Published in final edited form as:

Anal Chim Acta. 2010 July 19; 673(2): 117–125. doi:10.1016/j.aca.2010.05.042.

Recent developments in cyanide detection: A review

Jian Ma and Purnendu K. Dasgupta*

Department of Chemistry and Biochemistry, University of Texas, 700 Planetarium Place, Arlington, Texas 76019-0065, United States

Abstract

The extreme toxicity of cyanide and environmental concerns from its continued industrial use continue to generate interest in facile and sensitive methods for cyanide detection. In recent years there is also additional recognition of HCN toxicity from smoke inhalation and potential use of cyanide as a weapon of terrorism. This review summarizes the literature since 2005 on cyanide measurement in different matrices ranging from drinking water and wastewater, to cigarette smoke and exhaled breath to biological fluids like blood, urine and saliva. The dramatic increase in the number of publications on cyanide measurement is indicative of the great interest in this field not only from analytical chemists, but also researchers from diverse environmental, medical, forensic and clinical arena. The recent methods cover both established and emerging analytical disciplines and include naked eye visual detection, spectrophotometry/colorimetry, capillary electrophoresis with optical absorbance detection, fluorometry, chemiluminescence, near-infrared cavity ring down spectroscopy, atomic absorption spectrometry, electrochemical methods (potentiometry/ amperometry/ion chromatography-pulsed amperometry), mass spectrometry (selected ion flow tube mass spectrometry, electrospray ionization mass spectrometry, gas chromatography-mass spectrometry), gas chromatography (nitrogen phosphorus detector, electron capture detector) and quartz crystal mass monitors.

Keywords

Cyanide

1. Introduction

The cyanide anion consists of a carbon atom triply bonded to a nitrogen atom with a net negative charge. Cyanides occur naturally both in the geologic and biologic world; the production of cyanides by certain plants is believed to be a natural means of defense against pests. Over 2000 plants species, including fruits and vegetables, contain cyanogenic glycosides that release cyanide on acid hydrolysis (e.g., as occurs when ingested). Among them, cassava (tapioca, manioc) and sorghum are staple foods for hundreds of millions in tropical countries [1]. In this review, we focus on hydrogen cyanide (HCN) and simple cyanide salts (NaCN, KCN, etc.); these are also the most toxic and most likely to be in the environment [2]. Cyanides are industrially made in large quantities and used in

*Corresponding author: Phone: 817-272-3171, Fax: 817-272-3808, Dasgupta@uta.edu (P.K. Dasgupta).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.aca.2010.xx.xxx

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

electroplating, metallurgy, production of organic chemicals, and plastics, photographic developing, fumigation, and mining [3]. Cyanides have been used for unusual and not always admirable activities. Concentrated NaCN solutions have been used to stun colorful fish near the Philippine reefs (they are caught and then (for the most part) revived after release in fresh seawater) to supply fish for aquaria. Despite the fact this practice is illegal in all the relevant countries, an estimated 1 million kilograms of cyanide have been used in waters around Philippines since the 1960's [4].

Cyanide is acutely toxic to mammals by all routes of administration, with a very steep and rate-dependent dose-response curve that involves inactivation of cytochrome oxidase and inhibition of cellular respiration and consequent cellular anoxia. In humans and animals cardiovascular, respiratory and central nervous systems are primarily affected [1]. There are many international, national, and local regulations and guidelines regarding cyanide in air, water and other media [5]. As an example, the maximum contaminant level for cyanide set by the US EPA in drinking water is 200 µg/L [6]; while the European Union has an even lower limit of 50 µg/L [7]. The maximum concentration allowed in mineral waters is 70 µg/L [8]; this is the same as the World Health Organization limit in drinking water [9]. For ecosystems, one needs to have lower limits; the Australian and New Zealand Environmental and Conservation Council set a standard of trigger values for freshwater and marine water (that provides for protection of 99% of the species) as 4 and 2 µg/L, respectively [10]. To check compliance to such standards, sub-µg/L LODs are obviously necessary.

Official methods for the determination of cyanides include titration [11,12], spectrophotometry [11,12], potentiometry with cyanide-selective electrodes [11,13], flow injection (FI) - amperometry [14] and the best case LOQs range from 2 to 5 µg/L. Although most legislated requirements are met by these techniques, operationally they are complex, time-consuming and often require significant preconcentration and/or organic solvents. Consequently alternative and more sensitive methods that can directly measure cyanide from sub- µg/L to mg/L levels in different matrices are competitive. Measurement of cyanide in different matrices including water, soil, air, exhaled breath, food and biological fluids (blood, urine, saliva, etc.) have been reviewed in official documents [1,15], books [2,16] and journal articles [4,17,18,19]; all are more than 5 years old (ref. 4, appeared in 2005 but was accepted in September 2004). Meanwhile, the interest in cyanide is growing; a large number of publications that cover from naked eye detection to almost all aspects of modern instrumental analysis have appeared during the last five years. Recently, Xu *et al* [20] and Zelder and Männel-Croisé [21] have respectively reviewed optical sensors and colorimetric measurement of cyanide.

We limit this review to papers that have appeared since 2005; a summary table (Table 1) is the heart of this paper; solution phase concentrations are cited in µg/L throughout. This review is not comprehensive with respect to the prior literature; the reader is therefore frequently referred to other prior reviews on specific topics. Some selected pre-2005 references may be cited to illustrate a specific point but the omission of another such paper in no way connotes that the latter is of lesser importance.

2. Optical Methods

2.1. Naked eye detection

Since antiquity, every culture has folklores about poisons being detected (generally in food) by some form of color reaction. Colorimetric detection kits for poisons in foods are presently commercially available [22]. In many instances simple visual confirmation of the presence or absence of a substance suffices and in many instances it is possible to get at least semi-quantitative information in comparison with a color chart, e.g., as with strips used for

