Analytical and Bioanalytical Chemistry (2018) 410:5331–5351
https://doi.org/10.1007/s00216-018-1195-3

REVIEW

# Hits and misses in research trends to monitor contaminants in foods

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Received: 3 May 2018 / Revised: 31 May 2018 / Accepted: 12 June 2018 / Published online: 27 June 2018
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## Abstract

Monitoring of chemicals of toxicological concern in food is commonly needed for many purposes, which include (in part) food safety, regulatory enforcement, risk assessment, international food trade, label claims, environmental protection, industry needs, academic research, and consumer confidence. Chemicals of current concern include a variety of toxins, pesticides, veterinary drugs, growth promoters, environmental contaminants, toxic metals, allergens, endocrine disruptors, genetically modified organisms, melamine, acrylamide, furans, nitrosamines, food additives, packaging components, and miscellaneous other chemicals. In light of past crises, the potential harm from known or unknown chemicals not currently monitored are a source of additional concern by the food industry, regulators, scientists, and consumers. As global food trade has expanded and detection techniques have improved, chemical contaminant analysis of foods has also increased in importance and activity. This critical review article is aimed to highlight current trends in the literature, including neglected research needs, on the analysis of chemicals of toxicological concern in foods.

**Keywords** Review · Food safety analysis · Chemical residues · Contaminants · Regulatory monitoring

## Introduction

Food safety is a central concern of everyone, and it fundamentally impacts all aspects of our lives. Acute health risks from toxins (chemicals of biological origin) and other highly toxic compounds in food can have an immediate impact after any meal, including allergens for a segment of the population. Furthermore, long-term effects from chronic exposure to carcinogenic, endocrine disrupting, and similar types of chemicals in food adversely affect human health, growth, and performance, causing insidious damage to individuals and society. Terroristic attacks on the food supply constitute another unfortunate possibility we must guard against in the food safety arena.

Food safety is not only a human health concern, but it also greatly contributes to domestic and global economies, involves a large, complex legal/regulatory framework, and implicates agricultural and food processing operations that affect the environment and ecosystem. Microbial resistance to antibiotics is just one example of the type of important issues impacted by food safety policies and monitoring programs [1]. In nearly every country, governmental registration of agrochemicals for commercial use in agriculture also requires development and testing of validated, approved methods of analysis for the active ingredients. Other underlying reasons for monitoring of chemical contaminants in food include: conducting research studies, implementing the capabilities of modern analytical instruments and techniques, meeting regulatory requirements, and addressing consumer concerns.

In the era of a rapidly growing global economy, food products are no longer just a local matter; rare regional delicacies can be obtained in much of the world any time of the year. According to the World Trade Organization (WTO), food and agriculture contributed $1.49 trillion and $1.76 trillion, respectively, to the $18.5 trillion world merchandise trade in 2015 [2]. Developed countries tend to have populations with

Published in the topical collection *Food Safety Analysis* with guest editor Steven J. Lehotay.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00216-018-1195-3) contains supplementary material, which is available to authorized users.

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high food quality standards, and major food importing countries have rigorous monitoring programs to verify food safety of imports. In many countries, agriculture and food play the dominant role in their economies [3]. Particularly for less developed countries, improvement in the human condition and environment depends greatly on food production, which is significantly driven by global food safety demands and associated monitoring programs.

Food safety is not only a high priority for governments, but it is also an utmost concern of the food industry for moral, business, and legal reasons. People want to feel assured that the food they buy (for themselves and their pets and livestock) meet their expectations. Ideally, food producers and industry would follow good agricultural practices, hazard analysis at critical control points, and similar measures to meet these obligations without need for oversight. However, many newsworthy events due to accidental, negligent, or intentional actions continue to periodically occur [4], demonstrating that we must still verify the safety (and label claims) of food/feed. Toxicological and ecological risk assessment also requires knowledge about exposure of chemicals in food and the environment, which lead to re-evaluation of monitoring priorities.

All of the above reasons require the development, validation, and implementation of methods to detect hazardous components in food. Monitoring capabilities directly depend on the resources, personnel, and performance of the analytical technologies and methods used. The cost of monitoring adds to the cost of the tested food but increased efficiencies provided by wider scope, enhanced sensitivity, higher selectivity, more reproducibility, better software, and greater reliability of modern instruments often serves to improve quality of analysis at lower cost per sample [5].

## Food safety monitoring trends

As indicated in Table 1, thousands of scientific articles have been published on food safety monitoring topics. However, growth has been high in nearly every scientific field, thus *relative* growth in the number of publications (no. pubs) on a given topic represents a better approximation of importance than actual growth. Table 1 lists the no. pubs and trends using different search terms in the Web of Science core collection in Feb 2018 (the search term "of" yielded ~ 45 million pubs in the database) [6]. A "hit" occurs if the search terms appear in the pub titles, abstracts, or keywords. The first row indicates that the no. pubs listed under "chemistry" grew from ~ 65,000 in the 6 years during 1994–1999 to ~ 183,000 between 2012 and 2017 (180% growth). At the same time, "food (analysis or detection)" and "food (contaminant or residue)" grew at rates of 520 and 357%, respectively (or 121 and 63% higher relative growth normalized to chemistry, as shown in Table 1). Figure 1 also demonstrates this higher growth in food analysis compared with: (A) the chemistry topic in general and (B) pubs in *Trends Anal. Chem*. Clearly, growth in food applications have outpaced environmental applications from the same starting point 15 years ago (albeit the latter is poised for a rebound). The same trends can be observed in other analytical journals, including *Anal. Bioanal. Chem*, and the no. pubs have also soared in several specialized journals such as *Food Anal. Methods*, *Food Control*, *Food Addit. Contam.*, and *Food Chem.*, further indicating the recent increasing relative importance of food analysis and safety.

A related trend with respect to broader internationalization of scientific efforts is also occurring, as described in the Electronic supplementary material (ESM). For example, the no. pubs (co-)authored by scientists from China has increased dramatically in the past two decades, as shown in Fig. S1 (see ESM).

The search terms in Table 1 are sorted by decreasing no. pubs in the 2012–2017 timeframe as a rough estimation about the relative attention being given by scientists in the field. Tremendous relative growth can be observed in the topics in italicized text, whereas topics set in bold underwent slower growth. For the sake of comparison, "food fraud and authenticity" and "pathogen detection and food" are also included to show their prominence, even though they generally fall outside the scope of this review.

The traditional concerns of toxic elements (e.g., Pb, Cd, As, Hg), pesticides, mycotoxins, environmental contaminants (e.g., dioxins and polychlorinated biphenyls), allergens, and veterinary drugs/antibiotics still lead the way in terms of the no. pubs on food safety monitoring topics, but newer issues such as nanoparticles, acrylamide, melamine, flame retardants, genetically modified organisms (GMOs), bisphenol A (BPA), endocrine disruptors, and others have skyrocketed from merely a handful of pubs just over a decade ago to hundreds of pubs more recently.

Of course, certain non-isolated factors in searches limit the ability to draw clear conclusions from this online literature search. In the case of nanoparticles, for example, the observed growth mainly arose from research papers describing the use of nanoparticles for food detection, not only papers about the detection of nanoparticles in food. However, the observed growth certainly reflects current events and changing dynamics of technology, toxicology, scientific funding, food production practices, research priorities, regulatory concerns, and consumer views.

As in environmental analysis, many analytical chemists in the food safety arena use the advanced technology gained from powerful detection tools to monitor "chemicals of interest" in foods, not necessarily just "chemicals of toxicological concern." This serves to provide exposure data for toxicologists and regulators to conduct risk assessment of the "emerging" contaminants. However, some analytical chemists continue to monitor certain chemicals at levels known to cause

**Table 1** Number of publications (pubs) found searching the Web of Science core database in Feb 2018 using given search terms and years

| Search terms | No. pubs 1994–1999 | No. pubs 2000–2005 (rel. growth vs. 1994–1999) | No. pubs 2006–2011 (rel. growth vs. 2000–2005 | No. pubs 2012–2017 (rel. growth vs. 2006–2011) | Rel. growth 2012–2017 vs. 1994–1999 (%) |
|---|---|---|---|---|---|
| Chemistry | 65,170 | 89,223 (37%)[a] | 130,159 (46%)[a] | 182,751 (40%)[a] | 180[a] |
| (Analysis or detection) + food | 12,692 | 21,517 (24%) | 41,696 (33%) | 78,771 (35%) | 121 |
| "Food safety" | 1043 | 2126 (49%) | 4887 (58%) | 10,826 (58%) | 270 |
| (Contaminant or residue) + food | 2296 | 3248 (3%) | 6084 (28%) | 10,500 (23%) | 63 |
| (Cadmium or Cd or mercury or Hg or Pb or arsenic) + food | 1537 | 2205 (5%) | 3911 (22%) | 7068 (29%) | 64 |
| (Pesticide or insecticide or herbicide or fungicide or miticide) + residue + food | 492 | 631 **(−6%)** | 1150 (25%) | 2063 (28%) | 50 |
| "*Antimicrobial resistance*" + *food* | 39 | 297 (*456%*) | 841 (94%) | 1811 (53%) | *1556* |
| (Fraud or authentic…) + food | 122 | 281 (68%) | 690 (68%) | 1806 (86%) | 428 |
| "Pathogen detection" + food | 140 | 407 (*112%*) | 908 (53%) | 1784 (40%) | 354 |
| Mycotoxin + food | 170 | 337 (45%) | 778 (58%) | 1614 (48%) | 239 |
| *Nanoparticle + food* | 1 | 17 (*1142%*) | 258 (*940%*) | 1193 (*229%*) | *42,443* |
| Allergen + food + (detection or analysis) | 167 | 401 (75%) | 787 (35%) | 1167 (6%) | 149 |
| (Adulteration or adulterant) + food | 77 | 147 (39%) | 314 (46%) | 1001 (*127%*) | 364 |
| BPA or "bisphenol A" + food | 52 | 183 (*157%*) | 359 (34%) | 867 (72%) | 495 |
| ("Veterinary drug" or antibiotic) + residue | 138 | 199 (5%) | 440 (52%) | 757 (23%) | 96 |
| *Acrylamide + food* | 15 | 271 (*1220%*) | 596 (51%) | 733 **(−12%)** | *1643* |
| *("Flame retardant" or PBDE or polybrominated) + food* | 14 | 93 (*385%*) | 486 (*258%*) | 684 (0%) | *1642* |
| **(Dioxin or PCDD or PCDF) + food** | 302 | 481 (16%) | 651 **(−7%)** | **608 (−33%)** | **−28** |
| **("Polychlorinated biphenyl" or PCB) + food** | 353 | 492 (2%) | 604 **(−16%)** | **558 (−34%)** | **−44** |
| Phthalate + food | 48 | 114 (73%) | 188 (13%) | 471 (78%) | 250 |
| ("Polycyclic aromatic hydrocarbon" or PAH) + food | 83 | 155 (36%) | 249 (10%) | 404 (16%) | 74 |
| GMO + food | 29 | 181 *(356%)* | 308 (17%) | 401 **(−7%)** | 393 |
| *Melamine + food* | 2 | 4 (46%) | 256 (*4287%*) | 368 (2%) | *6462* |
| Furan + food | 60 | 109 (33%) | 215 (35%) | 360 (19%) | 114 |
| "Food additive" + (detection or analysis) | 37 | 70 (38%) | 99 **(−3%)** | 276 (99%) | 166 |
| (PFC or PFOA) + food | 18 | 33 (34%) | 166 *(245%)* | 274 (18%) | 443 |
| Seafood + toxin | 61 | 106 (27%) | 177 (14%) | 273 (10%) | 60 |
| Paraffin + food | 39 | 56 (5%) | 116 (42%) | 184 (13%) | 68 |
| **Radionuclide + food** | 115 | 125 **(−21%)** | 143 **(−22%)** | 162 **(−19%)** | **−50** |
| Parabens + food | 9 | 35 (*184%*) | 43 **(−16%)** | 149 (*147%*) | 490 |
| "*Endocrine disruptor*" + *food* | 2 | 22 (*703%*) | 66 (*106%*) | 145 (56%) | *2485* |
| **Nitrosamine + food** | 95 | 98 **(−25%)** | 109 **(−24%)** | 134 **(−12%)** | **−50** |
| (PDE-5 or sildenafil or tadalafil or vardenafil) + food | 4 | 39 (*612%*) | 57 (0%) | 114 (42%) | 916 |
| "Ethyl carbamate" + food | 23 | **19 (−40%)** | 53 (91%) | 97 (30%) | 50 |
| Perchlorate + food | 11 | 26 (73%) | 76 (*100%*) | **68 (−36%)** | 120 |

Entries set in italics indicate highest growth topics and entries set in bold indicate topics growing at a slower rate than "chemistry" in general

[a] Actual growth results are shown for "chemistry" to which other rates of growth are normalized

no effect. There is actually much value in demonstrating that the chemicals pose no health risks and the food is safe, but there are some who engage in such efforts to gain notoriety, funding, and publications. This is because advocacy groups, news organizations, advertisers, contract labs, instrument/supply companies, publishers, and even regulatory agencies often benefit from consumer fears of "chemicals." Protection of domestic markets in international trade is another economic interest that sometimes infiltrates food safety monitoring, which can lead to contentious discussions among delegations in Codex Alimentarius and trade judgments by the WTO.

Ultimately, science-based decision-making should be followed, and the US Food and Drug Administration (FDA) on their website only lists those contaminants with levels of

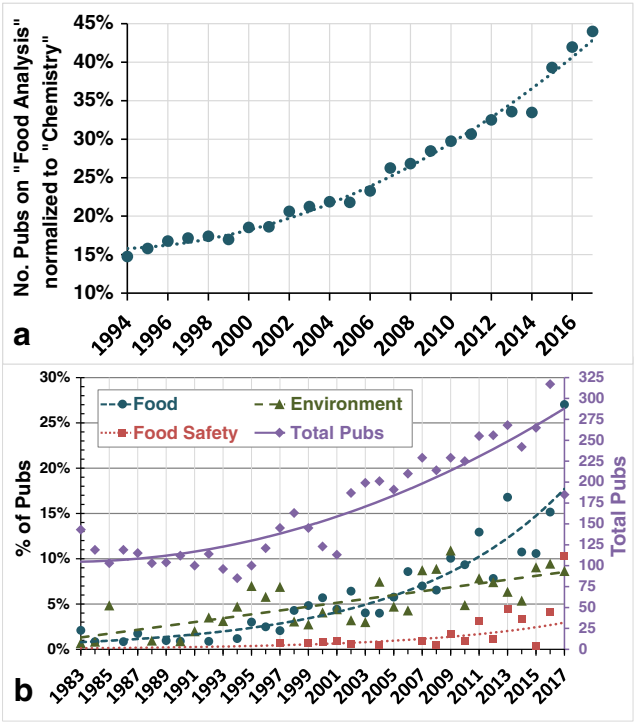



**Fig. 1** **a** Annual number of publications on the topic "food analysis" relative to "chemistry" in the Web of Science core collection database; **b** number of publications and their percentage on the given topics in *Trends Anal. Chem.* over time

concern derived from scientific risk assessments [7], consisting of As, Hg, Pb, mycotoxins, bio-security agents, pesticides, veterinary drugs, dioxins, PCBs, acrylamide, melamine, perchlorate, ethyl carbamate, and furan. The ESM contains additional discussion and review with citations on the analysis of those contaminants.

The monitoring of chemical contaminants in food is much too large of a subject to encompass in detail, thus in this critical review nearly all citations consist of other reviews. In keeping with the growth in no. pubs overall, the number of review articles on food safety analysis has also greatly increased from ~2/year in the early 1990s to 150 in 2017, according to Web of Science. However, few of these can match the excellent reviews by Borchers et al. [8] on food safety and Krska et al. [9] with respect to trends. This critical review is intended to supplement and update previous reviews [10], but with greater emphasis on general analytical trends and research gaps in the food safety arena. Otherwise, topical reviews about analysis of individual types of contaminants not listed on the FDA website [7] include: PAHs [11], flame retardants [12–15], seafood toxins [15–18], plastics [19–21], detection of nanoparticles [22–24], GMOs [25–27], allergens [8, 28, 29], nitrates [30], nitrosamines [31], radionuclides [32–34], food additives [35, 36], BPA and other food packaging migrants [37–41], perfluorinated compounds [42–44], and other emerging contaminants [45–47].

## Analytical techniques for contaminants in food

In an assessment of analytical trends in monitoring food contaminants, Table 2 shows results from a similar Web of Science search in Feb 2018 as shown in Table 1. In the case of Table 2, the first row lists the no. pubs arising from a broad search of: (residue or contaminant or adulterant or toxin or toxicant or pollutant) and (food or vegetable or fruit or meat or honey or milk or cereal or grain or meat or fish or seafood or feed) and (analysis or detection or determination or quantitation or quantification). Each subsequent row reflects a subset within the no. pubs in the first row ("+" represents "and"), and rows starting with "+ "" +" mean that a further subset of a previous row's search term is provided, such as "Liquid chromatog… or HPLC" in rows 4–8. The rates of growth for each row in Table 2 are relative to the first row in the same column.

The rows in Table 2 are generally grouped into categories of (a) chromatography, (b) mass spectrometry, (c) sample preparation, (d) data management, (e) bio-based methods, (f) general techniques, and (g) atomic analysis, which are each listed in order of the no. pubs during 2012–2017 for the top search term within the group. Despite the imperfect and overlapping nature of some of the search terms, much interesting information can be gleaned from the results.

## Chromatography

Foremost, a steady 36–37% of pubs in the field since 1994 have involved chromatography, with liquid chromatography (LC) growing from 25% of the pubs in 1994–1999 to 28% in 2012–2017. Meanwhile, the share of pubs involving gas chromatography (GC) slightly decreased from 13 to 11% recently after peaking at 14% during 2000–2005. Furthermore, thin-layer chromatography (TLC) has decreased from 1.8 to 0.8% as a share of pubs about chromatography in the field since the 1990s. Despite such trends, (ultra-)TLC continues to have parallel sample throughput advantages over column chromatography which makes it very useful when it meets application needs [48, 49]. Ion chromatography also listed in Table 2 maintains niche applicability [50] with less than average growth in the food safety analysis arena (reflecting the type of applications shown in Table 1).

According to Table 2, supercritical fluid chromatography (SFC) is another technology that appears to be languishing along with supercritical fluid extraction (SFE) with a consistent combined average of ~ 17 pubs/year since 1994 in the field. However, SFC has always had an advantageous capability to separate both LC- and GC-amenable analytes in the same analysis [51]. The group of Bamba has published exceptional results using SFC using modern mass spectrometry

**Table 2** Number of publications (pubs) found searching the Web of Science core database in Feb 2018 using given search terms and years

| Search terms | No. pubs 1994–1999 | No. pubs 2000–2005 (rel. growth vs. 1994–1999) | No. pubs 2006–2011 (rel. growth vs. 2000–2005 | No. pubs 2012–2017 (rel. growth vs. 2006–2011) | Rel. growth 2012–2017 vs. 1994–1999 (%) |
|---|---|---|---|---|---|
| Search terms listed in table footnote | 3819 | 5709 (49%)[a] | 10,500 (84%)[a] | 16,991 (62%)[a] | 345[a] |
| (a) Chromatography | | | | | |
| + Chromatog… | 1358 | 2041 (1%) | 3877 (3%) | 6089 **(−3%)** | 1 |
| + ("Liquid chromatog…" or HPLC) | 949 | 1476 (4%) | 2934 (8%) | 4748 (0%) | 12 |
| + "" + "Mass spectr…" | 263 | 767 (95%) | 2166 (54%) | 3620 (3%) | 209 |
| + "" + *("Tandem MS" or MS/MS or "triple quadrupole")* | 28 | 215 *(414%)* | 885 *(124%)* | 1833 (28%) | *1371* |
| + "" **not "mass spectr…"** | 686 | 709 **(−31%)** | 763 **(−41%)** | 1083 **(−12%)** | **−65** |
| + "" + HILiC | 0 | 2 | 37 *(634%)* | 52 (19%) | N/A |
| + "" + Monolithic | 0 | 2 | 29 *(688%)* | 45 **(−4%)** | N/A |
| + *(UHPLC or UPLC)* | 0 | 0 | 148 | 564 *(135%)* | N/A |
| + **"Gas chromatog…"** | 511 | 815 (7%) | 1422 **(−5%)** | 1940 **(−16%)** | **−15** |
| + "" + "Mass spectr…" | 245 | 531 (45%) | 1130 (16%) | 1648 **(−10%)** | 51 |
| + "" + *("Tandem MS" or MS/MS or "triple quadrupole")* | 8 | 77 *(544%)* | 254 (79%) | 497 (21%) | *1296* |
| + "" **not "mass spectr…"** | 266 | 284 **(−29%)** | 292 **(−44%)** | 292 **(−38%)** | **−75** |
| + "" + "Two-dimensional" | 3 | 7 (56%) | 28 *(117%)* | 36 **(−21%)** | 170 |
| + **(TLC or "thin-layer chromatog…")** | 67 | 99 **(−1%)** | **93 (−49%)** | 135 **(−10%)** | **−55** |
| + **Supercritical** | 94 | 103 **(−27%)** | 104 **(−45%)** | **103 (−39%)** | **−75** |
| + **"Ion Chromatog…"** | 12 | 19 **(−8%)** | 32 **(−8%)** | 45 **(−13%)** | **−16** |
| (b) Mass spectrometry | | | | | |
| + "Mass spectr…" | 495 | 1201 (62%) | 3191 (44%) | 5523 (7%) | 151 |
| + "" Not chromatog… | 65 | 118 (21%) | 354 (63%) | 816 (42%) | 182 |
| + "" + "*High resolution*" | 18 | 31 (15%) | 97 (70%) | 383 **(144%)** | 378 |
| + "" + Ambient | 5 | 5 **(−33%)** | 43 *(368%)* | 59 **(−15%)** | 165 |
| + *(Orbitrap or "orbital ion")* | 0 | 0 | 34 | 174 *(216%)* | N/A |
| + *("Q/TOF" or "quadrupole time-of")* | 1 | 9 *(502%)* | 45 *(172%)* | 122 (68%) | *2642* |
| + MALDI | 3 | 38 *(747%)* | 68 **(−3%)** | 118 (7%) | 784 |
| + **Ion trap not (Orbi… or "linear ion")** | 25 | 71 (90%) | 114 **(−13%)** | **88 (−52%)** | **−21** |
| + *(IMS or "ion mobility")* | 4 | 10 (67%) | 15 **(−18%)** | 52 *(114%)* | 192 |
| + "Linear ion trap" | 0 | 1 | 16 *(770%)* | 46 (78%) | N/A |
| (c) Sample preparation | | | | | |
| + (SPE or "solid-phase extraction") | 247 | 460 (25%) | 1223 (45%) | 2031 (3%) | 85 |
| + "" + *(d-SPE or dispersive)* | 0 | *9* | 119 *(619%)* | 415 *(116%)* | N/A |
| + *QuEChERS* | 0 | 3 | 187 *(3289%)* | 976 *(223%)* | N/A |
| + *(MIP or imprinted)* | 3 | 26 *(480%)* | 113 *(136%)* | 333 (82%) | *2395* |
| + (SPME or "solid-phase microextraction") | 6 | 92 *(926%)* | 238 (41%) | 294 **(−24%)** | *1001* |
| + "*Liquid-liquid microextraction*" | 0 | 0 | 35 | 249 *(340%)* | N/A |
| + Microwave | 26 | 63 (62%) | 140 (21%) | 190 **(−16%)** | 64 |
| + ("Accelerated solvent" or "pressur… liquid extraction") | 6 | 38 *(324%)* | 147 *(110%)* | 150 **(−37%)** | 462 |
| + **("Gel-permeation" or "size-exclusion")** | 73 | 86 **(−21%)** | 159 (1%) | **129 (−50%)** | **−60** |
| + (OASIS or HLB) | 2 | 28 *(837%)* | 115 *(123%)* | 129 **(−31%)** | *1350* |
| + "*Ionic liquid*" | 0 | 0 | 21 | 121 *(256%)* | N/A |
| + (MSPD or "matrix solid-phase disp…") | 21 | 77 *(145%)* | 111 **(−22%)** | 114 **(−37%)** | 22 |
| + Ultrasonic | 12 | 18 (0%) | 52 (57%) | 106 (26%) | 99 |
| + ("Graphit… carbon black" or carbonX) | 5 | 12 (61%) | 41 (86%) | 68 (2%) | 206 |
| + *(Zircon… or ZSep or "Z-Sep")* | 5 | 7 **(−6%)** | 13 (1%) | 50 *(138%)* | 125 |
| + (…WCNT or "carbon nanotube") | 0 | 1 | 17 *(824%)* | 38 (38%) | N/A |
| + (SBSE or Twister) | 0 | 3 | 20 *(262%)* | **16 (−51%)** | N/A |
| (d) Data management | | | | | |
| + Targeted | 143 | 316 (48%) | 889 (53%) | 1856 (29%) | 192 |
| + (Non-targeted or untargeted) | 0 | 0 | 8 | 64 *(394%)* | N/A |
| + (Screening or qualitative) | 360 | 553 (3%) | 1101 (8%) | 1777 (0%) | 11 |
| + Validation | 81 | 251 *(107%)* | 876 (90%) | 1628 (15%) | 352 |
| + **("Quality control" or "Q… assurance")** | 63 | 78 **(−17%)** | 147 (2%) | 251 (6%) | **−10** |
| + Chemometric… | 12 | 29 (3%) | 70 (8%) | 193 (0%) | 261 |
| + ("Standard reference" or "certified reference" or "reference material") | 32 | 34 **(−29%)** | 72 (15%) | 156 (34%) | 10 |
| + "Proficiency test…" | 4 | 9 (51%) | 39 *(136%)* | 80 (27%) | 350 |
| + "Measurement uncertainty" | 0 | 10 | 39 *(112%)* | 66 (5%) | N/A |
| (e) Bio-based methods | | | | | |
| + **Immuno…** | 498 | 673 **(−10%)** | 1290 (4%) | 1839 **(−12%)** | **−17** |
| + (PCR or "polymer… chain reaction") | 194 | 452 (56%) | 943 (13%) | 1278 **(−16%)** | 48 |
| + (Multiplex or "multi-plex") | 17 | 83 *(227%)* | 182 (19%) | 348 (18%) | 360 |
| + **Bioassay** | 97 | 183 (26%) | 306 **(−9%)** | 328 **(−34%)** | **−24** |
| + Aptamer | 0 | 1 | 16 *(770%)* | 174 *(572%)* | N/A |
| + "Quantum dot" | 0 | 0 | 25 | 143 *(253%)* | N/A |
| + **Immunomagnetic** | 16 | 36 (51%) | 38 **(−43%)** | 52 **(−15%)** | **−27** |
| (f) General techniques | | | | | |
| + (Sensor or sensing) | 33 | 102 (107%) | 280 (49%) | 697 (54%) | 375 |
| + (Fluoresc… or luminesc… or phosphoresc…) not "chromatog… | 81 | 156 (29%) | 302 (5%) | 576 (18%) | 60 |
| + Electrophoresis | 105 | 208 (33%) | 430 (12%) | 553 **(−21%)** | 18 |

**Table 2** (continued)

| Search terms | No. pubs 1994–1999 | No. pubs 2000–2005 (rel. growth vs. 1994–1999) | No. pubs 2006–2011 (rel. growth vs. 2000–2005 | No. pubs 2012–2017 (rel. growth vs. 2006–2011) | Rel. growth 2012–2017 vs. 1994–1999 (%) |
|---|---|---|---|---|---|
| + (Infrared or "infra-red") | 34 | 67 (32%) | 179 (45%) | 547 (89%) | 262 |
| + Electrochemical | 53 | 68 **(−14%)** | 190 (52%) | 461 (50%) | 96 |
| + ("Nuclear magnetic resonance" or NMR) | 77 | 110 **(−4%)** | 237 (17%) | 353 **(−8%)** | 3 |
| + *Raman* | 6 | 14 (56%) | *52 (102%)* | *315 (274%)* | *1080* |
| + **(Automat… or robot…)** | 107 | 124 **(−22%)** | 211 **(−7%)** | 272 **(−20%)** | **−43** |
| + **Derivatization** | 119 | 120 **(−33%)** | 214 **(−3%)** | 255 **(−26%)** | **−52** |
| + Laser | 30 | 65 (45%) | 128 (7%) | 214 (3%) | 60 |
| + (Lipidomic or metabolomic or proteomic) | 0 | 13 | 79 *(230%)* | 184 (44%) | N/A |
| + "Surface plasmon" | 9 | 48 *(257%)* | 103 (17%) | 144 **(−14%)** | 260 |
| + **Absorbance** | 28 | 41 **(−2%)** | 52 **(−31%)** | 84 (0%) | **−33** |
| + "**Flow injection**" | 22 | 41 (25%) | 67 **(−11%)** | 70 **(−35%)** | **−28** |
| + Cytometry | 10 | 16 (7%) | 45 (53%) | 65 **(−11%)** | 46 |
| + Hyperspectral | 0 | 3 | 22 *(299%)* | 61 (71%) | N/A |
| + Microfluidic | 0 | 4 | 25 *(240%)* | 60 (48%) | N/A |
| (g) Atomic analysis | | | | | |
| + "Atomic absor…" | 32 | 36 **(−25%)** | 74 (12%) | 150 (25%) | 5 |
| + (ICP or "inductively-coupled") + (ICP-MS or "mass spectro…") | 10 | 25 (67%) | 59 (28%) | 101 (6%) | 127 |
| + **(ICP-AES or ICP-OES or "atomic emission" or "optical emission")** | 22 | 30 **(−9%)** | 46 **(−17%)** | 77 (3%) | **−21** |
| + (Atomic fluoresc…") | 2 | 10 *(234%)* | 13 **(−29%)** | 16 **(−24%)** | 80 |

Entries set in italics indicate highest growth topics, and entries set in bold indicate topics growing at a slower rate than the following search terms in the first row: (residue or contaminant or adulterant or toxin or toxicant or pollutant) and (food or vegetable or fruit or meat or honey or milk or cereal or grain or meat or fish or seafood or feed) and (analysis or detection or determination or quantitation or quantification)

[a] Actual growth results are shown to which other rates of growth are normalized

(MS) tools to overcome some of the past detection limitations [52–54]. Shimadzu, Waters, Agilent, and other companies manufacture updated SFC instruments, and perhaps SFC will become more prominent in the future to reduce instrument, lab space, and operational costs compared to separate LC and GC analyses that cover the same scope of analytes.

