Analytical Method for Simultaneous Determination of Pesticides and Pesticide Transformation Products in Water Environment Using GC-MS and LC-MS/MS

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ABSTRACT

Exposure to chemicals and their transformation products is important for evaluating environmental risk. In this study, the analytical method for both pesticides and pesticide transformation products (PTP) in water environments was developed. Eleven pesticides were selected based on the amount of their use in Kanagawa, Japan. According to previous literature research for PTP which have been found in hydrolysis and/or photolysis, 77 PTP could be enumerated. Among them, 30 commercially available PTP and their 11 parent pesticides were tested in this study. The detection sensitivity for pesticides and PTP was evaluated using GC-MS and LC-MS/MS. Using GC-MS, 31 compounds could be detected with a limit of quantification (LOQ) of 10 – 50 ng/mL. To achieve detection of GC-MS-unfavorable compounds and more sensitive detection by LC-MS/MS, two atmospheric pressure ionization methods (electron spray ionization (ESI) and atmospheric pressure chemical ionization (APCI)) were assessed. Comparison of the LOQs demonstrated that the ESI method achieved more sensitive analysis than the APCI method. Also, LC-ESI-MS/MS showed higher sensitivity (< 1 ng/mL) for the 11 compounds. As a result, except for 3 PTP, all pesticides and PTP were detected by the method developed. This analytical method can be applied to determine pesticides and PTP in environmental water samples.

Keywords: GC-MS, LC-MS/MS, pesticide, pesticide transformation product in water environments, simultaneous analysis

INTRODUCTION

Pesticides, which are widely used in agriculture for a consistent food supply, belong to many different chemical groups. These chemicals can be transformed in natural environments by hydrolysis and photolysis among other means. Spraying of a variety of pesticides further creates various pesticide transformation products (PTP) in water environments and pollution by these substances is thus now an increasing concern with regard to not only environmental risk but also health risk. Because of this concern, pesticides and their PTP in water matrices including groundwater and surface water have been determined elsewhere (Albanis *et al.*, 1998; U. S. Geological Survey, 2003; Hladik *et al.*, 2008; Iwafune *et al.*, 2010). These studies demonstrated that PTP could be found in higher concentrations than their parent pesticides in water environments; however, these studies mainly focused on the major PTP of target pesticides. On the other hand, the molecular structure of some PTP, which are not mutagens and are thus

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Received May 10, 2012, Accepted July 24, 2012.

neglected by regulations, could change to become mutagenic by chlorination in water purification plants (Kishida *et al.*, 2010). Kishida *et al.* (2010) reported that 3-methyl-4-nitrophenol (3M4NP), a PTP of the organophosphorus insecticide fenitrothion, has 19 times greater mutagen formation potential (MFP) than the MFP of the parent, fenitrothion. Our recent monitoring results have shown that 3M4NP was found in higher concentrations than fenitrothion in rivers in Kanagawa, Japan (Kameya *et al.*, 2012); thus, besides the identification of such substances, the fate of pesticides and all their possible PTP in water environments should be assessed. However, such a method development and a monitoring report for multiclass pesticides and PTP in water environment have not reported. Therefore, the method development to identify and quantify these substances simultaneously is indispensable.

To detect pesticides and PTP, gas chromatography (GC) and liquid chromatography (LC) equipped with mass spectrometer(s) (MS) have been widely accepted. The GC-MS system provides a robust analytical method for the detection of volatile and thermally stable compounds with high selectivity and sensitivity. For non-volatile or thermally unstable compounds, LC-tandem mass spectrometry (LC-MS/MS) is a powerful method. For most polar pesticides, LC-MS/MS has achieved much better selective and sensitive detection than GC-MS (Alder *et al.*, 2006). As for LC-MS/MS analysis, there are two types of ionization: electron spray ionization (ESI) and atmospheric pressure chemical ionization (APCI).

Hence, the objective of this study is the development of an analytical method for both pesticides and PTP simultaneously using GC-MS and LC-MS/MS. First, to develop such a method, selected pesticides and PTP were subjected to the development of the method by using GC-MS. Retention time, monitoring ion and characterization ions of each substance were identified. After that, limit of quantification (LOQ) in GC-MS analysis was determined. For further sensitive detection, LC-MS/MS analysis was performed for both the ESI and APCI methods. After identification of transition ions and retention time, LOQs in each ionization methods were determined. The developed method in this study should contribute to the monitoring of multiclass pesticides and PTP in water matrices simultaneously, and to the understanding of their environmental fate.

