that PCBs, as further of chemical environmental factors, affect antipyrine metabolism in man. The plasma half-life of antipyrine was significantly shorter in workers exposed to PCBs than in control subjects for both the control group from the same factory and control group of student volunteers. However, in control subjects from the factory antipyrine had a significantly shorter half-life in plasma than in control subjects represented by student volunteers. Although the mean of half-life of antipyrine in students is 25 % longer than that in large group of 307 healthy male subjects reported by VESTAL et al. /1975/, the range in this our control group, 9.4 to 29.1 hours, is smaller than their data 4.8 to 41.7 hours.

Our observations suggest that hepatic enzyme induction by PCBs occurs in man. If the assumption is right, this phenomenon could affect significantly the toxicity of PCBs themselves by accelerating their metabolism. However, recently SHIMADA /1976/ and latest SEYMOUR et al. /1976/ have brought some evidence to previous assumptions of different investigators, that activated intermediate metabolites of PCBs can induce the chronic liver injury. Furthermore, our data demonstrate that these factors of industrial environment may play a role in regulating the rate of drug metabolism, what is important from a therapeutic aspect.

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