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Research Gaps In Contaminants Of Emerging Concern (CECs): Routes To The Standardization Of Chemical Test Methods By GC/LC-Mass Spectrometry: A Review

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Literature review

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Abstract

A literature review was undertaken with a focus on 1) identifying the research gaps regarding CECs, 2) identifying the most common ones, and 3) identifying the typical analytical methods/technologies employed, for their analysis. A total of 214 papers were noted, with a total of 21 review articles (9.8%). Of this total, a surprisingly high number were from South Africa alone: 117 (54.7%), of which 44 (20.6%) reports were associated with South Africa's Water Research Commission (WRC). The top three CECs research gaps were (decreasing rank: Number of "gaps", %): 1) Toxicity/Risk/Impact (260, 21.5%), 2) Analysis/Tests/Methods (118, 9.8%) and 2) Future research/studies (118, 9.8%), and 3) Monitoring (89, 7.4%). The common classes of CECs that were reported on, were : (i) Chemical: pharmaceuticals, personal care products, steroids, chlorinated and brominated contaminants, PAHs, PCBs, phthalates, alkyl phenols, herbicides, organochlorine pesticides, engineered nanomaterials and (ii) "Microbiological": antibiotic resistance genes, human enteric bacteria and viruses, microbial pathogens (e.g., E Coli, rotavirus, Crypto, etc.), infectious biological water contaminants (e.g., E Coli isolates), cyanobacterial blooms (Microcystis). Common test methods used for analysis of the chemical contaminants were found to be chromatography (gas, liquid)-mass spectrometry; for the microbial contaminants, they were culture-based methods, ELISA, fluorescence microscopy, qPCR, RT-qPCR, gel electrophoresis, Raman spectroscopy, and also chromatography (largely liquid)-mass spectrometry, were also used. Some proposals were additionally made to address the very common, significant research gaps noted in CECs research, especially the standardization of analytical chemical test methods, based on chromatography-mass spectrometry, for quantification.

Introduction

The importance of water quality worldwide, especially for sustainable socio-economic development cannot be over-emphasized (1-3). The South African region has experienced drought for consecutive years (4-6) – water scarcity is becoming a reality and recent water rationing attests to this enormous challenge. There is therefore increasing pressure to reuse wastewater and to consider and use non-traditional sources of raw water supply (7-9). Erratic rainfall patterns, global

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warming and the global challenge (10-11) of continuous discharge of both chemical and pathogenic contaminants into water systems remains a threat to water safety and quality (12-15). This is a human health risk that requires urgent intervention.

The Emerging Contaminants (ECs), or Contaminants of Emerging Concern (CECS) (16-21), also referred to as Persistent Organic Pollutants (POPs), are synthetic or naturally occurring chemicals, and include any microorganisms that are not commonly monitored in the environment but which have the potential to enter the environment – air, water and soil. They subsequently cause known or suspected adverse ecological or human health effects after exposure. They are generally present in very low concentrations in water bodies. For most of them, their effects on humans at low concentrations are still to be established. As a result, they are a global concern.

The CECs include industrial and manufacturing chemicals, pharmaceuticals and personal care products (PPCPs: for example, endocrine disrupting compounds, artificial sweeteners, food additives, nanomaterials, sunscreens, UV filters), flame retardants, biocides, plant and animal protection products, pesticides, hormones, pathogens (bacteria, viruses and protozoa, which are normally detected in water and they have a detrimental effect on human health). They are constantly being found and reported in various matrices, like groundwater, surface water, municipal wastewater, landfill leachate and sediment, drinking water and food sources.

Regarding the CECs, it must be noted that, in South Africa (SA) as well as elsewhere, 1) There are no regulatory requirements to monitor them, 2) Our national drinking water quality guide , the South African National Standards (SANS) 241 (22), although it is aligned to the World Health Organization (WHO) guidelines for drinking water quality (23), merely covers a very limited number of target compounds. Hence, any potential risk mitigation is hardly, if any, addressed, and 3) They are generally present in very low concentration in water bodies.

South Africa is ranked as the 30th driest country, worldwide (24). The South African region has experienced drought for consecutive years. The water scarcity is becoming a reality in South Africa and the recent water rationing attests to this enormous challenge. There is therefore increasing pressure in South Africa to reuse wastewater and to consider and to use non-traditional sources of raw water supply. Umgeni Water (25), located in Pietermaritzburg, province of KwaZulu-Natal, is the largest supplier of bulk potable water in the province, and it is one of the largest bulk drinking water suppliers in South Africa. As a state-owned entity, it is also one of Africa's most successful organizations involved in water management. The organization was established in 1974 to provide water services (water supply and sanitation) to other water services institutions in its area of service. The Process Services Department of Umgeni Water is currently involved in a Water Research Commission (WRC)-funded re-use project to treat wastewater effluent to potable standards, at the Darvill Wastewater Works, a treatment plant in Pietermaritzburg, which is managed by Umgeni Water. This work is of critical importance due to increasing pressure to reuse wastewater and to use non-traditional sources of raw water supply.

Umgeni Water also has a newly developing Research and Development (R&D) Unit, with a comprehensive five-year R&D Master Plan (26), covering research areas to address some of the water sector and related area challenges. The provision of the required resources for this new Unit (state-of-art research infrastructure (laboratories), high-end analytical equipment procurement (e.g., 2D GCXGC-TOF-MS, GC-MS/MS, etc.), human resources recruitment, etc.) has already commenced. In response to the potential risks of these CECS to our drinking water catchments, our recently formulated R&D Plan has therefore included at least one priority project on the CECs (26). The latter project entails,

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inter alia, the screening, identification and quantification of CECs in our catchments (e.g., raw water (dams, rivers), drinking water, etc.); this has not been done before. To this end, we have already procured some of the required analytical equipment, for non-target analysis, like the 2D-GCXGC-TOF-MS, for the analysis of the relatively non-polar, volatile organic contaminants. Our future plans include purchase of a complimentary advanced LC-MS system, e.g., consideration of the trapped in mobility spectrometry (tims)-LC-TOF-MS, to cover the analysis of the relatively polar, non-volatile organic contaminants. The latter project necessitated a prior need to find out the current state of knowledge on the CECs, via a literature search review, with a focus on the research gaps pertaining to the CECs.

Whilst there is a large number of research publications on the CECs, including various review papers, to the author's knowledge, there has been no comprehensive report covering almost all of the possible research gaps regarding CECs.

The aims of this current study was therefore, to undertake a detailed review of the literature on CECs, with a focus on 1) noting the research gaps, 2) identifying the most common, significant ones, 3) identifying the typical analytical methods/technologies employed for their analysis, and 4) to address some of the very common, important gaps.

Materials and methods

Journal publications, for the search of the key word/s/phrases: "contaminants of emerging concern, review" were searched in Science Direct, Google, and our national (South African) Water Research Commission (27) "Knowledge Hub" portal (28), covering the last 5-6 years: for the period: ± 2014 to 2020. This search also provided technical briefs and power point presentations from Conference proceedings. The raw data were captured, and analyzed. For convenience of the data presentation, similar gaps were subsequently grouped into numbered classes (categories), with combinations of fairly similar classes, where it was deemed appropriate. The frequency of the actual research gaps were noted and the resulting Classes were ranked accordingly.

Results and Discussion

Data presentation

The Supplementary Material 1 file (not available in the manuscript) contains the following data:

1) The 214 references (literature papers) that were consulted for this research study.

2) Table S2: The initial raw data, which excludes the research gaps, showing CEC class, sampling mode, matrix, analytical method, etc.

3) Table S3: The initial raw data, which details the research gaps: high level class description, actual research gaps, and the relative frequency (number, percentage of total).

4) Table S4: Some typical classes of CECs.

5) Table S5: Some of the reported matrices analysed for CECs.

6) Table S6: Reported definition of a CEC and references.

7) Table S7: Summary of other reported descriptions (properties) of CECs.

8) Table S8: The International Organisation for Standardisation (ISO) requirements as per ISO ISO/IEC Directives Part 2 Principles and rules for the structure and drafting of ISO and IEC documents: Clauses on subdivisions of the document only.

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The Supplementary Material 2 file contains Table S1: The initial raw data for the research gaps information only (Excel version).

Only two tables are provided in the manuscript:

Table 1: Summary of the reported CECs research gaps and the relative frequency.

Table 2: Quantitative chemical test method validation and key accreditation criteria comparison among some reputable international standard bodies.

The literature findings

From the literature review, a total of 214 papers were noted, with a total of 21 review articles (9.8%) (Supplementary Material 1). Of this total, a surprisingly high number were from South Africa alone: 117 (54.7%), just over 50%, of which 44 (20.6%) reports were associated with South Africa's Water Research Commission (WRC) (27-28).

The WRC was established in South Africa in terms of the Water Research Act (Act No 34 of 1971), following a period of serious water shortage. It was deemed to be of national importance to generate new knowledge and to promote the country's water research purposefully, owing to the view held that water would be one of South Africa's most limiting factors in the 21st century. Its vision is to have highly informed water decision-making through science and technology at all levels, in all stakeholder groups, and innovative water solutions through research and development, for South Africa, Africa and the world. Its Mission, Values and primary functions are available on its web site.

The CECs that were reported

The common classes of CECs (Table S3) that were reported on, were 1) Chemical: pharmaceuticals, personal care products, steroids, chlorinated and brominated contaminants, PAHs, PCBs, phthalates, alkyl phenols, herbicides, organochlorine pesticides, engineered nanomaterials, etc., and

2) "Microbiological": antibiotic resistance genes, human enteric bacteria and viruses, microbial pathogens (e.g., E Coli, rotavirus, Crypto, etc.), infectious biological water contaminants (e.g., E Coli isolates), cyanobacterial blooms (e.g., Microcystis), etc.

Findings on Sampling

The sampling methods that was reported in the 214 references.(Table S1) was predominantly "grab", with the following breakdown: Grab samples: ± 178 (± 82.4%), Composite samples: ± 11 (± 5.1%), Grab and Composite samples: ± 5 (± 2.3%), Polar Organic Chemical Integrative Samplers (POCIS): 1 (± 0.5%), and 24 hr flow proportional sampling: 1 (± 0.5%).

Matrices

The reported matrices (Table S4) in the 214 studies, appeared to be quite extensive: from the most common, typical raw and treated drinking water, raw and treated wastewater, sludge, through to the less common ones: e.g., other solids, various biota and even human-based matrices.

