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以超高效能液相層析/串聯式飛行時間質譜術篩查血漿中環境汙染物

Screening of environmental pollutants in human plasma using ultra-high performance liquid chromatography / quadrupole time-of-flight mass spectrometry

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國立臺灣大學碩士學位論文
口試委員會審定書

以超高效能液相層析/串聯式飛行時間質譜術篩查血漿中環境汙染物

Screening of environmental pollutants in human plasma using ultra-high performance/quadrupole time-of-flight mass spectrometry

本論文係 陳儒佑 君（學號 R04844022）在國立臺灣大學環境與職業健康科學研究所完成之碩士學位論文，於民國 109 年 7 月 23 日承下列考試委員審查通過及口試及格，特此證明

口試委員：陳家揚（簽名）

李慶國（指導教授）　郭錦樺

陳安彰

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中文摘要

人們可能從環境中暴露到各種有害汙染物質並造成不良健康效應。不論暴露途徑為何，人體生物偵測可以得到暴露化學物質於人體內濃度。利用極致高效液相層析高解析質譜儀進行無選擇性的資料蒐集可以用來篩查關切的化學物質。此研究發展並建立以非標的物方式偵測血漿樣品中的環境汙染物篩查平台。

血漿樣品與 1%甲酸乙腈溶液混合並經由 96 孔 Ostro 萃取盤濾除蛋白質與磷脂質，濃縮回溶後的樣品利用正離子與負離子電灑游離法與超高效能液相層析/四極柱飛行時間串聯質譜儀進行分析，儀器分析時間為 20 分鐘。化合物於 Phenomenex Luna Omega Polar C18 管柱進行分離分析，質譜以全離子碎片模式 (三種撞擊能量 0, 20, 40 伏特) 收集質荷比 70 至 1100 的資料。方法以樣品前處理、管柱選擇與品質管制評估進行最佳化。

此研究分析 500 個來自中研院人體生物資料庫的血漿樣品，受試者為 30 至 70 歲正常台灣人。血漿樣品包含品管樣品皆添加 6 種同位素標記標準品以評估批次內與批次間樣品的分析再現性。除了 $^{13}C_4$-PFBA 受到質量接近的干擾物影響，大部分同位素內標的質量精確度落在 5 ppm 以內；同位素標準品的積分面積批次內相對標準偏差落在 5.9% 至 18.9% 之間 (n = 43 及 26)，批次間相對標準偏差落在 22.0-43.1%之間 (n = 12)；於 2 個月 12 批次的樣品分析期間 (n = 572)，正電分析模式下同位素標準品的滯留時間差異在 0.3 分鐘內，於負電模式下在 1 分鐘內。

500 個樣品分析資料與 3500 個化合物資料庫進行二次質譜的比對，比對標準為質量準確度在 10 ppm 以內，除母離子之外至少再比對到一個同位素或加成物、以及至少有一個子離子與母離子共層析疊合(coelution)。ToxPi 計分系統被用做試探性比對到的化合物質排序，包含利用化合物偵測頻率、訊號豐度、暴露資料及毒性資料來進行化學物質排序。於此研究樣品中比對到計分較高的關切物質為 (1) 對羥基苯甲酸酯類 (parabens); (2) 塑化劑: 己二酸酯、鄰苯二甲酸酯、磷酸酯阻燃

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劑; (3) 全氟碳化合物及 (4) 其他: 殺蟎劑 (metolcarb)、8-羥基喹啉及、對特辛基苯酚等。

此研究於樣品前處理及儀器分析上建立了人體血漿樣品的篩查平台，提供一個新的篩查工具來調查人體常暴露到的關切化學物質且收集到的樣品資料具有可回溯的特性。所得到的排序化合物清單可幫助暴露評估、化學物控制及人體健康。

關鍵字: 環境汙染物、人體生物偵測、血漿、篩查平台、液相層析飛行時間質譜儀、化學物質排序

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Abstract

People may expose to many concerned chemicals from the environment and cause health effects. Biomonitoring of human specimens can reflect internal doses of exposed chemicals regardless of the exposure route. With data-independent acquisition using a UHPLC-HRMS, we can screen concerned compounds without chemical standards. This study developed and established a platform for identifying environmental pollutants in human plasma using a non-targeted approach.

Plasma samples were mixed with 1% formic acid/acetonitrile, then were extracted with Waters Ostro 96-well plates for removing proteins and phospholipids; The concentrated and reconstituted filtrates were analyzed with an Agilent UHPLC-QTOF MS in both positive and negative electrospray ionization. Compounds were separated on a Phenomenex Luna Omega Polar C18 column (100 × 2.1 mm, 1.6 μm) within 20 minutes. Information at all ion MS/MS (AIM) mode from m/z 70 to m/z 1100 were collected at three collision energies (CE = 0, 20, and 40 V). The analytical method was optimized on sample preparation, column selection, and quality assurance.

This study analyzed 500 plasma samples obtained from the Taiwan Biobank, and the age of subjects was from 30 to 70 years old. Samples including quality control samples were pre-spiked with six stable isotope-labeled surrogate standards for evaluating the

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reproducibility within and between batches of analysis. Most of the mass accuracy was within 5 ppm except for $^{13}C_4$-perfluorobutanoic acid, which resulted from a very close m/z in backgrounds. The %RSD of peak areas of the six surrogates were 5.9%-18.9% within batches (n = 43 or 26) and were 22.0-43.1% between batches (n = 12). The differences of retention time of the three surrogate isotope standards were lower than 0.3 minute in positive ion mode and lower than 1 minute in negative ion mode in 12 batches through two-month analysis.

The 500-sample data were compared with MS/MS spectral libraries of about 3,500 suspect chemicals. The criteria for tentative identification were a compound precursor ion co-eluted with at least one of the product ions, mass accuracy within ± 10 ppm, and at least one isotope or adduct founded. A novel ToxPi scoring system was used for the prioritization of tentatively identified compounds based on detection frequency, abundance, exposure, and bioactivity data. The concerned chemicals tentatively identified in this study with higher priority scores were (1) Parabens: propylparaben, butylparaben, isobutylparaben, and methylparaben; (2) Plasticizer: tri-(2-chloroisopropyl) phosphate (TCPP), tributylphosphate (TBP), Tris(2-butoxyethyl) phosphate (TBEP), dinonyl phthalate (DNP), di(2-ethylhexyl)phthalate (DEHP) and di (2-ethylhexyl) adipate (DEHA); (3) Perfluorochemicals (PFCs): perfluorooctanoic acid (PFOA), perfluoro-

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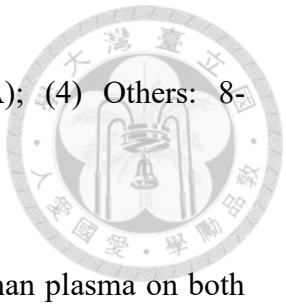

octanesulfonic acid (PFOS), and perfluorodecanoic acid (PFDA); (4) Others: 8-hydroxyquinoline, metolcarb, and 4-tert-Octylphenol.

This research set up the procedure of suspect screening on human plasma on both sample preparation and instrumental analysis with UHPLC-QTOF MS, offering a new screening tool to find the chemicals that people are commonly exposed to with a “known unknown” pattern and retrospective data. The prioritized chemicals, which could be utilized to facilitate the exposure assessment, chemical regulations, and human health.

Keywords: Environmental pollutants; Human biomonitoring; Plasma; LC-QTOF MS; Suspect screening; Chemicals prioritization

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Chapter 1. Introduction

1.1 The basic of environmental pollutants

Environmental pollutants from different anthropogenic or natural sources are widely distributed. These pollutants may be mobile and persistent in air, water, soil, sediments and organisms even at low concentrations [1-2]. Environmental pollutants could be harmful or toxic for humans, either persistent and bio-accumulative in the environment or what humans are continually exposed to, especially for the susceptible group [3-5].

For example, endocrine disruptors, one of the most concerned environmental pollutants, constitute a topic of extensive research [6]. An endocrine-disrupting compound has been described by the U.S. Environmental Protection Agency (EPA) as “an agent that interferes with the synthesis, secretion, transport, binding, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development or behavior”[7]. Endocrine disrupting chemicals (EDCs) are usually highly heterogeneous and synthesized, presenting in the products that people use in daily life, from children products, electronics, personal care products, clothing to building materials, as shown in the Table 1 [8-9].

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Table 1. Common endocrine disrupting chemicals (EDCs) and their uses.

Common EDCs	**Uses**
BPA, phthalates, phenol	Food contact materials
Phthalates	Personal care products, medical tubing
Perfluorochemicals	Textiles, clothing
Parabens, phthalates, glycol ethers, fragrances, cyclosiloxanes	Cosmetics, personal care products, cleaners
Tributylin	Antifoulants used to paint the bottom of the ship
Nonylphenol (alkylphenols)	Surfactants- detergents used for removing oil and their metabolites
Ethinyl estradiol (Synthetic steroid)	Contraceptive
Brominate flame retardants, PCBs	Electronics and building materials
DDT, chlorpyrifos, atrazine, 2,4-dichlorophenoxyacetic acid, glyphosate	Pesticides
Triclosan	Antibacterials

Endocrine disruptors exhibit the same characteristics as hormones and could exercise their effects mainly in two pathways: either a directly on hormone-receptor complex or on the specific proteins that are involved in the control of delivery of hormones [10]. Endocrine disruptors could obstruct thyroid function [11], cause corticoid dysfunction [12-13], have effect on nervous system as neuroendocrine disruptors [14], and also affect male and female reproduction [15-16].

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Environmental pollutants can enter human body by a variety of routes, such as oral consumption, contact with skin or inhalation. Exposure to these chemicals is widespread globally, through air, water, food contamination, and many consumer goods including plastics and personal care products. Usually ingestion of foods is deemed as the primary exposure route to those concerned chemicals, and environmental contaminants [17].

Over 160 million unique organic and inorganic compounds are currently listed on the Chemical Abstracts Service (CAS) Registry [18]. Further, between 1930 and 2000 global production of anthropogenic chemicals increased from 1 million to 400 million tons per each year [19]. Statistics published by EUROSTAT in 2018 reveal that, between 2004 and 2018, over 50% of the total production of chemicals are chemicals with significant environmental impact and over 70% of these reveals hazardous or toxic to human health [20]. And it is known that greater than 80% of human diseases are linked to environmental exposures as well [3, 21].

An environmental monitoring or systematic post-market monitoring of foods and products for regulated chemical substances helps a lot for risk assessment. Owing to the development and refinement of many techniques, detection and analysis of trace pollutants during recent years have been progressed a lot, but a wide

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array of undetected and emerging concerned chemicals needs to be identified and quantified.

1.2 The basic of human biomonitoring and the exposome

Human biomonitoring (HBM) measures the levels of chemical substances, their metabolites, or reaction products in human specimens such as blood, urine, hair, adipose tissue, teeth, saliva, breast milk, and semen. HBM is an approach for assessing human exposures to natural and synthetic compounds from the environment, occupation, and lifestyle. The main advantage of HBM is that they represent the internal dose, an integrative measurement of exposure to a given substance, regardless complex pathways of exposure [22-23]. Many countries have conducted HBM studies, established cross-sectional nationwide HBM surveys and programmed to monitor and track the chemical concentrations within their general populations, such as the United States of America (USA), Canada, Germany, France, Belgium, South Korea, and so on [24]. For example, National Health and Nutrition Examination Survey (NHANES), conducted by the USA CDC, was devoted to the monitoring of toxic substances and essential nutrients in the US population, published the yearly National Report on Human Exposure to Environmental Chemicals with more than 300 substances regularly monitored [25].

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Human biomonitoring, the direct measurement of a biomarker, is an approach used to measure exposures to environmental chemicals [23, 26]. Figure 1 summarizes the relationships among exposures, biomarkers, and adverse health outcomes, adapted from [24]. Risk assessment incorporates exposure to chemicals from different sources in the environment, leading to the absorption, distribution, metabolism, and excretion of chemicals in the human body, and following with health effects. The internal dose or target organ dose of biomarkers are regarded as more closely related to adverse health effects.

HBM is progressively deemed as an efficient and cost-effective way of assessing human exposure to food contaminants, including mycotoxins, pesticides, heavy metals and environmental pollutants [17, 24, 27].

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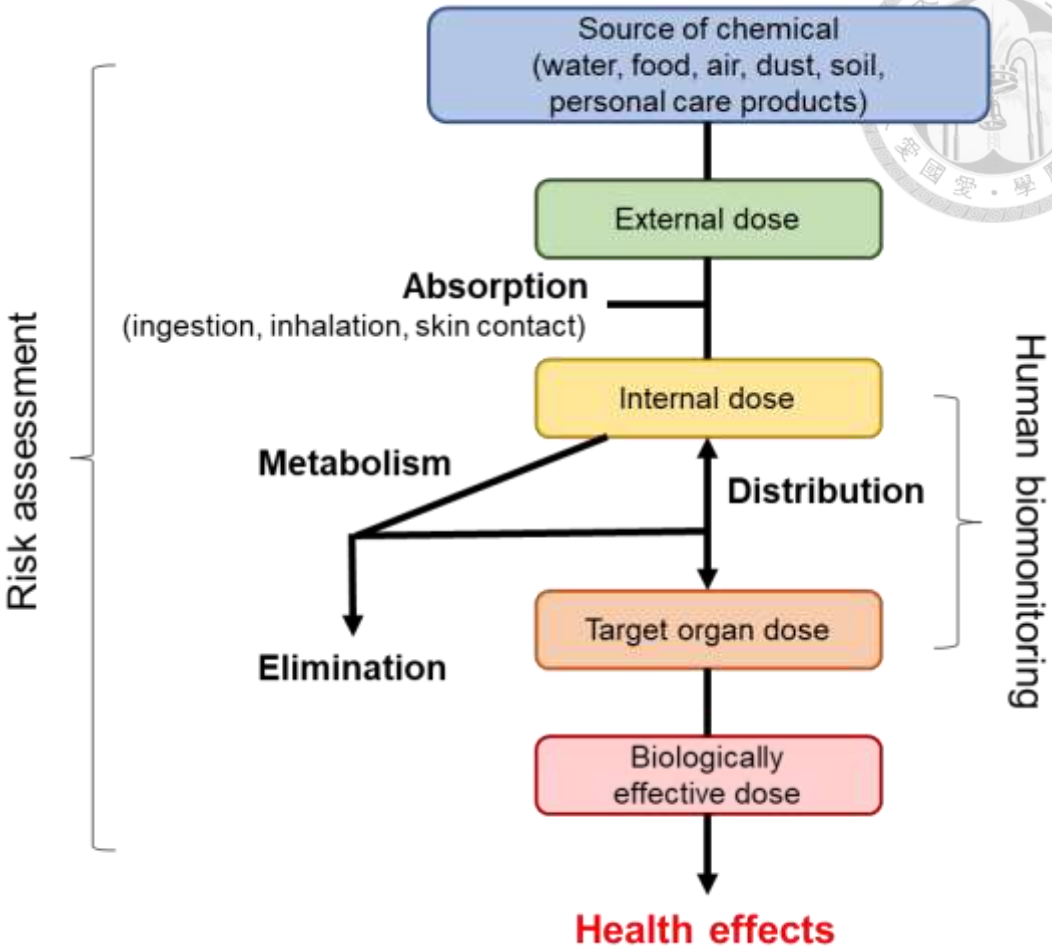

Figure 1. The scheme of the relationship from source to biomarkers to health effects, risk assessment and human biomonitoring (adapted from [24]).

In the human biomonitoring, there is a concept introduced in 2005, the exposome, which reflects the totality of chemical and nonchemical exposures that an individual accumulates over a lifetime, beginning during prenatal period [28]. Exposomic approaches include quantifying hundreds or thousands of analytes simultaneously in what is known as non-targeted analysis and measuring even a greater number of metabolites [29].

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A new commentary discusses why both traditional and exposomic approaches are critical to advancing the science of exposure assessment [30-31]. Method development for traditional biomonitoring can be quite rigorous and robust, developing analysis protocols for new chemicals of interest is relatively a slow and expensive process. While traditional biomonitoring aims at specific analytes to measure in samples, Limitations are also evident to discover new chemicals that are hazardous. Exposomic approaches go beyond traditional biomonitoring, expecting to capture all exposures that potentially affect disease and health. A comprehensive study of the exposome incorporates environmental exposures and associated biological responses including from environmental factors, diet, behavior, to metabolomic processes [32]. The challenge would be to detect and identify low-abundance chemicals in samples and to differentiate between endogenous and exogenous molecules [30].

HBM can establish distribution of exposure among the general population, recognize new chemical exposures, trends and changes in exposure, and identify vulnerable groups and populations with higher exposures [33-34].

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1.3 Analytical method for suspect screening in biospecimens

Liquid chromatography mass spectrometry (LC-MS) is an important technique for biomonitoring and quantitative analysis of biological fluids, offering high-efficiency separations of compounds, sensitive detection across a broad range of chemical species. High resolution mass spectrometry (HRMS), such as time-of-flight (ToF), quadrupole-time-of-flight (Qq-ToF), or Orbitrap, provides opportunities to screen target, suspect, and non-target molecular features with improved sensitivity, mass resolution, reliability and robustness [35]. Liquid chromatography coupled to high resolution mass spectrometry (LC–HRMS) allows for the screening of targeted contaminants, their metabolites, degradation products or other non-targeted compounds by measuring the exact mono isotopic mass in full-scan mode. [36-37]

To include comprehensive profile of substances in specimens, minimal sample preparation is usually preferred, especially for non-targeted applications while for targeted approaches a relative selective sample-preparation protocol can be used [38-40]. Most studies on biofluids reported in the literature are based on plasma/serum and urine, which are more easily obtainable and considered to be representative of overall metabolic behavior [39]. Simple sample clean-up and pre-concentration of analytes is preferred to remove interfering matrix components and for trace analysis. The

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challenges of sample preparation for non-targeted analysis of biospecimens include efficiency, reproducibility and coverage, among others [41].

