

## Comparative Studies on Tissue Distributions of Organophosphorus, Carbamate and Organochlorine Pesticides in Decedents Intoxicated with These Chemicals

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**ABSTRACT:** This paper describes the tissue distributions of dichlorvos, an organophosphate, chlorpyrifos-methyl, an organophosphorothioate, methomyl, a carbamate, and endrin, an organochlorine, in three individuals (Cases 1–3) who died after ingesting insecticidal preparations containing these chemicals.

In Case 1 involving dichlorvos and chlorpyrifos-methyl, no dichlorvos was detected in most of the blood and tissue samples. Tiny amounts of dichlorvos (0.067 mg/L and 0.027 mg/L) were detected in the vitreous humor and cerebrospinal fluid, respectively. The chlorpyrifos-methyl concentrations in the blood samples were very site-dependent with a range of 0.615–2.24 mg/L. The tissue concentrations of chlorpyrifos-methyl were within the range 0.379–8.60 mg/kg. The total amounts of dichlorvos and chlorpyrifos-methyl in the stomach were 879 and 612 mg, respectively. The serum cholinesterase activity was 3 IU/L/37°C.

In Case 2 involving methomyl, the methomyl concentrations in the blood samples were very site-dependent with a range of 0.56–4.75 mg/L. The tissue concentrations of methomyl were 2.61 mg/kg or less, no methomyl being detected in the spleen, liver and kidney. The methomyl concentrations in the cerebrospinal fluid and vitreous humor were 5.37 and 4.75 mg/L, respectively. The stomach contained 85 mg methomyl. The serum cholinesterase activity was 73 IU/L/37°C.

In Case 3 involving endrin, the victim underwent medical treatment for 7 h after ingesting an endrin preparation. The differences in the endrin concentrations among the blood samples were small, with a range of 0.353–0.615 mg/L. The tissue concentrations of endrin were within the range 0.467–13.3 mg/kg. The endrin in the stomach (66 mg) was adsorbed almost completely on the activated charcoal that was administered for medical treatment.

**KEYWORDS:** forensic science, forensic toxicology, dichlorvos, chlorpyrifos-methyl, methomyl, endrin, tissue distributions of pesticides, postmortem stability of pesticides, esterases, gas chromatography

In Japan, more than 5000 agricultural chemical preparations are available; approximately 400 active ingredients are used. Based on

the purpose of usage, agricultural chemicals are categorized into insecticides, fungicides, herbicides, rodenticides, and plant growth regulators. There is an urgent need for the development of agricultural chemicals with high effectiveness, but with low toxicity to humans and animals. Insecticidal preparations that contain ethyl parathion, methyl parathion, tetraethyl pyrophosphate, dichlorodiphenyltrichloroethane (DDT), aldrin, endrin, etc. are no longer available in Japan because of their high toxicity. However, many farmers still store such insecticidal preparations, which were purchased previously, but not used. Yamashita et al. (1) reported that malathion was one of the organophosphorus chemicals involved most frequently in patients with acute poisoning admitted to their hospital. Thus, forensic and clinical toxicologists should be aware that poisoning by agricultural chemicals that are no longer being produced can still occur to a great extent, because of the deliberate ingestion of stored chemicals.

Determining the tissue distributions of drugs and chemicals is an important part of establishing how toxicological findings can be used for assessing the toxicity of drugs and chemicals in relation to pathological findings. However, only limited data about the tissue distributions of agricultural chemicals are available. In this study, we investigated the tissue distributions of dichlorvos, chlorpyrifos-methyl, methomyl, and endrin in persons who died after ingesting insecticidal preparations containing these chemicals.

### Case Histories

*Case 1*—An 84-year-old man (161 cm tall and weighing 46.5 kg) was found dead in a prone position in the living room of his house. A container of a liquid pesticide consisting of 2% w/v dichlorvos and 5% w/v chlorpyrifos-methyl was found in the room. At autopsy, the postmortem interval was estimated to be approximately 28 h. No miosis was observed; the diameters of the left and right pupils were 0.4 and 0.3 cm, respectively. The mucosae from the root of the tongue to the esophagus were whitish gray. The heart weighed 370 g and contained a moderate volume of liquid blood. The lungs were heavily edematous; the left weighed 600 g and the right 750 g. The stomach contained 300 g whitish gray pulpy food material with a pungent odor, and the gastric mucosa was macerated and congested with a large number of petechial hemorrhages. No marked changes, other than congestion, of other organs were observed. The serum cholinesterase activity was 3 IU/L/37°C (normal range for male: 203–460 IU/L/37°C). The cause of death was diagnosed as fatal organophosphorus chemical poisoning.