testing urinary glucose. Most such techniques can be made more quantitative by using a reflectance or transmittance reader that can be based on a light emitting diode emitting at an appropriate wavelength. The majority of new reagents introduced in the last few years react with cyanide with a visible change in color, some may require a completely non-aqueous medium that makes it less practical [23]. Some others also must use large fraction of organic solvents, typically methanol or acetonitrile [24–27] but occasionally other solvents such as dimethylsulfoxide (DMSO) [28,29], reducing their attractiveness. Some chromogenic reactions that take place reasonably fast in mixed aqueous media become unacceptably slow in pure water, making it impractical to work in pure water [30]. Article titles can be misleading: those claiming to determine cyanide in an “aqueous environment” or “aqueous solution” turns out to be working in 95% acetonitrile [31] or 50% DMSO [32]! Cyanide is a powerful ligand for many metal ions and can thus affect the color of metal indicator complexes; this principle has been applied to both previously known [33] and new [34] copper-indicator complexes. Hamza *et al.* [35] proposed a completely aqueous chemistry in which a novel imine reagent reacts with cyanide to produce a brown-red product. Other direct approaches have been advanced by Männel-Croisé *et al.* [36,37] where water coordinated to cobalt in a complex is displaced by cyanide. Zelder earlier proposed the color reaction of Vitamin B₁₂ with cyanide [38] that allows ready visual detection of mM levels of cyanide in water or down to 600 μ M cyanide in a medium of 5% methanol. Vitamin B₁₂ and related cobalt complexes, often called corrinoids, have been studied for cyanide detection for some time. Daunert and Bachas [39] studied several vitamin B₁₂ derivatives to make a cyanide sensitive electrode. Referring to Figure 1, Freeman and Bachas [40] used compound I in their efforts to make a fiber optic sensor. Männel-Croisé and Zelder [36] studied compounds II (aquocyanocobinamide), III, IV and Männel-Croisé *et al.* [37] carried out more extensive studies the most promising of these, compound III. Hydroxoaquocobinamide (compound V) has an –OH group instead of the axial cyanide. This markedly increases its affinity for cyanide [41] and also provides easily visually discernible color change (see Figure 2). Unlike most other papers in which no real applications were demonstrated, some of these corrinoid based methods [37,39,42] have actually demonstrated applicability to the measurement of cyanide in biological samples. We have recently used an hydroxoaquocobinamide-based assay to determine the temperature dependent solubility of gaseous HCN in water [43].

2.2. Colorimetry and spectrophotometry

Of course, all of the reagents that can be used for simple visual estimation of cyanide can also be used to make a more quantitative measurement using a colorimeter or a spectrophotometer. In some cases, measuring absorbance at a second wavelength provides for a more accurate measurement [35].

Zelder and Männel-Croisé [21] have classified colorimetric sensing of cyanide into four mechanistic types: sensors that rely on hydrogen bonding, sensors based on coordination to boron, sensors based on transition metal coordination and sensors that rely on an organic binding reaction that does not fit into the above categories. In a more recent review Xu *et al* [20] use a somewhat different classification of optical sensors for cyanide: (a) those in which the binding sites and signaling subunits are covalently attached; binding of cyanide causes a change in optical properties of the signaling subunit; (b) a coordination complex where cyanide binds and displaces a moiety, the optical signal of which is monitored; and (c) a cumulative “chemodosimeter” where cyanide generally binds irreversibly.

Because spectrophotometry/colorimetry involves simple and largely inexpensive instruments, such techniques are generally popular. For the most part, many of the methods published during the last 5 years are adaptation of previously known chemistries that have been improved or automated. This is not to say that they are without merit. Phenolphthalin is

oxidized to pink phenolphthalein by cyanogen that is liberated as cyanide reduces Cu(II) to form Cu^ICN. This chemistry is well known but has many practical difficulties that are solved by addition of a small amount of EDTA [44]. Hassan et al. [45] looked at the same class of cobalt complexes with ester functionalities on the side chains that was later examined more systematically by Männel-Croisé and Zelder [36]. Interestingly, these authors reported a better LOD in manual spectrophotometry than by flow injection analysis (FIA); this may well, however, be caused by the limitations of their particular equipment. Themelis et al [46] have looked at matrix isolation by gas diffusion FIA, on-line standard addition and determination by reaction with ninhydrin; one-stage [47] and two-stage [48] membrane differentiated measurement of HCN in the presence of large amounts of H₂S had been described a decade ago. Triarylmethane dyes in general are decolorized by cyanide [34], the nucleophilic analyte adds on to the central carbon leading to loss of color. While one-shot “dosimetric” sensors have been advocated based on the decolorization of methyl violet [49], well-established chemistry makes it clear that cyanide is not the only nucleophile that will be able to do this and for those applications where this specificity is adequate, there may be better choices in terms of more intensely absorbing dyes [50]. The Chloramine-T/Pyridine-barbituric acid colorimetric method for measuring cyanide is one of the most well-established standard methods. Afkhami et al. [51] has shown that if the initial reaction with Chloramine-T is carried out at pH 4, thiocyanate also decomposes to make CNCl but at a different rate. This can be used to kinetically discriminate between SCN[−] and CN[−] and determine both simultaneously. Zvinowanda et al. [52] used another kinetic method based on the formation of an intensely purple compound as *p*-nitrobenzaldehyde and *o*-dinitrobenzene reacts with cyanide in a strongly alkaline medium. They applied this method to mining wastes; they determined cyanate by an independent method and concluded that with exposure to air, cyanide is oxidized to cyanate in the environment.

We have been enamored by the chromogenic attributes of hydroxoaquocobinamide and its intense absorbance. Our automated approach involves adjacent reagent-sample zone FI that is implemented with a 10 port valve and hydroxoaquocobinamide is injected in the sample slug; this minimizes consumption of hydroxoaquocobinamide [53]. A white light emitting diode (LED) is used as a light source and the measurement cell is a 50 cm long Teflon AF based liquid core waveguide [54]. Multiwavelength detection with an inexpensive CCD minispectrometer allows baseline correction and an LOD of 40 nM cyanide without preconcentration, performance that is rarely possible with absorbance detection.

Reagents that undergo a change in fluorescence properties upon reaction with cyanide also undergo a change in absorbance characteristics. Thus, virtually all the methods listed under fluorometry can also be used for absorbance based measurements. 2.2.1. Optical detection of cyanide following capillary electrophoresis (CE). High separation efficiency, small sample/electrolyte requirement and waste production are advantages that CE offers. For complex real samples, separation can be a prerequisite and CE is helpful. Optical absorption is most commonly used for detection in CE but cyanide does not absorb strongly. Papežová and Glatz [55] described the determination of cyanide by CE using a thiosulfate based background electrolyte and an in-capillary reaction with the electromigratively driven *rhodanese*, a mitochondrial enzyme that converts cyanide to the much more strongly absorbing thiocyanate that is determined at 200 nm. The LOD is 78 µg/L with a linear quantitation range of 0.39 to 13 mg/L (r^2 0.9970). Jermak et al [56] described a headspace single-drop microextraction method where a drop of Ni(II)-NH₃ complex, containing pyromellitate as an internal standard, is used to form Ni(CN)₄^{2−}. This is then separated by CE and detected at 254 nm. Because the pK_a of HCN is well above 9, this headspace microextraction technique can effectively measure free cyanide from neutral solutions without acidification. The authors claim that acidification-based procedures are often error-prone due either to incomplete liberation/capture or artifact cyanide production. The method

provided an LOD of 80 nM. Human saliva and urine samples were analyzed with spiked recoveries of 91.7–105.6%. Recently, Meng et al [57] used essentially the same chemistry and internal standard but used a hollow fiber to contain the extractant solution. They reported an LOD of 10 nM; the general use of membrane interfaces for vapor phase sampling in CE was described long ago [58].