The strategy "suspect screening analysis" refers to analytical chemistry techniques that compare molecular features observed within samples to databases of known chemical agents to identify potential matches. This strategy enables investigation of thousands of chemicals within a sample [42-43]. The Figure 2 illustrates the workflow of non-target screening, suspect screening, and target screening for HRMS approaches [36].

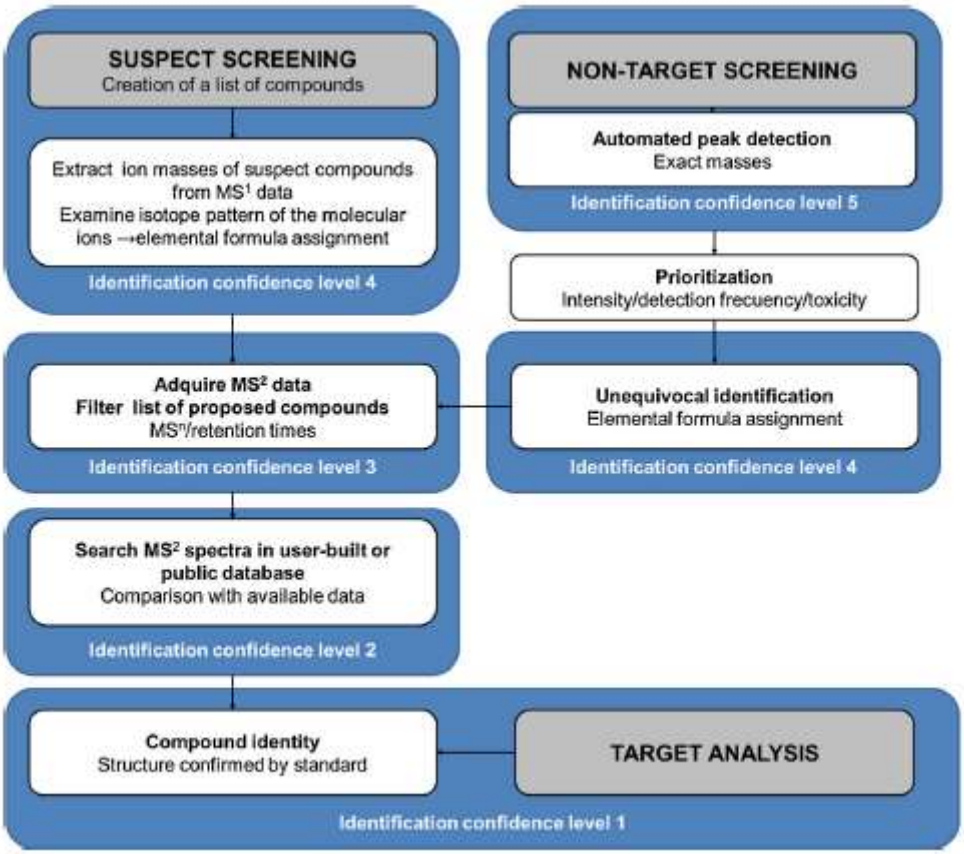

Figure 2. The workflow illustrates from non-target screening, suspect screening, to target screening for HRMS approaches (from [36]).

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There were more and more applications of suspect screening using HRMS on multi-residue detection method of foods [44-47] and environmental samples [48-51], or bioanalysis on clinical/forensic toxicology [52-55] or metabolomics [56-58]. HRMS also has become an increasingly used tool for broad exposome-level characterization [35, 59].

1.4 Objectives

People may expose to many concerned chemicals from foods, water, air, soil and personal care products, such as organochlorines, polychlorinated biphenyls, polybrominated diphenyl ethers, endocrine disruptors, pesticides, veterinary drugs, mycotoxins et al., leading to health effect. A systemic post market monitoring and environmental monitoring is helpful for exposure and risk assessment, but many uncertainties among exposure, absorption and metabolism from person to person due to different living environment, lifestyle factors, individual genomes and susceptibility. Human biomonitoring represents the internal dose regardless the exposure routes and could be used to find out emerging concerned chemicals which people usually expose to. Plasma/serum are representative of overall metabolic behavior in body and are suitable as biomonitoring samples. Appropriate bioanalysis method was non-targeted analysis/ suspect screening using LC-HRMS and

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corresponding sample preparation method. So far, not much non-targeted analysis and suspect screening protocol for human biomonitoring of environmental pollutants was used in blood sample yet. Therefore, the aim of this study is to:

(1) Establish a non-targeted analysis platform based on UHPLC-QTOF MS for human plasma.

(2) Apply the platform on real human plasma samples.

(3) Tentatively identify the concerned chemicals in human plasma and set up a workflow for suspect screening from large-scale datasets.

(4) Prioritize and characterize the chemicals which humans are frequently exposed to and may cause health concerns.

To promote the health of people in Taiwan, this study would apply the screening platform to 500 normal human plasma, and prioritize these identified chemicals, which could be utilized in further investigations on exposure assessment, reducing environmental pollution, better agricultural practices, and improving the food safety.

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Chapter 2. Material and methods

2.1 Reagents and materials

Formic acid (A.C.S. reagent grade, ≧98%), ammonium acetate (BioUltra, ~5M in H_2O), acetic acid (glacial, ACS grade, ≧99.7%) were from Sigma-Aldrich (Saint Louis, MO, U.S.A.). HPLC-grade acetone and methanol, LC/MS-grade acetonitrile were provided by J.T Baker (Philipsburg, NJ, USA). LC-MS grade Methanol used in instrumental analysis was from Fluka (Steinheim, Germany). Milli-Q water was from a Milli-Q integral water purification system (Merck Millipore, Darmstadt, Germany). The isotope standard perfluoro-*n*-[$^{13}C_4$] butanoic acid ($^{13}C_4$-PFBA), perfluoro-*n*-[$^{13}C_8$] octanoic acid ($^{13}C_8$-PFOA), perfluoro-*n*-[1,2,3,4,5,6,7-$^{13}C_7$] undecanoic acid ($^{13}C_7$-PFUnDA) were from Wellington Laboratories (Ontario, Canada) with purity > 98%, concentration 50 ± 2.5 μg/mL in methanol. And isotope standard cocaine-D3 (C-004), diazepam-D5 (D-902) and morphine-D3 (M-003) were from Cerilliant Corpotation (Round Rock, Texas, USA) with purity > 98%, concentration 100 μg/mL in methanol. Six isotopic chemicals ($^{13}C_4$-PFBA, $^{13}C_8$-PFOA, $^{13}C_7$-PFUnDA, cocaine-D3, diazepam-D5 and morphine-D3) were mixed in methanol which final concentration was 300 ng mL^{-1} as isotopic standard working solution (ISTDs). Ostro 96-well plate, 25 mg, 1/pk was from Waters Corporation (Wexford, Ireland). For accurate mass calibration and tuning of

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TOF MS, a mass calibration solution was prepared with a ESI-L Low Concentration Tuning Mix and ES-TOF Biopolymer Analysis Reference Mass Standards Kit (Agilent, Santa Clara, CA, USA) in 95:5 aetonitrile: water solution (v/v). TOF Reference Mix (Agilent, Santa Clara, CA, USA), prepared in 95:5 aetonitrile: water solution, provided internal reference masses for accurate mass correction in operation.

2.2 Sample collection

Human plasma samples were collected by Academia Sinica Taiwan Biobank from 2008 to 2016, including 500 subjects from four different regions in Taiwan, and subjects' age were from 30 to 70. This study used left samples, results are not able to link with personal information of individuals, and the health risk of the subjects didn't increase. The usage of 500 left samples was approved by Institutional Review Board (IRB, IRB number: 104-007-F). The demographic data of samples was listed in

Table 2. Four-hundred microliters of 500 samples transferred from Taiwan Biobank in 2016 and were froze at -20℃ before usage.

Table 2. The demographic data of 500 plasma samples.

Age	Gender		Total
	Male	Female	
30-39	65	65	130
40-49	65	65	130
50-59	60	60	120
60-70	60	60	120
total	250	250	500

Regions in Taiwan	Number
Greater Taipei	160
Taichung	120
Southern Taiwan	120
Eastern Taiwan	100
total	500

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2.3 Sample preparation

To make aliquots and prepare pooled human plasma as quality control samples, all of the 500 samples were thawed to room temperature and vortexed. One aliquot (150 μL) of each sample in Eppendorf was used to sample preparation afterwards, and the other one aliquot (20 μL) of all samples were mixed together in a clean container to prepare pooled human plasma. The pooled human plasma was also distributed to 150 μL each aliquot in Eppendorf. The pooled human plasma samples were used for method development and as quality control samples through sample analysis. All of the samples and aliquots were frozen back to -20℃. The aliquots were thawed to room temperature in batches before sample preparation.

One hundred fifty microliters of serum/plasma samples were spiked with 50 μL ISTDs in methanol, followed by adding 400 μL of 1% formic acid in acetonitrile, then were vortexed homogeneously for 30 seconds. Each sample mixture was loaded onto Ostro 96-well plate (Waters, Wexford, Ireland) and applied 2.5 to 4 psi (5–8 ”Hg) of vacuum to help the samples passed through the plate and collected into a 96-well polypropylene collection plate with a volume capacity of 2 mL in each cell. The collected filtrate was transferred into deactivated vials, evaporated by Savant SPD1010 SpeedVac (Thermo Scientific, Holbrook, New York, U.S.A.) to nearly dry. Samples were reconstituted with 50 μL methanol with vortex for 30 seconds, then 50 μL water was

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added and vortexed for another 30 seconds. The reconstituted samples were transferred into 150 μL inserts, centrifuged 10 minutes at 4000 rpm using Kubota Compact Tabletop Centrifuge 2010 (Kubota, Fujioka, Japan) and were ready for the instrumental analysis.

Each sample preparation batch included one solvent sample, one pooled human plasma (no ISTDs), three pooled human plasma spiked with ISTDs, and 43 real samples spiked with ISTDs, while the last one sample batch (batch 12) contained 26 real samples. Total 12 batches of samples were analyzed in 2 months for sample preparation and instrumental analysis.

2.4 Instrumental analysis

The accurate mass of Q-TOF MS was calibrated using MS calibrator solution before analysis of a sample batch or after TOF MS polarity switching. The m/z used to calibrate accurate mass are showed in Table 3.

Table 3. The list of MS calibrator solution m/z.

	Positive	Negative
Mass 1	118.086255	112.98587
Mass 2	322.048121	301.998139
Mass 3	622.028960	301.978977
Mass 4	922.009798	601.978977
Mass 5	1221.990637	1033.988109
Mass 6	1521.971475	1333.968947
Mass 7	1821.952313	1633.949786

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Liquid Chromatography (LC) - Time-of-Flight (TOF) HRMS analysis was carried out using an Agilent 1290 HPLC (Agilent Technologies, Palo Alto, CA), interfaced with an Agilent 6545 TOF HRMS (Agilent Technologies, Santa Clara, California). The prepared samples were placed in autosampler at 10℃. The injection volume was 6 μL. Chromatographic separation was accomplished using a Luna omega polar C18 column (100 × 2.1 mm, 1.6 μm) fitted with corresponding guard column from Phenomenex (Torrance, CA, USA). The LC method in positive electrospray ionization mode consisted of the following conditions: 0.3 mL/min flow rate; column at 40℃; mobile phase A as ammonium acetate buffer (5 mM) in Milli-Q water (pH = 6.40), and mobile phase B as methanol; gradient: from initial to 0.5 min hold at 95:5 A:B, 0.5−7 min linear gradient from 95:5 A:B to 40:60 A:B; 7−14 min a linear gradient to 100% B; 14-17 min hold at 100% B; then back to 95:5 A:B for 2.5-min equilibrium. The LC gradient in negative electrospray ionization mode was the same, except for the mobile phase A as 0.04 % (v/v) acetic acid in Milli-Q water (pH = 3.40). The analytical LC condition is summarized in Table 4 (p. 17).

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Table 4. LC analytical condition.

Column	Luna omega polar C18 (100 × 2.1 mm, 1.6 μm)	
Column temperature	40 ℃	
Flow rate	0.3 mL/min	
Injection volume	6 μL	
Mobile phase / Gradient (min)	Methanol	ESI^+: 5 mM ammonium acetate (pH = 6.40) ESI^-: 0.04 % acetic acid (pH = 3.40)
Initial	5	95
0.5	5	95
7.0	60	40
14.0	100	0
17.0	100	0
17.1	5	95
19.6	5	95

The TOF-HRMS was fitted with an electrospray ionization source, which operated in both positive and negative ionization modes (separate sample injection for each mode), using a fragmentor voltage of 125 V. The other MS source parameters are showed in Table 5 (p.18). Data acquisition was at all ion MS/MS (AIM) mode, which all the precursor ions (CE = 0) and all the product ions (CE = 20, 40), from m/z 70 to m/z 1100 were collected, achieving non-target screening purpose. The dwell time of each spectrum (CE = 0, 20, 40) was 0.2 sec and the cycle time was 0.6 sec. Data was collected in 2 GHz high dynamic range mode in centroid data format.

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Table 5. Ion source parameters

	Method ESI+	Method ESI−	Tuning ESI+	Tuning ESI−
Drying gas temperature (℃)	340	340	325	325
Drying gas flow (L/min)	10	10	5	5
Neubulizer gas (psig)	50	50	20	20
Sheath gas temperature (℃)	360	360	275	275
Sheath gas flow (L/min)	11	11	12	12
Nozzle voltage (V)	2000	1500	2000	2000
Capillary voltage (V)	4500	3500	4000	3500

Reference solution was infused to TOF MS at dual AJS ESI through analysis to calibrate the accurate mass of TOF MS online. The reference m/z were 121.050873 and 933.009798 in positive ion mode, while the reference m/z were 112.985587 and 1033.988109 in negative ion mode.

The MS acquisition batch was the same as sample preparation batch, while analyzed in positive ion mode first and negative ion mode afterwards. All samples were analyzed in both positive ion and negative ion mode separately after sample preparation in five days. One QC sample was injected every ten real samples at least and each prepared pooled QC sample was injected twice.

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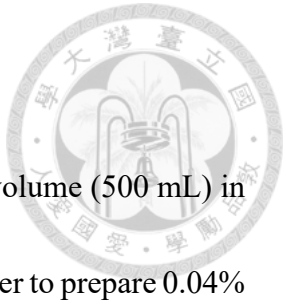

2.5 Quality assurance

The aqueous mobile phase was prepared freshly with the same volume (500 mL) in volumetric flask, while 200 μL of acetic acid was added to Milli-Q water to prepare 0.04% acetic acid solution (pH= 3.40), and 500 μL of commercial 5 M ammonium acetate solution (stocked at 4℃) was added to prepare 5 mM ammonium acetate solution (pH = 6.40). One liter of commercial methanol was directly used for organic mobile phase without transfer, minimizing contaminant. The mobile phase preparation process was executed consistently due to their ease of volumetric preparation or direct use of commercial product in large batches, mitigating concern for solvent preparation as a cause for batch effects.

As standard practice, TOF MS was tuned to achieve high resolution and maximum sensitivity at low mass (m/z 50-750) prior to conducting each batch of assay or after polarity switching. The electrospray spray chamber was cleaned by Kimwipes (Kimtech Science, Roswell, GA) and a mixture of isopropanol and water (50%, V/V) after analysis of each one or two batches.

Deactivated (silanized) glass vials and inserts (Agilent) were used to prevent the analytes from adsorbing on the glass surface. Polypropylene 96-well collection plates were rinsed by acetone and methanol twice before use. Glassware was washed using

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Milli-Q water twice and was rinsed by acetone and methanol twice sequentially after use, then was covered with alumina foli and placed in a chemical fume hood for drying.

2.6 Data analysis and compound identification

The peaks of six isotope-labeled standard were extracted within 35 ppm, using software Profinder 8.0 with 'Batch Target Features Extraction' function. The mass accuracy, peak area and retention time of six isotope-labeled standard across all data were recorded and used to check 12 batches in positive and negative ESI mode (3 isotopic standards each).

Molecular features were identified using the Molecular Feature Extraction (MFE) tool in MassHunter Workstation Software Qualitative Analysis (Agilent Software, v.B.07.00). The MFE method used in the analysis was achieved based on user-specified criteria (Table 6a) (p.21). These criteria are similar to those used in previously published studies [60-61]. This MFE deconvolution step removes the chemical background that could be attributed to instrument "noise", and finds the true ion signals (retention time, m/z and ion intensities). It is noteworthy that single molecular feature (with a discrete mass and retention time) was defined to include all peaks (m/z) that were detected as belonging to the same analyte, including the peaks representing isotopes, and adducts.

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Table 6: Criteria used to identify molecular features and compounds.

(a) Molecular feature extraction criteria

Peak Filters	**Ion Species**	**Charge State**	**Compound Filters**	**Quality Filter**
height ≥ 100 counts	Positive ions: $+H^+$, $+NH_4^+$	Isotope peak spacing tolerance: 0.0025 plus 7.0 ppm	Absolute peak height ≥ 1000 counts	Compound quality score ≥ 70
	Negative ions: $-H^+$, $+CH_3COO^-$	Charge states limit: 2		

(b) Find by formula extraction criteria used for tentative identificaiton.