MATERIALS AND METHODS

Reagents and Chemicals

The pesticides and their PTP were purchased from Wako Pure Chemical Industries (Osaka, Japan), Tokyo Chemical Industry (Tokyo, Japan), Sigma-Aldrich (Tokyo, Japan), Nacalai Tesque (Kyoto, Japan) and CosmoBio (Tokyo, Japan). Purity of these chemicals ranged from 95% to 99% except for diethyl phosphate (75%). Acenaphthene-d10, naphthalene-d8, fluoranthene-d10 and phenanthrene-d10 were supplied as a mixture from RESTEK (Bellefonte, PA, USA) and utilized as internal standards (ITSDs) for GC-MS analysis. Each stock standard solution (100 to 2,000 µg/mL, depending on the solubility of each) and ITSD were prepared by dissolving in acetone or methanol and storing at -25°C. Standard solutions were diluted with adequate solvent (acetone for GC-MS and methanol for LC-MS/MS) prior to fragmentation analysis. The working standard solutions of the mixtures were prepared

by the appropriate dilution of the stock solutions at concentrations ranging from 10 ng/mL to 10 µg/mL for GC-MS and from 100 pg/mL to 100 ng/mL for LC-MS/MS. Acetone for residual pesticide analysis, methanol and ultra-pure water of HPLC-grade, and ammonium formate were obtained from Wako Pure Chemical Industries (Osaka, Japan).

GC-MS analysis

For the observation of fragment patterns, each standard solution was loaded to a GC-MS system (QP2010 plus, Shimadzu, Kyoto, Japan) which was operated under the following conditions: column, Agilent Technologies J&W DB-5ms (30 m × 0.25 mm, 0.25 µm; Tokyo, Japan); carrier gas, helium with a flow rate of 2.13 mL/min at constant flow; injector temperature, 220°C; transfer line, 250°C; ion source, electron impact (EI) at 70 eV; source temperature, 230°C; injection volume, 1 µL; injection mode, splitless; programmed oven temperature, 50°C for 2 min and ramped to 170°C at 10°C/min, then to 200°C at 3°C/min, finally to 300°C at 10°C/min, and kept for 10 min. These conditions were determined for the detection of much target analytes as referred to the methods by Kadokami *et al.* (2004). Also, ITSDs were also utilized according to Kadokami *et al.* (2004) and adequate ITSD for each substance was automatically fixed by GC-MS software (GCMS solution ver. 2.71, Shimadzu) according to retention time. After the determination of fragment ions for monitoring ion and characteristic ions, the complete mixed standards were analyzed using the selected ion monitoring (SIM) mode. The LOQ was set to the lowest concentration, which gave a signal-to-noise (S/N) ratio of ≥ 10 for the most intense peak.

LC-MS/MS analysis

The sensitivity of LC-MS/MS was assessed using a triple quadrupole mass spectrometer (TSQ Quantum Access MAX, Thermo Fisher Scientific, Yokohama, Japan) equipped with Accela HPLC (Thermo Fisher Scientific). For each ionization method, ESI and APCI, two multiple reaction monitoring (MRM) transitions and adequate collision energy for all substances were determined by direct injection of standard solutions (≥ 50 ng/mL) with methanol/2 mM-ammonium formate buffer (50 : 50).

After that, LC was operated using a Hypesil GOLD column (50 mm × 2.1 mm, 1.9 µm; Thermo Fisher Scientific, Yokohama, Japan) and the column temperature was kept at 40°C. The mobile phase consisted of 2 mM ammonium formate (A) and methanol (B). The applied gradient elution was set as follows: start with 1% B, increase to 30% B within 3 min, maintain the isocratic condition for 3 min, further increase to 99% B within 6 min, return to the initial condition within 1 min, and hold for the last 5.5 min. The flow rate was kept constant at 200 µL/min and the injection volume was 5 µL. The operational conditions for the ESI method were set as follows: spray voltage, 3,000 V; tube lens voltage, 78 V; ion transfer capillary temperature, 270°C; vaporizer temperature, 450°C; sheath gas (N₂) pressure, 50 psi; auxiliary gas (N₂) pressure, 15 units. The operational conditions for the APCI method were as follows: corona discharge current, 4 µA; tube lens voltage, 78 V; ion transfer capillary temperature, 300°C; vaporizer temperature, 300°C; sheath gas pressure, 30 psi; auxiliary gas pressure, 0 units. The collision gas (argon) pressure was set at 1.5 mTorr for both operational methods.