2.3. Fluorometry

Many cyanine dyes are both colored and fluorescent. They contain two nitrogen centers (one of which is positively charged) connected by a polymethine bridge containing an odd number of carbons. They have large extinction coefficients ($\epsilon > 10^5 \text{ M}^{-1} \text{ cm}^{-1}$) in many cases and strong fluorescence in the near infrared. Niu et al. [59] showed that cyanide readily adds to the carbon next to the iminium cation, leading to loss of color and fluorescence in the dye Cy5. The naked eye detection limit based on the color reaction can be $< 1.5 \text{ } \mu\text{M}$ but it requires a two phase system (dichloromethane containing the dye and aqueous buffered cyanide bearing sample in the presence of a tetrabutylammonium salt as a phase transfer agent. The mode of implementation and negative chromogenic/fluorogenic response make this method less attractive than it would otherwise be. Shang and Dong [60] have described a singularly interesting way of measuring cyanide that relies on the fact that in an oxygen-bearing solution (air exposure is sufficient), cyanide will readily attack gold forming the aurocyanide complex. Consider that one has a combination of a fluorescent dye and a gold nanoparticles in the same solution and the gold nano particles are of a size that they efficiently absorb the fluorescence emission. If cyanide is added to this solution, it rapidly attacks the gold nanoparticles, reducing their size and detuning the size-controlled absorption and the observed fluorescence emission increases. An LOD of $0.6 \text{ } \mu\text{M}$ was reported.

The same group reported an analogous and another similarly interesting approach to measure cyanide [61]. The fluorescence of CdTe quantum dots (QDs) are dramatically reduced by the presence of small amounts of Cu^{2+} as the Cu^{2+} adsorbs on the CdTe QDs and the paramagnetic Cu^{2+} quenches the fluorescence. In the presence of cyanide, this fluorescence is restored as CN^- complexes the Cu^{2+} and removes it from the QD surface. The LOD is reported to be $0.15 \text{ } \mu\text{M}$.

Jo and Lee [62] synthesized a series of diphenylacetylene derivatives in which the π -conjugated backbone was functionalized with an aldehyde group to render the molecule nonfluorescent. When cyanide adds to the carbonyl group forming a cyanohydrin, the fluorescence (λ_{max} 375 nm), optimally excited at 270 nm, is restored. The best of the probes provide an LOD better than $2.5 \text{ } \mu\text{M}$ cyanide.

Sun et al. synthesized [32] a salicylidenehydrazide derivative of 4-(N,N-dimethylamino)benzamide; the latter is intensely fluorescent but this fluorescence is quenched upon derivatization. The derivative reacts with cyanide and the fluorescence is restored upon reaction ($\lambda_{\text{ex,max}}$ 385 nm; $\lambda_{\text{em,max}}$ 460 nm). The reaction is carried out in 1:1 DMSO:H₂O and an LOD of $0.2 \text{ } \mu\text{M}$ is reported. The same group also condensed 2-hydroxy-1-naphthaldehyde with 4-(N,N-dimethylamino)benzoylhydrazine [29]. The intrinsic fluorescence of the dimethylaminobenzamido moiety is quenched upon this coupling and cyanide restores this fluorescence ($\lambda_{\text{ex,max}}$ 334 nm; $\lambda_{\text{em,max}}$ 495 nm). The reaction is carried out in 1:1 DMSO:H₂O and an LOD of $0.2 \text{ } \mu\text{M}$ is reported. From a practical point of view, although the second compound obviously has a much larger Stokes shift, it may be easier to build a practical detector based on a compound that is excited at 385 nm as opposed to 334 nm because of facile availability of solid state high intensity LEDs at the longer wavelength.

2.4. Chemiluminescence (CL)

Gavrilov et al. [63] found that alkaline solutions of luminol containing *p*-nitrobenzaldehyde (*p*-NBA) and hemin exhibit enhanced CL when cyanide is present. The *p*-nitrobenzaldehyde cyanohydrin likely reduces dissolved oxygen to superoxide which induces luminol CL at a high rate. An extremely low LOD of ~4 nM was claimed but no real samples were analyzed or interferences were studied.

Lv et al [64] presented a reactant volume self-controlled micro-device, which was applied to the FI-CL determination of cyanide in whole blood using a mini distiller for cyanide extraction from blood samples. The described system showed the features of facile fabrication, undiluted sample injection, safe analytical operation and suitability for automatic cyanide analysis. The linear range is from 0.5 to 50 μM with an LOD of 0.2 μM and relative standard deviation (RSD) of 1.9% ($n=11$ @ 26 $\mu\text{g/L}$). The results of analyses of rabbit whole blood agreed well with those obtained from an official method.

2.4. Near-infrared cavity ring down spectroscopy (NI-CRDS)

A particular transition of gaseous HCN (the first H-C stretching overtone) is at 1.5374192 μm that is accessible by a tunable diode laser. This absorption was used, through a cavity ring-down spectroscopy arrangement to monitor HCN in exhaled breath. Exhaled breath HCN has been suggested as a diagnostic tool for cyanide poisoning and for cyanide-producing bacterial infections. First, baseline data for breath HCN are needed to establish normalcy criteria. Stamyr et al [65] utilized NI-CRDS, which is nondestructive, highly specific and offers high sensitivity by directly measuring analyte concentrations in breath. They measured exhaled breath from 40 healthy subjects; female subjects had slightly higher average breath HCN concentrations. The 50 cm base path NI-CRDS exhibited an LOD of 1.5×10^{-9} atm (1.5 ppbv) HCN.

2.5. Atomic absorption spectrometry (AAS)

Cyanide cannot obviously be measured directly by AAS. The first report of injecting a cyanide bearing sample through a column packed with essentially insoluble CuS and releasing the copper as the soluble cuprocyanide and measuring the copper by AAS as a measure of cyanide was first advocated by Haj-Hussein et al [66]. The new entries work on similar principles; it is not clear whether the better LODs observed in the more recent papers are as a result of instruments that have improved over the intervening years or better choice of chemistry. Compared to a reported LOD of 1 mg/L 2+ decades ago, Noroozifar et al [67] use a CdCO_3 on silica gel bed and achieve an LOD of 0.2 mg/L. Dadfarnia et al [68] used a micro-column of immobilized (N,N'-bis(salicylidene)ethylenediamine) on sodium dodecyl sulphate -coated alumina saturated with silver ion. With a carrier of dilute NaOH, they inject a 250 μL aliquot of the cyanide bearing sample. A detection limit of 0.06 mg/L cyanide was reported.

