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Excretion and Tissue Distribution Properties of PCB-126 for Establishing a Bioaccumulation Model in Mice

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Polychlorinated biphenyls (PCBs) are persistent environmental pollutants, and their harmful effects on humans and animals are a major concern. Although the mechanisms of PCB toxicity have been studied, and they are known to largely accumulate in adipose tissue and liver, no therapy for PCB exposure has been established. To develop excretion-enhancing methods or antidotes for PCBs, animal models reflecting actual PCB bioaccumulation should be used. To establish such a model, we administered four levels of [^{3}H]-labeled PCB-126 (710.4×10^4, 142.1×10^4, 28.4×10^4, and 5.7×10^4 dpm) to mice and investigated their excretion and tissue distribution. Lindane was used as a readily excreted comparator. 28.4×10^4 or 5.7×10^4 dpm [^{3}H]PCB-126 resulted in excretion and tissue-distribution levels that were close to the detection limit. Administration of the maximum dose of [^{3}H]PCB-126 resulted in continual excretion in feces and urine over the 8-day experimental period. In the mouse administered 142.1×10^4 dpm [^{3}H]PCB-126, the fecal and urinary excretion were reduced to a constant low level by day 8 after exposure, suggesting that the distribution of [^{3}H]PCB-126 into the tissues had almost been completed. Our results suggest that mice administered 142.1×10^4 dpm [^{3}H]PCB-126 could be suitable as a PCB-126 bioaccumulation model for research to facilitate methods to enhance PCBs excretion and to develop therapies for PCBs toxicity.

Key words persistent organic pollutants, fecal excretion, polychlorinated biphenyls, bioaccumulation model, lindane

INTRODUCTION

Polychlorinated biphenyls (PCBs) have been widely used as insulators, electrical energy transformers, heaters, and coolers in industrial fields[1] because of their excellent chemical stability and electrical insulation. PCBs comprise approximately 200 isomers, some of which exhibit dioxin-like toxic effects (dioxin-like PCBs). PCBs exhibit high environmental persistence and bioaccumulation, and their harmful effects on humans and animals are a major concern. In the 1970s, PCB contamination occurred in Japan, Taiwan, Belgium, and other countries[2–4]; the most representative PCB poisonings have been "YUSHO" in Japan and "Yuchen" in Taiwan. These induced various health effects including chloracne and hyperlipidemia[5,6] due to the ingestion of PCB-contaminated rice oil. Therefore, PCBs have been regulated for manufacture, use, and transport by the Stockholm Convention on Persistent Organic Pollutants.[7]

PCBs have been reported to exhibit strong carcinogenicity, teratogenicity, immunotoxicity, and endocrine-disrupting effects.[8–11] Aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor, is known to play an important role in the toxicity of PCBs because PCB toxicity is abolished in AhR-knockdown cells and knockout mice.[12–14] AhR is activated by ligands including PCBs, dioxins, polyaromatic hydrocarbons, heterocyclic amines, and tryptophan metabolites and induces the expression of AhR-regulated genes such as cytochrome P450 (CYP) 1A1, CYP1A2, and CYP1B1,[15–17] which are enzymes involved in PCB metabolism. In addition, reactive oxygen species (ROS) can be generated. Because PCBs are minimally metabolized, ROS generation can continue for a long time[18] and can result in oxidative stress followed by damage to DNA, proteins, and lipids and the release of pro-inflammatory cytokines. In fact, YUSHO patients showed high blood ROS levels compared with a non-exposed group.[19]

Like dioxins, PCBs exhibit high lipophilicity and capacity for binding to the CYP1A2 protein, which functions as a reservoir for dioxins in the liver. PCBs therefore mainly accumulate in the adipose tissue and liver.[20,21] To develop therapies for PCB exposure and toxicity, it is necessary to establish methods to enhance PCB excretion by using appropriate animal models. Intraperitoneally or orally administered PCB-136 is excreted in urine and feces of rats, dogs, and monkeys.[22,23] In humans, PCBs are excreted mainly in feces and sebum, and they are excreted slightly in urine.[24,25] Therefore, PCBs are excreted primarily in feces and sebum with minor excretion in urine. Methods for enhancing PCB excretion from experimental animals have commonly used activated charcoal and dietary fiber.[26–28] Although these have the ability to adsorb PCBs

