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Alkylnaphthalenes. I. Absorption, Tissue Distribution and Excretion of 2,6-Diisopropylnaphthalene in Rats

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Upon a single oral administration of 2,6-DIPN (100 mg/kg) to rats, about 85% of the dose was absorbed from the gastrointestinal tract during 48 hr after the administration. Only a small amount of unchanged 2,6-DIPN was excreted in urine. The maximum levels of 2,6-DIPN in the liver, kidney, heart, spleen, brain and muscle were obtained within 4 hr after the administration and then the levels decreased with time. However, the time for reaching the maximum level of 2,6-DIPN in the skin and adipose tissue was longer than that in the other tissues. In addition, the content and disappearance of 2,6-DIPN in the adipose tissue were higher and slower than those in the other tissues.

Keywords——alkylnaphthalene; 2,6-diisopropylnaphthalene; absorption; distribution; excretion; rat

Recently, alkylnaphthalenes have been used for duplicating papers, heat-transfer media, *ect*, as a substitute for polychlorinated biphenyls (PCB's). Accompanying with the increase of the use of alkylnaphthalenes, the release of the compound into environment appears to be inevitable.

The purpose of the present study was to examine the absorption, tissue distribution and excretion of 2,6-diisopropylnaphthalene (2,6-DIPN) in adult male rats.

Experimental

Materials——Pure 2,6-DIPN (mp 69.5°) was a gift of Kureha Chemical Ind. Co., Tokyo. All other chemicals and solvents used in this study were of reagent grade.

***In Vivo* Rat Experiments**——2,6-DIPN (100 mg/kg) was given as olive oil solution (40 mg/ml) to male Wistar rats, weighing 230—270 g, by stomach tube. The feces and urine were collected separately 2, 4, 6, 8, 14, 24 and 48 hr after administration of 2,6-DIPN. The rats were sacrificed by decapitation at each designated time period as mentioned above. The various tissues were collected and stored in a freezer until they were applied to analysis.

Analytical Procedure——Whole blood (10—15 ml) containing 5 ml of 3.8% sodium citrate solution or 10 ml of urine was extracted three times with 8 ml of *n*-hexane. The *n*-hexane extracts were pooled and then evaporated to dryness *in vacuo* at temperature under 30°. The residue was dissolved in an adequate volume of *n*-hexane containing 0.003% of acenaphthene as internal standard and then applied to gas-liquid chromatography (GLC). The liver, kidney, spleen, heart, brain, muscle, skin, adipose tissue, gut or feces was homogenized with an equal amount of anhydrous Na_2SO_4 in a motor with a pestle, and then extracted three times with 10 ml of *n*-hexane. The *n*-hexane extracts were treated and analyzed by the same procedure as mentioned above. When 2,6-DIPN (1.0—20 μg/g wet tissue) was added to these specimens and then analyzed by the method described above, the recovery of 2,6-DIPN was 90 to 95%.

Apparatus and Experimental Conditions of GLC——A Shimadzu gas chromatograph (Model GC-3BF) equipped with a hydrogen flame ionization detector was used for analysis. The column was 2.1 m × 3 mm glass spiral-tube containing 60—80 mesh Shimalite W coated with 10% Apiezon-L. The column temperature was maintained at 190°. The flow rate of carrier gas (N_2) was 135 ml/min. The calibration curve was obtained by plotting the concentration of 2,6-DIPN (10—100 μg/ml) against the peak height ratio of 2,6-DIPN to acenaphthene.