3. Electrochemical methods: Potentiometry and amperometry

Ion selective electrodes (ISEs) are convenient, they involve no chemistry, offer a fast response time and hence are widely used; commercial ISEs for cyanide are available. The cyanide ISE, however, has numerous interferences such as halides, pseudohalides sulfide and various metals that are complexed by cyanide, e.g., cadmium, silver, zinc, copper, nickel and mercury [15]. A chemically modified carbon paste electrode with 3,4-tetra pyridinoporphyrazinatocobalt(II) was developed by Abbaspour et al. [69] that had no response to halides, pseudohalides, or oxalate. They demonstrated accurate determination of spiked cyanide in spring water. The electrode displayed a Nernstian slope (60 ± 1.5 mV/decade) from 0.015–10 mM CN^- and an LOD of 9 μM .

Amperometry is also very popular and can be very sensitive. Taheri et al [70] developed a novel cyanide sensor. A silver doped silica nanocomposite was synthesized by self-assembly of a sol-gel network and silver nanoparticles. A precleaned gold electrode (GE) was immersed in a hydrolyzed mercaptopropyltrimethoxysilane (MPS) sol-gel solution containing Ag nanoparticles (AgNPs) to assemble a three-dimensional structure around the gold electrode (GE/sol-gel/AgNPs). The electrochemical reaction occurs between the Ag nanoparticle and CN^- . The LOD was reportedly 14 nM but the lower limit of the linear range was $>100\times$ at 1.5 μM . Different industrial electroplating waste waters were analyzed and the results were statistically indistinguishable with those obtained by accepted standard methods. Lindsay and O'Hare [71] utilized a Nafion coated Au electrode for amperometric determination of free cyanide at physiological pH in a variety of real and simulated biological samples. The LOD was 4 μM and the upper dynamic range extended to beyond 400 μM . Recently, Zacharis et al [72] described a fully automated ultrasensitive assay based on automated gas diffusion of HCN liberated by HCl from a 250 μL cyanide containing sample and absorbed in a NaOH acceptor. After up to a total of 5 repeated sample injections during which the acceptor remains stationary, the acceptor is propelled to an amperometric detector with a silver working electrode. The LOD ranged from 2 to 5 nM. Water samples spiked with 40 to 400 nM showed recoveries of 88–112%.

Amperometric detection of cyanide is not free of interferences and the electrode response changes over time. The electrode must be frequently reconditioned and recalibrated. The first is ameliorated by carrying out an actual chromatographic separation prior to amperometric detection. The second problem is solved by rapidly cycling the electrode through pre-measurement, measurement and cleaning potentials. The two techniques together have come to be used as ion chromatography with pulsed amperometric detection (IC-PAD) that is particularly popular. Research publications from the manufacturer have addressed IC-PAD for measuring cyanide. Cheng et al [73] described the preparation of disposable silver electrodes that dispenses with polishing of permanent electrodes; the LOD was 75 nM cyanide. Christison and Rohrer [74] treated the sample with sodium hydroxide to stabilize cyanide and then removed transition metals with a cation-exchange cartridge. Analysis of this sample with IC-PAD provided an LOD less than 40 nM cyanide.

4. Mass Spectrometry

Mass spectrometry is well known for its ability to provide unambiguous qualitative identification and superb quantitative sensitivity. Several types of mass spectrometry have been used for the measurement of cyanide.

Selected ion flow tube mass spectrometry (SIFT-MS) has been used particularly for the measurement of exhaled breath constituents, including HCN. SIFT-MS uses three selected reagent ions, H_3O^+ , NO^+ and O_2^+ , and utilizes fast flow tube technology along with accurate quantitative mass spectrometry. Španel et al [75,76] utilized a modified ion source and the SIFT-MS optimized specifically for the purpose, to offer real time analysis without sample storage by operating the device in the multiple ion monitoring mode. HCN concentration of exhaled breath from subjects with age ranges of 4–6, 17–18, and 60–83 years was measured and compared with another set of measurements of subjects aged 20–60 years. There was no systematic variation of breath HCN with age.

Electrospray ionization tandem mass spectrometry (ESI-MS-MS) is one of the most commonly used forms of mass spectrometry. Minakata et al [77] reacted cyanide in biological fluids with NaAuCl_4 to produce the dicyanogold anion, $\text{Au}(\text{CN})_2^-$. This was extracted into methyl isobutyl ketone (MIBK) in presence of tetramethylammonium ion as a paring agent and the extract was injected directly into a negative ion mode ESI-MS-MS

instrument. The transition $248.9 \rightarrow 26.2$ ($\text{Au}(\text{CN})_2^- \rightarrow \text{CN}^-$) was monitored. The LOD was 1.04 $\mu\text{g/L}$. Isotope dilution for better quantitation was not pursued.

4.1. Gas chromatography-mass spectrometry

While MS is one of the most sensitive analytical methods, quantitation accuracy often leaves much to be desired; this is particularly true for complex samples where co-elution is possible. While there may not be a qualitative interference by the co-elution on the analyte peak of interest, quantitation will almost certainly be affected because the ionization of the desired molecule will be affected by the presence of the other molecules. To the non-mass spectrometrists, the great sensitivity with which analytes can be detected often hides this Achilles heel of quantitation. This problem is most easily solved by the use of isotopically labelled versions of the analyte which are chemically the same as the analyte but produce different and distinct signatures on the mass spectrometer. They cannot be significantly present in the sample initially and thus can act as internal standards. Isotope dilution mass spectrometry (IDMS) as it is called, is particularly easy to practice for cyanide, as instead of the common isotopic variety of cyanide, $^{12}\text{C}^{14}\text{N}$, one can use singly labelled tracers e.g., $^{13}\text{C}^{14}\text{N}$ or $^{12}\text{C}^{15}\text{N}$, or preferably the doubly labelled standard $^{13}\text{C}^{15}\text{N}$. This is of particular value in the analysis of cyanide in complex biological samples. Dumas et al [78] and Murphy et al [79] established similar GC-IDMS method for determination of cyanide in blood. The latter group used a cryogenically cooled oven, this could focus the HCN better, improving the sensitivity and decreased the analytical cycle time. Løbger et al [80] used a headspace-GC-IDMS method and cyanide carryover via absorption on the needle surface was prevented by automated flushing of the needle between each analysis. Frison et al [81] utilized a 75 μm carboxen/polydimethylsiloxane solid phase micro extraction (SPME) fiber for headspace sample extraction and detected cyanide with GC-MS. Liu et al [82] utilized solid-supported liquid-liquid extraction (SLE) and a two-step derivatization protocol prior to GC-MS for the determination of cyanide in plasma and urine. The sample was buffered and benzaldehyde was added to form the cyanohydrin. 1,3,5-tribromobenzene was also added at this time as an internal standard. The mixture was now absorbed on a small column of diatomaceous earth and then eluted with *n*-hexane containing 0.4% of heptafluorobutyl chloride whereupon the final derivative and the final analyte, α -cyanobenzyl heptafluorobutyrate, was formed. The authors state that conversion of cyanide to such a larger mass molecule greatly improves sensitivity and prevents interference from thiocyanate and N_2 (m/z 28, similar to HCN at m/z 27), (such derivatization will also greatly increase sensitivity for detection by an electron capture detector, ECD). But for routine analysis this is a complex procedure.

