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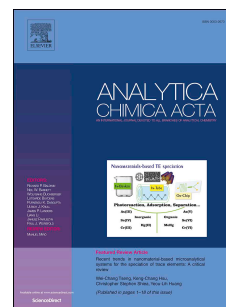
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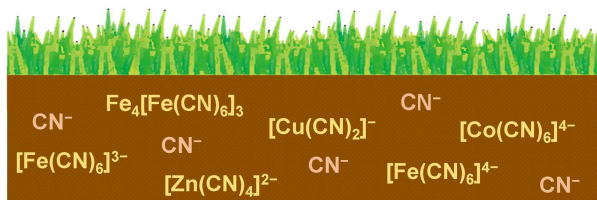
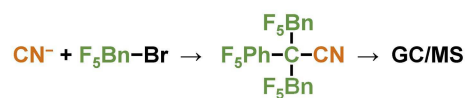
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GRAPHICAL ABSTRACT



Determination of Total Cyanide in Soil by Isotope Dilution GC/MS Following Pentafluorobenzyl Derivatization

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ABSTRACT

The high toxicity of cyanide, along with its widespread industrial use, has fuelled interest in the development of analytical methods for its determination in complex matrices. In this study, we propose a novel approach for the measurement of total cyanide in soil samples based on single-step derivatization with pentafluorobenzyl bromide (F_5Bn-Br) followed by quantitation with gas chromatography mass spectrometry in negative chemical ionization mode.

The reaction between CN^- and F_5Bn-Br resulted in the identification of several derivatives such as F_5Bn-CN , $(F_5Bn)(F_5Ph)CH-CN$, and $(F_5Bn)_2(F_5Ph)C-CN$. The relative proportion between such compounds was dependent on experimental conditions. When a 100 μL aliquot of an alkaline-aqueous extract was reacted with 700 μL of 1.3% F_5Bn-Br in acetone, the tri-alkylated derivative was the most abundant. In such conditions a detection limit of 0.5 ng/g of CN^- was attained.

Soil samples were initially spiked with an alkaline solution of $K^{13}C^{15}N$ internal standard and suspended in 7.5% aqueous NaOH. Determination of total cyanide was achieved by digestion of the alkaline extract with H_3PO_4 to produce HCN which was then trapped in 0.1% NaOH in a sealed double vial system, followed by reaction with F_5Bn-Br . Isotope dilution calibration was chosen for quantitation, and the validity of the novel method was demonstrated by analysis of soil Certified Reference Materials (CRMs) and by spike recovery tests.

Keywords

Cyanide; pentafluorobenzyl bromide; soil; isotope dilution; gas chromatography-mass spectrometry.

1. Introduction

Hydrogen cyanide and its salts are well known powerful toxic agents for living organisms. Chronic exposure to cyanide can lead to liver and kidney damage, permanent paralysis, nervous lesions, hypothyroidism, and miscarriages.[1] Despite the potential hazard, cyanide is widely used for gold mining, where 90,000 tons of cyanide are employed every year in the USA for heap leaching extraction of gold from ore.[2] Furthermore, sites of former manufacturing gas plants or coke ovens – which are widespread in the industrialised world – are often contaminated by cyanide.[3] For these reasons, cyanide monitoring in soil has been of interest since the beginning of the 20th century.[4] The determination of cyanide in soil helps to assure national food safety and support the development of soil specific and crop-specific remedies for contaminated sites. Since the availability of soil for cultivation and farming is affected by potential contamination with cyanide, several countries have established guidelines for its maximum allowable concentration. These regulations (Table 1) take into consideration the chemical form of the cyanide and the intended use of the soil. Cyanide may be present in soil in several chemical forms such as (i) ionic cyanide salts (NaCN, KCN) weakly adsorbed onto soil particles at $\text{pH} > 9.2$, (ii) weak metal-cyanide complexes (such as $[\text{Zn}(\text{CN})_4]^{2-}$ and $[\text{Cd}(\text{CN})_3]^-$), (iii) moderately strong metal-cyanide complexes (such as $[\text{Cu}(\text{CN})_2]^-$ and $[\text{Ag}(\text{CN})_2]^-$), (iv) strong metal-cyanide complexes (such as $[\text{Fe}(\text{CN})_6]^{3-}$, $[\text{Fe}(\text{CN})_6]^{4-}$, $[\text{Co}(\text{CN})_6]^{4-}$, $[\text{Au}(\text{CN})_2]^-$, and $[\text{Hg}(\text{CN})_4]^{2-}$) and (v) Prussian Blue, $\text{Fe}_4[\text{Fe}(\text{CN})_6]_3$. [3] There is no an unanimous definition for metal cyanide complexes, but as a general rule we can consider the compounds having a $\log K$ between 10 and 20 as weak complexes, between 20 and 30 moderately strong complexes and over 30 as strong complexes.[5]

Since these metal complexes have different stability toward hydrolysis, their toxicity varies from one compound to another and depends upon environmental conditions. In this regard, speciation of cyanide compounds plays an important role in understanding mobility, toxicity and fate of cyanide in soil.[6] For example, Fe(III) cyanide complexes – which have been associated with low environmental risk[7] – may decompose under solar light to the toxic free cyanide form.[8]

Furthermore, changes in the physico-chemical properties of the soil may result in the remobilization of adsorbed cyanide complexes leading to migration in groundwater or the atmosphere.[6] Therefore, attention should be given to the quantification of total cyanide in soil monitoring schemes.