1) Location: *5–1 Ohe Honmachi, Kumamoto.*

Results and Discussion

In order to investigate the absorption, tissue distribution and excretion of 2,6-DIPN, the compound (100 mg/kg) was administered to rats. As shown in Table I, unchanged

Table I. Blood Level, Gut Content, and Fecal and Urinary Excretions of 2,6-DIPN

Time (hr)	2,6-DIPN			
	Blood level (μg/ml)	Gut content (mg)	Feces (mg)	Urine (μg)
2	2.87±0.05	16.27±2.80	—	—
4	1.64±0.65	13.46±3.87	0	0.41±0.28
6	0.87±0.33	10.41±1.59	—	—
8	0.49±0.26	4.90±4.34	1.54±0.56	0.52±0.20
10	0.22±0.08	3.00±0.69	1.57±0.06	0.63±0.33
14	0.08+0.04	—	—	—
24	0.05±0.01	0.45±0.43	1.86±1.13	1.12±0.85
48	0.03±0.00	0.03±0.00	3.76±1.79	0.90±0.40

2,6-DIPN (100 mg/kg) was given to rats by a single oral administration. The values represent the mean±standard deviation for 3 to 5 animals.

2,6-DIPN excreted into feces during 48 hr was approximately 3.76 mg (about 15% of the dose). That the unchanged 2,6-DIPN detected in the intestinal lumen and faces is not attributed to the biliary excretion of 2,6-DIPN absorbed from the gastrointestinal tract has been confirmed by us (data not shown). Accordingly, these facts suggest that about 85% of the dose during 48 hr after administration of 2,6-DIPN is absorbed from the gastrointestinal tract.

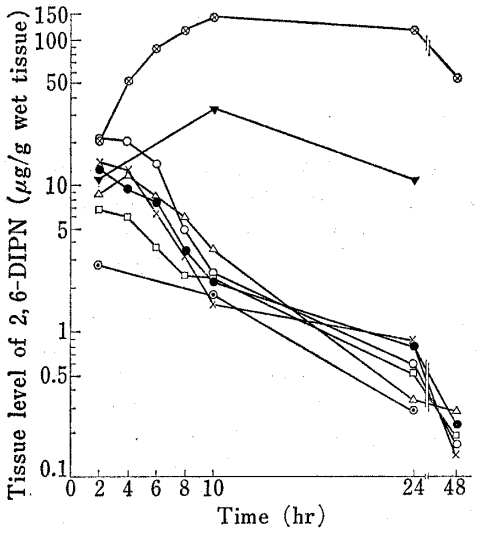

Fig. 1. Tissue Level of 2,6-DIPN following Single Oral Administration

The dose of 2,6-DIPN was 100 mg//kg. The values represent the mean for 3 or 4 animals Key: ○, liver; ●, kidney; □, spleen; ×, heart; △, brain; ⊙, muscle; ▼, skin; ⊗, adipose tissue.

The first-order rate constant for the gastrointestinal absorption of 2,6-DIPN was computed to be 0.170 hr^{-1} from the slope of the straight line on the semilogarithmic plots of 2,6-DIPN amount in the rat gut and feces against time. Also, the maximum blood level of 2,6-DIPN was observed within 2 hr after the administration. Thus, the gastrointestinal absorption of 2,6-DIPN appears to be considerably rapid.

Furthermore, unchanged 2,6-DIPN in the urine was almost excreted during the first 24 hr after the administration but its amount was extremely small. Iwahara[2] have reported that upon oral administration of ^{3}H–DIPN to mice, the radioactivity in the urine and feces was approximately 25% and 70%, respectively, of the dose during 24 hr after the administration. These facts suggest that most of 2,6-DIPN administered to rats is excreted as the form of its metabolites. However, at present, the detailed information on the metabolites of 2,6-DIPN in rats are not available.

2) S. Iwahara, *National Defence Medical J.*, **21**, 273 (1974).

The unchanged 2,6-DIPN contents in the major organs and tissues of rats are shown in Fig. 1. The maximum levels of 2,6-DIPN in the liver, kidney, heart, spleen, brain and muscle were observed within 4 hr after the administration and then decreased with time. On the other hand, the time required for reaching the maximum level of 2,6-DIPN in the skin and adipose tissue was considerably longer than that in the other tissues as described above. The maximum levels for both the tissues were obtained approximately 10 hr after the administration and then the levels decreased slowly. The order of the extent of the maximum levels (μg per g wet tissue) in these tissues was adipose tissue >skin>liver>heart, kidney, brain>spleen>muscle.

