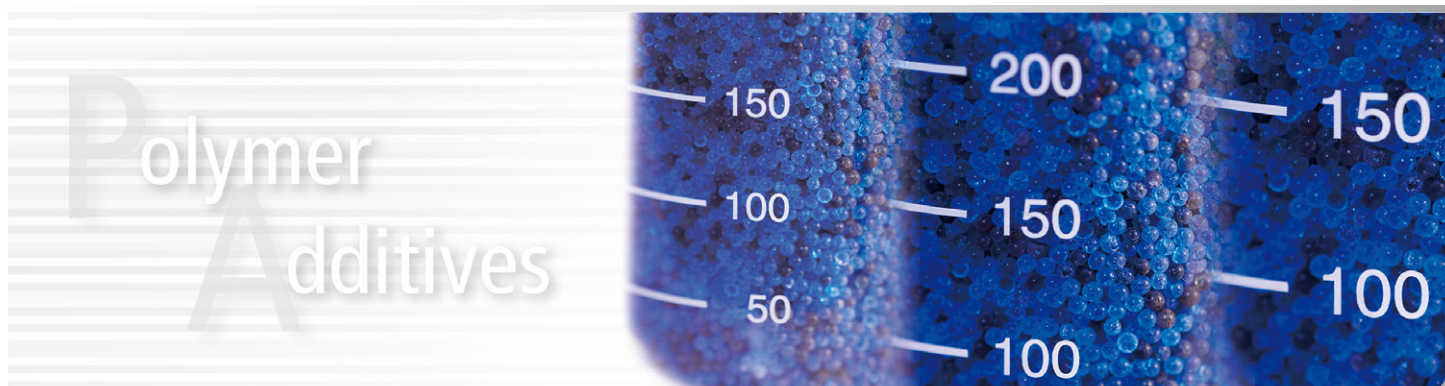# SHIMADZU
Excellence in Science

Analytical Solutions for Analysis of Polymer Additives

Polymer Additives

Introduction

Polymer additives are compounds added to plastic products to increase their durability and functionality.
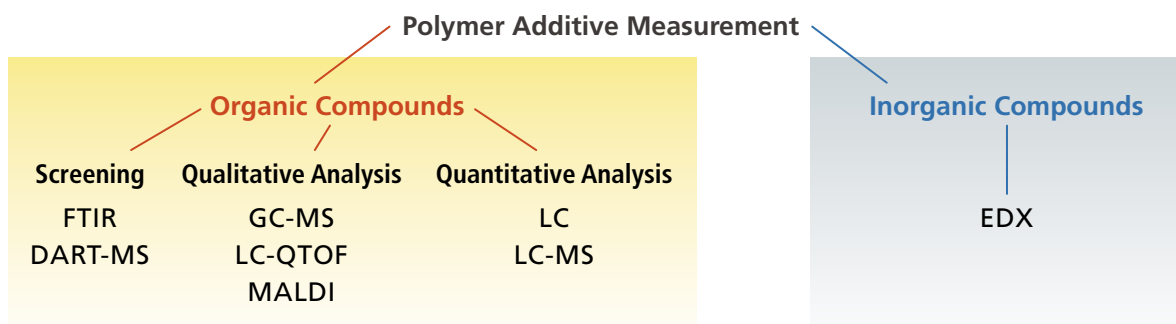
Although plastic products are used in a wide range of fields, including as packaging containers for pharmaceuticals and food, and as materials in transportation equipment and home appliances, the adoption of SDGs by the United Nations and the promotion of a circular economy is leading to an increased emphasis on recycling.

Polymer additives are an important element in the recycling of plastic products and ensuring the quality of recycled goods.

There is also an increasing focus on the leaching and transfer of additives from plastic products and their effects on the human body and environment, with some countries establishing regulations in this area.

This application book gathers together example analyses of polymer additives performed using Shimadzu products.

Classification of Analytical Instruments by Intended Use

Polymer Additive Measurement

Organic Compounds

Screening	**Qualitative Analysis**	**Quantitative Analysis**
FTIR	GC-MS	LC
DART-MS	LC-QTOF	LC-MS
	MALDI	

Inorganic Compounds

EDX

Contents

Quantitative Analysis of Polymer Additives

Analysis of Additives in Plastic Pellets (LC-MS/MS)

Polymer materials are used every day in packaging and containers for food and pharmaceuticals. In recent years, various countries have established regulations on additives that leach into pharmaceuticals and foods because of their impact on the human body and the environment, resulting in an increasing demand for quantitative analysis of these additives.

Presented here is a case study of a quantitative analysis of additives in plastic using the LCMS-8045 triple quadrupole mass spectrometer.

MRM analysis was performed on a standard solution containing 22 additives. Fig. 1 shows a chromatogram of the solution and Table 1 shows the MRM conditions, retention time, and calibration curve information for each additive. Good results were achieved with a coefficient of determination (R^2) of 0.995 or higher for all additives.

The additives present in four different plastic pellets were identified. Table 2 shows quantitative results for the additives and Fig. 2 shows MRM chromatograms of the compounds detected in polybutylene plastic pellets.
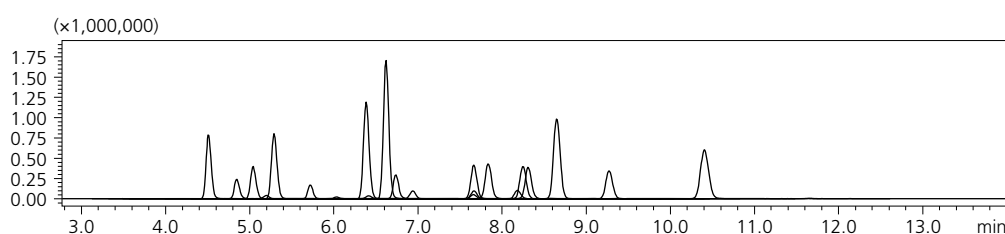

Fig. 1   MRM Chromatogram of Standard Solution of 22 Additives

Table 1   MRM Results from a Standard Solution of 22 Additives

Compound Name	m/z	Retention Time	Calibration Point	R^2
Irganox 1222	357 > 301	4.508	0.1–100	0.999986
Irganox 245	605 > 177	4.852	0.1–500	0.999048
Irganox 1024	570 > 181	5.039	0.1–100	0.999068
Tinuvin P	226 > 120	5.209	1–1000	0.999830
Irganox 1098	637 > 321	5.303	0.1–100	0.999799
Irganox 1035	660 > 249	6.381	0.1–100	0.999939
Cyanox 1790	717 > 191	6.407	5–100	0.998250
Tinuvin 120	439 > 233	6.619	0.1–100	0.999804
Irganox 259	657 > 416	6.743	0.1–500	0.998642
Tinuvin 399	324 > 212	6.934	0.5–1000	0.999575
Tinuvin 320	324 > 268	7.658	0.1–100	0.999606
Tinuvin 326	316 > 260	7.652	0.5–500	0.999256
Tinuvin 234	449 > 371	7.84	0.1–100	0.999613
Tinuvin 327	358 > 302	8.176	0.5–1000	0.999091
Tinuvin 328	352 > 282	8.243	0.1–500	0.999299
Irganox 1010 d	1195 > 1195	8.311	0.5–500	0.999881
Irganox 1330	792 > 219	8.655	0.5–100	0.997701
Irganox 565	589 > 250	9.272	0.1–100	0.997243
Irganox 1076	549 > 475	10.415	0.5–100	0.999436
Irgafos 168_648	648 > 147	11.672	1–100	0.998962
Cyanox 2246	339 > 163	5.724	0.1–1000	0.999503
Cyanox 425	367 > 177	6.033	0.5–500	0.999346

Table 2   Quantitative Results for Additives in Plastic

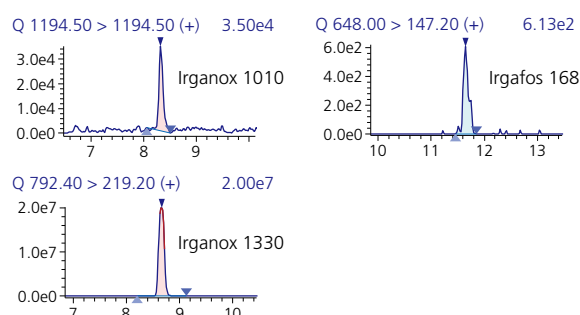| Compound Name	Concentration (mg/g)			
	PP	Polybutylene	LDPE	ABS
Irganox 1010	0.66	1.30	0.55	16.64
Irganox 1330	—	9.70	—	—
Irgafos 168	12.61	0.24	—	8.65
Cyanox 2246	—	—	—	0.68

Fig. 2   MRM Chromatograms of Additives in Plastic

LCMS-8045

Four additives were detected in the samples. Irganox 1010 was detected in all samples at 0.55 to 16.64 mg/g, Irganox 1330 was detected in polybutylene at 9.70 mg/g, Irgafos 168 was detected in PP, polybutylene, and ABS plastic at 0.24 to 12.61 mg/g, and Cyanox 2246 was detected in ABS plastic at 0.68 mg/g. This analytical system enables simple and highly selective analysis. LC-MS/MS is expected to be utilized in the development of polymer materials and in manufacturing processes, and to confirm the safety of containers and packaging materials.

Quantitative Analysis of Antimony (Sb) in Plastic (EDX)

Similar to the five elements restricted under the RoHS Directive (Cd, Pb, Cr, Hg, and Br), the need has arisen to test for antimony (Sb) chemicals used as flame-retardant synergists in plastics. This need has arisen due to companies adding their own regulations on top of official regulations.

Presented here is an example of the quantitative analysis of polyethylene (PE) adopted with an antimony standard using an X-ray fluorescence spectrometer.