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*Case 2*—A 60-year-old woman (159 cm tall and weighing 52.5 kg) who had suffered from depressive psychosis was found lying in a prone position on the ground outside her house. A vinyl rope used for strangling herself and a cup containing an aqueous solution of methomyl were found near her body. At autopsy, the postmortem interval was estimated to be approximately 28 h. No miosis was observed; the diameters of the left and right pupils were 0.4 and 0.35 cm, respectively. Ligature marks encircling the neck were observed. The face was markedly congested and there were many petechiae on the mucosae of the left and right eyes and the buccal cavity. There were no fractures of the hyoid bone and thyroid cartilages. The heart weighed 280 g and contained a large volume of liquid blood. The lungs had acute emphysema; the left weighed 300 g and the right 350 g. The stomach contained 250 g of brownish pulpy food material. No marked changes, other than congestion, of other organs were observed. The serum cholinesterase activity was 73 IU/L/37°C (normal range for female: 179–354 IU/L/37°C). The cause of death was thought to be asphyxia due to self-strangulation with the ligature.

*Case 3*—An 86-year-old woman (146 cm tall and weighing 48 kg) who had suffered from senile dementia was found lying in bed in her house and rushed to a hospital. She died about 7 h after being hospitalized. Three bottles of a liquid pesticide containing endrin were found outside her house. An autopsy was performed approximately 20 h after death. The mucosa of the esophagus was whitish gray. The heart weighed 380 g and contained a moderate volume of liquid blood containing small amounts of chicken fat clots. The lungs had acute emphysema; the left weighed 270 g and the right 330 g. The stomach contained 60 g of pulpy material composed mainly of activated charcoal and a clear liquid, and the gastric mucosa had a laceration (2 cm long) and a small number of petechial hemorrhages. Marked hemorrhages were observed in the iliopsoas muscles. The cause of death was diagnosed as fatal endrin poisoning.

## Toxicological Analysis

### Apparatus

A gas chromatograph (Shimadzu GC-14B, Kyoto, Japan) equipped with a TC-1 capillary column [dimethyl silicone, 15 m by 0.53 mm internal diameter, 1.5  $\mu$ m film thickness (GL Sciences Inc., Tokyo, Japan)], a TC-17 capillary column [50% phenylmethyl silicone, 15 m by 0.53 mm internal diameter, 1  $\mu$ m film thickness (GL Sciences Inc., Tokyo, Japan)] and a flame thermionic detector (FTD) or flame ionization detector (FID) was employed for screening and quantification of the agricultural chemicals. The temperature of both the injection port and detector was 260°C. The column temperatures were programmed as follows: the initial temperature of 100 or 150°C was maintained for 0 or 2 min, respectively, then increased to 260°C at a rate of 10°C/min and the final temperature was maintained for 27 min. The carrier gas was nitrogen at a flow pressure of 15 kPa.

A gas chromatography/mass spectrometry (GC/MS) system comprising a gas chromatograph (Shimadzu GC-9A, Kyoto, Japan) equipped with a 2 m by 0.26 cm internal diameter glass column packed with 2% OV-1 on 60–80 mesh Chromosorb W AW DMCS, and a mass spectrometer (Shimadzu QP 1000 D, Kyoto, Japan) was employed for confirmation of the agricultural chemicals. The column temperatures were programmed as follows: the initial temperature of 100 or 150°C was maintained for 2 min and then increased to 280°C at a rate of 10°C/min. The tem-

perature of both the injection port and separator was 280°C, the electron impact ionization energy and accelerating voltage were 70 eV and 3 kV, respectively, and the carrier gas was helium, at a flow rate of 40 mL/min.

### GC Quantification of Dichlorvos and Chlorpyrifos-methyl

A quantity of 1 mL each body fluid, 1 g each tissue homogenate (tissue:water = 1:3 by weight) or 1 g homogenate of the stomach contents (stomach contents:water=1:99 by weight) was mixed with a 50- $\mu$ L aliquot of 50 mg/L chlorpyrifos in acetone (internal standard) and 1 mL 0.5 M phosphate buffer (pH 5.5). Each mixture was extracted with 4 mL diethyl ether for 20 min using a mechanical shaker, centrifuged, the upper organic phase was transferred to a glass tube, reduced to 1 mL at 38–40°C and then evaporated to dryness at room temperature under a gentle stream of air. The residue was dissolved in 0.4 mL acetonitrile and partitioned with 0.4 mL n-hexane for 1 min using a vortex mixer. The upper n-hexane phase was aspirated, this partition step was repeated, the residue was evaporated to dryness at room temperature under a gentle stream of air, and reconstituted with 0.2–1 mL acetone. A 1- $\mu$ L aliquot of this mixture was injected into the GC. The sensitivities of the GC assays for both dichlorvos and chlorpyrifos-methyl in body fluids and tissues were about 0.005 mg/L and 0.020 mg/kg, respectively.