Out of curiosity, the no. pubs of three often touted developments in LC are tracked in Table 2: ultrahigh-performance liquid chromatography (UHPLC or UPLC) [55], monolithic columns [56], and hydrophilic interaction liquid chromatography (HILiC) [57]. UHPLC has exceptional advantages in speed and/or selectivity over HPLC, and since its commercial introduction by Waters in 2004, UHPLC has currently grown to > 12% of LC pubs in the field. This share is actually higher because UHPLC is now sometimes assumed when LC is mentioned. However, monolithic columns and HILiC have not been the subject of nearly as many pubs as UHPLC.

Those two topics follow a relatively frequent pattern observable in Table 2 in which an initial surge of papers takes place soon after a technique is introduced, then growth subsides. If the new technique is shown to work better than alternatives in food safety analysis applications, then the greater growth continues, such as in the case of UHPLC. But if the technique does not provide robustness, then it will not be used no matter what other advantages it may possess. Similarly, if "good enough" alternatives are available with practical advantages in sample throughput, ease of use, and cost, then the more practical technique will be used more often than a less practical one that is "better than good enough."

## Mass spectrometry

MS is the marquee example of a technique that has been demonstrated to be useful leading to high sustained growth. The no. pubs involving MS grew from 13% of pubs in row 1 of Table 2 during 1994–1999 to 33% during 2012–2017. MS is coupled with chromatography in 85–90% of the pubs involving MS, and as shown in italicized text in Table 2, the most growth even within chromatography since at least the mid-1990s has involved MS, particularly triple quadrupole tandem MS/MS. As shown in bold text in Table 2, the rates of growth in LC and GC not involving MS has been ~ 70% less than growth in food safety analysis overall. Within the subset of "chromatography," Fig. 2 indicates how LC has grown from 70% of papers in 1994–1999 to 78% in 2012–2017, with LC-MS growing from 28 to 76% of those publications within the same time-frame. In the case of the LC-MS subset, the share of LC-MS/MS grew from 11 to 51%, which is surely much higher because MS/MS has become so commonplace in LC that the descriptor "LC-MS" may often be assumed to actually entail tandem MS using electrospray ionization.

Even more dramatic growth in the percent of pubs involving GC-MS and GC-MS/MS occurred within the GC subset. As can be surmised by the converging solid and dashed blue lines in Fig. 2, the GC-MS subset grew from 48 to 85% of total pubs on GC given in Table 2 since 1994–1999, and the share of the GC-MS/MS subset of pubs grew from 3 to 30% among GC-MS pubs in the same time-frame. These trends

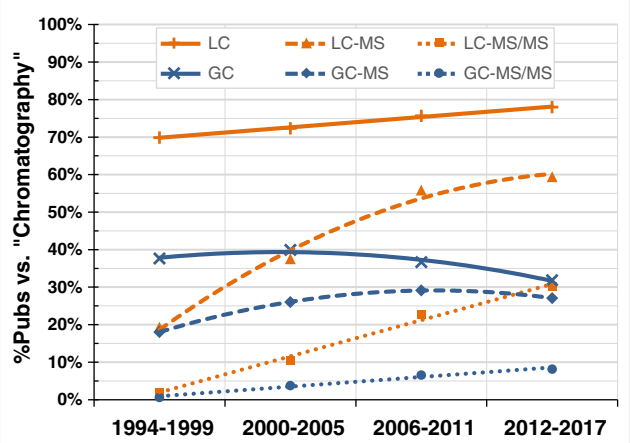



**Fig. 2** Percent of LC- and GC-((MS)/MS) publications with respect to publications involving chromatography over time according to Web of Science searches in Table 2

correspond closely with the commercial introduction of several bench-top triple quadrupole MS/MS instruments first in LC starting in the 1990s followed by GC in the 2000s. In conjunction with the plots shown in Fig. S2 (see ESM), the use of MS coupled with inductively coupled plasma (ICP) analysis of metals also began increasing dramatically when commercial instrumentation became available.

Indeed, the trends in pubs using the techniques and technologies shown in Table 2 track closely with the introduction and/or termination of commercial products. For example, commercial ion trap MS instruments capable of MS/MS have been available in both LC and GC since the late 1980s, but wider manufacture of these instruments ceased soon after ThermoFisher introduced orbital ion trap (Orbi) technology starting in 2005 and Agilent bought Varian in 2009. Bruker still markets ion trap MS instruments, and Sciex manufactures hybrid triple quadrupole instruments employing linear ion traps, but independent of the pros and cons of the technology itself relative to other approaches, researchers in the field are highly dependent on commercial vendors, patents, and particular products. The rise and decline in traditional ion trap MS can be observed in Table 2 under the MS category, which coincides with rapid growth in pubs using high-resolution (HR) time-of-flight (TOF) or Orbi technologies. Similarly, the highly advantageous MS concept based on supersonic molecular beams [58–60], has not been adequately commercialized, which has precluded interested analytical chemists from evaluating the approach.

Just as GC-MS is making a transition into GC-MS/MS, at least for analysis of targeted analytes, hybrid quadrupole-HRMS (Q/TOF or Q/Orbi) are gaining prominence in LC-MS food safety applications due to the greater selectivity of HRMS and its additional non-targeted monitoring capability [61–63]. HRMS only constituted ~ 3% of MS pubs in the field from 1994 to 2011 but jumped to 7% from 2012 to 2017. First-generation GC-Q/TOF and GC-Q/Orbi [64–66] commercial instruments have been recently introduced, which may lead to similar future gains in GC as it has in LC. Capital expense of instruments used to be a greater impediment in the food safety analysis arena, but food trade is so important and lucrative that many of the top government and contract labs can afford to purchase the newest instruments despite the cost. Instrument companies continue to consolidate, including broader incorporation of instrumentation with sample prep, reference standards, methods, consumables, software, training, and other means that has made them proactively integral in the food safety analysis arena.

Despite the growing role of the instrument manufacturers, their products must prove to be useful in validation trials among multiple labs to be successful. Table 2 shows how "ambient MS" outpaced average growth by 368% in the 2006–2011 timeframe soon after desorption electrospray ionization (DESI) [67], direct analysis in real time (DART) [68], atmospheric solid analysis probe (ASAP), and other similar direct ionization MS techniques were introduced, but in 2012–2017, 15% less than average relative growth in no. pubs took place. Many labs obtained ambient MS instruments to test their potential for high-throughput monitoring of contaminants with minimal sample prep and no chromatography, but despite publications by the FDA showing promise [69], the approach did not meet real-world monitoring demands in a field trial for pesticide screening. Analytical scope was too narrow and rates of false positives and negatives were too high for routine implementation.

The need for rapid and reliable field screening with wide analytical scope remains. The verdict is still pending on newer approaches, and it would be interesting to see the trends in another 6 years. For example, ion mobility spectrometry (IMS), including stand-alone devices, field asymmetric (FA)IMS in the source, or a hybrid MS-IMS-MS version within the analyzer, has recently seen a large increase in pubs [70].

Matrix-assisted laser desorption ionization (MALDI), typically coupled with TOF, is another type of approach that went through an initial surge in pubs 6 years earlier than ambient MS. It is mainly used for large molecule analysis, such as allergens and biomarkers for microbial pathogens [71–74], thus has a different niche in food safety applications than analytical techniques for small molecules. MS-based imaging using MALDI and other means, such as rapid evaporative ionization (REI)MS [75] will continue to grow as data handling technologies and techniques improve, but it remains to be seen if imaging will be useful in food safety analysis. However, laser ablation electrospray ionization (LAESI) for MS-based analysis of samples contained in 96-well plates has shown potential real-world applicability in high-throughput analysis of small molecule contaminants in food [76].

## Sample preparation

The next section of Table 2 in terms of no. pubs involving food safety analysis relates to sample prep, which mainly consists of extraction and cleanup. Of course, nearly all methods and pubs entail some form of sample prep, often even in the direct analysis of samples, but authors do not always highlight this critical aspect in the overall analysis for it to appear as a topic in literature searches. Raynie [77] reviewed trends in sample prep based on biennial surveys of *LCGC* readers since 1991, which provides an interesting comparison of surveyed usage of different sample prep techniques vs. pubs on the topic. In short, only solid-phase microextraction (SPME) appeared in pubs at a higher relative rate (> 3-fold) than actual usage according to survey respondents. Otherwise, the usages of different sample prep techniques listed in Table 2 were under-highlighted in the scientific literature (which also likely holds true for other established methods).

**Solid-phase extraction** As shown in Table 2, solid-phase extraction (SPE) dominates sample prep techniques in the analysis of food contaminants, and mention of SPE in the food safety analysis literature has doubled from 6% of pubs in 1994–1999 to 12% of pubs in 2012–2017. Unlike water analysis in which SPE actually serves to "extract" the analyte(s) from the sample, SPE in food analysis is mostly used for cleanup of initial liquid extracts. SPE persists as the default approach for cleanup in food analysis, and dozens of vendors sell SPE products containing a wide variety sorbents and formats, which is a very rich area of study and development [78, 79]. So many options of formats, sorbents, and solvents exist among the myriad analytes, matrices, and applications are possible that it is virtually impossible to sufficiently review them. Even a company's primer about SPE requires 212 pages [80]. Table 2 tracks a few sorbents of interest in the literature, such as "Oasis or HLB" polymers [81], carbons [82–85], and zirconia [86]. Each so far follows the common pattern of an initial surge in pubs followed by relatively flat or decreasing growth, albeit unpublished usage continues.

Traditionally, SPE involves sorbent(s) packed into cartridges, and cleanup is accomplished by retention of the analytes in the extracts by the sorbent, in which case the matrix components would ideally be unretained and washed away. Then, a different solvent would be used to elute the analytes from the cartridge, serving as the final extract for analysis. However, this multi-step approach is rather inefficient, and many diverse analytes in multi-class, multi-residue GC- and LC-MS analysis methods could not be retained and/or eluted using the same sorbent/solvent combinations. Since foods tend to consist of the same major components (water, carbohydrates, lipids, and proteins), it is often much more efficient and effective to design sample prep methods to selectively retain co-extracted food matrix components (e.g., fatty acids, chlorophyll, sterols) onto sorbents (i.e., chemical filtration), rather than retaining then eluting the analytes.

In the chemical filtration approach, the extract serves as the SPE elution solvent, and the sorbent no longer needs to be contained in a cartridge. Along that line, the dispersive (d-)SPE format involves adding cleanup sorbent(s) to the extract and then separating the loose material by centrifugation, filtration, magnetism [85, 87], flow, and/or other means. d-SPE can be conducted conveniently in a vial, tube, syringe, pipette tip [88], or other novel format. The concept of d-SPE has always been an option in cleanup of extracts, but it is less effective than column-bed adsorption, thus d-SPE was rarely useful before the commercial introduction of bench-top GC- and LC-MS instruments. These broadly applicable, selective, sensitive, qualitative, quantitative, and reliable means of analysis require less cleanup than previous detection methods. The merging of multiple methods into a single method to cover the same analytes is the best way by far to lower costs and ease lab operations, and use of MS detection in multi-class, multi-residue methods lowers overall costs despite the initial capital expense for instrumentation [5]. For MS-based analysis, multi-class, multi-residue extraction methods must provide a wide analytical scope, which inherently sacrifices a degree of cleanup, thus d-SPE is often tailored to provide "just-enough" cleanup.

**QuEChERS** During the time of widespread transition to MS detection in 2003, Anastassiades et al. [89] introduced the "quick, easy, cheap, effective, rugged, and safe" (QuEChERS) approach, which included d-SPE to streamline sample prep. Table 2 shows how QuEChERS and d-SPE have grown rapidly in the food safety analysis field in the 15 years since their introduction. Initially devised for analysis of pesticide residues in fruits and vegetables, QuEChERS has grown to encompass a widening range of applications, as described in recent reviews [90–92]. One important advance among several in the QuEChERS approach involves the development and multi-laboratory validation of a single method, known as the quick polar pesticides (QuPPe) method, for analysis of several pesticides previously analyzed only in single-analyte methods (e.g., glyphosate, ethephon, mepiquat, etc.) [93].

Analytical chemists almost universally revile sample prep and seek to minimize it both during method development and routine analyses. QuEChERS is one of the current sample prep options that helps analysts to avoid what is felt to be an otherwise onerous task. Basically, QuEChERS is "just enough" sample prep in a centrifuge tube to cover a wide range of analytes amenable to both GC and LC analysis (or the full range in SFC) without leading to excessive instrument maintenance problems. QuEChERS is simultaneously: a fixed set of thoroughly validated methods with commercial kits

available from dozens of vendors worldwide and a highly flexible sample prep approach that can be readily adapted to work in many applications. Either way, very little time, cost, or effort is involved for a lab to try QuEChERS for a particular application to see how well it works.

Previous methods generally required many steps, including large volume solvent transfers, exchanges, and evaporation, and a lot of lab space, reagents, glassware, manual labor, and other inconveniences. Sufficient selectivity in the initial extraction is commonly achieved in QuEChERS by shaking with acetonitrile, which minimizes co-extraction of fat, protein, and sugars, followed by its partitioning (or not) from water in moist samples (or added water for dry samples) using salt-out partitioning, or other means such as refrigeration [94]. The selectivity of extraction can be tailored by use of different solvent(s), salts, and their relative amounts in the tube [89]. If needed, further cleanup of extracts can be conducted using (d-)SPE or many other options.

**Solid-phase microextraction** Since SPME was introduced by Arthur and Pawlisyn in 1990 [95], it has been a subject of > 16,300 pubs, typically involving the GC analysis of (semi-)volatiles in a variety of applications. For comparison, Fig. 3 plots the annual no. pubs involving SPME vs. "QuEChERS or d-SPE" and citations to the introductory article according to Web of Science. No discussion of sample prep can be complete without mentioning SPME, but despite its scientific and commercial successes, the initial spike and declining relative growth shown in Table 2 indicates how SPME is not as readily applicable to food safety analysis as QuEChERS and d-SPE. SPME is highly applicable to qualitative food analysis, including authenticity testing, but it is not easily applied in quantitative analysis due to incomplete extractions often affected by matrix components and environmental parameters. Furthermore, SPME is not particularly fast, rugged, or cheap, which is also why it is not widely used in food safety monitoring even for volatiles such as ethyl carbamate and nitrosamines. However, SPME has been generally adopted in furan analysis, as reviewed in the ESM. The commercial exclusivity of SPME products to Supelco (part of Millipore-Sigma) has expired, and perhaps a variety of concepts presented in recent reviews [96, 97] will spur adaptations and higher relative growth of SPME in additional food safety applications.

**Liquid-liquid microextraction** Liquid-liquid partitioning (or extraction) of the initial extracts to separate matrix components from analytes has been a common approach in sample prep since the beginning of analytical chemistry. Miniaturization has also been a continuing general trend in technological development, including sample prep in analytical chemistry [98]. Thus, more sensitivity and selectivity provided by modern instruments and unique solvents, such as ionic liquids [99, 100], has led to the development and wider usage of liquid-liquid microextraction (LLME). Kokosa [101] has written an excellent review of solvent microextraction, which encompasses its many variations and terminology.

LLME methods have many choices of immiscible solvent combinations with a liquid sample (water in the case of foods) or initial organic solvent sample extract, which can provide a degree of selectivity to separate analytes from matrix components prior to analysis. As in SPME, a major advantage is that the analytes are typically highly concentrated from the milliliter sample volume into the microliter partitioning solvent (or absorption) volume. Another option is to combine use of salts and/or d-SPE with LLME to yield greater flexibility and selectivity [102, 103], which is essentially micro-QuEChERS. LLME can be easily automated using common autosampler robotic systems, but this is also the case for SPME and QuEChERS [86, 104].

Raynie and Qiu [105] reviewed a variety of sample prep methods listing their advantages and disadvantages, and conceptually, LLME tends to be more useful for a narrow range of analytes that strongly partition into the particular immiscible solvent, such as metals into ionic liquids [99–101] or lipophilic organics into non-polar solvents [106]. This serves a different and overlapping niche with SPME, which has some advantages in the analysis of (semi-)volatiles. Meanwhile, QuEChERS is intended to cover a broad scope of analytes in the same procedure.

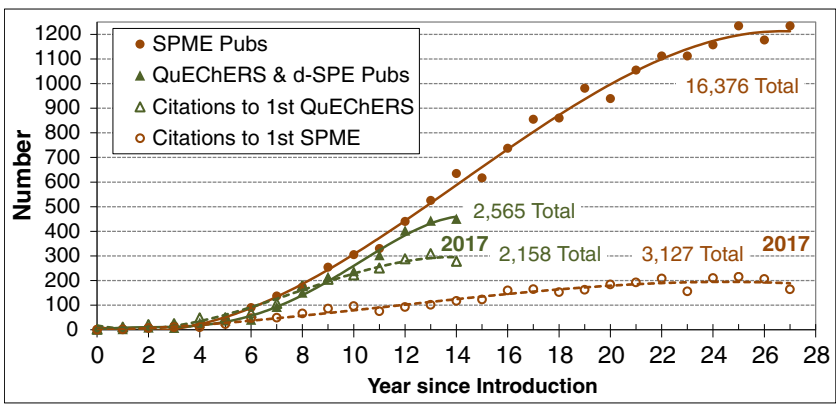



**Fig. 3** Growth in the scientific literature according to Web of Science searches of SPME [95] and QuEChERS [89] techniques for sample preparation since their introduction (as cited)

**Sampling considerations** An inherent problem with miniaturization of any method in food safety analysis is that the test sample portion must be representative of the original bulk sample. Lehotay and Cook [107] reviewed the importance of this need to meet regulatory purposes (the same as in any application). If a microextraction method yields an accurate result for a test portion that does not acceptably reflect the actual sample for the intended purpose, then the result is worthless at best and deceptive at worst. The amount of food that can be sampled is rarely limiting, and actually, the sample is often so overwhelming (such as ship, train, or truck containers, agricultural fields, silos, vats, flocks, etc.) that rigorous statistical sample collection methods must be used to obtain kilograms bulk sample portions [108, 109].

Furthermore, this collected sample must be comminuted to provide a test portion that reliably yields a meaningful result. Very few food safety applications listed in Table 1 require knowledge of analyte concentrations in individual food items, or on their surfaces, but an inordinate number of researchers propose sampling methods that either ignore or misconstrue real-world needs. Others may justify their novel analytical approaches by proposing new purposes that cater to consumer fears or political trade situations rather than actual food safety needs.

Ironically, truly novel sample processing and subsampling technologies and techniques that may reliably yield exceptionally small representative test portions for use in automated, high-throughput analyses are rarely investigated or published. For example, Riter et al. [110] studied cryomilling to provide sufficiently representative test portions as small as 75 mg, but only a few analytes and food commodities were evaluated, and although the approach worked well in several cases, it was still rather time-consuming, tricky to conduct, expensive, and not universally acceptable in all analyte/matrix pairs.

A technological breakthrough in the performance and efficiency of sample processing is definitely needed for many applications, not just food safety, which would expand the real-world applicability of miniaturized methods in general. Otherwise, nearly all research involving micromethods have no practical value in food safety applications. Despite its predominant priority, the current climate in which researchers, funding sources, and journal gatekeepers do not value this type of "mundane" research provides little incentive for investigators to even propose working on the topic. Perhaps no efficient solution to the problem exists, thus it is easier to ignore the challenge rather than fail in trying to overcome it. In the meantime, investigators must honestly recognize and accept the current reality, and journal reviewers should at least require a statement to this effect in all applicable pubs.

**Other sample prep techniques** Others have already reviewed common sample prep methods in food safety analysis [105, 111], and Table 2 shows the relative popularity of the different methods over time in the scientific literature. Microwave-assisted (solvent) extraction (MAE or MASE) [111, 112], pressurized liquid or accelerated solvent extraction (PLE or ASE) [113], matrix solid-phase dispersion (MSPD) [114], and stir-bar sorptive extraction (SBSE) or Twister [115] in food applications each went through periods of initial higher relative growth followed by less growth more recently as they are implemented (or not) more routinely. Each has its niche applications, such as MAE for extraction of metals, PLE for strongly bound matrix-analyte situations (e.g., polar pesticides in dry feeds), and SBSE for beverages. Interestingly, growth in publications calling attention to "old-fashioned" ultrasonic extraction [111, 116] continues to steadily outpace those more modern approaches (see Table 2).

A major concern among regulators and analytical chemists in the field is that an extraction method yields 100% analyte recoveries for spiked samples but only partial extraction of the analyte(s) incurred in actual samples. For this reason, extraction methods must be shown for regulatory and drug/pesticide registration purposes to achieve acceptably high recoveries in real samples. This is known as "total extractability," which involves radiolabeling in the most rigorous assessments, but use of incurred and/or reference materials to assess and compare different conditions, repeated extractions, and comparison of methods can also be done. Journal reviewers should be aware of this concern when judging the acceptability of new extraction methods, which also relates to the discussion of acceptable data management practices later in this review.

Unlike LLME, SPME, and QuEChERS, a frequent drawback when using more exhaustive extraction techniques, such as blending, ultrasonics, MAE, or PLE, is that extracts typically need greater cleanup. Lipids tend to cause the most difficulty due to their potential to foul analytical columns and instruments, and extra care must be taken with fatty foods to avoid this problem. In particular, separation of lipophilic analytes from co-extracted fat can be notoriously difficult [117]. For example, analysis of dioxins (polychlorinated dibenzo-*p*-dioxins and dibenzofurans) often takes many hours and much solvent using multi-layer silica columns to provide a final extract reasonably free of lipids to meet commonly needed picograms per gram detection limits [118]. Use of more selective extraction solvents and/or sorbents in PLE (e.g., in-vessel PLE/MSPD, in-line PLE-SPE, or post-PLE d-SPE) can efficiently provide the requisite high recoveries in sufficiently clean final extracts [119], but this kind of approach would only be used if easier options do not meet analytical needs. The domination of MS-based analysis has led to an eruption in the commercial availability of isotopically-labeled reference standards for use as internal standards to improve quantification by MS analysis [120] even when analyte recoveries are not 100% (e.g., SPME), but total analyte extractability remains paramount to obtain accurate results for real samples.

In a possible alternative to gel-permeation chromatography (GPC), a new commercial product known as enhanced-matrix removal of lipids (EMR-L) has been demonstrated to separate many food contaminants from co-extracted lipids [121]. EMR-L entails a unique size-dependent and adsorption mechanism in aqueous solvent solutions to trap and retain long-chain hydrocarbons, such as fatty acids and other lipids. Due to an extra post-cleanup partitioning step needed in the d-SPE format to remove the dissolved EMR-L material, a more streamlined option using the traditional cartridge SPE format has been introduced [122]. It is too early to assess the impact of EMR-L, but it is likely to follow the pattern of Oasis and Z-Sep products observable in Table 2.

Molecularly imprinted polymers (MIPs) is the only remaining row in the sample prep section of Table 2 that has yet to be discussed. Although MIP was first mentioned in 1985 [123], it took several years to develop. The concepts and applications of MIPs in food and other applications have been reviewed elsewhere [124–126]. In the food safety arena, no. pubs involving MIPs grew from about 4/year during the early 2000s to nearly 20 pubs/year from 2006 to 2011, to currently > 55 pubs/year, which places it among the highest growing techniques listed in Table 2. As in the case of SPME, the original exclusive availability of commercial MIP sorbents with a single vendor may have limited diversity and availability of products, but partnerships with larger chemical supplies companies starting in 2010 led to an expansion in applications (and pubs) that is likely to continue. The easier use and lower cost of MIPs rather than antibodies in sensor-based nanotechnology approaches [124] has also contributed to the growth of pubs, but the problems remain as mentioned above with respect to sample sizes and general applicability for real-world implementation.

A major limitation with MIPs originate with its major strength as being selective for targeted (imprinted) analytes, much akin to antibodies (but typically with much weaker interactions). An additional problem is that the imprinted analyte has to be thoroughly removed from the MIP, but the unwashed analyte may still be detected in ultra-trace methods leading to false positives. Therefore, it is better conceptually in many food safety applications to imprint the polymeric sorbent with matrix components for their removal from extracts, as in chemical filtration by (d-)SPE, rather than retain analytes followed by elution (which can be difficult if its binding with the MIP is actually *too* strong).

## Data management

For lack of a better term, data management in the context of this critical review refers to signal processing (e.g., peak integration), data handling and mining, software, statistical treatments (e.g., measurement uncertainty), quantification, screening, qualitative chemical identification, chemometrics, quality assurance and control (QA/QC), method validation, lab accreditation, proficiency testing and inter-lab trials, reference materials, reporting and monitoring results, and other aspects in lab management. Trends in the no. pubs involving several of these terms are grouped together in Table 2. Of course, all analyses require data management, but just as in the case of sample prep, only pubs using the search terms in the title, abstract, and keywords are counted.

**Method validation** In theory, all pubs about newly developed methods should involve method validation, but unfortunately, this is not always the case. Understandably, standards of top-tier analytical journals require research novelty, which is not met if the work only involves method validation of a previously described method. However, the acceptance standards of those same journals often require validation and use of the method for real-world analysis. Surprisingly, < 10% of the ~ 17,000 pubs between 2012 and 2017 in Table 2 line 1 included validation in the title, abstract, or keywords. Perhaps many studies already use validated methods, though, and most new methods are being properly validated. Indeed, validation is being increasingly featured in pubs, growing 352% faster than food safety analysis in general since 2000.

Practicing analytical chemists abide by the expression that the "proof of the pudding is in the eating." Trust in method performance is not freely given based on published validation results, and current practices call for analytical chemists to independently validate methods for their own use. Unfortunately, corresponding to another common expression, too many analytical chemists treat methods like toothbrushes by only using their own. In just one example, there are seemingly countless QuEChERS variations for analysis of typical pesticide residues in common foods [91, 92], but how can all of them have advantages over previous versions? The "publish or perish" incentives placed on many investigators stresses novelty for novelty's sake, not necessarily for better utility in meeting real-world needs. Impartial "apple-to-apple" comparisons of different methods and techniques using shared real samples are publishable studies of great value, but too few pubs of this nature exist.

The traditional use of fixed official methods in food safety monitoring has given way to the performance-based method validation concept coupled with lab accreditation, in which any method that has been sufficiently demonstrated in-house to meet desired data quality objectives may be used. Most monitoring labs follow ISO 17025 accreditation principles (updated in 2017) [127], which specify that individual analysts must demonstrate through method validation that they can achieve acceptable results. In today's climate, advanced regulatory and private labs cannot manage without accreditation in food monitoring applications. Yet, the no. pubs on either "ISO 17025" or "accreditation" was too low to be

included in Table 2. Investigators can still publish and not perish by reporting novel, peer-reviewed studies that improve quality of analyses and lab operations.

Valcárel and Lucena [128] reviewed the important relationship between data management principles in analytical chemistry, but they also found few papers to cite on the topic. In addition to "validation" as already mentioned, the real-world growth in lab accreditation can be observed in Table 2 by the much higher than average increase in the no. pubs on "measurement uncertainty" [129], "proficiency testing" (PT) [130], and "reference material" (to a lesser extent). In recognition of the frequent disconnect between analytical pubs and real-world practices, Wise [131] recently described how novelty can be improved or reconsidered with respect to certified (or standard) reference materials (CRMs or SRMs) for publication. If CRMs and/or PT samples are available, accredited labs must periodically analyze them in blind fashion and consistently achieve statistically acceptable results [132]. These samples must also contain at least some incurred analytes to check total extractability, as discussed earlier in this review. The greater availability of these type of samples provides an excellent service to increase accuracy of methods and results, not only in accredited labs, but in all labs that analyze the samples. Authors and journal reviewers should check the availability of CRM and PT sample types for use in studies intended for publication.

**Quality assurance and control** QA/QC is central to all analyses to help ensure accuracy of the results; therefore, one would expect that QA/QC procedures are described in all analytical pubs. Usually, reviewers take it for granted that authors follow proper QA/QC practices unless detailed descriptions and/or raw analytical data are provided, which becomes too unwieldy and time-consuming in common practice. However, an even larger typically unexamined question is "What is proper QA/QC?"

QA/QC constitutes one of the few topics that grew more slowly than other search terms listed in Table 2, and current QA/QC practices tend to be excessive without necessarily impacting the quality of results. Research studies with the goal to minimize time, effort, and cost associated with QA/QC while still achieving trustworthy results should be a highly valued (and cited) endeavor. Currently accepted QA/QC practices should also undergo scientific evaluation for both effectiveness and efficiency.

Although QA/QC may be under-reported, perhaps the term chemometrics shown in Table 2 better captures the growth in pubs involving computerized data processing techniques. The growth in pubs involving chemometrics since 1994 has kept a steady pace with the other terms listed, but the starting point of merely 2 pubs/year in the late 1990s has expanded to 32 pubs/year during 2012–2017, which is 261% faster than average among listed terms in Table 2.

Unlike traditional quantitative analysis, the QA/QC practices are not firmly established with respect to data processing for making chemical identifications and fingerprints of complex foods. Several reviews have been published about of this evolving area of investigation [133–136]. The complexity of presented information from "omics" type applications distances the final results from the raw data, which requires much trust by others in the validity of the data treatments. Foremost, the foundation of the experimental design must be assessed to guard against broad conclusions being made from information gained from too few experiments lacking diversity of samples [136].