Fig. 3 shows the PP standard samples. Fig. 4 shows the internal standard-corrected calibration curve for Sb created from four standard sample concentrations and Table 3 shows the concentration of Sb in each sample. An integration time of 100 seconds resulted in good accuracy (0.8 ppm) and a theoretical lower detection limit of 9.8 ppm, allowing quantitative analysis at the ppm level. Table 4 shows the results of a repeatability test that analyzed sample (3) (630 ppm) ten times using the internal standard-corrected correlation curve method described above.
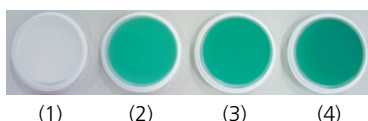

Fig. 3　PP Standard Samples

Table 3　Concentration of Each Standard Sample
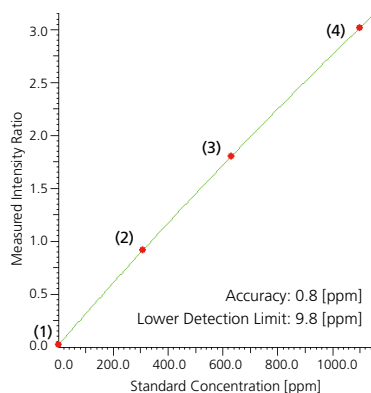
Sample	Sb Content [ppm]
(1)	0
(2)	310
(3)	630
(4)	1100

Fig. 4　Calibration Curve of Sb in Plastic

Accuracy: 0.8 [ppm]
Lower Detection Limit: 9.8 [ppm]

Table 4　Repeatability

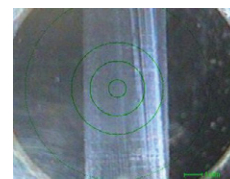| Mean	630.9 ppm
Standard Deviation	14.0 ppm
Coefficient of Variation	2.2 %

Fig. 5　Plastic Fragment Sample

Conditions for analyzing seven elements were created by adding Sb to analysis conditions for six elements: the five listed in the RoHS Directive plus Cl. Quantitative analysis was performed on plastic fragments (Fig. 5). Table 5 shows data excerpted from the quantitative analysis and judgment sections of the results report. Since analysis conditions for Sb are the same as for Cd, the total analysis time is unchanged from analyzing the five or six elements mentioned above.

Currently, samples are often evaluated by a screening analysis that quickly determines whether the five RoHS elements and Cl are outside reference values that are set for each material or product, or within an intermediate gray zone. Fig. 6 shows the window displaying these judgments ("OK" and "GRAY") after screening analysis was performed on a plastic fragment using conditions for 7-element analysis (five RoHS elements, Cl, and Sb). The judgments for Cd, Pb, Cr, Hg, Br, Cl, and Sb were obtained in around two minutes. When the Sb upper limit level is set to 500 ppm, the judgment is "OK" based on the following conditions.

Quantified level + 3σ = 242.3 + 26.1 = 268.4 < 500 => OK

Similar to other heavy elements such as Cd, Pb, Cr, Hg, and Br, Sb was quantitatively analyzed at the ppm level. The total analysis time remained unchanged, and throughput was the same as before.

Thus, a wide range of inorganic components can be analyzed by adding target components to existing analysis conditions or by modifying those conditions.

Table 5　Excerpt from 7-Element Analysis Results

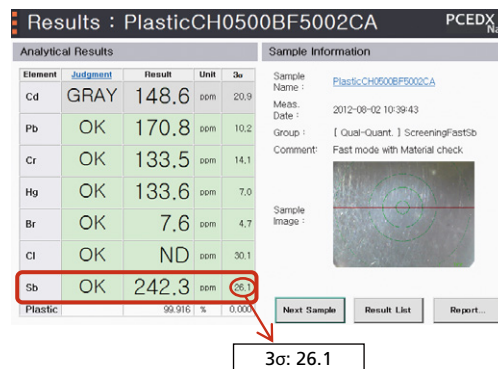| Element	Content	3σ	Unit	Judgment
Cd	132.0	9.3	ppm	GRAY
Pb	351.2	10.1	ppm	OK
Cr	116.4	7.3	ppm	OK
Hg	147.0	6.5	ppm	OK
Br	5.6	3.9	ppm	OK
Cl	97.4	30.7	ppm	OK
Sb	207.2	12.5	ppm	OK

3σ: 26.1

Fig. 6　Window Showing Screening Analysis and Outcome Judgments for Plastic Fragment

Analysis of PIP (3:1) in Plastic (GC-MS)

Phenol, isopropyl phosphate (3:1) (PIP (3:1)) (CAS Registry Number: 68937-41-7), is used in various materials, such as polyvinyl chloride (PVC), polyurethane, other plastics, lubricants, and sealants, to impart plasticity and fire resistance. The U.S. Environmental Protection Agency (US EPA) has recently started to regulate the domestic manufacture and trade of products and molded goods containing PIP (3:1).

Pyrolysis (thermal desorption)–GC-MS (Py/TD–GC-MS) has been adopted for the international standard IEC 62321-8 and is currently attracting attention as an analytical method that is friendly to both the environment and instrument operators since it does not require large amounts of organic solvents, unlike the solvent extraction-GC/MS method. Presented here is confirmation that Py/TD–GC-MS can be used to analyze PIP (3:1) in plastic (Fig. 7).
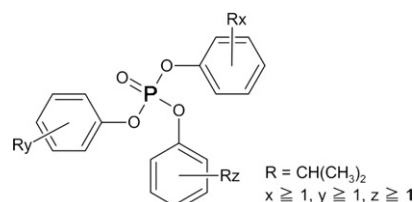
Molded articles that use PIP (3:1) were analyzed. A 0.5-mg fragment was cut from a PVC cap with a utility knife, placed in a sample cup, and analyzed. A polyurethane sponge was also analyzed by the same procedure. As shown in Fig. 8 and Fig. 9, peaks representing PIP (3:1) with the same retention time as a standard solution were detected in both samples. Furthermore, as shown in Fig. 9, cross-referencing the scan mode spectra from this analysis against Shimadzu's Polymer Additives Library revealed that tris(1,3-dichloro-2-propyl) phosphate (TDCPP), a phosphorus-based fire retardant, was used in the sponge sample (spectral similarity: 95).

Since Toxic Substances Control Act (TSCA) regulations do not set permissible levels for PIP (3:1), analytical instruments must be capable of detecting very small amounts of PIP (3:1). Py/TD–GC-MS can measure PIP (3:1) in plastic with a simple procedure and without the need for organic solvents or complex sample pretreatment.

Using Fast Automated Scan/SIM Type (FASST) mode allows PIP (3:1) levels to be measured with high sensitivity (detection limit: 10 mg/kg) while simultaneously performing a qualitative analysis of other additives. Shimadzu's Polymer Additives Library contains approx. 4900 scan mode spectra and additive classifications (fire retardants, plasticizers, etc.), enabling the qualitative analysis of additives even without detailed specialist knowledge.

This analysis also showed the potential for PIP (3:1) carryover, and the need to analyze a blank sample after detecting a high concentration of PIP (3:1).

Fig. 7   Structural Formula of PIP (3:1)
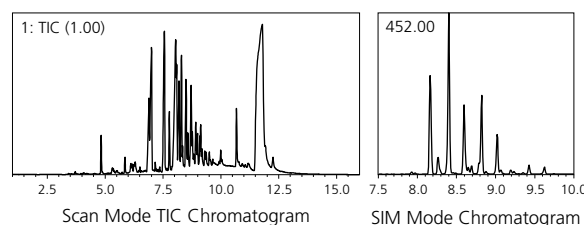
Fig. 8   Analytical Results from PVC Cap

CAS#:   13674 - 84 - 8   Mol Wt: 428   Serial#: 8
Cmpd Name: Tris(1,3-dichloro-2-propyl) Phosphate
Formula: C9H15Cl6O4P   Class Flag: Fire retardant

Scan mode mass spectra and information on TDCPP found in library

Fig. 9   Results from Analysis of a Polyurethane Sponge

Analyzing Plastics Using a Polymer Additives Library (GC-MS)

The analysis of additives in polymer materials is important for quality control of polymer materials, quality improvement, and compliance with regulations on chemicals. Shimadzu's **Polymer Additives Library** is a GC/MS mass spectra library that contains information on a wide range of additives used in polymer materials.
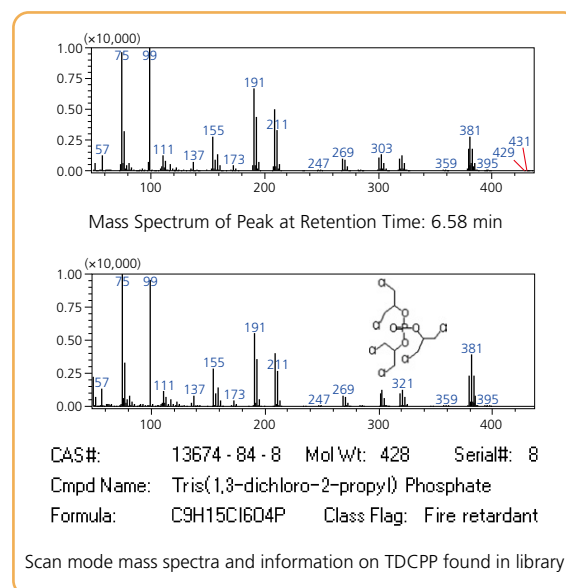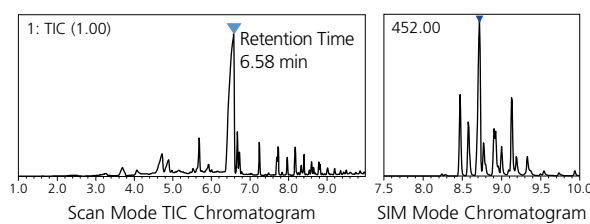
Presented here is an analysis of an unknown plastic using different analysis modes on a Py–GS/MS system (evolved gas MS and thermal extraction GC/MS) and the Polymer Additives Library to estimate the additives and polymer base material of the plastic.

A sheet of vulcanized rubber (thickness: 2 mm) of unknown base material and unknown additive formulation was used as the sample.