### GC Quantification of Methomyl

A quantity of 1 mL each body fluid, 1 g each tissue homogenate (tissue:water = 1:3 by weight) or 1 g homogenate of the stomach contents (stomach contents:water=1:99 by weight) was mixed with 1 mL 0.5 M phosphate buffer (pH 5.5). Each mixture was extracted with 4 mL dichloromethane for 20 min using a mechanical shaker and centrifuged. The lower organic phase was transferred to a glass tube, this extraction step was repeated, the combined organic phase was reduced to 1 mL at 40–42°C and then evaporated to dryness at room temperature under a gentle stream of air. The residue was dissolved in 0.4 mL acetonitrile and partitioned with 0.4 mL n-hexane for 1 min using a vortex mixer. The upper n-hexane phase was aspirated, this partition step was repeated, the residue was evaporated to dryness at room temperature under a gentle stream of air and reconstituted with 0.1 mL 0.1 N NaOH. This mixture was heated at 80°C for 30 min to hydrolyze methomyl to S-methyl-N-hydroxythioacetimidate, neutralized with 0.05 mL 0.2 N H<sub>2</sub>SO<sub>4</sub> and mixed with a 20- $\mu$ L aliquot of 25 mg/L dichlorvos in acetone (external standard). The mixture was extracted with 0.2 mL ethyl acetate for 30 s using the vortex mixer and centrifuged. A 1- $\mu$ L aliquot of the upper organic phase was injected into the GC. The sensitivities of the GC assays for methomyl in body fluids and tissues were about 0.01 mg/L and 0.04 mg/kg, respectively.

### GC Quantification of Endrin

A quantity of 2 mL each body fluid, 2 g each tissue homogenate (tissue:water = 1:3 by weight) or 2 g homogenate of the stomach contents (stomach contents:water=1:99 by weight) was mixed with a 50- $\mu$ L aliquot of 120 mg/L methaqualone in methanol (internal standard) and 2 mL 0.5 M phosphate buffer (pH 5.5). Each mixture was extracted with 8 mL diethyl ether for 20 min using a mechanical shaker, centrifuged, the upper organic phase was transferred to a glass tube and then evaporated to dryness at 50°C. The residue was dissolved in 0.4 mL acetonitrile and partitioned with

0.4 mL n-hexane for 1 min using a vortex mixer. The upper n-hexane phase was aspirated, this partition step was repeated, the residue was evaporated to dryness at 70°C under a gentle stream of air, reconstituted with 50 µL methanol and a 1-µL aliquot of this mixture was injected into the GC. The sensitivities of the GC assays for endrin in body fluids and tissues were about 0.025 mg/L and 0.100 mg/kg, respectively.

## Results

Table 1 shows the concentrations of dichlorvos, chlorpyrifos-methyl, methomyl, and endrin in the body fluids and tissues of the poisoning victims.

In Case 1, no dichlorvos was detected in blood samples from the cardiac chambers, pulmonary vessels or right femoral vein, cerebrum, lungs, myocardium, liver, right kidney, right femoral muscle, or urine. Tiny amounts (0.027–0.082 mg/L) were detected in the cerebrospinal fluid, vitreous humor, thoracic aortic blood and inferior vena caval blood, and substantial amounts (0.438–8.99 mg/L or mg/kg) were present in the pericardial fluid, spleen and bile. The chlorpyrifos-methyl concentrations in the blood samples were very site-dependent with a maximum concentration of 4.15 mg/L in the pulmonary arteries and a minimum concentration of 0.615 mg/L in the right femoral venous blood. Negligible amounts of chlorpyrifos-methyl (0.008–0.012 mg/L) were detected in the cerebrospinal fluid, vitreous humor and pericardial fluid and none was detected in the bile or urine. Large amounts of dichlorvos and chlorpyrifos-methyl, 879 and 612 mg, respectively, were detected in the stomach.