RESULTS AND DISCUSSION

Selected pesticides and PTP

According to the amount of pesticides in Kanagawa, Japan (Japan Plant Protection Association, 2007), and literature search for PTP using the ISI Web of Science database, 11 target pesticides were selected (Table 1). All the selected pesticides are regulated by Waterworks Law of Japan (Ministry of Health, Labour and Welfare) and the target values are also shown in Table 1. Although there are 77 PTP for the target pesticides, only 30 PTP listed in Table 1 were commercially available. Summary for the number of available and unavailable PTP of each pesticide is shown in Table 2. Commercially available PTP are roughly divided into two types: higher molecular weight PTP, which are primary metabolites such as oxon metabolites, and the lower molecular weight PTP, which have simple structures and could be sold for other research purposes. For example, there are 5 PTP for the organophosphorus insecticide acephate (Fig. 1). Only 1 higher molecular weight PTP (methamidophos) and 1 lower molecular weight PTP (dimethyl disulfide) were available. Other unavailable PTP were not tested in this study and further development of the method for the detection of these PTP is necessary.

Table 1 - Pesticides and PTP tested in this study and parameters of GC-MS analysis.

Pesticide PTP	CAS RN.	Target value ^a [mg/L]	Retention time [min]	Monitoring ion [m/z]	Characterization ions [m/z]	ITSD ^b	LOQ [ng/mL]
Acephate	30560-19-1	0.08	12.8	136	42, 94	A	<10
Methamidophos	10265-92-6		10.0	94	95, 47, 141	N	<10
Dimethyl disulfide	624-92-0		N.D.	N.D.	N.D.	N.D.	N.D.
Chlorothalonil	1897-45-6	0.05	18.1	266	264, 268	P	<10
Isophtalaldehyde	626-17-5		10.6	128	101, 129	N	<10
Diazinon	333-41-5	0.005	18.0	179	137, 152	P	<10
Diazoxon	962-58-3		17.6	137	273, 134	P	<10
Diethyl phosphate	598-02-7		N.D.	N.D.	N.D.	N.D.	N.D.
2-Isopropyl-6-methyl-pyrimidine-4-ol	2814-20-2		13.0	137	84, 151	A	<10
Dichlorvos	62-73-7	0.008	10.2	109	185, 145	N	<10
Dimethyl phosphate	813-78-5		N.D.	N.D.	N.D.	N.D.	N.D.
Disulfoton	298-04-4	0.004	18.3	88	89, 60	P	<10
Disulfoton-oxon	126-75-0		16.9	88	60, 89	P	<10
Disulfoton-sulfoxide	2497-07-6		11.4	97	125, 153	N	<10
Fenitrothion	122-14-5	0.003	21.0	125	277, 109	F	<10
Fenitrooxon	2255-17-6		19.5	109	244, 231	P	<10
Methyl parathion	298-00-0		20.0	109	263, 125	P	<10
Methyl paroxon	950-35-6		18.3	109	96, 217	P	<10
3-Methyl-4-nitroanisole	5367-32-8		13.4	150	109, 165	A	<10
3-Methyl-4-nitrophenol	2581-34-2		14.7	136	77, 153	A	<10
Trimethylphosphate	512-56-1		N.D.	N.D.	N.D.	N.D.	N.D.
<i>m</i> -Cresol	108-39-4		N.D.	N.D.	N.D.	N.D.	N.D.
Malathion	121-75-5	0.05	21.6	127	173, 125	F	<10
Malaonon	1634-78-2		20.0	127	99, 125	F	<10
D-(-)-Tartaric acid diethyl ester	13811-71-7		11.7	104	76, 29, 133	A	<10
L-(+)-Tartaric acid diethyl ester ^c	87-91-2		11.7	104	76, 133	A	<10
Diethyl L-(-)-malate	691-84-9		10.5	117	89, 71	N	<10
Diethyl maleate	141-05-9		9.1	99	127, 126	N	<10
Diethyl fumarate ^c	623-91-6		9.1	127	99, 126, 29	N	<10
Methidathion	950-37-8	0.004	24.6	145	85, 93, 15	F	<10
Methidathion-oxon	39856-16-1		22.5	85	145, 142	F	<10
Thiobencarb	28249-77-6	0.02	21.8	100	72, 125	F	<10
<i>p</i> -Chlorobenzyl alcohol	873-76-7		10.2	77	107, 142	N	<10
<i>p</i> -Chlorobenzaldehyde	104-88-1		N.D.	N.D.	N.D.	N.D.	N.D.
<i>p</i> -Chlorobenzoic acid	74-11-3		11.4	139	156, 111	N	50
Thiophanate-methyl	23564-05-8	0.3	N.D.	N.D.	N.D.	N.D.	N.D.
Carbendazim	10605-21-7		N.D.	N.D.	N.D.	N.D.	N.D.
2-Aminobenzimidazole	934-32-7		N.D.	N.D.	N.D.	N.D.	N.D.
Pencycron	66063-05-6	0.1	16.3	125	127, 180	P	<10
Phenylurea	64-10-8		14.9	93	136, 66	A	<10
Aniline	62-53-3		N.D.	N.D.	N.D.	N.D.	N.D.

a. Target value has been set by Waterworks Law of Japan. b. Each ITSD is shown by abbreviation (retention time): A, acenaphthene-d10 (13.5 min); N, naphthalene-d8 (9.4 min); F, fluoranthene-d10 (23.7 min); P, phenanthrene-d10 (17.9 min). c. The isomer was determined with another isomer. N.D., not determined.