The sample was analyzed by the evolved gas MS method, and temperature regions in which volatile components and polymer pyrolysates were detected were evaluated. Fig. 10 shows a thermogram obtained from this analysis. Additives and other volatile components were detected between 100 °C and around 340 °C, and polymer-derived pyrolysates were detected at higher temperatures.
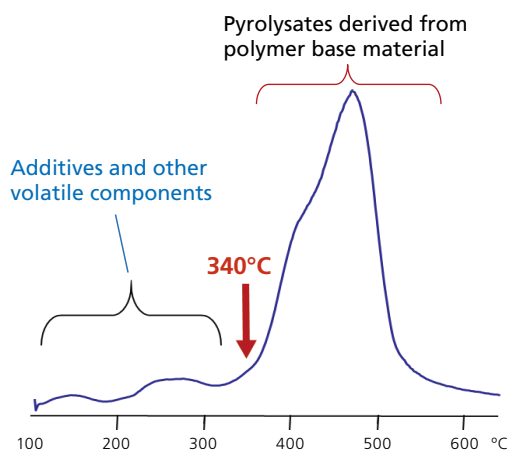
Fig. 10 Thermogram Obtained by Evolved Gas MS Analysis

Based on the information in the evolved gas MS analysis thermogram, thermal extraction GC/MS analysis was performed using the temperature range that extracted volatile components (100 to 340 °C), then qualitative analysis was performed on major peaks using the NIST Library and the Polymer Additives Library (Fig. 11).
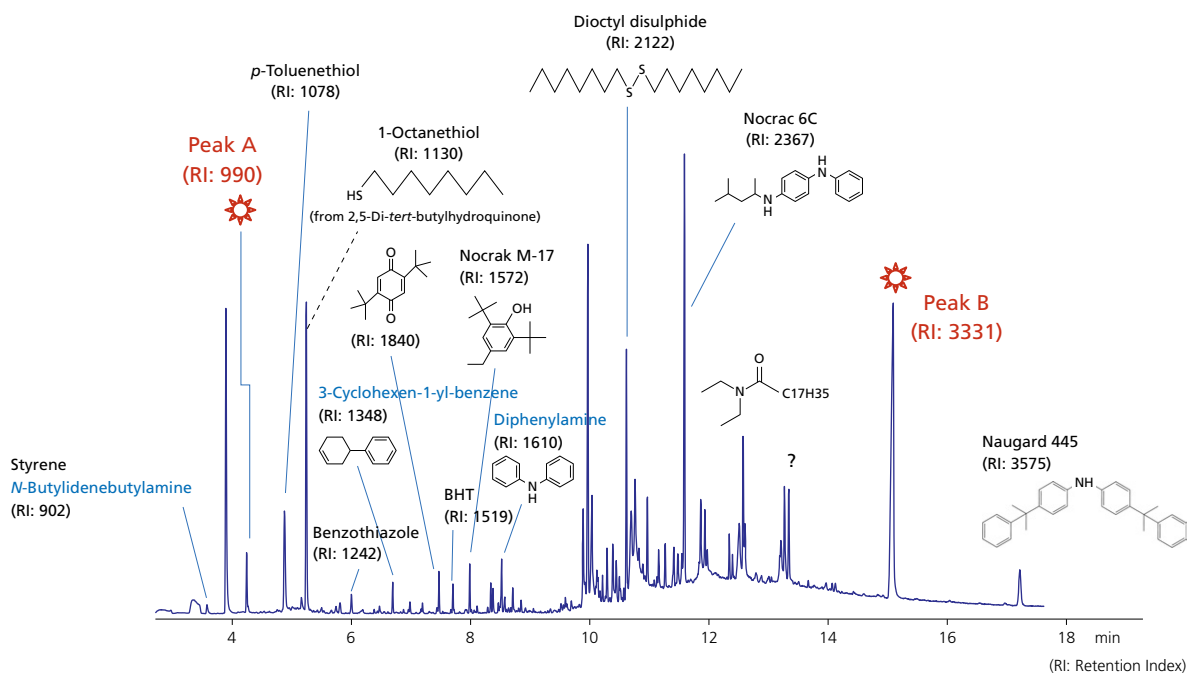
Fig. 11 Total Ion Current Chromatogram Obtained by Thermal Extraction GC/MS Analysis, and Results from Qualitative Analysis of Detected Peaks

The presence of the cross-linking agent Irgacure and the use of the antioxidants BHT, Nocrac M-17, Nocrac 6C, and Nocrac CD were estimated based on search results obtained from both the NIST Library and the Polymer Additives Library. For peaks A and B, the NIST Library produced low hit rates and inconclusive results. Peak A was estimated to be butyl isocyanate, and based on original information included in the Polymer Additives Library, the compound was estimated to be derived from tributylthiourea, an antioxidant. Peak B was estimated to be *p*-(*p*-toluene sulfonylamido)-diphenylamine, an antioxidant that is also called Nocrac TD.

Fig.12   Results from Qualitative Analysis of Peaks A and B Using the Polymer Additives Library

Analysis of Inorganic Additives in Plastic (FTIR, EDX)

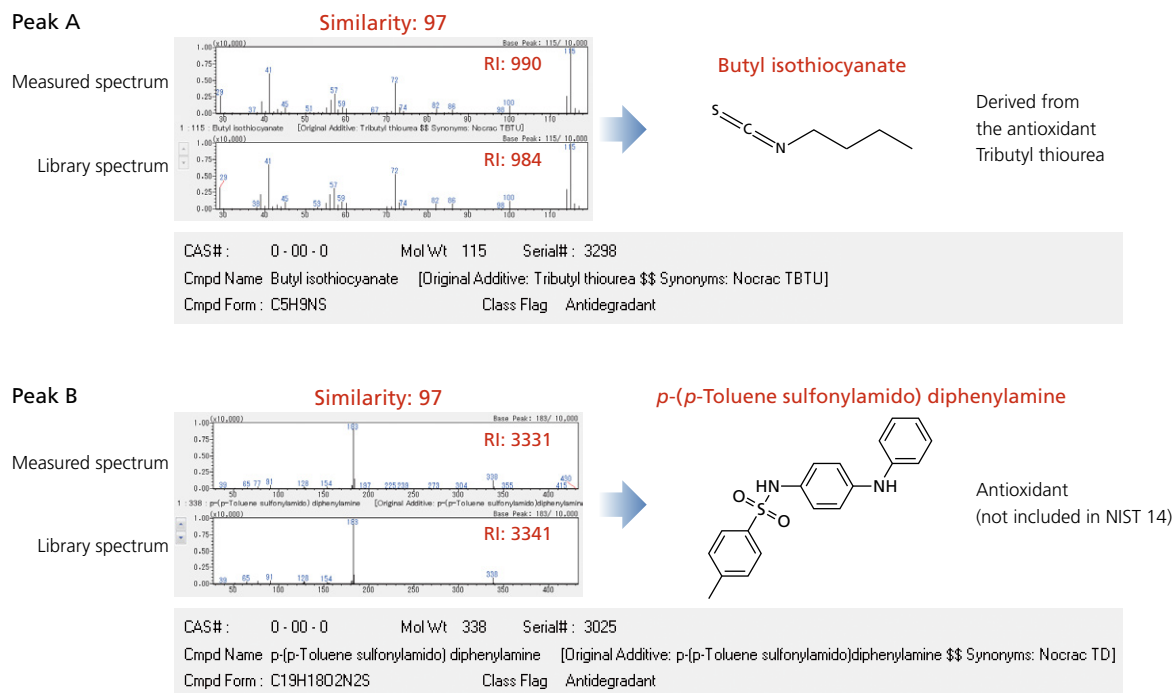When analyzing additives, the approach differs depending on whether the additive is organic or inorganic. For inorganic additives, the additive is identified based on an overall judgment and the results of elemental analysis and infrared spectroscopic analysis or morphological observation.

Presented here is an example analysis of a plastic containing an inorganic additive by FTIR and EDX.

A connector cover was used as the plastic sample, which was analyzed by FTIR. Fig. 13 shows a photo of the sample. The infrared spectrum and search results shown in Fig. 14 indicate the connector cover was mostly made from polyvinyl chloride (PVC) with phthalate esters. The infrared spectrum of the sample also contains a peak near 1415 cm^{-1}, a peak position that suggests the sample contains the additive calcium carbonate (CaCO$_3$).

Fig. 13   Connector Cover

Search results from Shimadzu standards library
• Polyvinyl chloride with phthalate esters
• Calcium carbonate
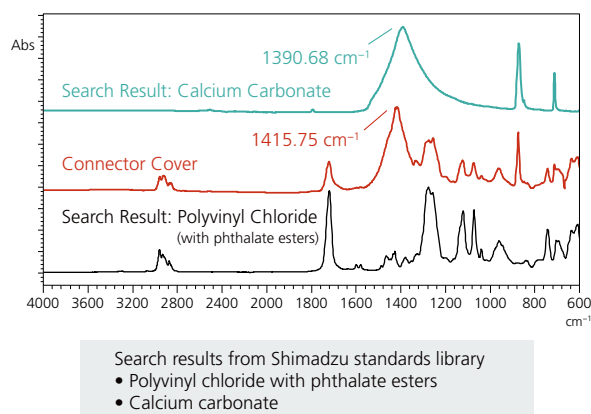
Fig. 14   Connector Cover Infrared Spectrum and Search Results

However, the connector cover peak at 1415 cm^{-1} is 25 cm^{-1} away from the position of the peak in a spectrum obtained from only calcium carbonate (1390 cm^{-1}). Therefore, an infrared spectrum alone did not provide a sufficient basis to determine that the sample contained calcium carbonate as an additive.

More evidence was obtained by using EDX to perform an elemental analysis. Fig. 15 shows the results of qualitative analysis and Table 6-1 and Table 6-2 show the results of quantitative analysis by the fundamental parameter (FP) method.

Table 6-1 shows that chlorine (Cl) and calcium (Ca) are the main constituent elements. This is consistent with the FTIR finding that the sample is polyvinyl chloride and supports the presence of calcium carbonate in the sample. Table 6-2 shows the results of quantitative analysis of the compound that was identified using the standards library and results from both FTIR and EDX. Other detected elements were assumed to be oxides. Thus, the combination of FTIR and EDX provided a sufficient basis to show the sample contained calcium carbonate as an additive.
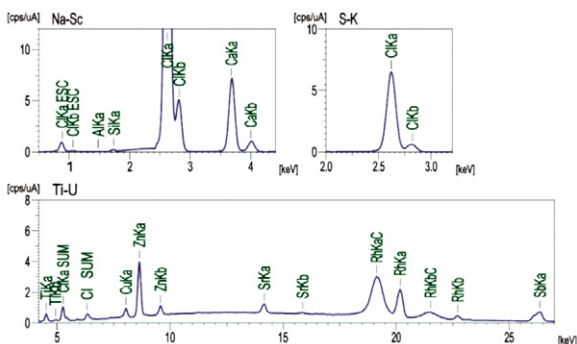
Fig. 15   Results of Qualitative Analysis of a Connector Cover by EDX

Table 6-1   Results (A) of Quantitative Analysis of a Connector Cover by EDX

[%]

Element	Cl	Ca	Sb	Zn	Ti	Si	Al	Cu	Sr
Quantified Value	72.56	26.11	0.40	0.31	0.23	0.21	0.096	0.054	0.030

Table 6-2   Results (B) of Quantitative Analysis of a Connector Cover Based on FTIR and EDX Findings

[%]

Element	C$_2$H$_3$Cl	CaCO$_3$	SiO$_2$	Sb$_2$O$_3$	TiO$_2$	ZnO	Al$_2$O$_3$	CuO	SrO
Quantified Value	73.14	25.55	0.31	0.30	0.25	0.25	0.13	0.046	0.024

Qualitative and Quantitative Analysis of Additives in Food Containers (LC-QTOF)

Using additives, such as antioxidants, ultraviolet absorbers, and fire retardants, during development and manufacture can increase the performance of polymer materials. To evaluate this performance, it's important to know which additives are present in a specific material.