Fundamentally, all analytical chemists must know the difference between precision (random error) and bias (systematic error), which when combined refer to accuracy of methods and their results. In real-world practice, a result with 0% bias but 20% RSD (precision) should be much preferred over a result with 20% bias and 0% RSD. However, the reality of common QA/QC practices (and reviewer acceptance standards for pubs) leads to a greater incentive and likelihood for the latter situation.

In a critical assessment using actual results from different methods and labs conducting elemental analysis, Andersen [137] demonstrated how the greater emphasis that current QA/QC procedures place on the precision of individual analyses can lead to greater bias in the results. This in turn leads to worse long-term precision and reduced accuracy. Andersen pinpointed the desire for more precise calibration and excessive removal of outliers, which yield better *reported* precision, as prominent reasons for the worse reliability of individual and overall results. Analysts who follow accepted QA/QC practices should achieve better results, not worse; thus, the problem resides with the QA/QC procedures, not with the analysts who usually take the blame [137].

Solutions to the problem include use of greater diversity in calibration via replicate standard solutions (not just duplicate injections), without excluding outliers. Also, more analyses of blind samples with concentrations known by a second-party should be conducted during method development and validation studies, both in the case of quantitative and/or qualitative methods. Furthermore, journal reviewers should not accept studies for publication that only present single-day validation experiments with few replicates; multi-day ruggedness studies provide better assessment of real-world results using the method.

Ironically, dogmatic views about the degree of precision that is "good enough," independent of the reality of true needs and method performance attributes, makes implementation of less stringent data acceptability criteria more difficult, even if *looser* standards lead to *better* accuracy. The desire of analysts to report the best possible precision also contributes to the situation. A fallacy that supports dogmatic beliefs is that ultratrace analysis of many diverse analytes in complex food

samples *should* and *can* achieve results with near 0% uncertainty. Currently, this expectation is unrealistic and unattainable except in rare circumstances of high importance, which require much expense and expertise (e.g. dioxins analysis) [118]. The increased participation in PT programs should lead to a better understanding by QA/QC officers (and journal reviewers) to devise analytical acceptability standards to achieve better long-term results rather than merely precise results in individual analyses.

**Mistakes** Random and systematic errors are commonly addressed, but the third main type of error in analytical chemistry, namely spurious or gross error (human mistakes), is barely mentioned in the scientific literature and generally ignored in most QA/QC guidelines. For example, the SANTE/11813/2017 [138] guidance document on QA/QC for pesticide analysis mentions systematic and random errors but does not contain the words, "human" "mistake," "spurious," or "gross." A search of human, gross, or spurious error in the Web of Science core collection uncovered 3324 pubs (0.0074%). Only 53 (1.6%) of these were categorized under analytical chemistry, which was 27th among the fields of science listed. With respect to trends, though, the 31 pubs during 2011–2017 was 288% more than the 8 pubs during the previous 6 years, so perhaps this issue is starting to gain some attention commensurate with its importance in analytical chemistry.

Spurious error is by far the most common source of false results, as any practicing analytical chemist can attest [139, 140]. Whenever a strange finding is encountered (after the fact, of course), investigation of its cause generally points to a mistake in calculations, preparations of solutions, transcription errors, or other common human error. Even sneakier are the unnoticed small errors that unknowingly lead to more uncertainty than the method actually achieves (albeit analyst error can be construed as part of the method). Each step in a method not only increases the systematic and random error contributing to overall method uncertainty, but it also increases the chances of mistakes when performing so many steps. Even if a mistake is immediately realized, sample throughput is often slowed, possibly leading to higher reagent and labor costs and dissatisfied clients (and bosses). Thus, if a method contains too many unwieldy or unneeded steps, more blame should fall on the method developer than on an analyst who makes an average rate of errors.

In an interesting study involving a voluntary survey of analysts who reported unacceptable PT results, Ellison and Hardcastle [141] surmised that ~44% of causes were due to simple operator errors. Considering the tendency of people to blame mistakes on other factors, and because many chemists did not respond to the survey, the rates of spurious error is likely much higher. When the reason for a curious result is unknown, some sort of human error is more likely to be the cause than the facetiously attributed "phase of the moon." Ultimately, someone signs the report and takes responsibility for the analytical results, thus 100% of false results may be broadly interpreted as human error, which include the wisdom (or not) in making analytical and data management choices and the ability to carry out those choices.

One of the reasons that spurious error is so rarely mentioned is that it is difficult to assess scientifically. Ambrus et al. [142] at least discuss gross error as a factor in pesticide residue analysis, and Kuselman et al. [143–145] are leading proponents and investigators to incorporate human error as a factor in metrology and data management guidelines. The intent of these efforts is not to embarrass analysts, because after all, "to err is human," but analytical chemists should strive to implement efficient practices to reduce all forms of error over time, including human error.

Even more rarely mentioned among analytical chemists are the insidiously "correct" results generated falsely. Unfortunately, unethical behavior exists among analytical chemists just as any other subset of people. Yet, the role of scientists is to objectively seek and report truth, and dishonesty undermines the foundations of public trust in scientific research. Kovac gives an excellent overview of ethical responsibilities of chemists including common examples faced by many analytical chemists [146]. Research to replicate the findings of others is essential to the scientific method, and studies of this nature should also be highly valued.

A suggested QA/QC practice to test honesty of analysts is to have them analyze a test sample of a stated concentration that is substantially different from its actual concentration. If the reported result corresponds to the stated rather than actual concentration, then the integrity of the analysis, including the analyst, needs to be questioned. Journal reviewers also need to ask authors to provide supporting documentation when reported results are exceptionally better than the norm, which if true, help the authors also convince skeptical readers.

**Quantitative and qualitative analysis** The terms used to create Table 2 already contain both qualitative and quantitative expressions within the search parameters. Only qualitative aspects are separated into its own row, and quantitative can be assumed to make up most of the remainder. Qualitative and screening have remained a consistent 9–10% of pubs since 1994, whereas expressions of quantitative analysis grew steadily among the share of pubs from 35 to 39% over that time. This is more an indication of word use by authors, and in actuality, all analyses must encompass some degree each of qualitative and quantitative aspects to yield a legitimate result. In particular, MS analysis for most food safety purposes simultaneously provides an exceptional degree of quantitative and qualitative information. The issues of screening, determination, identification, and confirmation in food safety applications (including method validation), particularly when using

MS-based methods, have already been described extensively elsewhere [138–140].

Rather than quant/qual(itative), other terms increasingly being stated in analytical applications are targeted or non-targeted (or untargeted); the use of which are tracked in Table 2. Conventionally, all "analytes" are "targeted" by definition, but the capabilities of modern HRMS instruments and software for improved non-targeted analysis [61–66], particularly in "omics" applications, has led to a rethinking of terms [147]. This type of qualitative analysis has been performed almost since the advent of electronic data acquisition and storage, but only now have the distinctions become more practically important. What universe of possible chemicals that can be potentially detected and identified be considered an analyte? Are all constituents of an MS library/database potential analytes? Can a previously "unknown" chemical be an analyte?

Despite improving technology, "non-targeted" approaches are mostly limited to leaders in the field due to the high instrument costs, dedicated expertise required, large data storage needs, and slower processing times. For routine monitoring, the same advanced tools can be used in targeted analysis (or "quantidentification") much more easily. In the reference lab approach used in the EU, previously non-targeted chemicals (possibly previously unknown) that rise to the level of regulatory concern, can be added to the listed of targeted analytes for more widespread monitoring. This process requires confirmation of any findings using a well-characterized reference standard to determine concentration and ensure that the analytical method and conditions lead to a matching identification. The chemical reference standard needs to be available for other labs to also characterize the new analyte using their methods and instruments, and the quantitative monitoring results can then be used to provide exposure information for toxicological risk assessment purposes.

Journal reviewers need to be cognizant of this intensive multi-step process when evaluating author claims about the broad applicability of non-targeted methods. Even if an approach can be streamlined for reliable chemical identification without confirmation using a reference material, which does not meet current regulatory guidelines, its concentration and food safety risk would also have to be assessed [148]. Very high economic, legal, and political stakes may be involved in food safety analyses, and great care should be made to avoid the risk of false positives. Regulatory levels of concern already incorporate a large safety factor when they are set, thus the consumer health risk due to false negatives is not likely as severe. Toxicologists and food safety regulators need be consulted when analytical chemists have concerns about a confirmed new contaminant [148].

**Signal and data processing** Instrument manufacturers are expected to design, build, and install instruments that meet stated specifications. Analysts must maintain the instrument properly, and a common QA/QC practice calls for a system suitability check prior to initiating each analytical sequence. However, most analysts trust that the basic instrument functions and software work as expected, but even this cannot be trusted blindly. Due to a feedback from an observant analyst, one company recently alerted customers that their software made a math error when adding the integrated areas from two or more chromatographic peaks. Software bugs are expected for any complicated program, and analysts in the field using instruments in unique ways are often the ones to encounter bugs. Even if the software works as intended, analyst input using the software may not be correct, such as data treatments using Excel spreadsheets or laboratory information management systems. Thus, data inputs and processing should be checked for accuracy before reporting final results.

One of the most time-consuming and mind-numbing tasks in working labs is to ensure that chromatographic peaks are integrated properly. Development and use of data processing approaches is an active area of investigation [149–151], but practical implementation of advanced methods relies on instrument companies. Frankly, many papers on the topic are written by and for statisticians, and the information is indecipherable by most analytical chemists. Unless analysts are willing and able to create or find a compatible alternative, they are at the mercy of the manufacturer's software. Thus, instrument integration software tends to be a black box to the analyst, and although numerous choices of algorithms may be available, practicing chromatographers in the field know from experience that no automatic peak integration program is to be trusted completely, especially for ultratrace analysis of complex foods. QA/QC practices generally require visual review and manual re-integrations, and despite advanced data treatments being realized by powerful computing [151], highly reproducible chromatography and very selective detection actually make it feasible to return to the simplest approach to peak integration: sum the signal above a line drawn at the baseline just before and after the expected analyte peak. If the analyte retention times are consistent, then this simple "summation" integration approach obviates review and manual re-integrations, as described previously [104, 152].

After assuring that the signal has been reliably acquired, a staggering number of data processing and statistical treatment options may be followed to yield the final results. Asnin published an excellent review about the importance of calibration and common pitfalls to avoid in quantitative analysis [149]. RSDs > 20% is the norm in PT studies involving different labs, reagents, methods, and analysts [132], but substantial variations can result even when using the same raw data but different validated data handling approaches. For instance, the typically default choice of a regression algorithm can lead to notable statistical differences [153, 154]. Additional options to normalize analyte signals to internal standard(s), employ matrix-matching, plot calibration blanks, use quadratic

calibration, etc. (or not), further complicate supposedly straight-forward quantitative methods.

Authors of analytical pubs rarely or barely mention the details or nuances in their data handling processes that can affect the reported results, but Andersen [137] demonstrated how such choices can be very important. In single-lab method development and/or validation, in which the correct result of a spiked sample or CRM is already known by the analyst, then the analyst tends to choose the treatment option that yields the most accurate result. However, the actual analytes present and their concentrations are unknown in real-world (or PT) samples, and the previously validated data processing method may lead to a less accurate result than other choices.

Ideally, such issues would not matter and all options lead to the same result, which in fact leads to a great way to assess the reliability of a method. If several different data processing options still lead to much the same result, then the overall method and result are more likely to be accurate. If the different procedures yield rather variable results, the analyst could report the range and average result to better express uncertainty in the method, which includes data processing factors. This can be likened to existing validation protocols to assess method ruggedness by using different conditions and reagents to see how they affect the final result.

## Bio-based and general analytical techniques

Due to significant overlap, discussion of the next two sections in Table 2 concerning immunochemical, sensing, and general analytical techniques are being combined. Only a few of the terms will be discussed in this section, and the reader can view the trends in Table 2 and form their own conclusions about them. Despite the thousands of pubs on these topics in food safety analysis applications, monitoring labs rarely employ the techniques except for specific analytes that are not easily detected by MS-based methods. The number of these niches is decreasing as MS technology continues to make gains in performance, commercial availability, and multi-analyte scope, among other advantages. For example, rapid MS-based detection when coupled with flow-injection analysis [155] rather than chromatography may be useful in quantitative screening applications that traditionally fall within the niche of immunoassays. In a likely consequence of greater relative growth of the no. pubs involving MS, lower relative growth has occurred in the case of immuno- and bioassay techniques, as indicated by the terms set in bold in Table 2. However, the use of alternative chemical mechanisms for analysis is highly desirable when making analyte confirmations [139, 140], as one example, and there are very good reasons to use diverse tools in food safety applications.

Despite the lower relative growth, there is no shortage of pubs or reviews [156–161] about immunochemical analysis in food safety applications. It can be very interesting to retrospectively compare comments from older review articles with newer ones. In 1991, Samarajeewa et al. [156] wrote an extensive review with 381 references about immunoassays in food applications. Twenty-six years later, Li et al. [157] began their review of 178 references by stating "Immunoassay is an emerging technique..." despite that the first of > 66,000 pubs in the Web of Science core collection using the term "immunoassay" appeared in 1959 [162]. Indeed, multiplexing (multi-analyte analysis) using immunochemical methods has been undergoing higher growth as indicated in Table 2, but that trend has been occurring for at least 20 years.

Strengths of immunochemical methods include the selectivity and sensitivity of analysis for the particular analyte(s), flexibility of formats, and the ease of performing analyses. However, general weaknesses of common immuno-based methods include limited scope of analytes, semi-quantitative nature, adverse matrix and solvent effects, difficulty to distinguish or identify individual analytes, long incubation times, and high cost of assays. The quality of results and practical aspects of all immunological assays depend on the selectivity, binding strength, and stability of the antibodies, which are not easily generated for many small molecule applications, such as analysis of food contaminants. Immunoassays are known to work very well in water and biological fluids, especially for large molecules and microbes, but food contaminant extracts generally contain organic solvents and matrix components that interfere in immunoassays. Even in the type of ideal food safety applications for immunochemical analyses, such as allergens, toxins (seafood, fungal, microbial), GMOs, and pathogens [157–161], MS-based methods are gaining traction due to their overall advantages [16, 17, 55, 62, 72–75, 163, 164].

Not only have MS detection methods expanded into traditional immunochemical food safety applications, but so has real-time PCR (polymerize-chain reaction). As shown in Table 2, PCR grew from a 39% fraction of the no. pubs relative to immunoassays in 1994–1999 to a 70% fraction since 2000. Akin to UHPLC-MS/MS in the case of small molecule analysis, PCR has become a standard commercialized technique for biomonitoring using extensively validated methods. Any new method designed for the same application as PCR must possess significant practical and measurement advantages over PCR to be implemented. De Medici et al. [165] published an extensive critical review of PCR describing its advantages and disadvantages in food analysis.

Italicized text in Table 2 highlight the areas of food safety analysis in which trends in the relative no. pubs more than double in the most recent or two consecutive 6-year periods. Currently, this includes aptamers [166, 167], quantum dots [168, 169], and Raman spectroscopy [170, 171]. As in the case of MIPs discussed earlier, it is questionable if these techniques, among other sensing technologies listed in Table 2, have significant real-world advantages over existing methods

for implementation in food safety monitoring. For example, (surface-enhanced) Raman spectroscopy is much weaker and less quantitative than other forms of molecular spectroscopy and not nearly as selective or widely applicable as MS.

Also, electrochemical detection notoriously tends to lack day-to-day reproducibility, ruggedness, robustness, and the broad analytical scope that can be achieved by other analytical techniques. Perhaps recent reviews [172–174] on electrochemical sensors describe modern twists that make those perceptions false, but virtually no authors or vendors present electrochemical methods at food safety workshops, and practicing analysts in the field tend to avoid electrochemistry.

As noted in a book review on the topic [175], no shortage exists in the amount of information or research being conducted in the area of sensing techniques. Yet, very little if any research is being done to overcome the concerns described in the sample prep and data management sections of this review. Soares et al. [176] also conclude "…it becomes apparent that … sample preparation … still present[s] major technical challenges…. that has been so far insufficiently explored in the literature. An added difficulty is the prior sampling and grinding process required for solid samples … yet to be tackled in miniaturized systems. … [It] is also clear that many recent approaches rely on excessively complex procedures, inevitably resulting in high costs and several sequential assay steps … result[ing] in lower precision due to cumulative experimental error [and] assay times longer than desired…"

There is much value in advancing science, disseminating research, gaining grants, teaching students, getting patents, starting businesses, etc. Fundamental research to satisfy human curiosity and meet technical challenges akin to climbing mountains ("because they are there!") has led to tremendous improvements in the human condition. Unless the well-known common-sense (but widely ignored) real-world limitations mentioned above are overcome by serious research efforts to meet the challenges, rather than simply acknowledge the problems, then the "potential" for food safety analysis is just at an umbrella justification for falsely calling fundamental research as being applied. Furthermore, a method with ten real advantages but just one critical weakness, such as lack of robustness or prohibitive cost, will not be widely implemented.

## Atomic analysis

The only remaining undiscussed section of Table 2 relates to atomic analysis. According to the no. pubs in Table 1, analysis of toxic metals constitutes the most important category in food safety analysis. Indeed, the acute and chronic toxicity of heavy metals makes their abatement in sources of human exposure an important public health service. For example, the reduction of Pb in food, drinking water, and environment stands as one of the greatest accomplishments in human health history.

In this respect, sensitive and accurate methods for the analysis Pb, Cd, and other elements in foods have been long established, and most of the current pubs in the literature involve studies in which monitoring results from existing analytical methods are used for other purposes. Recent reviews [177–182] discuss new analytical developments, particularly for multi-elemental analysis and speciation in food and other applications. The ESM contains a further review of the topic, including Fig. S2, which shows the no. pubs over time with respect to different analytical techniques for toxic metals of most concern (Pb, Cd, Hg, and As) in foods.

## Conclusions

Food safety analysis is currently undergoing a period of higher growth than average in the field of chemistry. This trend is likely to continue globally as populations and international food trade continue to increase, with more food exports coming from developing countries in particular. As economies grow, more countries will be able to afford rigorous food safety monitoring programs to ensure that not just their food exports, but also their imported and domestic foods meet international regulatory standards. Food safety testing and enforcement lead to better public health along with many peripheral benefits, including good jobs and business for those involved in the food safety arena.

Scientists can truly provide a great service to humanity if they develop better analytical technologies and techniques that meet food safety monitoring needs, but only if their efforts lead to implemented improvements. A major reason for this critical review is to help researchers understand real-world needs and encourage investigation of the highest priority topics that are currently lacking in the scientific literature. All analytical chemists should know that any analysis originates with a purpose and follows a series of steps starting with sampling and ending with reported results of sufficient accuracy to fulfill the intended purpose. Just as a chain is only as strong as its weakest link, all aspects in the overall analysis need to be addressed to meet the intended need with the highest efficiency.

Despite the common sense understanding of the overall problem, a critical review of the scientific literature leads to the conclusion that too many (but not all) researchers are missing (or ignoring) the true needs for their efforts. Similarly, too many (but not all) researchers are focusing on the same link in the chain, namely detection technologies, without enough recognition of the capabilities of existing methods for the same purpose. Too much research in food safety analysis involves development of "novel" methods intended only for publication that may (at best) only slightly improve upon existing methods, whereas major gaps exist in the chain links related to sample processing and data

management (e.g., data processing, QA/QC, spurious error, and method validation). More emphasis needs to be placed on rigorous method validation, reproducibility assessments, and impartial comparisons. Lastly, greater appreciation among journal editors and reviewers should be given to the type of useful scientific studies designed to advance food safety by overcoming current practical monitoring challenges.

**Disclaimer** The opinions expressed in this article are those of the authors and do not reflect the views of the US Dept. of Agriculture (USDA). Mention of brand or firm name does not constitute an endorsement by the USDA above others of a similar nature not mentioned.

**Funding information** This project was supported in part by a subaward from the University of Kentucky Research Foundation (UKRF) in grant no. 3048108028-11-342 from the National Institute for Hometown Security.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Hudson JA, Frewer LJ, Jones G, Brereton PA, Whittingham MJ, Stewart G. The agri-food chain and antimicrobial resistance: a review. Trends Food Sci Technol. 2017;69:131–47.
2. World Trade Organization. International trade statistics 2015. www.wto.org/english/res_e/statis_e/its2015_e/its15_toc_e.htm. Accessed Feb 2018.
3. US Central Intelligence Agency. The world factbook 2017. www.cia.gov/library/publications/the-world-factbook/. Accessed Feb 2018.
4. Randall E. Food, risk and politics: scare, scandal and crisis - insights into the risk politics of food safety. Manchester: Manchester University Press; 2009. 272 pp
5. De Brabander HF, Vanden Bussche J, Verbeke W, Vanhaecke L. The economics of residue analysis. Trends Anal Chem. 2011;30:1088–94.
6. Clarivate Analytics. Web of science. clarivate.com/products/web-of-science. Accessed Feb 2018.
7. US Food and Drug Administration. Contaminants and adulteration. www.fda.gov/Food/FoodborneIllnessContaminants. Accessed Feb 2018.
8. Borchers A, Teuber SS, Keen CL, Gershwin ME. Food safety. Clin Rev Allergy Immunol. 2010;39:95–141.
9. Krska R, Becalski A, Braekevelt E, Koerner T, Cao XL, Dabeka R, et al. Challenges and trends in the determination of selected chemical contaminants and allergens in food. Anal Bioanal Chem. 2012;402:139–62.
10. Amelin VG, Lavrukhina OI. Food safety assurance using methods of chemical analysis. J Anal Chem. 2017;72:1–46.
11. Purcaro G, Moret S, Conte LS. Overview on polycyclic aromatic hydrocarbons: occurrence, legislation and innovative determination in foods. Talanta. 2013;105:292–305.
12. Cruz R, Cunha SC, Marques A, Casal S. Polybrominated diphenyl ethers and metabolites—an analytical review on seafood occurrence. Trends Anal Chem. 2017;87:129–44.
13. Pietron WJ, Malagocki P. Quantification of polybrominated diphenyl ethers (PBDEs) in food. A review. Talanta. 2017;167:411–27.
14. Fromme H, Becher G, Hilger B, Volkel W. Brominated flame retardants—exposure and risk assessment for the general population. Int J Hyg Environ Health. 2016;219:1–23.
15. Nicolas J, Hoogenboom RLAP, Hendricksen PJM, Bodero M, Bovee TFH, Rietjens IMCM, et al. Marine biotoxins and associated outbreaks following seafood consumption: prevention and surveillance in the 21st century. Global Food Secur Agric Policy Econ Environ. 2017;15:11–21.
16. Rodriguez I, Vieytes MR, Alfonso A. Analytical challenges for regulated marine toxins. Detection methods. Curr Opin Food Sci. 2017;18:29–36.
17. Gomes T, Albergamo A, Costa R, Mondello L, Dugo G. Potential use of proteomics in shellfish aquaculture: from assessment of environmental toxicity to evaluation of seafood quality and safety. Curr Org Chem. 2017;21:402–25.
18. Biji KB, Ravishankar CN, Venkateswarlu R, Mohan CO, Gopal TKS. Biogenic amines in seafood: a review. J Food Sci Technol. 2016;53:2210–8.
19. Wright SL, Kelly FJ. Plastic and human health: a micro issue? Environ Sci Technol. 2017;51:6634–47.
20. Hahladakis JN, Velis CA, Weber R, Iacovidou E, Purnell P. An overview of chemical additives present in plastics: migration, release, fate and environmental impact during their use, disposal and recycling. J Hazard Mater. 2018;344:179–99.
21. Bouwmeester H, Hollman PCH, Peters RJB. Potential health impact of environmentally released micro- and nanoplastics in the human food production chain: experiences from nanotoxicology. Environ Sci Technol. 2015;49:8932–47.
22. Mattarozzi M, Suman M, Cascio C, Calestani D, Weigel S, Undas A, et al. Analytical approaches for the characterization and quantification of nanoparticles in food and beverages. Anal Bioanal Chem. 2017;409:63–80.
23. Pico Y, Alfarham A, Barcelo D. Analysis of emerging contaminants and nanomaterials in plant materials following uptake from soils. Trends Anal Chem. 2017;94:173–89.
24. Guo HY, He LL, Xing BS. Applications of surface-enhanced Raman spectroscopy in the analysis of nanoparticles in the environment. Environ Sci-Nano. 2017;4:2093–107.
25. Arulandhu AJ, van Dijk JP, Dobnik D, Holst-Jensen A, Shi JX, Zel J, et al. DNA enrichment approaches to identify unauthorized genetically modified organisms (GMOs). Anal Bioanal Chem. 2016;408:4575–93.
26. Lin CH, Pan TM. Perspectives on genetically modified crops and food detection. J Food Drug Anal. 2016;24:1–8.
27. Arugula MA, Zhang YY, Simonian AL. Biosensors as 21st century technology for detecting genetically modified organisms in food and feed. Anal Chem. 2014;86:119–29.
28. Alves RC, Barroso MF, Gonzalez-Garcia MB, Oliveira MBPP, Delerue-Matos C. New trends in food allergens detection: toward biosensing strategies. Crit Rev Food Sci Nutr. 2016;56:2304–19.
29. Prado M, Ortea I, Vial S, Rivas J, Calo-Mata P, Barros-Valazques J. Advanced DNA- and protein-based methods for detection and investigation of food allergens. Crit Rev Food Sci Nutr. 2016;56:2511–42.
30. Chiou JC, Leung AHH, Lee HW, Wong WT. Rapid testing methods for food contaminants and toxicants. J Integr Agric. 2015;14:2243–64.
31. Crews C. The determination of N-nitrosamines in food. Qual Assur Safety Crops Foods. 2010;2:2–12.
32. Iwaoka K. The current limits for radionuclides in food in Japan. Health Phys. 2016;111:417–8.

33. Kolacinska K, Trojanowicz M. Application of flow analysis in determination of selected radionuclides. Talanta. 2014;125:131–45.
34. Maxwell SL, Culligan BK, Kelsey-Wall A, Shaw PJ. Rapid determination of actinides in emergency food samples. J Radioanal Nucl Chem. 2012;292:339–47.
35. Iammarino M, Marino R, Albenzio M. How meaty? Detection and quantification of adulterants, foreign proteins and food additives in meat products. Int J Food Sci Technol. 2017;52:851–63.
36. Maffini MV, Alger HM, Olson ED, Neltner TG. Looking back to look forward: a review of FDA's food additives safety assessment and recommendations for modernizing its program. Compr Rev Food Sci Food Saf. 2013;12:439–53.
37. Sanchis Y, Yusa V, Coscolla C. Analytical strategies for organic food packaging contaminants. J Chromatogr A. 2017;1490:22–46.
38. Yang T, Huang HF, Zhu F, Lin QL, Zhang L, Liu JW. Recent progresses in nanobiosensing for food safety analysis. Sensors. 2016;16:1118.
39. Mantovani A. Endocrine disrupters and the safety of food chains. Horm Res Paediatr. 2016;86:279–88.
40. Careghini A, Mastorgio AF, Saponaro S, Sezenna E. Bisphenol a, nonylphenols, benzophenones, and benzotriazoles in soils, groundwater, surface water, sediments, and food: a review. Environ Sci Pollut Res. 2015;22:5711–41.
41. Harunarashid NZIH, Lim LH, Harunsani MH. Phthalate sample preparation methods and analysis in food and food packaging: a review. Food Anal Methods. 2017;10:3790–814.
42. Brambilla G, D'Hollander W, Oliaei F, Stahl T, Weber R. Pathways and factors for food safety and food security at PFOS contaminated sites within a problem based learning approach. Chemosphere. 2015;129:192–202.
43. Domingo JL, Nadal M. Per- and polyfluoroalkyl substances (PFASs) in food and human dietary intake: a review of the recent scientific literature. J Agric Food Chem. 2017;65:533–43.
44. Trojanowicz M, Koc M. Recent developments in methods for analysis of perfluorinated persistent pollutants. Microchim Acta. 2013;180:957–71.
45. Naughton DP, Nepusz T, Petroczi A. Network analysis: a promising tool for food safety. Curr Opin Food Sci. 2015;6:44–8.
46. Alves A, Kucharska A, Erratico C, Xu F, Den Hond E, Koppen G, et al. Human biomonitoring of emerging pollutants through non-invasive matrices: state of the art and future potential. Anal Bioanal Chem. 2014;406:4063–88.
47. Farre M, Barcelo D. Analysis of emerging contaminants in food. Trends Anal Chem. 2013;43:240–53.
48. Habe TT, Morlock GE. Miniaturization of instrumental planar chromatography with focus on mass spectrometry. Chromatographia. 2016;79:797–810.
49. Morlock GE. Miniaturized planar chromatography using office peripherals – office chromatography. J Chromatogr A. 2015;1382:87–96.
50. Liu JM, Liu CC, Fang GZ, Wang S. Advanced analytical methods and sample preparation for ion chromatography techniques. RSC Adv. 2015;72:58713–26.
51. Cutillas V, Martínez Galera M, Rajski Ł, Fernández-Alba AR. Evaluation of supercritical fluid chromatography coupled to tandem mass spectrometry for pesticide residues in food. J Chromatogr A. 2018;1545:67–74.
52. Fujito Y, Hayakawa Y, Izumi Y, Bamba T. Importance of optimizing chromatographic conditions and mass spectrometric parameters for supercritical fluid chromatography/mass spectrometry. J Chromatogr A. 2017;1508:138–47.
53. Ishibashi M, Izumi Y, Sakai M, Ando T, Fukusaki E, Bamba T. High-throughput simultaneous analysis of pesticides by supercritical fluid chromatography coupled with high-resolution mass spectrometry. J Agric Food Chem. 2015;63:4457–63.
54. Ishibashi M, Ando T, Sakai M, Matsubara A, Uchikata T, Fukusaki E, et al. High-throughput simultaneous analysis of pesticides by supercritical fluid chromatography/tandem mass spectrometry. J Chromatogr A. 2012;1266:143–8.
55. Garrido Frenich A, Romero-Gonzalez R, del Mar Aguilera-Ruiz M. Comprehensive analysis of toxics (pesticides, veterinary drugs and mycotoxins) in food by UHPLC-MS. Trends Anal Chem. 2014;63:158–69.
56. Jandera P. Advances in the development of organic polymer monolithic columns and their applications in food analysis—a review. J Chromatogr A. 2013;1313:37–53.
57. Bernal J, Ares AM, Pol J, Wiedmar SK. Hydrophilic interaction liquid chromatography in food analysis. J Chromatogr A. 2011;42:7438–52.
58. Keshet U, Alon T, Fialkov AB, Amirav A. Open probe fast GC-MS—combining ambient sampling ultra-fast separation and in-vacuum ionization for real-time analysis. J Mass Spectrom. 2017;52:417–26.
59. Seemann B, Alon T, Tsizin S, Fialkov AB, Amirav A. Electron ionization LC-MS with supersonic molecular beams—the concept, benefits and applications. J Mass Spectrom. 2015;50:1252–63.
60. Amirav A, Gordin A, Poliak M, Fialkov AB. Gas chromatography-mass spectrometry with supersonic molecular beams. J Mass Spectrom. 2008;43:141–63.
61. Rochat B. From targeted quantification to untargeted metabolomics: why LC-high-resolution-MS will become a key instrument in clinical labs. Trends Anal Chem. 2016;84:151–64.
62. Senyuva HZ, Gokmen V, Sarikaya EA. Future perspectives in Orbitrap™-high-resolution mass spectrometry in food analysis: a review. Food Addit Contam A. 2015;32:1568–606.
63. Wang J, Chow W, Chang J, Wong JW. Development and validation of a qualitative method for target screening of 448 pesticide residues in fruits and vegetables using UHPLC/ESI Q-Orbitrap based on data-independent acquisition and compound database. J Agric Food Chem. 2017;65:473–93.
64. Uclés S, Uclés A, Lozano A, Martínez Bueno MJ, Fernández-Alba AR. Shifting the paradigm in gas chromatography mass spectrometry pesticide analysis using high resolution accurate mass spectrometry. J Chromatogr A. 2017;1501:107–16.
65. Mol HGJ, Tienstra M, Zomer P. Evaluation of gas chromatography - electron ionization—full scan high resolution Orbitrap mass spectrometry for pesticide residue analysis. Anal Chim Acta. 2016;935:161–72.
66. Barcaru A, Mol HGJ, Tienstra M, Vivó-Truyols G. Bayesian approach to peak deconvolution and library search for high resolution gas chromatography–mass spectrometry. Anal Chim Acta. 2017;983:76–90.
67. Bylinski H, Gebicki J, Dymerski T, Namiesnik J. Direct analysis of samples of various origin and composition using specific types of mass spectrometry. Crit Rev Anal Chem. 2017;47:340–58.
68. Guo TY, Yong W, Jin Y, Zhang LY, Liu JH, Wang S, et al. Applications of DART-MS for food quality and safety assurance in food supply chain. Mass Spectrom Rev. 2017;36:161–87.
69. Kern SE, Lin LA, Fricke FL. Accurate mass fragment library for rapid analysis of pesticides on produce using ambient pressure desorption ionization with high-resolution mass spectrometry. J Am Soc Mass Spectrom. 2014;25:1482–8.
70. Hernandez-Mesa M, Escourrou A, Monteau F, Le Bizec B, Dervilly-Pinel G. Current applications and perspectives of ion mobility spectrometry to answer chemical food safety issues. Trends Anal Chem. 2017;94:39–53.