The relative, approximate distribution was noted to be, in decreasing rank: 1) water (raw, source) (31%), 2) biota (26.6%), 3) waste water (13.3%), 4) food (11.4%), 5) solid (10.1%) and lastly, 6) air and human (7.6%).

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These findings indicate and confirms that the CECs are rather widespread in the environment. We would also expect the most commonly tested matrix to be drinking (tap) water, which was ranked 1), at 31%. Surprisingly, the second most common matrix was not wastewater or similar, but rather the biota (26.6%).

Sample preparation

The complexity of environmental matrices and the relatively low concentrations generally detected, require efficient, optimized sample pre-concentration-extraction techniques, and also, removal of any interferences that may be present before chromatographic analysis.

Whilst this aspect was not covered in this review, it should be briefly noted that Solid Phase Extraction (SPE) has been traditionally used for multi-residue analysis due to some advantages, such as preconcentration of the analytes (29). Despite the drawbacks of SPE, such as, (i) the use of large volumes of organic solvents in comparison with miniaturized techniques, (ii) it is time- consuming and (iii) high cost, it is still the most used technique due to the high enrichment factors and efficient reduction of interferences and matrix effects (30-32). Other reported extraction techniques include: online SPE, solid phase micro extraction (SPME), multilayer SPE, fabric-phase sorptive extraction (FSPE) and liquid-liquid extraction, the latter being used for the analysis of volatile compounds (33- 34). The direct injection (DI) technique (35) is an alternative to reduce solvent consumption and analysis costs. Several authors have reported the use of specific ion exchange or graphitized carbon SPE, alone, or in tandem with HLB sorbent cartridges or pH adjustments prior to sample filtration-extraction (36). One technique that has not been extensively researched for the CECs application is QueChERS, which was originally applied to the multiresidue analysis of polar and nonpolar pesticide in fruit and vegetables (37). One recent QuEChERs approach was reported by Martinez-Piernas et al (38), for multiresidue- determination of 107 CECs in treated wastewater, using LC-quadrupole-linear ion trap tandem mass spectrometry.

Analysis and analytical methods

There were far more studies reporting on the analysis of chemical contaminants as compared to analysis of microbiological contaminants: 172 (80.4%) vs 42 (19.6%) (Table S1). This finding is somewhat expected as the common perception is that the CECs are largely chemical, and organic, in nature. Furthermore, relatively larger amounts of synthetic organic chemicals, rather than microbials, are used for the manufacture of products, goods, personal care products and others, for daily life use.

The analytical test methods used were both targeted and non-targeted, but the bulk was targeted: Targeted: 172 (80.4%), Non-targeted: 18 (8.4%) and both Targeted/Non-targeted: 9 (4.2%) (Table S1). This is somewhat expected as standards are available for some, but not all, organic, or microbiological, pollutants. For non-target analyses, by mass spectrometry-based methods, additional confirmation of the observed identification ("hit", usually by the library search software) is required, generally by analysis of the relevant standard, which is in most cases, not available.

The common test methods reported for the chemical contaminants were gas and liquid chromatography, and even 2-dimensional (2D) Gas Chromatography, coupled to various detection systems, like the Electron Capture and the Mass Spectrometer: e.g., single quad, tandem mass spectrometry ("triple quad"), high resolution, magnetic sector, etc. These included GC-MS, GC-MSMS, GC-ECD, GC-Q-TOF, GCXGC-TOF-HRMS, HPLC-MS, HPLC-MSMS, UHPLC-TOF-HRMS, UHPLC-Orbitrap,

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LC-FT-MS, FT-ICR-MS, GC-HR- magnetic sector-MS (Table S1). At least 101 references (47.2%) reported the use of mass spectrometric-based test methods.

The bulk of the test methods were based on the quantitative determination of the chemical concentration of the compounds.

The environmental analysis of micro pollutants is a complex challenge for analytical chemistry researchers, due to: the large number of CECs, the complexity of matrices, the diversity of their physico-chemical properties and concentrations (some are present at relatively low (ng/L) concentrations) (39), etc. The determination of organic pollutants in environmental samples is generally performed by liquid or gas chromatography, according to compound volatility, polarity and stability (40). In general, many tests are target, multi-residue methods, with the aim of monitoring and screening for as many pollutants as possible. Mass spectrometry is the preferred identification and quantification method of choice due to its superior specificity, sensitivity, and it being able to achieve very low detection limits (41). It is well known that liquid chromatography coupled to tandem mass spectrometry is the preferred technique for the analysis of CECs in environmental water, due to its high selectivity, high sensitivity and the relatively medium-high polarity of the CECs contaminants (33).

The common test methods that were reported for the "microbial" contaminants (Table S1) were: culture-based methods, ELISA, fluorescence microscopy, qPCR, RT-qPCR, gel electrophoresis, Raman spectroscopy, and also chromatography (LC and GC)-mass spectrometry: MALDI-TOF-MS, LC-MSMS, UPLC-MSMS, LC-HR-MS, LC-QTOF, Q-Orbitrap, LC-MS, GC-MS.

Research gaps for the CECs

Combination of similar gap Classes (Categories)

Due to some similarity, some Classes (Categories) were grouped together, giving a final total of 36 classes (Categories). The resulting data is is summarized in Table 1:

The following 11 Classes represent similar gaps: Toxicity/Risk/Impact,

Analysis/tests/methods, Studies/Research, Removal/reduction/remediation/treatment/Purification, Fate/ Degradation/transformation-products/metabolites, Distribution/spatial-temporal variability/occurrence, Source/evaluation of additional sources, Ecology/trophic transfer, Use/consumption, Water pollution/ mitigation, and Resistance/Persistence.

The most common research gaps (Classes)

The resultant top five, or the most common areas noted (6 in total) were the following Classes, in decreasing rank (Number of "gaps", %): (i) Toxicity/Risk/Impact (260, 21.5%),(ii) Analysis/Tests/Methods (118, 9.8%) and (ii) Future research/studies (118, 9.8%), (iii) Monitoring (89, 7.4%), (iv), Removal/ reduction/remediation/treatment/purification (81, 6.7%), and (v) Fate/degradation/transformation-products/metabolites (67, 5.6%). The remaining Classes are summarized, in decreasing Rank based on frequency, in Table 1.

The top 2 ranking research gaps (Classes) are further discussed below, with a focus on the actual details that were reported:

1 Toxicity/Risk/Impact (21.5%)

In this gap Class, the contaminants referred to were both chemical: e.g., pharmaceuticals, agricultural

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Table 1.Summary of the reported CECs research gaps and the relative frequency

Research gap Class Number	Research gap Class	Frequency: Number of gaps reported per Class	% of Total Gaps	Class Rank
1	Toxicity/Risk/Impact	260	21.5	1
2	Analysis/tests/methods	118	9.8	2
3	Studies/Research	118	9.8	2
4	Monitoring	89	7.4	3
5	Removal/reduction/remediation/treatment/Purification	81	6.7	4
6	Fate/Degradation/transformation-products/ /metabolites	67	5.6	5
7	Distribution/spatial-temporal variability/occurrence	58	4.8	6
8	Data	51	4.2	7
9	Regulation	51	4.2	7
10	Source/evaluation of additional sources	31	2.6	8
11	Knowledge	29	2.4	9
12	Ecology/trophic transfer	26	2.2	10
13	Management	21	1.7	11
14	Sampling	19	1.6	12
15	Use/consumption	17	1.4	13
16	Models	17	1.4	13
17	Scope	15	1.2	14
18	Mixtures	15	1.2	14
19	Epidemiology	12	1.0	15
20	Bioaccumulation	11	0.9	16
21	Collaboration of expertise	11	0.9	16
22	Information	11	0.9	16
23	Priority Contaminant List	9	0.7	17
24	Water pollution/mitigation	9	0.7	17
25	Transfer mechanism of antibiotic resistance genes	6	0.5	18
26	Resources	6	0.5	18
27	Education	6	0.5	18
28	Behavior	6	0.5	18
29	Interaction	6	0.5	18
30	Policy	5	0.4	19
31	Resistance/Persistence	5	0.4	19
32	Bioassay	5	0.4	19
33	Reporting	5	0.4	19
34	Partitioning of CECs to solid matter	4	0.3	20
35	Chiral contaminants	4	0.3	20
36	Retention of contaminants by plastic particles	3	0.2	21

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chemicals (pesticides), PCB, engineered nanomaterials, personal care products (PCPs), micro plastics, metal-elements, etc., and microbiological: e.g., anti-microbial resistance genes, mycotoxins, etc.

Some of the gaps reported included: risks for human health, tests for toxicology, tests for risk assessment, impact on human health and the environment, additive effects, guidelines and strategies for environmental risk assessment, research on the health impacts of micro-plastics, both human and non-human, determining exposure levels and possible standards for drinking water and food products, measurement of internal concentrations in biota, that will enable more reliable risk assessment for pharmaceuticals in the environment than those based solely on concentrations in water, limited reviews have investigated sources, behavior and health risks of antimicrobial resistance genes (ARGS) in the wastewater-human pathway, pathogens: their threats to human health and ecosystems from these compounds (ARGs) occurring in sewage sludge, anti-TB drugs: since antimicrobial compounds are mostly non-biodegradable (e.g., INH), they may be toxic to sludge bacteria and kill them; this could decrease the efficiency of WWTP biological processes since sludge bacterial population will be decreased, TCS, TCC: additional investigations are required on their toxicity, micro plastics: globally, freshwater systems are among the most threatened of habitats and it is important that this emerging threat is recognized and mitigated, relationship between general health status and PFAA exposure in wildlife and humans is an area greatly understudied, the survival of microbial pathogens in chlorinated effluents is a cause of concern over and above the potential health hazards associated with exposure to poorly treated effluents, agricultural pesticides: numerous chronic and acute environmental health risks are associated with agricultural pesticide exposure, other microbial communities such as fungi, viruses, and protozoans should be investigated to identify the recurrent biomarkers and their toxigenic compounds, antibiotic resistant bacteria and genes: a considerable body of knowledge is being generated to establish the occurrence of antibiotics, ARB and ARGs in aquatic systems, particularly in drinking water distribution systems; how environmental conditions affect the associated genetic and metabolic changes is not clearly understood, pharmaceutical and personal care products: establishing the possible endocrine-disrupting effects of commonly detected PPCPs and other micro-pollutants through a tiered eco-toxicological approach, CECs in recycling/reuse: combined effects and concentrations are mostly unknown, CECS in recycling/reuse: carefully test drinking water from the seawater desalination plants or reused sewage water for toxicity, micro plastics: to develop methods for toxicity testing to study micro plastics in South African freshwater systems, agricultural chemicals: it is recommended that a manual providing guidelines on choosing agricultural chemicals that minimize effects in non-target environments (both human and ecological health) be produced, urban wastewater epidemiology: need to broaden our understanding on CEC presence, fate, risk, micro plastic pollution: the full impact and risks of micro plastics pollution in water is yet to be discovered, etc.