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released to the intestine by the gastrointestinal circulation, and these absorbates are finally excreted in feces, the amount of non-metabolized PCBs released to the bile duct and intestine can be very small. Thus, another, more effective, approach is needed to promote PCB release from the liver and adipose tissue. Animal models that reflect actual PCB bioaccumulation should be used; however, currently no such model has been established.[29)]

Here, we administered four amounts of radiolabeled PCB-126 (710.4×10^4, 142.1×10^4, 28.4×10^4, and 5.7×10^4 disintegrations per minute [dpm]) to mice and analyzed the toxicokinetics of PCB-126 in comparison with lindane as a reference chemical that exhibits low bioaccumulation. Only in the mouse administered 142.1×10^4 dpm [^{3}H]PCB-126 did the fecal and urinary excretion decrease to a constant low level by day 8 after administration. In addition, [^{3}H]PCB-126 accumulated largely in the adipose tissue and liver. Our results suggest that mice administered 142.1×10^4 dpm [^{3}H]PCB-126 could be used as a PCB bioaccumulation model.

MATERIALS AND METHODS

Chemicals [^{14}C]lindane and [^{3}H]PCB-126 were purchased from American Radiolabeled Chemicals, Inc. (St. Louis, MO, USA). They had specific activities of 5 mCi (1.11×10^{10} dpm)/mmol and 5 Ci (1.11×10^{13} dpm)/mmol, respectively, and both had radiochemical purity >97%. Both [^{14}C]lindane and [^{3}H]PCB-126 were diluted with olive oil. Soluene-350 tissue solubilizer and Hionic-Fluor solution were purchased from Packard Bioscience (Groningen, The Netherlands). Clear-sol II scintillator reagent was purchased from Nacalai Tesque (Kyoto, Japan). All other chemicals used were of the best commercially available grade.

Animals Eleven-week-old C57BL/6J mice were purchased from Jackson Laboratory and were housed in a room maintained at 23 ± 2°C with 50% ± 10% humidity and a 12 h light–dark cycle (lights on from 8:00 a.m. to 8:00 p.m.). Food and water were provided ad libitum. All animal care and handling procedures were approved by the Institutional Animal Care and Use Committees of Gifu Pharmaceutical University. All efforts were made to minimize both suffering and the number of animals used. At the time of the study, mice were housed individually in stainless-steel metabolic cages designed for the separate collection of feces and urine. CE-2 (CLEA, Tokyo Japan) was used as the diet in all experiments.

Animal Experiments Each dose of both chemicals was administered to a single mouse. All mice intraperitoneally injected on day 0 with one of four doses of [^{3}H]PCB-126 (208.91, 41.78, 8.36, or 1.67 ng) or [^{14}C]lindane (186.12, 37.22, 7.44, or 1.49 μg), equivalent to 710.4×10^4, 142.1×10^4, 28.4×10^4, and 5.7×10^4 dpm. Total urine and total feces were collected on days 2, 4, 6, and 8 following the [^{14}C]lindane or [^{3}H]PCB-126 treatment. All animals were euthanized on day 8, and blood samples were collected. Various tissues were then removed and weighed. Fecal samples were air-dried and then weighed. All collected blood samples were immediately centrifuged, and the serum in the supernatant was transferred to another tube for measurement of ^{3}H or ^{14}C content by liquid scintillation counting.