5. Gas chromatography

Chromatography, notably gas chromatography, has been particularly important in the measurement of cyanide in complex, especially biological samples. Uses with MS detectors have already been discussed in the foregoing; here we discuss use with two selective detectors, the nitrogen-phosphorus detector (NPD), and the ECD.

5.1. GC-NPD

Matrix isolation of analyte cyanide is typically achieved by acidification of the sample to produce HCN. The headspace can then be sampled either directly or via an SPME fiber. Further derivatization is not needed because the NPD responds sensitively to HCN. The GC-NPD approach has been widely used for cyanide determination in clinical and forensic needs. Many methods based on this principle and incremental improvements thereof have been published in the past. While during the period of this review no major novelties in GC-NPD based approaches were reported, the following are noteworthy. Gambaro et al. [83]

compared results from a classical spectrophotometric method with those from an automated headspace GC-NPD approach and found them to be statistically equivalent. Boadas-Vaello et al. [84] reported headspace SPME sampling followed by GC-NPD analysis for the simultaneous determination of cyanide, acetonitrile, *cis*- and *trans*- crotononitrile, allylnitrile and butyronitrile at low $\mu\text{g/L}$ concentration on rat and mice blood. The maximum RSD was less than 12% across the analytes and LOD less than 3 $\mu\text{g/L}$ throughout.

5.2 GC-ECD

The ECD is more sensitive for appropriately derivatized analytes and tends to be more robust and stable than the NPD. HCN does not directly respond to the ECD and must be derivatized. While there was no dramatic new development, there were some important application papers. Zhang et al [85] applied headspace GC-ECD to measure cyanide and reported on cyanide distribution in various in human blood, kidney, brain, urine, and stomach content. Xu et al [86] used chloramine-T to convert cyanide in cigarette smoke to cyanogen chloride, which is taken up in *n*-hexane. This was then analyzed by capillary GC coupled to a micro ECD. Felby [87] utilized the same derivatization principle to determine cyanide in blood except that the derivatization was conducted on a strip of filter paper in the sample vial headspace.

6. Quartz crystal mass monitor (QCMM)

QCMMs are typically quartz crystals cut with certain facets. They vibrate naturally and the resonant frequency can be readily determined by appropriate electrical excitation. The exact resonant frequency is acutely dependent on the total mass of the crystal, decreasing with increasing mass of the crystal. If such a crystal is metalized by Au or Ag for example, and cyanide in an oxic solution contacts the crystal, the metal will dissolve to form a cyano complex, the mass will decrease and the resonant frequency will increase.

Sun et al [88] developed a sensitive and inexpensive QCMM based cyanide sensor. The sensing layer consisted of photochemically generated nano-sized silver particles on a titanium dioxide film at the electrode surface of the QCMM. The fresh nanoparticulate Ag is easily attacked by cyanide, leading to improved sensor performance with a LOD of 85 nM. Timofeyenko et al [89] developed an online flow-based real-time cyanide sensor that relies on the dissolution of gold electrodes on a QCMM placed in a flow cell. The resulting loss of gold from the electrode is detected by the piezoelectric crystal as a resonant frequency change. The detection limits were 0.6 and 0.6 and 0.1 μM for analysis times of 10 min and 1 h, respectively. However, no real samples were analyzed.

7. Conclusions and future outlook

In conclusion, a broad range of detection techniques used for practical analysis and detection of cyanide are available. There is the adage that if there are too many methods in the literature, none are probably outstanding. Zelder and Männel-Croisé [22] put forward three criteria of desirability: sensitivity, selectivity and straightforwardness – few meet these goals. The new colorimetric/fluorometric reagents have a lot of promise: they clearly can replace the extant standard methods that need complex equipment or organic solvents. It is a little wonder therefore that the most active area in cyanide sensing in recent years has been in designing new sensing molecules. As greater applicability to real samples, e.g., natural waters, industrial wastewater, biological fluids like urine, blood, saliva etc. are demonstrated; these approaches will become more mainstream.

Because of the importance in clinical, forensic and very likely, security and antiterrorism applications, rapid cyanide analysis in blood or breath is ripe for new attractive approaches.

There are fast acting antidotes for cyanide poisoning, whether from smoke inhalation or exposure to a weapon of terrorism. It is vital to determine blood or breath cyanide levels fast and accurately so that an appropriate dose of the antidote can be readily determined. Physiological half-life of free cyanide is short ($t_{1/2} = 0.34\text{--}1.28\text{ h}$) [90] and concentration can be affected by storage conditions and many other factors. It is crucial to rapidly analyze such samples, perhaps *in-situ*. Techniques that involve much manipulation such as microdiffusion, extraction, etc. prior to measurement will not be able to meet these needs. As the sensing technique, electrochemical methods provide the basis of small and portable analyzers but robustness leaves much to be desired. If electrodes are to be frequently replaced or reconditioned or recalibrated, effective analysis time suffers. In the wake of increased acts of terrorism, it has become urgent to establish rapid, sensitive, specific and robust point of care (POC) blood and breath cyanide analyzers that can be used in the field.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by the National Institutes of Health CounterACT Program Grant No. NINDS U01 NS058030-S2 and in part through National Science Foundation Grant No. CHE-0821969.