Presented here is an example of the qualitative and quantitative analysis of polymer additives in food containers using the **LCMS-9030** liquid chromatograph–quadrupole time-of-flight (Q-TOF) mass spectrometer.

The polymer additives present in five food containers were analyzed. Samples were prepared by adding 1 mL of THF to 0.1 g of a finely cut-up food container (pack and film), subjecting the mixture to ultrasonic treatment for 1 minute, adding 1 mL of methanol, then filtering the supernatant through a 0.2 µm filter and diluting with methanol.

Fig. 16 shows results from using the LabSolutions Insight Explore compound detector feature to perform peak picking on the extracted ion chromatogram (EIC) of the food A film sample. EIC peaks were detected at m/z 637.4941, 386.3057, 1194.8190, 548.5039, and 647.4591. These peaks correspond with the m/z of ions derived from Irganox 1098, Cyanox 425, Irganox 1010, Irganox 1076, and Irgafos 168, respectively. As an example, Fig. 17 shows the estimated composition of peak X (m/z 637.4941). According to the data, the compositional formula of peak X is $C_{40}H_{64}N_2O_4$.
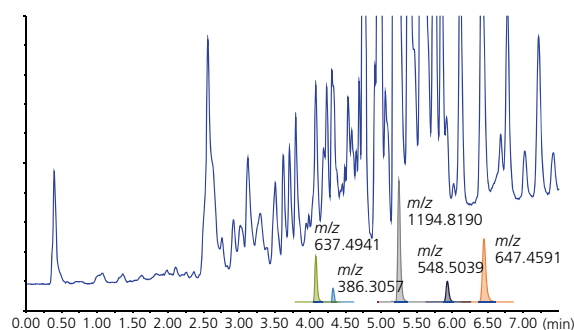
Fig. 16　Result of Peak Picking of Food A Film Using Insight Explore
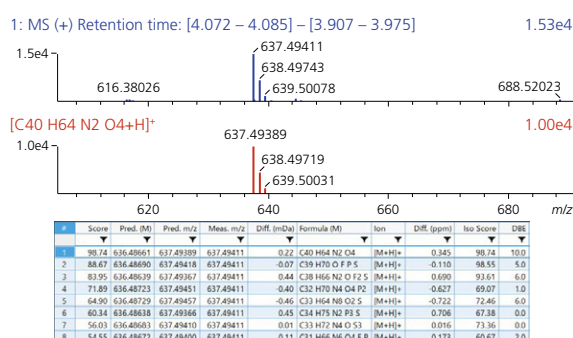
Fig. 17　Result of Composition Estimation of Peak X (Top: Measured Spectrum, Middle: Theoretical Spectrum, Bottom: Candidates of Compositional Formula)

ACD/MS Structure ID Suite (Advanced Chemistry Development) was also used to verify the structural formula and name of the compound represented by this peak. Fig. 18 shows ranked results for candidate compounds from a database search.

PubChem CID 90004 has the highest "Assignment Score."

An online search of PubChem revealed this compound to be Irganox 1098 (Fig. 19).
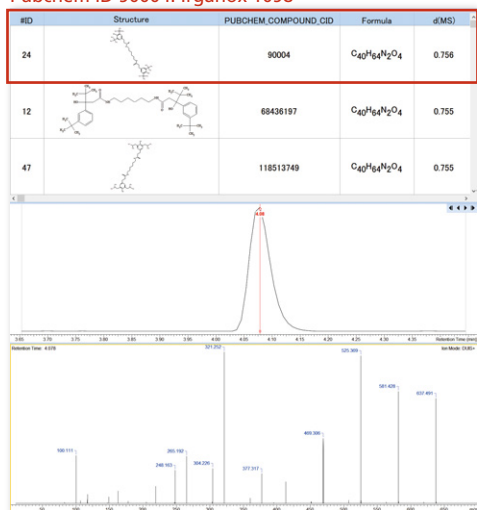
Fig. 18　Results of Database Search and Ranking of Assignment Rates Using ACD/MS Structure ID Suite

Fig. 19　Result of Compound Search Using an Online Database

An additive standard was also analyzed to obtain a reliable qualitative result.

The retention time of Irganox 1098 was checked and found to match the retention time of peak X. The MS/MS spectra of Irganox 1098 and peak X were also compared and found to be almost identical (Fig. 20).

The above results confirmed that peak X was Irganox 1098.

MS/MS chromatograms were obtained for a quantitative analysis of the polymer additives present in the food containers. Table 7 shows the calibration curve range and coefficient of determination (R^2) of each polymer additive.
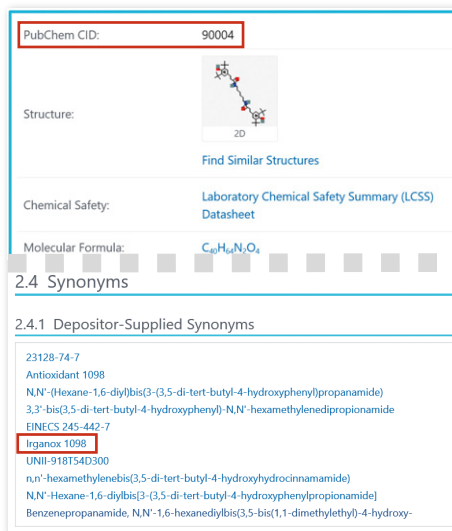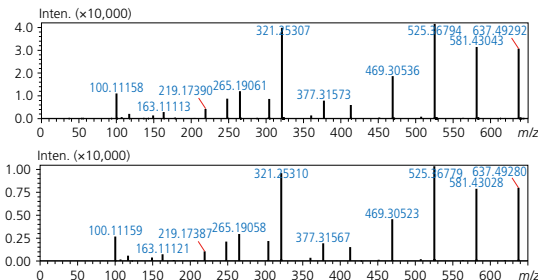

Fig. 20　MS/MS Spectra of Irganox 1098 Standard (Top) and Peak X (Bottom)

Table 7　Calibration Curve Range and Coefficient of Determination of 14 Polymer Additives

Compound Name	Ionization Method	Precursor Ion	Monitored Ion	Calibration Curve Range (ppb)	Coefficient of Determination (R^2)
Tinuvin P	ESI positive	226.0975	120.0556	1–1000	0.999
Irganox 245	ESI positive	604.3844	177.1279	0.05–50	0.998
Irganox MD 1024	ESI positive	570.4265	181.0972	0.1–100	0.995
Irganox 1098	ESI positive	637.4939	321.2537	0.1–100	0.996
CYANOX 2246	ESI negative	339.2330	163.1128	0.1–100	0.999
CYANOX 425	ESI negative	367.2643	367.2643	0.1–100	0.999
Irganox 1035	ESI positive	660.4292	249.1485	0.05–50	0.998
Tinuvin 120	ESI positive	439.3207	233.1531	0.01–10	0.999
Tinuvin 328	ESI positive	352.2383	282.1601	0.1–100	0.999
Irganox 1010	ESI positive	1194.8179	1194.8179	0.1–100	0.995
Irganox 1330	ESI positive	792.6289	219.1743	0.05–50	0.995
Irganox 565	ESI positive	589.3968	250.1009	0.5–100	0.993
Irganox 1076	ESI positive	548.5037	475.4146	0.5–100	0.997
Irgafos 168	ESI positive	647.4588	647.4588	0.5–100	0.999

Food container samples were extracted using the above-described procedure and diluted 10 to 1000 times with methanol. Quantitative calculations revealed the concentration of Irgafos 168 in samples diluted 1000 times ranged from 1.85 to 40 ppb, showing the concentration of Irgafos 168 in food container packs and films ranged from 37 to 800 mg/g. Fig. 21 shows a typical MS/MS chromatogram that was obtained from food A film and Table 8 shows the quantitative results.
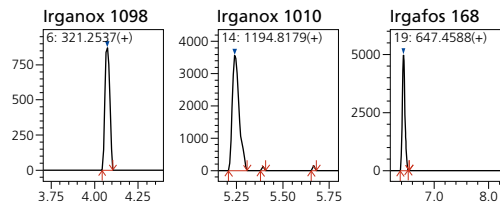

Fig. 21　Typical MS/MS Chromatogram (Food A Film)

Table 8　Quantitative Results for Polymer Additives in Food Containers

Compound Name	Concentration (mg/g)									
	Food A Pack	Food A Film	Food B Pack	Food B Film	Food C Pack	Food C Film	Food D Pack	Food D Film	Food E Pack	Food E Film
Tinuvin P	—	—	—	—	—	—	—	—	—	—
Irganox 245	—	—	—	0.043	—	—	—	—	—	—
Irganox MD 1024	0.823	0.695	0.627	0.486	0.479	0.430	0.376	0.400	0.318	0.278
Irganox 1098	—	7.104	—	8.64	—	—	—	—	—	—
CYANOX 2246	—	0.021	—	—	—	—	—	—	—	—
CYANOX 425	0.130	3.132	—	0.069	—	—	—	—	—	—
Irganox 1035	0.011	0.012	—	—	—	—	—	—	—	—
Tinuvin 120	—	0.005	—	—	—	—	—	—	—	—
Tinuvin 328	0.024	—	—	—	—	—	0.268	—	—	—
Irganox 1010	9.544	51.094	1.698	—	14.054	76.426	6.260	58.466	15.218	113.920
Irganox 1330	—	—	—	—	—	—	—	—	—	0.004
Irganox 565	—	0.159	—	—	—	—	—	—	—	0.135
Irganox 1076	2.140	8.366	—	25.450	2.636	2.482	7.994	9.644	1.484	8.438
Irgafos 168	111.04	339.94	119.64	37.1	253.68	799.66	350.10	616.62	205.24	126.96

Using the LCMS-9030 and analysis software such as LabSolutions Insight Explore and ACD/MS Structure ID Suite provided an analytical workflow that included detection, qualitative analysis, and quantitative analysis of functional additives in polymer materials.