Table 2 - Summary for the number of commercially available PTP and unavailable PTP.

Pesticide	Commercially available PTP	Unavailable PTP	Total
Acephate	2	3	5
Chlorotalonil	1	7	8
Diazinon	3	3	6
Dichlorvos	1	0	1
Disulfoton	2	1	3
Fenitrothion	7	11	18
Malathion	6	5	11
Methidathion	1	8	9
Pencycuron	2	5	7
Thiobencarb	3	4	7
Thiophanate-methyl	2	0	2

Fig. 1 - PTP of acephate. Commercially available PTP are underlined.

GC-MS analysis for pesticides and PTP selected

Residual pesticides analysis using GC-MS has been widely utilized. Among the tested 41 substances (11 pesticides and their 30 PTP), fragmentation patterns and their retention time were determined for 31 substances. The retention time for these substances ranged from 9.1 to 24.6 min, indicating that good separation was achieved. In Waterworks Law of Japan, GC-MS analysis has been utilized for the detection of all pesticides except for acephate and thiophanate-methyl. In this study, acephate and its PTP methamidophos could be detected the same as GC-MS-favorable pesticides, whereas thiophanate-methyl and its PTP were not detected. Two pairs of isomers (D,L-tartaric acid diethyl; diethyl maleate and diethyl fumarate), which are the PTP of malathion, were not distinguishable, so their LOQs were obtained by each representative (D-tartaric acid diethyl and diethyl maleate). Phosphoric esters, *p*-chlorobenzaldehyde, dimethyl disulfide and aniline were not detected by GC-MS in this study. For all the detectable substances, except for *p*-chlorobenzoic acid, LOQs were less than 10 ng/mL (Table 1).

Detection of selected pesticide and PTP using LC-MS/MS

For the detection of pesticides and their PTP, LC-MS/MS analysis was applied. The MS spectra of substances tested in this study showed strong signals at $[M+H]^+$ or $[M+NH_4]^+$. The MRM transitions of 28 substances using the ESI method are shown in Table 3 since those using APCI method for most substances did not differ significantly. For the detectable 27 substances, LOQs were equal to or less than 10 ng/mL, whereas it was 20 ng/mL for dimethyl phosphate (Table 3). Furthermore, among them, LOQs for 11 substances were less than 1 ng/mL. The organochlorine fungicide chlorothalonil and its PTP were not observed. The MRM transitions of fenitrothion, methylparathion, 3-methyl-4-nitroanisol in positive mode, and 3-methyl-4-nitrophenol in negative mode, were confirmed by the infusion analysis in LC-ESI-MS/MS analysis; however, the LOQs were higher than the standard concentration tested in this study (data not shown). As for other carboxylic acids and alcohols, MRM transitions were confirmed in negative mode but these signals were very weak (data not shown).

Table 3 - Parameters in LC-MS/MS for pesticides and PTP analysis.