2 Analysis/Tests/Methods (9.8%)

The reported gaps in this Class covered both chemical and microbiological contaminants.

The chemical contaminants included: DEET, insecticides, pharmaceuticals, personal care products, anti-TB drugs, ARVD metabolites, rare earth elements, chiral APIs, PBDEs, 1,4-dioxane, mercury, fluoride, PAH, PCB, OC-pesticide, engineered nanomaterials, brominated flame retardants, alkyl phenol ethoxylates (APEs), CECs in recycling/re-use, micro plastics, plasticizers, agricultural chemicals (glyphosate), etc.

Some of the reported microbiological contaminants were: algal toxins, RABs, antibiotic resistant

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bacteria (arb) and genes, antimicrobials/antibiotic resistant bacteria.

Some of the gaps reported included: speed, optimization, non-target/unknown compound methods, sensitivity, accuracy, standardized method validation guidelines, development of enantioselective methods for profiling chiral APIs, need for metabolomics, guidelines for method validation using HRMS are lacking, instrumental reference methods that are essential to verify the presence of an analyte at the level of interest, etc.

Some proposed solutions to address some gaps in CECs research

This section will attempt to address some of the significant, common gaps identified in this study.

Definition of a CEC

Whilst this was not identified as a gap in the literature that was reviewed, a brief, preliminary literature search was subsequently undertaken to establish the current definition of a CEC. After a Science Direct search, using the key word: "definition of a CEC", a total of 19 published papers, covering the last 5 years, were reviewed. The preliminary findings are summarized in Table S3 (Some reported definitions for a Contaminant of Emerging Concern (CEC)).

Of the 19 publications: all 19 (100%) defined them as chemical in nature, 10 (52.6%) further defined them as also including chemical-inorganic contaminants. It was further noted that only 3 (15.8%) references defined them to include all three contaminant classes: organic, inorganic and microbial.

This preliminary study confirms the general, current perception that the CECs are "chemical" compounds, and they are organic, in nature.

From this research, the following is now proposed as a definition of a CEC that should encompass, as a minimum, the following 6 attributes: their composition, source, occurrence, concentration, toxicity and regulation, which are further described below:

1 Their composition: they are synthetic, manufactured, man-made, anthropogenic, artificial or naturally occurring chemicals (both organic and inorganic), materials, microbial substances; a wide range of substances, including each of their metabolites/transformation products; includes any compound for which a conceptual model is missing: Conceptual models intend to describe and optionally quantify systems, processes and their interactions and are developed to different incremental degrees of complexity; any high-priority compound that critically requires further, toxicological studies or for which regulatory measures could be envisaged..

Some examples of the chemical contaminants, not exhaustive, which also include the different Classes, are summarized in Table S3.

2 Their source: they are derived from various sources, notably wastewater works, wastes recycling, and pharmaceutical facilities; from non-point sources such as run-off from streets and agricultural land, for example, concentrated animal feeding operations and treated-effluent discharge from wastewater treatment plants.

3 Their occurrence: they are present, and accumulate, in the environment; are found in environmental compartments, especially aquatic; are found in biota, fauna, flora and in humans.

4 Their concentration: they are present at typically mg/L, µg/L, down to ng/L (ppt) concentrations in the

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environment (environmental) compartments.

5 Their toxicity: they cause known, or show some potential to pose risks to human health or the environment (e.g., they can significantly alter the metabolism, biological disruption (dysfunction), including endocrine dysfunction).

6 Their regulation: they are generally not yet subjected to regulatory criteria, (or are recently regulated), or to norms for the protection of human health or the environment.

Some of the other descriptions and properties that have been used to describe CECs are summarized in Table S6.

Towards the standardization of method validation guidelines and chemical test methods for CECs in various matrices using chromatography-mass spectrometry

One way of assessing the hazard posed by chemical pollution is by component-based methods (CBMs) – comparing the measured environmental concentrations (MECs) and toxicological endpoints from Eco toxicological studies (42).

As risk assessment (toxicity) is one of the most important end points of CECs research, the actual chemical measurement, which should be fairly accurate, precise and reliable, is a vital piece of information for subsequent risk assessments, especially those involving prior knowledge of chemical concentration for the subsequent calculations, e.g., the Risk Quotient method (43-44).

This study revealed that toxicity and the lack of comprehensive, standardized test method validation guidelines are the top 2 gap "classes" in CECs research. Additionally, as CECs are generally present at low (ng/L) concentration, there is therefore a need for sensitive, accurate, and precise analytical methods that are adequately validated and deemed to be "fit-for-purpose".

For general water quality monitoring requirements, the test methods used should ideally meet the requirements for being relevant, simple, reliable, accurate, and cost-effective. Analytical test methods that are method-validated (45-46) to meet the full ISO/IEC 17025- accredited (47), technical competency requirements are deemed to be "fit- for-purpose" (46).

Accuracy is the closeness of the agreement between a test result and the reference value (47-48). The recovery of a target analyte from a matrix is generally affected by the extraction technique. Ideally, one aims to use an optimized method that will result in maximum (100%) recovery of the target analyte. In the water sector, many decisions are based on the results of test measurements. It is critical that such results are accurate, for public health safety, and now, more so, in the context of CECs screening, quantification, risk assessment, any health-safety implications, and final reporting to the relevant authorities.

The required measurement quality (49) can be achieved by achieving method validation that meets international accreditation standards or requirements, (e.g., ISO/IEC 17025) (45-47), by establishing traceability of the measured test results to stated references and by an estimate of the measurement uncertainty (MU) (Uncertainty of Measurement (UOM)) (50). The Uncertainty of Measurement (UOM) is the parameter associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand (47, 50). For ISO/IEC 17025 accreditation of test methods, UOM is a requirement (47).

Standards contain technical specifications and criteria designed to be used consistently. One route to

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standardization of test methods is the one minimum requirement of test method validation, defined as a process that demonstrates suitability of an analytical method for its intended purpose (45-47). This can be further followed by suitable international accreditation, like ISO/IEC 17025 (47).

Method validation and accreditation

Method validation is defined as "the process of establishing the performance characteristics and limitations of a method and the identification of the influences which may change these characteristics and to what extent".

Validation (45-47) is the process that is followed to demonstrate with the provision of objective evidence, that a specified test method is suitable for the intended purpose. Performance characteristic "means functional quality that can be attributed to an analytical method". Examples of typical performance characteristics (45-47, 51), for chemical test methods, include: selectivity, accuracy, trueness, recovery, precision, repeatability, reproducibility, limit of detection, limit of quantitation, ruggedness and stability. The differences due to matrices ("scope") must be taken into account when testing different types of samples. The raw data should be evaluated with appropriate statistical methods.

Quality control and quality assurance includes interlaboratory comparisons, blind test samples analyzed by the laboratory and proficiency testing schemes (48, 52). Proficiency testing is an accreditation requirement for laboratories (47-48), for the scope of accreditation (tests) being performed, and it should conform to the requirements of ISO 17043 (51). It also includes internal quality control, which consists of all the procedures undertaken by a laboratory for the continuous evaluation of its testing work (45-47). The main objective is to ensure the consistency of test results produced day-to-day and their conformity to defined criteria, or internal limits. A program of periodic checks is necessary to demonstrate that variability (e.g., between analysts and between equipment or materials, etc.) is under control.

One of the major CECs research gaps regarding the "Class (category) Number 2 (Table 1) "analytical tests" is the lack of comprehensive, standardized method validation guidelines, standardized tests, or standards. The availability of an internationally accepted standard for method validation will no doubt promote the development and availability of many more tests for CECs in various water, and other related, environmental matrices.

ISO/IEC 17025 accreditation

Many testing laboratories have achieved ISO/IEC 17025 accreditation for various chemical tests on water, and even on wastewater, soil, sludge, etc.

Accreditation is the confirmation by an accreditation body that the organization is competent to conduct its technical activities (tests or calibration) and to produce valid reliable results to specified requirements. Implementation of the requirements of a recognized standard as a management system gives confidence that the technical activities of an organization will consistently produce valid results. It is competence-based.

The ISO/IEC 17025:2017(E) document, titled General requirements for the competence of testing and calibration laboratories (47), is an international standard that has been developed with the objective of promoting confidence in the operation of testing and calibration laboratories. This standard covers both the technical and management system requirements that need to be fully met, for the accreditation of a

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test method; the generic requirements are summarized in Table 2. Testing laboratories that are ISO/IEC 17025-accredited are deemed competent to generate valid test results for their accredited test methods. In order for a test method to be ISO/IEC 17025-accredited, there is the prior need for method validation (technical), in addition to the laboratory complying with all the other technical and management requirements as per the ISO/IEC 17025 standard (47). The generic test method validation and ISO 17025 accreditation data requirements (45-46), are summarized in Table 2.

For a country like South Africa, the South African National Accreditation System (SANAS) (53) is the single, national ISO/IEC 17025 Accreditation Body that gives formal recognition that Laboratories (e.g., testing, calibration), Certification Bodies, Inspection Bodies, Proficiency Testing Scheme Providers and Good Laboratory Practice (GLP) test facilities are competent to carry out specific tasks. SANAS is responsible for the accreditation of Certification bodies to ISO/IEC 17021, ISO/IEC 17024 and 65 (and the IAF interpretation thereof), and laboratories (testing and calibration) to ISO/IEC 17025.

Some of the key technical requirements, by some international scientific bodies, like the United States Environmental Protection Agency (US EPA) (54), the American Society for Testing and Materials (ASTM) (55), and the Association of Official Analytical Collaboration (AOAC) (56), compared with the requirements of the ISO/IEC 17025 guide, are summarized in Table 2.

The earlier version (2005), and this 2017 updated, current version document, was developed with the objective of promoting confidence in the operation of laboratories. It contains requirements (both management and technical) to enable them to demonstrate that they operate competently, and that they are able to generate valid test results. Use of this document will facilitate cooperation between laboratories and other bodies, will assist in the exchange of information and experience, and in the harmonization of standards and procedures. The acceptance of results between countries is facilitated if laboratories conform, by way of being accredited, to the standard.