This workflow is anticipated to aid in the efficient development and improvement of better synthetic polymer materials.

Identification of Additives in Food Containers (GC-MS)

In recent years, there have been increasing reports of contaminants in foods and an increasing need for manufacturers to analyze contaminants. When using GC-MS to perform contaminant analysis, the primary methods used to identify plastic materials and additives are pyrolysis GC/MS and thermal extraction GC/MS.

Presented here are results of an analysis of additives in food packaging materials performed using the thermal extraction GC/MS method.

Thermal extraction was performed using an **OPTIC-4 multimode injection system for GCMS**.

The sample used was a small piece (approx. 0.2 mg) of commercially available food container packaging prepared with a utility knife. The small piece of food container was placed in a designated microvial, which was set in the OPTIC-4 liner, and underwent thermal extraction by heating the liner in the injection inlet (Difficult Matrix Introduction [DMI]) (Fig. 22). Fig. 23 shows the total ion chromatogram (TIC) obtained by this thermal extraction GC/MS method.

Sample

DMI microvial containing the sample is set in the insert liner
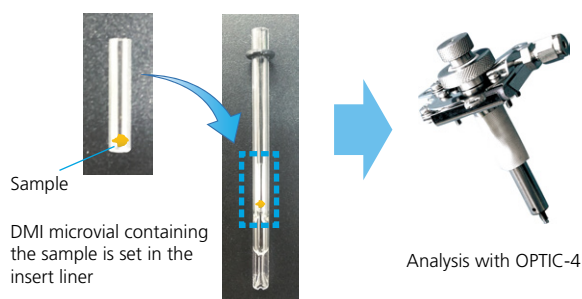
Analysis with OPTIC-4

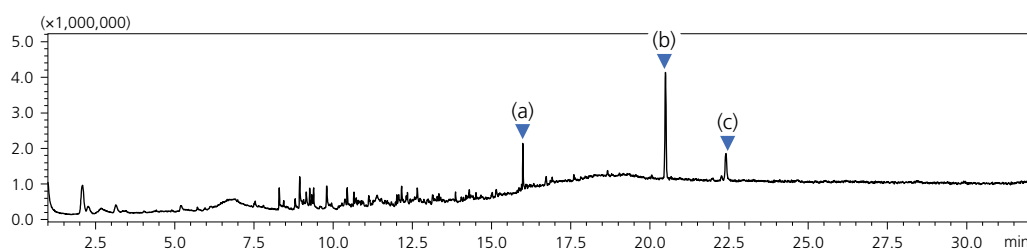Fig. 22   Sampling with OPTIC-4 for Thermal Extraction Analysis

Fig. 23   TIC Obtained by Thermal Extraction GC/MS

Fig. 24 shows the peaks of compounds that were search hits in the Polymer Additives Library. Multiple antioxidants and their degradation products were identified. In this case, using retention indices to narrow down the number of additives enabled a highly accurate qualitative analysis of the additives in the sample, and the Polymer Additives Library was used to perform a library search for the detected peaks. The Polymer Additives Library contains the mass spectra of a wide range of additives used in polymer materials and the degradation products of those additives.

Peak (a)

Similarity score: 91

Measured spectrum — RI: 3411

Library spectrum — RI: 3401

Bis(3,5-di-*tert*-butyl-2-hydroxyphenyl)methane

Degradation product of 2,2'-Methylene bis(4,6-di-*tert*-butylphenyl) octylphosphite (ADK STAB HP-10) (antioxidant)

Peak (b)

Similarity score: 94

Measured spectrum — RI: 3447

Library spectrum — RI: 3452

Tris(2,4-di-*tert*-butylphenyl)phosphite ($C_{42}H_{63}O_3P$)

Antioxidant (Irgafos 168)

Peak (c)

Similarity score: 85

Measured spectrum — RI: 3623

Library spectrum — RI: 3632

Tris(2,4-di-*tert*-butylphenyl)phosphite ($C_{42}H_{63}O_4P$)

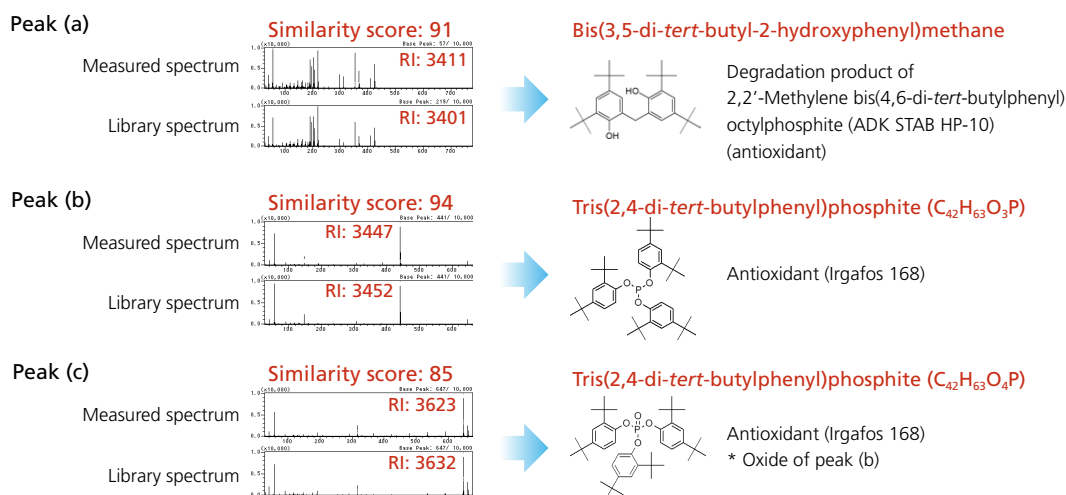Antioxidant (Irgafos 168)
* Oxide of peak (b)

Fig. 24   Results from Qualitative Analysis of Peaks Using the Polymer Additives Library

Analysis of Extractables in Pharmaceutical Packaging

(GC, GC-MS)

An important issue in pharmaceutical packaging is interaction between the pharmaceuticals and packaging material. Compounds produced under extreme storage conditions are called extractables, and substances that transfer from packaging to pharmaceuticals under normal storage conditions are called leachables. Table 9 shows the classification for both. When selling pharmaceuticals, extractables and leachables must be checked in a comprehensive manner and the risk posed by packaging must be understood.

Due to the increasing use of biopharmaceuticals, in 2020 the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) established a working group for the evaluation and management of extractables and leachables. Biopharmaceuticals are high molecular weight molecules and almost always injected due to problems associated with oral administration. Presented here is an example of GC-MS analysis of a polyvinyl chloride (PVC) plastic bag used for liquid formulations in which samples were prepared by two methods: solvent extraction and high-temperature extraction.

Table 9   Overview of Extractables and Leachables

	Extractables	Leachables
Overview	Anything that may be extracted from packaging materials	Anything that leaches during normal conditions of use
Extraction Conditions	Harsher than normal usage or storage conditions. High-temperature extraction and solvent extraction are used.	Under normal usage or storage conditions.
Object of Analysis	Packaging materials	Pharmaceuticals

Solvent extraction was performed using ethanol, which is in common use in pharmaceutical production, and dichloromethane (DCM) and hexane, which are often used to extract plastic components. A 1-cm square piece of a PVC bag weighing approx. 400 mg was prepared, placed in vials containing 5 mL of each solvent, and caps were placed on the vials. Extraction was performed by exposing vials to ultrasonic treatment for five hours and then leaving the vials at room temperature for three days. The organic solvent supernatant was then analyzed by GC-MS. Fig. 25 shows the total ion current chromatograms (TICCs) obtained by analyzing hexane, DCM, and ethanol extraction liquids.

High-temperature extraction was performed using headspace–GC-MS analysis and results were compared at different extraction temperatures. Fig. 26 shows the TICCs obtained at each temperature.
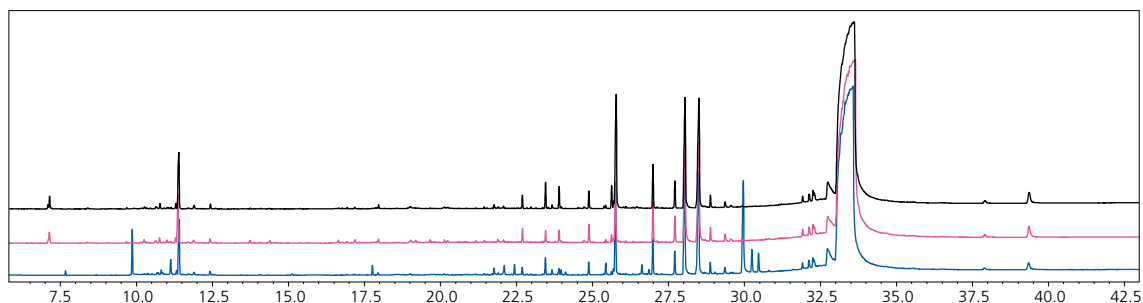

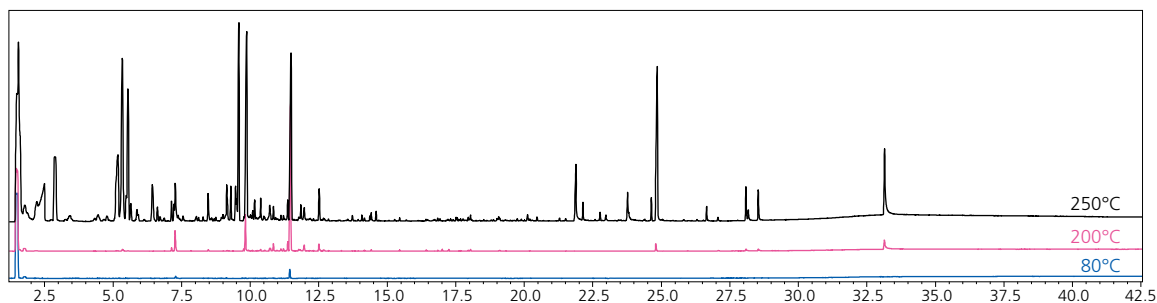Fig. 25   TICCs Obtained Using Solvent Extraction (Black: Hexane, Pink: DCM, Blue: Ethanol)

Fig. 26   TICCs Obtained Using High-Temperature Extraction (Black: 250 °C, Pink: 200 °C, Blue: 80 °C)

Table 10 shows the compounds detected using solvent extraction. Plasticizers, such as tris(2-ethylhexyl) trimellitate (TOTM), bis(2-ethylhexyl) phthalate (DEHP), and bis(2-ethylhexyl) adipate (DEHA), and lubricants, such as palmitic acid and ethyl palmitate, were detected. Different components were detected depending on the extraction solvent used. This was due to the different polarities of the extraction solvents and because low polarity solvents such as hexane are more efficient at extracting low polarity compounds, and high polarity solvents such as ethanol are more efficient at extracting high polarity compounds. In this analysis, the largest number of compounds were detected after extraction with ethanol.