Formula matching	**Ion Species**	**Charge State**	**Compound Filters**	**Quality Filter**	**Fragment confirmation**
Maximum matches per formula: 3	Positive ions: $+H^+$, $+NH_4^+$	Isotope peak spacing tolerance: 0.0025 m/z plus 7.0 ppm	Absolute peak height ≥ 1000 counts	Compound quality score ≥ 70	RT difference +/- 0.1 min S/N ratio≧ 3.0
Mass tolerance: 10 ppm	Negative ions: $-H^+$, $+CH_3COO^-$	Charge states limit: 2			Coelution score: > 90 Minimum number of qualified fragments: 1

The compound database and the high-resolution MS/MS spectrum library was established in MassHunter Personal Compound Database Library (PCDL) version B.07 (Agilent). We used MassHunter Qualitative Analysis B.07 (Agilent) “Find by Formula” (FBF) to identify suspect compounds in samples and this function could compare the sample data with libraries data in PCDL. The criteria for tentative identification were a compound precursor ion co-eluted with at least one product ion, mass accuracy within ±

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10 ppm, at least one isotope or adduct founded, and the others are shown in Table 6b. Five databases (one custom-established and the other four from manufacturer) were used for suspect screening in sample data, the number of compound and MS/MS was listed in Table 7. It is notable that only compounds with accurate MS/MS spectra were used for tentative identification and the number was about 3500.

Table 7. The number of MS and MS/MS spectra in five databases used for compound identification.

Library name	The compound number with formula (accurate mass)	**The compound number of accurate MS/MS spectra**
Commercial Library		
Mycotoxins	455	302
Pesticides	1684	770
Water	1451	1083
Vetdrugs	2107	1428
Established Library		
Concerned Chemicals	480	233

2.7 Chemical prioritization

The tentatively identified chemicals suspected of being in the plasma samples were prioritized using ToxPi scoring system mainly according to Rager et al. [62] and Newton, S.R., et al. [43]. To prioritize suspect concerned chemicals, identified compounds was linked with exposure prediction and *in vitro* bioassay data. The equation as shown below calculates for each compound as a normalized weighted combination of the averaged

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abundance (A), detection frequency (N), exposure (E), and bioactivity (B) data if the latter two available from US EPA 's ExpoCast and Tox21 project.

$$\text{ToxiPi Score}_i = w_A \frac{A_i - A_{min}}{A_{max} - A_{min}} + w_N \frac{N_i - N_{min}}{N_{max} - N_{min}} \left(+ w_E \frac{E_i - E_{min}}{E_{max} - E_{min}} + w_B \frac{B_i - B_{min}}{B_{max} - B_{min}}\right)$$

Here, abundance and exposure data were weighted 1 ($W_A = W_E = 1$) while detection frequency and bioactivity were given twice as much weight ($W_N = W_B = 2$), considering uncertainty in the relationship between observed peak abundance and true sample concentration, and uncertainty in difference of estimated exposure data between US population and Taiwanese. Values for average abundance were log-transformed before applying to equation due to the extreme right-skewed nature of their distribution to provide better balance across the distributions of A, N, E and B. Visualizations and scores were generated using ToxPi Software (v 1.3, from https://toxpi.org/). Compounds with available exposure and bioactivity data were labeled as "Group A", whereas compounds missing one or both of these data were labeled as Group B". All final data sets used in the ToxPi algorithm showed positively skewed distributions, thus allowing chemicals with large values to be highlighted, as previously recommended [63-64].

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2.7.1 Exposure information for ToxPi scoring

Exposure categories were calculated from ExpoCast daily exposure estimates described by Rager et al [62]. Briefly, High-throughput models had been developed within EPA's ExpoCast program for predicting human exposure across thousands of analytes [65-66]. Wambaugh et al. [65] first used exposure descriptors to predict exposures assumed from the U.S. National Health and Nutrition Examination Survey (NHANES) biomarker data, and developed a model based on this work to estimate human exposure to approximately 8000 chemicals. For each chemical a 95% credible interval was estimated for the median exposure rate (mg/kg/day) for the total U.S. population. These chemical-specific exposure rates were grouped into discrete categories, where:

Category 1: $< 1 \times 10^{-8}$ mg/kg/day;

Category 2: $\geq 1 \times 10^{-8}$ mg/kg/day and $< 1 \times 10^{-7}$ mg/kg/day;

Category 3: $\geq 1 \times 10^{-7}$ mg/kg/day and $< 1 \times 10^{-6}$ mg/kg/day;

Category 4: $\geq 1 \times 10^{-6}$ mg/kg/day and $< 1 \times 10^{-5}$ mg/kg/day;

Category 5: $\geq 1 \times 10^{-5}$ mg/kg/day and $< 1 \times 10^{-4}$ mg/kg/day;

Category 6: $\geq 1 \times 10^{-4}$ mg/kg/day and $< 1 \times 10^{-3}$ mg/kg/day; and

Category 7: $\geq 1 \times 10^{-3}$ mg/kg/day and $< 1 \times 10^{-2}$ mg/kg/day.

Exposure category values for tentatively identified chemicals were used to generate ToxPi scores (with Ei ranging from 1 to 7), according to the equation above.

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2.7.2 Bioactivity information for ToxPi scoring

In short, bioactivity data were downloaded from the EPA's online ToxCast data repository [67]. For this analysis, Tox21 results were used from assays testing the activity of five transcription factors known to play important roles in disease pathogenesis, plus a set of cytotoxicity/viability assays to represent general cell-stress and toxicity. The selected assays of interest when evaluating chemical stressors in environmental media included the aryl hydrocarbon receptor (AhR), the androgen receptor (AR), estrogen receptor alpha (ERα, one of the two forms of ER), nuclear factor of kappa light polypeptide gene enhancer in B cells 1 (NFκB1), and the peroxisome proliferator-activated receptor gamma (PPARγ). Pathways regulated by AhR, AR, ER, NFκB, and PPARγ are known to be changed upon exposure to environmental contaminants [68]. These assays which showed positive or negative (1 or 0) were used here and represent the overall activity in response to each chemical, with a value of 1 representing an “active” chemical, and a value of 0 representing an “inactive” chemical. It is noteworthy that the number of assay technologies was not equal across all five proteins, with AR and ERα having greater coverage (AhR = 1 assay, AR = 4 assays, ERα = 4 assays, NFκB1 = 2 assays, PPARγ = 2 assays, and cytotoxicity/viability = 3 assays) across the full suite of 16 assays. The assay data were averaged for each chemical, resulting in a percent activity estimate. These final

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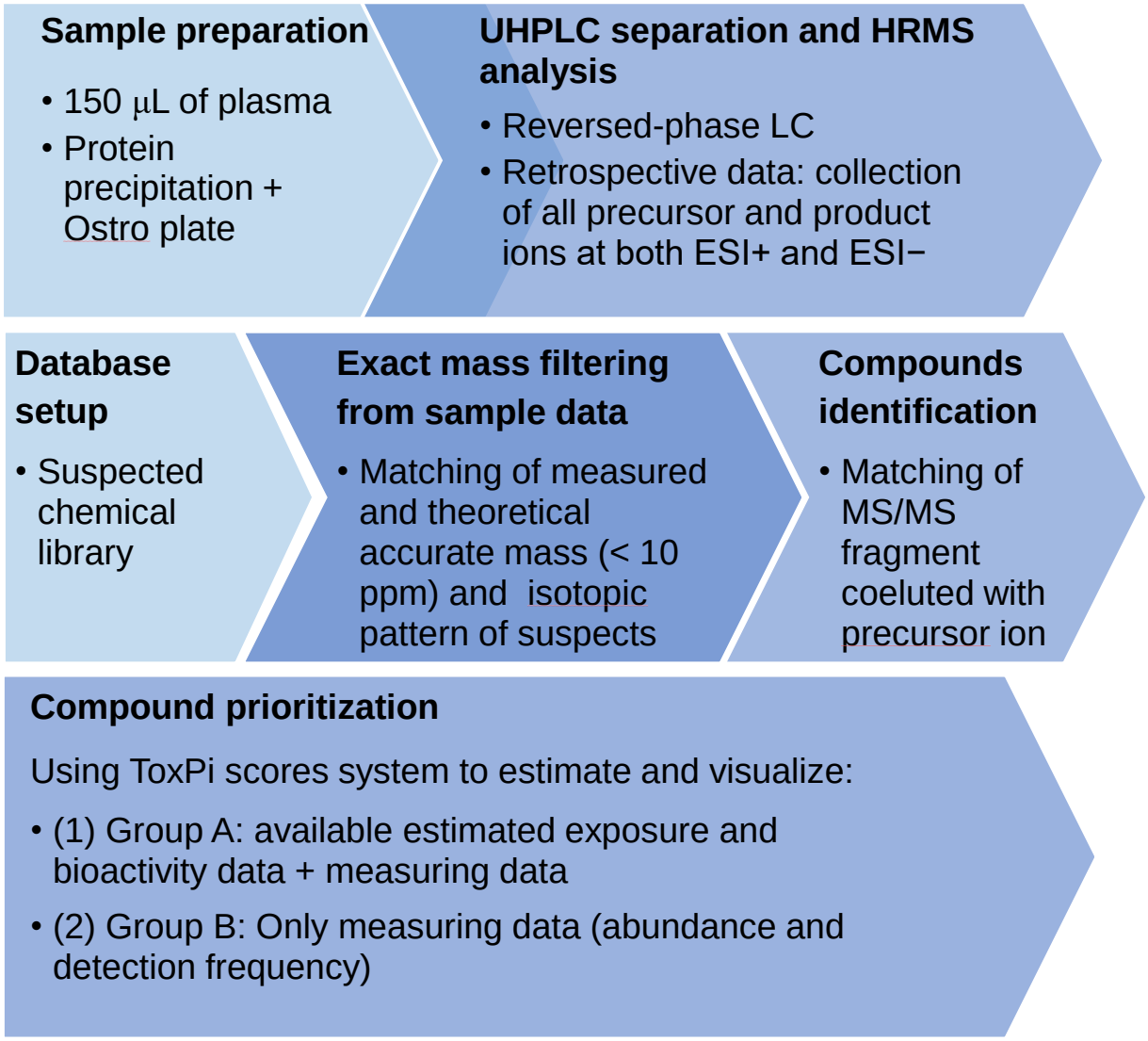
bioactivity values were used for ToxPi scoring, with possible values ranging from 0% (no observed bioactivity) to 100% (all assay tests indicated activity).

Figure 3. The workflow of concerned chemical identification in human plasma.



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Chapter 3. Results and Discussion

3.1 Sample preparation method

The target analytes of our study were comprehensive xenobiotics in human plasma, most importantly environmental pollutants. Less selective extraction or sample clean-up procedure was preferred but considering to removing some interferences in sample. The Ostro 96-well plate was used as sample preparation method in this study. The Ostro plate, a pass-through sample preparation technique, is designed for handling blood samples such as plasma or serum, to remove protein and phospholipids in plasma. Phospholipids (PLs) are a primary component of cell membranes and found in different levels in many biological fluids. Plasma and serum samples are the most effected by PL interference in analysis, owing to the possibility of approximately 17,000 different types of lipids and fatty acids being present [44]. PLs are problematic when they are not the analytes of interest due to highly interfering with analysis, especially on reverse-phase chromatographic methods coupled with mass spectrometric detection [69].

The Ostro 96-well plates design and the procedure without centrifugation significantly improved the throughput. It was widely used in analysis of pharmacokinetics, metabolomics [70-71], and emerging contaminants [72-74], decreasing the matrix effect and interference of phospholipids in a fast and convenient way [69, 75]. The sample preparation

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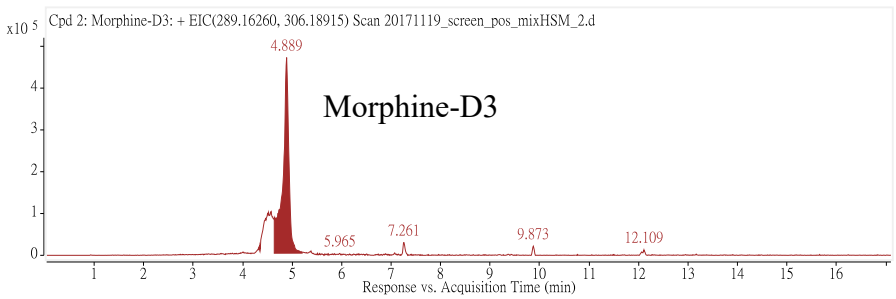
procedures were mainly from the manufacturer instruction and a validated method developed by our team to analyze 20 emerging contaminants in serum samples [76]. Only the reconstitution solvent was modified. Because we found that some of hydrophilic compounds are not retained well under reversed-phase column if the constitution solvent was methanol. For example, there was a significant front shoulder on the peak of morphine-D_3 reconstituted in methanol, one of the isotope standards added in sample used as quality control and surveillance of analysis. This phenomenon, which might be appliable to other hydrophilic and early-eluent compounds on reversed-phase column, might lead to incorrect or missing automated integration of these peaks. Therefore, to balance the solvent effect on retention of early-eluent and the solubility of some known hydrophobic environment contaminants, like perfluoroalkyl substances (PFASs), the reconstitution procedure was that we first added 50 μL methanol to nearly-dry extract, vortexed, and then added 50 μL of water in, following by another 30-sec vortex. Figure 5 shows that the peak of morphine-D_3 is retained more consistently and performs better peak shape, while reconstituted in 50% methanol/water (v/v, %).

(a)



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(b)

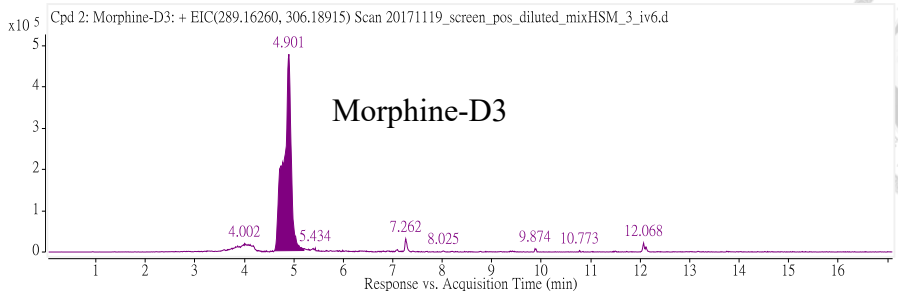

Figure 5. The peak of morphine-d3 in prepared pooled human plasma reconstituted (a) in methanol and (b) in 50% methanol/water (v/v, %).

3.2 Column selection

Reversed-phase (RP) LC columns are in wide use for the analysis of non-polar and medium-polar xenobiotics. The reversed-phase chromatography was chosen for the analysis because many of the environmental pollutants are more hydrophobic, which demonstrate more persistent and bio-accumulative property in organisms and cause more concerns. We compared the analytical efficiency of different reversed-phase columns with different coating materials or length. A general LC gradient from aqueous to organic phase was used. In positive ESI mode, we analyzed prepared pooled human plasma samples (n=3) in five different columns under 5 mM ammonium acetate solution (aqueous phase) and methanol (organic phase), including ACE Excel 2 C18-PFP (50 x 2.1mm, 2 μm), Luna omega polar C18 (50 x 2.1mm, 1.6 μm), Luna omega polar C18 (100 x 2.1mm, 1.6 μm), HSS T3 (100 x 2.1 mm, 1.8 μm), and Chromolith RD-18e (100 x 2.1 mm). In negative ESI mode, four different columns with 0.04% acetic acid solution (aqueous

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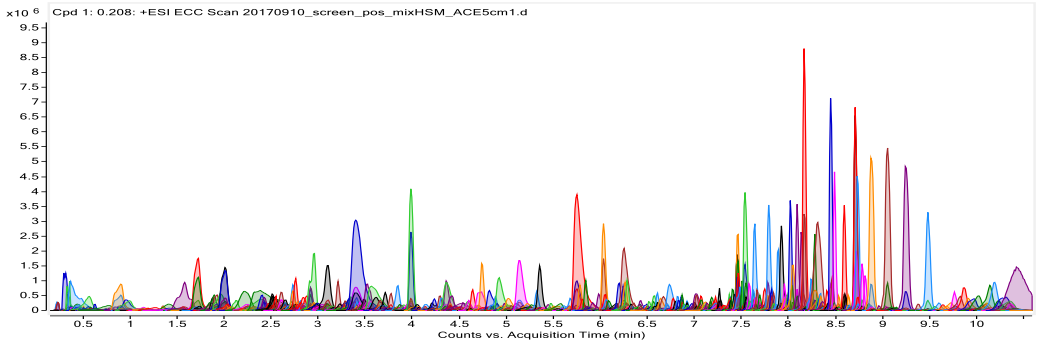
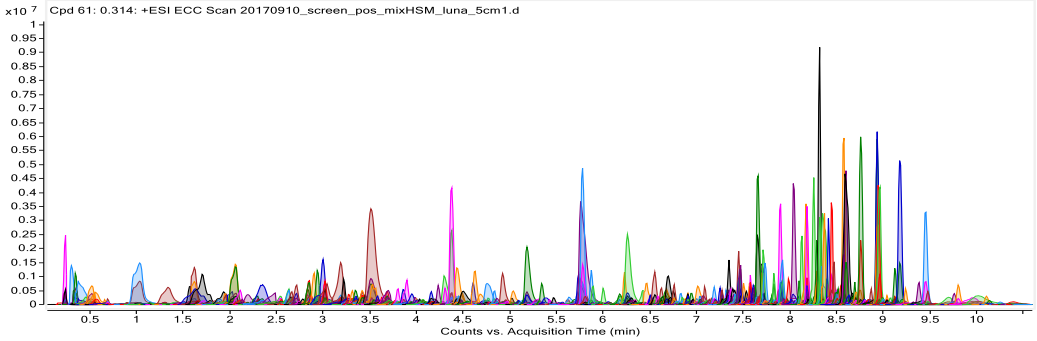
phase) and methanol (organic phase) were evaluated, including CORTECS C18 (50 x 2.1 mm, 1.6 μm), ZORBAX Eclipse Plus C18 (50 x 2.1 mm, 1.8 μm), Luna Omega Polar C18 (50 x 2.1 mm, 1.6 μm) and Luna Omega Polar C18 (100 x 2.1 mm, 1.6 μm). The number of molecular features (MFs) of pooled human plasma sample was used to evaluate the efficiency of different columns in positive and negative ion mode relatively, extracted by Agilent MassHunter B7.0 software: Molecular Feature Extraction. The overlaid peaks of pooled human plasma MFs analyzed by different columns are showed in Figure 4, with the number of MFs from 4936 to 6715 in positive ion mode; and Figure 5, with the number of MFs from 4116 to 5612 in negative ion mode.