The Clauses 4 to 8 are listed in Table 2. In addition to the international ISO 17025 guide, the South African national ISO 17025 accrediting body SANAS has further supplementary documents, for assisting and guiding laboratories (e.g., water testing) with meeting the accreditation requirements: e.g., for chemical tests: SANAS TR 26 03 and SANAS R 80-04.The corresponding supplementary SANAS requirements for validation and quality assurance in microbiological testing, are specifically outlined in the SANAS document TR 28-03 (57).

The generic method validation requirements are fairly comprehensive. Some of the key performance characteristics, and others, recommended for validation, are: accuracy, trueness, bias, precision, selectivity, specificity, LOD, LOQ, ruggedness, range, linearity, calibration, sensitivity, and also Measurement Uncertainty (MU). However, there is no additional identification requirements specifically for chromatographic tests, using mass selective detectors, which is now very commonly used for the CECs screen and for their quantification.

Standardization options and brief discussion

A standard is an agreed, repeatable way of doing something. A published document contains a technical specification or other precise criteria designed to be used consistently as a rule, guideline, or definition. Standards help to make life simpler and to increase the reliability and the effectiveness of many goods and services we use. Standards are created by bringing together the experience and expertise of all interested parties, such as the producers, sellers, buyers, users and regulators of a particular material, product, process or service.

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Table 2.Quantitative chemical test method validation and key accreditation criteria comparison among some reputable international standard bodies

Num-ber/ *ISO 17025 Clause*	**Parameter**	**ISO/ IEC 17025 (2017)**	**US EPA[a] (FEM 2016)**	**US EPA ATP Protocol (1996)**	**Eura=chem (2014)**	**SANTE 11312/ 2021 (2021)**	**Journal publica-tion[b] (2020)**	**ASTM**	**AOAC**	***Standard Methods[c] (2023)***
4	General requirements	√				√				
4.1	Impartiality	√				√				
4.2	Confidentiality	√				√				
5.1-5.7	Structural requirements	√			√	√				
6	Resource requirements	√			√	√				
6.1	General	√			√	√				
6.2	Personnel	√			√	√				
6.3	Facilities and environmental conditions	√			√	√				√
6.4	Equipment	√		√	√	√				
6.5	Metrological traceability	√				√				
6.6	Externally provided products and services	√				√				

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7	Process requirements	√		√		√				
7.1	Review of requests, tenders, contracts	√				√				
7.2	Selection, verification and validation of methods	√		√		√				√
7.3	Sampling	√		√		√				√
7.4	Handling of test or calibration items	√		√		√				√
7.5	Technical records	√		√		√				
7.6	Evaluation of measurement uncertainty	√			√					√
7.7	Ensuring the validity of results	√		√		√				
7.8	Reporting of results	√		√		√				√
7.9	Complaints	√				√				
7.1	Non-conforming work	√				√				
7.11	Control of data and information management	√				√				
8	Management system requirements	√				√				
8.1	Options	√				√				
8.2	Management system documentation	√				√				
8.3	Control of management system documents	√				√				

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8.4	Control of records	√				√				
8.5	Actions to address risks and opportunities	√				√				
8.6	Improvement	√								
8.7	Corrective actions	√				√				
8.8	Internal audits	√				√				√
8.9	Management reviews	√				√				√
	Reason for an ATP	√		√						
	Method development									
	Addressed in guidance document	√	√			√				
	To be planned	√				√				
1	**Method validation**	√		√		√				√
	Commences only after method development		√							

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	Within-intra-lab method validation addressed by guide		√	√		√				
	Multiple inter-lab method validation addressed by guide		√							
	Guide addresses validation of field activities, e.g., sampling	√	√							
	Criteria to consider if validation is necessary		√							
	Selection of methods: Standard, rapid, Non-standard	√	√			√				
	Qualified and competent staff	√	√		√	√				
	Procedures for assuring quality of results generated by test methods used for routine/ad hoc/ non routine testing	√				√				
	Procedure for method validation	√				√				
	Staff assigned for validation	√			√	√				
	Staff training to carry out validation and evaluation of raw validation data	√			√	√				

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	Staff training to carry out validation and evaluation of raw validation data	√			√	√				
	Appropriateness of equipment used	√				√				
	Acceptance criteria and basis of acceptance	√				√				
	Extent of validation	√				√				
	Standard operating procedure for validation	√				√				
	Identification of uncertainty sources	√				√				
	Identification of validation parameters	√				√				
2	**Test method**									
	Method development	√			√					√
	ATP case number			√						
	Date	√		√		√		√		
	Revision number	√		√		√				
	Method summary		√	√				√		

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	Introduction/principle	√				√				
	Scope and application	√	√	√		√		√		
	Definitions and acronyms	√	√	√		√		√		
	Interferences/sources of error	√	√	√		√		√		
	Facilities and environmental conditions	√	√			√				
	Safety, health and environment	√	√	√		√		√		√
	Sample collection/ sampling	√		√		√		√		
	Sample handling	√				√				
	Sample transport	√				√				
	Sample preservation	√	√	√		√				
	Sample storage			√						
	Equipment	√	√	√		√		√		
	Maintenance and services	√				√				
	Reagents and standard solutions	√	√	√		√		√		
	Preparation of samples	√				√				
	Calibration and standardisation	√	√	√		√		√		
	Analytical procedure	√	√	√		√		√		
	Quality control	√	√	√		√				

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	Calculation of results	√	√	√		√		√		
	Data analysis		√	√				√		
	Method performance		√	√						
	Reporting of results	√				√				
	References	√		√		√		√		
	Appendix	√				√		√		
	Document revision and change history	√				√				
	Pollution prevention		√	√						
	Waste management		√	√						
	Operational limits		√					√		
	Table, diagrams, flow charts, validation data			√				√		
3	**Validation Plan**	√	√		√					
	Validation procedure used	√				√				
	Measurement process components to be validat-ed to be described, e.g., sub-sampling, instrumental		√							
	Any known limitations and assumptions to be de-		√							
3.1	A description of how the method and analytical parameters cho-sen meet the data quality objectives for the specific application		√							
	Method title Include Reference	√	√		√	√				

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	Method to be validated: a detailed written procedure (such as a standard operating procedure) describing the method to be evaluated should be available. The formal validation should be considered separately from any method development activities. It is the 'final' version of the method – after completion of method development – that is validated.		√		√					
	Critical steps in the method and instrument requirements				√	√				
	Supporting information (e.g., data from participation in interlaboratory comparisons (ILC), such as proficiency testing (PT) schemes, results from internal quality control (IQC) and results from previous routine use of similar methods).				√	√				
	Experiments				√					
	The materials that will be analysed – e.g. (C)RMs, test samples, calibration standards				√					
	The experimental design, including: 1) The number of replicate measurements that will be made on each material 2) The measurement conditions and order of analysis (e.g. if the measurements are to be made on different days, and/or by different analysts, and/or using different measuring instruments)				√					

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3.2	**Analytical Requirement**				√					
	Analyte/s specified		√		√					√
	Description of measurand/s	√	√		√	√			√	√
	Description of matrice/s typically analysed, and form of samples	√	√	√	√	√			√	√
	Expected levels/required working range specified?		√		√					√
	Purpose of method described, and/or well understood?		√		√					√
	Intended use of data		√							
	Use of results clearly specified?				√					
	Any specific regulatory requirements?				√					
	Are results to be used for critical decisions?				√					
	Performance characteristics to be studied identified?		√		√					
	Validation parameter (description of samples, experimental approach	√			√					
	Accuracy /Analysis of unknown samples or Standards (e.g.,	√	√							√
	Trueness	√	√							
	Bias	√	√	√	√			√		√
	Recovery (as a measure of Trueness/Bias)					√ (70-120%, ≤ 20%				

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	Bias - matrix matched (as close as possible) certified reference material,	√								
	Bias- by recovery experiments using spiked samples,	√								
	Bias - by comparison with another validated (standard or reference) method or through PTS	√								
	Selectivity	√	√		√					
	Specificity	√								
	Limit of detection/method detection limit	√	√	√	√					√
	Limit of quantification	√	√		√	√				
	Ruggedness (Robustness)	√	√		√					
	Precision: Repeatability	√	√		√	√		√		√
	Precision: Intermediate	√			√			√		
	Precision: Reproducibility	√	√		√	√ Within-lab RSDwR ≤ 20%)				
	Measurement Uncertainty	√			√	√		√		
	Analytical Sensitivity		√		√					
	Instrument calibration (calibration model, e.g., first- order linear, curvilinear, or nonlinear)	√	√							

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	Calibration curve	√	√	√						
	Linearity/R2 statistic	√	√							
	Sensitivity	√				√				
	Working/measurement Range (Method)	√	√		√					
	Working Range (Instrument)				√					
	Analyte stability/sample holding time/ruggedness (robustness)		√	√	√					√
	Storage condition of sample -stability		√	√						
	Equivalency testing (samples at 3 different concentrations by the standard and by the new alternate method)									√
	Analyte stability in extracts		√			√				
	Identification (MS-based methods)									
	Specificity					√				
	Ion ratio					√				
	Retention time					√ (± 0.1 min)	√			
	Matrix effect					√				
	Decision limit						√			
	Detection capability						√			
	Mass accuracy					√	√			

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	Isotopic fit						√			
	Fragmentation						√			
	Target values for performance characteristics stated?				√					
	Data evaluation									
	Outline how the data will be evaluated. Include information on: 1) Any statistical parameters to be calculated from the data (e.g. mean, standard deviation) 2) How values for performance characteristics are to be calculated form the data 3) Any statistical tests that will be used 4) How the 'fitness for purpose' of the performance characteristic will be assessed				√					
	Comparison of results achieved with other validated methods	√								
	Extent of routine use of the method known?				√					
	Purpose of validation study									
	Purpose of validation exercise stated?				√					
	Method to be validated for use in another laboratory?				√					
	Method/similar methods well known in lab?				√					
	Clear and unambiguous method description available (e.g. standard operating procedure)?				√					
	Any known/foreseen critical steps?				√					
	Any supplemental standard operating procedures required?				√					
	Any health/safety issues?				√					
	Specific requirements for performing the method				√					