Pesticide PTP	Retention time [min]	Precursor ion [m/z]	1st transition		2nd transition		ESI	APCI
			[m/z]	CE [V]	[m/z]	CE [V]	LOQ [ng/mL]	LOQ [ng/mL]
Acephate	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Methamidophos	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Dimethyl disulfide	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chlorothalonil	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Isophthalonitrile	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Diazinon	7.49	305	169	21	153	21	0.2	0.5
Diazoxon	5.89	289	153	17	84	32	0.5	5
Diethyl phosphate	0.72	155	99	14	81	32	0.5	0.5
2-Isopropyl-6-methyl-pyrimidine-4-ol	4.04	153	84	17	70	19	5	5
Dichlorvos	5.13	221	109	17	127	14	2	N.D.
Dimethyl phosphate	0.63	127	109	14	95	18	20	100
Disulfoton	7.97	275	89	11	61	14	10	20
Disulfoton-oxon	5.91	259	89	10	61	34	0.5	5
Disulfoton-sulfoxide	5.43	291	185	11	157	19	0.5	2
Fenitrothion	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Fenitrooxon	5.19	279	216	23	104	24	0.2	50
Methyl parathion	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Methyl paraoxon	4.85	248	202	15	109	26	10	N.D.
3-Methyl-4-nitroanisol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
3-Methyl-4-nitrophenol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Trimethylphosphate	3.42	141	109	15	79	20	5	2
<i>m</i> -Cresol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Malathion	6.25	331	127	11	99	20	10	2
Malaoxon	5.15	315	99	20	127	31	1	5
D-(-)-Tartaric acid diethyl ester	4.18	224	133	12	161	10	10	100
L-(+)-Tartaric acid diethyl ester ^a	4.18	224	133	12	161	8	10	100
Diethyl L-(-)-malate	4.49	208	117	14	145	10	5	20
Diethyl maleate	4.89	173	99	15	127	5	1	1
Diethyl fumarate ^a	4.89	173	99	13	127	8	1	1
Methidathion	5.71	303	145	6	85	17	1	2
Methidathion-oxon	4.72	287	145	8	85	18	<0.1	2
Thiobencarb	6.37	258	125	19	89	42	1	2
<i>p</i> -Chlorobenzyl alcohol	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
<i>p</i> -Chlorobenzaldehyde	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
<i>p</i> -Chlorobenzoic acid	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Thiophanate-methyl	5.00	343	151	20	311	10	1	5
Carbendazim	4.58	192	160	17	132	29	0.5	5
2-Aminobenzimidazole	4.23	134	92	92	65	32	0.5	5
Pencyron	8.04	329	125	22	89	59	0.5	2
Phenylurea	3.81	137	94	15	77	26	0.5	20
Aniline	3.80	94	77	17	51	33	10	5

a, The isomer was determined with another isomer. N.D., not determined.

Compared to the APCI method, the ESI method achieved high sensitivity analysis for most substances (Table 3). Although higher sensitivity using the ESI method has also been reported (Wick *et al.*, 2010; Maragou *et al.*, 2011), both studies also reported that significant ionization suppression was confirmed using the ESI method due to the presence of non-volatile materials that inhibit the release of analytes into the gas phase (King *et al.*, 2000). Thus, using environmental samples, an adequate ionization method could be optimized for each pesticide and its PTP.

Greater sensitivity and selectivity was obtained in LC-ESI-MS/MS rather than GC-MS in most pesticides and PTP. This result is consistent with the review by Alder *et al.* (2006) that LC-ESI-MS/MS achieved better performance than GC-MS in the analysis of all chemical classes of pesticides except for organochlorine pesticides such as chlorothalonil. However, different from the review, the organophosphate insecticide acephate and its PTP methamidophos exhibited very broad peaks between 0.7 to 4.0 min. One reason for this phenomenon may be solvent suitability. Mol *et al.* (2003) reported that peak broadening was confirmed in a larger injection volume when methanol was used as a solvent. Thus, solvent optimization would improve the sensitivity in future study. Using both GC-MS and LC-ESI-MS/MS, all pesticides and most of the PTP used in this study could be detected except for 3 PTP (dimethyl sulfide, *m*-cresol and *p*-chlorobenzaldehyde). The summary of LOQs is shown in Fig. 2. Most substances could be identified and quantified with LOQs of 0.1 ng/mL to 10 ng/mL. Considering pre-concentration such as solid phase extraction (SPE), these LOQs are sufficient for the required pesticide analysis regulated by the Waterworks Law of Japan, and are enough to detect pesticides and PTP with trace concentrations in water environments.

Fig. 2 - LOQs of pesticides and PTP tested in this study. The numbers in the figure indicate the numbers of substances.

CONCLUSIONS

To develop an analytical method for both pesticides and PTP simultaneously, 11 pesticides and their 30 PTP were selected and subjected to analytical method development using GC-MS and LC-MS/MS. Parameters such as fragment patterns and retention times for each substance were determined (Table 1 and 3). All substances except for the 3 PTP (dimethyl sulfide, *m*-cresol and *p*-chlorobenzaldehyde) were detected by both GC-MS and LC-MS/MS. For environmental water samples, concentration using SPE is necessary due to their trace concentrations. Therefore, LOQs determined in this study are sufficient for the monitoring of pesticides and PTP in water environments. Although further method development such as addition of detectable substances, estimation of recovery ratio in SPE procedure and evaluation of matrix effect in LC-MS/MS analysis are required, this analytical method can be a powerful tool in understanding the environmental fate of pesticides and PTP.

ACKNOWLEDGEMENTS

This research was supported by the Environment Research and Technology Development Fund (B-1104) of the Ministry of the Environment, Japan.

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