References

1. World Health Organization. Concise international chemical assessment document 61, Hydrogen cyanide and cyanides: human health aspects. Geneva: 2004 [Accessed January 09, 2009]. p. 4-5.<http://www.who.int/ipcs/publications/cicad/en/cicad61.pdf>
2. Dzombak, DA.; Ghosh, RS.; Wong-Chong, GM. Cyanide in water and soil: Chemistry, risk and management. CRC press; Boca Raton, FL: 2006. p. 2
3. The Agency for Toxic Substances and Disease Registry. Toxicological profile for cyanide. Atlanta, GA: US Department of Health and Human Services; [Accessed January 9, 2010]. p. 1-2.<http://www.atsdr.cdc.gov/toxprofiles/tp8-c1.pdf>
4. Mak KKW, Yanase H, Renneberg R. Biosens Bioelectron. 2005; 20:2581. [PubMed: 15854827]
5. The Agency for Toxic Substances and Disease Registry. Toxicological profile for cyanide. Atlanta, GA: US Department of Health and Human Services; [Accessed January 9, 2010]. p. 221-228.<http://www.atsdr.cdc.gov/toxprofiles/tp8-c8.pdf>
6. United States Environmental Protection Agency (EPA). Methods for chemical analysis of water and wastes. Environmental Monitoring and Support Laboratory; Cincinnati, OH: 1983 [Accessed January 9, 2010]. <http://www.epa.gov/ogwdw000/contaminants/basicinformation/cyanide.html>
7. Official Journal of the European Union, Commission Directive 1998/83/EC. 1998 [Accessed January 9, 2010]. p. L30-42.<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:330:0032:0054:EN:PDF>
8. Official Journal of the European Union, Commission Directive 2003/40/EC. 2003 [Accessed January 9, 2010]. p. L126-37.<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:126:0034:0039:EN:PDF>
9. World Health Organization. Guidelines for drinking-water quality. 3. Geneva: 2008 [Accessed January 9, 2010]. p. 188http://www.who.int/water_sanitation_health/dwq/fulltext.pdf
10. Australian and New Zealand Environmental and Conservation Council (ANZECC). Agriculture and Resource Management Council of Australia and New Zealand. Australian Water Quality Guidelines for Fresh and Marine Water; 2000 [Accessed January 9, 2010]. p. 3.4-5.http://www.mincos.gov.au/__data/assets/pdf_file/0019/316126/wqg-ch3.pdf

11. American Public Health Association. Standard Methods for the Examination of Water and Wastewater. 21. Washington, DC: 2005. Method 4500-CN-
12. United States Environmental Protection Agency (EPA). Titrimetric and manual spectrophotometric determinative methods for cyanide. Method 9014. 1996 [Accessed January 9, 2010]. <http://www.epa.gov/waste/hazard/testmethods/sw846/pdfs/9014.pdf>
13. United States Environmental Protection Agency (EPA). Potentiometric determination of cyanide in aqueous samples and distillates with ion-selective electrode. Method 9213. 1996 [Accessed January 9, 2010]. www.epa.gov/waste/hazard/testmethods/sw846/pdfs/9213.pdf
14. United States Environmental Protection Agency (EPA). Available cyanide by flow injection, ligand exchange and amperometry. Method OIA-1677. 2004 [Accessed January 9, 2010]. <http://www.epa.gov/waterscience/methods/method/cyanide/1677final.pdf>
15. The Agency for Toxic Substances and Disease Registry. Toxicological profile for cyanide. Atlanta, GA: US Department of Health and Human Services; [Accessed January 9, 2010]. p. 201-219. <http://www.atsdr.cdc.gov/toxprofiles/tp8-c7.pdf>
16. Smith, A.; Mudder, T. The chemistry and treatment of cyanidation wastes. Mining Journal Books, Ltd; London: 1991. p. 21-46.
17. Singh HB, Wasi N, Mehra MC. Int J Environ Anal Chem. 1986; 26:115. [PubMed: 3531047]
18. Out EO, Byerley JJ, Robinson CW. Int J Environ Anal Chem. 1996; 63:81.
19. Lindsay AE, Greenbaum AR, O'Hare D. Anal Chim Acta. 2004; 511:185.
20. Xu Z, Chen X, Kim HN, Yoon J. Chem Soc Rev. 2010; 39:127. [PubMed: 20023843]
21. Zelder FH, Männel-Croisé C. Chimia. 2009; 63:58.
22. Detection of Poison in Food. http://www.chemsee.com/members/569947/download/fpd_k_instruction.pdf
23. Zhang X, Li C, Cheng X, Wang X, Zhang B. Sens Actuators, B. 2008; 129:152.
24. Ren J, Zhu W, Tian H. Talanta. 2008; 75:760. [PubMed: 18585143]
25. Cho D, Kim JH, Sessler JL. J Am Chem Soc. 2008; 130:12163. [PubMed: 18698844]
26. Tomasulo M, Raymo FM. Org Lett. 2005; 7:4633. [PubMed: 16209497]
27. Tomasulo M, Sortino S, White AJP, Raymo FM. J Org Chem. 2006; 71:744. [PubMed: 16408989]
28. Sun Y, Wang G, Guo W. Tetrahedron. 2009; 65:3480.
29. Sun Y, Liu Y, Chen M, Guo W. Talanta. 2009; 80:996. [PubMed: 19836585]
30. Kaur P, Sareen D, Kaur S, Singh K. Inorg Chem Commun. 2009; 12:272.
31. Niu H, Su D, Jiang X, Yang W, Yin Z, He J, Cheng J. Org Biomol Chem. 2008; 6:3038. [PubMed: 18698458]
32. Sun Y, Liu Y, Guo W. Sens Actuators, B. 2009; 143:171.
33. Lou X, Zhang L, Qin J, Li Z. Chem Commun. 2008; 11:5848.
34. Kaur P, Kaur S, Singh K. Inorg Chem Commun. 2009; 12:978.
35. Hamza A, Bashammakh AS, Al-Sibaai AA, Al-Saidi HM, El-Shahawi MS. Anal Chim Acta. 2010; 757:69. [PubMed: 19951759]
36. Männel-Croisé C, Zelder F. Inorg Chem. 2009; 48:1272. [PubMed: 19161297]
37. Männel-Croisé C, Probst B, Zelder F. Anal Chem. 2009; 81:9493. [PubMed: 19842647]
38. Zelder FH. Inorg Chem. 2008; 47:1264. [PubMed: 18205304]
39. Daunert S, Bachas LG. Anal Chem. 1989; 61:499.
40. Freeman MK, Bachas LG. Anal Chim Acta. 1990; 241:119.
41. Blackledge WC, Blackledge CW, Griesel A, Mahon SB, Brenner M, Pilz RB, Boss GR. Anal Chem. 2010; 82:4216. [PubMed: 20420400]
42. Powell SC. Anal Chem. 2009; 81:9535.
43. Ma J, Dasgupta PK, Blackledge W, Boss GR. Environ Sci Tech. 2010; 42:2688.
44. Cacace D, Ashbaugh H, Kouri N, Bledsoe S, Lancaster S, Chalk S. Anal Chim Acta. 2007; 589:137. [PubMed: 17397664]
45. Hassan SSM, Hamza MSA, Kelany AE. Talanta. 2007; 71:1088. [PubMed: 19071417]