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	Any specific requirements for sample handling/storage?				√					
	Any specific requirements for sample preparation?				√					
	Any specific requirements for equipment calibration?				√					
	Any specific requirements for environmental monitoring?				√					
	Competence for validation				√					
	Responsible person for the study appointed?				√					
	Analyst(s) carrying out validation familiar with the method?				√					
	Supplementary training required?				√					
	Supervision during validation required?				√					
	Equipment and facilities				√					
	Particular equipment required for sample preparation?				√					
	Required measuring equipment available?				√					
	Measuring equipment properly calibrated?				√					
	Measuring equipment properly maintained?				√					
	Facilities appropriate for the application of the method?				√					
	Environmental conditions under control?				√					
	Tools available for validation				√					
	Suitable blanks available?				√					
	RMs/CRMs available?				√					

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	Spiking of samples possible/ required?				√					
	Surplus test samples available?				√					
	Stability of validation materials under control?				√					
	Reference method (s) available?				√					
	Evaluation of individual performance characteristics				√					
	Performance target specified?				√					
	Materials to be analysed specified and sufficient material available?				√					
	Experimental plan defined (number of replicates, order of analysis)?				√					
	Data analysis defined (including statistical tests)?				√					
	Criteria for assessing fitness for purpose specified?				√					
	Supplementary information to support assessment of method performance				√					
	Any historical data available (e.g. IQC or results from routine application of method)?				√					
	Possible to participate in PT during validation?				√					
	Possible to participate in/ arrange other ILC?				√					
	Multilaboratory validation studies		√							
	Standard Operating procedure									√
	Tier 1 single laboratory, 1 or more matrix		√							
	Tier 2 multiple laboratory, 1 matrix		√							√
	Tier 3 nation-wide laboratory, all matrices		√							
	Primary validation/laboratory performance study		√							
	Secondary validation/method		√							

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	Participating (Interlab) laboratories	√	√			√				
	Test materials: CRMS, laboratory prepared spiked materials, reference standards/materials	√	√			√				
	Replication of test materials: ≥ 2		√	√						√
	Precision: 6 analysts, not more than 2 per laboratory									√
	Concentration levels: ≥ 3 over the entire method Range									√
	Approval of validation plan Validation plan signed off by appropriate person?				√					
	On completion of study				√					
	Assessment of fitness for purpose completed for each performance characteristic and method as a whole?				√					
	Validation report signed off?				√					
	Final method documentation (e.g. standard operating procedure) prepared and signed off?				√					
	Ongoing quality control requirements established?				√					
4	**Validation Report**	√	√		√					
	Guidelines and format for method to be proposed			√						
	Title page			√				√		
	Acknowledgements			√						
	Disclaimer			√						
	Table of contents			√						
	Introduction			√				√		
	Notice of performance-based method			√						
	Body of Method (EMMC format)			√						
	Format			√						

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	Conventions			√						
	Content (must contain 17 specific topical sections			√						
	Summary of Method			√						
	Definitions			√						
	Interferences			√						
	Safety			√						
	Method Validation report									
	Report of method validation studies/Summary	√		√		√				
	Validation plan used to generate test method performance characteristic	√				√				
	Identification of participant laboratory/laboratories		√	√						
	Description of reagents, spiking materials, reference standards and source/s, calibration, equipment	√	√	√		√				
	Study design summary		√	√					√	
	Test materials used: collection and preparation details	√	√	√	√	√				
	Sample preservation and storage			√						
	Quality control			√						
	Calibration and standardisation			√						
	Procedure			√						
	Data analysis and calculations (interpretation), reporting			√						
	Procedure/s used for analyses of results	√	√		√	√				
	Statistical method/s used for analyses of results		√		√					

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	Method Title The determination of A {analyte or measurand} in the presence of B {interference} in C {sample type/matrix} using D {principle} Include method reference number if applicable A: What quantity is being measured? B: Are there any known interferences that can be accommodated by the method? C: What sample types/matrices will be analysed using the method? D: What measurement technique/ measuring instrument will be used?	√			√	√				
	Method status Is the method, e.g. a published standard method (unmodified), based on a published standard method (with modification), a method developed in-house?		√		√					
	Introduction	√			√	√				
	Purpose of study Outline the purpose of the study, e.g. to validate a new in-house method, to verify the performance of a published standard method, to validate the extension of the scope of the method.		√	√	√					
	Analytical requirement: Analyte: Specify the analyte(s) (e.g. copper, creatinine, hexavalent chromium). Measurand: State the measurand (the quantity intended to be measured), e.g., is it the 'total' concentration of the analyte(s) present that is of interest, the 'amount extracted' under specified conditions, or the result obtained from a specified (standard) measurement procedure? State the units in which the measurement results will be reported. State required range (e.g. concentration range in samples). Matrix and form: State the matrix/ matrices of the samples and their physical form. Purpose of measurement: Specify why the measurements are required (e.g. to check compliance with a particular regulation or a manufacturing specification). Scope of method, application, purpose of study, materials available for the study		√		√					

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	Other considerations: 1 Is there any historical data on method performance available? 2 Is sampling/subsampling required (and will this be done within the laboratory)? 3 Are there any restrictions on sample size or availability? 4 Is the analyte dispersed or localised within the samples? 5 Are there any known interferences? 6 List any CRMs that are commercially available with a matrix and property values that are similar to the test samples. 7 Identify any other (C)RMs that may be used during the validation study (e.g. pure substance reference materials used for preparing spiked samples).				√					
	Purpose of study State the purpose of the study, e.g.: 1) Full validation of a method developed in-house 2) Verification of implementation of a published method for which data on performance characteristics are available 3) Validation of change of scope of a method 4) Re-validation following change in operating conditions 5) Re-validation after period of non-use.				√					
	Validation parameter/performance characteristics to be investigated/ method performance: 1 List the performance characteristics (e.g. selectivity, LOD, LOQ, precision, accuracy, bias, etc.) to be evaluated during the study. 2 Justify any omissions (e.g. ruggedness not relevant as a published standard method is being used).	√	√	√	√	√				
	Method performance: Collaborative study (can be additionally done)			√						
	Interlaboratory study		√							

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	Experiments Outline the experiments that will be carried out to evaluate each performance characteristic Materials to be analysed: e.g. (C)RMs, test samples, calibration standards The experimental design, including: 1) The number of replicate measurements that will be made on each material 2) The measurement conditions and order of analysis (e.g. if the measurements are to be made on different days, and/or by different analysts, and/or using different measuring instruments).				√					
	Method performance requirements/ Criteria against which performance characteristics will be accessed How does the method need to perform to deliver results that are fit for purpose? Summarise the performance target values for the performance characteristics to be evaluated during the study. State and justify how the performance requirements were defined. Performance target values may be: 1 Defined in standards/regulations 2 Stated in a published standard method (can the stated performance be achieved?) 3 Related to a product specification in manufacturing quality control 4 Based on performance of similar procedures that are known to be fit for purpose 5 Defined as the current state-of-the-art (what is the method capable of? (e.g. target values for precision, bias or limit of detection (LOD)).				√					
	Notes Any existing performance data available				√					
	Evaluation of data Outline how the data will be evaluated. Include information on: 1 Any statistical parameters to be calculated from the data (e.g. mean, standard deviation) 2 How values for performance characteristics are to be calculated form the data 3 Any statistical tests that will be used 4 How the 'fitness for purpose' of the performance characteristic will be assessed	√			√	√				

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	Methods		√	√						
	Validation data			√						
	Results and discussion	√	√	√	√	√				
	Specifications – method performance summary	√	√	√	√	√				
	Development of quantitative QC criteria		√							
	Statement on whether aims of study have been achieved				√					
	Conclusion Statement on whether the performance criteria have been met, and whether the method is fit-for- purpose	√		√	√	√				
	Statistical assessment of method's comparability with any available reference method		√	√						
	Location of raw data	√		√		√				
	References (e.g., relevant section/s of Eurachem Guide 2014)	√		√	√	√				
	Approval: Signoff of Validation Report				√					
	Notes/Key Information: To highlight any key information that has arisen from the validation, such as critical steps in the method, any other information relevant to the evaluation of the performance characteristic or requirements for future quality control				√					
	Pollution prevention			√						
	Waste management			√						√
	Glossary			√						
5	**Quality control and quality assurance**	√			√	√				√
	Internal quality control	√			√	√				√
	QC samples									√
	Test samples				√					
	Blanks				√					√
	Standard solutions (calibration samples)				√					
	Use of spiked samples	√			√	√				√
	Use of reference materials replicate testing	√			√	√				

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	Replicate evaluation of test results/routine samples	√			√	√				
	Intralaboratory comparisons	√			√	√				√
	Blind samples				√					√
	External quality control				√					
	Proficiency testing	√			√	√				√
	Interlaboratory comparisons	√			√	√				√
	Blind test samples analysed by the laboratory	√				√				
	Proficiency Testing Schemes (PTS)	√				√				√
6	**Post-validation activity**									
	Records: raw data, results obtained	√				√				
	Records: validation procedure used	√				√				
	Peer review of method before publication	√	√			√				
	Evidence that method has been transferred to routine use	√				√				
	Periodic verification that documented performance can be met	√				√				
	Method performance verification during routine analysis AQC, on-going method validation					√				
	Equivalency testing (to Standard Methods)									√
	Conversion to a Standard Method Collaborative testing (different laboratories, Apparatus/Equipment, Operators, Concentration/Levels, Matrix)									√

[a] For internal use only, by US EPA personnel

[b] Gago-Ferrero et al (40)

[c] *Standard Methods for the Examination of Water and Wastewater*

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Various international guideline options, technical documents, etc., and even test methods, are already available. These include: 1) ISO/IEC 17025 (47), 2) US EPA (54), 3) Eurachem (58), 4) SANTE 11312/2021 (59), 5) ASTM (55), 6) AOAC (56) and 7) The Standard Methods For The Examination of Water and Wastewater textbook (60). Routine testing laboratories that are accredited to ISO/IEC 17025 standard, research institutes, academia, health and environmental protection institutes, etc., are already, in a very favorable position to submit their developed and validated chemical tests to ISO for standardization. It is hereby proposed that use is made of the current available guides.

These options, considered as possible candidates for proposed routes towards the standardization of chemical test methods for CECs, specifically by chromatography-mass spectrometry, will be briefly discussed and reviewed below. The criteria for each option are indicated by a "tick" (√). An overall comparison is summarized in Table 2.

i) ISO/IEC 17025

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO- member bodies), including the South African Bureau of Standards (SABS) (61), South Africa's national standardization body.