Table 11 shows the compounds detected after high-temperature extraction. Extractables from pharmaceutical packaging were identified using both the solvent extraction method and the high-temperature extraction method. By using a variety of solvents, solvent extraction can be used to identify compounds with a wide range of properties. In contrast, high-temperature extraction with a headspace sampler offers quicker and simpler sample pretreatment than solvent extraction. In either case, compounds were identified by a library search of the NIST Library (2020 release) and the Polymer Additives Library.

Table 10   Compounds Detected after Solvent Extraction

Compound Name	Retention Time (min)			Remarks
	Hexane	DCM	Ethanol	
2-Ethylhexanol	—	—	9.86	
Isophorone	11.37	11.40	11.40	Solvent
Palmitic acid	—	21.77	21.77	Lubricant
Ethyl palmitate	—	—	22.10	Lubricant
2-Ethylhexyl methyl isophthalate	23.46	23.46	23.46	
Stearic acid	—	23.67	23.67	Lubricant
Butyl palmitate	—	23.91	23.90	Lubricant
Ethyl stearate	—	23.90	23.97	Lubricant
Terephthalic acid, ethyl 2-ethylhexyl ester	—	—	24.12	
Methyl 9,10-epoxystearate	24.89	24.89	24.88	
Butyl stearate	—	25.63	—	Lubricant
Bis(2-ethylhexyl) adipate	25.75	25.78	25.78	Plasticizer (DEHA)
Ethyl stearate, 9,12-diepoxy	—	—	26.63	
Bis(2-ethylhexyl) phthalate	27.00	26.99	26.99	Plasticizer (DEHP)
Bis(2-ethylhexyl) isophthalate	28.03	28.05	28.04	Plasticizer
Bis(2-ethylhexyl) terephthalate	28.48	28.51	28.50	Plasticizer
Epoxidized 2-ethylhexyl oleate	29.37	—	29.36	
Tris(2-ethylhexyl) Trimellitate	33.67	33.65	33.59	Plasticizer (TOTM)

Table 11   Compounds Detected after High-Temperature Extraction

Compound Name	Retention Time (min)	Remarks
Benzene	2.87	Solvent
2-Ethyl-1-hexene	5.52	Degradation products of TOTM
2-Chloro-octane	9.27	Degradation products of PVC
3-(Chloromethyl)heptane	9.57	Degradation products of PVC
2-Ethylhexanol	9.85	Degradation products of TOTM
Isophorone	11.47	Solvent
Palmitic acid	21.85	Lubricant
Stearic acid	23.73	Lubricant
Butyl palmitate	23.95	Lubricant
Unidentified	24.80	Degradation products of TOTM
Bis(2-ethylhexyl) adipate	25.79	Plasticizer
Bis(2-ethylhexyl) phthalate	27.03	Plasticizer (DEHP)
Bis(2-ethylhexyl) isophthalate	28.05	Plasticizer
2-Ethylhexyl stearate	28.14	
Bis(2-ethylhexyl) terephthalate	28.50	Plasticizer
Tris(2-ethylhexyl) Trimellitate	33.10	Plasticizer (TOTM)

The HS-20 NX Trap headspace sampler used for high-temperature extraction was equipped with an electronically-cooled trap and capable of heating to a maximum temperature of 300 °C, offering at least 20 times the sensitivity of conventional static headspace (SHS) methods. This sensitivity is comparable to that of heat desorption methods. Presented here is a comparison of results obtained from analyzing pyrolysates from an eye-drop container by SHS and trap headspace (THS) methods.

Fig. 27 shows the principle behind the THS method. For a solid sample, the pressure inside the vial is 10 kPa at 80 °C and 22 kPa at 100 °C. Thus, the vial was pressurized at more than twice this pressure for one minute (pressurizing time). Next, the headspace is introduced to the trap (load time) and approx. 50 % of molecules in the headspace are concentrated in the trap. This cycle of pressurization and loading is then repeated.

Fig. 28 shows results obtained by analyzing different parts of the eye-drop container. Pyrolysates from the nozzle and bottle, which are made of low-density polyethylene, give less intense results than those from the cap, which is made of high-density polyethylene. Fig. 29 compares results obtained by analyzing the nozzle using SHS and THS methods. When using the THS method, components that were almost undetectable using the SHS method were detected with peaks of sufficient intensity to provide a library search hit.
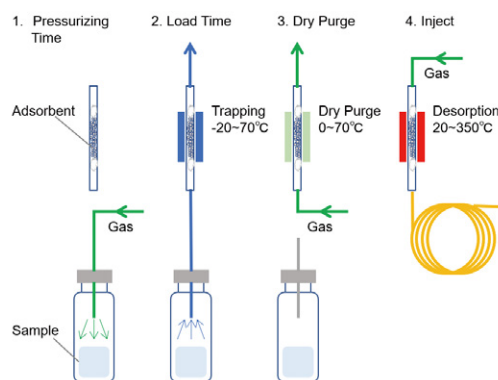

Fig. 27　Principle behind the THS Method

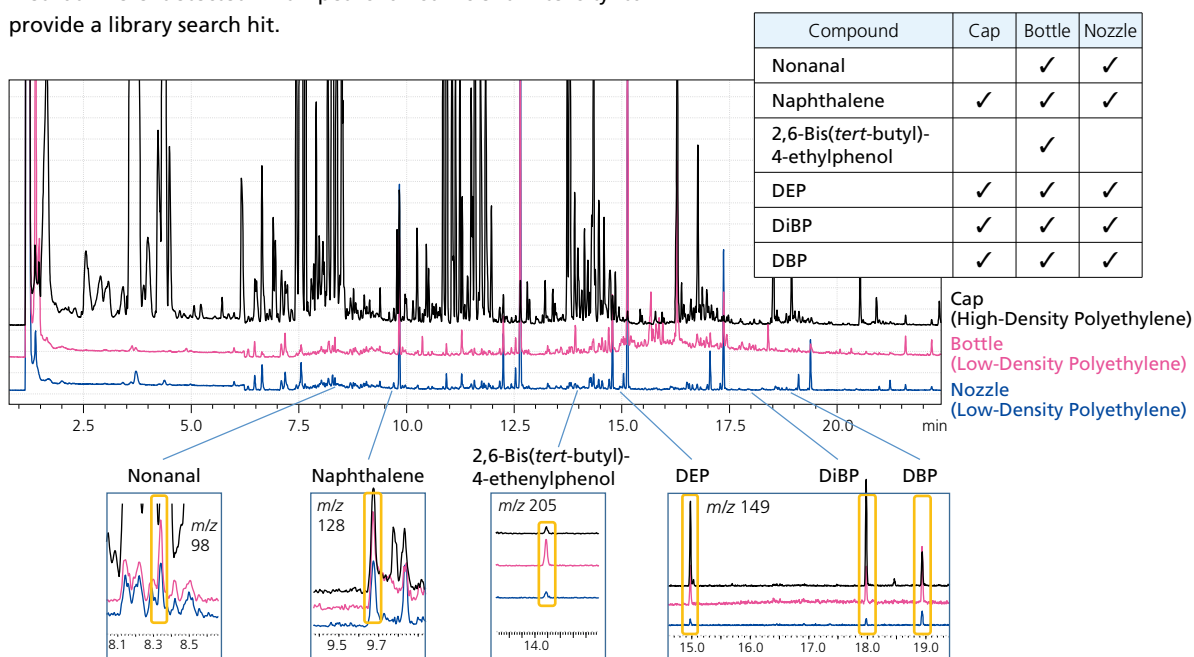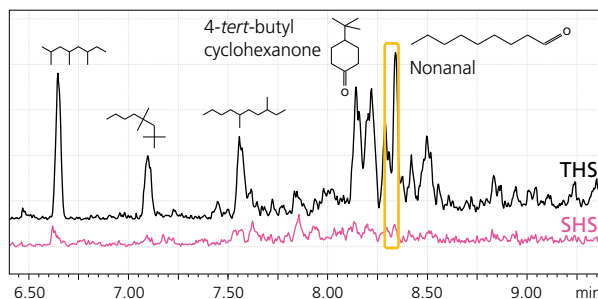| Compound	Cap	Bottle	Nozzle
Nonanal		✓	✓
Naphthalene	✓	✓	✓
2,6-Bis(*tert*-butyl)-4-ethylphenol		✓	
DEP	✓	✓	✓
DiBP	✓	✓	✓
DBP	✓	✓	✓

Fig. 28　Eye-Drop Container Pyrolysates

Fig. 29　Comparison of SHS and THS Methods

Rapid Analysis of a Residual Solvent (*N*-Methylpyrrolidone) in Prepreg CFRP

(DART-MS)

Carbon fiber reinforced plastics (CFRP) combine desirable material attributes such as light weight, high strength, and high rigidity. CFRPs are used in a wide range of industries, including aircraft, automobiles, and other transportation equipment, industrial materials, and construction. CFRPs that use polyimide resins were developed to increase the thermal resistance of the resin matrix in CFRPs for aircraft applications.

Prepreg is an intermediate CFRP consisting of carbon fibers impregnated with resin that is used to form a CFRP by laying prepreg sheets and autoclaving or otherwise treating the resulting laminate. *N*-methyl-2-pyrrolidone (NMP) is used to increase resin flow during the production of thermoset polyimide prepreg. Although NMP improves resin moldability by improving the flowability of polyimide resin, residual NMP in CFRPs after molding can create voids and reduce strength.