Detection of Radioactivity Fecal samples were air-dried and homogenized; then they were treated with isopropanol and 30% H_2O_2 as a bleaching agent. All tissues, serum, and fecal samples were then dissolved in Soluene-350 tissue solubilizer. Hionic-Fluor solution was then added, and ^{3}H or ^{14}C radioactivity was quantified with a liquid scintillation counter (Nippon Raytech Co., Tokyo, Japan). Urine samples were mixed with Clear-sol II (Nacalai Tesque, Inc., Kyoto, Japan) for measurement of radioactivity by the liquid scintillation counter. The blank value was quantified before the measurement of samples.

RESULTS

Analysis of Fecal Excretion Levels of [^{3}H]PCB-126 and [^{14}C]lindane Previously, we investigated the toxicokinetics of [^{3}H]2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in male mice early after intraperitoneal exposure to establish a bioaccumulation model of TCDD, and we demonstrated that the distribution and the daily excretion of [^{3}H]TCDD in urine and feces reached a constant from post-exposure day 8 onward.[30)] Similarly, to establish a bioaccumulation model of PCBs, in the current study we investigated the tissue distribution and excretion of [^{3}H]PCB-126, one of the most toxic PCBs, for 8 days after exposure. We report the excretion levels in two ways: the absolute amounts and the percentage of administered doses.

In absolute amounts, fecal excretion levels of [^{3}H]PCB-126 increased in a dose-dependent manner. The mouse administered 710.4×10^4 dpm showed the highest fecal excretion level compared with other groups (Table 1), but the amounts excreted decreased each day (Table 1 and Fig. 1A). In terms of the percentage of administered doses, the mouse administered 5.7×10^4 dpm excreted the highest percentage on day 2 compared with the other mice (Fig. 1A). However, in the mice administered 5.7×10^4 and 28.4×10^4 dpm, the fecal excretion levels were around the detection limit (almost the same value as the blank) except for days 2 and 4 (Table 1). In the mouse administered 142.1×10^4 dpm, the daily fecal excretion level was maximal on day 2 (2.1×10^4 dpm or 1.5% of administration) and gradually decreased from day 2 to day 8, and [^{3}H]PCB-126 was sufficiently detectable on each day (Table 1 and Fig. 1A). Moreover, the cumulative fecal excretion level almost reached a plateau on day 6 and increased little from day 6 to day 8 (Table 1 and Fig. 1B). These results indicated that a dose of 142.1×10^4 dpm was sufficient to detect excreted [^{3}H]PCB-126 in feces, and the fecal excretion reached a relatively constant low level on day 8.

We further examined the daily fecal excretion of the same radioactive dosage of [^{14}C]lindane as a positive control that was rapidly excreted from the body. For all tested dosages, daily fecal excretion levels reached a maximum on day 2 (0.1×10^4 to 0.6×10^4 dpm or 0.09% to 1.52% of the administered doses) and decreased sharply from days 2 to 4 (Table 1 And Fig. 1C). Moreover, in absolute amounts, the cumulative fecal excretion levels of [^{14}C]lindane increased only slightly from days 2 to 8 in all groups (Table 1 and Fig. 1D). These results indicated that most fecal excretion of [^{14}C]lindane occurred by day 2, and little [^{14}C]lindane was excreted in feces from day 4 onward.

Analysis of Urinary Excretion Levels of [^{3}H]PCB-126 and [^{14}C]lindane We next investigated the levels of [^{3}H]PCB-126 and [^{14}C]lindane excretion in urine. In mice administered either 5.7×10^4 or 28.4×10^4 dpm of [^{3}H]PCB-126, the urinary excretion levels were around the detection limit dur-

Table 1. The absolute amounts of fecal and urinary excretion of [^{3}H]PCB-126 and [^{14}C]lindane