71. Piras C, Roncada P, Rodrigues PM, Bonizzi L, Soggiu A. Proteomics in food: quality, safety, microbes, and allergens. Proteomics. 2016;16:799–815.
72. Fagerquist CK. Unlocking the proteomic information encoded in MALDI-TOF-MS data used for microbial identification and characterization. Expert Rev Proteomics. 2017;14:97–107.
73. Huber I, Pavlovic M, Maggipinto M, Konrad R, Busch U. Interlaboratory proficiency test using MALDI-TOF MS for identification of food-associated bacteria. Food Anal Methods. 2018;11:1068–75.
74. Wang X, Wang SJ, Cai ZW. The latest developments and applications of mass spectrometry in food-safety and quality analysis. Trends Anal Chem. 2013;52:170–85.
75. Golf O, Strittmatter N, Karancsi T, Pringle SD, Speller AVM, Mroz A, et al. Rapid evaporative ionization mass spectrometry imaging platform for direct mapping from bulk tissue and bacterial growth media. Anal Chem. 2015;87:2527–34.
76. Beach DG, Walsh CM, Cantrell P, Rourke W, O'Brien S, Reeves K, et al. Laser ablation electrospray ionization high-resolution mass spectrometry for regulatory screening of domoic acid in shellfish. Rapid Commun Mass Spectrom. 2016;30:2379–87.
77. Raynie DE. Trends in sample preparation. LCGC N Am. 2016;34:174–88.
78. Wen YY, Chen L, Li JH, Liu DY, Chen LX. Recent advances in solid-phase sorbents for sample preparation prior to chromatographic analysis. Trends Anal Chem. 2014;59:26–41.
79. Plotka-Wasylka J, Szczepanska N, de la Guardia M, Namiesnik J. Modern trends in solid-phase extraction: new sorbent media. Trends Anal Chem. 2016;77:26–43.
80. Arsenault JC. Beginner's guide to SPE: solid-phase extraction. Milford: Waters Corp; 2012. 212 pp
81. Andrade-Eiroa A, Canle M, Leroy-Cancellieri V, Cerda V. Solid-phase extraction of organic compounds: a critical review. Trends Anal Chem. 2016;80:655–67.
82. De Toffoli AL, Soares Maciel EV, Fumes BH, Lancas FM. The role of graphene-based sorbents in modern sample preparation techniques. J Sep Sci. 2018;41:288–302.
83. Jakubus A, Paszkiewicz M, Stepnowski P. Carbon nanotubes application in the extraction techniques of pesticides: a review. Crit Rev Anal Chem. 2017;47:76–91.
84. Herrero Latorre C, Álvarez Méndez J, Barciela García J, García Martín S, Peña Crecente RM. Carbon nanotubes as solid-phase extraction sorbents prior to atomic spectrometric determination of metal species: a review. Anal Chim Acta. 2012;749:16–35.
85. Herrero-Latorre C, Barciela-García J, García-Martín S, Peña-Crecente RM, Otarola-Jimenez J. Magnetic solid-phase extraction using carbon nanotubes as sorbents: a review. Anal Chim Acta. 2015;892:10–26.
86. Morris BD, Schriner RB. Development of an automated column solid-phase extraction cleanup of QuEChERS extracts, using zirconia-based sorbent, for pesticide residue analyses by LC-MS/MS. J Agric Food Chem. 2015;63:5107–19.
87. Khezeli T, Daneshfar A. Development of dispersive micro-solid phase extraction based on micro and nano sorbents. Trends Anal Chem. 2017;89:99–118.
88. Bordin DCM, Alves MNR, de Campos EG, De Martinis BS. Disposable pipette tips extraction: fundamentals, applications, and state of the art. J Sep Sci. 2016;39:1168–72.
89. Anastassiades M, Lehotay SJ, Štajnbaher D, Schenck FJ. Fast and easy multiresidue method employing acetonitrile extraction/partitioning and "dispersive solid-phase extraction" for the determination of pesticide residues in produce. J AOAC Int. 2003;86:412–31.
90. González-Curbelo MÁ, Socas-Rodríguez B, Herrera-Herrera AV, González-Sálamo J, Hernández-Borges J, Rodríguez-Delgado MÁ. Evolution and applications of the QuEChERS method. Trends Anal Chem. 2015;71:169–85.
91. Rejczak T, Tuzimski T. A review of recent developments and trends in the QuEChERS sample preparation approach. Open Chem. 2015;13:980–1010.
92. Bruzzoniti MC, Checchini L, De Carlo RM, Orlandini S, Rivoira L, Del Bubba M. QuEChERS sample preparation for the determination of pesticides and other organic residues in environmental matrices: a critical review. Anal Bioanal Chem. 2014;406:4089–116.
93. Steinborn A, Alder L, Spitzke M, Doerk D, Anastassiades M. Development of a QuEChERS-based method for the simultaneous determination of acidic pesticides, their esters, and conjugates following alkaline hydrolysis. J Agric Food Chem. 2017;65:1296–305.
94. Shao G, Agar J, Giese RW. Cold-induced aqueous acetonitrile phase separation: a salt-free way to begin quick, easy, cheap, effective, rugged, safe. J Chromatogr A. 2017;1506:128–33.
95. Arthur CL, Pawliszyn J. Solid-phase microextraction with thermal-desorption using fused-silica optical fibers. Anal Chem. 1990;62:2145–8.
96. Reyes-Garcés N, Gionfriddo E, Gómez-Ríos GA, Alam MN, Boyacı E, Bojko B, et al. Advances in solid-phase microextraction and perspective on future directions. Anal Chem. 2018;90:302–60.
97. Souza-Silva EA, Gionfriddo E, Pawliszyn J. A critical review of the state of the art of solid-phase microextraction of complex matrices II. Food analysis. Trends Anal Chem. 2015;71:236–48.
98. Costa R. Newly introduced sample preparation techniques: towards miniaturization. Crit Rev Anal Chem. 2014;44:299–310.
99. Martín-Calero A, Pino V, Afonso AM. Ionic liquids as a tool for determination of metals and organic compounds in food analysis. Trends Anal Chem. 2011;30:1598–619.
100. Trujillo-Rodríguez MJ, Rocío-Bautista P, Pino V, Afonso AM. Ionic liquids in dispersive liquid-liquid microextraction. Trends Anal Chem. 2013;51:87–106.
101. Kokosa JM. Advances in solvent-microextraction techniques. Trends Anal Chem. 2013;43:2–13.
102. Hernández-Hernández AA, Álvarez-Romero GA, Contreras-López E, Aguilar-Artega K, Castañeda-Ovando A. Food analysis by microextraction methods based on the use of magnetic nanoparticles as supports: recent advances. Food Anal Methods. 2017;10:2974–93.
103. Bendicho C, Costas-Mora I, Romero V, Lavilla I. Nanoparticle-enhanced liquid-phase microextraction. Trends Anal Chem. 2015;68:78–87.
104. Lehotay SJ, Han L, Sapozhnikova Y. Automated mini-column solid-phase extraction cleanup for high-throughput analysis of chemical contaminants in foods by low-pressure gas chromatography–tandem mass spectrometry. Chromatographia. 2016;79:1113–30.
105. Raynie DE, Qiu C. The use of extraction technologies in food safety studies. LCGC N Am. 2017;35:158–69.
106. Lawal A, Tan GH, Alsharif AMA. Recent advances in analysis of pesticides in food and drink samples using LPME techniques coupled to GC-MS and LC-MS: a review. J AOAC Int. 2016;99:1383–94.
107. Lehotay SJ, Cook JM. Sampling and sample processing in pesticide residue analysis. J Agric Food Chem. 2015;63:4395–404.
108. Whitaker TB. Sampling foods for mycotoxins. Food Addit Contam. 2006;23:50–61.
109. Bodnar M, Namieśnik J, Konieczka P. Validation of a sampling procedure. Trends Anal Chem. 2013;51:117–26.
110. Riter LS, Lynn KJ, Wujcik CE, Bucholz LM. Interlaboratory assessment of cryomilling sample preparation for residue analysis. J Agric Food Chem. 2015;63:4405–8.

111. Mandal V, Tandey R. A critical analysis of publication trends from 2005-2015 in microwave assisted extraction of botanicals: how far have come and the road ahead. Trends Anal Chem. 2016;82:100–8.
112. Wang H, Ding J, Ren NQ. Recent advances in microwave-assisted extraction of trace organic pollutants from food and environmental samples. Trends Anal Chem. 2016;75:197–208.
113. Sun HW, Ge XS, Lv YK, Wang AB. Application of accelerated solvent extraction in the analysis of organic contaminants, bioactive and nutritional compounds in food and feed. J Chromatogr A. 2012;1237:1–23.
114. Capriotti AL, Cavaliere C, Giansanti P, Gubbiotti R, Samperi R, Lagana A. Recent developments in matrix solid-phase dispersion. J Chromatogr A. 2010;1217:2521–32.
115. He M, Chen BB, Hu B. Recent developments in stir bar sorptive extraction. Anal Bioanal Chem. 2014;406:2001–26.
116. Seidi S, Yamini Y. Analytical sonochemistry; developments applications, and hyphenations of ultrasound in sample preparation and analytical techniques. Central Eur J Chem. 2012;10:938–76.
117. Ma F, Wu R, Li PW, Li Y. Analytical approaches for measuring pesticides, mycotoxins and heavy metals in vegetable oils: a review. Eur J Lipid Sci Technol. 2016;118:339–52.
118. Hoogenboom R, Traag W, Fernandes A, Rose M. European developments following incidents with dioxins and PCBs in the food and feed chain. Food Control. 2015;50:670–83.
119. Subedi B, Aguilar L, Robinson EM, Hageman KJ, Bjorklund E, Sheesley RJ, et al. Selective pressurized liquid extraction as a sample-preparation technique for persistent organic pollutants and contaminants of emerging concern. Trends Anal Chem. 2015;68:119–32.
120. Bylda C, Thiele R, Kobold U, Volmer DA. Recent advances in sample preparation techniques to overcome difficulties encountered during quantitative analysis of small molecules from biofluids using LC-MS/MS. Analyst. 2014;139:2265–76.
121. Han L, Matarrita J, Sapoznikova Y, Lehotay SJ. Evaluation of a recent product to remove lipids and other matrix co-extractives in the analysis of pesticide residues and environmental contaminants in foods. J Chromatogr A. 2016;1449:17–29.
122. Zhao L, Lucas D, Long D, Richter B, Stevens J. Multi-class multiresidue analysis of veterinary drugs in meat using enhanced matrix removal lipid cleanup and liquid chromatography-tandem mass spectrometry. J Chromatogr A. 2018;1549:14–24.
123. Sellergren B, Ekberg B, Mosbach K. Molecular imprinting of amino-acid derivatives in macroporous polymers–demonstration of substrate-selectivity and enantio-selectivity by chromatographic resolution of racemic mixtures of amino-acid derivatives. J Chromatogr. 1985;347:1–10.
124. Ashley J, Shahbazi MA, Kant K, Chidambara VA, Wolff A, Bang DD, et al. Molecularly imprinted polymers for sample preparation and biosensing in food analysis: progress and perspectives. Biosens Bioelectron. 2017;94:606–15.
125. Speltini A, Scalabrini A, Maraschi F, Sturini M, Profumo A. Newest applications of molecularly imprinted polymers for extraction of contaminants from environmental and food matrices: a review. Anal Chim Acta. 2017;974:1–26.
126. Wang PL, Sun XH, Su XO, Wang T. Advancements of molecularly imprinted polymers in the food safety field. Analyst. 2016;141:3540–53.
127. International Standards Organization. ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories. Mar. 2018 (corrected version), www.iso.org/standard/66912. Accessed Apr 2018.
128. Valcárel M, Lucena R. Synergistic relationships between analytical chemistry and written standards. Anal Chim Acta. 2013;788:1–7.
129. Esbensen KH, Wagner C. Theory of sampling (TOS) versus measurement uncertainty (MU)—a call for integration. Trends Anal Chem. 2014;57:93–106.
130. Madeiros de Albano F, Schwengber ten Caten C. Proficiency tests for laboratories: a systematic review. Accred Qual Assur. 2014;19:245–57.
131. Wise SA. What is novel about certified reference materials? Anal Bioanal Chem. 2018;410:2045–9.
132. Ferrer C, Lozano A, Uclés S, Valverde A, Fernández-Alba AR. European Union proficiency tests for pesticide residues in fruit and vegetables from 2009 to 2016: overview of the results and main achievements. Food Control. 2017;82:101–13.
133. Franceschi P, Giordan M, Wehrens R. Multiple comparisons in mass-spectometry-based—*omics* technologies. Trends Anal Chem. 2013;50:11–21.
134. Ropodi AI, Panagou EZ, G-JE N. Data mining derived from food analyses using non-invasive/non-destructive analytical techniques; determination of food authenticity, quality & safety in tandem with computer science disciplines. Trends Food Sci Technol. 2016;50:11–25.
135. Burfield R, Neumann C, Saunders CP. Review and application of functional data analysis to chemical data—the example of the comparison, classification, and database search of forensic ink chromatograms. Chemom Intell Lab Syst. 2015;149:97–106.
136. Rodionova OY, Titova AV, Pomerantzev AL. Discriminant analysis is an inappropriate method of authentication. Trends Anal Chem. 2016;78:17–22.
137. Andersen JET. On the development of quality assurance. Trends Anal Chem. 2014;60:16–24.
138. European Commission Directorate General for Health and Food Safety, Guidance document on analytical quality control and method validation procedures for pesticide residues and analysis in food and feed. SANTE/11813/2017.
139. Lehotay SJ, Sapozhnikova Y, Mol HGJ. Current issues involving screening and identification of chemical contaminants in foods by mass spectrometry. Trends Anal Chem. 2015;69:62–75.
140. Lehotay SJ, Mastovska K, Amirav A, Fialkov AB, Alon T, Martos PA, et al. Identification and confirmation of chemical residues in food by chromatography-mass spectrometry and other techniques. Trends Anal Chem. 2008;27:1070–90.
141. Ellison SLR, Hardcastle WA. Causes of error in analytical chemistry: results of web-based survey of proficiency testing participants. Accred Qual Assur. 2012;17:453–64.
142. Ambrus Á, Zentai A, Sali J, Ficzere I. Hidden contributors to uncertainty and accuracy of results of residue analysis. Accred Qual Assur. 2011;16:3–11.
143. Kuselman I, Pennechi F, Epstein M, Fajgelj A, Ellison SLR. Monte Carlo simulation of expert judgments on human errors in chemical analysis—a case study of ICP-MS. Talanta. 2014;130:462–9.
144. Kuselman I, Pennecchi F, Bich W, Hibbert DB. Human being as a part of measuring system influencing measurement results. Accred Qual Assur. 2016;21:421–4.
145. Kuselman I, Pennecchi F. Human errors and measurement uncertainty. Metrologia. 2015;52:238–43.
146. Kovac J. What is an ethical chemist? Chimia. 2017;71:38–43.
147. Knolhoff AM, Croley TR. Non-targeted screening approaches for contaminants and adulterants in food using liquid chromatography hyphenated to high resolution mass spectrometry. J Chromatogr A. 2016;1428:86–96.
148. Koster S, Boobis AR, Cubberly R, Hollnagel HM, Richling E, Wildemann T, et al. Application of the TTC concept to unknown substances found in analysis of foods. Food Chem Toxicol. 2011;49:1643–60.
149. Asnin LD. Peak measurement and calibration in chromatographic analysis. Trends Anal Chem. 2016;81:51–62.

150. Van Stee LLP, Brinkman UAT. Peak detection methods for GC × GC: an overview. Trends Anal Chem. 2016;83:1–13.
151. Isaacman-VanWertz G, Sueper DT, Aikin KC, Lerner BM, Gilman JB, de Gouw JA, et al. Automated single-ion peak fitting as an efficient approach for analyzing complex chromatographic data. J Chromatogr A. 2017;1529:81–92.
152. Lehotay SJ. Utility of the summation chromatographic peak integration function to avoid manual reintegrations in the analysis of targeted analytes. LCGC N Am. 2017;35:391–402.
153. Andrade JM, Estévez-Pérez MG. Statistical comparison of the slopes of two regression lines: a tutorial. Anal Chim Acta. 2014;838:1–12.
154. Francq BG, Govaerts BB. Measurement methods comparison with errors-in-variables regressions. From horizontal to vertical OLS regression, review and new perspectives. Chemom Intell Lab Syst. 2014;134:123–39.
155. Nanita SC, Kaldon LG. Emerging flow injection mass spectrometry methods for high-throughput quantitative analysis. Anal Bioanal Chem. 2016;408:23–33.
156. Samarajeewa U, Wei CI, Huang TS, Marshall MR. Application of immunoassay in the food-industry. Crit Rev Food Sci Nutr. 1991;29:403–34.
157. Li YF, Sun YM, Beier RC, Lei HT, Gee S, Hammock BD, et al. Immunochemical techniques for multianalyte analysis of chemical residues in food and the environment: a review. Trends Anal Chem. 2017;88:25–40.
158. Jha SN, Jaiswal P, Grewal MK, Gupta M, Bhardwaj R. Detection of adulterants and contaminants in liquid foods—a review. Crit Rev Food Sci Nutr. 2016;56:1662–84.
159. McGrath TF, Elliott CT, Fodey TL. Biosensors for the analysis of microbiological and chemical contaminants in food. Anal Bioanal Chem. 2012;403:75–92.
160. Liu AP, Anfossi L, Shen L, Li C, Wang XH. Non-competitive immunoassay for low-molecular-weight contaminants detection in food, feed and agricultural products: a mini-review. Trends Food Sci Technol. 2018;71:181–7.
161. Yan X, Li HX, Yan Y, Su XG. Developments in pesticide analysis by multi-analyte immunoassays: a review. Anal Methods. 2014;6:3543–54.
162. Unger RH, Eisentraut AM, McCall MS, Keller S, Lanz HC, Madison LL. Glucagon antibodies and their use for immunoassay for glucagon. Proc Soc Exp Biol Med. 1959;102:621–3.
163. Hird SJ, Lau BPY, Schuhmacher R, Krska R. Liquid chromatography-mass spectrometry for the determination of chemical contaminants in food. Trends Anal Chem. 2014;59:59–72.
164. Gomaa A, Boye J. Simultaneous detection of multi-allergens in a food matrix using ELISA, multiplex flow cytometry and liquid chromatography mass spectrometry (LC-MS). Food Chem. 2015;175:585–92.
165. De Medici D, Kuchta T, Knuttson R, Angelov A, Auricchio B, Barbanera M, et al. Rapid methods for quality assurance of foods: the next decade with polymerase chain reaction (PCR)-based food monitoring. Food Anal Methods. 2015;8:255–71.
166. Goudreau DN, Smith M, EM MC, Ruscito A, Velu R, Callahan J, et al. Aptamer-based sensing techniques for food safety and quality. In: Lu X, editor. Sensing techniques for food safety and quality control. Cambridge: Royal Society of Chemistry; 2017. p. 200–71.
167. Duan N, Wu SJ, Dai SL, Gu HJ, Hao LL, Ye H, et al. Advances in aptasensors for the detection of food contaminants. Analyst. 2016;141:3942–61.
168. Wegner KD, Tran MV, Massey M, Algar WR. Quantum dots in the analysis of food safety and quality. In: Lu X, editor. Sensing techniques for food safety and quality control. Cambridge: Royal Society of Chemistry; 2017. p. 17–60.
169. Zhou JW, Zou XM, Song SH, Chen GH. Quantum dots applied to methodology on detection of pesticide and veterinary drug residues. J Agric Food Chem. 2018;66:1307–19.
170. Yaseen T, Sun DW, Cheng JH. Raman imaging for food quality and safety evaluation: fundamentals and applications. Trends Food Sci Technol. 2017;62:177–89.
171. Yaseen T, Pu HB, Sun DW. Functionalization techniques for improving SERS substrates and their applications in food safety evaluation: a review of recent research trends. Trends Food Sci Technol. 2018;72:162–74.
172. Hao N, Wang K. Recent development of electrochemiluminescence sensors for food analysis. Anal Bioanal Chem. 2016;408:7035–48.
173. Rotariu L, Lagarde F, Jaffrezic-Renault N, Bala C. Electrochemical biosensors for fast detection of food contaminants trends and perspective. Trends Anal Chem. 2016;79:80–7.
174. Reverte L, Prieto-Simon B, Campas M. New advances in electrochemical biosensors for the detection of toxins: nanomaterials, magnetic beads and microfluidic systems. A review. Anal Chim Acta. 2016;908:8–21.
175. Lehotay SJ, Lu X. Sensing techniques for food safety and quality control. Anal Bioanal Chem. 2018;410:2271–2.
176. Soares RG, Ricelli A, Fanelli C, Caputo D, de Cesare G, Chu V, et al. Advances, challenges and opportunities for point-of-needs screening of mycotoxins in foods and feeds. Analyst. 2018;143:1015–35.
177. Marcinkowska M, Baralkiewicz D. Multielemental speciation analysis by advanced hyphenated technique—HPLC/ICP-MS: a review. Talanta. 2016;161:177–204.
178. Hajeb P, Sloth JJ, Shakibazadeh S, Mahyudin NA, Afsah-Hejri L. Toxic elements in food: occurrence, binding, and reduction approaches. Compr Rev Food Sci Food Saf. 2014;13:457–72.
179. Peng JY, Liu F, Zhou F, Song KL, Zhang C, Ye LH, et al. Challenging applications for multi-element analysis by laser-induced breakdown spectroscopy in agriculture: a review. Trends Anal Chem. 2016;85:260–72.
180. Markiewicz-Keszycka M, Cama-Moncunill X, Casado-Gavalda MP, Dixit Y, Cama-Moncunill R, Cullen PJ, et al. Laser-induced breakdown spectroscopy (LIBS) for food analysis: a review. Trends Food Sci Technol. 2017;65:80–93.
181. Butcher DJ. Atomic fluorescence spectrometry: a review of advances in instrumentation and novel applications. Appl Spectrosc Rev. 2016;51:397–416.
182. Taylor A, Barlow N, Day MP, Hill S, Patriarca M, White M. Atomic spectrometry update: review of advances in the analysis of clinical and biological materials, foods and beverages. J Anal At Spectrom. 2017;32:432–76.

**Analytical and Bioanalytical Chemistry**

**Electronic Supplementary Material**

# Hits and misses in research trends to monitor contaminants in foods

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A trend with respect to broader internationalization of scientific efforts is taking place in analytical chemistry, and surely other fields of science, too. In particular, the no. pubs (co-) authored by Chinese scientists has increased dramatically in the past two decades, as shown in Fig. S1 displays the percentage of total pubs in *Anal. Chem.* linked to region and/or country since 1992 according to the Web of Science. The total no. pubs in Anal. Chem. increased from 640 in 1992 to 1,815 in 2017, but the growth in no. pubs by (co-)authors from China far outpaced any other country by far, as shown in Fig. S1. The work may not have been done in China, but countries of origin for the author institutions are recorded in the Web of Science core database. Notably, international collaborations have also skyrocketed, with only a 6% greater no. pubs listed by country than actual in 1992, rising in a quadratic curve to 32% in 2017. The average annual change in country share of pubs in *Anal. Chem.* from North America (USA and Canada) fell by 3.7% from 1993 to 2017 (see Fig. S1), which was made up by 2.8% average annual growth in the share from Western Europe, 6.7% from East Asia, 7% from Africa, 9.7% from Eastern Europe, 10.7% from Central/West Asia, 13.9% from Latin America, and 14.7% from Oceania (Australia and New Zealand). However, double counting of pubs within regions inflates these rates, such as co-authors from both Australia and New Zealand on the same paper would count toward two pubs for Oceania (and a pub by co-authors from 6 different Western European countries would count as 6 pubs in this accounting).