In Case 2, the methomyl concentrations in the blood samples were very site-dependent, with a maximum concentration of 4.75 mg/L in the pulmonary vein and a minimum concentration of 0.56 mg/L in the inferior vena caval blood. Various concentrations of methomyl (1.17–5.37 mg/L or mg/kg) were detected in the cerebrospinal fluid, vitreous humor, pericardial fluid, brain, lungs, and femoral muscle, but none was detected in the spleen, liver and right kidney. A relatively large amount of methomyl, 85 mg, was detected in the stomach.

In Case 3, the differences in the endrin concentrations among the blood samples were small, with a range of 0.353–0.615 mg/L. The endrin concentration in the cerebrospinal fluid was within the range for the blood endrin concentrations. The endrin concentrations in the vitreous humor, pericardial fluid and bile were higher than those in the blood samples. Various concentrations of endrin (0.467–13.8 mg/kg) were detected in the cerebrum, lungs, myocardium, liver and right femoral muscle, but none was detected in the right kidney. The stomach contained 66 mg endrin, 99.9% of which had been adsorbed on the activated charcoal used for medical treatment.

## Discussion

Data on the tissue distributions of drugs and chemicals in humans are very useful not only for toxicokinetic and pharmacokinetic studies, but also for determining the specimens of choice for postmortem toxicological analysis. However, special caution should be exercised in the analysis of postmortem body fluids and tissues for drugs and chemicals because the drug and chemical con-

TABLE 1—Concentrations of dichlorvos, chlorpyrifos-methyl, methomyl, and endrin in various body fluids and tissues of three individuals (Cases 1–3) who died after ingesting insecticidal preparations containing these chemicals.

Sample	Concentration (mg/L or mg/kg)			
	Case 1		Case 2	Case 3
	Dichlorvos	Chlorpyrifos-methyl	Methomyl	Endrin
Blood				
Left cardiac chambers	ND	1.01	4.89	0.615
Right cardiac chambers	ND	1.71	1.08	0.568
Pulmonary arteries	ND	4.15	4.75	—
Pulmonary veins	ND	2.83	4.09	—
Thoracic aorta	0.043	0.987	7.00	0.542
Thoracic inferior vena cava	0.082	2.24	0.56	0.453
Right femoral vein	ND	0.615	3.91	0.353
Cerebrospinal fluid	0.027	0.008	5.37	0.515
Vitreous humor	0.067	0.009	4.75	1.67
Pericardial fluid	0.438	0.012	3.67	1.00
Bile	8.99	ND	5.68	2.06
Urine	ND	ND	4.76	—
Cerebrum	ND	0.379	2.26	1.93
Lung				
Left hilus	ND	8.60	1.17	6.20
Right hilus	—	—	1.86	1.19
Myocardium	ND	0.491	0.08	0.467
Liver				
Deep within right lobe	ND	1.41	ND	13.8
Spleen	0.542	0.666	ND	—
Right kidney	ND	0.472	ND	ND
Right femoral muscle	ND	0.392	2.61	2.08
Stomach contents	2929 (879*)	2041 (612*)	340 (85*)	1100 (66*)

\* The total amount in the stomach.

ND = not detectable.

centrations in body fluids and tissues can vary postmortem, even in apparently non-decomposed bodies. There are three main reasons for this variation: (i) chemical and/or enzymatic degradation of drugs and chemicals (2,3), (ii) postmortem redistribution of drugs and chemicals (4,5), and (iii) postmortem diffusion from the stomach containing large amounts of drugs and chemicals (6,7).

In Case 1, the presence of dichlorvos in the cerebrospinal fluid and vitreous humor suggests strongly that dichlorvos had been absorbed antemortem to some degree, although it was not detected in the blood samples obtained from the cardiac chambers, pulmonary vessels and femoral vein or in organs other than the spleen. The cerebrospinal fluid and vitreous humor are spared from postmortem diffusion of drugs and chemicals in the stomach or postmortem redistribution of drugs and chemicals. The liver and serum are known to possess high A-esterase (paraoxygenase) activities (8) and A-esterases can hydrolyze organophosphates, but are not inhibited by them, whereas B-esterases, such as ali-esterases and cholinesterases, are inhibited strongly by organophosphorus chemicals, but do not hydrolyze organophosphates (9). The *in vitro* half-lives of dichlorvos in whole blood (10 mg/L) at 15–25°C are approximately 3 and 18 h at pH 7.4 and 6.2, respectively (10). Thus, dichlorvos that was present in the blood and tissues of our subject at the time of death might have been degraded almost completely before toxicological analysis. We found that the cholinesterase activities in the cerebrospinal fluid, vitreous humor and pericardial fluid in healthy humans ( $n = 3-4$ ) were  $1.3 \pm 1.5$ ,  $0.7 \pm 1.2$  and  $67.0 \pm 12.6$  IU/L/37°C, respectively. This suggests strongly that the cerebrospinal fluid and vitreous humor have little A-esterase activities as well, although A-esterase activities in these fluids were not determined. Thus, it is suggested that enzymatic metabolism of organophosphates in the cerebrospinal fluid and vitreous humor may be negligible. The pH value of the cerebrospinal fluid, as well as that of blood, rapidly decreases below 7.0 postmortem due to anaerobic glycolysis (11,12). The pH of the vitreous humor, however, remains around 7.4 postmortem. Thus, the extent of chemical degradation of organophosphates may be a little smaller in the cerebrospinal fluid than in the vitreous humor. For these reasons, the cerebrospinal fluid may be the specimen of choice for detecting parent organophosphates in corpses with longer postmortem intervals, and the next best may be the vitreous humor. The dichlorvos detected in the thoracic aortic blood, thoracic inferior vena caval blood, pericardial fluid, bile, and spleen is thought to have resulted mainly from the postmortem diffusion of dichlorvos from the stomach, because these fluids and tissue are very close to the stomach.