	[^{3}H]PCB-126				[^{14}C]lindane			
Administration dose (dpm)	5.7×10^4	28.4×10^4	142.1×10^4	710.4×10^4	5.7×10^4	28.4×10^4	142.1×10^4	710.4×10^4
Daily fecal excretion level(dpm)								
Day 2	5078	4067	20908	147355	863	905	1612	6416
Day 4	1241	3555	13953	82652	126	111	124	41
Day 6	453	N.D.	6235	67889	396	312	104	457
Day 8	N.D.	453	1974	58647	554	382	637	503
Cumulative fecal excretion level(dpm)								
Day 2	5078	4067	20908	147355	863	905	1612	6416
Day 4	6318	7622	34860	230007	989	1016	1736	6457
Day 6	6771	7622	41096	297896	1385	1328	1840	6914
Day 8	6771	8075	43070	356543	1939	1710	2477	7417
Daily urinary excretion level(dpm)								
Day 2	911	2138	7286	103055	2096	4080	11744	60179
Day 4	1241	1924	7495	66971	247	596	1419	2608
Day 6	1577	2260	6743	64545	240	366	482	860
Day 8	1667	1666	5005	60173	158	234	318	288
Cumulative urinary excretion level(dpm)								
Day 2	911	2138	7286	103055	2096	4080	11744	60179
Day 4	2152	4062	14781	170026	2343	4676	13164	62787
Day 6	3728	6322	21524	234571	2583	5042	13646	63647
Day 8	5395	7988	26529	294745	2741	5276	13963	63934

