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

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

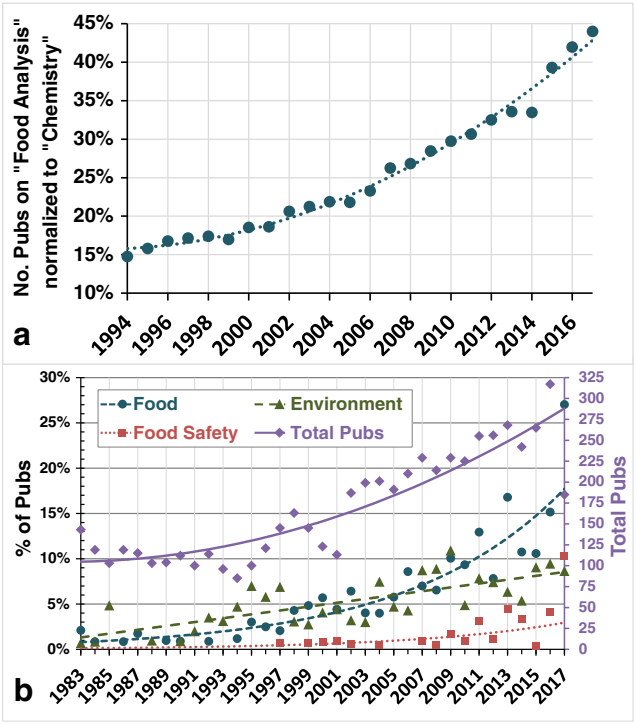

Fig. 1 **a** Annual number of publications on the topic "food analysis" relative to "chemistry" in the Web of Science core collection database; **b** number of publications and their percentage on the given topics in *Trends Anal. Chem.* over time

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

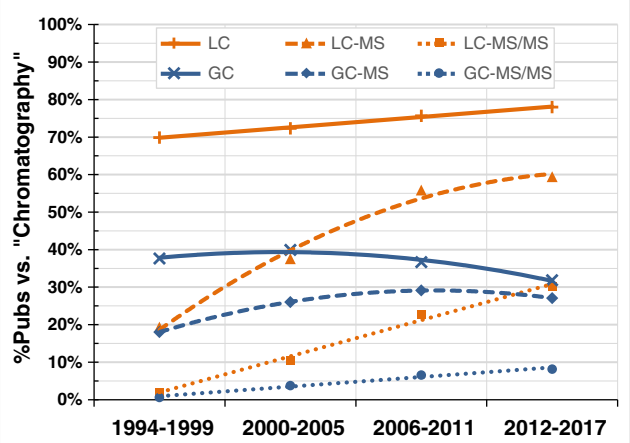

Fig. 2 Percent of LC- and GC-((MS)/MS) publications with respect to publications involving chromatography over time according to Web of Science searches in Table 2

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.

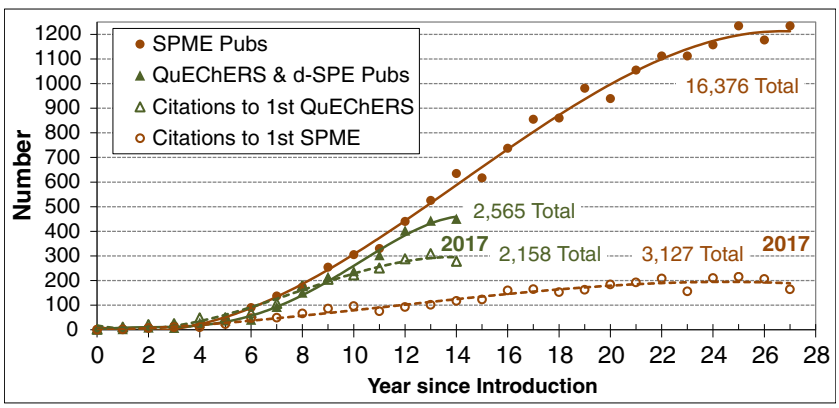

Fig. 3 Growth in the scientific literature according to Web of Science searches of SPME [95] and QuEChERS [89] techniques for sample preparation since their introduction (as cited)

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.