46. Themelis DG, Karastogianni SC, Tzanavaras PD. *Anal Chim Acta*. 2009; 632:93. [PubMed: 19100887]
47. Olson DC, Bysouth SR, Dasgupta PK, Kuban V. *Process Control Qual*. 1994; 5:259.
48. Kuban V, Dasgupta PK. *Anal Chem*. 1992; 64:1106.
49. Afkhami A, Sarlak N. *Sens Actuators, B*. 2007; 122:437.
50. Dasgupta PK, DeCesare K, Ullrey JC. *Anal Chem*. 1980; 52:1912.
51. Afkhami A, Sarlak N, Zarei AR. *Talanta*. 2007; 71:893. [PubMed: 19071391]
52. Zvinowanda CM, Okonkwo JO, Gurira RC. *J Hazard Mater*. 2008; 158:196. [PubMed: 18313212]
53. Ma J, Dasgupta PK, Blackledge W, Boss GR. (in preparation).
54. Dallas T, Dasgupta PK. *Trends Anal Chem*. 2004; 23:385.
55. Papežová K, Glatz Z. *J Chromatogr A*. 2006; 1120:268.
56. Jermak S, Pranaitytė B, Padarauskas A. *Electrophoresis*. 2006; 27:4538. [PubMed: 17058310]
57. Meng L, Liu X, Wang B, Shen G, Wang Z, Guo M. *J Chromatogr B*. 2009; 877:3645.
58. Bao L, Dasgupta PK. *Anal Chem*. 1992; 64:991.
59. Niu H, Jiang X, He J, Cheng J. *Tetrahedron Lett*. 2009; 50:6668.
60. Shang L, Dong S. *Anal Chem*. 2009; 81:1465. [PubMed: 19140677]
61. Shang L, Zhang L, Dong S. *Analyst*. 2009; 134:107. [PubMed: 19082182]
62. Jo JY, Lee DW. *J Amer Chem Soc*. 2009; 131:16283. [PubMed: 19831355]
63. Gavrilov AV, Druzhinin AA, Zakharov KI, Ishutin VA, Nemkov AA, Pushkin IA. *J Anal Chem*. 2005; 60:1029.
64. Lv J, Zhang Z, Li J, Luo L. *Forensic Sci Int*. 2005; 148:15. [PubMed: 15607585]
65. Stamy K, Vaittinen O, Jaakola J, Guss J, Metsälä M, Johanson G, Halonen L. *Biomarkers*. 2009; 14:285. [PubMed: 19480566]
66. Haj-Hussein AT, Christian GD, Ruzicka J. *Anal Chem*. 1986; 58:38.
67. Noroozifar M, Khorasani-Motlagh M, Hosseini SN. *Anal Chim Acta*. 2005; 528:269.
68. Dadfarnia S, Shabani AMH, Tamadon F, Rezaei M. *Microchim Acta*. 2007; 158:159.
69. Abbaspour A, Asadi M, Ghaffarinejad A, Safaei E. *Talanta*. 2005; 66:931. [PubMed: 18970074]
70. Taheri A, Noroozifar M, Khorasani-Motlagh M. *J Electroanal Chem*. 2009; 628:48.
71. Lindsay AE, O'Hare D. *Anal Chim Acta*. 2006; 558:158.
72. Zacharis CK, Tzanavaras PD, Voulgaropoulos AN, Karlberg B. *Talanta*. 2009; 77:1620. [PubMed: 19159774]
73. Cheng J, Jandik P, Avdalovic N. *Anal Chim Acta*. 2005; 536:267.
74. Christison TT, Rohrer JS. *J Chromatogr A*. 2007; 1155:31.
75. Španel P, Dryahina K, Smith D. *J Breath Res*. 2007; 1:011001. [PubMed: 21383426]
76. Španel P, Dryahina K, Smith D. *J Breath Res*. 2007; 1:026001. [PubMed: 21383435]
77. Minakata K, Nozawa H, Gonmori K, Suzuki M, Suzuki O. *Anal Chim Acta*. 2009; 651:81. [PubMed: 19733739]
78. Dumas P, Gingras G, LeBlanc A. *J Anal Toxicol*. 2005; 29:71. [PubMed: 15808018]
79. Murphy KE, Schantz MM, Butler TA, Benner BA Jr, Wood LJ, Turk GC. *Clin Chem*. 2006; 52:458. [PubMed: 16439606]
80. Løbger LL, Petersen HW, Anderson JET. *Anal Lett*. 2008; 41:2564.
81. Frison G, Zancanaro F, Favretto D, Ferrara SD. *Rapid Commun Mass Spectrom*. 2006; 20:2932. [PubMed: 16941546]
82. Liu G, Liu J, Hara K, Wang Y, Yu Y, Gao L, Li L. *J Chromatogr B*. 2009; 877:3054.
83. Gambaro V, Arnoldi S, Casagni E, Dell'Acqua L, Pecoraro C, Foldi R. *J Forensic Sci*. 2007; 52:1401. [PubMed: 18093070]
84. Boadas-Vaello P, Jover E, Llorens J, Bayona JM. *J Chromatogr B*. 2008; 870:17.
85. Zhang C, Zheng H, Ouyang J, Feng S, Taes YEC. *Anal Lett*. 2005; 38:247.
86. Xu J, Tong H, Yan X, Du S, Yao Z, Liu D. *Chromatographia*. 2006; 64:609.
87. Felby S. *Forensic Sci Med Pathol*. 2009; 5:39. [PubMed: 19291430]

88. Sun H, Zhang YY, Si SH, Zhu DR, Fung YS. *Sens Actuators, B*. 2005; 108:925.
89. Timofeyenko YG, Rosentreter JJ, Mayo S. *Anal Chem*. 2007; 79:251. [PubMed: 17194148]
90. Hartung, R. Cyanide and nitriles. In: Clayton, GD.; Clayton, E., editors. *Patty's Industrial Hygiene and Toxicology*. John Wiley & Sons; New York, NY: 1982. p. 4845-4900.

Figure 1.

Cobalt complexes related to Vitamin B₁₂ studied for cyanide determination, after Männel-Croisé and Zelder [36]. Compound **I** (aquocyanocobinamide) was used in [40], **II–IV** in [36], **III** studied more extensively in [37] and **V** (hydroxoaquocobinamide) in [41].

Figure 2.

Color of solutions of 50 μM cobinamide treated with increasing amounts of cyanide (1: 0, 2: 15, 3: 30, 4: 45, 5: 60, 6: 75 and 7: 90 μM cyanide, from left to right) prepared in 1 mM NaOH solution at room temperature. The medium is fully aqueous.