ISO is an independent, non-governmental international organization with a membership of 167 national standards bodies. Through its members, it brings together experts to share knowledge and develop voluntary, consensus-based, market relevant International Standards, currently 24 599, that support innovation and provide solutions to global challenges. The standards cover almost all aspects of technology, management and manufacturing.

Electro technical standards are harmonized internationally by the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). The work of preparing International Standards is normally carried out through ISO technical committees, currently 809. In the field of conformity assessment, ISO and the IEC form the specialized system for standardization. Before submission of a new test method for approval to ISO, the country needs to approach their national ISO body.

ISO has a guidance document for submission of new work: ISO Guidance on new work, with 3 Parts, covering: Part 1 New standardization areas, Part 2: New fields of work – proposals for new committees, and Part 3: New work item proposals within existing committees. The relevant Form is: ISO FORM 1 PROPOSAL FOR A NEW FIELD OF TECHNICAL ACTIVITY, and the proposal must follow the guidelines as per the ISO document: ISO/IEC Directives, comprising two Parts. Part 1 is titled: Consolidated Supplement - Procedure for the technical work – procedures specific to ISO, 13th Edition 2022 and the ISO/IEC Directives. Part 2 is titled: Principles and rules for the structure and drafting of ISO and IEC documents. This contains the principles and rules for the structure and drafting of International Standards, Technical Specifications and Publicly Available Specifications. As far as is practicable, these principles and rules also apply to Technical Reports and Guides. The ISO/IEC Directives, Part 2 (edition 9, 2021) Principles and rules for the structure and drafting of ISO and IEC documents (Table S8), states the general principles by which ISO and IEC documents are drafted and stipulates certain rules that shall always be applied in order to ensure that they are clear, precise and unambiguous. These rules are also important for ensuring that each document contributes effectively to the consistent and interdependent body of knowledge that ISO and IEC produce.

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There is even a simple draft template for ISO standards. The purpose of this template is to simplify the drafting of International Standards and similar publications by providing a document "skeleton" that incorporates a range of predefined stylistic and structural rules, as well as ensuring that the electronic files of the document can be processed easily by the ISO Central Secretariat and other members of the ISO infrastructure. This aid to authoring is designed to save time and effort in the preparation and processing of standards by providing on-the-spot help concerning the drafting rules specified in the ISO/ IEC Directives. There is even a model document available on the ISO web site, which demonstrates a simple application of the ISO/IEC Directives, Part 2, 2016, Principles and rules for the structure and drafting of ISO and IEC documents.

For standardization at a national level, e.g., for South Africa, the relevant authority is the South African Bureau of Standards (SABS) (61). As a founder member of the International Organization for Standardization (ISO), the SABS has built a reputation globally as a long-standing and widely respected role player in international standardization, and the leading standardization body in Africa.

In South Africa, the national process for the submission of a new test method, to ISO, is firstly via the SABS: a proposal is submitted, for the development of the standard in which a detailed justification for the need of the standard has been identified and how this will have an impact on the South African economy (SABS Project proposal and registration Form (AZ 96.22_2021/04/08 sabs pta)). The SABS is also a full participating member of the ISO technical committee on Water Quality, ISO/TC 147. The Technical Committee SABS/TC 147/SC 02 deals with “Water - Physical, chemical and biochemical methods”.

ii) The United States Environmental Protection Agency (US EPA) (2016): Validation and Peer Review of U.S. Environmental Protection Agency Chemical Methods of Analysis

The US EPA program offices publish a wide variety of measurement methods for use by EPA personnel, other government agencies, and the private sector. These methods may originate from many sources, such as the EPA laboratories, EPA contractors, scientific organizations, other government laboratories, and from the private sector. Since these methods may be published as regulations, incorporated by reference in regulations, or published as guidance, they must be thoroughly tested and peer reviewed prior to publication as US EPA methods.

This document provides Agency-wide guidance for EPA personnel who will evaluate the performance and suitability of new chemical methods of analysis before EPA publication. The method validation principles contained herein are based on current, international approaches and guidelines for intralaboratory (single laboratory) and interlaboratory (multiple laboratory) method validation studies. This guide is referenced to some documents by the following relevant, international bodies: Eurachem 1998, IUPAC 2002, ISO 5725-1 1994, ISO (VIM) 1993, ASTM 2003, and AOAC International 2002.

Peer review is required for the EPA chemical methods of analysis. The EPA Science Policy Council Peer Review Handbook provides Agency-wide requirements and options for that process.

The key performance characteristics that are covered are: accuracy, trueness, bias, selectivity, LOD, LOQ, ruggedness, precision (repeatability and reproducibility), sensitivity, calibration, linearity, range, analyte stability, sample stability. Whilst the Measurement Uncertainty is defined at the end of the guide, it appears not to be a mandatory requirement. Interlaboratory studies determine whether an analytical method can be transferred for use in other laboratories and whether it can be used for regulatory testing. A method that proved rugged for use in one laboratory may lose that characteristic when tried in several

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other laboratories. This guide does state that an interlaboratory method validation study should be completed prior to publishing an EPA method for general use; it is an expected topic area of the method validation summary (report). The extent of the study will vary, depending on available resources and the intended use and applicability of the method. An interlaboratory method validation study is a practical testing of the written method on identical test materials (samples), usually derived from split samples, by a number of laboratories. The study is not intended to evaluate laboratories; it is intended to evaluate method reproducibility among laboratories.

Here again, there is no specific, additional identification requirements for chromatographic tests, with mass selective detectors, now commonly used for CECs screen, identification and quantification.

iii) The US EPA Alternate Test Procedure (ATP)

The Clean Water Act Alternate Test Procedure (ATP) program is described at 40 CFR 136.4 and 136.5. This program provides a mechanism for the submission and review of an application for nationwide use or limited use of an ATP for measurement of a pollutant as an alternative to the methods approved at 40 CFR Part 136. An ATP may fall into one of two categories: 1) A method using a determinative technique (e.g., a pollutant detector) different from that in an existing Part 136 method (for method validation and evaluation purposes, this type of method is referred to as a new method**)**, or 2) A modification to a Part 136 method that falls outside the scope of the modification flexibility described in the Part 136 method, or at 40 CFR 136.6 (for validation and evaluation purposes, this type of method is referred to as an ATP**).** A method developer may apply for review of a method modification or a new method through the ATP program.

The EPA has provided detailed guidance about the kind of information it needs to evaluate methods for potential approval. The Agency conducts a notice-and-comment rulemaking process for methods evaluated under the ATP program, before they are incorporated into the Part 136 regulations. The types of information required for an application are described in three protocol documents: two for chemical methods, and one for microbiological methods.

EPA finalized the protocols in 2018 for the review of ATPs and new methods for chemical analytes, based on public comments submitted on the 2016 draft protocols: Protocols for EPA Review of Alternate Test Procedures (February 2018).

Before submitting a method to the US EPA for an ATP review, a developer confers with the EPA to design a method validation study. This study tests the new or modified method in several representative matrices and independent laboratories. The method must also be written in a standard format that includes all of the steps in an approved method, such as sample and data handling, and quality assurance requirements.

The US EPA has 4 guide documents related to its Clean Water Act, the CWA Alternate Test Program: for test methods, namely:

1) Protocol for Review and Validation of Alternate Test Procedures for Regulated Organic and Inorganic Analytes in Wastewater Under EPA's Alternate Test Procedure Program (pdf) (807.67 KB, February 2018, 821-B-18-002). The protocol provides guidance for validation, submission, and EPA review of ATP applications under EPA's National ATP Program submitted for modifications of an EPA-approved method or a procedure that uses the same determinative technique and measures the same analyte(s) of interest as an approved method.

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2) Protocol for Review and Validation of New Methods for Regulated Organic and Inorganic Analytes in Wastewater Under EPA's Alternate Test Procedure Program (pdf) (854.53 KB, February 2018, 821-B-18 -001). This protocol represents EPA's "best thinking" about the information that is useful in making the determination of whether or not to approve use of any new method for organic and inorganic analytes.

3) EPA Microbiological Alternate Test Procedure (ATP) Protocol for Drinking Water, Ambient Water, Wastewater and Sewage Sludge Monitoring Methods (pdf) (830.84 KB, September 2010, 821-B-10-001) and

4) Guidelines and Format for Methods to be Proposed at 40 CFR Part 136 or Part 141 (1996).

The EPA has already developed 12 test methods by GC- and LC-MS, covering pharmaceuticals (Method 542), pesticides (Method 1699) and even per-and polyfluoroalkyl substances (Method 533, 537.1), in various matrices (water, soil, sediment, bio solid).

iv) *Eurachem (2014) The Fitness for Purpose of Analytical Methods A Laboratory Guide to Method Validation and Related Topics and Planning and Reporting Method Validation Studies (2019) Supplement to Eurachem Guide on the Fitness for Purpose of Analytical Methods*

This Guide, like the first Edition (1998) is based on, and is consistent with, the principles of ISO 17025. It further cross-references other relevant international guide documents, like ISO 9001 2008, VIM 2012, AOAC 2002, ASTSM 2012, IUPAC 2001, USP 2003, IUPAC 1995, and the Council Directive EC 2009 and Commission Decision EC 2002.

An initiative in the UK to promote good practice in analytical measurement has identified six principles of analytical practice which, taken together, are considered to constitute best practice. This document is principally intended to assist laboratories in implementing Principle 2, by giving guidance on the evaluation of testing methods to show that they are "fit-for-purpose". The additional 2019 Supplement serves as guidance for, specifically, the planning and reporting of validation studies. This supplementary document is not intended to be used in isolation; it should be used in conjunction with the Guide. The aim is to provide a clear plan for the entire validation study, covering the performance characteristics that will be studied, the target value for each performance characteristic, the materials that will be analyzed, the level of replication and order of the experiments, any statistical analysis that will be used, and how the method will be judged as being "fit- for- purpose".

It includes the typical performance characteristics: bias, selectivity, LOD, LOQ, ruggedness, precision (repeatability, intermediate, reproducibility), sensitivity, range, analytic stability, and MU.