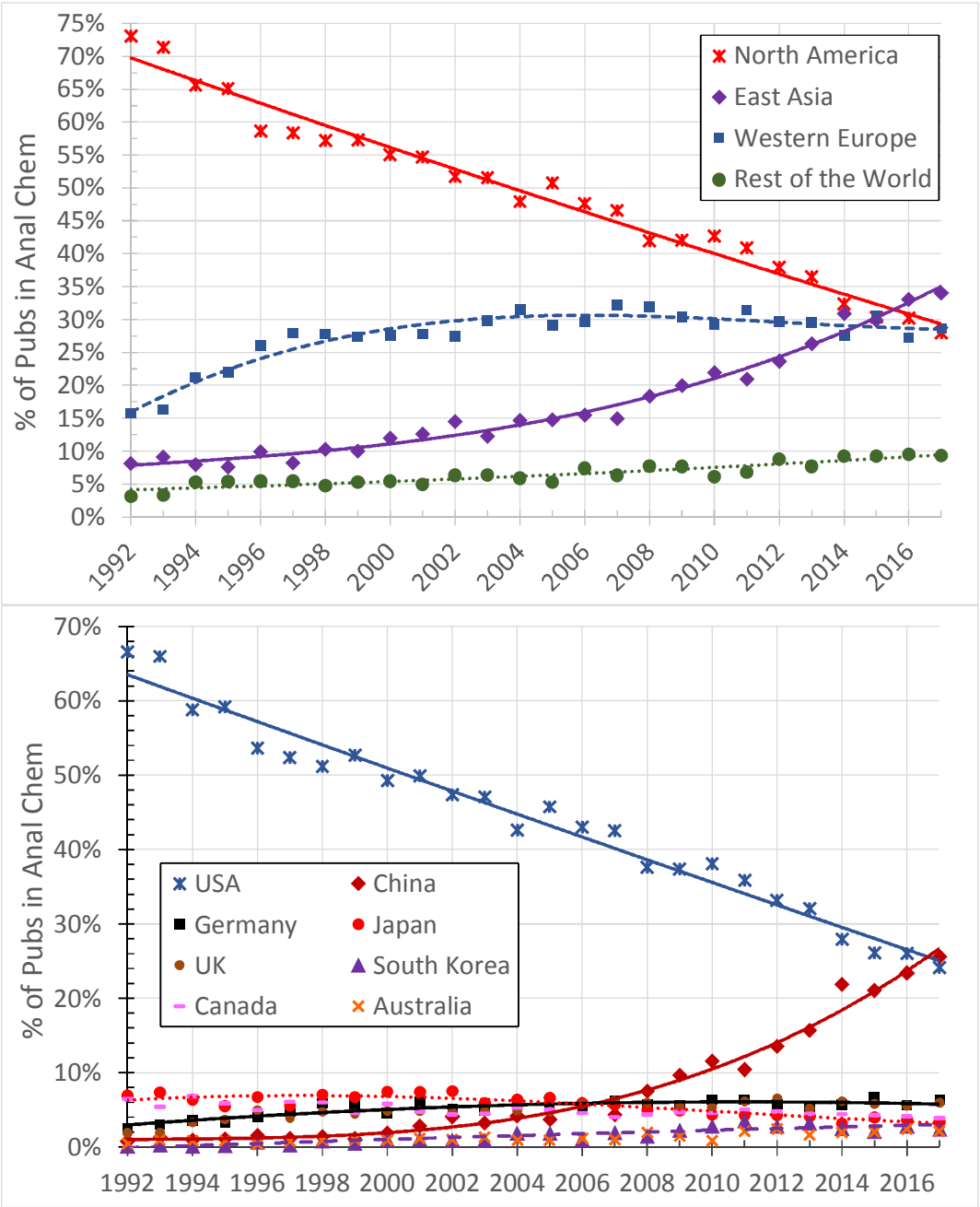



**Fig. S1** Trends in (co-)author countries of origin of pubs in *Anal. Chem.* since 1992 according to the Web of Science: (top) most common regions; and (bottom) most common countries. East Asia surpassed North America in 2016 and China exceeded the USA in 2017 for the first time

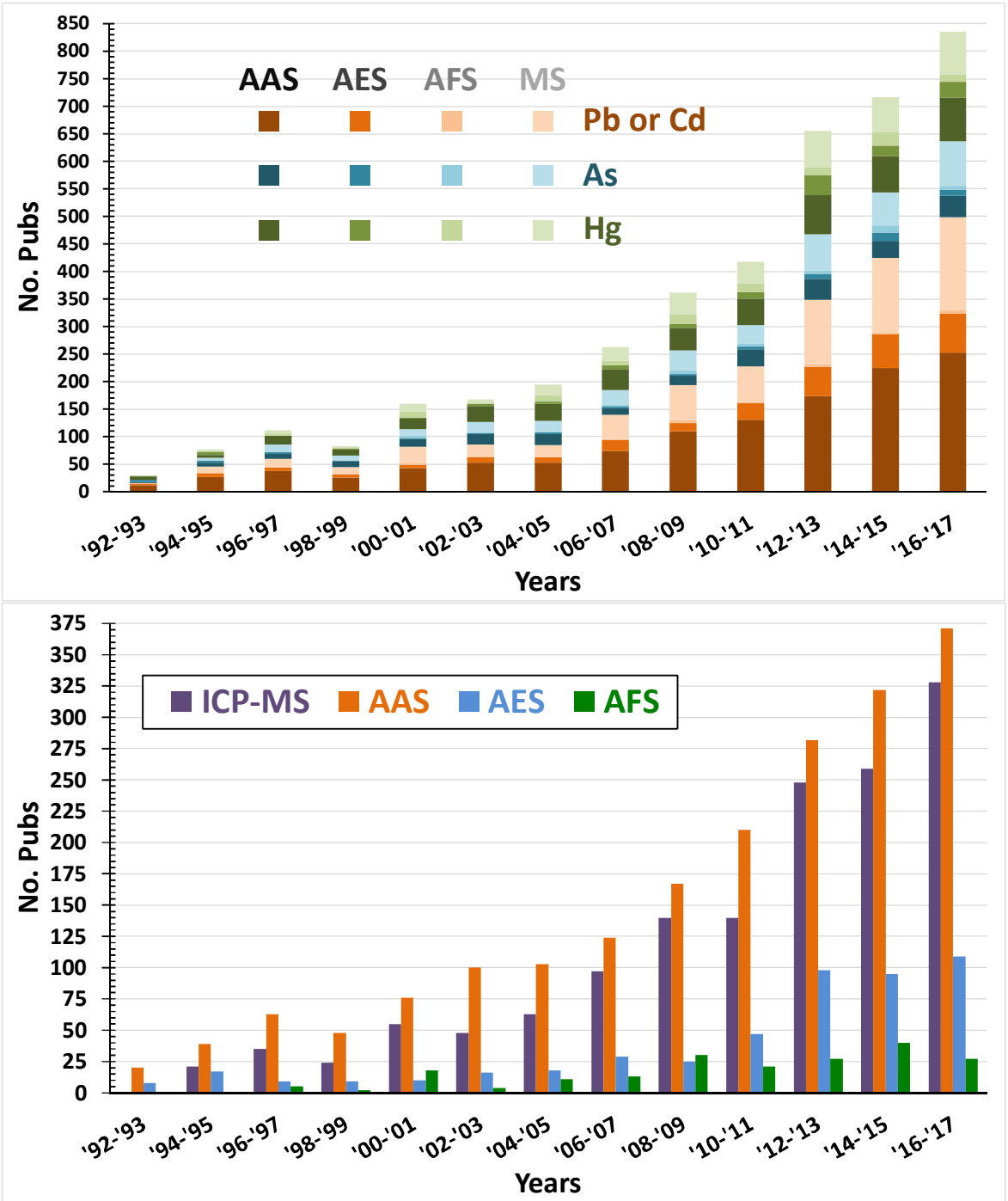



**Fig. S2** No. pubs over time in Web of Science searches of food analysis for the given metals using different means of spectrometry

**Toxic metals**

In the case of metals, ICP-MS has the advantage to permit very accurate multi-elemental analysis simultaneously at very low concentrations. For example, Costas et al. were able to quantitatively determine up to 40 elements (Ag, As, Ba, Cd, Co, Cr, Cu, Ga, Mn, Mo, Nb, Ni, Pb, Rb, Sb, Se, Sn, Sr, Ta, Te, Th, Ti, U, V. Zn, Zr and the lanthanides Ce, Dy, Er, Eu, Gd, Ho, La, Lu, Nd, Pr, Sm, Tm, Y, and Yb) in seafood using quadrupole-ICP-MS.[1] Improvements in ICP-MS technology include improved aerosol generation, optimization of the MS collision cell, and combination of ICP-MS with organic-based MS, all of which were described in a review by Taylor et. al.[2] The authors also emphasized the benefits increased selectivity gained by combining separation techniques with ICP-MS for improved speciation of organometallic compounds in food products.

Elemental methods of analysis typically involve rather different approaches for sample preparation and detection compared to organic chemicals in foods. The analysts may work in the same monitoring labs with colleagues who conduct methods for pesticides, veterinary drugs, and/or other contaminants, but analytical chemists who specialize in metals analysis tend to focus only on that topic. The same trends of rapid, streamlined, automated sample preparation of complex samples and increasingly sensitive and selective, multi-analyte analysis using advanced technologies are occurring in the atomic analysis arena. Analysis of the toxic metals of most concern listed below have already been reviewed.[3]

**Arsenic.** Arsenic (As) is a poisonous element that occurs naturally in soil, water, plants, and other sectors in the environment. Recent extensive reviews of methods for analysis for As, including its speciation, have already been published.[4, 5] While inorganic forms of As are the most toxic, the methylated As species have intermediate toxicity, and the tetraalkylate is relatively non-toxic.[6] The modern scientific community has developed many sophisticated analytical techniques to determine As species in food and other matrices.[6-9] As commonly exists in four oxidation states (-3, 0, +3 and +5), and it is well documented that As species can alter their oxidation states during sample collection, storage, extraction, and chromatographic separation.[7]

Rice is a staple food in many human diets worldwide, and it also contains the highest concentration level of inorganic As due to its relative high uptake from water and soil by rice. Extracting arsenic from rice a critical step in the analysis has been the focus of many studies.[10-14] For example, a rapid sample treatment method was developed using an ultrasonic probe to accelerate enzymatic hydrolysis thereby enhancing extraction of As.[11] This novel extraction procedure reduced sample preparation time from hours[15] to a few minutes. The ultrasonic-assisted enzymatic extraction method has been extended to other food groups as well.[16] One study demonstrated that using partial digestion with nitric acid could achieve complete As extraction from a variety of brown rice samples. The optimized conditions were devised so that no organic As species were converted to inorganic As.[12] Narukawa and co-workers developed a MAE technique using water as the extraction solvent for As speciation analysis, claiming that it was the most suitable such method for rice.[13] They also developed a more universal approach by replacing MAE with a simple heat-assisted aqueous extraction. Another study involved the investigation of MAE, concluding that closed microwave digestion under optimized conditions was very successful for As analysis in rice.[14] To address the issue whether determination of inorganic As in rice is method dependent or not, a study was conducted designed involving 98

labs around the world.[17] The results indicated that the determined concentration of inorganic As in rice was independent of the analytical method used.

HPLC-ICP-MS is most common As speciation method due to its high degree of selectivity and low detection limits achieved.[7, 8, 18] This technique was applied to As determination and new species identification in many types of foods.[19-22] Yet, the method has been continuously modified and improved to be faster, more efficient, and yield higher quality results.[23-25] Alternately, hydride generation atomic fluorescence spectrometry (HG-AFS) is a lower cost technique that provides similar selectivity, sensitivity, linear dynamic range, but lacks the multi-element capability of ICP-MS.[26, 27]

Another low cost approach, based on AAS detection, has also been developed by Rasmussen et al.[28] They incorporated hydrochloric acid/$H_2O_2$ for extraction to convert As(III) to As(V), subsequently selectively eluted As(V) using strong anion exchange in SPE, and quantified the inorganic As with HG-AAS. This method was applied to 20 marine foods and feed samples with acceptable sensitivity and excellent recoveries. Another rapid and efficient screening procedure for As speciation in fish-based baby foods was developed by García et al. using electrothermal AAS.[29]

An identification method of As species was developed based on monitoring different behaviors of organic and inorganic As atomization using different chemical modifiers.[29, 30] A very elaborate As speciation approach was reported by Sartal et al. who applied a two-dimensional HPLC-ICP-MS and ESI-MS/MS to reveal that the only 12-16% of As was bioavailable in edible seaweed.[31] In another study, Yang et al. demonstrated that LC with Orbitrap MS detection provided better confidence to identify arsenic species based on high mass accuracy than ICP-MS.[32]

**Mercury.** Mercury (Hg) is a toxic volatile heavy metal existing in several forms: zero oxidation state $Hg^0$, mercurous state $Hg_2^{2+}$ and mercuric state $Hg^{2+}$. In general, methylmercury ($MeHg^+$) is considered a greater concern than inorganic Hg due to the bioaccumulation of $MeHg^+$ through the food chain. Hg is one of the most toxic elements to humans,[33, 34] and seafood is the predominant food monitored on account of MeHg bioaccumulation, but analysis of Hg is notoriously difficult. A review described isotope dilution analysis in seafood applications.[35] The review presented advantages and limitations of isotope dilution for species-unspecific and species-specific Hg analytes in tuna samples. Ferreira et al. recently reviewed Hg analysis of foods.[36]

In terms of sample preparation, avoiding inter-conversions between Hg species is an important consideration. A comprehensive evaluation of 8 different sample preparation procedures was presented by Reyes and co-workers in 2008.[37, 38] They concluded that MAE using alkaline conditions was among the best techniques to avoid transformation of Hg species. A similar conclusion was drawn based on good analyte recoveries in other studies.[38, 39] Ultrasound assisted extraction is another approach causing minimal Hg transformations, which has been evaluated using GC-ICP-MS with isotope dilution analysis. The method was applied to real samples and showed high species preservation rate.[40]

Additionally, SPE can be used to extract and pre-concentrate Hg from the sample in the field to avoid problems associated with sample stability of Hg during lengthy sample transportation and storage times.[41] A re-usable SPE sorbent was developed using magnetic nanoparticles doped with 1,5-diphenylcarbazide,[42] which not only has high capacity and

selectivity for Hg, but it also can be easily separated from matrix extracts by applying an external magnetic field.

Hg can be detected through various spectrometric methods such as AAS,[43, 44] atomic emission spectrometry (AES),[45] AFS,[46] and ICP-MS.[47, 48] Independent of the detection method, cold-vapor atomization was tailored for Hg due to its high vapor pressure at room temperature. This serves to lower detection limits in Hg to ng/g levels using the spectrometric techniques mentioned above. Cold vapor generation also has been conveniently incorporated with on-line Hg speciation to rapidly provide pre-concentrated prior to detection.[49, 50] Using a gold trap in a conventional electrothermal atomizer, graphite furnace AAS was shown to be an effective way to determine organic and inorganic forms of Hg in fish tissues.[51]

In an electrochemical method, novel modification of a graphite electrode was developed using L-cysteine based on the property of strong Hg-S affinity. Inside the graphite electrode, organic and inorganic Hg can be converted to Hg vapor, resulting in an accurate and sensitive Hg speciation method using AFS for analysis.[46]

**Lead.** Lead (Pb) is a heavy metal and a toxic element which contaminates food mainly from industrial release .into the environment. AAS and ICP-AES are common techniques for determining Pb in foods and other environmental substances, and oftentimes Pb is analyzed at the same time as cadmium and other toxic heavy metals in food.[1, 2, 52, 53] A sample pre-concentration step is often required before submitting samples for trace analysis. A list of conventional sample preparation procedures and common analytical methods for Pb were reviewed by Korn et al.[54] The report described pros and cons associated with the sample pre-concentration methods such as liquid-liquid extraction, SPE, co-precipitation, and cloud point extraction. Since then, a different chelating reagent was used to enrich Pb from a wide variety foods using the co-precipitation method.[55] An on-line pre-concentration method for determination of Pb was developed by coupling cloud point extraction with a flow injection system.[56] A flotation separation technique based on forming a Pb-Fe ion complex was able to pre-concentrate Pb in water and vegetable samples.[57]

SPE is a popular technique for the enrichment of Pb prior to its detection, and advancements in SPE have involved the development of sorbents with large adsorption capacity and high selectivity. Xiang et al described how chemically-modified peanut shell contained activated carbon that could be used to extract Pb from tea, liquor, and milk powder.[58] A new hybrid inorganic-organic mesoporous silica was synthesized for SPE pre-concentration and determination of Pb followed by flame AAS.[59] Novaes et al. demonstrated a rapid, simple, and sensitive method of extracting Pb in water samples using a minicolumn packed with functionalized sorbent.[60] Sorbents with similar concept such as functionalized forms of polyurethane were also evaluated.[61, 62] Novel materials such as macrocyclic crown ethers and nano-carbonstructure graphene have been introduced as sorbents for Pb enrichment.[63, 64]

Novel solvent combinations have also been developed to improve liquid-liquid extraction methods for Pb.[65] DLLME has improved technique provides higher extraction speed and lower solvent consumption compared to the conventional liquid-liquid extraction.[66, 67] The ionic liquid $[C_4tmsim][PF_6]$ was used to replace an organic solvent extraction procedure for large water sample analysis to reduce environmental impact. Due to the high viscosity, thermal stability, and low volatility of ionic liquids, they have been successfully applied to single-drop micro-extraction for electrothermal AAS determination of Pb in water samples.[68, 69]

1. M. Costas, F. Pena, S. Gil, C. Bendicho and I. Lavilla, *At. Spectrosc.*, 2011, **32**, 114-126.
2. A. Taylor, M. P. Day, S. Hill, J. Marshall, M. Patriarca and M. White, *J. Anal. At. Spectrom.*, 2013, **28**, 425-459.
3. J. Sardans, F. Montes and J. Penuelas, *Spectrochim. Acta B*, 2010, **65**, 97-112.
4. B. Sadee, M. E. Foulkes and S. J. Hill, *J. Anal. At. Spectrom.*, 2015, **30**, 102-118.
5. T. Llorente-Mirandes, R. Rubio, J. F. Lopez-Sanchez, *Appl. Spectrosc.*, 2017, **71**, 25-69.
6. V. Sele, J. J. Sloth, A.-K. Lundebye, E. H. Larsen, M. H. G. Berntssen and H. Amlund, *Food Chem.*, 2012, **133**, 618-630.
7. K. A. Francesconi and D. Kuehnelt, *Analyst*, 2014, **129**,373-395.
8. I. Komorowicz and D. Baralkiewicz, *Talanta*, 2011, **84**, 247-261.
9. H. M. Anawar, *Talanta*, 2012, **88**, 30-42.
10. B. E. S. Costa, L. M. Coelho, C. S. T. Araújo, H. C. Rezende, N. M. M. Coelho, *J. Chem.*, 2016, #1427154, 11 pp.
11. E. Sanz, R. Munoz-Olivas and C. Camara, *Anal. Chim. Acta*, 2005, **535**, 227-235.
12. M. Hamano-Nagaoka, T. Nishimura, R. Matsuda and T. Maitani, *J.Food Hyg. Soc. Jpn*, 2008, **49**, 95-99.
13. T. Narukawa and K. Chiba, *J. Agric. Food Chem.*, 2010, **58**, 8183-8188.
14. P. Alava, T. Van de Wiele, F. Tack and G. Du Laing, *Anal. Methods*, 2012, **4**, 1237-1243.
15. M. D'Amato, G. Forte and S. Caroli, *J. AOAC Int.*, 2004, **87**, 238-243.
16. V. Dufailly, M. Nicolas, J. Richoz-Payot and E. Poitevin, *J. AOAC Int.*, 2011, **94**, 947-958.
17. M. B. de la Calle, H. Emteborg, T. P. J. Linsinger, R. Montoro, J. J. Sloth, R. Rubio, M. J. Baxter, J. Feldmann, P. Vermaercke and G. Raber, *Trends Anal. Chem.*, 2011, **30**, 641-651.
18. M. Contreras-Acuna, T. Garcia-Barrera, M. A. Garcia-Sevillano and J. L. Gomez-Ariza, *J. Chromatogr. A*, 2013, **1282**, 133-141.
19. Y. L. Chu and S. J. Jiang, *J. Chromatogr. A*, 2011, **1218**, 5175-5179.
20. S. K. V. Yathavakilla, M. Fricke, P. A. Creed, D. T. Heitkemper, N. V. Shockey, C. Schwegel, J. A. Caruso and J. T. Creed, *Anal. Chem.*, 2008, **80**, 775-782.
21. N. P. Vela and D. T. Heitkemper, *J. AOAC Int.*, 2004, **87**, 244-252.
22. S. D. Conklin and P. E. Chen, *Food Addit. Contam. A*, 2012, **29**, 1272-1279.
23. A. Terol, F. Ardini, M. Grotti and J. Luis Todoli, *J. Chromatogr. A*, 2012, **1262**, 70-76.
24. G. Raber, N. Stock, P. Hanel, M. Murko, J. Navratilova and K. A. Francesconi, *Food Chem.*, 2012, **134**, 524-532.
25. A. H. Petursdottir, H. Gunnlaugsdottir, H. Joerundsdottir, A. Mestrot, E. M. Krupp and J. Feldmann, *Anal. Bioanal. Chem.*, 2012, **404**, 2185-2191.
26. P. Vinas, I. Lopez-Garcia, B. Merino-Merono, N. Campillo and M. Hernandez-Cordoba, *Chromatographia*, 2003, **57**, 611-616.
27. S. Garcia-Salgado, M. A. Quijano and M. M. Bonilla, *Anal. Chim. Acta*, 2012, **714**, 38-46.
28. R. R. Rasmussen, R. V. Hedegaard, E. H. Larsen and J. J. Sloth, *Anal. Bioanal. Chem.*, 2012, **403**, 2825-2834.
29. I. Lopez-Garcia, M. Briceno and M. Hernandez-Cordoba, *Anal. Chim. Acta*, 2011, **699**, 11-17.

30. C. G. Bruhn, C. J. Bustos, K. L. Saez, J. Y. Neira and S. E. Alvarez, *Talanta*, 2007, **71**, 81-89.
31. C. Garcia-Sartal, S. Taebunpakul, E. Stokes, M. del Carmen Barciela-Alonso, P. Bermejo-Barrera and H. Goenaga-Infante, *Anal. Bioanal. Chem.*, 2012, **402**, 3359-3369.
32. L. Yang, J. Ding, P. Maxwell, M. McCooeye, A. Windust, L. Ouerdane, S. Bakirdere, S. Willie and Z. Mester, *Anal. Chem.*, 2011, **83**, 3371-3378.
33. Y. Gao, Z. M. Shi, Z. Long, P. Wu, C. B. Zheng and X. D. Hou, *Microchem J.*, 2012, **103**, 1-14.
34. C. Ibanez-Palomino, J. F. Lopez-Sanchez and A. Sahuquillo, *Anal. Chim. Acta*, 2012, **720**, 9-15.
35. S. Clemens, M. Monperrus, O. F. X. Donard, D. Amouroux and T. Guerin, *Talanta*, 2012, **89**, 12-20.
36. S. L. C. Ferreira, V. A. Lemos, L. O. B. Silva, A. F. S. Queiroz, A. S. Souza, E. G. P. da Silva, W. N. L. dos Santos and C. F. das Virgens, *Microchem. J.*, 2015, **121**, 227-236.
37. L. H. Reyes, G. M. M. Rahman, T. Fahrenholz and H. M. S. Kingston, *Anal. Bioanal. Chem.*, 2008, **390**, 2123-2132.
38. L. H. Reyes, G. M. M. Rahman and H. M. S. Kingston, *Anal. Chim. Acta*, 2009, **631**, 121-128.
39. L. H. Reyes, J. L. G. Mar, A. Hernandez-Ramirez, J. M. Peralta-Hernandez, J. M. A. Barbosa and H. M. S. Kingston, *Microchim. Acta*, 2011, **172**, 3-14.
40. D. Esteban-Fernandez, M. Mirat, M. I. M. de la Hinojosa and J. I. G. Alonso, *J. Agric. Food Chem.*, 2012, **60**, 8333-8339.
41. K. Leopold, M. Foulkes and P. J. Worsfold, *Trends Anal. Chem.*, 2009, **28**, 426-435.
42. Y. H. Zhai, S. E. Duan, Q. He, X. H. Yang and Q. Han, *Microchim. Acta*, 2010, **169**, 353-360.
43. Y. L. Zhang and S. B. Adeloju, *Anal. Chim. Acta*, 2012, **721**, 22-27.
44. A. Q. Shah, T. G. Kazi, J. A. Baig, H. I. Afridi and M. B. Arain, *Food Chem.*, 2012, **134**, 2345-2349.
45. T. Frentiu, A. I. Mihaltan, E. Darvasi, M. Ponta, C. Roman and M. Frentiu, *J. Anal. At. Spectrom.*, 2012, **27**, 1753-1760.
46. W. B. Zhang, X. A. Yang, Y. P. Dong and J. J. Xue, *Anal. Chem.*, 2012, **84**, 9199-9207.
47. M. Wojciechowski, A. Krata and E. Bulska, *Chem. Anal.*, 2008, **53**, 797-808.
48. L. R. Drennan-Harris, S. Wongwilawan and J. F. Tyson, *J. Anal. At. Spectrom.*, 2013, **28**, 259-265.
49. E. V. Alonso, M. T. S. Cordero, A. G. de Torres, P. C. Rudner and J. M. C. Pavon, *Talanta*, 2008, **77**, 53-59.
50. M. V. B. Krishna, K. Chandrasekaran and D. Karunasagar, *Talanta*, 2010, **81**, 462-472.
51. F. A. Duarte, C. A. Bizzi, F. G. Antes, V. L. Dressler and E. M. D. Flores, *Spectrochim. Acta B*, 2009, **64**, 513-519.
52. S. Bakirdere, F. Aydin, E. G. Bakirdere, S. Titretir, I. Akdeniz, I. Aydin, E. Yildirim and Y. Arslan, *Appl. Spectrosc. Rev.*, 2011, **46**, 38-66.
53. S. G. Capar, W. R. Mindak and J. Cheng, *Anal. Bioanal. Chem.*, 2007, **389**, 159-169.
54. M. D. A. Korn, J. B. de Andrade, D. S. de Jesus, V. A. Lemos, M. Bandeira, W. N. L. dos Santos, M. A. Bezerra, F. A. C. Amorim, A. S. Souza and S. L. C. Ferreira, *Talanta*, 2006, **69**, 16-24.

55. T. Oymak, S. Tokalioglu, V. Yilmaz, S. Kartal and D. Aydin, *Food Chem.*, 2009, **113**, 1314-1317.
56. R. A. Gil, J. A. Salonia, J. A. Gasquez, A. C. Olivieri, R. Olsina and L. D. Martinez, *Microchem J.*, 2010, **95**, 306-310.
57. M. S. Hosseini and R. Hassan-Abadi, *Int. J. Environ. Anal. Chem.*, 2008, **88**, 199-207.
58. G. Q. Xiang, Y. Huang and Y. F. Luo, *Microchim. Acta*, 2009, **165**, 237-242.
59. D. Perez-Quintanilla, A. Sanchez, I. del Hierro, M. Fajardo and I. Sierra, *Microchim. Acta*, 2009, **165**, 291-298.
60. C. G. Novaes, J. S. Santos, S. L. C. Ferreira and V. A. Lemos, *J. AOAC Int.*, 2010, **93**, 1609-1615.
61. N. Burham, S. M. Abdel-Azeem and F. El-Shahat, *Int. J. Environ. Anal. Chem.*, 2008, **88**, 775-789.
62. V. A. Lemos, A. D. Lima, J. S. Santos, J. T. Castro and S. L. C. Ferreira, *Int. J. Environ. Anal. Chem.*, 2012, **92**, 1121-1134.
63. H. Mizuguchi, M. Ishida, T. Takahashi, A. Sasaki and J. Shida, *Anal. Sci.*, 2011, **27**, 85-89.
64. Y. K. Wang, S. T. Gao, X. H. Zang, J. C. Li and J. J. Ma, *Anal. Chim. Acta*, 2012, **716**, 112-118.
65. Z. J. Li, Q. P. Peng and H. X. Shan, *J. AOAC Int.*, 2007, **90**, 1191-1196.
66. M. T. Naseri, M. R. M. Hosseini, Y. Assadi and A. Kiani, *Talanta*, 2008, **75**, 56-62.
67. D. Afzali, A. R. Mohadesi, M. Falahnejad and B. Bahadori, *J. AOAC Int.*, 2013, **96**, 161-165.
68. J. L. Manzoori, M. Amjadi and J. Abulhassani, *Anal. Chim. Acta*, 2009, **644**, 48-52.
69. E. M. Martinis, P. Berton, J. C. Altamirano, U. Hakala and R. G. Wuilloud, *Talanta*, 2010, **80**, 2034-2040.

**Mycotoxins**

Toxins are chemicals naturally produced by organisms that are harmful to other organisms. Even though the public generally believe "natural" chemicals to be safer, toxins tend to be some of the most toxic chemicals known, thus pose higher risk than other chemicals in food. Mycotoxins are produced by fungi that can grow on crops in the field or during storage, thereby affecting many agricultural products including cereals, animal feed, nuts, fresh and dried fruit, coffee, cocoa, spices, oilseeds, and milk. Common mycotoxins found in human consumption are aflatoxins, ochratoxin A, fumonisins, trichothecenes, zearalenone, ergot alkaloids, and patulin. Table 1 shows a 6-fold increase in the no. pubs on the detection of mycotoxins in food over the past 20 years, which is undoubtedly due in part to improvements in commercial LC-MS instruments.

The determination of mycotoxins in human foods is the subject of multiple reviews in the literature.[70-80] In keeping with the trend in other food safety applications, advancements are often devised to monitor for as many mycotoxins as possible in the same method.[81] Modern analytical tools are starting to allow analytical chemists to meet that challenge, but it is still very difficult to devise a universal method. Matrix interferences complicate sample preparation because the mycotoxins have a high degree of structural diversity which limits the amount of clean-up that can be done without losing analytes.

In any case, modern methods and techniques have enabled mycotoxin analysis beyond the cereal food matrix traditionally of greatest concern, and chemists have taken advantage of QuEChERS-based sample preparation[82] and DART[83] to evaluate many other food types as well.[84-86] QuEChERS,[87] was applied for the screening of mycotoxins in eggs.[85] Cigić et al. presented an overview of conventional and emerging analytical methods for studying mycotoxins with emphasis on sample preparation.[79] They summarized in detail the methodologies applied for the most important mycotoxins in different matrices. For example, 91 different teas and herbal infusion products were analyzed using UHPLC-MS/MS.[84] Similarly, 35 mycotoxins were routinely monitored in traditional Chinese medicines using pressurized liquid extraction (PLE) and UHPLC-MS/MS for analysis.[86] Moreover, LC coupled with a commercial triple quadrupole that utilizes a linear ion trap in the third quadrupole (Q-trap) is considered another promising technique in the field. Although triple quadrupoles, ion-trap, and Q-trap instruments can determine several mycotoxins in a single analysis, LC-TOF-MS has the advantage of covering a wide mass range to help identify nontargeted analytes. One study showed the ability to monitor up to 474 mycotoxins simultaneously.[88] Furthermore, atmospheric pressure photoionization (APPI) has been shown to eliminate sodium or potassium adducts when analyzing aflatoxins in peanuts, red pepper, and corn.[89]

Despite the use of state-of-the-art technology, pitfalls occur in mycotoxin analysis of which analytical chemists should be cognizant. Important issues include: transformation (or "masking") of mycotoxins, how to collect representative subsamples from very large samples, and biases introduced during sample preparation and analysis.[75-77, 80, 90, 91] With respect to sampling, if proper practices are not followed to achieve a representative sample (collected from a series of subsamples), then the analytical result may be misleading. As technology has advanced, newer strategies in sample preparation for mycotoxin analysis have been introduced.[80] Among them, sol-gel immunoaffinity chromatography (IAC), immuno-ultrafiltration, and molecularly imprinted polymers (MIPs)[92] using aptamers as templates are a few innovative approaches of note. A developing trend involving HRMS with an Orbitrap instrument, coupled with highly efficient sample treatment, has much potential to produce both qualitative and quantitative results.[90] The unique feature of this technique is that it can perform nontargeted qualitative analysis to potentially "fish out" degradation products, or "masked" mycotoxins.