dpm: Disintegrations per minute; N.D.: Not detected

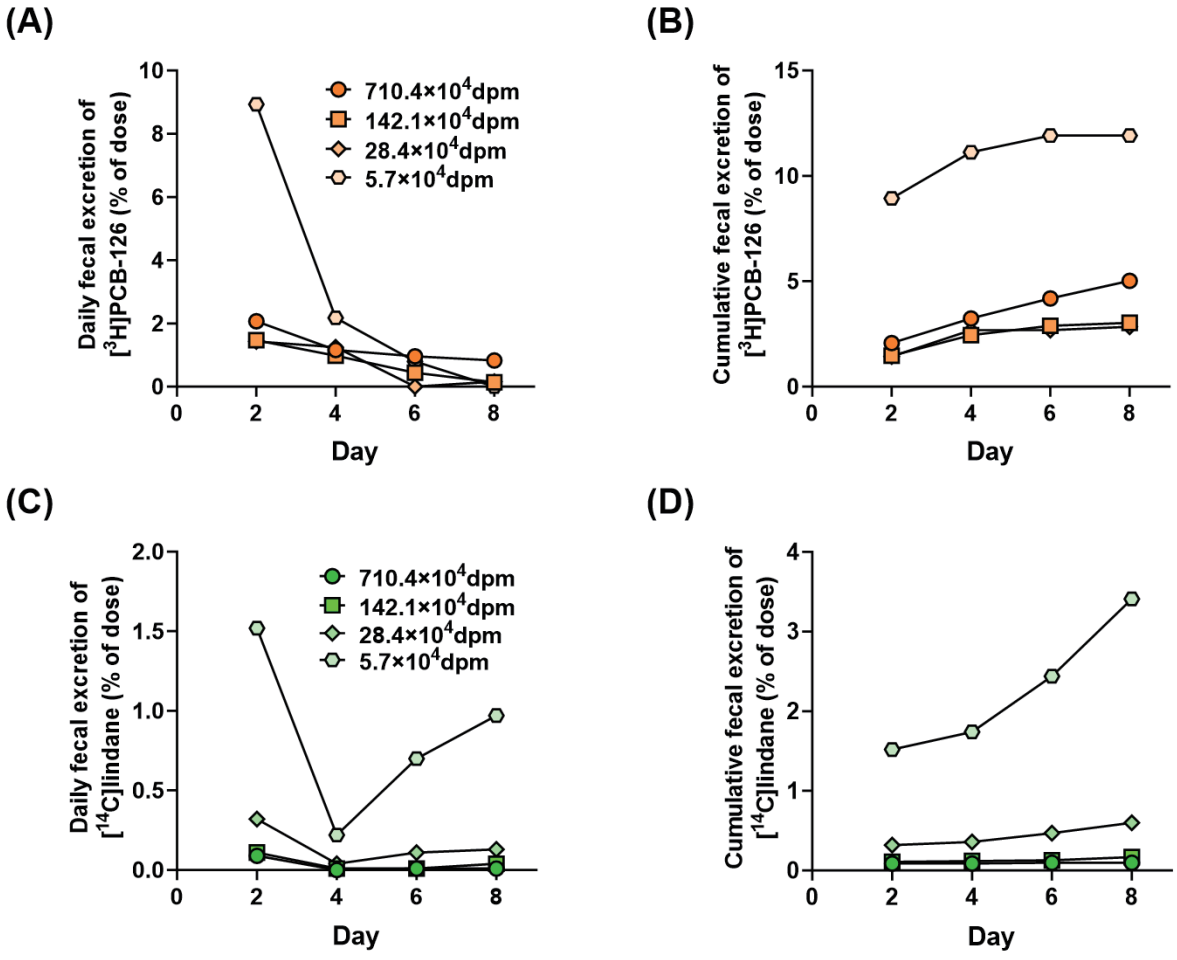

Fig. 1. Fecal Excretion of [^{3}H]PCB-126 and [^{14}C]lindane

Mice were intraperitoneally injected with one of four doses of [^{3}H]PCB-126 or [^{14}C]lindane on day 0. (A, C) Daily fecal excretion levels of [^{3}H]PCB-126 and [^{14}C]lindane shown as the percentage of administered dose. (B, D) Cumulative fecal excretion levels of [^{3}H]PCB-126 and [^{14}C]lindane shown as the percentage of administered doses.

