# Clearance and Tissue Distribution of Polychlorinated Dibenzofurans in Mice

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Polychlorinated dibenzofurans (PCDFs) are known to be highly toxic substances. (BAUER et al. 1961, HOFMANN 1958) Chicks fed on 5ug/kg/day of 2,3,7,8-tetrachlorodibenzofuran died within 8-15 days.( GOLDSTEIN et al. 1974) Chick embryo bioassays have demonstrated that the ability of 2,3,7,8-tetrachlorodibenzofuran and 2,3,4,7,8-pentachlorodibenzofuran to affect induction of aryl hydrocarbon hydroxylase is comparable to that of 2,3,7,8-tetrachlorodibenzodioxin (TCDD). (KENDE et al. 1975) The latter compound is known in its high acute toxicity and strong teratogenecity.

The presence of PCDFs in commercial PCB preparations has been first shown by Vos et al.(1970) Subsequent researches revealed that PCDFs were contained in all PCB preparations including American, French,German and Japanese preparations. ( BOWES et al 1973, 1975, ROACH and PoMERANTZ 1974, NAGAYAMA et al., 1976) Despite that PCBs are known as a ubiquitous pollutant and that PCDFs have discharged to the environment concomittingly with PCBs, ditailed studies have not been made on the metabolism, distribution, clearance, effect on reproduction etc. of PCDFs in mammals. This paper will report on the distribution and clearance rate of PCDFs in mice.

## Materials and Method

Reagent of PCDFs was synthesized through the chlorination of dibenzofuran in chloroform under the presence of catalytic amount of ferric chloride and iodine. Average chlorine number of aromatic ring substitution was 4.7.

Mice used for animal experiment was ICR male mice, 9 weeks of age and weighing 40 grams. 30 mice were given single dose of 0.50 mg of PCDFs per mouse. PCDFs were dissolved in rice oil in the concentration of 2.5mg/ml and dosed intraperitoneally. Water and food were given ad libitum.

The animals were killed by decapitation and blood, brain, heart, lungs, liver, kidneys, testes, spleen and fat tissues were collected. Each tissues was weighed and homogenized with 2 grams of anhydrous



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sodium sulfate in 10 ml of n-hexane-acetone mixture (95:5) using Polytron brender ®. Hexane extracts were vigourously shaken with concentrated sulfuric acid. Supernatant hexane layer was injected to gaschromatography equipped with ECD detector (Ni $^{63}$). GLC condition was as follows. Column Dexil 2% on Chromosorb WAW DCMS (80/100) Temp. 250°C Carrier gas $N_2$ 60 ml/min. Detector ECD(Ni $^{63}$, 10 mCi) Temp. 270°C. Injection Port Temp. 270°C.

## Results and Discussion

No mice died during the experimental period. The acute toxicity of PCDFs seems to be considerably weaker than TCDD.

Gaschromatographic patterns of PCDFs of starting sample and in various organs in mice 3 days after administration are given in Fig. 1. PCDFs used in this experiment was a mixture of two tetrachloro-(Peaks 41 and 42), four pentachloro-(Peaks 51,52,53 and 54) and four hexachloro-(Peaks 61,62,63 and 64)dibenzofurans.