**Aflatoxins.** A highly carcinogenic type of mycotoxins named aflatoxins were discovered in 1960 due to the outbreak of "Turkey 'X' disease" in the UK.[93] Two overviews of strategies for their sample preparation and analysis were published.[94, 95] HPLC with fluorescence detection combined with IAC for purification commonly remains the method of choice for official analyses. In particular, this approach has been applied to many oil-based food matrices, such as olive oil, peanut oil, sesame oil, and black and white sesame seeds.[96-98] In order to increase sample throughput, IAC clean-up could be incorporated in-line with HPLC-fluorescence and LC-MS detection.[99, 100] This configuration enabled the analysis to be automatic, rapid, selective and sensitive. For analysis of ultratrace levels of aflatoxins in edible oils, a procedure using dispersive liquid-liquid microextraction (DLLME)[101] preconcentration after IAC clean-up proved to be very effective in eliminating matrix effects and providing high selectivity.[102]

Also, LC column technology has significantly improved, with smaller particle size packing materials (<2 μm) introduced for UHPLC and improved packing sorbents. A detailed comparison study showed that 2.7 μm solid-core particle columns, coated with porous material, can reduce analysis time by ~1/2 compared to columns of 5μm and ~1/3 vs. columns with 3 μm

particles.[103] In another report, use of a silica-based monolithic column enabled >4-fold faster separation of aflatoxins in chili, peanuts, and rice than using a conventional C18 column.[104]

Despite the high selectivity of using IAC for sample clean-up, there are other alternative means to analyze aflatoxins in food matrices. Solid-phase microextraction (SPME) has become a common sample preparation method for volatiles, and it is gaining in usage for semi-volatiles.[105] A novel SPME device based on a sol-gel process for hollow-fiber SPME overcomes the draw-backs of conventional SPME.[106] Using the hollow-fiber SPME procedure, the authors were able to produce a reliable qualitative and quantitative analysis of aflatoxins $B_1$, $B_2$ in cereals at low concentrations. Matrix solid-phase dispersion (MSPD)[107] also enables extraction of aflatoxins from different cereals. Optimization of MSPD for simultaneous extraction of multiple aflatoxins in cereals was described.[108] Combining solid-liquid extraction and DLLME was shown to be a fast and simple novel procedure applied to aflatoxins analysis in maize flour, rice, and pasta.[109] In the case of animal-derived foods, PLE was successfully applied to analysis of aflatoxins and other mycotoxins.[110] Microwave-assisted extraction (MAE) is also useful in sample preparation for determination of aflatoxins in grain products, with the advantages of reduced extraction time and solvent consumption.[111]

One major advantage of using LC-MS/MS for quantifying aflatoxins is the elimination of the derivatization step. Therefore, LC-MS/MS combined with IAC has become more commonly used for analysis of aflatoxins not only in conventional grain food matrixes, but also in other type of foods such as medicinal herbs.[112] UHPLC-MS/MS has been successfully applied in the determination of aflatoxin $M_1$, which is the hydroxylated metabolite of aflatoxin $B_1$ in milk and milk products.[113, 114] In one study, 4 UHPLC columns were compared, demonstrating that UHPLC reduced the separation time and lowered detection limits up to 58 times compared to HPLC.[113] In some cases, aflatoxins can be analyzed by MS without chromatography. A simple and multiplexed method to measure them using TOF combined with secondary ion MS (TOF-SIMS) exhibited the capability to quantify aflatoxin $B_1$ in corn.[115]

**Fumonosins.** Although they are not the most toxic mycotoxins, fusarium toxins are important to monitor because they are often associated with illness of humans and farm animals. Studies of fumonisins and trichothecenes are well-represented in the literature,[116-119] but research on other emerging fusarium toxins is scarce.[120] The presence of fusarium toxins affects the growth and yield of agricultural foods for human and livestock consumption. Intense efforts have been invested to enable fast and reliable analyses of a large number of samples for surveillance and monitoring purposes. As in the case of aflatoxins, HPLC-fluorescence is one of the common techniques for the analysis of fumonisins in food, but it is necessary to derivatize fumonisins with fluorescence reagents to reach an adequately low detection limit. An on-line post-column derivatization method enabled efficient analysis of fumonisins in 112 spices, aromatic and medicinal herbs using HPLC-fluorescence.[121]

PLE was applied to the analysis of fumonisins $B_1$, $B_2$ and $B_3$ in corn-based baby food.[122] This sample extraction technique overcame the drawbacks of the labor-intensive conventional methods using solvent extraction followed by various clean-up steps such as SPE and IAC. Determination of fumonisins B in masa, maize, and their derived products could be challenging due to the difficulties to obtain satisfactory recoveries. A simple phosphate buffer aqueous extraction method was developed to effectively extract fumonisins with average recoveries of 96 ± 2%.[123] A novel modified QuEChERS method for extracting fumonisins from corn was reported by Yang et.al.[124] The mycotoxins were first extracted with methanol-water and then purified

using primary secondary amine (PSA) sorbent. The analytes were released from PSA using 1% formic acid in methanol.

**Masked Mycotoxins.** To carry out a thorough measurement of mycotoxins in food, researchers often have to face another challenge in that a number of mycotoxins can exist in different forms through metabolism. This can potentially cause a public health threat if the human and animal food supplies are exposed to both primary and "masked forms" of mycotoxins, such as DON glycosyl derivatives. A study demonstrated that using HPLC coupled with a linear ion trap MS could monitor for the co-occurrence of DON and the deoxynivalenol-3-glucoside (DON-3G) in different processed cereal-derived products. DON-3G was present between 12-30 μg/kg.[91]

Glucoside derivatives of type A trichothecenes, T-2 and HT-2, present in wheat and oats were first reported by Lattanzio et. al.[90] They used HPLC combined with Orbitrap MS to identify one monoglucoside derivative T-2 and two monoglucoside derivatives of HT-2 in naturally contaminated cereal grain samples. They found that the glucoside derivatives were more likely to be present in wheat than in oats based on the peak area ratios between the derivatives and their free forms. Monaci et al. presented a study of simultaneous determination of DON, T-2 and HT-2 in a processed cereal-based food matrix using Orbitrap technology equipped with a high-energy collision dissociation cell.[125] With this advanced instrumentation, they were able to identify and quantify all three mycotoxins with high confidence while achieving a mass accuracy of 0.5 ppm.

In a unique study, the authors compared direct analysis of crude extracts of deoxynivalenol (DON), zearalenone (ZON), T-2 and HT-2 toxins in animal feed with acetonitrile extracts after IAC cleanup.[126] The acceptability of this approach depended upon whether or not the ion suppression due to the matrix effects were too severe or not. The conclusion was that sample preparation without cleanup was acceptable for screening purposes. Perhaps a more practical approach would be to automate sample clean-up coupled to LC-MS/MS, which would allow direct injection of sample extracts and minimize matrix effects using online chromatographic-based clean-up/separation. Such a method has been developed for the routine analysis of DON, ZON, T-2, HT-2, fumonisins $B_1$ and $B_2$ from maize, wheat, and animal feeds.[127] In this method, a solution of 43:57 water with 0.1% formic acid:acetonitrile provided satisfactory extraction for all target mycotoxins. The extracts were cleaned up, separated, and detected in only 18 min total using turbulent flow chromatography (TFC) coupled with HRMS.


70. F. Berthiller, B. Cramer, M. H. Iha, R. Krska, V. M. T. Lattanzio, S. MacDonald, R. J. Malone, C. Maragos, M. Solfrizzo, M. Stranska-Zachariasova, J. Stroka and S. A. Tittlemier, *World Mycotoxin J.*, 2018, **11**, 5-31.
71. F. Berthiller, C. Brera, M. H. Iha, R. Krska, V. M. T. Lattanzio, S. MacDonald, R. J. Malone, C. Maragos, M. Solfrizzo, M. Stranska-Zachariasova, J. Stroka and S. A. Tittlemier, *World Mycotoxin J.*, 2017, **10**, 5-29.
72. F. Berthiller, C. Brera, C. Crews, M. H. Iha, R. Krska, V. M. T. Lattanzio, S. MacDonald, R. J. Malone, C. Maragos, M. Solfrizzo, M. Stranska-Zachariasova, J. Stroka and T. B. Whitaker, *World Mycotoxin J.*, 2016, **9**, 5-29.
73. F. Berthiller, C. Brera, C. Crews, M. H. Iha, R. Krska, V. M. T. Lattanzio, S. MacDonald, R. J. Malone, C. Maragos, M. Solfrizzo, M. Stranska-Zachariasova, J. Stroka and T. B. Whitaker, *World Mycotoxin J.*, 2015, **8**, 5-35.

74. G. S. Shephard, *Chem. Soc. Rev.*, 2008, **37**, 2468-2477.
75. P. Songsermsakul and E. Razzazi-Fazeli, *J. Liq. Chromatogr. Rel. Technol.*, 2008, **31**, 1641-1686.
76. R. Koppen, M. Koch, D. Siegel, S. Merkel, R. Maul and I. Nehls, *Appl. Microbiol. Biotechnol.*, 2010, **86**, 1595-1612.
77. C. M. Maragos and M. Busman, *Food Addit. Contam. A*, 2010, **27**, 688-700.
78. A. L. Capriotti, G. Caruso, C. Cavaliere, P. Foglia, R. Samperi and A. Lagana, *Mass Spectrom. Rev.*, 2012, **31**, 466-503.
79. I. K. Cigic and H. Prosen, *Int. J. Mol. Sci.*, 2009, **10**, 62-115.
80. M. Cichna-Markl, *World Mycotox. J.*, 2011, **4**, 203-215.
81. P. A. Martos, W. Thompson and G. J. Diaz, *World Mycotox. J.*, 2010, **3**, 205-223.
82. J. Rubert, Z. Dzuman, M. Vaclavikova, M. Zachariasova, C. Soler and J. Hajslova, *Talanta*, 2012, **99**, 712-719.
83. L. Vaclavik, M. Zachariasova, V. Hrbek and J. Hajslova, *Talanta*, 2010, **82**, 1950-1957.
84. S. Monbaliu, A. B. Wu, D. B. Zhang, C. Van Peteghem and S. De Saeger, *J. Agric. Food Chem.*, 2010, **58**, 12664-12671.
85. A. L. Capriotti, C. Cavaliere, S. Piovesana, R. Samperi and A. Lagana, *J. Chromatogr. A*, 2012, **1268**, 84-90.
86. Z. Han, Y. P. Ren, J. F. Zhu, Z. X. Cai, Y. Chen, L. J. Luan and Y. J. Wu, *J. Agric. Food Chem.*, 2012, **60**, 8233-8247.
87. M. Anastassiades, S. J. Lehotay, D. Stajnbaher and F. J. Schenck, *J. AOAC Int.*, 2003, **86**, 412-431.
88. K. F. Nielsen and J. Smedsgaard, *J. Chromatogr. A*, 2003, **1002**, 111-136.
89. A. L. Capriotti, P. Foglia, R. Gubbiotti, C. Roccia, R. Samperi and A. Lagana, *J. Chromatogr. A*, 2010, **1217**, 6044-6051.
90. V. M. T. Lattanzio, A. Visconti, M. Haidukowski and M. Pascale, *J. Mass Spectrom.*, 2012, **47**, 466-475.
91. M. Suman, E. Bergamini, D. Catellani and A. Manzitti, *Food Chem.*, 2013, **136**, 1568-1576.
92. L. Ye and K. Mosbach, *Chem. Mat.*, 2008, **20**, 859-868.
93. G. N. Wogan, T. W. Kensler and J. D. Groopman, *Food Addit. Contam. A*, 2012, **29**, 249-257.
94. G. S. Shephard, *Anal. Bioanal. Chem.*, 2009, **395**, 1215-1224.
95. E. Reiter, J. Zentek and E. Razzazi, *Mol. Nutr. Food Res.*, 2009, **53**, 508-524.
96. L. Bao, M. W. Trucksess and K. D. White, *J. AOAC Int.*, 2010, **93**, 936-942.
97. L. Bao, C. Z. Liang, M. W. Trucksess, Y. L. Xu, N. Lv, Z. X. Wu, P. Jing and F. S. Fry, *J. AOAC Int.*, 2012, **95**, 1689-1700.
98. G. H. Liu, Z. Zhu, J. Q. Cheng and H. Z. Senyuva, *J. AOAC Int.*, 2012, **95**, 122-128.
99. Y. Nonaka, K. Saito, N. Hanioka, S. Narimatsu and H. Kataoka, *J. Chromatogr. A*, 2009, **1216**, 4416-4422.
100. S. Jinap, T. C. De Rijk, S. Arzandeh, H. C. H. Kleijnen, P. Zomer, G. Van der Weg and J. G. J. Mol, *Food Control*, 2012, **26**, 42-48.
101. V. Andruch, I. S. Balogh, L. Kocurova and J. Sandrejova, *Appl. Spectrosc. Rev.*, 2013, **48**, 161-259.

102. D. Afzali, M. Ghanbarian, A. Mostafavi, T. Shamspur and S. Ghaseminezhad, *J. Chromatogr. A*, 2012, **1247**, 35-41.
103. A. Medina and N. Magan, *J. Chromatogr. B*, 2012, **889**, 138-143.
104. W. S. Khayoon, B. Saad, T. P. Lee and B. Salleh, *Food Chem.*, 2012, **133**, 489-496.
105. H. H. Jelen, M. Majcher and M. Dziadas, *Anal. Chim. Acta*, 2012, **738**, 13-26.
106. Z. Es'haghi, H. Sorayaei, F. Samadi, M. Masrournia and Z. Bakherad, *J. Chromatogr. B*, 2011, **879**, 3034-3040.
107. A. L. Capriotti, C. Cavaliere, P. Giansanti, R. Gubbiotti, R. Samperi and A. Lagana, *J. Chromatogr. A*, 2010, **1217**, 2521-2532.
108. J. Rubert, C. Soler and J. Manes, *Talanta*, 2010, **82**, 567-574.
109. L. Campone, A. L. Piccinelli, R. Celano and L. Rastrelli, *J. Chromatogr. A*, 2011, **1218**, 7648-7654.
110. D. M. Chen, X. Q. Cao, Y. F. Tao, Q. H. Wu, Y. H. Pan, L. L. Huang, X. Wang, Y. L. Wang, D. P. Peng, Z. L. Liu and Z. H. Yuan, *J. Chromatogr. A*, 2012, **1253**, 110-119.
111. S. Chen and H. Zhang, *Anal. Bioanal. Chem.*, 2013, **405**, 1623-1630.
112. L. N. Liu, H. Y. Jin, L. Sun, S. C. Ma and R. C. Lin, *Phytochem. Anal.*, 2012, **23**, 469-476.
113. W. L. Chen, T. F. Hsu and C. Y. Chen, *J. AOAC Int.*, 2011, **94**, 872-877.
114. E. Beltran, M. Ibanez, J. V. Sancho, M. A. Cortes, V. Yusa and F. Hernandez, *Food Chem.*, 2011, **126**, 737-744.
115. J. H. Ahn, Y. S. Jeong, T. G. Lee, Y. P. Kim and H. S. Kim, *Biochip J.*, 2012, **6**, 34-40.
116. C. Falavigna, M. Cirlini, G. Galaverna, S. Sforza, A. Dossena and C. Dall'Asta, *J. Mass Spectrom.*, 2012, **47**, 1170-1176.
117. P. M. Scott, *Food Addit. Contam. A*, 2012, **29**, 242-248.
118. H. Tanaka, M. Takino, Y. Sugita-Konishi, T. Tanaka, A. Toriba and K. Hayakawa, *Rap. Commun. Mass Spectrom.*, 2009, **23**, 3119-3124.
119. F. M. Valle-Algarra, E. M. Mateo, R. Mateo, J. V. Gimeno-Adelantado and M. Jimenez, *Talanta*, 2011, **84**, 1112-1117.
120. A. Santini, R. Ferracane, G. Meca and A. Ritieni, *Anal. Bioanal. Chem.*, 2009, **395**, 1253-1260.
121. W. J. Kong, T. T. Xie, J. Y. Li, J. H. Wei, F. Qiu, A. D. Qi, Y. G. Zheng and M. H. Yang, *Analyst*, 2012, **137**, 3166-3174.
122. G. D'Arco, M. Fernandez-Franzon, G. Font, P. Damiani and J. Manes, *J. Chromatogr. A*, 2008, **1209**, 188-194.
123. A. Pietri and T. Bertuzzi, *Food Anal. Methods*, 2012, **5**, 1088-1096.
124. Q. F. Yang and Y. L. Wu, *Chromatographia*, 2012, **75**, 1075-1080.
125. L. Monaci, E. De Angelis and A. Visconti, *J. Chromatogr. A*, 2011, **1218**, 8646-8654.
126. H. Z. Senyuva, J. Gilbert, G. Turkoz, D. Leeman and C. Donnelly, *J. AOAC Int.*, 2012, **95**, 1701-1708.
127. E. Ates, K. Mittendorf, J. Stroka and H. Senyuva, *Food Addit. Contam. A*, 2013, **30**, 156-165.

**Bio-Security Agents**

Toxins with high lethality and ease of production can be potentially used as biological weapons for terror attacks. Most of these type of toxins are peptides and/or proteins, such as ricin, staphylococcal enterotoxins B and A (SEB and SEA), and botulinum neurotoxins (BoNT). MS-based proteomics can serve as a better technique for detection rather than conventional DNA-based technologies because it can provide three functions in one system: detection, identification and quantification.[128-130] In one study, researchers developed an MS method to successfully detect all 7 toxin types of BoNT (A-G).[131] Matrix-assisted laser desorption ionization (MALDI) coupled with TOF or ion trap MS enabled the researchers to isolate and identify the subtype of BoNT A from spiked milk. Knowing the toxin subtype, the investigators were able to track down the source of multiple botulism outbreaks.[131] Similarly, Fagerquist et al. performed a top-down proteomic study using MALDI-TOF-TOF MS/MS to identify the disulfide-intact and disulfide-reduced β-subunit of Shiga toxin 2 from *Escherichia coli* O157:H7.[132] Pedersen et al. recently questioned the ability of current food safety monitoring schemes to detect deliberate contamination with chemical agents.[133]

*Bacillus anthracis* is one of the most dangerous toxins, and ranks the highest bioterrorism concern according to the Centers for Disease Control (CDC) in the US. A sensitive method of detecting B. *anthracis* spores at the level of the infectious dose in milk was developed by combining immunocapture and targeted MS.[134] With further improvement, the scientists proposed that the total experimental time could be reduced to a few hours, which can be an important factor in a crisis situation. They fulfilled their goal in a subsequent quantification of epsilon toxin (ETX) by a thorough optimization of the protocol.[135] A rapid quantification of ETX in complex food matrices by immunopurification and UHPLC-MS/MS was achieved in <4 h without losing sensitivity.

Some foodborne pathogens are difficult to identify because of the complex food matrix. Ion suppression of proteins extracted from bacteria can be so severe that sometimes it is infeasible to directly identify the toxins. Using a zirconium hydroxide immobilization approach, Chen et al. were able to isolate both Gram-positive and Gram-negative bacteria cells from foods then followed a proteomic method to identify microorganisms in nonfat dry milk, pudding, and coffee using MALDI-TOF and LC-MS/MS.[136]

Using apple juice as the food model, a proteomics-based MS approach was applied to detect, identify, and quantify SEB.[137] The procedure involved ultrafiltration to remove low molecular weight substances, enzymatic digestion of high molecular weight proteins, and analysis of the digested peptides by LC-MS. This method showed difficulties with milk samples due to the high protein content. This shortcoming was soon overcome by a protein precipitation followed by gel electrophoresis for separation. The extraction method used a mixture of dichloromethane and acidified water to accomplish two tasks: 1) dissolve the milk fat, and 2) sink the fat layer beneath the casein precipitate. In this way, the top protein layer is separated from casein and fat.[138]

To reduce sample preparation time and improve quantification, SEB and SEA can also be measured in whole protein forms. By eliminating the enzymatic digestion step, the quantification process was very efficient, and digestion was avoided.[139] Dupuis et al. demonstrated that using isotope-labeled proteins as isotope-dilution standards could offer the largest sequence coverage for quantification of SEA in coco-pearls (Chinese dessert) thereby avoiding differences in the digestion yields between the internal standard and the protein analyte.[140]

Ricin is a highly toxic protein toxin from the castor oil plant. MALDI-TOF is the typical approach used for detecting ricin due to its advantages of high sensitivity, ease of operation, and rapid speed of analysis. By combining immunoaffinity capture with MALDI-TOF, ricin could be detected in milk at low-ng levels,[141] which was further improved by Kalb and co-workers.[142] They developed a method with three separate ways to confirm the presence of ricin in food matrices. Firstly, ricin was immunoaffinity-captured and the activity of ricin was examined with a DNA substrate. Secondly, the DNA substrate was analyzed using MALDI-TOF MS. Lastly, ricin was identified through peptide mapping using LC-MS/MS. This approach provided unambiguous detection of ricin in milk, apple juice, and clinical samples tested. Quantification of ricin in tap water, 2% milk, and apple and orange juices was later performed using isotope dilution MS by the same group of researchers.[143] The method was able to quantify ricin 100,000-fold lower than the estimated $LD_{50}$.

In an outbreak situation, a rapid sensitive screening method of multiple toxins would be very desirable. Kull and co-workers developed a method using selected antibodies to simultaneously capture ricin, SEB, BoNT/A, and BoNT/B from foods.[144] By combining this multiplex-immunoaffinity purification strategy with MALDI-TOF detection, the sensitivity of monitoring toxin was as low as 500 fmol within 8 h.


128. P. A. Demirev and C. Fenselau, *J. Mass Spectrom.*, 2008, **43**, 1441-1457.
129. S. G. Ler, F. K. Lee and P. Gopalakrishnakone, *J. Chromatogr. A*, 2006, **1133**, 1-12.
130. Y. P. Ho and P. M. Reddy, *Mass Spectrom. Rev.*, 2011, **30**, 1203-1224.
131. S. R. Kalb, M. C. Goodnough, C. J. Malizio, J. L. Pirkle and J. R. Barr, *Anal. Chem.*, 2005, **77**, 6140-6146.
132. C. K. Fagerquist and O. Sultan, *Analyst*, 2011, **136**, 1739-1746.
133. B. Pedersen, A. A. Gorzkowska-Sobas, M. Gerevini, R. Prugger, J. Belenguer, M. Maletti, M. Ljønes, B. H. Gilljam, J. Tønsager, A. M. Opstad and R. K. Davidson, *Trends Anal. Chem.*, 2016, **85**, 42-46.
134. J. Chenau, F. Fenaille, E. Ezan, N. Morel, P. Lamourette, P. L. Goossens and F. Becher, *Anal. Chem.*, 2011, **83**, 8675-8682.
135. A. Seyer, F. Fenaille, C. Feraudet-Tarisse, H. Volland, M. R. Popoff, J. C. Tabet, C. Junot and F. Becher, *Anal. Chem.*, 2012, **84**, 5103-5109.
136. C. T. Chen, P. M. Reddy, Y. R. Ma and Y. P. Ho, *Int. J. Mass Spectrom.*, 2012, **312**, 45-52.
137. J. H. Callahan, K. J. Shefcheck, T. L. Williams and S. M. Musser, *Anal. Chem.*, 2006, **78**, 1789-1800.
138. I. Sospedra, C. Soler, J. Manes and J. M. Soriano, *Anal. Bioanal. Chem.*, 2011, **400**, 1525-1531.
139. I. Sospedra, C. Soler, J. Manes and J. M. Soriano, *J. Chromatogr. A*, 2012, **1238**, 54-59.
140. A. Dupuis, J. A. Hennekinne, J. Garin and V. Brun, *Proteomics*, 2008, **8**, 4633-4636.
141. E. Duriez, F. Fenaille, J. C. Tabet, P. Lamourette, D. Hilaire, F. Becher and E. Ezan, *J. Proteome Res.*, 2008, **7**, 4154-4163.
142. S. R. Kalb and J. R. Barr, *Anal. Chem.*, 2009, **81**, 2037-2042.
143. S. C. McGrath, D. M. Schieltz, L. G. McWilliams, J. L. Pirkle and J. R. Barr, *Anal. Chem.*, 2011, **83**, 2897-2905.

144. S. Kull, D. Pauly, B. Stormann, S. Kirchner, M. Stammler, M. B. Dorner, P. Lasch, D. Naumann and B. G. Dorner, *Anal. Chem.*, 2010, **82**, 2916-2924.

**Pesticides**

**Background.** Pesticides are substances used to kill insects (insecticides), ticks and mites (acaricides) weeds (herbicides), fungi (fungicides), microorganisms (bactericides), slugs and snails (molluscicides), roundworms (nematicides) and animal pests (e.g. rodenticides and avicides). Contrary to popular belief, control of pesticide residues in food is primarily devised to assure proper usage of the pesticides in agriculture, for environmental purposes as well as food safety.[145] The topic of pesticides in food is already the subject of reviews,[146, 147] including analytical aspects.[148-158]

Usage of pesticides and monitoring/control of their residues has been a subject of regulations for at least a century. In that time, an elaborate regulatory process has evolved in each country and among countries worldwide, such as through the United Nations' *Codex Alimentarius* Commission.[159] In developed countries, crop (or plant) protection products (pesticides) must first be approved by the governing body before they may be applied for the specified usages in the field, and the registrant must demonstrate that the labeled application rate of the active ingredient(s) does not lead to residues in food or environmental samples above the regulatory limits after the defined pre-harvest interval. The registration process typically involves many millions of dollars and several years to obtain approval of the products. To improve efficiencies, save costs, and ease the registration processes, pesticide manufacturers are seeking to harmonize the registration process and set uniform maximum residue limits (MRLs, or tolerances in the US). This is now being done among EU countries,[160, 161] but it is a complex issue due to national sovereignty issues, and because different pesticides are applied in different crops at different rates in different climates to control different pests in different countries. Total dietary intakes in regulatory risk assessments for (re-)registrations also depend on the amounts of different foods that different populations eat. Furthermore, the risk assessments have evolved over time to take toxicologically synergistic pesticides into account, which has caused some countries to change MRLs/tolerances and ban certain pesticides.[162, 163]

Importers/exporters of foods greatly desire uniform worldwide MRLs for pesticides in given crops because it is often a great complexity for farmers to know regulatory limits for different countries and follow different pre-harvest intervals depending on the country of destination.[164] High economic stakes are involved if a shipment is denied due to pesticide residue violations, and many exporters hire contract labs to test the commodity for residues prior to shipment. A common complaint by exporting countries concerns the rejection of shipments due to the presence of pesticide residues that are permitted in some commodities, but not for the particular crop in the shipment. Exporting producers typically follow good agricultural practices within their countries, and health risks are low for imported foods,[165, 166] but the economic costs of violations based on technicalities can be high. In light of toxicological studies of pesticides and infants,[167] a customary limit of 10 ng/g is used for commodities containing pesticides that are registered in other commodities. In practice, the 50% measurement uncertainty concept in the EU[168] means that a single measurement that identifies common pesticides in unregistered usages above 15 ng/g is a violation, and in the US, two analyses (one confirming the other) that give concentrations above 10 ng/g indicate a violation.

**Sampling and Analytical Quality.** As in the case of mycotoxins, the quality of the results involves intricate steps starting with representative sampling, sample homogenization, and subsampling for analysis, all of which are equally critical if meaningful results are to be achieved.[169, 170] The critical issue of sampling is often neglected in studies to show quality of analyses (e.g. spiked samples and proficiency tests check only the analytical method, not the sampling processes or sample homogenization). This may become a greater focus to determine real-world uncertainties in the results, which would undoubtedly show worse precision, but better trueness for regulatory enforcement and risk assessment purposes. Measured uncertainties are typically 20-30% RSD based on bottom up (step-by-step) lab measurements[171] and top down (empirical) results from inter-lab proficiency test.[172] Field trials conducted for registration processes measure the full uncertainty in controlled experiments, and an investigation using field data from multiple labs showed up to 100% RSD in the results.[173] The evaluation in uncertainties from multiple measurements among multiple labs using common sampling and handling practices for the same shipment may lead to results that call current real-world practices into question.

An excellent guide for all labs worldwide that monitor pesticide residues in food is provided by the European Commission's Directorate General for Health and Food Safety (DG SANTE) on the Internet.[168] This document has been produced by a team of analytical and regulatory experts in Europe who have spent their careers on the topic of pesticide residue monitoring. The EU tends to set the bar for the world on pesticide monitoring issues due to their investments into labs, regulatory framework, and the extensive food imports into Europe. The team of experts meets every two years to update the DG SANTE quality assurance document, which evolves over time to address validation and quality control policies as new approaches and technologies are implemented. The issue of qualitative analysis (screening, identification, and confirmation by MS methods)[174] for pesticides is becoming one of the most important aspects for regulatory applications, and the two-year revision cycle for the EU guidelines gives it much prominence in the monitoring community due to its adaptability, practicality, and authority.

**Current Trends.** The major trends in pesticide residue monitoring follow the same broader trends in the analytical sciences: better quality of results achieved through greater detectability (improved selectivity and sensitivity) using faster, easier, streamlined sample preparation methods that provide wider scope of targeted and/or nontargeted analytes. The use of multiclass, multiresidue methods tend to increase lab efficiency to better afford the high cost of sophisticated MS instruments, potentially coupled with automated sample preparation systems.[175] High throughput screening using GC- and UHPLC-MS/MS and/or -HRMS capable of analyte identification is becoming more prominent for initial pesticide identification purposes[176, 177] followed by quantification and confirmation of suspected violations using a separate determinative method.