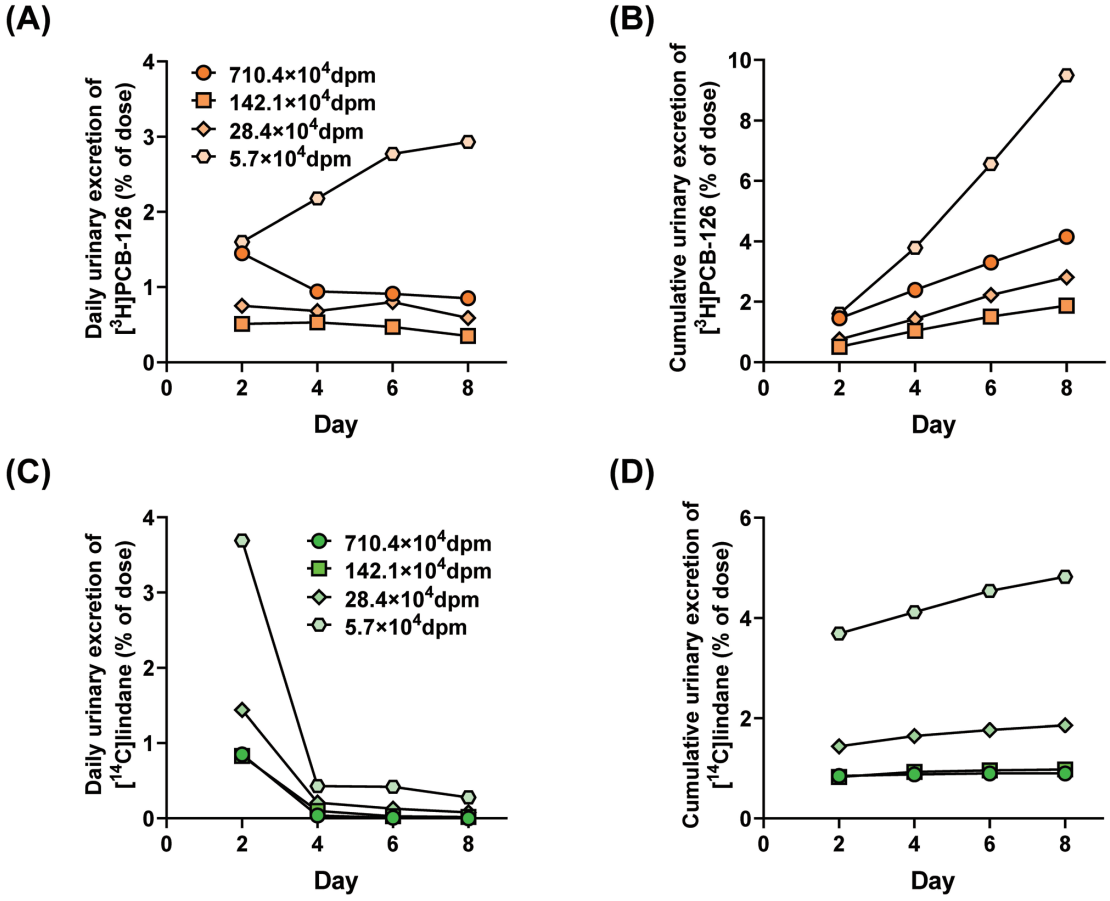

Fig. 2. Urinary Excretion Level of [3H]PCB-126 and [14C]lindane

Mice were intraperitoneally injected with one of four doses of [3H]PCB-126 or [14C]lindane on day 0. (A,C) Daily urinary excretion levels of [3H]PCB-126 and [14C]lindane shown as a percentage of administered doses. (B,D) Cumulative urinary excretion levels of [3H]PCB-126 and [14C]lindane shown as a percentage of administered doses.

ing the experimental period (Table 1 and Fig. 2A). The mouse administered 710.4 × 10^4 dpm showed the maximum urinary excretion level on day 2, and the daily urinary excretion level gradually decreased from days 2 to 8 (Table 1 and Fig. 2A). Moreover, the cumulative urinary excretion level in the mouse administered 710.4 × 10^4 dpm reached 30 × 10^4 dpm or 4.2% of administration on day 8 (Table 1 and Fig. 2B). The excretion amount of [3H]PCB-126 in the urine (Table 1 and Fig. 2) was lower than that in the feces (Table 1 and Fig. 1).

In all mice administered [14C]lindane, daily urinary excretion levels were maximal (0.2 × 10^4 to 6 × 10^4 dpm or 0.9% to 3.7% of administered doses) on day 2 and decreased sharply from days 2 to 4 (Table 1 and Fig. 2C). Although this pattern of urinary excretion was similar to that of fecal excretion, the amount of [14C]lindane excreted in urine was higher than that excreted in feces (Table 1 and Fig. 1C, 2C). Moreover, the cumulative urinary excretion levels of [14C]lindane were increased slightly or not changed from days 2 to 8 in all groups (Table 1 and Fig. 2D). These results indicated that urine, rather than feces, was the major excretion route of lindane.

Investigation of [3H]PCB-126 Concentrations in the Tissues To determine the optimal [3H]PCB-126 doses that reflect the actual tissue accumulation properties of PCBs, we investigated the concentration of [3H]PCB-126 in the serum and tissues including the major accumulation tissues (adipose tissue and liver). The concentration of [3H]PCB-126 increased in a dose-dependent manner in all tested tissues (Fig. 3A and B). The concentrations of [3H]PCB-126 in the livers and adipose tissue of all groups were shown in Fig. 3A. In the other tissues, [3H]PCB-126 was also detectable in the mice administered 710.4 × 10^4 and 142.1 × 10^4 dpm (Fig. 3B); however, the concentrations of [3H]PCB-126 in these tissues were lower than those in the liver and adipose tissues. In contrast, in the mice administered 28.4 × 10^4 and 5.7 × 10^4 dpm, [3H]PCB-126 levels were around the detection limit in the lung, brain, heart, and kidney (approximately 0.005 × 10^4 to 0.015 × 10^4 dpm/g tissue) (Fig. 3B). These results indicated that doses of PCB-126 of 142.1 × 10^4 dpm or higher would be necessary to investigate the effects of test chemicals on its toxicokinetics in its target organs.