Table 1
Analytical performance of the recently published methods for cyanide detection (2005-present)

Ref.	Method	Application	LOD, µg/L	range, µg/L	r ²	RSD %	Recovery %	Analysis Time, min	Interferences/Comments
23	UV-Vis	-	130	-	-	-	-	-	See Figure S1
24	Visual	tap, drinking water	26	26–260	-	5	-	-	See Figure S2
25	Visual	-	44.2	-	-	-	-	-	See Figure S3
26	Visual	-	26	-	-	-	-	-	See Figure S4
27	Visual	-	26	-	-	-	-	-	See Figure S5
28	Visual	-	lower than 50	-	-	-	-	-	See Figure S6. Up to 200 µM H ₂ PO ₄ ⁻ tolerated for 20 µM CN ⁻
29	UV-Vis	drinking water	1.9	5.2–52	0.9935	-	-	-	See Figure S7
30	Visual	-	~50	-	-	-	-	-	See Figure S8. Up to 250 µM F ⁻ tolerated on 250 µM CN ⁻
31	Visual	-	13	260–1300	-	-	-	-	See Figure S9.
32	UV-Vis	-	39	520–2600	-	-	-	-	See Figure S10.
33	Visual	-	130	-	-	-	-	-	See Figure S11A,B.
34	UV-Vis	-	-	6500	-	-	-	-	See Figure S12.
35	UV-Vis	tap, bottle, ground water	16	50–2000	0.999	2.3, n=5	99–109	-	See Figure S13.
36	Visual	-	39	-	-	-	-	-	See Figure S14A,B.
37	Visual	cassava	-	52–1170	-	-	-	-	See Figure S15 A,B,C.
38	UV-Vis	-	520	-	-	-	-	-	See Figure S16.
41	Visual	rabbit blood	26	65–7800	0.99	-	-	~5	See Figure S17.
44	UV-Vis	pond, ocean, river water	5	10–3000	0.9988	0.48, 1.93, n=10	94.6–102	>3	See Figure S18. High sulfide concentrations interfere by forming polysulfides and thiocyanate.
45	UV-Vis	industrial waste water	20	40–1200	0.9995	0.37, n=6	97.6–99.2	0.33	See Figure S19. Up to 36 mg/L SO ₃ ²⁻ on 0.52 mg/L CN ⁻ is tolerated.
46	UV-Vis	tap, mineral water	2.5	7.5–200	0.9994	2.4, n=8	94.2–103.6	7.5	-See Figure S20.
49	UV-Vis	water, serum	63000	100000–2500000	0.9964	3.15, n=5	100–104	5	See Figure S21. Up to 100 mg/L S ²⁻ , SO ₃ ²⁻ , Cr ₂ O ₇ ²⁻ and 30 mg/L Mg ²⁺ ,

Ref.	Method	Application	LOD, µg/L	range, µg/L	r ²	RSD %	Recovery %	Analysis Time, min	Interferences/Comments
51	UV-Vis	well, tap water	8.7	10-900	0.9988	5.6, n=11	98.3	>3	Fe ³⁺ , Ce ⁴⁺ tolerated for 500 mg/L CN ⁻
52	UV-Vis	mine effluent	50	10-80000	0.974	-	88.1-96.4	15	See Figure S22. Up to 10 mg/L S ²⁻ tolerated for 500 mg/L CN ⁻
55	CE	lysed erythrocyte samples	78	390-13000	0.994	3.2, n=10	93-106	7	See Figure S23.
56	CE	urine and saliva	2.08	6.5-520	0.997	7.5-8.4, n=3	91.7-105.6	~30	See Figure S24.
57	CE	urine and saliva	0.26	2.6-520	0.9987	5.3-7.0, n=3	92-103.4	~20	-
59	Fluor	-	49.4	-	-	-	-	-	-
60	Fluor	tap water	15.6	26-15600	-	3.7, n=5	97.6	20	See Figure S25.
61	Fluor	-	3.9	7.8-312	0.9936	3.19, n=3	94-108	-	See Figure S26.
62	Fluor	-	65	-	-	-	-	-	See Figure S27.
63	CL	-	0.1	0.1-10, 50-5000	-	12-31, n=5	-	>5	See Figure S28.
64	FL-CL	whole blood	6	13-1300	0.9801	1.9, n=11	-	-	-
65	CRDS	breath	1.5 ppbv	-	-	-	-	~2	-
67	FI-AAS	industrial wastewater	180	up to 15000	0.9960	<1.2, n=7	98.2-101	0.83	-
68	FI-AAS	well, tap water, industrial waste effluent	60	100-10000	0.9994	4.1-4.7, n=7	95-105	-	-
69	Potentiometry	spring water	234	390-260000	0.988	4.57, n=7; 7.88, n=5	101.0-101.9	5	-
70	Voltammetry	industrial wastewater	0.36	39-5460	0.9829	1.6, n=7	-	30	-
71	electrode	albumin, blood	98.8	up to 10400	-	-	-	8	-
72	Anperometry	tap, mineral, table water	0.05-0.12	0.17-200	0.9991-0.9999	2.8-5.1, n=9	88-112	6.7-20	S ²⁻ , OCl ⁻ interfere.
73	IC-PAD	-	2	2-100000	0.9996	3.6, n=25	-	20	-
74	IC-PAD	drinking and surface water	1	2-100	0.9995	-	80.6-99.5	25	-
75	SIFT-MS	breath	1 ppbv	-	-	-	-	~5	-
76	SIFT-MS	breath	1 ppbv	-	-	-	-	~5	-
77	ESI-MS/MS	urine and gastric content	1.04	2.6-1300	0.9980	1.3-13.3	-	10	-
78	GC-MS	blood	7.8	up to 2600	-	4.4 and 3.9, n=10	98	20	-
79	GC-MS	blood	3-7 ng/g	0.01-2.9 µg/g	0.9999	1.2-4.4, n=4	NS	15	-
80	GC-MS	whole blood	7-12	Oct-00	0.99	2.0, n=10	73-108	30	-
81	GC-MS	blood	6	50-10000	0.9992	4.7-7.9, n=3	76.5-80.1	>50	-

Ref.	Method	Application	LOD, µg/L	range, µg/L	r ²	RSD %	Recovery %	Analysis Time, min	Interferences/Comments
82	GC-MS	plasma and urine	10	20–100000	0.9988, 0.9993	3.19–7.24, n=20	90.58–115.56	25	-
83	GC-NPD	blood	50	50–5000	0.9754–0.9990	13.8, n=3	91.4	~50	-
84	GC-NPD	whole blood	2.8	1.4–400	>0.99	12, n=3	-	~60	-
85	GC-ECD	blood, liver, kidney, brain, urine, stomach content	0.5	200–3000	0.9958	6.39, n=8	84.6	> 120	-
86	GC-µECD	cigarette smoke	0.57	25–15000	0.9992	4.68, n=5	86–116	10	-
87	GC-ECD	blood	10	10–1000	0.9989–0.9996	3.3–7.2, n=6	84–96	30	-
88	QCM	drinking water	2.2	2.6–260	-	3.2, n=3	98.8	5	Tolerates 1 µM Cu ²⁺ , Co ²⁺ , Zn ²⁺ for 5 µM CN ⁻
89	QCM	-	2.7	100–2000	0.9992	0.56–22.22	98.8–103	60	-