Here again, this guide has no specific, additional identification requirements for chromatographic tests, with mass selective detectors, now commonly used for CECs screen, identification and quantification.

v) SANTE (2021)

This document (59) is intended for laboratories involved in the official control of pesticide residues in food and feed across the European Union (EU). It describes the method validation and analytical quality control (AQC) requirements to support the validity of data reported within the framework of official controls on pesticide residues, including monitoring data sent to the European Food Safety Authority (EFSA), and is used for checking compliance with maximum residue levels (MRLs), enforcement actions, or the assessment of consumer exposure. This document is more importantly, complementary and integral to the requirements specified in the ISO/IEC 17025 guide.

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It specifies that within-laboratory method validation should be performed to provide evidence that a method is fit for the intended purpose. As per this guide, method validation is a requirement of accreditation bodies, and must be supported and extended by method performance verification during routine analysis (analytical quality control and on-going method validation). Typically, with each batch of samples routinely analyzed, one or more samples of different commodities from the applicable commodity category are spiked with the analytes and analyzed concurrently with the samples.

Sample extracts are normally analyzed using capillary gas chromatography (GC) and/or high performance or ultra-performance liquid chromatography (HPLC or UPLC) coupled to mass spectrometry (MS) for the identification and quantification of pesticides in food and feed samples. There are options for the use of various MS detection systems. For unit mass resolution, the typical systems listed are single MS (quad, ion trap, TOF) and MS/MS (triple quadrupole, ion trap, Q-trap, Q-TOF, Q-Orbitrap). For accurate mass measurement resolution, the corresponding typical systems listed are High resolution MS ((Q-)TOF, (Q-)Orbitrap). The Acquisition modes are listed for each mass resolution option. There are also specific requirements for identification for each mass resolution type used.

Typical ionization techniques are electron ionization (EI), chemical ionization (CI), atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI). Different acquisition modes may be used, such as full-scan, selected ion monitoring (SIM), selected reaction monitoring (SRM) and multiple reaction monitoring (MRM).

The guide specifies the following generic method validation parameters, with criteria: sensitivity (linearity), matrix effect, LOQ, specificity, recovery, precision (repeatability RSDr and within-lab reproducibility RSDwR) and robustness, ion ratio and retention time.

Besides quantitative validation aspects, the guide also specifies the identification parameters that must be assessed for MS-based methods: 1) Specificity, 2) Ion ratio, 2) Retention time, 3) Matrix effect. Of note is a specific section titled "Identification of analytes and the confirmation of results", covering the following sub-categories: Mass spectrometry coupled to chromatography, Requirements for chromatography, Requirements for mass spectrometry (MS), Recommendations regarding identification using MS spectra, and the Requirements for identification using selected ions, for different MS techniques (single quad MS, triple quad MS/MS, high resolution MS). There is also a specific section for the "Confirmation of results", and for "Reporting results" (expression, calculation, correction for method bias, rounding off data, and Qualifying results with).

vi) Miscellaneous Journal publication 2020 (40): Wide-scope target screening of>2000 emerging contaminants in wastewater samples with UPLC-Q-ToF-HRMS/MS and smart evaluation of its performance through the validation of 195 selected representative analytes

The determination of the CECs in environmental samples constitutes a great challenge. The most common choice has been the use of multiresidue methods that include a limited number of compounds (normally < 100). This automatically reveals a gap in environmental analysis concerning methods and techniques that can analyze simultaneously, a higher number of CECs. Advances in the high resolving power mass analyzers (HRMS) have contributed towards the development of real wide-scope multi-residue screening methods, that also offer the potential of retrieving information about new analytes in post-acquisition approaches (retrospective analysis).

To date, one of the main deficiencies in wide-scope target screening analysis by HRMS methods is the lack of standardized criteria and harmonized guidance for the accurate identification and quantitation of

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the analytes. For a comprehensive target analysis the use of reference standards is necessary in order to compare (i) retention times (RTs), (ii) MS spectra profiles (precursor ion, adducts and in-source fragments) and (iii) MS/MS spectra (fragment ions and ratios). To reduce the number of false negative and false positive findings, a careful optimization of the data processing parameters (mass accuracy, RT or signal thresholds) is essential. Since the size of HRMS data is enormous, automated solutions are required. Regarding the identification and quantitation, the resolving power of the mass analyzer is of great significance. The criteria defined in the 1) Commission Decision 2002/657/EC (EC, 2002) (62), and in 2) SANCO 12571/2013 (SANCO, 2013) (63) and the previous version of SANTE 11813/2017(SANTE, 2017) (64) do not take full advantage of the available instrumentation capabilities and are still more low-resolution oriented. In addition, the compounds used as a validation dataset should be selected upon well-defined criteria and follow a uniform protocol.

This work (40) references the deficiencies in these guides: in addition to the specified Retention time, it has the following additional criteria for MS-based methods regarding "Identification": 1) Decision Limit, 2) Detection capability, 3) Mass accuracy, 4) Isotope fit ,5) Fragmentation.

vii) ASTM

More than 30,000 people from 150 countries create and update standards through ASTM

International, one of the world's most respected standards development organizations. The high quality of ASTM International standards is driven by the expertise and judgment of its members who represent industry, governments, academia, trade groups, consumers, and others. Their contributions are why ASTM International standards are known for high quality and market relevance across many industries.

The Types of Standards are the following: 1) test method, 2) specification, 3) guide, 4) practice, 5) classification, and 6) terminology.

Over 50 Proficiency Testing programs help laboratories evaluate, improve, and document their performance in conducting test methods when compared to other laboratories. More than 5,000 participants worldwide are involved in these statistical quality assurance programs that help laboratories to meet accreditation requirements.

The Memorandum of Understanding program promotes: 1) communication among standards bodies, 2) awareness of standardization systems, 3) development of national standards, 4) reduced duplication of efforts, and 5) broader economic development efforts.

The process used by ASTM to develop standards is extremely flexible, honed over 111 years to accommodate a diverse collection of activities. Test methods, specifications, classifications, practices, guides, and terminology are different categories of standards offered by ASTM. Areas ranging from petroleum, steel, and plastics to homeland security, unmanned vehicles, and sustainability have all achieved standards-based solutions via ASTM's process.

ASTM receives a variety of requests for new standards development activities, ranging from a single standard to a new main technical committee. It is important to note that not all requests ultimately reach fruition. As the organizational process evolves, it may be determined that the stakeholder interest is insufficient, other standards may exist that satisfy the particular need, or that it is premature for a consensus standards program. When a request is initially submitted, ASTM maps the scope and subject area to the existing committee population. If they are able to find an appropriate venue, they coordinate

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with the officers of the committee and subcommittee(s) in question. If the request covers an area unrepresented within ASTM, they proceed with their new activity organizational process.

ASTM has the guide titled: Form and style for ASTM Standards (September 2022).

This manual is the basic textbook for anyone writing an ASTM standard. A study of Parts A, B, C, or E will show the proper form for the principal types of standards, including a detailed explanation of how to write each section, from the title to the appendices.

If one is drafting a new ASTM standard (Test Method, Specification, Guide/Practice, Classification, or Terminology) the pre-formatted MS Word templates that will help to speed up the process, are available. These templates insert all of the required form and style elements as specified in The Form and Style for ASTM Standards manual, also known as "The Blue Book". They are built on the existing functionality of MS Word 97/2000; one can alter them to suit individual needs.

viii) AOAC

The Legal name is: AOAC INTERNATIONAL, and the Long-form name is: ASSOCIATION OF OFFICIAL ANALYTICAL COLLABORATION (AOAC) INTERNATIONAL. AOAC INTERNATIONAL is a 501(c) (3), independent, third party, not-for-profit association and voluntary consensus standards developing organization.

AOAC INTERNATIONAL brings together government, industry, and academia to establish standard methods of analysis that ensure the safety and integrity of foods and other products (dietary supplements, pharmaceuticals) that impact public health around the world. As a leader of analytical excellence, AOAC INTERNATIONAL advances food safety, food integrity, and public health, by bringing together members, organizations, and experts dedicated to developing and validating standards, methods, and technologies of global relevance.

Their key initiatives are:

1) Official Methods of Analysis Program: is the AOAC INTERNATIONAL's premier methods program. Approved methods undergo rigorous, systematic, scientific scrutiny to ensure they are highly credible, defensible and that can be used with confidence by industry, regulatory agencies, research organizations, testing laboratories, and academic institutions.

2) AOAC Research Institute: is a division of AOAC INTERNATIONAL that promotes and conduct activities to help develop, improve, and validate proprietary testing methods and products.

3) Proficiency Testing (PT): helps laboratories to compete in the global marketplace by demonstrating and certifying that they meet the highest international standards for accuracy, reliability, and compliance.

The Appendix F: Guidelines for Standard Method Performance Requirements (SMPR) (AOAC, 2016) are intended to provide basic information for working groups assigned to prepare SMPRs. The guidelines consist of the standard format of an SMPR, followed by a series of informative tables and annexes.

Information about method requirements is itemized into nine categories: (1) intended use, 2) applicability, 3) analytical technique, 4) definitions, 5) method performance requirements, 6) system suitability, 7) reference materials, 8) validation guidance, and 9) maximum time-to-determination.

For a Quantitative method (trace or contaminant (Single Lab Validation)), the prescribed generic guidelines for standard method performance requirements are: Applicable Range, Bias, Precision, Recovery, LOQ, Reproducibility: RSD_R or Target Measurement Uncertainty.

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ix) Standard Methods for the Examination of Water & Wastewater textbook (Standard Methods)

This comprehensive reference covers all aspects of water and wastewater analysis techniques. *Standard Methods* is a joint publication of the American Public Health Association (APHA), the American Water Works Association (AWWA), and the Water Environment Federation (WEF). The work of the Standard Methods committees of APHA, AWWH and WEF is coordinated by a Joint Editorial Board (JEB), on which all three are represented.

For each new edition, both the technical criteria for selection and the formal procedures for their approval are reviewed critically. With regard to approval procedure, standard methods presented have been peer reviewed and are supported by the largest number of qualified people. In this way, *Standard Methods* represent a true consensus of expert opinion.

The methods presented in *Standard Methods* are believed to be the best available, and broadly accepted procedures for analyzing (physical, chemical, microscopic, bacteriological) water, wastewaters and related materials. They represent the recommendations of specialists, ratified by a large number of analysts, and others of more general expertise. As such, they are truly consensus standards, which offer a valid and recognized basis for control and evaluation.