DISCUSSION

The toxicokinetics of some PCB isomers have been reported. For example, PCB-136 and PCB-153 are metabolized and excreted in the urine and feces when intravenously administered to rats.[23] On day 1 after administration, 2% and 0.2% of the PCB-136 and PCB-153 administered, respectively, are excreted in the urine, and 40% and 30% of the doses are excreted in the feces.[23] In guinea pig, intraperitoneally administered PCB-187 is maximally excreted in the feces on day

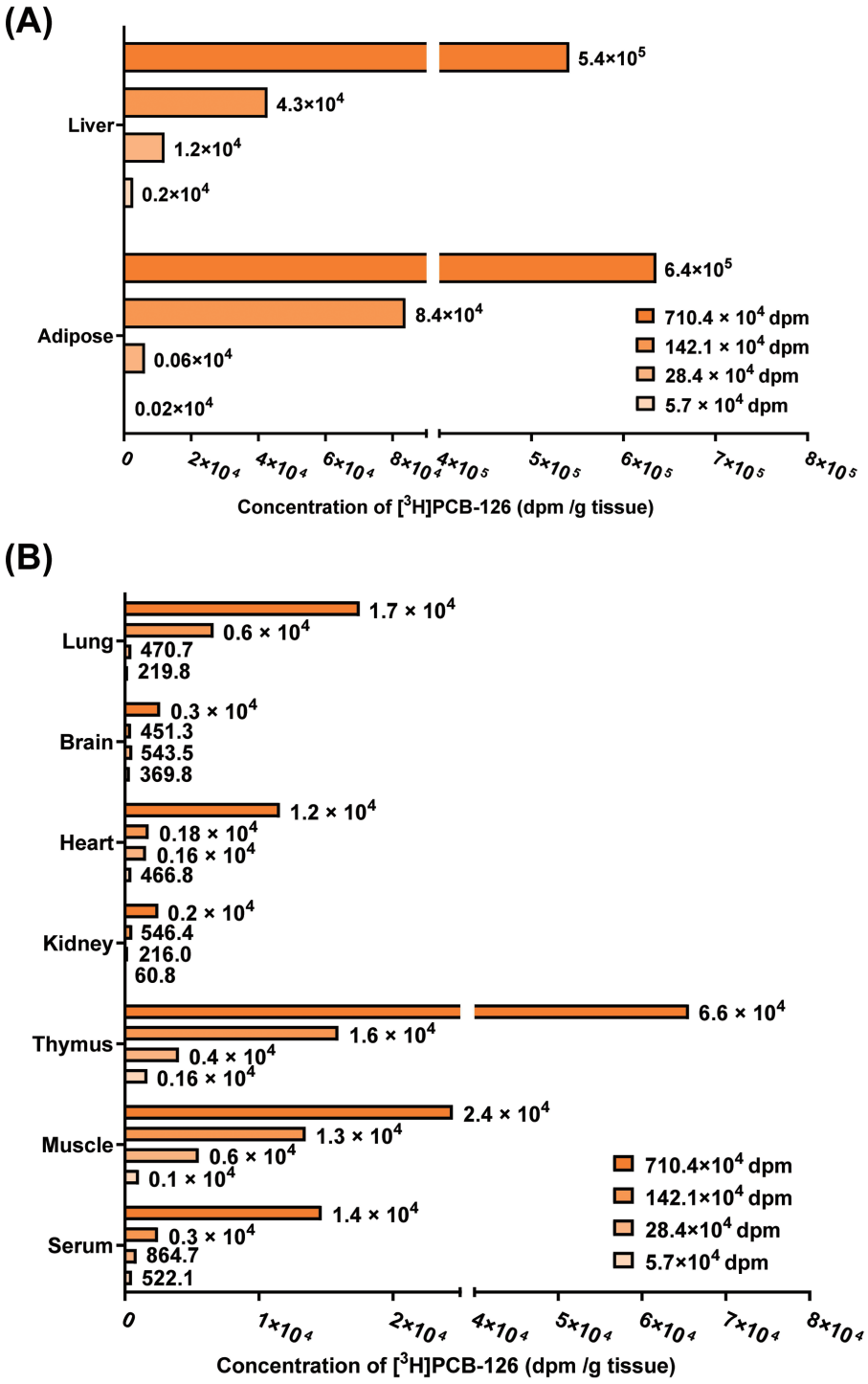

Fig. 3. [³H]PCB-126 Concentration in Tissues and Serum in from Mice Administered [³H]PCB-126