(a)



(b)



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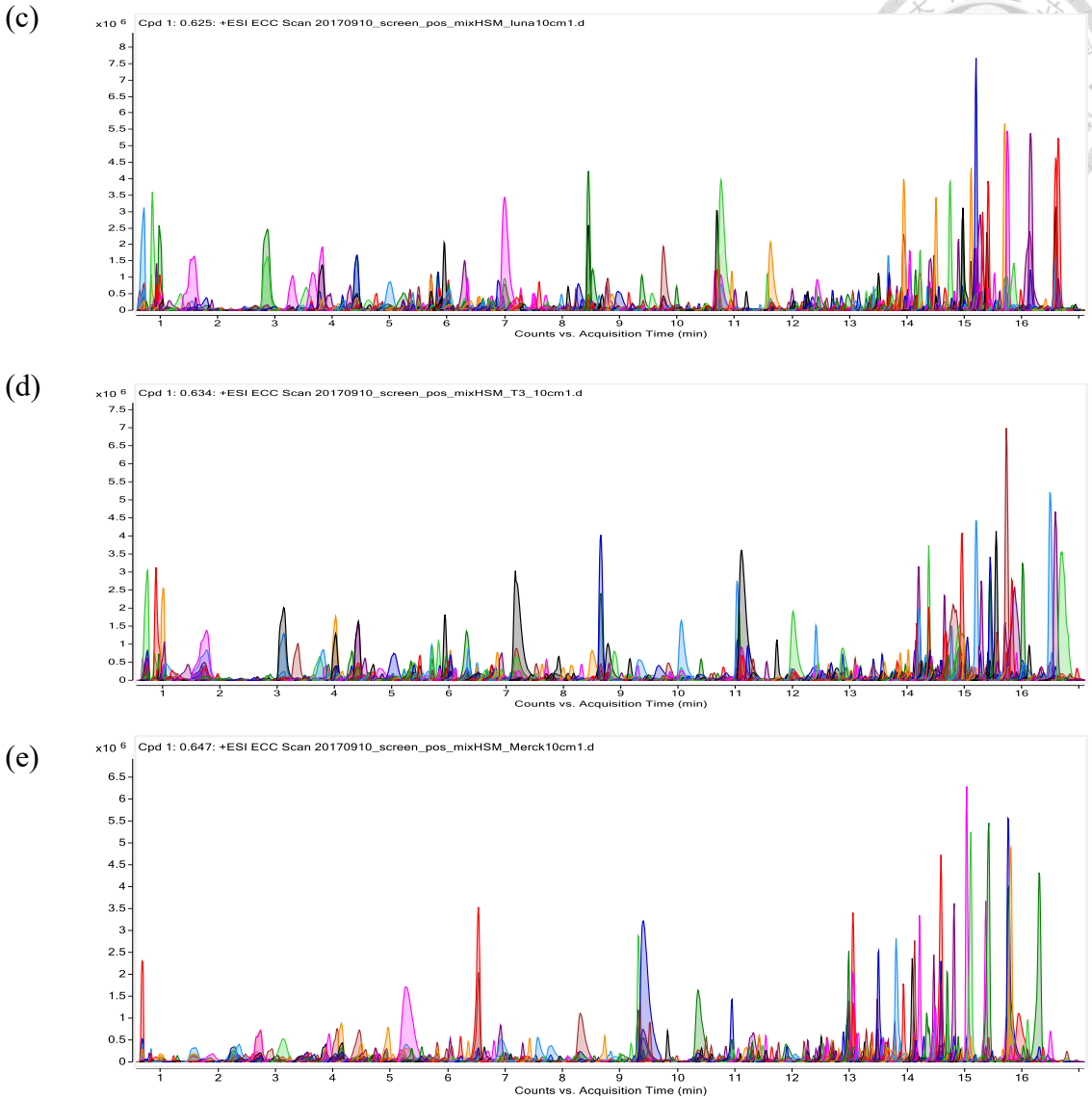

Figure 4. The overlaid of pooled human plasma molecular features (MFs) analyzed with five different LC columns and QTOF ESI$^+$. The column and the number of MFs is shown as (a) ACE Excel 2 C18-PFP (50 x 2.1mm, 2 µm), total 6110 molecular features; (b) Luna Omega Polar C18 (50 x 2.1 mm, 1.6 µm), total 6429 molecular features; (c) Luna Omega Polar C18 (100 x 2.1 mm, 1.6 µm), total 6715 molecular features; (d) HSS T3 (100 x 2.1 mm, 1.8 µm), total 5486 molecular features; (e) Chromolith RD-18e (100 x 2.1 mm), total 4936 molecular features.

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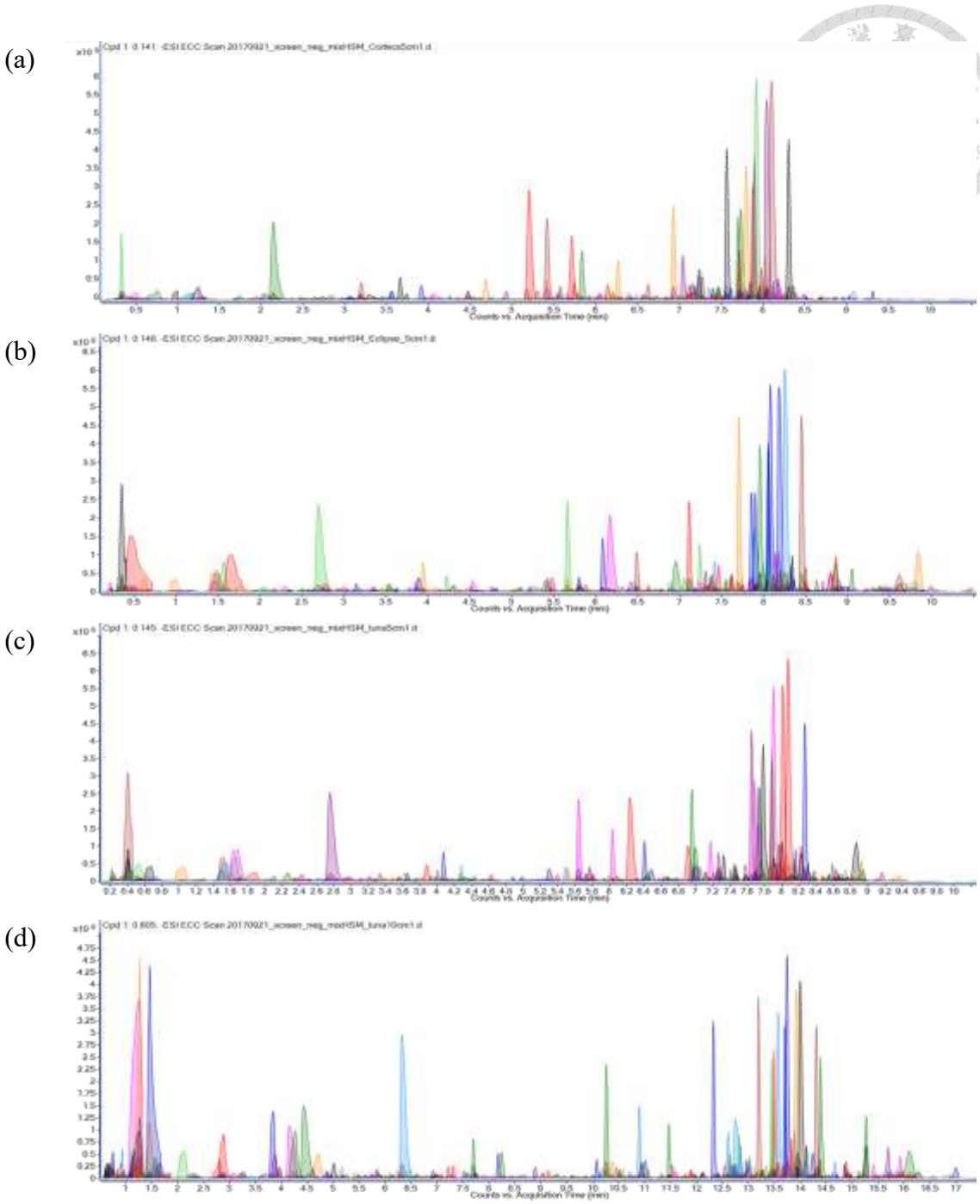

Figure 5. The overlaid of pooled human plasma molecular features (MFs) analyzed with four different LC columns and QTOF ESI⁻. The column and the number of MFs is shown as (a) CORTECS C18 (50 x 2.1 mm, 1.6 µm), total 4116 molecular features; (b) ZORBAX Eclipse Plus C18 (50 x 2.1 mm, 1.8 µm), total 4917 molecular features (c) Luna Omega Polar C18 (50 x 2.1 mm, 1.6 µm), total 5218 molecular features; (d) Luna Omega Polar C18 (100 x 2.1 mm, 1.6 µm), total 5612 molecular features.

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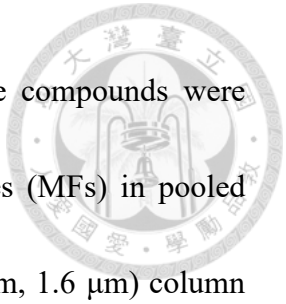

Columns with more molecular features represented that more compounds were better retained on. We found that the number of molecular features (MFs) in pooled human plasma analyzed by the Luna omega polar C18 (100 x 2.1mm, 1.6 μm) column was the highest in both positive ion mode (6715 MFs) and negative ion mode (5612 MFs).

We also accessed the peak width of pooled human plasma MFs in different columns and fitted with the TOF acquisition method. It would be better to acquire a minimum of six to eight data points across an LC peak to define its shape and to enable reproducible quantitation or semi-quantitation based on the area under the peak. The cycle time of TOF-MS acquisition was 0.6 sec (0.01 min). The number and percentage of MFs with peaks more than 8 data points (peak width greater than 0.08 min) were 4397 (72.0%), 4060 (63.2%), 5633 (83.9%), 4870 (88.8%), and 4128 (83.6%) in positive ion mode in five columns mentioned in Figure 4 (page 31) respectively; and were 2873 (69.8%), 3166 (64.4%), 3096 (59.3%) and 4599 (81.9%) in negative ion mode in four columns mentioned in Figure 5 (p. 32) respectively. The peak widths of MFs analyzed on different columns, sorting from narrow to broad, are shown in Figure 6 (p.34). We found that 10-cm long columns were better than 5-cm long columns at the number of data points acquired by TOF-MS method, while there were more than 8 data points at greater than 80% peaks acquired, and more than 6 data points at greater than 95% of peaks in 10-cm long columns.

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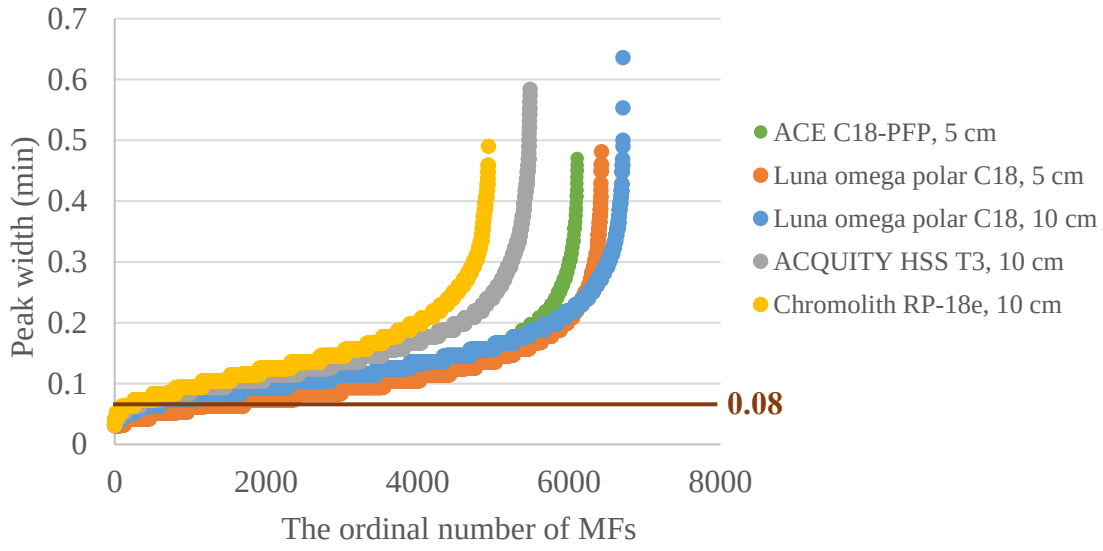
(a)



(b)

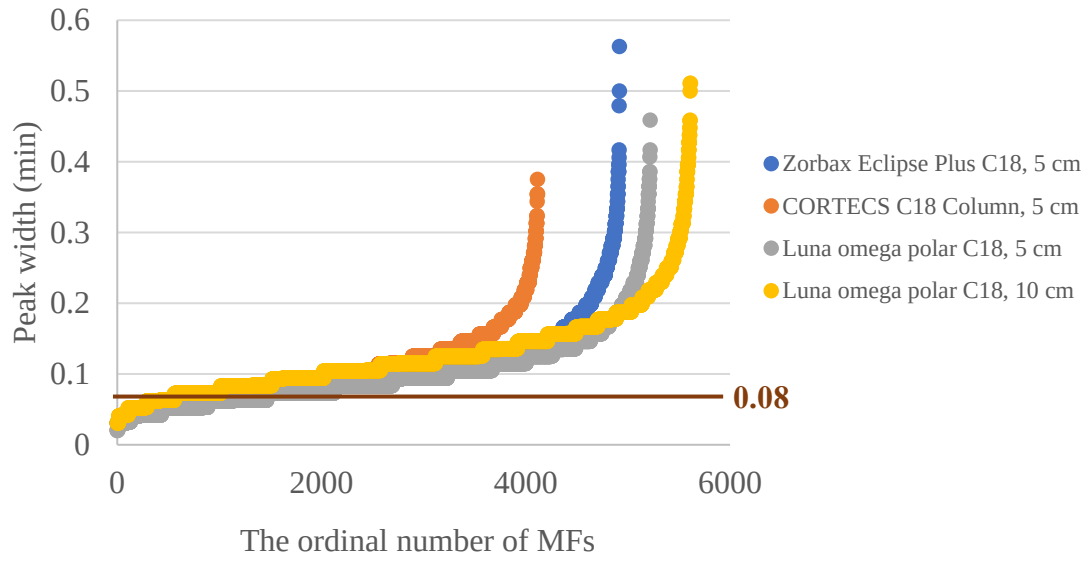


Figure 6. The peak widths sorting from small to large to the ordinal number of pooled human plasma molecular features (MFs) in different columns, analyzed in (a) positive ion mode and (b) negative ion mode.

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To sum up, we chose 10-cm Phenomenex Luna omega polar C18 column (100 x 2.1mm, 1.6 μm) to analyze samples in both positive and negative ESI mode with better performance on separation of compounds and data quality in our study.

3.3 UHPLC-QTOF method

An LC gradient from aqueous phase to organic phase (flow rate 0.3 mL/min) was used in the untargeted reversed-phase chromatography analysis, and the runtime for 10-cm long column was 19.6 min, including 2.5 min equilibrium (the column back pressure around 6000-6500 psi). We directly used one liter of commercially packed methanol as organic mobile phase without transfer or preparation in both positive and negative ion mode, designed to minimizing contamination. The 5 mM ammonium acetate solution (pH 6.4) was chosen as aqueous mobile phase in positive ion mode because theoretically fewer compounds in nearly neutral pH condition are protonated than in acidic condition and could be better retained on reversed-phase column, but later compounds might be easy to be positively charged under positive electrospray ionization (ESI+) condition when high voltage was applied, and then detected by TOF-MS. The 0.04% acetic acid solution (pH 3.4) was chosen in negative ion mode due to the similar reasons.

To achieve the purpose of suspect screening and collect more information in samples, the acquisition method of TOF-MS was all ion MS/MS (AIM) / all ion fragmentation

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(AIF), collecting all information of the precursor ions and product ions without mass selection of quadrupole. The dwell time of each spectrum was set as 0.2 sec and the cycle time was 0.6 sec, considering the balance between MS sensitivity and reliable peak shape defined with enough data points.

Three different isotope chemicals in positive and negative ion mode relatively were added to samples at the start of sample preparation to monitor the reproducibility within batch and between batches. These six isotope chemicals are barely existed in nature. The peaks of these isotope chemicals distributed in front, middle and back of retention time in both ESI positive and negative mode respectively, as shown in Figure 7.