Direct analysis in real time (DART) ionizes samples directly and allows rapid analysis of samples in gaseous, liquid, or solid form without pretreatment, thus enabling non-destructive and rapid screening of samples that are otherwise difficult to dissolve, such as CFRPs. Presented here is an example of the rapid analysis of residual solvents in a CFRP using DART in combination with a triple quadrupole mass spectrometer.

Fig. 30 shows the appearance of the prepreg product used for analysis. Prepreg samples with a resin matrix of thermo-plastic polyimide resin without NMP (#1), thermoset polyimide resin exposed to the atmosphere for an extended period after production (#2), and thermoset polyimide resin stored frozen after production (#3) were analyzed by DART-MS. Fig. 31 shows the MS spectra of the prepreg samples.
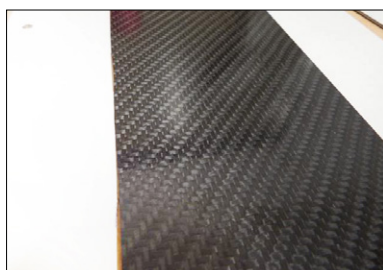

Fig. 30   Prepreg Appearance

DART-MS Ion Source (IonSense) and
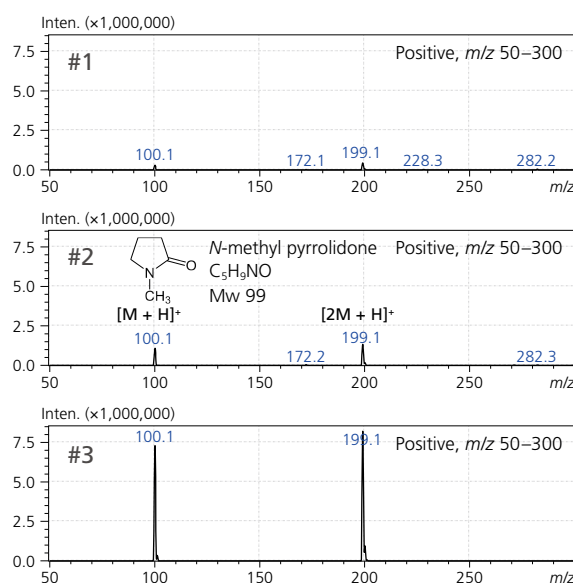Triple Quadrupole LCMS

Fig. 31   Prepeg MS Spectra Obtained by DART-MS
(#1: Thermoplastic polyimide resin, #2: Thermoset polyimide resin after extended exposure to atmosphere, #3: Thermoset polyimide resin after frozen storage)

The spectrum of each sample was acquired in positive mode in the range of *m/z* 50 to 300. The MS spectrum of prepreg with thermoset polyimide resin stored frozen (#3) shows that an [M + H]$^+$ (*m/z* 100) peak and [2M + H]$^+$ (*m/z* 199) peak associated with NMP were detected with very high intensity. Components associated with NMP were also detected in the MS spectrum of prepreg exposed to the atmosphere for an extended period (#2), though their intensity was lower than detected in #3. Almost no NMP was detected in the MS spectrum of prepreg with a thermoplastic polyimide resin without NMP (#1).

NMP screening analysis by DART-MS detected residual NMP with high sensitivity in prepreg exposed to the atmosphere for an extended period. NMP that remains in a CFRP after molding leads to reduced strength, and DART-MS enables easy NMP screening analysis of samples without pretreatment.

Molecular Weight Analysis of Synthetic Polymers and Simultaneous Analysis of Polymer Additives

Simultaneous Analysis of Polymer Additives by GPC (HPLC)

Measuring the molecular weight distribution of polymers is a branch of HPLC analysis performed in size exclusion mode that has long been called **gel permeation chromatography (GPC)**. The recent demand for improved throughput by increasing analysis speed is considered important even for GPC, which has an established analytical procedure. Presented here is an example of using overlapped injection on a normal column to improve efficiency and, simultaneously, perform a quantitative analysis of polymer additives.

A weight-responsive refractive index detector (RID) is often used in GPC analysis when determining the mean molecular weight and polydispersity of polymer compounds. UV detectors are often used when analyzing additives with antioxidant properties because many of the compounds have double bonds. Fig. 32 shows the chromatogram obtained from GPC analysis of the polystyrene sample and three additives used in this investigation. Table 12 shows results for the polystyrene sample.
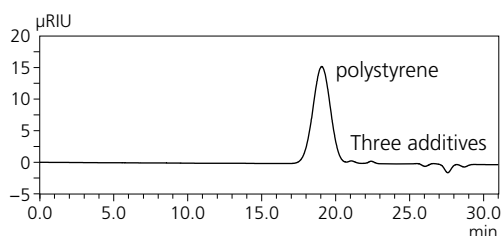

Fig. 32　Chromatogram of Polystyrene and Additives

Table 12　Analytical Results for the Polystyrene Sample (n = 6)

	Number average molecular weight Mn	Weight average molecular weight Mw	Polydispersity Mw/Mn
Polystyrene	2.63×10^4	4.89×10^4	1.86
%RSD	1.41	0.89	0.52

When multiple additives are present, achieving complete separation of small molecule additives from each other can be difficult even on columns with small exclusion limits, and an accurate quantitative analysis is almost always difficult to achieve. Therefore, a photodiode-array (PDA) detector that also provides spectral information was used as the UV detector, and a peak deconvolution function was used to improve the separation of unresolved additives. A LabSolutions (workstation) feature called **i-PDeA II** separates unresolved peaks based on three-dimensional spectral information obtained with a PDA. Fig. 33 shows the chromatogram of the peak detected at UV 240 nm by the PDA and a superimposed chromatogram of each individual component obtained with the peak deconvolution function. Only two peaks could be detected by UV detection alone, but three peaks were identified after processing with i-PDeA II. Furthermore, the peak areas obtained with the deconvolution function represent the contribution of each component in the original unresolved data and can be used without processing for quantitative calculations.

Calibration curves were made for the three additives in the range of 0.01 to 0.1 % (w/v) and used to calculate the quantities of additives added to the polystyrene sample. Table 13 shows the linearity of each calibration curve and the quantitative results of repeat analysis (six times). Quantitative calculations by i-PDeA II, which compensates for the separation performance of GPC columns in the low molecular weight range, demonstrated how GPC can potentially provide value-added, high-throughput analysis.
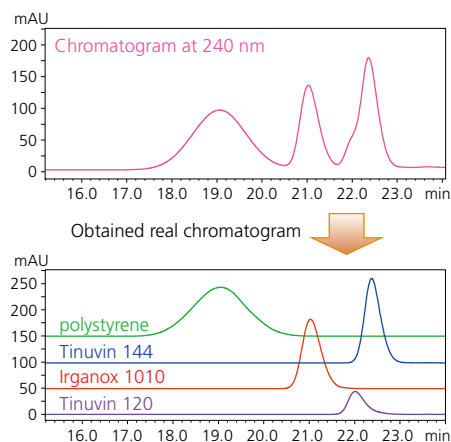

Fig. 33　Deconvolution Results for Three Additives (PDA)

Table 13　Analytical Results for Additives in a Polystyrene Sample (n = 6)

Additive	Irganox 1010	Tinuvin 144	Tinuvin 120
Linearity of calibration curve (r^2)	0.999	0.995	0.998
Determined content (mg/g)	49.2	23.1	27.4
%RSD	1.28	1.93	1.47

Analysis of Oligomers and Additives in an Acrylic Sheet (MALDI)

Many additives, including antioxidants, UV absorbers, hindered amine light stabilizers (HALS), and heat stabilizers, are used to prevent the degradation of polymer materials. The amount of additive added to polymer materials is normally small and no more than approx. 1 % (w/w). Polymer materials of the same type can also have different additives depending on the material grade and the manufacturer. As a result, analyzing additives in polymer materials is very important for investigating and improving the performance of various polymer materials.

Presented here is an example analysis of a dissolved sample of commercially available acrylic sheet performed using AccuSpot, a device that automatically mixes matrix with eluate from size-exclusion chromatography (SEC) and spots a MALDI sample plate with the mixture.

A piece of commercially available acrylic sheet cut to approx. 1 g was immersed in 1 mL of tetrahydrofuran (THF) and subjected to ultrasonic treatment for one minute. The supernatant solution was then collected and analyzed (Fig. 34). Fig. 35 shows a chromatogram of this sample extracted from the acrylic sheet. AccuSpot was used to fractionate 6-second samples from the detected peaks between the beginning and end of peak elution (7 min to 17 min 30 sec). These 6-second fractions were then used to create 105 sample spots on a MALDI sample plate.
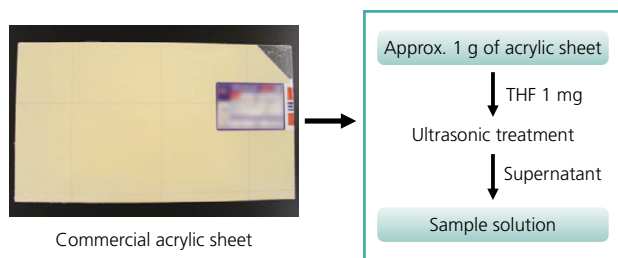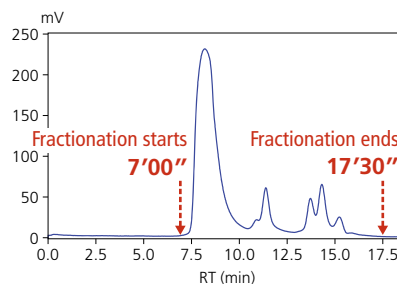

Fig. 34   Sample Preparation

Fig. 35   Chromatogram of Acrylic Sheet Extract

Each spot was analyzed by a MALDI-TOF MS system to obtain mass spectra based on elution times (Fig. 36). Each mass spectra showed a different molecular weight distribution. Looking closely at fractions collected after 11 min 10 sec showed the detection of an additive peak ([Irganox 1010 + Na]$^+$, m/z 1200) not observed before fractionation, even when results were magnified five times (Fig. 37). At the same time, three molecular distributions with a peak of around m/z 2000 (●■▲) were also detected. Since the gaps between adjacent peaks are all m/z 100, these molecular weight distributions are probably oligomers composed of the same monomer unit. The difference between the three molecular weight distributions is due to different terminal structures on each oligomer.