Four mice were each intraperitoneally injected with one of four doses of [³H]PCB-126 on day 0. After the mice were euthanized on day 8, the tissues were removed. The concentrations of [³H]PCB-126 in (A) the liver and adipose tissue, and (B) the lung, brain, heart, kidney, thymus, muscle, and serum are shown.

2.[31] These lines of evidence suggest that the degree of chlorination can affect the rate of metabolism and excretion of PCBs.

In order to develop antidotes and detoxification methods for PCBs, it will first be necessary to establish bioaccumulation models of PCBs; however, to our knowledge, no such model has been established. In the current study, we proposed a PCB bioaccumulation model using mice administered [³H]PCB-126. Our experiments were performed with N = 1 because PCB-126 is a class I designated chemical substance and is restricted in use. However, our results showed dose-dependent excretion levels. And urinary and fecal excretion and tissue distribution of [³H]PCB-126 were all stable 8 days after administration of a dose of 142.1 × 10⁴ dpm. An excess dose of [³H]PCB-126 administration resulted in persistent excretion in feces, perhaps because it was in excess of the volume of distribution and may have overflowed from the adipose tissue and liver, the major storage tissues. In contrast, an insufficient dose resulted in low excretion and tissue-distribution lev-

els close to the detection limit.

Both lindane and PCB-126 are organochlorine compounds, but they have different excretion characteristics: lindane is excreted mainly in urine,[32] whereas PCB-126 is excreted mainly in feces.[33] More than 99% of the composition of lindane, a neurotoxic chemical used as an agricultural and residential pesticide, is the γ-benzene hexachloride (BHC) isomer. BHC is an organochlorine compound with nine stereoisomers, each of which exhibits different characteristics. For example, the γ-BHC isomer has the most pronounced insecticidal properties,[34] whereas the β and ε isomers are non-toxic to insects.[35] In mammals, both the γ and β isomers induce liver enlargement.[36] Although γ-BHC is known for its extreme acute toxicity, it does not accumulate in the body and is rapidly excreted into the urine. In the current study, we therefore used lindane as a positive control for an excreted for a chlorinated compound that excretes quickly. Our results demonstrated that lindane was excreted mainly in urine early after its administration. This result is consistent with previous report[37] and showed that lindane was rapidly distributed to the whole body by 5 min after exposure. Approximately 50% of the dose was excreted in urine by day 1 after exposure.[37] Therefore, in our experiments, most of the lindane was probably excreted by day 2 after exposure.

The fecal [^{3}H]PCB-126 excretion plateaued at a low level by day 8 in the mouse administered 142.1×10^4 dpm. Moreover, the fact that the urinary excretion level of [^{3}H]PCB-126 was lower than the fecal excretion level was consistent with the results of previous reports about PCBs, polychlorinated dibenzo-*p*-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs).[23,30,38] The fact that PCBs, PCDDs, and PCDFs are preferentially excreted in feces instead of urine might be attributed to their high lipophilicity and limited metabolism.

In summary, we investigated the fecal and urinary excretion of [^{3}H]PCB-126, which showed the same excretion pattern as other PCBs in previous reports. We proposed that administration of 142.1×10^4 dpm [^{3}H]PCB-126 might be a suitable for PCB-126 bioaccumulation model, because the fecal and urinary excretion reached a constant low level by day 8 after administration, and [^{3}H]PCB-126 largely accumulated in the adipose tissue and liver, although there were detectable levels in other tissues. This model could contribute to establishment of excretion-enhancing methods and subsequent development of therapy for PCB toxicity.

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Conflict of interest The authors declare no conflict of interest.

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