There is a debate in the analytical monitoring community, especially in the case of pesticide residues, about targeted (or known) vs. nontargeted (unknown) screening detection/analysis. In terms of semantics and practicality, the targeted argument wins the debate because once a chemical has been identified, it becomes a known target (and potential analyte). Also, to use a mass spectral database (or library) to help make identifications, it is already known (or targeted) within the library,[178] and a reference spectrum exists from a pure standard. For regulatory work, a certified reference standard must be analyzed contemporaneously as the sample at the same conditions and meet pre-defined criteria (e.g. retention time, spectral

matching factors, ion ratios, peak characteristics).[179] It is an important but difficult balance to avoid both false positives and false negatives in the analyses, which is why the preferred approach is to employ full spectral acquisition to screen for as many analytes as possible in the first analysis, and then quantify and confirm in the second analysis.[174, 180, 181]

True identification of unknowns, such as the case in natural products research, requires structural elucidation including as much other information as can be obtained, which typically involves both full spectral and high mass resolution analyses.[182] Then, the proposed chemical would have to be synthesized and purified to generate a reference standard, which would have to give the same qualitative results as the suspected chemical found in the original sample. In food contaminant applications it is not acceptable to make identifications of nontargeted compounds only using spectral deconvolutions,[183] molecular formula, library matching, and/or proposed fragmentation elucidations. To take enforcement actions, re-analysis of the sample to confirm the violative findings should be done, ideally using a different orthogonally-selective method.[184]

A well-known instance within the pesticide community occurred in 2006 when the identification process described above was followed, but the "unknown" was not initially detected by MS; it was found as an extraneous peak in traditional GC analysis with a nitrogen-phosphorus detector (NPD).[185] GC-MS was used to help with structural elucidation based on retention time and elemental information gained from the GC-NPD results, and the suspected compound was synthesized to provide a reference standard. Peppers were found to be contaminated with a banned pesticide, isofenphos-methyl, which was not registered for usage thus had not been targeted in monitoring schemes.[186] Now, it is included as a targeted pesticide in many labs worldwide, which serves as an example of how the monitoring system works in practice.

Currently, chromatography combined with MS/MS detection often achieves the best quantitative performance, lowest detection limits, and highest selectivity for making identifications of targeted analytes in foods. The high speed of modern chromatography and electronics make it possible to analyze hundreds of analytes within 10 min,[187-189] but this approach is guaranteed to miss any chemical that is not targeted. The better approach for wider scope is to use fast, full spectral MS(/MS) acquisition, ideally with HRMS or isotope abundance analysis of molecular ions,[190] but detection limits and quantitative facets are usually limiting.[191, 192] However, the state-of-the-art Orbitrap[177, 193-195] and TOF[196-200] systems are starting to improve in those regards. Supersonic molecular beam MS technology also holds promise for full scan identification purposes.[190, 201] Rather than trying to immediately identify unknowns, the advantage of the nontargeted approach is that data can be stored and re-processed to target chemicals of future interest in the samples based on changing priorities.[181, 195]

**Sample Preparation.** The highest degree of efficiency that can be achieved in monitoring labs is to reduce the number of different methods that need to be conducted for the same sample. Analytical chemists in monitoring applications have always tried to detect as many compounds as possible in the same method, but technology and instrument maintenance demands have always been limiting. Serving to minimize those longstanding problems, current MS-based instruments give greater selectivity and detectability for relatively complex food, thus affording analysis of more dilute extracts. The use of MS-based detection has led to the proliferation of different multiclass, multiresidue methods for sample preparation of pesticides in food.[202-205] In the past 10 years since its introduction, QuEChERS, which includes dispersive-SPE for clean-up, has become the most popular sample preparation method for pesticide residue

analysis.[151, 154, 206] QuEChERS not only refers to official methods for pesticides analysis in foods,[207, 208] but also has become a concept of streamlined sample preparation for many different applications, such as mycotoxins,[209] veterinary drugs,[210] PAHs,[211] acrylamide,[212] environmental contaminants,[213] and a variety of others.[206] QuEChERS and dispersive-SPE products are commercially available from more than 35 vendors worldwide, and only takes a few dollars and about 10 min to try, so it can be used as an initial sample preparation approach for new applications to save time and trouble in method development.

Mega-methods[214] provide even broader scope of applicability than QuEChERS, with the drawback of reduced clean-up. Some matrices such as spices,[215] tea,[200, 204, 216] coffee,[217] and botanicals[218] are so complex that more extensive clean-up is often required when using typical chromatography-MS/MS instrumentation. However, enhanced selectivity provided by coupling MS(/MS) and/or HRMS with GC×GC,[219] UHPLC,[188] or 2-dimensional LC[220] analytical separation techniques typically meets analytical needs for hundreds of pesticides even in very complicated extracts.

Another major advantage provided by modern (HR)MS(/MS) instruments is their ability to ionize and detect traditionally very difficult pesticides that are too nonvolatile or thermally-labile for GC analysis and lack chromophores for analysis by LC without MS detection. These type of pesticides include glyphosate, glufosinate, quaternary ammoniums, morpholine, phenoxy acids, ethephon, and dithiocarbamates. Traditionally, complicated, laborious, and time-consuming single analyte methods using derivatization are needed for these type of pesticides. Pesticide metabolites are also often included as part of the residue definitions for MRLs, but these additional pertinent analytes are often ignored in practice because they are not typically recovered in common monitoring methods. In the case of dithiocarbamates, Crnogorac and Schwack have extensively studied and reviewed the issues involved in their analyses.[158]

Methods have been developed using simple dilution extraction with minimal cleanup followed by minimal chromatography (or flow injection) and MS-based detection for difficult pesticides together or individually.[221] This concept is called “quick polar pesticides” (QuPPe) method, which has been validated and implemented for many analytes.[222] Nanita has pioneered flow injection-MS/MS which holds promise for even faster analyses of MS-amenable analytes,[223, 224] but this complicates MS identification because retention time is no longer a facet in the analysis. Matrix interferences, ion suppression, and instrument maintenance problems have hampered use of this concept in the past, but broad implementation of any approach in food monitoring programs requires extensive validation within and among labs.


145. A. Felsot, *Pesticides and Health: Myths vs. Realities*, American Council on Science and Health, New York, NY; USA, 2011.
146. D. J. MacLachlan and D. Hamilton, *Pest Manag. Sci.*, 2011, **67**, 609-615.
147. C. A. Damalas and I. G. Eleftherohorinos, *Int. J. Environ. Res. Public Health*, 2011, **8**, 1402-1419.
148. A. Stachniuk and E. Fornal, *Food Anal. Methods*, 2016, **9**, 1654-1665.
149. A. Masia, M. Morales Suarez-Varela, A. Llopis-Gonzalez and Y. Pico, *Anal. Chim. Acta*, 2016, **936**, 40-61.
150. A. Garrido Frenich, R. Romero-González and M. del Mar Aguilera-Luiz, *Trends Anal. Chem.*, 2014, **63**, 158-169.

151. L. J. Zhang, S. W. Liu, X. Y. Cui, C. P. Pan, A. L. Zhang and F. Chen, *Cent. Eur. J. Chem*, 2012, **10**, 900-925.
152. L. B. Abdulra'uf, W. A. Hammed and G. H. Tan, *Crit. Rev. Anal. Chem.*, 2012, **42**, 152-161.
153. E. Watanabe, *Jpn. Agric. Res. Q.*, 2011, **45**, 359-370.
154. A. Wiilkowska and M. Biziuk, *Food Chem.*, 2011, **125**, 803-812.
155. M. LeDoux, *J. Chromatogr. A*, 2011, **1218**, 1021-1036.
156. L. Pareja, A. R. Fernandez-Alba, V. Cesio and H. Heinzen, *Trends Anal. Chem.*, 2011, **30**, 270-291.
157. D. Sharma, A. Nagpal, Y. B. Pakade and J. K. Katnoria, *Talanta*, 2010, **82**, 1077-1089.
158. G. Crnogorac and W. Schwack, *Trends Anal. Chem.*, 2009, **28**, 40-50.
159. M. A. Livermore, *N. Y. Univ. Law Rev.*, 2006, **81**, 766-801.
160. E. Erlacher and M. Wang, *Environ. Pollut.*, 2011, **159**, 3357-3363.
161. J. Bale, *J. Appl. Entomol.*, 2011, **135**, 503-513.
162. *Science*, 2013, **340**, 531-531.
163. N. Lubick, *Science*, 2010, **328**, 1466-1466.
164. A. Engler, L. Nahuelhual, G. Cofre and J. Barrena, *Food Policy*, 2012, **37**, 162-170.
165. C. K. Winter, *J. Agric. Food Chem.*, 2012, **60**, 4425-4429.
166. J. M. Katz and C. K. Winter, *Food Chem. Toxicol.*, 2009, **47**, 335-338.
167. B. Koletzko, P. J. Aggett, C. Agostoni, K. Baerlocher, J. L. Bresson, R. J. Cooke, T. Decsi, J. Deutsch, J. Janda, F. Manz, M. Moya, J. Rigo and J. Socha, *Arch. Dis. Child.*, 1999, **80**, 91-92.
168. DG SANTE, *Method Validation and Quality Control Procedures for Pesticide Residues Analysis in Food and Feed*, www.eurl-pesticides.eu/docs/public/tmplt_article.asp?CntID=727
169. P. Y. Omeroglu, A. Ambrus and D. Boyacioglu, *Food Anal. Methods*, 2013, **6**, 238-247.
170. P. Y. Omeroglu, A. Ambrus, D. Boyacioglu and E. S. Majzik, *Food Addit. Contam. A*, 2013, **30**, 116-126.
171. A. Ambrus, A. Zentai, J. Sali and I. Ficzere, *Accredit. Qual. Assur.*, 2011, **16**, 3-11.
172. P. Medina-Pastor, C. Rodriguez-Torreblanca, A. Andersson and A. R. Fernandez-Alba, *Trends Anal. Chem.*, 2010, **29**, 70-83.
173. S. C. Nanita, M. Ziegler, L. Giammarrusti, A. Huber, E. Astor and J. C. Ruhl, *J. Environ. Sci. Health B*, 2009, **44**, 640-648.
174. S. J. Lehotay, K. Mastovska, A. Amirav, A. B. Fialkov, T. Alon, P. A. Martos, A. de Kok and A. R. Fernandez-Alba, *Trends Anal. Chem.*, 2008, **27**, 1070-1090.
175. P. Kaewsuya, W. E. Brewer, J. Wong and S. L. Morgan, *J. Agric. Food Chem.*, 2013, **61**, 2299-2314.
176. J. Zweigenbaum, *Agro. Food Ind. Hi-Tech.*, 2011, **22**, 4-6.
177. M. M. Gomez-Ramos, C. Ferrer, O. Malato, A. Aguera and A. R. Fernandez-Alba, *J. Chromatogr. A*, 2013, **1287**, 24-37.
178. K. Zhang, J. W. Wong, P. Yang, D. G. Hayward, T. Sakuma, Y. Y. Zou, A. Schreiber, C. Borton, T. V. Nguyen, B. Kaushik and D. Oulkar, *Anal. Chem.*, 2012, **84**, 5677-5684.
179. US Food and Drug Administration, Guidance for Industry #118, *Mass Spectrometry for Confirmation of the Identity of Animal Drug Residues*,

www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052658.pdf
180. D. N. Heller, S. J. Lehotay, P. A. Martos, W. Hammack and A. R. Fernandez-Alba, *J. AOAC Int.*, 2010, **93**, 1625-1632.
181. O. Malato, A. Lozano, M. Mezcua, A. Aguera and A. R. Fernandez-Alba, *J. Chromatogr. A*, 2011, **1218**, 7615-7626.
182. E. M. Thurman, I. Ferrer, P. Zavitsanos and J. A. Zweigenbaum, *J. Agric. Food Chem.*, 2013, **61**, 2340-2347.
183. H. R. Norli, A. Christiansen and B. Holen, *J. Chromatogr. A*, 2010, **1217**, 2056-2064.
184. S. J. Lehotay, A. R. Lightfield, L. Geis-Asteggiante, M. J. Schneider, T. Dutko, C. Ng, L. Bluhm and K. Mastovska, *Drug Test. Anal.*, 2012, **4**, 75-90.
185. CVUA-Stuttgart, *Residues of the unauthorized insecticide isofenphos-methyl detected in sweet peppers from Spain*, www.cvuas.de/pub/beitrag.asp?ID=646&subid=1&Thema_ID=5.
186. European Crop Protection Association, *Counterfeit Pesticides Across Europe - 2008*, www.environmentportal.in/files/counter.pdf
187. J. Wang, W. Chow and W. Cheung, *J. Agric. Food Chem.*, 2011, **59**, 8589-8608.
188. J. O'Mahony, L. Clarke, M. Whelan, R. O'Kennedy, S. J. Lehotay and M. Danaher, *J. Chromatogr. A*, 2013, **1292**, 83-95.
189. U. Koesukwiwat, S. J. Lehotay and N. Leepipatpiboon, *J. Chromatogr. A*, 2011, **1218**, 7039-7050.
190. T. Alon and A. Amirav, *Rap. Commun. Mass Spectrom.*, 2009, **23**, 3668-3672.
191. S. J. Lehotay, U. Koesukwiwat, H. van der Kamp, H. G. J. Mol and N. Leepipatpiboon, *J. Agric. Food Chem.*, 2011, **59**, 7544-7556.
192. M. Kellmann, H. Muenster, P. Zomer and H. Mol, *J. Am. Soc. Mass Spectrom.*, 2009, **20**, 1464-1476.
193. J. Wang, W. Chow, D. Leung and J. Chang, *J. Agric. Food Chem.*, 2012, **60**, 12088-12104.
194. L. Alder, A. Steinborn and S. Bergelt, *J. AOAC Int.*, 2011, **94**, 1661-1673.
195. H. G. J. Mol, P. Zomer and M. de Koning, *Anal. Bioanal. Chem.*, 2012, **403**, 2891-2908.
196. Y. Akiyama, *J. Pest. Sci.*, 2012, **37**, 215-221.
197. M. I. Cervera, T. Portoles, E. Pitarch, J. Beltran and F. Hernandez, *J. Chromatogr. A*, 2012, **1244**, 168-177.
198. R. Diaz, M. Ibanez, J. V. Sancho and F. Hernandez, *Anal. Methods*, 2012, **4**, 196-209.
199. M. Mezcua, O. Malato, M. A. Martinez-Uroz, A. Lozano, A. Aguera and A. R. Fernandez-Alba, *J. AOAC Int.*, 2011, **94**, 1674-1684.
200. J. Wang, W. Chow and D. Leung, *J. AOAC Int.*, 2011, **94**, 1685-1714.
201. A. Amirav, A. Gordin, M. Poliak and A. B. Fialkov, *J. Mass Spectrom.*, 2008, **43**, 141-163.
202. T. Pihlstrom, G. Blomkvist, P. Friman, U. Pagard and B. G. Osterdahl, *Anal. Bioanal. Chem.*, 2007, **389**, 1773-1789.
203. H. G. J. Mol, A. Rooseboom, R. van Dam, M. Roding, K. Arondeus and S. Sunarto, *Anal. Bioanal. Chem.*, 2007, **389**, 1715-1754.
204. C. L. Fan, Q. Y. Chang, G. F. Pang, Z. Y. Li, J. Kang, G. Q. Pan, S. Z. Zheng, W. W. Wang, C. C. Yao and X. X. Ji, *J. AOAC Int.*, 2013, **96**, 432-440.

205. A. G. Frenich, I. M. Salvador, J. Martinez Vidal and T. Lopez-Lopez, *Anal. Bioanal. Chem.*, 2005, **383**, 1106-1118.
206. S. J. Lehotay, M. Anastassiades and R. E. Majors, *LCGC N. Am.*, 2010, **28**, 504-+.
207. P. Paya, M. Anastassiades, D. Mack, I. Sigalova, B. Tasdelen, J. Oliva and A. Barba, *Anal. Bioanal. Chem.*, 2007, **389**, 1697-1714.
208. S. J. Lehotay, *J. AOAC Int.*, 2007, **90**, 485-520.
209. N. Arroyo-Manzanares, A. M. Garcia-Campana and L. Gamiz-Gracia, *J. Chromatogr. A*, 2013, **1282**, 11-19.
210. L. Geis-Asteggiante, S. J. Lehotay, A. R. Lightfield, T. Dutko, C. Ng and L. Bluhm, *J. Chromatogr. A*, 2012, **1258**, 43-54.
211. Y. S. Johnson, *J. Food Sci.*, 2012, **77**, T131-T137.
212. K. Mastovska and S. J. Lehotay, *J. Agric. Food Chem.*, 2006, **54**, 7001-7008.
213. Y. Sapozhnikova and S. J. Lehotay, *Anal. Chim. Acta*, 2013, **758**, 80-92.
214. R. Romero-Gonzalez, A. G. Frenich, J. L. M. Vidal, O. D. Prestes and S. L. Grio, *J. Chromatogr. A*, 2011, **1218**, 1477-1485.
215. L. K. Chai and F. Elie, *Food Control*, 2013, **32**, 322-326.
216. X. A. Zhang, N. Mobley, J. G. Zang, X. M. Zheng, L. Lu, O. Ragin and C. J. Smith, *J. Agric. Food Chem.*, 2010, **58**, 11553-+.
217. I. R. Pizzutti, A. de Kok, C. D. Cardoso, B. Reichert, M. de Kroon, W. Wind, L. W. Righi and R. C. da Silva, *J. Chromatogr. A*, 2012, **1251**, 16-26.
218. D. G. Hayward, J. W. Wong, F. Shi, K. Zhang, N. S. Lee, A. L. DiBenedetto and M. J. Hengel, *Anal. Chem.*, 2013, **85**, 4686-4693.
219. P. Q. Tranchida, F. A. Franchina, M. Zoccali, S. Panto, D. Sciarrone, P. Dugo and L. Mondello, *J. Chromatogr. A*, 2013, **1278**, 153-159.
220. S. Kittlaus, J. Schimanke, G. Kempe and K. Speer, *J. Chromatogr. A*, 2013, **1283**, 98-109.
221. D. I. S. Kolberg, D. Mack, M. Anastassiades, M. T. Hetmanski, R. J. Fussell, T. Meijer and H. G. J. Mol, *Anal. Bioanal. Chem.*, 2012, **404**, 2465-2474.
222. C. Stuttgart, *QuPPe Method*, www.eurl-pesticides.eu/docs/public/tmplt_article.asp?CntID=887&LabID=200&Lang=EN.
223. S. C. Nanita, *Analyst*, 2011, **136**, 285-287.
224. S. C. Nanita, J. J. Stry, A. M. Pentz, J. P. McClory and J. H. May, *J. Agric. Food Chem.*, 2011, **59**, 7557-7568.

**Veterinary Drugs**

Many veterinary drugs are the same as those used to treat human illnesses, which include common antibiotics (e.g. β-lactams, aminoglycosides, sulfonamides, fluoroquinolones, tetracyclines, macrolides, phenicols), analgesics (e.g. nonsteroidal anti-inflammatory drugs, corticosteroids), anthelmintics, coccidiostats, tranquilizers, diuretics, and miscellaneous others. Growth promoters, such as β-agonists, hormones, and steroids, are also treated as veterinary drugs. A number of reviews appear in the literature to give the background about regulations, residues, and monitoring of veterinary drugs in animal-derived foods.[149, 150, 225-231]

As in the case of pesticides, there is a long, involved history with respect to veterinary drug regulations and monitoring policies. The main purpose for veterinary drug regulations and residue monitoring is to ensure that farmers and veterinarians do not use improper practices that

lead to potentially harmful chemicals in the food. When the regulations were originally devised, pharmaceuticals in the environment were not a consideration, but subsequent developments of microbial resistance and ecotoxicological risks[232] have changed the landscape in the veterinary drug (re-)registration process. Previously approved drug applications for animals have been disallowed in certain cases due to the critical importance of the same antibiotics used to treat microbial infections in humans.

Despite many similarities in the issues and nature of the chemical, veterinary drugs have been traditionally regulated by government agencies with different missions and scientific backgrounds than the case for pesticides. The veterinary drug regulators tend to have training in veterinary medicine, pharmaceutical sciences, and microbiology moreso than analytical, environmental, and food chemistry, which are the fields of study that dominate the other food safety topics covered in this review. Even though veterinary drugs are generally less toxic than pesticides, the regulatory and quality assurance policies tend to be stricter and more complex for veterinary drug residues than for pesticides. There is also a greater divide between policies in the US and the EU on veterinary drug issues than in other cases. There are many reasons for this, including differences in European and North American consumer opinions about chemical residues in food, but political/economic pressures to protect domestic markets from foreign imports also influence veterinary drug residue policies. For example, the banning by the EU of many growth promoters approved for use in the U.S. (and other countries) has long been a source of contention in trade of meat products. Toxicological risk assessments have not shown the substances to cause health risks when used in accordance with approved practices, but the EU has a philosophical view that animal drugs should be used to treat illnesses, not as a sub-therapeutic prophylactic or growth promoter to increase production. These issues are a matter of debate in *Codex Alimentarius* when MRLs for veterinary drugs are being considered, and high economic stakes are often involved in the voting decisions made by the regulatory and scientific representatives from many countries.

As in the case of other residue monitoring programs, the EU has invested in a large infrastructure of regulatory agencies, labs, and policies for veterinary drug monitoring. Regulation of food trade between countries within Europe led to rapidly evolving EU standards over time culminating in new legislation to define their performance-based method and lab validation standards.[233, 234] European Commission Decision 2002/657/EC "concerning the performance of analytical methods and the interpretation of results" made a large departure from the "official method" approach still used in the US for enforcement actions. In any case, these rules have served as a model for single lab method validation for many monitoring applications in general, and a Web of Science search of "2002/657/EC" in April of 2018 listed 808 pubs on the topic. Technically, the rules only apply to monitoring of residues in animal food products by EU regulatory labs, but many analysts worldwide have been confused by the regulatory distinctions between which rules (2002/657/EC)[233] or guidelines (SANTE/11813/2017) to follow depending on the food matrix and type of contaminants being monitored. In truth, labs can use any approach their client will accept to meet their purposes. This is made even more complex due to ISO 17025 and lab accreditation requirements, and Kay provides a case study for the approach taken in the UK.[235]

Due to the decision to put fixed rules into legislation rather than more flexible guidelines, the 2002/657/EC rules have fallen behind the pace of technology over the course of 15 years and need to be modified.[234] Independently, the changing economic climate in the EU and creation of

the European Food Safety Authority in 2002 has caused greater consolidation of veterinary drug, pesticide, and other monitoring programs with greater emphasis on science-driven priorities. It is foreseeable that both sets of EU policies for monitoring labs will be consolidated in the future, and the more practical and adaptable guide used for pesticides has several advantages. Time spent on method validation and quality assurance is important to help achieve high quality results, but this costs time and money without guarantees that quality will be better. High quality results come from good chemists who have enough resources using proven methods with suitable, working instruments in a lab being managed by knowledgeable and realistic professionals. Independent of method or validation requirements, widespread comparisons of results using blind inter-lab proficiency testing of shared, real-world samples has provided the needed incentive and feedback to help improve quality of results over time.

In practice, veterinary antibiotics are often screened on-site using microbial inhibition bioassays, and better commercial tests have been introduced to speed the process and achieve lower detection limits for more drugs.[236-238] This approach only works for a range of antibiotics, but it serves as an easy, fast, and affordable way to screen a large number of samples at their source, and only positives are sent to the lab for further analysis. In an excellent resource, FSIS provides the latest approved protocols for all the lab methods used in their National Residue Program.[239] Immunochemical methods and biosensors are another type of approach that can be used for screening in the field and lab,[240] but they tend to have niche applicability due to their narrowly selective inherent nature.

The same technologies and approaches that permit rapid screening analysis of hundreds of pesticides and mycotoxins in foods are also being applied to veterinary drugs.[241-243] In the past, the diverse nature of the polar drugs and greater difficulty of the animal tissue matrices (high fat and protein contents) made multiclass, multiresidue monitoring impossible. There are still difficult drug/matrix combinations, just as in the case of other monitoring applications,[244] but the luxuries afforded by some veterinary drug monitoring programs of the past to use many single-analyte or single-class methods is giving way to the broad screening approaches always preferred in pesticide residue monitoring. Even though the MS-based instruments are expensive and entail high operating costs, the labor and time savings to screen for hundreds of analytes lowers the overall costs.


225. S. B. Turnipseed, J. J. Lohne and J. O. Boison, J. AOAC Int., 2015, 98, 550-558.
226. J. C. Barreiro, A. L. Luiz, S. C. Fernandes Maciel, E. V. Soares Maciel and F. M. Lancas, *J. Sep. Sci.*, 2015, **38**, 1721-1732.
227. S. J. Lehotay, K. Mastovska and N. Thiex, in *Improving the Safety of Fresh Meat*, ed. J. N. Sofos, Woodhead, Boca Raton, FL; USA, 2005, pp. 102-131.
228. B. Kinsella, J. O'Mahony, E. Malone, M. Moloney, H. Cantwell, A. Furey and M. Danaher, *J. Chromatogr. A*, 2009, **1216**, 7977-8015.
229. H. F. De Brabander, H. Noppe, K. Verheyden, J. V. Bussche, K. Wille, L. Okerman, L. Vanhaecke, W. Reybroeck, S. Ooghe and S. Croubels, *J. Chromatogr. A*, 2009, **1216**, 7964-7976.
230. B. Le Bizec, G. Pinel and J. P. Antignac, *J. Chromatogr. A*, 2009, **1216**, 8016-8034.
231. R. J. B. Peters, A. A. M. Stolker, J. G. J. Mol, A. Lommen, E. Lyris, Y. Angelis, A. Vonaparti, M. Stamou, C. Georgakopoulos and M. W. F. Nielen, *Trends Anal. Chem.*, 2010, **29**, 1250-1268.

232. L. F. Du and W. K. Liu, *Agron. Sustain. Dev.*, 2012, **32**, 309-327.
233. E. Commission, *Off. J. Eur. Comm.*, 2002, **L221**.
234. L. Vanhaecke, P. Gowik, B. Le Bizec, L. Van Ginkel, E. Bichon, M. Blokland and H. F. De Brabander, *J. AOAC Int.*, 2011, **94**, 360-372.
235. J. F. Kay, *Drug Test. Anal.*, 2012, **4**, 25-27.
236. Z. S. Goffova, I. Kozarova, D. Mate, S. Marcincak, Z. Gondova and D. Sopkova, *Czech. J. Food Sci.*, 2012, **30**, 314-320.
237. H. Ashwin, S. Stead, M. Caldow, M. Sharman, J. Stark, A. de Rijk and B. J. Keely, *Anal. Chim. Acta*, 2009, **637**, 241-246.
238. M. J. Schneider, K. Mastovska, S. J. Lehotay, A. R. Lightfield, B. Kinsella and C. E. Shultz, *Anal. Chim. Acta*, 2009, **637**, 290-297.
239. USDA Food Safety and Inspection Service, *Chemistry Laboratory Guidebook*, www.fsis.usda.gov/wps/portal/fsis/topics/science/laboratories-and-procedures
240. T. F. McGrath, C. T. Elliott and T. L. Fodey, *Anal. Bioanal. Chem.*, 2012, **403**, 75-92.
241. P. A. Martos, F. Jayasundara, J. Dolbeer, W. Jin, L. Spilsbury, M. Mitchell, C. Varilla and B. Shurmer, *J. Agric. Food Chem.*, 2010, **58**, 5932-5944.
242. M. M. Aguilera-Luiz, J. L. M. Vidal, R. Romero-Gonzalez and A. G. Frenich, *Food Chem.*, 2012, **132**, 2171-2180.
243. M. L. Gomez-Perez, P. Plaza-Bolanos, R. Romero-Gonzalez, J. L. Martinez-Vidal and A. Garrido-Frenich, *J. Chromatogr. A*, 2012, **1248**, 130-138.
244. J. Wang and D. Leung, *Drug Test. Anal.*, 2012, **4**, 103-111.

**PCBs**

PCBs are a group of highly stable man-made organic compounds that have become ubiquitous pollutants in the environment. They are lipophilic and thus bioconcentrate up the food chain. There are 209 PCB congeners (although the number found in real samples is slightly above 100) with a combination of 1 to 10 chlorine atoms attached to two benzene rings. They are widely used in industry and consumer products due to the desirable physicochemical properties. The analysis of PCBs involves challenges with the large number of isomer target analytes, complexity of food matrices, and regulatory demand for low detection limits. Progress and advances in the analysis of PCBs has been previously reviewed.[245-248]

Historically, sample preparation in PCBs analysis involves the most labor and time in the analysis, and it also typically requires high solvent consumption. The goals for improved sample preparation are to speed and ease the process, increase both selectivity and recoveries in extraction, reduce costs and solvent usage, and provide automation. The sample preparation options for the analysis of PCBs in food are liquid-liquid extraction (LLE), Soxhlet extraction, SPE, SBSE, SPME, MSPD, supercritical fluid extraction (SFE), PLE, and MAE.[246-251] No single universal method can "fit" all applications for determining PCBs in food, but of course, the search for a better sample preparation procedure continues. DLLME was reported for the extraction of PCBs in fish samples by Hu and co-workers.[252] The extraction conditions were optimized and they were able to miniaturize sample preparation by only using 1 mL of acetone as the disperser solvent and 30 μL of chlorobenzene as the extraction solvent for PCBs in fish. Another innovative approach was reported by Helaleh et. al.[253, 254] who used automated PLE to automate extraction and clean up prior to GC-MS detection. PLE also can be streamlined by adding sorbents to the samples prior to extraction.[255] A study shows that using this technique,

only 0.25 g of sample provides accurate determination of PCBs in a variety of feeds.[256] One research group used PLE to demonstrate that PCBs and food packaging materials can be analyzed in the same efficient method to support food safety risk assessments.[257]

GC and multidimensional GC coupled with electron-capture detection (ECD) and various MS techniques are the common analytical methods for PCBs.[246-248] Comprehensive two-dimensional gas chromatography (GC×GC) coupled with μECD has gained wider acceptance in the analysis of PCBs and many other halogenated pollutants.[258, 259] A novel approach for the identification of potentially unknown halogenated pollutants in GC-HRMS by plotting the mass defect of detected ions was presented by Jobst and co-workers.[260]


245. I. Spanik and A. Machynakova, *J. Sep. Sci.*, 2018, **41**, 163-179.
246. F. E. Ahmed, *Trends Anal. Chem.*, 2003, **22**, 170-185.
247. A. Beyer and M. Biziuk, *Crit. Rev. Food Sci. Nutr.*, 2008, **48**, 888-904.
248. O. N. Zabelina, V. I. Saloutin and O. N. Chupakhin, *J. Anal. Chem.*, 2010, **65**, 1098-1108.
249. A. Beyer and M. Biziuk, *Food Chem.*, 2008, **108**, 669-680.
250. D. Garcia-Rodriguez, A. Maria Carro-Diaz and R. Antonia Lorenzo-Ferreira, *J. Sep. Sci.*, 2008, **31**, 1333-1345.
251. F. A. Esteve-Turrillas, E. Caupos, I. Llorca, A. Pastor and M. de la Guardia, *J. Agric. Food Chem.*, 2008, **56**, 1797-1803.
252. J. Hu, Y. Li, W. Zhang, H. Wang, C. Huang, M. Zhang and X. Wang, *J. Sep. Sci.*, 2009, **32**, 2103-2108.
253. M. I. H. Helaleh, A. Al-Rashdan and A. Ibtisam, *Talanta*, 2012, **94**, 44-49.
254. M. I. H. Helaleh and A. Al-Rashdan, *Anal. Methods*, 2013, **5**, 1617-1622.
255. J. J. Ramos, C. Dietz, M. J. Gonzalez and L. Ramos, *J. Chromatogr. A*, 2007, **1152**, 254-261.
256. M. Pena-Abaurrea, J. J. Ramos, M. J. Gonzalez and L. Ramos, *J. Chromatogr. A*, 2013, **1273**, 18-25.
257. Z. H. Li, D. Li, J. L. Ren, L. B. Wang, L. J. Yuan and Y. C. Liu, *Food Control*, 2012, **27**, 300-306.
258. A. M. Muscalu, E. J. Reiner, S. N. Liss, T. Chen, G. Ladwig and D. Morse, *Anal. Bioanal. Chem.*, 2011, **401**, 2403-2413.
259. L. R. Bordajandi, J. J. Ramos, J. Sanz, M. J. Gonzalez and L. Ramos, *J. Chromatogr. A*, 2008, **1186**, 312-324.
260. K. J. Jobst, L. Shen, E. J. Reiner, V. Y. Taguchi, P. A. Helm, R. McCrindle and S. Backus, *Anal. Bioanal. Chem.*, 2013, **405**, 3289-3297.