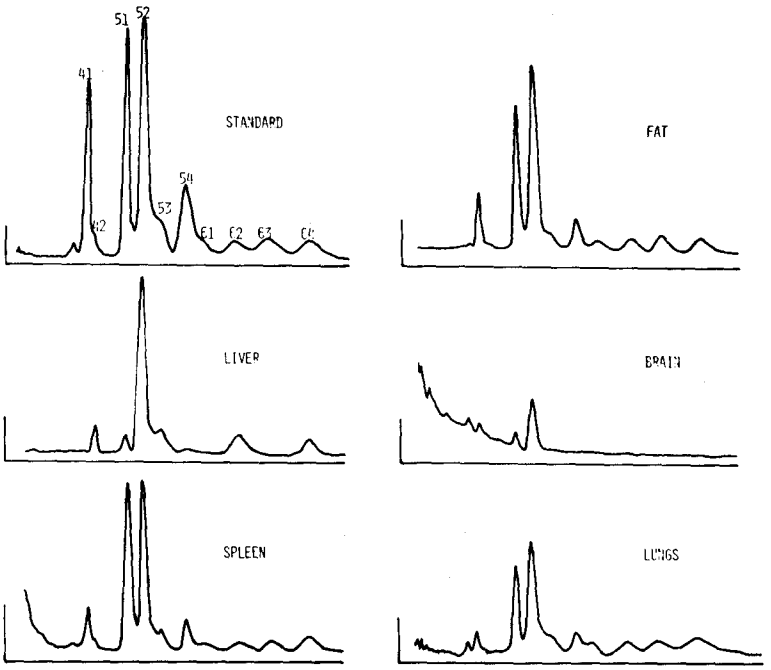


Fig.1 GLC patterns of PCDFs in various organs of mice three days after administration.

In most organs except liver, the GLC peak patterns were quite similar with each other. While, several peaks were diminished or disapperaed in the chromato-

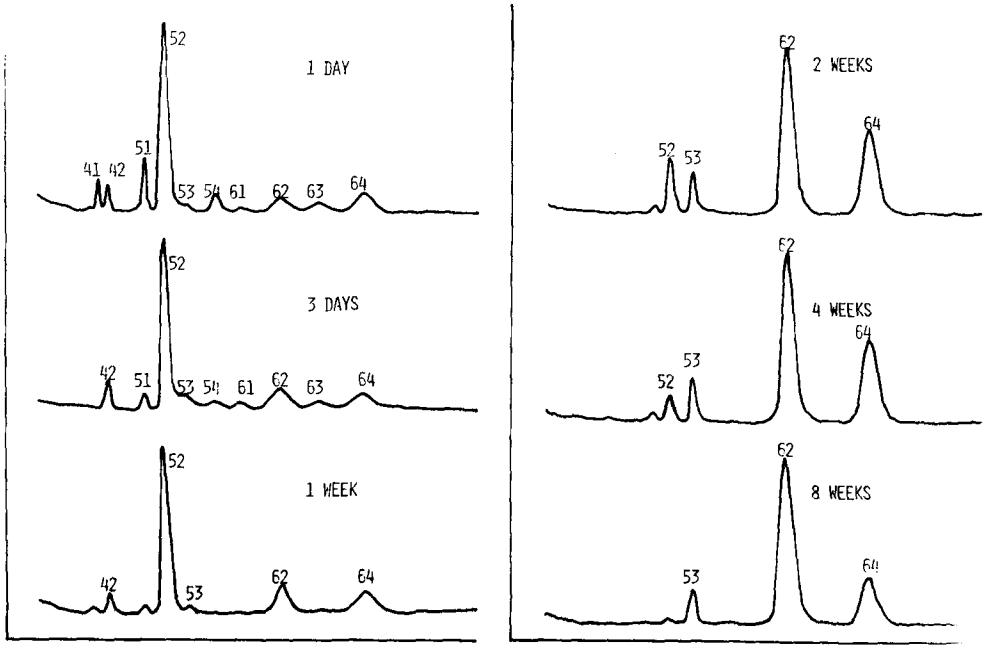


Fig. 2 Gaschromatographic pattern change of PCDFs in mouse liver. PCDFs were administered intraperitoneally.

gram of liver suggesting that PCDFs were metabolized in liver with different rate relating to the chemical structures.

Analysis of organs indicated that PCDFs were mainly located in liver, spleen and fat tissue.

Table 1. Organ Distribution of PCDFs in mice administered intraperitoneally.

| Organs | 3 days | | 4 weeks | |
|---|---|---|---|---|
| | ug | (ppm) | ug | (ppm) |
| Brain | 0.078 | (0.164) | | |
| Lungs | 0.262 | (1.33 ) | 0.008 | (0.011) |
| Heart | 0.068 | (0.71 ) | 0.002 | (0.006) |
| Spleen | 5.18 | (55.7 ) | 0.061 | (0.359) |
| Testes | 1.59 | (6.46 ) | 0.017 | (0.061) |
| Kidneys | 3.70 | (6.69 ) | 0.028 | (0.048) |
| Liver | 87.2 | (36.1 ) | 17.6 | (4.37 ) |
| Fat | | (147.5) | | (3.15 ) |

Lower concentrations were found in kidneys, testes and lungs. Minimal amounts of PCDFs appeared in heart, lungs and brain. The distribution pattern is different from that of PCBs or TCDD. It is interesting that PCDFs are deposited in spleen in high concentration.