A Joint Task Group (JTG) is established for each section; appointment of an individual to the Team is based on their recognized expertise and interest. The Group reviews the pertinent methods, or methods from the previous edition, reviews current methodology in the literature, evaluate new methods relevant to a particular Section, and address any specific issues of concern received by the Standard Methods Committee. Once a Joint Task Group has finished with and approved the work on its specific Section, the manuscript is edited and submitted to the relevant Standard Methods Committee members who review and vote on Sections in a given Part. The JEB makes a final decision on how an issue is to be handled.

The technical criteria for selecting methods are applied by the Joint Task Groups and the individuals reviewing their recommendations; the JEB only provides general guidelines. In addition to the classical concepts of precision, bias and Minimum Detectable Concentration, test method selection also must consider other issues like: the time required to obtain a result, specialized equipment and analyst training needs, cost of analysis and the feasibility of its widespread use.

Methods published in *Standard Methods* are divided into two fundamental classes: Proposed and Standard. Regardless of class, all methods must be approved by the Standard Methods Committee:

1 Proposed: this method must undergo development and validation that meets the requirements of Section 1040A of *Standard Methods.*

2 Standard: a procedure qualifies as a Standard Method in one of two ways: a) the procedure has undergone development, validation and collaborative testing that meet the requirements set forth in Section 1040B and C of Standard Methods, and it is “widely used” or b) the procedure is “widely used” and it has appeared in *Standard Methods* for at least 5 years.

When an entirely new method is developed by accepted research procedures or an existing method is modified to meet special requirements, method validation by a 3-step process is required:

1) Determination of single operator characteristics: precision and bias: requires determining detection and reporting levels, analytical range, method bias (its systematic error), matrix effects, and interferences.

2) Analysis of independently prepared unknown samples: requires the analysis of independently prepared

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standards, by the standard operating procedure for the test method, whose value is unknown to the analyst. Unknown samples are obtained from other personnel in the laboratory, using either purchased analytical-grade reagents, or standards traceable to the National Institute of Standards Technology (NIST). Performance evaluation samples, if available, from accredited proficiency test (PT) providers (schemes) are also recommended.

3) Determination of method ruggedness: is the stability of the result produced when steps in the method are varied. It is especially important to determine this characteristic if the method will be proposed as a standard or reference method.

4) Equivalency testing: after a new method has been validated by the above procedures, it may be necessary to test it for equivalency to the standard method, unless they do not exist. Statistical steps with references are further provided in the textbook.

5) Collaborative multi-laboratory testing: After a new method has been developed and validated, it is then determined whether it should be made a "Standard method", via the Collaborative Multilaboratory test. Here multiple laboratories collaborate by using the same SOP to analyse a select number of samples to determine the method's bias and precision. Factors to be considered are a precisely written SOP, the number of variables to be tested (laboratories, apparatus, operators, levels (concentration)), the number of levels to be tested, the number of replicates required, and possibly matrix effects.

Table 2 gives a snapshot summary of some of the main criteria prescribed by the well-known, international technical bodies in the field of analytical chemical test method development-validation.

It appears that the technical requirements specified in the ISO/IEC, and the SANTE guides (followed by the US EPA/Eurachem) are fairly extensive, compared to that in the ASTM/AOAC/*Standard Methods*. Whilst all guides address the minimum generic method validation/performance requirements/criteria fairly well, the additional "Identification for MS-based methods" requirements are only prescribed by the SANTE guide and by the recent work by Gago-Ferrero et al (40).

It is proposed that researchers working towards the development-validation of standardized chemical test methods by chromatography-mass spectrometry can use any combination of these guides, in a complementary manner, preferably the SANTE and the ISO/IEC 17025, and also address the additional MS requirements, as described by Gago-Ferrero et al (40), during the test method development-validation.

Other research gaps in CECs research

The following are, inter alia, deserving of similar attention, that may have been partially covered here, and warrant further research:

1) Alternative descriptions for the definition of a CEC: This was partially addressed in this study (Table S6).

2) Risk assessment/toxicity testing: the reader can consult various reported references (65).

3) The management of CECs: This is another broad area that covers: reduction, removal, regulation, education, advanced treatment options, etc.

4) Target/Contaminant List: The US EPA has, for example, a Contaminant Candidate List 5 (CCL 5) (66). CCL 5 includes 66 chemicals, 3 chemical groups (cyanotoxins, disinfection byproducts (DBPs), and per- and polyfluoroalkyl substances (PFAS)), and 12 microbial contaminants. It is proposed that

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researchers can begin with a proposed list, at national level, based on potential sources.

For a potential target list of priority CECs to quantify, or screen for, a good starting point would be the potential source/s of the contaminants that needs to be first identified. For example, with the HIV and Tuberculosis (TB) disease burden in South Africa, it can be expected that relatively more related treatment drugs, like the anti-retro virals and anti-TB drugs/pharmaceuticals, will be found in raw source water, raw or treated wastewater, and in drinking water.

5) Complementary use of 2-dimensional (2-D) gas chromatography (GCxGC) (67): Test methods can be a combination of targeted analysis, like tandem mass spectrometry, and non-target screen, using 2-dimensional GCXGC-Q-TOF-MS, LC-QTOF-MS. Some of the major advantages of 2D-GCXGC, coupled to a mass spectrometric detector, include the following:

i) The chromatographic separation space is significantly increased compared to a standard 1D-GC analysis, yielding a big leap in potential peak capacity.

ii) Besides increased resolution, the resulting chromatogram is also structured so that similar compounds elute in clustered bands throughout the chromatogram plane.

iii) The clustering of structurally and chemically similar compounds offers a helpful clue that can help in peak identification.

iv) Increased compound detectability, or signal-to-noise ratio (S/N) (sensitivity).

v) Saves time with Multi-Class compound analyses possible in a single analysis.

vi) Reduced solvent usage with simplified sample preparation.

vii) Decreased manual labor with “Automated Peak Identification”.

With a non-specific detector like the ECD or FID, the contour plot can be used for grouping compounds based on their chemical class. When a mass spectrometer (MS) is used as a detector, unknown peaks can be further identified by searching a mass spectral library (for example, NIST).

viii) Automated identification of unknowns (analyte peaks) with time reduction.

ix) Accelerate discovery with increased peak capacity.

x) Savings on costs with the use of economical detectors.

Increasing the chromatographic resolution with GCxGC reduces the need for expensive mass spectrometer detectors; the FID is a robust, economical, and simple to operate detector.

xi) Viability in a routine laboratory setting.

Saving time in sample preparation, instrumental analysis, and non-target data review can be an immediate payoff when a GCxGC system is implemented. The ability to analyze an extensive range of complex samples with the simultaneous target and non-target detection is an attractive prospect that can be leveraged in a competitive landscape.

6) An international Data Base for CECs.: The possible matrix elements could include: already published research, technical application notes from analytical equipment vendors, validated or partially validated test methods, “hot spots” and identified CECs at a national level, etc.

7) Chlorine-resistant pathogens (bacteria) in disinfected drinking water (68):

Umgeni Water has at least one project addressing this area in the 5-year R&D Master Plan.

8) Per- and poly-fluoro alkyl substances, the “forever chemicals: PFAS (PFOS and PFOA). Whilst this

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review identified 19 research papers, there has been subsequently a tremendous increase in publications, covering their source, occurrence, toxic effects (69), analytical techniques for their determination (70), their degradation (71), their removal (72), etc.

The U.S EPA SW-846 Test Method 8327: Per-and Polyfluoroalkyl Substances (PFAS) by Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS) (73) is now standardized for a selected 24 PFAS contaminants in non-potable water. The method was validated with real water samples testing, in a multilaboratory (eight) study, at 200 ng/L and at 60 ng/L for recovery (range = 75-130% at 60 ng/L) and precision.

There is additionally at least two WRC-funded PFAS monitoring-related projects in South Africa; one study has just been completed and the relevant research reports (Project No. 2019/2020-00187) will be available (28) once they are finalized.

Human exposure to PFAS alternatives and emerging PFAS, which were proposed as substitutes for legacy PFAS is unknown. Short-chain PFSA and PFCA homologues, like PFBS and PFHxA, are just as persistent as legacy and historical PFAS in the environment. There are limited data and information available on the occurrence, sources and fate of emerging PFAS in the environment than there is for the legacy PFAS. It is necessary to create a complete and trustworthy inventory of alternatives for legacy PFAS.

Some recently reported gaps include their potentially large number present in the environment that is yet to be identified, the unknown extent of their environmental pollution, further research to improve our understanding of their behavior and hazards they pose to the environment and human health, and whether they can be degraded or metabolized by humans in environmentally relevant conditions.

Limitations of the current study

Between the time of this study inception (2019) and the present, various other publications have appeared on this, and related topics, that are not addressed here. Various other pertinent publications have also not been referenced here due to journal space requirements.

Conclusion

A literature review was undertaken with a focus on finding out the most common CECs research gaps. The top three CECs research gaps (Classes) were found to be: (Number of "gaps", %): 1) Toxicity/Risk/ Impact (260, 21.5%), 2) Analysis/Tests/Methods (118, 9.8%) and 2) Future research/studies (118, 9.8%), and 3) Monitoring (89, 7.4%). The most common test methods used for the analysis of the chemical contaminants were found to be: chromatography (gas, liquid)-mass spectrometry; for the microbial contaminants: culture-based methods, ELISA, fluorescence microscopy, qPCR, RT-qPCR, gel electrophoresis, Raman spectroscopy, and also chromatography (largely liquid)-mass spectrometry were also used.

A revised definition for the CECs was proposed. Some proposals were additionally made to address the very common, significant research gaps in CECs research: for example, the standardization of analytical, chromatographic-mass spectrometric test methods for CECs quantification, risk assessment/toxicity testing, management of the CECs, Target/Contaminant List, etc.

This research attempted to develop a framework for the prioritization of CECs research efforts. Large

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knowledge gaps persist regarding the significance of many constituents of emerging concern (CECs), which may occur in drinking water and wastewater systems. This research has to some extent confirmed the apparent perception that there is indeed concern about the toxicity/risk /impact of CECs to the environment and to human health. It is very clear that much more research is needed to understand the health and environmental effects of CECs.

It is evident that many international technical and scientific experts (e.g., natural, regulatory, environmental scientists, water treatment process scientists/engineers, chemists, toxicologists, microbiologists, etc.), and bodies, for drafting and developing consensus chemical test method development-validation guidelines, and/or standard test methods, are already available: they comprise staff or members from ISO, SANTE, US EPA, Eurachem, etc. It is proposed that a joint meeting and collaboration of them, with a view to finalizing these, be a way forward, to address this global, significant environmental issue: CECs.

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