TABLE II. Distribution of 2,6-DIPN in Various Tissues

Tissue	2,6-DIPN (% of dose), hr		
	2	10	24
Blood	0.215±0.072	0.020±0.007	0.005±0.001
Liver	0.781±0.207	0.081±0.022	0.026±0.010
Kidney	0.094±0.026	0.016±0.005	0.007±0.001
Spleen	0.018±0.004	0.006±0.005	0.002±0.0005
Heart	0.043±0.013	0.004±0.001	0.004±0.003
Brain	0.016±0.013	0.025±0.009	0.003±0.0005
Muscle	1.417±0.367	0.890±0.403	0.140±0.041
Skin	1.840±0.460	5.250±0.500	1.675±0.285
Adipose tissue	1.266±0.483	10.066±0.725	8.211±2.560

The values represent the mean± standard deviation for 3 or 4 animals.

The distribution of 2,6-DIPN in various tissues (percentage of 2,6-DIPN content per tissue) are shown in Table II. The major sites for the distribution of 2,6-DIPN during the early period after the administration appeared to be the liver, muscle, adipose tissue and skin. Assuming that muscle and skin in the body weight of rats occupied approximately 50% and 16%, respectively,[3,4] the both tissues may act as the major sites of the deposition of 2,6-DIPN at early time periods. At the longer time periods after the administration, 2,6-DIPN was mainly deposited in the adipose tissue and skin. In particular, most of 2,6-DIPN was observed in the adipose tissue.

These results suggest that the adipose tissue is the major site for the storage of 2,6-DIPN in the rats as well as that in PCB's.[5]

The semilogarithmic plots of the blood level of 2,6-DIPN against time showed a biphasic disappearance curve (Fig. 2). The component 1 may be due to the rapid disappearance of 2,6-DIPN from the tissues except for the adipose tissue and skin. On the other hand, the component 2 may be due to the slower disappearance of 2,6-DIPN from the adipose tissue. This assumption may be supported by the result that the component 2 is observed after the 2,6-DIPN content in the adipose tissue reached the maximum level. However, since the disappearance rate of 2,6-DIPN was considerably rapid as compared with that of PCB's in rats,[4,5] the accumulation of 2,6-DIPN in the adipose tissue may be lower than that of PCB's.

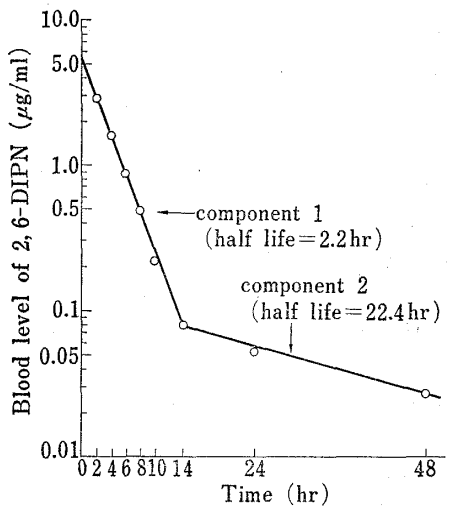

Fig. 2. Blood Level of 2,6-DIPN following Single Oral Administration

The dose of 2,6-DIPN was 100 mg/kg. The values represent the mean for 3 or 4 animals.

3) K.B. Bischff, R.L. Dedrick, D.S. Zaharko, and J.A. Longstreet, *J. Pharm. Sci.*, 60, 1128 (1971).
4) H.B. Matthews and M.W. Anderson, *Drug Metab. Dispos.*, 3, 211 (1975).
5) H.B. Matthews and M.W. Anderson, *Drug Metab. Dispos.*, 3, 371 (1975).