**Dioxins**

Dioxins and dioxin-like compounds are a group of environmental pollutants including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), dioxin-like PCBs, and 1,4-dioxin. Dioxins analysis is a very specialized type of analyses conducted for decades typically by dedicated experts using high resolution GC and HRMS with sector instruments. Comprehensive overviews of analysis of dioxins and related compounds have been published,[245, 261] detailing current practices and future trends, which involves more automation,

greater selectivity, higher sensitivity, expanded coverage of many closely related compounds, and multi-sample screening.

Currently, some analytical methods are designed to determine dioxins at the same time as PCBs, but a difficulty is that the dioxins occur at orders of magnitude lower concentrations than PCBs. GC-HRMS is the common approach for the determination of dioxins in food and feed, but GC×GC with ECD, TOF, and/or MS/MS are potential alternatives if the newer technologies can be satisfactorily demonstrated and accepted.[262-265] GC×GC The novel combination of GC – tandem quadrupole-Fourier transform ion cyclotron resonance MS (GC-MS/MS-FTICRMS) has also been evaluated for analysis of dioxins.[266] The feasibility of the technique was demonstrated by screening mixed halogenated dioxins in vegetation. Fatty samples tend to yield the most difficulties due to the need to concentrate the extracts and separate fats making up the bulk of the sample from the ultratrace analytes.


261. E. J. Reiner, *Mass Spectrom. Rev.*, 2010, **29**, 526-559.
262. J. Malavia, F. J. Santos and M. T. Galceran, *J. Chromatogr. A*, 2008, **1186**, 302-311.
263. E. Hoh, S. J. Lehotay, K. Mastovska and J. K. Huwe, *J. Chromatogr. A*, 2008, **1201**, 69-77.
264. P. Haglund, P. Korytar, C. Danielsson, J. Diaz, K. Wiberg, P. Leonards, U. A. T. Brinkman and J. de Boer, *Anal. Bioanal. Chem.*, 2008, **390**, 1815-1827.
265. G. Eppe, J. F. Focant, C. Pirard and E. De Pauw, *Talanta*, 2004, **63**, 1135-1146.
266. V. Y. Taguchi, R. J. Nieckarz, R. E. Clement, S. Krolik and R. Williams, *J. Am. Soc. Mass Spectrom.*, 2010, **21**, 1918-1921.


**Acrylamide**

Acrylamide is an odorless and colorless compound that is a known neurotoxin and carcinogen in animal models. In 2002, acrylamide was reported by Swedish scientists to occur at µg/g levels in starchy foods when cooked.[267] This report immediately raised scientific and public concern about unknown effects due to ingestion of acrylamide at greater amounts than previously thought (regulatory limits in water were often 100-fold lower than concentrations found in some fried foods). As reflected by the rise in the number of pubs for "acrylamide + food" in Table 1, the food industry, regulatory officials, and the scientific community jumped into action. Much effort was initially placed into developing methods and monitoring acrylamide in various foods. Research developments on acrylamide including analytical methods, formation mechanisms, and its chemistry have been reviewed numerous times.[268-273] The source of acrylamide formation was shown to be conversion of the common amino acid, asparagine, via the Maillard reaction in the presence of heat and reducing sugars. Acrylamide is not typically monitored routinely in regulatory labs, but analytical methods used by industry are designed to monitor precursors and intermediates. This is valuable to the food industry as demonstrated in a shortbread case study.[274] Ways are being sought to reduce or eliminate acrylamide formation without affecting the taste or quality of the food product.

Acrylamide analysis was initially carried out using GC-MS with or without derivatization, but it was found that heat during the injection was causing formation of acrylamide from starting materials in the extracts. This can be overcome by using programmable temperature vaporization during injection in GC.[212] Using a 2-column GC-MS/MS approach, Xu et al. were able to separate and detect both acrylamide and 3-monochloropropane-1,2-diol (3-

MCPD) without derivatization.[275] Each analytical technique has strengths and limitations in the analysis of acrylamide.[276, 277] GC, LC, and CE each could be employed for separations coupled to MS analysis, as previously reviewed.[273] The review summarized sample preparation, separation, and detection of acrylamide in different food matrixes. Additionally, a different report reviewed the detection of acrylamide in the human diet.[272] It surveyed analytical methods used in acrylamide quantification, concluding that a universal procedure could not be used to detect acrylamide in all types of food due to their diversity and complexity. Feasible MS-based methods are currently too expensive and lack portability, and the greatest need by industry is for a simple, inexpensive, and fast quantitative screening test that can be used in the food processing plant.

A derivatization method was developed to detect acrylamide using xanthydrol instead of bromine, which is the most popular acrylamide derivatization agent.[278] This method was applied to a variety of processed foods, such as potato and corn snacks, biscuits, instant noodles, coffee, soy sauces and miso. The advantage of performing xanthydrol instead of bromine derivatization is that the researchers could use the less expensive $d_3$-acrylamide rather than $^{13}C_3$-acrylamide as the internal standard. In addition, it can avoid potential deuterium hydrogen exchange reaction that can occur during bromination. Derivatization is commonly practiced in GC-MS, however, it also can be applied to LC methods. Geng and co-workers[279] found that improved reversed-phase retention of acrylamide and increased UV absorption at 215 nm could be achieved after bromine derivatization, which provided a low-cost and robust option to MS-based methods to determine acrylamide in starch-based foods, albeit the detection limit was not as low. For sample clean-up prior to LC-UV detection, several SPE sorbents have been evaluated including activated silica, carbon nanotubes, magnetic chitosan, modified chitosan, and C18. The authors concluded that C18 sorbent was the best choice for the enrichment of acrylamide in food extracts.


267. J. Rosen and K. E. Hellenas, *Analyst*, 2002, **127**, 880-882.
268. Y. Xu, B. Cui, R. Ran, Y. Liu, H. P. Chen, G. Y. Kai and J. X. Shi, *Food Chem. Toxicol.*, 2014, **69**, 1-12.
269. A. A. Elbashir, M. M. A. Omar, W. A. W. Ibrahim, O. J. Schmitz and H. Y. Aboul-Enein, *Crit. Rev. Anal. Chem.*, 2014, **44**, 107-141.
270. Y. Zhang, Y. Ren and Y. Zhang, *Chem. Rev.*, 2009, **109**, 4375-4397.
271. J. Keramat, A. LeBail, C. Prost and N. Soltanizadeh, *Food Bioprocess Technol.*, 2011, **4**, 340-363.
272. J. Oracz, E. Nebesny and D. Zyzelewicz, *Talanta*, 2011, **86**, 23-34.
273. S. E. K. Tekkeli, C. Onal and A. Onal, *Food Anal. Methods*, 2012, **5**, 29-39.
274. O. Marconi, E. Bravi, G. Perretti, R. Martini, L. Montanari and P. Fantozzi, *Anal. Methods*, 2010, **2**, 1686-1691.
275. X.-m. Xu, H.-l. He, Y. Zhu, L. Feng, Y. Ying, B.-f. Huang, H.-t. Shen, J.-l. Han and Y.-p. Ren, *Anal. Chim. Acta*, 2013, **760**, 93-99.
276. Q. D. Chen, W. F. Zhao and Y. S. Fung, *Electrophoresis*, 2011, **32**, 1252-1257.
277. P. Singh, P. Singh and R. B. Raja, *Af. J. Biotechn.*, 2010, **9**, 8085-8091.
278. K. Yamazaki, S. Isagawa, N. Kibune and T. Urushiyama, *Food Addit. Contam. A*, 2012, **29**, 705-715.
279. G. Zhiming, W. Peng and L. Aiming, *J. Chromatogr. Sci.*, 2011, **49**, 818-824.

**Melamine**

Melamine is a triazine that contains 67% nitrogen by mass. The Kjeldahl test, which measures nitrogen, has been commonly used by the food industry to assess protein content of ingredients, and melamine was used fraudulently as an additive to boost the apparent protein content. This practice was exposed in 2007 when some pets died due to melamine adulteration of pet food. The lethal effect of melamine comes from its chemical reaction with cyanuric acid, another nitrogen containing adulterant, which combine to precipitate as crystals in the kidneys and block renal functions. Other food products including milk and infant formula were found to contain melamine, leading to illnesses and deaths of infants in China in 2008. As can be interpreted from Table 1, no monitoring of melamine was done prior to 2007, but the crisis led to hundreds of pubs in following years about melamine in food, plus many others concerning the screening and identification of unknown chemicals in foods.

Development of analytical techniques in the detection of melamine and related compounds in foods has been reviewed numerous times.[280-284] Common methods of analysis for melamine use LC, LC-MS/MS, GC-MS, MALDI-MS, NMR, and several screening techniques. They share similar challenges to analyze melamine and cyanuric acid, including matrix effects, insolubility of analytes, and lengthy sample preparation procedures. One review lists advantages and disadvantages associated with various techniques.[284] Surface-enhanced Raman spectroscopy (SERS) has shown potential as an approach for rapid, real-time, on-site testing melamine food adulteration.[285-288] SERS enhances Raman emissions by factors up to $10^{14}$ by integrating samples with metal nanostructures, such as gold and silver. Portable SERS devices have been developed by multiple groups, and melamine detection is one of many proposed applications of the devices.

Another on-site routine monitoring technique was developed by Sun and co-workers, using a hand-held immunochromatographic strip.[289] Their method uses gold nanoparticle-labelled monoclonal antibody probes to gather melamine from milk. In another approach, surface-assisted laser desorption/ionization mass spectrometry (SALDI-MS) uses gold nanoparticles to transfer energy from laser irradiation to the analytes thereby inducing desorption and ionization.[290] This technique can perform simultaneous analysis of melamine and its byproducts without separation or time-consuming sample preparation. DART-TOFMS is another approach that can be used to rapidly detect both melamine and cyanuric acid in milk products.[291]

GC-MS is a more traditional means of melamine detection, and using mixed-mode SPE enabled investigators to simultaneously detect melamine and cyanuric acid in dairy products.[292] With respect to LC-based techniques, hydrophilic interaction liquid chromatography (HILiC) is able to separate highly polar and hydrophilic compounds better than traditional reversed-phase chromatography.[293] Ligand-exchange properties in HILiC have been applied to determine melamine in milk and milk products without sample pretreatment.[294] Another HILiC approach using an $-NH_2$ stationary phase[295] and polymer-based monolithic columns[296] have also been successfully applied to analysis of melamine and other possible nitrogen-containing adulterants. The Canadian Food Inspection Agency, for example, has compiled a list of such chemicals that could be used as potential adulterants in place of protein, and HILiC-MS/MS was used to perform multi-compound analysis.[297] After all, the protein labeling fraud must also be addressed, and industry has generally replaced the Kjeldahl approach with more specific method to measure protein content of foods and their ingredients, but this aspect falls outside the scope of this review of monitoring for chemical food safety purposes.

280. T. T. Wang, J. F. Ma, Y. H. Chang, Y. Li, L. H. Zhang, Y. K. Zhang, *J. Sep. Sci.*, 2017, **40**, 170-182.
281. Y. Lu, Y. Q. Xia, G. Z. Liu, M. F. Pan, M. J. Li, N. A. Lee, and S. Wang, *Crit. Rev. Anal. Chem.*, 2017, **47**, 51-66.
282. Y. Liu, E. E. D. Todd, Q. Zhang, J. R. Shi and X. J. Liu, *J. Zhejiang U.-Sci. B*, 2012, **13**, 525-532.
283. P. W. S. Chu, K. M. Chan, S. T. C. Cheung and Y. C. Wong, *Trends Anal. Chem.*, 2010, **29**, 1014-1026.
284. F. X. Sun, W. Ma, L. G. Xu, Y. Y. Zhu, L. Q. Liu, C. F. Peng, L. B. Wang, H. Kuang and C. L. Xu, *Trends Anal. Chem.*, 2010, **29**, 1239-1249.
285. N. N. Yazgan, I. H. Boyaci, A. Topcu and U. Tamer, *Anal. Bioanal. Chem.*, 2012, **403**, 2009-2017.
286. A. M. Robinson, S. G. Harroun, J. Bergman and C. L. Brosseau, *Anal. Chem.*, 2012, **84**, 1760-1764.
287. L. C. Mecker, K. M. Tyner, J. F. Kauffman, S. Arzhantsev, D. J. Mans and C. M. Gryniewicz-Ruzicka, *Anal. Chim. Acta*, 2012, **733**, 48-55.
288. S. H. Yazdi and I. M. White, *Anal. Chem.*, 2012, **84**, 7992-7998.
289. F. X. Sun, L. Q. Liu, W. W. Ma, C. L. Xu, L. B. Wang and H. Kuang, *Int. J. Food Sci. Technol.*, 2012, **47**, 1505-1510.
290. Y. T. Hsieh, W. T. Chen, I. Tomalova, J. Preisler and H. T. Chang, *Rap. Commun. Mass Spectrom.*, 2012, **26**, 1393-1398.
291. L. Vaclavik, J. Rosmus, B. Popping and J. Hajslova, *J. Chromatogr. A*, 2010, **1217**, 4204-4211.
292. X. D. Pan, P. G. Wu, D. J. Yang, L. Y. Wang, X. H. Shen and C. Y. Zhu, *Food Control*, 2013, **30**, 545-548.
293. A. L. N. van Nuijs, I. Tarcomnicu and A. Covaci, *J. Chromatogr. A*, 2011, **1218**, 5964-5974.
294. J. Tan, R. Li and Z. T. Jiang, *Food Anal. Methods*, 2012, **5**, 1062-1069.
295. X. L. Zheng, B. S. Yu, K. X. Li and Y. N. Dai, *Food Control*, 2012, **23**, 245-250.
296. H. Y. Huang, C. L. Lin, S. H. Jiang, B. Singco and Y. J. Cheng, *Anal. Chim. Acta*, 2012, **719**, 96-103.
297. S. Mac Mahon, T. H. Begley, G. W. Diachenko and S. A. Stromgren, *J. Chromatogr. A*, 2012, **1220**, 101-107.

**Perchlorate**

The primary applications of man-made perchlorate is the production of solid rocket fuels, military munitions, and fireworks. Perchlorate is extremely soluble in water and has a negative impact on the thyroid function, thus it is considered an environmental pollutant of concern by various government agencies.[298] Water is the main source of perchlorate contamination of food, and it is also regulated in drinking water. The common approach for perchlorate in water entails ion chromatography coupled with conductivity detection (IC-CD), which is the method of choice proposed by the EPA.[299] However, many other analytical methods have been developed to monitor perchlorate in water.[300] IC-MS helps avoid matrix interferences to improve detectability even without sample clean-up.[301] Using large volume injection and on-line SPE coupled with MS/MS, Lin et al. demonstrated an alternative technique to quantify perchlorate in bottled water

and tea.[302] To avoid interfering ions (e.g. chloride, carbonate, and sulfate), Martinelango et al. developed a strategy by forming a positively charged ion pair of perchlorate with a dicationic agent so that the perchlorate complex serving as the analyte shifted to a higher *m/z* of 300 and 400.[303, 304] Highly sensitive electrochemical approaches have also made its way to the trace analysis of perchlorate in water.[305, 306] The desirable features associated with the technique are low cost and field portability.

Food crops and dairy products can also contain perchlorate through contaminated water and soil. Emphasis has been placed on milk, milk powder, and infant formula due to the greater concern of health impacts on infants.[307-309] The determination of perchlorate in milk and related products is more difficult than in water samples due to the presence of fats, proteins, and carbohydrates. Dyke and co-workers used ultrafiltration and high molecular weight cutoff filters to separate the low mass perchlorate from high mass matrix components.[309] However, the method gave <50% analyte recovery from milk. Use of SPE combined with isotope dilution IC-MS/MS could better meet perchlorate analysis needs.[307] SPE followed by HILIC-MS/MS has been shown to be an effective method to quantitatively measure perchlorate in milk and milk powder.[308] Aribi et al. developed a method using minimum sample preparation to analyze perchlorate in a wide variety foods including fruits and vegetables, milk products, wine, and beer.[310] The method measured the chlorine isotope ratio ($^{35}Cl/^{37}Cl$) to identify perchlorate, also using ion transitions of $^{35}Cl^{16}O_4^-$ (*m/z* 98.9) to $^{35}Cl^{16}O_3^-$ (*m/z* 82.9) for quantification vs. the ion transition of $^{35}Cl^{18}O_4^-$ (*m/z* 107.0) to $^{35}Cl^{18}O_3^-$ (*m/z* 89.0) serving as the internal standard.


298. S. D. Richardson, *Anal. Chem.*, 2010, **82**, 4742-4774.
299. D. P. Hautman, D. J. Munch, A. D. Eaton and A. W. Haghani, *Determination of Perchlorate in Drinking Water Using Ion Chromatrography*, US Environmental Protection Agency, Cincinnati, OH; USA, 1999.
300. V. V. Goncharuk, O. V. Zui and N. F. Kushchevskaya, *J. Water Chem. Technol.*, 2009, **31**, 186-194.
301. M. Kamoshita, K. Kosaka, M. Asami and Y. Matsuoka, *Anal. Sci.*, 2009, **25**, 453-456.
302. S. L. Lin, C. Y. Lo and M. R. Fuh, *J. Chromatogr. A*, 2012, **1246**, 40-47.
303. P. K. Martinelango and P. K. Dasgupta, *Anal. Chem.*, 2007, **79**, 7198-7200.
304. P. K. Martinelango, J. L. Anderson, P. K. Dasgupta, D. W. Armstrong, R. S. Al-Horr and R. W. Slingsby, *Anal. Chem.*, 2005, **77**, 4829-4835.
305. E. J. Parra, G. A. Crespo, J. Riu, A. Ruiz and F. X. Rius, *Analyst*, 2009, **134**, 1905-1910.
306. Y. Kim and S. Amemiya, *Anal. Chem.*, 2008, **80**, 6056-6065.
307. Z. Wang, B. P. Y. Lau, B. Tague, M. Sparling and D. Forsyth, *Food Addit. Contam. A*, 2011, **28**, 799-806.
308. L. Chen, H. Chen, M. Shen, Z. Zhou and A. Ma, *J. Agric. Food Chem.*, 2010, **58**, 3736-3740.
309. J. V. Dyke, A. B. Kirk, K. Martinelango and P. K. Dasgupta, *Anal. Chim. Acta*, 2006, **567**, 73-78.
310. H. El Aribi, Y. J. C. Le Blanc, S. Antonsen and T. Sakuma, *Anal. Chim. Acta*, 2006, **567**, 39-47.


**Ethyl Carbamate**

Ethyl carbamate (EC) is a chemical that occurs naturally at low levels in fermented and baked foods and alcoholic beverages, and its analysis has been recently reviewed.[311] EC is considered genotoxic and carcinogenic in animals and a potential carcinogen for humans.[312] GC - flame ionization detection (FID) or MS are the commonly used methods for EC determination. Among these, GC-MS/MS typically achieves the lowest detection limits to quantify EC in food products.[313, 314] A common technique to improve detectability in GC-MS analysis is to derivatize EC with 9-xanthydrol. One study demonstrated the feasibility of derivatization of EC directly in food and beverages to avoid potential analyte loss during evaporation.[315] An alternative derivatization of EC using silylation after liquid-liquid extraction was developed by Xu and co-workers.[316] After carefully evaluating three types of common silylation reagents, *bis*-(trimethylsilyl)trifluoroacetamide (BSTFA) provided the best result in terms of low detection limit and silylation efficiency.

An international inter-laboratory study indicated that the analysis results of EC in alcoholic beverages using GC-FID were comparable to those using GC-MS.[317] The study also showed that the GC-FID method was much simpler than the official GC-MS method, and could be an alternative choice for EC analysis. With minimal sample preparation and derivatization using 9-xanthydrol, GC-FID was capable of routine analysis in wide variety fermented food matrices.[318, 319]

SPE is used routinely for sample preparation in EC determination. Alberts et al. described a novel SPE procedure by adding an optimized amount of sodium chloride to wine samples. The SPE procedure was simple, avoided toxic solvents, and could be applied to a variety of foods.[320] EC in vinegars has been investigated using SPE with a polymeric sorbent, which required optimization of the pH to improve results.[321]

SPME has also been applied to EC determination from homemade cachaça, Chinese rice wine, and other alcoholic beverages.[322-324] Despite the ease of SPME, only a small portion of the analyte was originally extracted, and a more exhaustive extraction approach was developed by performing a series of headspace-SPME exposures to the same sample container.[325, 326]

Deák et al. developed a method by using xanthydrol derivatization in LC-MS/MS to quantify EC in double-distilled fruit brandies.[327] Using this more selective hyphenated analytical technique, they were able to obtain a low quantification limit of EC without sample clean-up.


311. Q. Xia, C. J. Yang, C. D. Wu, R. Q. Zhou and Y. F. Li, *Food Control*, 2018, **84**, 499-512.
312. J. V. Weber and V. I. Sharypov, *Environ. Chem. Lett.*, 2009, **7**, 233-247.
313. D. W. Lachenmeier, W. Frank and T. Kuballa, *Rap. Commun. Mass Spectrom.*, 2005, **19**, 108-112.
314. C. G. Hamlet, S. M. Jayaratne and C. Morrison, *Rap. Commun. Mass Spectrom.*, 2005, **19**, 2235-2243.
315. H. S. Shin and E. Y. Yang, *Chem. Central J.*, 2012, **6**.
316. X. J. Xu, Y. H. Gao, X. J. Cao, X. Wang, G. X. Song, J. F. Zhao and Y. M. Hu, *J. Sep. Sci.*, 2012, **35**, 804-810.
317. S. de Melo Abreu, A. Alves, B. Oliveira and P. Herbert, *Anal. Bioanal. Chem.*, 2005, **382**, 498-503.
318. R. Rodriguez Madrera and B. Suarez Valles, *Food Control*, 2009, **20**, 139-143.
319. A. M. D. Machado, M. D. Cardoso, A. A. Saczk, J. P. dos Anjos, L. M. Zacaroni, H. S. Dorea and D. L. Nelson, *Food Chem.*, 2013, **138**, 1233-1238.

320. P. Alberts, M. A. Stander and A. De Villiers, *Food Addit. Contam. A*, 2011, **28**, 826-839.
321. C. Ubeda, C. Balsera, A. M. Troncoso, R. M. Callejon and M. L. Morales, *Talanta*, 2012, **89**, 178-182.
322. A. M. D. Machado, M. D. Cardoso, E. S. Emidio, V. D. Prata, H. S. Dorea, J. P. dos Anjos, Z. M. Magriotis and D. L. Nelson, *Anal. Lett.*, 2012, **45**, 1143-1155.
323. J. Liu, Y. Xu and G. A. Zhao, *J. Inst. Brewing*, 2012, **118**, 217-222.
324. Y. Zhang and J. Zhang, *Anal. Chim. Acta*, 2008, **627**, 212-218.
325. C. W. Ye, X. N. Zhang, J. Y. Huang, S. S. Li, S. Y. Pan, Y. L. Wang and X. J. Li, *J. Chromatogr. A*, 2011, **1218**, 5063-5070.
326. F. F. Lei, X. N. Zhang, Y. L. Gao, Y. H. Han, X. J. Li and S. Y. Pan, *J. Sep. Sci.*, 2012, **35**, 1152-1159.
327. E. Deak, A. Gyepes, E. Stefanovits-Banyai and M. Dernovics, *Food Res. Int.*, 2010, **43**, 2452-2455.

**Furan**

Furan is a highly volatile organic compound that can be a thermally-induced food contaminant which is carcinogenic.[328] Furan is difficult to analyze due to its high volatility, low molecular weight, and trace detection levels. In 2004, the FDA proposed a method to analyze furan in foods using automated headspace sampling followed by GC-MS detection.[329] In this approach, *d4*-furan served as the internal standard in the method of standard additions. Since the method was time-consuming and labor-intensive, several studies and reviews have been published since then in an attempt to improve furan analysis.[330-333]

GC-MS is the preferred analytical technique, and the two most commonly used sample preparation methods are direct headspace in the FDA approach and/or SPME.[334-336] A comparison study of furan analysis in foods indicated slightly better precision and lower detection limit using SPME than headspace alone for sample preparation.[337] However, direct headspace sampling still has merits of simplicity and low cost.[338-340] On the other hand, SPME has been applied to a great variety of applications[341, 342] due to its advantages of ease and commercial availability. One study showed advanced performance by using a fiber coated with sol-gel sorbent.[343] Optimization of various SPME parameters, such as sample size, amount of salt added, and extraction time, was eased by using a mathematical model called response surface methodology, which enabled the simultaneous detection and quantification of 4 different furans in deep-fried products.[344] The application of headspace and SPME with GC-MS analysis of furan in heat-treated, carbohydrate-rich food samples was carefully investigated by Altaki et al.[345] Another study demonstrated that using stir-bar sorptive extraction (SBSE) can extract furan at room temperature, thus avoiding the possibility of furan formation during analysis.[346] Bicchi and co-workers investigated a method for on-line monitoring during the food roasting process.[347] They used SPME-MS without GC separation to reduce analysis time by a factor of 5, but the outcome was limited by interferences.

328. N. Bakhiya and K. E. Appel, *Arch. Toxicol.*, 2010, **84**, 563-578.
329. US Food and Drug Administration, *www.cfsan.fda.gov/'dms/furan.html*, May 7, 2004.
330. M. S. Mariotti, K. Granby, J. Rozowski and F. Pedreschi, *Food & Function*, 2013, **4**, 1001-1015.

331. C. Crews, S. Hasnip, D. P. T. Roberts and L. Castle, *Food Addit. Contam.*, 2007, **24**, 108-113.
332. C. Crews and L. Castle, *Trends Food Sci. Technol.*, 2007, **18**, 365-372.
333. T. Wenzl, D. W. Lachenmeier and V. Gokmen, *Anal. Bioanal. Chem.*, 2007, **389**, 119-137.
334. A. Becalski and S. Seaman, *J. AOAC Int.*, 2005, **88**, 102-106.
335. F. Bianchi, M. Careri, A. Mangia and M. Musci, *J. Chromatogr. A*, 2006, **1102**, 268-272.
336. H. Kataoka, H. L. Lord and J. Pawliszyn, *J. Chromatogr. A*, 2000, **880**, 35-62.
337. M. S. Altaki, F. J. Santos and M. T. Galceran, *Talanta*, 2009, **78**, 1315-1320.
338. S. P. Nie, J. G. Huang, Y. N. Zhang, J. L. Hu, S. Wang, M. Y. Shen, C. Li, M. F. Marcone and M. Y. Xie, *Food Control*, 2013, **30**, 62-68.
339. E. Ruiz, M. I. Santillana, M. T. Nieto, M. E. Cirugeda and J. J. Sanchez, *Food Addit. Contam. A*, 2010, **27**, 1208-1214.
340. A. Becalski, S. Hayward, T. Krakalovich, L. Pelletier, V. Roscoe and E. Vavasour, *Food Addit. Contam. A*, 2010, **27**, 764-775.
341. T. K. Kim, S. Kim and K. G. Lee, *Food Chem.*, 2010, **123**, 1328-1333.
342. L. La Pera, A. Liberatore, G. Avellone, S. Fanara, G. Dugo and P. Agozzino, *Food Addit. Contam. A*, 2009, **26**, 786-792.
343. A. Sarafraz-Yazdi, M. Abbasian and A. Amiri, *Food Chem.*, 2012, **131**, 698-704.
344. T. Perez-Palacios, C. Petisca, A. Melo and I. Ferreira, *Food Chem.*, 2012, **135**, 1337-1343.
345. M. S. Altaki, F. J. Santos and M. T. Galceran, *J. Chromatogr. A*, 2007, **1146**, 103-109.
346. K. Ridgway, S. P. D. Lalljie and R. M. Smith, *Anal. Chim. Acta*, 2010, **657**, 169-174.
347. C. Bicchi, M. R. Ruosi, C. Cagliero, C. Cordero, E. Liberto, P. Rubiolo and B. Sgorbini, *J. Chromatogr. A*, 2011, **1218**, 753-762.