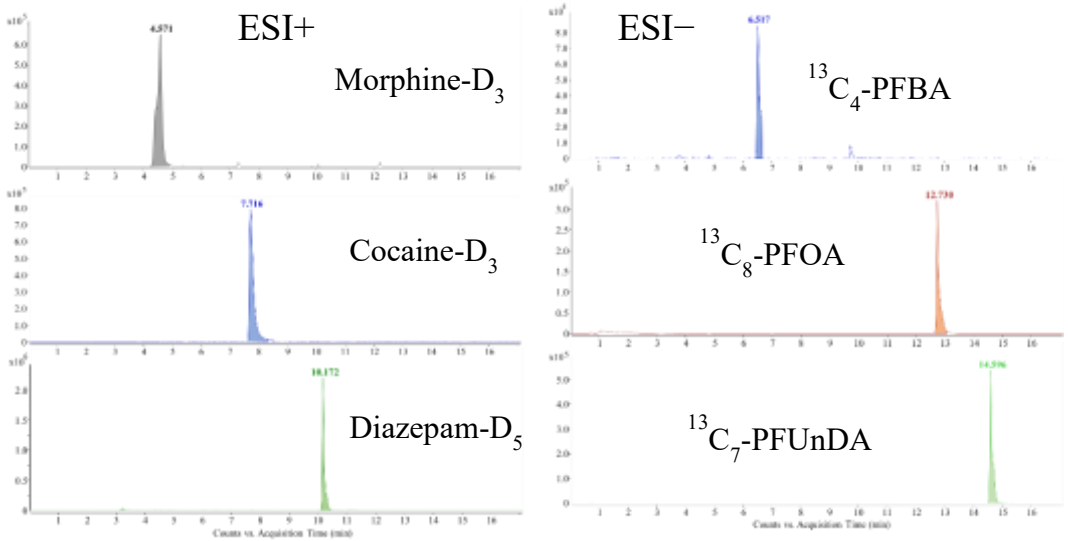

Figure 7. The peaks of isotope chemicals spiked in pooled human plasma with sample preparation and instrumental analysis.

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3.4 Self-established concerned chemical library

This study also set up the concerned chemical database that are feasible to be analyzed with ultra-high performance liquid chromatography/high-resolution tandem mass spectrometer (UHPLC-HRMS) from the following lists: (1) Restriction and authorization list of substances by European Chemicals Agency (ECHA) [77-79]; (2) Endocrine disruptors by the US EPA [80], European Commission [81], and Japan Ministry of the Environment [82]; (3) Banned or restricted pesticides based on the database of Taiwan Council of Agriculture [83-84]; (4) Toxic chemical substances by Taiwan EPA [85]. Total 480 parent compounds in the list included 233 MS^2 spectra, while most MS^2 spectra were from the library of MS manufacturer and some were set up from chemical standards in our lab. The established concerned chemicals are listed in Appendix 1 (p.62).

3.5 Quality controls within and between batches

The sample preparation and data acquisition had lasted two months. The samples were split into twelve batches, and each sample batch was analyzed in positive and negative ion mode separately. Quality controls are important, but typical quality assurance and quality control (QA/QC) measures of accuracy and precision for quantitative analytical methods are not necessarily applicable to non-targeted and suspect screening studies.

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We added six isotope standards to samples as described previously to evaluate the mass accuracy and the reproducibility of retention time and peak area within batch and between batches. The peaks of isotope standard in spiked samples were extracted by MassHunter Profinder B.08 (Agilent Technologies) using “Targeted Feature Extraction”. These results are summarized in Table 8 (p.39). Most of the mass accuracy of five spiked isotope standards were less than 5 ppm through all analysis (n = 572) in both positive and negative ion mode, while mass accuracy was a little higher than 5 ppm in only four sample data. But we found that most of the detected mass accuracy of $^{13}C_4$-PFBA, one spiked isotope standard in negative mode, were greater than 10 ppm owing to a close-accurate-mass contaminant in mobile phase. The retention time (RT) relative standard deviation (RSD) in all samples (n = 572) was less than 1.3% and the RT range difference was smaller than 0.22 min for reference isotope standards in the positive ion mode, while the retention time RSD was up to 3.74% and RT range difference was up to 0.98 min for reference isotope standards in the negative ion mode. The %RSD of isotope standard extracted ion chromatogram (EIC) peak areas within 12 batches (n = 43 or 26) were from 5.9% to 18.9%, while the %RSD of those within all spiked samples (n = 572) were 22.0%-28.4% in the positive ion mode and 39.7%-43.1% in the negative ion mode.

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Table 8. The data of spiked isotope standards in all samples.

	ESI+ (n = 572) [a]				ESI− (n = 572) [a]	
	Morphine-D3	Cocaine-D3	Diazepam-D5	$^{13}C_4$-PFBA	$^{13}C_8$-PFOA	$^{13}C_7$-PFUnDA
Formula	$C_{17}H_{16}D_3NO_3$	$C_{17}H_{18}D_3NO_4$	$C_{16}H_8D_5ClN_2O$	$[^{13}C]_4HF_7O_2$	$[^{13}C]_8HF_{15}O_2$	$C_4[^{13}C]_7HF_{21}O_2$
Accurate mass	288.1553	306.1659	289.1030	217.9999	422.0005	570.9876
Median mass accuracy [range] (ppm)	2.08 [-0.69 − 5.21] [b]	0.98 [-2.61 − 5.23] [b]	0.00 [-5.88 − 4.15] [c]	16.97 [4.13 − 39.45]	0.24 [-0.71 − 1.90]	-0.18 [-2.98 − 0.88]
Median RT (min) [%RSD]	4.58 [1.30%]	7.71 [1.08%]	10.19 [0.40%]	6.44 [3.38%]	12.71 [3.74%]	14.60 [3.33%]
Precision of peak area (n = 572) [a]	22.0%	22.6%	28.4%	43.1%	39.7%	42.4%
Median intra-day precision of peak area [range] [d]	10.7% [6.2% − 13.6%]	11.3% [7.5% − 17.1%]	13.3% [12.2% − 16.8%]	10.0% [5.9% − 13.6%]	10.5% [6.3% − 16.6%]	14.1% [6.6% − 18.9%]

a: Total 572 samples through 12 batches including spiked real samples and spiked pooled QC samples.

b: Mass accuracy of one sample was greater than 5 ppm.

c: Mass accuracy of two samples were less than -5 ppm.

d: Intra-day precision within each batch (n = 43 or 26), total 12 batches.

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We observed that the negative mode analysis generally produced higher measurement variations than those in the positive mode analysis at both retention time and EIC peak areas. The batch effect was also more obvious in negative mode analysis than positive mode analysis in long-term analysis, although we cleaned the MS ion source between batches after sample analysis. It was latter tested and suggested that the organic mobile phase using 0.04% acetic acid / methanol in replacement of pure methanol showed better ability to buffer and performed better reproducibility in negative mode through large-scale analysis.

Besides mass calibration of TOF-MS prior to analysis in each mode, instrumental drift in the mass accuracy of the TOF-MS was continuously corrected by infusion of two reference compounds during sample analysis as mentioned above, assuring the mass accuracy of TOF-MS instrument.

The high mass error of $^{13}C_4$-PFBA in negative ion mode was due to the contribution of interfering substance with close accurate mass. We analyzed the $^{13}C_4$-PFBA standard in solvent and in pooled human plasma in profile data format at TOF-MS with the same LC condition in this study. We observed that the interfering substance might be from mobile phase or LC system with a continuous appearance of its m/z. The extracted ion chromatography of 216.9926 (the accurate m/z of $^{13}C_4$-PFBA) with tolerance ± 35 ppm and the MS spectrums in front, middle and back of the $^{13}C_4$-PFBA peak are showed in

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Figure 8 (p.42). We could see that m/z of a close accurate mass interfering substance (about m/z 217.0028) was integrated with the m/z of $^{13}C_4$-PFBA (m/z 216.9926) and resulted in large positive mass error of $^{13}C_4$-PFBA through sample analysis. It reminded us that a clean system in an untargeted analysis is extremely important to data quality. Though we were dedicated to simplifying the procedure of the mobile phase prepared or directly using of commercial solvent stock, there were some inevitable contaminants from the system. This situation also showed that there could be some of the concerned chemicals in samples interfered by contaminants from systems are not able to be identified due to failing the criteria of matching. The isotope of five-carbon PFCs, perfluoro-*n*-[3,4,5-$^{13}C_3$] pentanoic acid ($^{13}C_3$-PFPeA), was suggested to replace the $^{13}C_4$-PFBA as an isotope-labelled surrogate standard for evaluating the reproducibility in the screening platform afterwards.

The overall results demonstrate an acceptable degree of analytical precision within most of the raw data across all assays in long-term study. These results were achieved despite the long duration of the studies and the consequential need to regularly supplement mobile phase buffer and solvent with freshly prepared or newly opened stock. We also observed from our results and suggested some modification at this analytical method.

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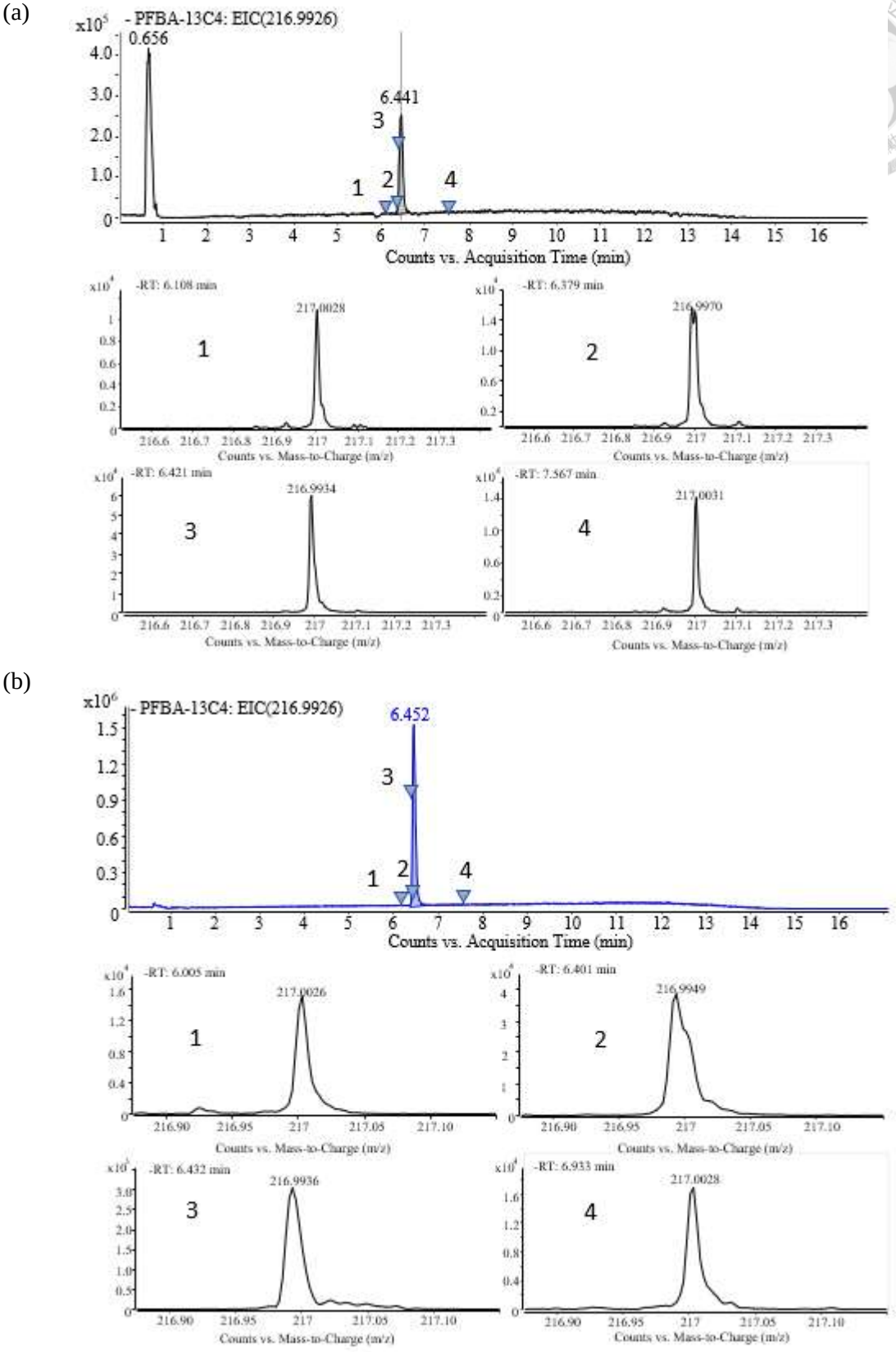

Figure 8. The peak and spectrum of $^{13}C_4$-PFBA in (a) plasma and (b) solvent, and a close accurate mass contaminant from LC system, acquired with profile data format.

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3.5 Compound identification in samples

The compound was tentatively identified in comparison with the MS/MS spectrum in five libraries. Here are some illustrations of compounds identified in pooled human plasma in Figure 9. At least one product ion coeluted well with the precursor ion, which overlaid peak trend matched with each other.

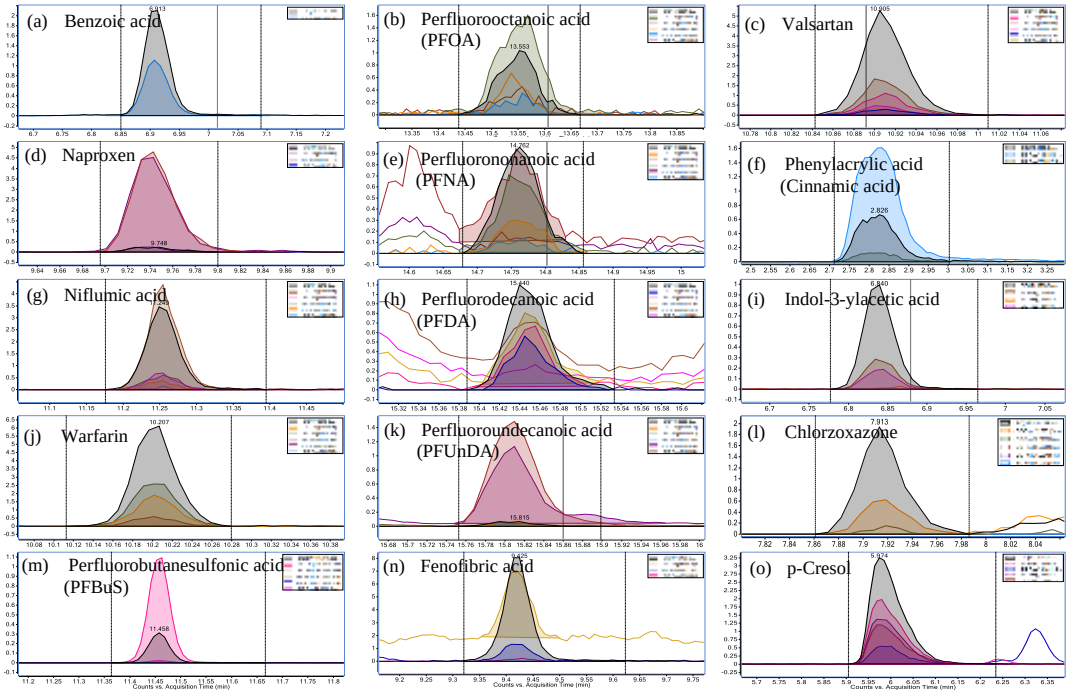

Figure 9. The figure illustrated compounds identified in the pooled human plasma which precursor ion coeluted with product ions.

The overall data processing of compound identification spent much time. There were 1192 sample data, 596 sample data in both ion mode, including prepared solvent blank, pooled human plasma, and real samples. Each sample data needed to be processed five times due to five different libraries. Merging all libraries into one didn't work because too

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many spectra to compare leading to serious lags and even errors when data processing. To process large amounts of sample datasets and compare with five different libraries separately, we applied automated batch processing to the large number of sample datasets using software DA preprocessor (Agilent).

There were 354 compounds met the criteria and tentatively identified in positive ion mode and 143 compounds identified in negative ion mode, found in at least one sample data, in comparison with total five libraries. There were 94 compounds repeatedly appeared in both ion mode. The number of unique compounds identified in real samples was 403. The overall sample datasets were exported to excel files including the information of sample name, compound name, integrated area, retention time, detected accurate mass, scores, and so on. From these identified compound data, we could see that detection frequency of most chemicals found in human plasma samples were really low. The detection frequency of about 100 compounds was one, and about 250 compounds were identified in lower than or equal to 5 samples (1%) in total 500 real samples.

3.6 Chemicals prioritizing

One purpose of this study was to find out emerging chemicals or concerned chemicals that people usually expose to. Detection frequency of chemicals higher than 10% in real samples ($n > 50$) were further investigated, while there were 48 compounds

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in positive ion mode, 35 compounds in negative ion mode, and 18 compounds repeatedly appeared in both ion mode. The datasets of which charge state compounds were more likely to be under ESI condition were left, determined by literature search. Sixty-five compounds left in the remaining chemical compound list.

The essential nutrient or endogenous compounds were excluded from this list, like tyrosine, alanine, serotonin, corticosterone, and chenodeoxycholic acid. It noteworthy that dibutyl phthalate (DBP) and diethyl phthalate (DEP), identified in solvent blank after sample preparation, were also excluded from the list due to difficulty to figure out the contribution of samples or backgrounds. The remaining 51 chemicals was prioritized using ToxPi score system.

Of these 51 chemicals, bioactivity data and exposure estimates were available for 13 chemicals, with bioactivity scores ranged from 0% to 22.7% and exposure categories ranged from 0 to 7. Chemicals were prioritized and scored in two separate groups, group A (n = 13) and group B (n = 39) according to the equation of ToxPi score calculations (p.23). Group A chemicals were evaluated using the full suite of exposure, bioactivity, and empirical measurement data (detection frequency and averaged abundance). Group B chemicals were evaluated using only empirical measures. The prioritized chemical results and visualized images of ToxPi scores are illustrated in Figure 10 (p.47) (Group A) and Figure 11 (p. 48) (Group B).