Chlorpyrifos-methyl, which was another organophosphorus compound detected in Case 1, is stable chemically and enzymatically in blood at pH 7.4 and 6.2 for at least 72 h (10). Thus, virtually no postmortem degradation of chlorpyrifos-methyl may have occurred. The postmortem diffusion of chlorpyrifos-methyl from the stomach seemed to be negligible, because no chlorpyrifos-methyl was detected in the bile and only a tiny amount was detected in the pericardial fluid; its concentration in the spleen was similar to those in the cerebrum, myocardium, right kidney, and right femoral muscle. The chlorpyrifos-methyl concentrations in the pulmonary vessels were higher than those in the other blood samples and this may have been due to postmortem redistribution of chlorpyrifos-methyl from the pulmonary tissues into the pulmonary vessels, because moderate deposition of chlorpyrifos-methyl in the lung was observed (4). The large amount of chlorpyrifos-methyl remaining in the stomach and the relationship among the chlorpyrifos-methyl concentrations in the blood samples obtained from

the cardiac chambers, thoracic inferior vena cava, thoracic aorta, and right femoral vein suggest strongly that the victim died at an early stage of chlorpyrifos-methyl absorption. For quantitative analysis for chlorpyrifos-methyl in postmortem specimens, peripheral blood may be better, and the cerebrum, myocardium, kidneys, and skeletal muscles of extremities may be alternative specimens to blood.

Methomyl can be metabolized postmortem by tissue carboxylesterases (13). Thus in Case 2, the tissue distributions of methomyl determined postmortem may not mirror those at the time of death. The methomyl concentrations in blood in fatal and serious poisoning cases were reported to be 0.7–1.4 mg/kg (14) and 3.24 mg/L (15), respectively. However, none of the reports discussed the postmortem stability of methomyl. In our case, it was suggested strongly that methomyl had been metabolized to various extents in body fluids and tissues postmortem, because the methomyl concentrations in the blood samples were very site-dependent and no methomyl was detected in the liver, spleen and kidney. High concentrations of methomyl in the cerebrospinal fluid and vitreous humor also suggest this possibility, because these samples may have low esterase activity as mentioned above. The methomyl in the stomach might have diffused into surrounding tissues and fluids only minimally, because no methomyl was detected in the spleen. The cerebrospinal fluid and vitreous humor may be the specimens of choice for detecting carbamates, as well as organophosphates, postmortem.

In Case 3, the victim received medical treatment for 7 h before death. In the stomach, a relatively large amount of endrin remained, and practically all the endrin was adsorbed on activated charcoal that had been administered for medical treatment. Thus in this case, a factor such as postmortem diffusion of endrin from the stomach into the surrounding fluids and tissues can be ignored. There was a large difference between the endrin concentrations in the left and right lungs. Agonal aspiration of the stomach contents might have occurred to some degree during medical treatment. Organochlorine compounds are very stable in biological specimens (13). The endrin concentrations in the postmortem peripheral blood samples can be used to assess the seriousness of poisoning by endrin. The cerebrospinal fluid may be an alternative sample to blood.

The results of this study led us to draw the following conclusions: (i) the cerebrospinal fluid and vitreous humor appear to be the specimens of choice in which to detect organophosphates and carbamates postmortem, because these specimens may have little esterase activity, and (ii) the concentrations of organophosphorothioates and organochlorine compounds in postmortem peripheral blood samples may mirror their concentrations in blood at the time of death.

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