Four weeks or eight weeks after single intraperitoneal administration, PCDFs disppeared from most of organs. Liver and fat tissue were the main depositing site of PCDFs. GLC patterns of liver samples were markedly changed during the experimental period. On the other hand. GLC patterns of fat tissues of eight weeks after administration was comparatively similar to that of initial day indicating that dosed PCDFs stayed persistently in fat tissue. GLC patterns of most organs four weeks after administration were similar to that of fat tissue and different from that of liver sample.

Fig. 2 shows the GLC patterns of PCDFs in liver after 1 day, 3 days, 1 week,2 weeks, 4 weeks and 8 weeks of administration. Peaks 41,42,51 and 54 were rapidly disappeared. Peaks 42,52,61 and 63 were metabolized less rapidly. Peaks 53 and 64 were quite slowly metabolized and peak 62 seemed to be almost non-metabolized. Peak 42 was tentatively assigned to be 2,3,7,8-tetrachlorodibenzofuran from GLC retention time. This compound seemed to have an approximate half life of 1 week in the liver of mouse. Since we had no further informations on the structure of PCDF isomers, we could not show a relationship between the metabolic rate and the chemical structures.

Fig. 3 shows the clearance of PCDFs in various organs. Clearance of PCDFs from brain, heart, lungs, and spleen proceeded rapidly. While that from liver roceeded less rapidly. Biological half life in mice may be estimated to be about two weeks.

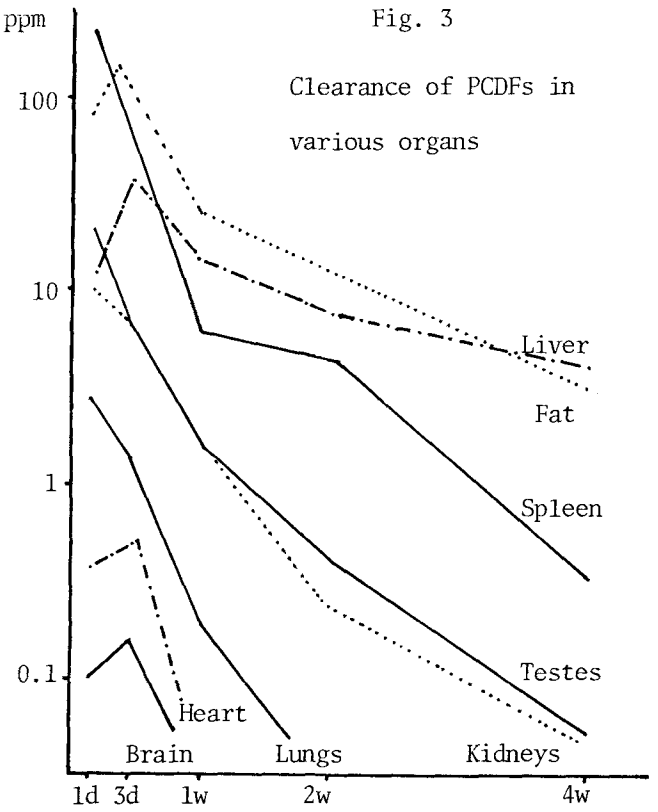


Fig. 3

Clearance of PCDFs in various organs

PCDF sample employed here was somewhat different in isomer components from that in commercial PCB preparations. However , several main peaks are often superposable on the gaschromatograms of both PCDFs. For example, major PCDF components in Chlophen a 40 corresponded to peak 42, 51 and 52. Therfore, the present result may reflect the clearance of PCDFs in PCB preparations. Further experiments are now under way on the structural determinations of PCDF isomers and also on the toxicologial effects on rats.

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