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Priority scoring of the group A chemicals (Figure 10) showed that the chemicals with the higher ToxPi scores were propylparaben, butylparaben, tri-(2-chloroisopropyl) phosphate (TCPP), cinnamic acid, isobutylparaben, 8-hydroxyquinoline, and tributylphosphate (TBP). Chemicals in group A can be roughly classified in to four groups: (1) Parabens: propylparaben, butylparaben, isobutylparaben, and methylparaben; (2) Plasticizers: tri-(2-chloroisopropyl) phosphate (TCPP), tributylphosphate (TBP), dinonyl phthalate (DNP), and di (2-ethylhexyl) adipate (DEHA); (3) Perfluorochemicals (PFCs): perfluorooctanoic acid (PFOA), perfluoro-octanesulfonic acid (PFOS), and perfluorodecanoic acid (PFDA); (4) Others: cinnamic acid and 8-hydroxyquinoline. Cinnamic acid was from oil of cinnamon, or from balsams such as storax, used in flavorings, synthetic indigo, and certain pharmaceuticals; 8-hydroxyquinoline is used as an antibacterial agent, an iron chelator, an antiseptic drug and an antifungal. It is an RNA synthesis inhibitor that interferes with transcription and have disinfectant properties.

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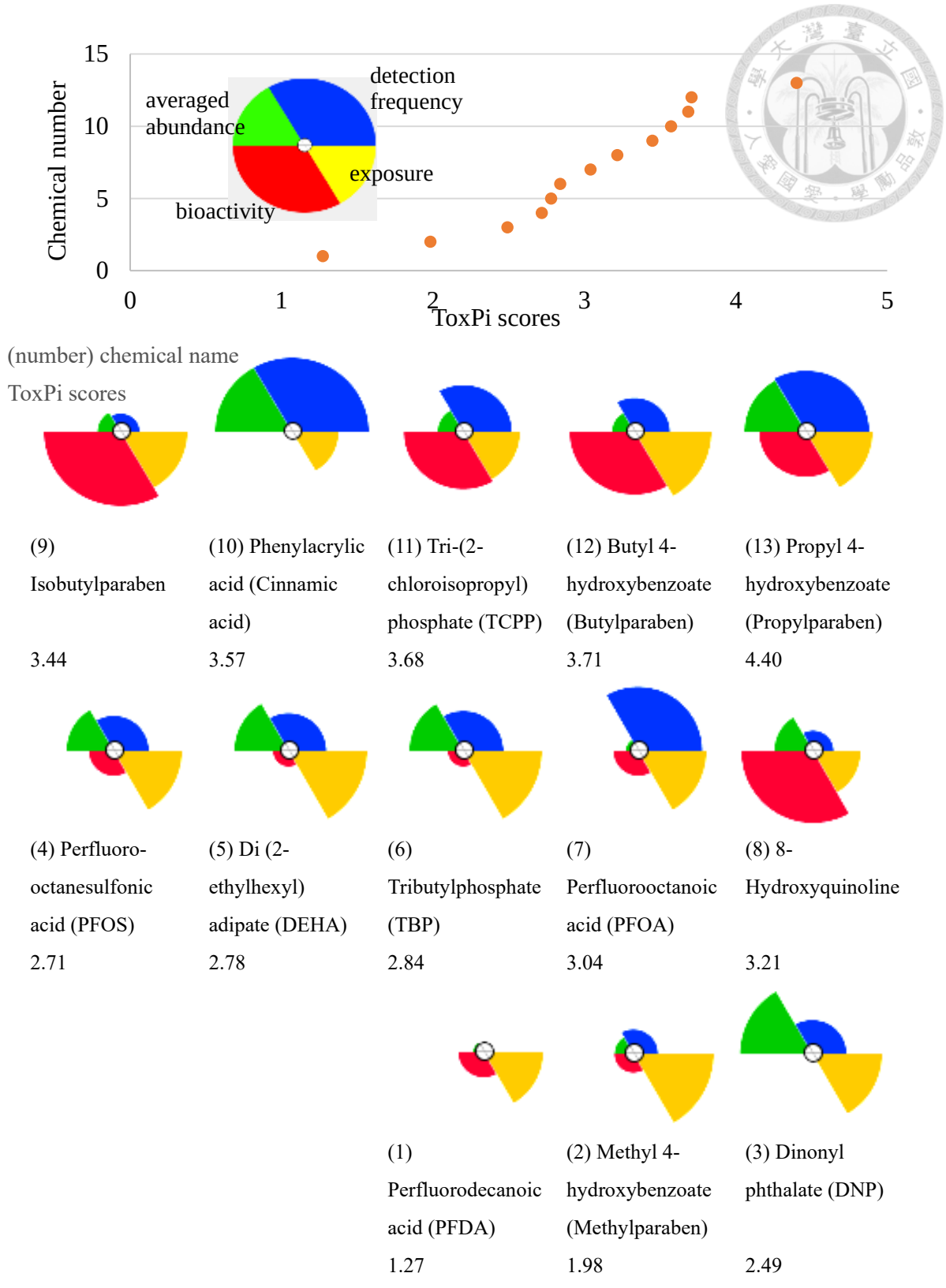

Figure 10. The prioritized chemicals identified in 500 plasma samples in Group A (with average abundance, detection frequency, exposure, and bioactivity data) and visualized images of ToxPi scores.

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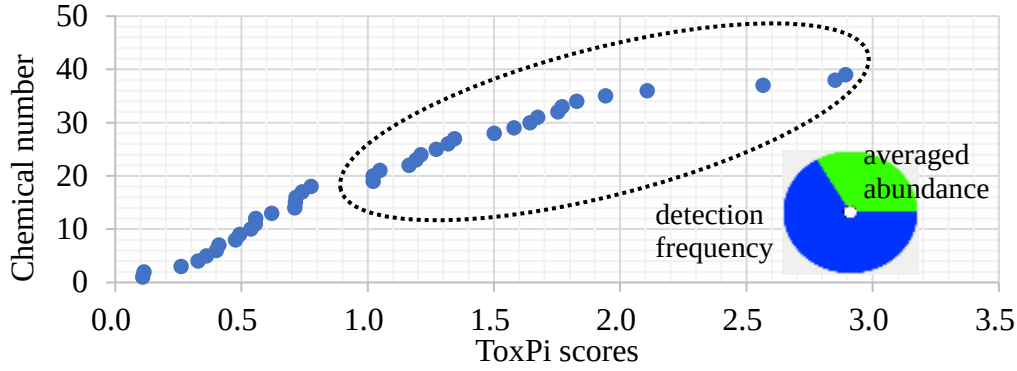

(35) 4-tert-Octylphenol 1.94 | (36) Indole-3-acetic acid 2.11 | (37) p-cresol 2.57 | (38) Metolcarb 2.85 | (39) Ethotoin 2.89

(30) TBEP 1.64 | (31) Ugurol 1.67 | (32) Theobromine 1.75 | (33) Caffeine 1.77 | (34) Pyrocatechol 1.82

(25) Cotinine 1.27 | (26) Gabapentin 1.32 | (27) DEHP 1.34 | (28) Carvone 1.50 | (29) Allopurinol 1.58

(20) Methylsalicylate 1.02 | (21) Triphenyl phosphate (TPPA) 1.02 | (22) Paraxanthine 1.16 | (23) Skatole 1.19 | (24) Benzoic acid 1.21

Figure 11. Top 20 prioritized chemicals identified in 500 plasma samples in Group B (with only average abundance and detection frequency) and visualized images of ToxPi scores.

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Figure 11 shows the top 20 compounds identified ToxPi scores in group B. We listed the possible characters and sources of these chemicals below, mainly from website HMDB and PubChem. Ethotoin is an anticonvulsant drug used in the treatment of epilepsy; Metolcarb is a kind of pesticide, an insecticide at killing members of the arachnid subclass Acari; P-cresol is produced by bacterial fermentation of protein in the human large intestine or constituent of tobacco smoke; Indole-3-acetic acid (IAA) is the most common naturally occurring plant hormone of the auxin class, biosynthetic pathway from tryptophan by plant; 4-tert-octylphenol (OP), a known environmental estrogen, an alkylphenol, is used to manufacture alkylphenol ethoxylates, which are anionic surfactants used in detergents, industrial cleaners, and emulsifiers; Pyrocatechol, first discovered in the plant extract catechin, is now synthetically produced as a commodity organic chemical, mainly as a precursor to pesticides, flavors, and fragrances, and also used in medicine as an expectorant; Caffeine and theobromine were mainly from coffee and chocolate, respectively; Ugurol, also tranexamic acid, is a medication used to treat or prevent excessive blood loss from major trauma, postpartum bleeding, surgery, tooth removal, nosebleeds, and heavy menstruation; Tris(2-butoxyethyl) phosphate (TBEP) are widely used as flame retardants and low temperature plasticizers in PVC and synthetic rubber, also in waxes, floor polishes and paper coatings; Allopurinol is a medication used to decrease high blood uric acid levels; Carvone is a member of a family of chemicals

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called terpenoids, found naturally in many essential oils; Bis(2-ethylhexyl) phthalate (DEHP) is the most common member of the class of phthalates, used as plasticizers; Gabapentin is an anticonvulsant medication used to treat partial seizures, neuropathic pain, hot flashes, and restless legs syndrome; Cotinine is the biomarker for exposure to tobacco smoke, predominant metabolite of nicotine; Benzoic acid is found a metabolic byproduct of phenylalanine or polyphenols from ingested fruits or beverages in gut bacteria. Appreciable amounts of benzoic acid have been found in most berries (around 0.05%). It is also a fungistatic compound, widely used as a food preservative; 3-Methylindole, or skatole, is foul smelling. It occurs naturally in feces, produced from tryptophan in the mammalian digestive tract; Paraxanthine is observed in nature as a metabolite of caffeine in animals; Triphenyl phosphate (TPPA) has been used widely as a flame retardant and plasticizer; Methyl salicylate produced by many species of plants, particularly wintergreens, and also produced synthetically, used as a fragrance, in foods and beverages, and in liniments.

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3.7 Limitation

There were some limitations on this study. About suspect screening approaches, two significant limitations of the are: (1) lower sensitivity of the HRMS instruments compared to instrumentation available for “target” quantification and, (2) limited number of compounds with known spectral features in the available databases. The prioritized chemical list was tentatively identified, which was needed to be further examined using chemical standards for confirmatory analysis. Still, this study provided the opportunity to portrait the exposure profile in human body.

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Chapter 4. Conclusion

In this study, we established a platform through non-target analysis of human plasma on both sample preparation and instrumental analysis using UHPLC-QTOF MS and set up the procedure of suspect screening to identify environmental pollutants in plasma.

We used this platform to screen 500 plasma samples of healthy adults in Taiwan. There were 403 compounds tentatively identified in this study. The ToxiPi software was used to visualize the priority of concerned chemicals. The prioritized chemicals included parabens, plasticizers, perfluorochemicals, and pesticides. These prioritized items could be further confirmed and utilized to exposure assessment. This information could offer to chemical regulations and environmental/food survey, reduce the future human exposure, and improve human health.

This study broke through the limits of the conventional target analysis approach and using a new screening tool to find the chemicals that Taiwan people are commonly exposed to with a “known unknown” pattern. This acquired data from HRMS also offers a unique opportunity for retrospective analysis of full-scan MS and the MS/MS data, which enables one to return to look for emerging chemicals and contaminants even years after the initial sample analysis. This feature shows a great advantage to human biomonitoring programs.

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Appendix

Appendix 1. Established library of concerned chemicals.

Compound Name	Formula	Mass	CAS	Spectrum
1,1,1,2-Tetrachloroethane	C2H2Cl4	165.891061	630-20-6	
1,1,1-Trichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane	C14H9Cl5	351.914689	789-02-6	
1,1,1-Trichloro-2,2-bis(4-hydroxyphenyl)ethane	C14H11Cl3O2	315.982463	2971-36-0	
1,1,1-Trichloroethane	C2H3Cl3	131.930033	71-55-6	
1,1,2,2-Tetrachloroethane	C2H2Cl4	165.891061	79-34-5	
1,1,2-Trichloroethane	C2H3Cl3	131.930033	79-00-5	
1,1-Dichloroethane	C2H4Cl2	97.969006	75-34-3	
1,1-Dichloroethylene	C2H2Cl2	95.953355	75-35-4	
1,2,3,7,8-Pentachlorodibenzodioxin	C12H3Cl5O2	353.857568	40321-76-4	
1,2,3,7,8-Pentachlorodibenzofuran	C12H3Cl5O	337.862653	57117-41-6	
1,2,3-Trichloropropane	C3H5Cl3	145.945683	96-18-4	
1,2,4-Trichlorobenzene	C6H3Cl3	179.930033	120-82-1	
1,2-Dibromo-3-chloropropane	C3H5Br2Cl	233.844654	1996/12/8	
1,2-Dichlorobenzene	C6H4Cl2	145.969006	95-50-1	
1,2-Dichloroethane	C2H4Cl2	97.969006	107-06-2	
1,2-Dichloropropane	C3H6Cl2	111.984656	78-87-5	
1,3-Dichlorobenzene	C6H4Cl2	145.969006	541-73-1	
1,3-Dichloropropene	C3H4Cl2	109.969006	542-75-6	
1,3-Dinitrobenzene	C6H4N2O4	168.017110	99-65-0	

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Compound Name	Formula	Mass	CAS	Spectrum
1,3-Propane sultone	C3H6O3S	122.003765	1120-71-4	
1,4-Dioxane	C4H8O2	88.052429	123-91-1	
1-Butanol	C4H10O	74.073165	71-36-3	
1-Chloro-2,2-bis(4'-chlorophenyl)ethylene	C14H9Cl3	281.976983	1022-22-6	
1-Hydroxychlordene	C10H6Cl6O	351.854981	2597/11/7	
1-Naphthylamine	C10H9N	143.073499	134-32-7	
2-(m-Chlorophenyl)-2-(p-chlorophenyl)-1,1-dichloroethane	C14H10Cl4	317.953661	4329/12/8	
2,2-(2-Chlorophenyl-4'-chlorophenyl)-1,1-dichloroethene	C14H8Cl4	315.938011	3424-82-6	
2,2',3,3',6,6'-Hexachlorobiphenyl	C12H4Cl6	357.844416	38411-22-2	
2,2',3,4,4',5',6-Heptabromodiphenyl ether	C12H3Br7O	715.446755	207122-16-5	
2,2',4,4',5,5'-Hexabromodiphenyl ether	C12H4Br6O	637.536242	68631-49-2	
2,2',4,4',5,5'-Hexachlorobiphenyl	C12H4Cl6	357.844416	35065-27-1	
2,2',4,4',5,6'-Hexabromodiphenyl ether	C12H4Br6O	637.536242	207122-15-4	
2,2',4,4'-Tetrachlorobiphenyl	C12H6Cl4	289.922361	2437-79-8	
2,2',4,5-Tetrachlorobiphenyl	C12H6Cl4	289.922361	70362-47-9	
2,2',5,5'-Tetrachlorobiphenyl	C12H6Cl4	289.922361	35693-99-3	
2,3,3',4,4',5-Hexachlorobiphenyl	C12H4Cl6	357.844416	38380-08-4	
2,3',4,4',5-Pentachlorobiphenyl	C12H5Cl5	323.883389	31508-00-6	
2',3',4',5'-Tetrachloro-3-biphenylol	C12H6Cl4O	305.917276	67651-37-0	
2,3,4,5-Tetrachloro-4'-biphenylol	C12H6Cl4O	305.917276	67651-34-7	
2,3,4,5-Tetrachlorobiphenyl	C12H6Cl4	289.922361	33284-53-6	
2,3,4,7,8-Pentachlorodibenzofuran	C12H3Cl5O	337.862653	57117-31-4	

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Compound Name	Formula	Mass	CAS	Spectrum
2,3,4-Trichlorobiphenyl	C12H7Cl3	255.961333	55702-46-0	
2,3,5,6-Tetrachloro-4,4'-biphenyldiol	C12H6Cl4O2	321.912190	100702-98-5	
2,3,7,8-Tetrachlorodibenzodioxin	C12H4Cl4O2	319.896540	1746-01-6	
2,3,7,8-Tetrachlorodibenzofuran	C12H4Cl4O	303.901626	51207-31-9	
2,4,4',6-Tetrachlorobiphenyl	C12H6Cl4	289.922361	32598-12-2	
2,4,5-T / 2,4,5-Trichlorophenoxyacetic acid	C8H5Cl3O3	253.930430	93-76-5	v
2,4,5-TCP / 2,4,5-Trichlorophenol	C6H3Cl3O	195.924948	95-95-4	
2,4,5-TP / Silvex (Fenoprop)	C9H7Cl3O3	267.946080	93-72-1	v
2,4,6-TCP / Trichlorophenol, 2,4,6-	C6H3Cl3O	195.924948	1988/6/2	
2,4,6-Trichloro-4'-biphenylol	C12H7Cl3O	271.956248	14962-28-8	
2,4-D / 2,4-Dichlorophenoxyacetic acid	C8H6Cl2O3	219.969400	94-75-7	v
2,4-DCP / 2,4-Dichlorophenol	C6H4Cl2O	161.963920	120-83-2	
2,4-Diaminotoluene	C7H10N2	122.084398	95-80-7	
2,4-Dichlorophenoxybutyric Acid	C10H10Cl2O3	248.000700	94-82-6	v
2,4-Dihydroxybenzophenone	C13H10O3	214.062994	131-56-6	
2,4-Dinitrophenol	C6H4N2O5	184.012020	51-28-5	v
2,4-DP / Dichloroprop	C9H8Cl2O3	233.985050	120-36-5	v
2-Chlorobiphenyl	C12H9Cl	188.039278	2051-60-7	
2-Ethoxyethanol	C4H10O2	90.068080	110-80-5	
2-Naphthylamine	C10H9N	143.073499	91-59-8	
2-Phenylphenol (Orthophenylphenol)	C12H10O	170.073160	90-43-7	v
2-tert-Butyl-4-methoxyphenol	C11H16O2	180.115030	25013-16-5	v