The above findings show that Irganox 1010 was added as an additive to the commercial acrylic sheet analyzed in this study. This analysis also simultaneously detected small amounts of oligomer compounds in the acrylic sheet.
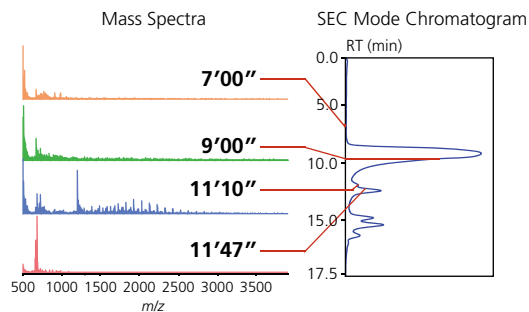

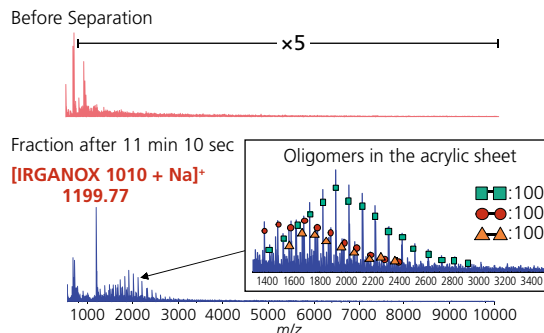Fig. 36   MS Spectra of Individual Fractions

Fig. 37   Detection of Additives in an Acrylic Sheet
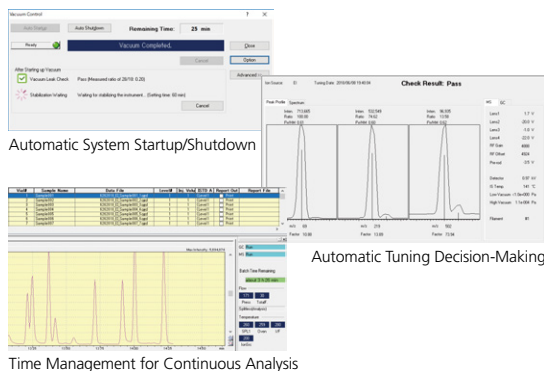
Overview of Related Instruments and Products

GCMS-QP2020 NX

Smart Solutions for Maximizing the Potential of Laboratories

GC-MS systems, which are used in all sorts of fields, have become a general-purpose analytical tool. Consequently, customers are increasingly demanding GC-MS systems that offer higher performance for the cost and enable a better work–life balance for operators. The GCMS-QP2020 NX maximizes the potential of laboratories by offering efficiency improvements for various aspects of analytical work.
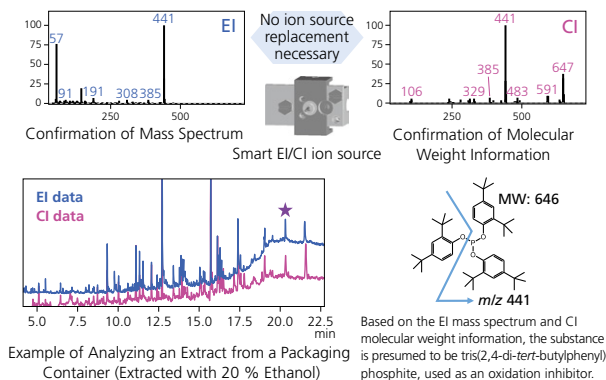
Active Time Management

Active time management helps visualize how much time was spent on maintenance, switching between systems, or performing analyses, for example, to help manage the instrument downtime more appropriately. By automating tasks previously performed by users, it enables more efficient system operation.

Automatic System Startup/Shutdown

Automatic Tuning Decision-Making

Time Management for Continuous Analysis

Smart EI/CI Ion Source

The newly developed Smart EI/CI ion source can be used to acquire CI data without exchanging ion sources or losing the general applicability of EI sensitivity. With the EI mode, even if identification is difficult using a mass spectral library, molecular weight information can be collected from the CI mode data, which is especially useful for predicting unknown compounds.

No ion source replacement necessary

Smart EI/CI ion source

Confirmation of Mass Spectrum

Confirmation of Molecular Weight Information

EI data
CI data

Example of Analyzing an Extract from a Packaging Container (Extracted with 20 % Ethanol)

MW: 646

m/z 441

Based on the EI mass spectrum and CI molecular weight information, the substance is presumed to be tris(2,4-di-tert-butylphenyl) phosphite, used as an oxidation inhibitor.

Fourier Transform Infrared Spectrophotometer
IRTracer-100

This system achieves excellent sensitivity with an S/N ratio of 60,000:1, high resolution at 0.25 cm^{-1}, and high-speed scanning capable of 20 spectra/second. The performance of medium and higher end models is supported by high reliability, achieved with advanced dynamic alignment and an interferometer with a dehumidifier. This system is applicable for in a variety of circumstances, with a library of approximately 12,000 spectra and data analysis programs for contaminant analysis, and time course and rapid scan programs for reaction tracking.

Energy Dispersive X-ray Fluorescence Spectrometer
EDX-7200

Equipped with an electronically-cooled high-performance semiconductor detector, the EDX-7200 offers lower running costs and easier maintenance, as well as better sensitivity, throughput, and resolution than previous models. Many optional features, such as a vacuum unit for light element analysis and a turret unit for continuous measurements, are available. PCEDX-Navi software, designed to enable easy operation, and PCEDX-Pro software, designed for general analysis applications, are included as standard. PCEDX-Navi can be optionally equipped with the screening features offered by EDX-LE and PCEDX-Pro can be optionally equipped with an FDA 21 CFR Part 11 system.

Polymer Additives Library

The Polymer Additives Library is a GCMS mass spectral library containing information on a wide range of additives utilized in polymer materials. In addition to approx. 4,900 mass spectra and retention indices, it contains information on the classification of additives and pyrolysates, so even without detailed knowledge of additives, users can see which additive is associated with a compound found in the library. The library can be used for a variety of GC/MS applications, including pyrolysis GC/MS and liquid sample injection GC/MS.

Filtering with Retention Index

Multiple compounds with similar mass spectra are listed as candidates when performing a library search using only the mass spectrum. Filtering with the retention index sorts the candidates by retention index, thereby providing highly accurate identification results.

Results of similarity search using mass spectrum

Hit#	Similarity	Register	Ret. Index	Compound Name	Mol Wt	Formula	Library
1	95	☑	1729	Ethylhexyl benzoate [Original Additive: Bi	234	C15H22O2	FLAB_ADD1
2	81	☐	2042	Undecyl benzoate [Original Additive: Diu	276	C18H28O2	FLAB_ADD1
3	81	☐	1796	Octyl benzoate [Original Additive: Tri-n-	234	C15H22O2	FLAB_ADD1
4	79	☐	2109	Tridecyl benzoate [Original Additive: Diun	304	C20H32O2	FLAB_ADD1
5	66	☐	793	1−Octene [Original Additive: Alkyl phosp	112	C8H16	FLAB_ADD1
6	65	☐	791	Isomer of C8H16 [Original Additive: Alkyl	112	C8H16	FLAB_ADD1

Results sorted using retention index filtering

Hit#	Similarity	Register	Ret. Index	Compound Name	Mol Wt	Formula	Library
1	95	☑	1729	Ethylhexyl benzoate [Original Additive: Bi	234	C15H22O2	FLAB_ADD1

Confirming the Additive Classification Information

The additive classification information (such as plasticizers and flame retardants) registered in the library plays a role in confirming the type of additive associated with the compounds included in search results.
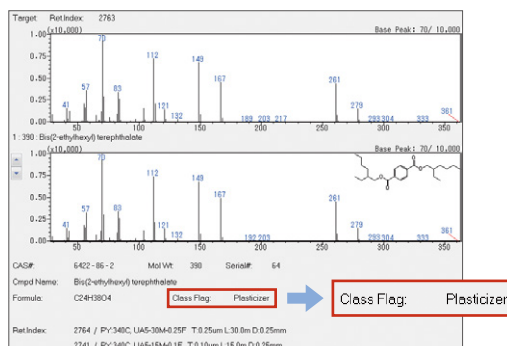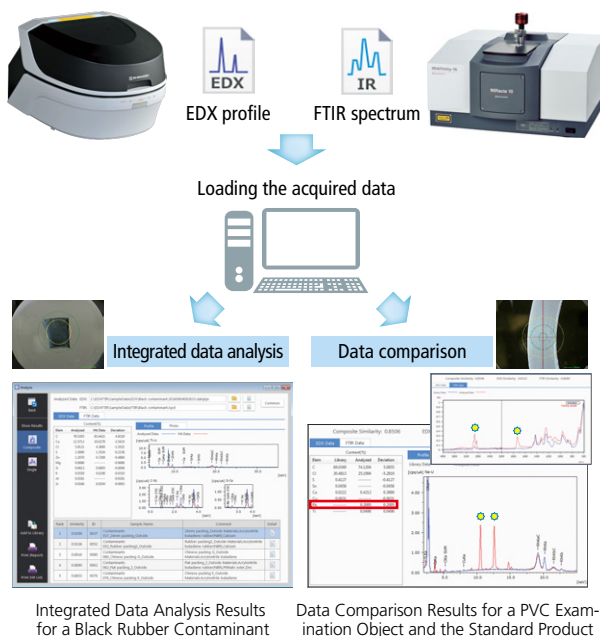

Integrated EDX–FTIR Analysis Software

EDXIR-Analysis

EDXIR-Analysis software has been especially for qualitative analysis, utilizing data acquired with energy dispersive X-ray (EDX) fluorescence spectrometers and Fourier transform infrared (FTIR) spectrophotometers. This software provides identification results and degrees of matching by performing an integrated analysis of data acquired with FTIR, which is ideal for the identification and qualitative analysis of organic compounds, and data acquired with EDX, which is ideal for the analysis of the elements contained in metals and inorganic compounds. It can also perform either EDX or FTIR analysis separately. Shimadzu's proprietary library (containing 485 data as standard), created through cooperation with waterworks agencies and food product manufacturers, is used for the data analysis. Additional data as well as image files and document files in PDF format can be registered in the library. It is also effective for linked storage with a variety of data as digital files.

EDX profile   FTIR spectrum

Loading the acquired data

Integrated data analysis   Data comparison

Integrated Data Analysis Results for a Black Rubber Contaminant

Data Comparison Results for a PVC Examination Object and the Standard Product

▶

SHIMADZU

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