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Compound Name	Formula	Mass	CAS	Spectrum
3,3',5,5'-Tetrachloro-4,4'-biphenyldiol	C12H6Cl4O2	321.912190	13049-13-3	
3,3'-Dichlorobenzidine	C12H10Cl2N2	252.022104	91-94-1	
3,3'-Dimethoxybenzidine	C14H16N2O2	244.121178	119-90-4	
3,3'-Dimethylbenzidine	C14H16N2	212.131349	119-93-7	
3,4,3',4'-Tetrachlorobiphenyl	C12H6Cl4	289.922361	32598-13-3	
3,4,5,3',4',5'-Hexachlorobiphenyl	C12H4Cl6	357.844416	32774-16-6	
3,4-Dichloraniline	C6H5Cl2N	160.979900	95-76-1	
4,3',5'-Trichloro-4'-biphenol	C12H7Cl3O	271.956248	4400-06-0	
4,4'-Bis(dimethylamino)benzophenone (Michler's ketone)	C17H20N2O	268.157560	90-94-8	v
4,4'-Dihydroxybenzophenone	C13H10O3	214.062994	611-99-4	
4,4'-Dihydroxybiphenyl	C12H10O2	186.068080	92-88-6	
4,4'-Methylene-bis-(2-chloroaniline)	C13H12Cl2N2	266.037754	101-14-4	
4,4'-Methylenedianiline	C13H14N2	198.115698	101-77-9	
4-Benzylphenol	C13H12O	184.088815	101-53-1	
4-Biphenylamine	C12H11N	169.089149	92-67-1	
4-Chloro-2-methylaniline (Chlordimeform artifact)	C7H8ClN	141.034527	95-69-2	
4-Chloro-2-methylphenol	C7H7ClO	142.018543	1570-64-5	
4-Chlorobiphenyl	C12H9Cl	188.039278	2051-62-9	
4-Hydroxybiphenyl	C12H10O	170.073165	92-69-3	
4-Nitrobiphenyl	C12H9NO2	199.063329	92-93-3	
4-Nonylphenol	C15H24O	220.182715	25154-52-3	v
4-Octylphenol	C14H22O	206.167070	1806-26-4	v

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Compound Name	Formula	Mass	CAS	Spectrum
4-sec-Butylphenol	C10H14O	150.104465	99-71-8	
4-tert-Butylphenol	C10H14O	150.104465	98-54-4	
4-tert-Octylphenol	C14H22O	206.167065	140-66-9	
4-tert-Octylphenol (4-(1,1,3,3-Tetramethylbutyl)phenol)	C14H22O	206.167070	140-66-9	v
5,6-Cyclopenteno-1,2-benzanthracene	C21H16	268.125201	7099-43-6	
7,12-Dimethylbenz[a]anthracene	C20H16	256.125201	57-97-6	
Acephate	C4H10NO3PS	183.011900	30560-19-1	v
Acetochlor	C14H20ClNO2	269.118257	34256-82-1	v
Acetochlor ESA	C14H21NO5S	315.114040	187022-11-3	v
Acetochlor OXA (Acetochlor OA)	C14H19NO4	265.131410	194992-44-4	v
Acrylamide	C3H5NO	71.037114	1979/6/1	
Alachlor	C14H20ClNO2	269.118257	15972-60-8	v
Alachlor ESA	C14H21NO5S	315.114040	142363-53-9	v
Alachlor OXA (Alachlor OA)	C14H19NO4	265.131410	171262-17-2	v
Aldicarb	C7H14N2O2S	190.077600	116-06-3	v
Aldicarb sulfoxide (Aldicarb sulphoxide)	C7H14N2O3S	206.072510	1646-87-3	v
Aldicarb-sulfone (Aldoxycarb)	C7H14N2O4S	222.067428	1646-88-4	
Aldoxycarb (Aldicarb Sulfone)	C7H14N2O4S	222.067430	1646-88-4	v
Aldrin	C12H8Cl6	361.875717	309-00-2	
Allethrin	C19H26O3	302.188190	584-79-2	v
Amitrole (Aminotriazole)	C2H4N4	84.043596	61-82-5	
Aniline	C6H7N	93.057850	62-53-3	

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Compound Name	Formula	Mass	CAS	Spectrum
Anthracene	C14H10	178.078250	120-12-7	
Atrazine	C8H14ClN5	215.093770	1912-24-9	v
Atrazine-desethyl (Desethylatrazine)	C6H10ClN5	187.062470	6190-65-4	v
Atrazine-desethyl-desisopropyl	C3H4ClN5	145.015520	3397-62-4	
Atrazine-desisopropyl (Deisopropylatrazine)	C5H8ClN5	173.046820	1007-28-9	v
Azinphos-methyl (Guthion)	C10H12N3O3PS2	317.005770	86-50-0	v
BADGE	C21H24O4	340.167459	1675-54-3	v
Benfluralin	C13H16F3N3O4	335.109290	1861-40-1	v
Benfuracarb	C20H30N2O5S	410.187540	82560-54-1	v
Bensulide	C14H24NO4PS3	397.060510	741-58-2	v
Benz[a]anthracene	C18H12	228.093900	56-55-3	
Benzidine	C12H12N2	184.100048	92-87-5	
Benzotrichloride	C7H5Cl3	193.945683	1998/7/7	
Benzyl chloride	C7H7Cl	126.023628	100-44-7	
Benzylbutylphthalate	C19H20O4	312.136159	85-68-7	v
Bifenthrin	C23H22ClF3O2	422.126040	82657-04-3	
Bis(2-butoxyethyl)phthalate	C20H30O6	366.204239	117-83-9	
Bis(4'-chlorophenyl)acetate	C14H10Cl2O2	280.005785	1983/5/6	
Bis(chloromethyl) ether	C2H4Cl2O	113.963920	542-88-1	
Bisphenol A	C15H16O2	228.115030	1980/5/7	
Bisphenol B	C16H18O2	242.130680	77-40-7	v
BP-2 / Benzophenone-2	C13H10O5	246.052820	131-55-5	v

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Compound Name	Formula	Mass	CAS	Spectrum
BPA / Bisphenol A	C15H16O2	228.115030	80-05-7	v
BPA-G	C21H24O8	404.147120		v
Bromodichloromethane	CHBrCl2	161.863868	75-27-4	
Bromoform	CHBr3	249.762839	75-25-2	
Bromophos	C8H8BrCl2O3PS	363.849220	2104-96-3	
Bromophos-ethyl	C10H12BrCl2O3PS	391.880520	4824-78-6	v
Bromoxynil	C7H3Br2NO	274.858140	1689-84-5	v
Butachlor	C17H26ClNO2	311.165207	23184-66-9	v
Butyl 4-hydroxybenzoate (Butylparaben)	C11H14O3	194.094290	94-26-8	v
Butyl acrylate	C7H12O2	128.083730	141-32-2	
Butylparaben (Butyl paraben)	C11H14O3	194.094290	94-26-8	
Captafol	C10H9Cl4NO2S	346.910810	2425/6/1	
Captan	C9H8Cl3NO2S	298.934130	133-06-2	
Carbaryl	C12H11NO2	201.078980	63-25-2	v
Carbendazim (Azole)	C9H9N3O2	191.069480	10605-21-7	v
Carbofuran	C12H15NO3	221.105190	1563-66-2	v
Carbofuran, - 3 hydroxy	C12H15NO4	237.100110	16655-82-6	v
Carbon disulfide	CS2	75.944141	75-15-0	
Carbon tetrachloride	CCl4	151.875411	56-23-5	
Carbophenothion	C11H16ClO2PS3	341.973860	786-19-6	v
Carbosulfan	C20H32N2O3S	380.213360	55285-14-8	v
Chloral Hydrate	C2H3Cl3O2	163.919860	302-17-0	

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Compound Name	Formula	Mass	CAS	Spectrum
Chlordane	C10H6Cl8	405.797770	57-74-9	
Chlordecone	C10Cl10O	485.683440	143-50-0	
Chlordimeform	C10H13ClN2	196.076730	6164-98-3	v
Chlorendic acid	C9H4Cl6O4	385.824075	115-28-6	
Chlorfenvinphos(I)	C12H14Cl3O4P	357.969530	470-90-6	
Chlorfenvinphos(II)	C12H14Cl3O4P	357.969530	470-90-6	v
Chlornitofen	C12H6Cl3NO3	316.941326	1836-77-7	
Chloroacetic acid	C2H3ClO2	93.982157	1979/11/8	
Chlorobenzene	C6H5Cl	112.007978	108-90-7	
Chlorobenzilate	C16H14Cl2O3	324.032000	510-15-6	
Chlorocresol	C7H7ClO	142.018543	59-50-7	v
Chloroform	CHCl3	117.914380	67-66-3	
Chloromethyl methyl ether	C2H5ClO	80.002892	107-30-2	
Chloroprene	C4H5Cl	88.007978	126-99-8	
Chlorothalonil	C8Cl4N2	263.881559	1897-45-6	
Chlorpyrifos	C9H11Cl3NO3PS	348.926280	2921-88-2	v
cis-1,2-Dichloroethene	C2H2Cl2	95.953355	156-59-2	
Clethodim	C17H26ClNO3S	359.132190	99129-21-2	v
Clofentezin	C14H8Cl2N4	302.012600	74115-24-5	v
Clomazone	C12H14ClNO2	239.071310	81777-89-1	v
CN gas (chloroacetophenone)	C8H7ClO	154.018543	532-27-4	
Coumaphos	C14H16ClO5PS	362.014460	56-72-4	v

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Compound Name	Formula	Mass	CAS	Spectrum
Coumaric acid	C9H8O3	164.047344	7400-08-0	
Crotonaldehyde	C4H6O	70.041865	4170-30-3	
Cumene	C9H12	120.093900	98-82-8	
Cyanazine (Fortrol)	C9H13ClN6	240.089020	21725-46-2	v
Cyclophosphamide	C7H15Cl2N2O2P	260.024820	50-18-0	v
Cyfluthrin(I)	C22H18Cl2FNO3	433.064780	68359-37-5	
Cypermethrin	C22H19Cl2NO3	415.074200	52315-07-8	v
Cyromazine	C6H10N6	166.096690	66215-27-8	v
Dalapon	C3H4Cl2O2	141.958830	75-99-0	
Daminozide	C6H12N2O3	160.084790	1596-84-5	v
DBP / Dibutyl phthalate	C16H22O4	278.151810	84-74-2	v
DBZP / Dibenzyl phthalate	C22H18O4	346.120510	523-31-9	v
DCHP / Dicyclohexyl phthalate	C20H26O4	330.183110	84-61-7	v
DCIP / Bis(2-chloro-1-methylethyl)ether	C6H12Cl2O	170.026520	108-60-1	
DCPA / Chlorthal-dimethyl (Dacthal)	C10H6Cl4O4	329.902020	1861-32-1	
Decabromodiphenyl oxide	C12Br10O	949.178294	1163-19-5	
DEHA / Di(2-ethylhexyl) adipate	C22H42O4	370.308310	103-23-1	v
Deltamethrin	C22H19Br2NO3	502.973169	52918-63-5	v
delta-Methrin (Decamethrin)	C22H19Br2NO3	502.973169	52918-63-5	
Demeton	C8H19O3PS2	258.051322	8065-48-3	v
Demeton-S-methyl	C6H15O3PS2	230.020020	919-86-8	v
Demeton-S-methylsulfoxide	C6H15O4PS2	246.014940	301-12-2	v

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Compound Name	Formula	Mass	CAS	Spectrum
DHB / 2,4-Dihydroxybenzophenone (Benzophenone-1)	C13H10O3	214.062990	131-56-6	v
DHP / Dihexyl phthalate (DHXP) (DnHP)	C20H30O4	334.214410	84-75-3	v
Di(2-ethylhexyl) adipate	C22H42O4	370.308310	103-23-1	
Diazinon (Dimpylate)	C12H21N2O3PS	304.101050	333-41-5	v
Dibenzofuran	C12H8O	168.057515	132-64-9	
Dibutyl phthalate	C16H22O4	278.151809	84-74-2	
Dicamba	C8H6Cl2O3	219.969400	1918-00-9	v
Dichlobenil	C7H3Cl2N	170.964250	1194-65-6	
Dichlorodiphenyldichloroethylene	C14H8Cl4	315.938011	72-55-9	
Dichlorodiphenyltrichloroethane	C14H9Cl5	351.914689	50-29-3	
Dichlorvos	C4H7Cl2O4P	219.945900	62-73-7	v
Dicofol	C14H9Cl5O	367.909600	115-32-2	
Dicrotophos (Bidrin)	C8H16NO5P	237.076610	141-66-2	v
Dicyclopentadiene	C10H12	132.093900	77-73-6	
Diethanolamine	C4H11NO2	105.078979	111-42-2	v
Diethyl phthalate	C12H14O4	222.089209	84-66-2	v
Diethyl sulfate	C4H10O4S	154.029980	64-67-5	
Dihydroxy-dimethoxybenzophenone	C15H14O5	274.084124	131-54-4	
Diisobutyl phthalate	C16H22O4	278.151809	84-69-5	
Diisodecyl phthalate	C28H46O4	446.339610	26761-40-0	
Diisononyl phthalate	C26H42O4	418.308310	28553-12-0	
Diisooctyl phthalate	C24H38O4	390.277010	27554-26-3	

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Compound Name	Formula	Mass	CAS	Spectrum
Dimethoate	C5H12NO3PS2	228.999620	60-51-5	v
Dimethyl phthalate	C10H10O4	194.057909	131-11-3	
Dimethyl sulfate	C2H6O4S	125.998679	77-78-1	
Dimethylcarbamoyl chloride	C3H6ClNO	107.013792	79-44-7	
Di-n-hexyl phthalate	C20H30O4	334.214409	84-75-3	
Di-n-octyl phthalate	C24H38O4	390.277010	117-84-0	
Dinoseb (Subitex)	C10H12N2O5	240.074620	88-85-7	v
DINP / Diisononylphthalate	C26H42O4	418.308310	28553-12-0	v
Di-n-pentyl phthalate	C18H26O4	306.183109	131-18-0	
Di-n-propylphthalate	C14H18O4	250.120509	131-16-8	
Dioctyl phthalate	C24H38O4	390.277010	117-81-7	v
DIOP / Diisooctyl phthalate	C24H38O4	390.277010	27554-26-3	v
Diphenylamine	C12H11N	169.089150	122-39-4	v
DIPP / Diisopentyl phthalate	C18H26O4	306.183110	605-50-5	v
Disulfoton (Ethylthiometon)	C8H19O2PS3	274.028480	298-04-4	v
Diuron	C9H10Cl2N2O	232.017018	330-54-1	v
DMDT / Metox (Methoxychlor)	C16H15Cl3O2	344.013760	72-43-5	
DMF / Dimethylformamide (DMFA)	C3H7NO	73.052760	68-12-2	v
DMP / Dimethyl phthalate (DMF)	C10H10O4	194.057910	131-11-3	v
DNOC / 2,4-Dinitro-o-kresol	C7H6N2O5	198.027670	534-52-1	
DNOP / Dioctyl phthalate	C24H38O4	390.277010	117-84-0	v
DNP / Dinonyl phthalate	C26H42O4	418.308310	84-76-4	v

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Compound Name	Formula	Mass	CAS	Spectrum
DPhP / Diphenyl phthalate	C20H14O4	318.089210	84-62-8	v
DPP / Dipentyl phthalate	C18H26O4	306.183110	131-18-0	v
EDPP / Edifenphos	C14H15O2PS2	310.025110	17109-49-8	v
Endosulfan	C9H6Cl6O3S	403.816881	115-29-7	
Endothal	C8H10O5	186.052820	145-73-3	v
Endrin	C12H8Cl6O	377.870631	72-20-8	
enzacamene	C18H22O	254.167065	36861-47-9	
EPN / Tsumaphos	C14H14NO4PS	323.038120	2104-64-5	v
EPTC / Epthame	C9H19NOS	189.118730	759-94-4	v
Erythromycin	C37H67NO13	733.461240	114-07-8	v
Esfenvalerat	C25H22ClNO3	419.128821	66230-04-4	
Ethiofencarb	C11H15NO2S	225.082350	29973-13-5	v
Ethion	C9H22O4P2S4	383.987620	563-12-2	v
Ethoprop (Ethoprophos)	C8H19O2PS2	242.056410	13194-48-4	v
Ethyl 4-hydroxybenzoate	C9H10O3	166.062990	120-47-8	v
Ethylbenzene	C8H10	106.078250	100-41-4	
Ethylendibromide	C2H4Br2	185.867976	106-93-4	
Etofenprox	C25H28O3	376.203840	80844-07-1	
Etridiazole (Echlomezole)	C5H5Cl3N2OS	245.918817	2593-15-9	
ETU / Ethylene thiourea (Imidazolidinethione)	C3H6N2S	102.025170	96-45-7	v
Fenamiphos - sulfone	C13H22NO5PS	335.095630	31972-44-8	v
Fenamiphos - sulfoxide	C13H22NO4PS	319.100720	31972-43-7	v

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Compound Name	Formula	Mass	CAS	Spectrum
Fenarimol	C17H12Cl2N2O	330.032670	60168-88-9	v
Fenbutatin oxide	C60H78OSn2	1038.414910	13356-08-6	
Fenchlorphos (Ronnel)	C8H8Cl3O3PS	319.899730	299-84-3	
Fenitrothion	C9H12NO5PS	277.017380	122-14-5	v
Fenobucarb (Baycarb)	C12H17NO2	207.125930	3766-81-2	v
Fenoxycarb	C17H19NO4	301.131408	72490-01-8	
Fenpropathrin	C22H23NO3	349.167790	39515-41-8	v
Fenthion	C10H15O3PS2	278.020020	55-38-9	v
Fentin acetate	C20H18O2Sn	402.035502	900-95-8	
Fentin hydroxide	C18H16OSn	360.024937	76-87-9	
Fenvalerate	C25H22ClNO3	419.128820	51630-58-1	
Fluazifop-P-butyl	C19H20F3NO4	383.134440	79241-46-6	v
Flumetsulam	C12H9F2N5O2S	325.044500	98967-40-9	v
Fluoroacetamide	C2H4FNO	77.027690	640-19-7	
Flutolanil	C17H16F3NO2	323.113310	66332-96-5	v
Fluvalinate	C26H22ClF3N2O3	502.127100	69409-94-5	v
Folpet	C9H4Cl3NO2S	294.902830	133-07-3	
Fomesafen	C15H10ClF3N2O6S	437.990020	72178-02-0	v
Fonofos (Dyfonate)	C10H15OPS2	246.030190	944-22-9	v
Fosetyl-aluminium	C6H15AlO9P3	350.974430	39148-24-8	
Glyphosate	C3H8NO5P	169.014010	1071-83-6	v
Heptachlor	C10H5Cl7	369.821094	76-44-8	

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Compound Name	Formula	Mass	CAS	Spectrum
Heptachlor epoxide	C10H5Cl7O	385.816009	1024-57-3	
Hexachloro-1,3-butadiene	C4Cl6	257.813116	87-68-3	
Hexachlorobenzene	C6Cl6	281.813116	118-74-1	
Hexachloroethane	C2Cl6	233.813116	67-72-1	
hexachlorophene	C13H6Cl6O2	403.849896	70-30-4	v
Hexaconazole(I)	C14H17Cl2N3O	313.074870	79983-71-4	
Hexaconazole(II)	C14H17Cl2N3O	313.074870	79983-71-4	v
Hexamethylphosphoramide	C6H18N3OP	179.118749	680-31-9	
Hexogen (RDX)	C3H6N6O6	222.034882	121-82-4	
Hexythiazox	C17H21ClN2O2S	352.101230	78587-05-0	v
Imidacloprid	C9H10ClN5O2	255.052300	138261-41-3	v
Ioxynil	C7H3I2NO	370.830400	1689-83-4	v
Iprobenfos	C13H21O3PS	288.094900	26087-47-8	v
Iprodione (Glycophen)	C13H13Cl2N3O3	329.033400	36734-19-7	v
Isophorone	C9H14O	138.104465	78-59-1	
Isoprocarb	C11H15NO2	193.110280	2631-40-5	v
Isoproturon	C12H18N2O	206.141910	34123-59-6	v
Isoxaben	C18H24N2O4	332.173610	82558-50-7	v
Isoxathion	C13H16NO4PS	313.053770	18854-01-8	v
Ketoconazole	C26H28Cl2N4O4	530.148760	65277-42-1	v
Lactofen	C19H15ClF3NO7	461.048910	77501-63-4	
Lambda-Cyhalothrin	C23H19ClF3NO3	449.100556	91465-08-6	

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Compound Name	Formula	Mass	CAS	Spectrum
Leptophos	C13H10BrCl2O2PS	409.869955	21609-90-5	
Lindane	C6H6Cl6	287.860066	58-89-9	
Linuron	C9H10Cl2N2O2	248.011930	330-55-2	v
Malathion	C10H19O6PS2	330.036070	121-75-5	v
MCiNP	C18H24O6	336.157290		v
MCPA (MCP)	C9H9ClO3	200.024020	94-74-6	v
MDA / 4,4'-Methylenedianiline	C13H14N2	198.115700	101-77-9	v
Mecoprop	C10H11ClO3	214.039672	93-65-2	
MECPP	C16H20O6	308.125990		v
Mefenacet (Rancho)	C16H14N2O2S	298.077600	73250-68-7	v
Mestranol	C21H26O2	310.193280	72-33-3	v
Metalaxyl	C15H21NO4	279.147060	57837-19-1	v
Metam	C2H5NS2	106.986341	137-42-8	
Methamidophos (Metamidophos)	C2H8NO2PS	141.001340	10265-92-6	v
Methidathion	C6H11N2O4PS3	301.961860	950-37-8	v
Methiocarb (Mercaptodimethur)	C11H15NO2S	225.082350	2032-65-7	v
Methomyl	C5H10N2O2S	162.046300	16752-77-5	v
Methyl 4-hydroxybenzoate	C8H8O3	152.047344	99-76-3	v
Methyl bromide	CH3Br	93.941813	74-83-9	
Methyl iodide	CH3I	141.927943	74-88-4	
Methyl isobutyl ketone	C6H12O	100.088815	108-10-1	
Methyl tert-butyl ether	C5H12O	88.088815	1634-04-4	

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Compound Name	Formula	Mass	CAS	Spectrum
Methylnitrosourea	C2H5N3O2	103.038176	684-93-5	
Metolachlor	C15H22ClNO2	283.133910	51218-45-2	v
Metolachloric acid	C15H21NO4	279.147060	152019-73-3	v
Metribuzin	C8H14N4OS	214.088830	21087-64-9	v
Mevinphos (Phosdrin)	C7H13O6P	224.044970	7786-34-7	v
MGK 264 (Synergist 264) (Pyrdone)	C17H25NO2	275.188529	113-48-4	
Mirex	C10Cl12	539.626233	2385-85-5	
Mitotane	C14H10Cl4	317.953660	53-19-0	
Molinate	C9H17NOS	187.103080	2212-67-1	v
Mono-(2-ethyl-5-hydroxyhexyl) phthalate	C16H22O5	294.146724	40321-99-1	v
Mono-(2-ethyl-5-oxohexyl)-phthalate	C16H20O5	292.131074	40321-98-0	v
Mono-(2-ethylhexyl) phthalate	C16H22O4	278.151809	4376-20-9	v
Mono-(3-carboxypropyl) phthalate	C12H12O6	252.063388	66851-46-5	v
Monobenzyl phthalate	C15H12O4	256.073559	2528-16-7	v
Monocrotophos (Azodrin)	C7H14NO5P	223.060960	6923-22-4	v
Mono-cyclohexyl phthalate	C14H16O4	248.104859		v
Mono-ethyl phthalate	C10H10O4	194.057910	2306-33-4	v
Mono-isobutyl phthalate	C12H14O4	222.089210	30833-53-5	v
Mono-isononyl phthalate	C17H24O4	292.167459		v
Mono-methyl phthalate	C9H8O4	180.042259	4376-18-5	v
Mono-n-butyl phthalate	C12H14O4	222.089209	131-70-4	v
Mono-n-octyl phthalate	C16H22O4	278.151809		v

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Compound Name	Formula	Mass	CAS	Spectrum
Myclobutanil	C15H17ClN4	288.114170	88671-89-0	v
NDMA / Nitrosodimethylamine	C2H6N2O	74.048010	62-75-9	v
Nitrilotriacetic acid	C6H9NO6	191.042987	139-13-9	
Nitrobenzene	C6H5NO2	123.032028	98-95-3	
Nitrofen	C12H7Cl2NO3	282.980299	1836-75-5	
Nitroglycerine	C3H5N3O9	227.002580	55-63-0	
Nitrophenol, 4-	C6H5NO3	139.026940	100-02-7	v
N-Methyl-2-pyrrolidinone	C5H9NO	99.068414	872-50-4	
N-Nitrosodiethylamine	C4H10N2O	102.079313	55-18-5	
N-Nitrosodimethylamine	C2H6N2O	74.048013	62-75-9	
Nonoxinol 9	C33H60O10	616.418648	9016-45-9	
Norflurazon	C12H9ClF3N3O	303.038620	27314-13-2	v
Octyl methoxycinnamate	C18H26O3	290.188190	5466-77-3	v
Omethoate	C5H12NO4PS	213.022470	1113-02-6	v
o-Toluidine	C7H9N	107.073499	95-53-4	
Oxamyl	C7H13N3O3S	219.067760	23135-22-0	v
Oxirane (chloromethyl)	C3H5ClO	92.002892	106-89-8	
Oxybenzone	C14H12O3	228.078644	131-57-7	v
Oxychlordane	C10H4Cl8O	419.777036	27304-13-8	
Oxyfluorofen	C15H11ClF3NO4	361.032870	42874-03-3	v
Paclobutrazol	C15H20ClN3O	293.129490	76738-62-0	v
Paradichlorobenzene (Benzene, 1,4-dichloro-)	C6H4Cl2	145.969006	106-46-7	

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Compound Name	Formula	Mass	CAS	Spectrum
Paraquat	C12H14N2	186.115698	4685-14-7	
Parathion	C10H14NO5PS	291.033030	56-38-2	v
Parathion-methyl	C8H10NO5PS	263.001730	298-00-0	
PCNB / Pentachloronitrobenzene (Quintozene)	C6Cl5NO2	292.837167	82-68-8	
PCP / Pentachlorophenol	C6HCl5O	263.847000	87-86-5	v
p-cresol	C7H8O	108.057515	106-44-5	v
Pencycuron	C19H21ClN2O	328.134240	66063-05-6	v
Pendimethalin (Penoxalin)	C13H19N3O4	281.137560	40487-42-1	v
Pentachlorobenzene	C6HCl5	247.852089	608-93-5	
Pentachlorophenol	C6HCl5O	263.847003	87-86-5	
Perfluorooctanesulfonic acid	C8HF17O3S	499.937494	1763-23-1	
Perfluorooctylsulfonyl fluoride	C8F18O2S	501.933158	307-35-7	
Permethrin(I)	C21H20Cl2O3	390.078950	52645-53-1	
Permethrin(I) ((1R)-trans-Permethrin)	C21H20Cl2O3	390.078950	61949-77-7	v
Permethrin(II) ((1R)-cis-Permethrin)	C21H20Cl2O3	390.078950	54774-46-8	v
PFNA / Perfluorononanoic acid	C9HF17O2	463.970510	375-95-1	v
PFOA / Perfluorooctanoic acid	C8HF15O2	413.973700	335-67-1	v
PFOS / Perfluorooctanesulfonic acid	C8HF17O3S	499.937490	1763-23-1	v
PFUnDA / Perfluoroundecanoic acid (PFUnA)	C11HF21O2	563.964120	2058-94-8	v
Phenolphthalein	C20H14O4	318.089209	77-09-8	v
Phenolphthalol	C20H18O3	306.125594	81-92-5	
Phenothrin	C23H26O3	350.188190	26002-80-2	v

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Compound Name	Formula	Mass	CAS	Spectrum
Phenthoate (Fenthoate)	C12H17O4PS2	320.030590	2597/3/7	v
Phorate (Isothioate)	C7H17O2PS3	260.012830	298-02-2	v
Phosalone	C12H15ClNO4PS2	366.986860	2310-17-0	v
Phosmet (Imidan)	C11H12NO4PS2	316.994540	732-11-6	v
Phosphamidon	C10H19ClNO5P	299.068940	13171-21-6	v
Phthalic acid Mono-2-ethylhexyl Ester	C16H22O4	278.151809	4376-20-9	v
Phthalic acid, dicyclohexyl ester	C20H26O4	330.183109	84-61-7	
Picloram	C6H3Cl3N2O2	239.926010	1918/2/1	v
Piperonyl butoxide	C19H30O5	338.209320	1951/3/6	
PIPP / Pentyl isopentyl phthalate (Isopentyl pentyl phthalate)	C18H26O4	306.183110	776297-69-9	v
Pirimicarb	C11H18N4O2	238.142980	23103-98-2	v
Pirimiphos-methyl (Pirimifos-methyl)	C11H20N3O3PS	305.096300	29232-93-7	v
p-nitrotoluene	C7H7NO2	137.047678	99-99-0	
p-Nonylphenol (4-Nonylphenol)	C15H24O	220.182720	104-40-5	v
Prochloraz	C15H16Cl3N3O2	375.030810	67747-09-5	v
Procymidone	C13H11Cl2NO2	283.016680	32809-16-8	v
Profenofos	C11H15BrClO3PS	371.935140	41198-08-7	v
Prometryn	C10H19N5S	241.136120	7287-19-6	v
Propanil	C9H9Cl2NO	217.006120	709-98-8	v
Propargite	C19H26O4S	350.155180	2312-35-8	
Propazine	C9H16ClN5	229.109420	139-40-2	v
Propiconazole(I)	C15H17Cl2N3O2	341.069780	60207-90-1	

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Compound Name	Formula	Mass	CAS	Spectrum
Propiconazole(II)	C15H17Cl2N3O2	341.069780	60207-90-1	v
Propiolactone	C3H4O2	72.021129	57-57-8	
Propionic acid	C3H6O2	74.036779	1979/9/4	
Propoxur	C11H15NO3	209.105190	114-26-1	v
Propyl 4-hydroxybenzoate (Propylparaben)	C10H12O3	180.078640	94-13-3	v
Propyzamide (Pronamide)	C12H11Cl2NO	255.021770	23950-58-5	v
Prothiofos	C11H15Cl2O2PS2	343.962810	34643-46-4	v
p-Salicylic acid	C7H6O3	138.031694	99-96-7	v
Pyrethrin II	C22H28O5	372.193670	121-29-9	
Pyriproxyfen (Pyriproxifen)	C20H19NO3	321.136490	95737-68-1	v
Quadrosilan	C18H28O4Si4	420.106465	33204-76-1	
Quinalphos (Diethquinalphione)	C12H15N2O3PS	298.054100	13593-03-8	v
Quinclorac	C10H5Cl2NO2	240.969730	84087-01-4	v
Quinoline	C9H7N	129.057849	91-22-5	
Quizalofop-p-ethyl	C19H17ClN2O4	372.087680	100646-51-3	v
Resmethrin(II)	C22H26O3	338.188190	10453-86-8	v
resorcinol	C6H6O2	110.036779	108-46-3	v
Roxarsone	C6H6AsNO6	262.941109	121-19-7	v
sec-Butylbenzene	C10H14	134.109550	135-98-8	
Simazine	C7H12ClN5	201.078120	122-34-9	v
Styrene	C8H8	104.062600	100-42-5	
Styrene oxide	C8H8O	120.057515	1996/9/3	

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Compound Name	Formula	Mass	CAS	Spectrum
Tau-fluvalinate	C26H22ClF3N2O3	502.127100	102851-06-9	v
TBTO / Bis(tributyltin) oxide	C24H54OSn2	582.227110	56-35-9	
TCEP / Tris(2-chloroethyl)phosphate	C6H12Cl3O4P	283.953880	115-96-8	v
TDA / 2,4-Toluene diamine (2,4-Diaminotoluene)	C7H10N2	122.084400	95-80-7	v
TDE	C14H10Cl4	317.953661	72-54-8	
Tebuconazole(I) (Terbuconazole)	C16H22ClN3O	307.145140	107534-96-3	
Tebuconazole(II) (Terbuconazole)	C16H22ClN3O	307.145140	107534-96-3	v
Temephos (Abate)	C16H20O6P2S3	465.989720	3383-96-8	v
Terbufos	C9H21O2PS3	288.044130	13071-79-9	v
Terbufos-sulfone	C9H21O4PS3	320.033958	56070-16-7	
Terbutryn	C10H19N5S	241.136120	886-50-0	v
Tetrachloroethene	C2Cl4	163.875411	127-18-4	
Tetrachlorvinphos (Dietreen T)	C10H9Cl4O4P	363.899260	22248-79-9	v
Thiobencarb	C12H16ClNOS	257.064110	28249-77-6	v
Thiofanox	C9H18N2O2S	218.108899	39196-18-4	
Thiophanate-methyl	C12H14N4O4S2	342.045650	23564-05-8	v
Thiourea	CH4N2S	76.009520	62-56-6	v
Thiram	C6H12N2S4	239.988330	137-26-8	v
Tinuvin 320	C20H25N3O	323.199760	3846-71-7	v
Tinuvin 327	C20H24ClN3O	357.160790	3864-99-1	v
Tinuvin 328	C22H29N3O	351.231060	25973-55-1	v
Toxaphene (Polychlorocamphene)	C10H8Cl8	407.813422	8001-35-2	

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Compound Name	Formula	Mass	CAS	Spectrum
trans-1,2-Dichloroethene	C2H2Cl2	95.953355	540-59-0	
trans-Nonachlor	C10H5Cl9	439.758800	39765-80-5	
Triadimefon	C14H16ClN3O2	293.093100	43121-43-3	v
Triazophos	C12H16N3O3PS	313.065000	24017-47-8	v
Tributyltin chloride	C12H27ClSn	318.084950	1461-22-9	
Trichlorfon (Dylox) (DEP)	C4H8Cl3O4P	255.922580	52-68-6	v
Trichloroethene	C2HCl3	129.914383	1979/1/6	
Triethylamine	C6H15N	101.120449	121-44-8	
Triflumizol	C15H15ClF3N3O	345.085570	68694-11-1	v
Trifluralin	C13H16F3N3O4	335.109290	1582-09-8	
Trinexapac-ethyl	C13H16O5	252.099770	95266-40-3	v
Triphenyltin chloride	C18H15ClSn	377.991050	639-58-7	
Tris(2,3-dibromopropyl) phosphate	C9H15Br6O4P	691.580823	126-72-7	
Tris(2-chloroethyl)phosphate	C6H12Cl3O4P	283.953878	115-96-8	
Urethane	C3H7NO2	89.047678	51-79-6	v
Vinclozolin	C12H9Cl2NO3	284.995949	50471-44-8	
Vinclozolin M2	C11H11Cl2NO2	259.016684	83792-61-4	
Vinyl acetate	C4H6O2	86.036779	108-05-4	
Vinyl bromide	C2H3Br	105.941813	593-60-2	
Zineb	C4H8N2S4	211.957031	12122-67-7	
Ziram (Ferbam)	C3H7NS2	121.001990	137-30-4	

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