The U.S. EPA developed several methods for cyanide determination, including titration[9], spectrophotometry[9], potentiometry with cyanide-selective electrodes[10] and flow injection with amperometric detection[11]. These methods can achieve detection limits that are sufficient for most regulatory needs (2 – 5 $\mu\text{g/L}$), but are complex, time-consuming, and require the manipulation of 20 – 40 grams of sample, from which large amounts of hydrogen cyanide can be released. Furthermore, spectrophotometric methods are not entirely compatible with high-alkaline solutions and are prone to matrix interferences from oxidizers and sulfur-bearing compounds.[12] Detection with cyanide-selective electrodes is severely affected by heavy matrices.[12] Ion chromatography with amperometric and conductometric detection has been proposed for the determination of cyanide.[13] However, fouling problems are reported with DC amperometric probes, whereas conductivity detection is rarely used due to the intrinsic nonlinear response with cyanide.[12]

The use of mass spectrometry (MS) can overcome most of the issues related to the selectivity and specificity of the classic approaches and has the advantage of allowing the use of isotopically labelled internal standards for high-precision quantitation. Mass spectrometry has been proposed in conjunction with high performance liquid chromatography (HPLC)[14-18] and also with gas chromatography (GC)[4], mainly for biological applications and for the determination of free cyanide. Both approaches require derivatization of cyanide before analysis. GC–MS appears most efficient because of the enormous abilities of high-resolution capillary column together with high selective detection system. The simplest chemistry proposed for GC entails acidification of the sample followed by headspace analysis of HCN.[19] Hydrogen cyanide, however, has poor retention on common GC columns and its low molar mass limits the performance of MS detection. To overcome the disadvantages, CN should be derived to a high-mass molecule, which can be

detected in an excellent mass range by GC–MS. Pentafluorobenzyl bromide ($\text{F}_5\text{Bn–Br}$) is a commercial and well-known alkylating agent for GC analysis of inorganic anions and allows for the conversion of cyanide into a derivative suitable for GC/MS.[20] Compared with the derivatization strategies proposed in the literature, the alkylation by PFBBR is a straightforward and rapid procedure, without liquid-liquid extraction of the analyte.

In this study, we present the general reactivity model for the $\text{CN}^-/\text{F}_5\text{Bn–Br}$ system and discuss the experimental parameters that influence the alkylation of CN^- . Despite $\text{F}_5\text{Bn–Br}$ being used in the past for GC work, the mechanistic aspects of its reactivity with CN^- indeed are not reported in the literature. The derivatization chemistry has been optimized to convert CN^- into $(\text{F}_5\text{Bn})_2(\text{F}_5\text{Ph})\text{C–CN}$ and applied for the determination of cyanide in contaminated soil samples by isotope dilution GC/MS with negative chemical ionization. The determination by mass spectrometry of a high molecular mass molecule reduces the problem of chromatographic interferences and allows an accurate quantitation of the analyte by isotope dilution methods. Derivatized cyanide may contain up to 15 F atoms, and NCI-MS is therefore a highly specific detection method with a linear response for cyanide, and allows reaching sub part-per-billion detection limits.

Table 1. Selected international quality guidelines for total cyanide in soil.

Country	Soil use				Ref.
	Natural Area (mg/kg)	Agricultural (mg/kg)	Residential (mg/kg)	Commercial/Industrial (mg/kg)	
<i>Argentina</i>	n.a.	5	50	500	[21]
<i>Australia</i>	1000	n.a.	500	2500	[22]
<i>Austria</i>	n.a.	5	5	n.a.	[23]
<i>Belgium</i>	5		5	12	[24]
<i>British Columbia</i> (Canada)	n.a.	5	50	500	[41]
<i>Czech Republic</i>	n.a.	5		n.a.	[26]
<i>Denmark</i>	n.a.	n.a.	500	n.a.	[27]
<i>Estonia</i>	n.a.	n.a.	50	500	[42]
<i>Finland</i>	n.a.	n.a.	50	n.a.	[29]
<i>Germany</i>	50	n.a.	50	100	[30]
<i>Lithuania</i>	n.a.	n.a.	5	n.a.	[32]
<i>Netherlands</i>	n.a.	n.a.	50	n.a.	[33]
<i>Poland</i>	5	5	n.a.	40	[36]
<i>South Africa</i>	n.a.	n.a.	1200	10000	[37]
<i>Tanzania</i>	n.a.	10	10	n.a.	[43]
<i>Thailand</i>	n.a.	11	11	35	[38]
<i>Turkey</i>	n.a.	n.a.	5	n.a.	[39]
<i>Korea</i>	n.a.	2	2	120	[40]

2. Materials and methods

2.1. Chemicals

Isotopically enriched cyanide, $K^{13}C^{15}N$ ($x(^{13}C) = 0.99$ mol/mol, $x(^{15}N) > 0.98$ mol/mol, $w(K^{13}C^{15}N) = 0.98$) was purchased from Cambridge Isotope Laboratories (Andover, MA, USA), whereas a primary standard solution of cyanide of natural isotopic composition was obtained from Fluka (996 ± 6 mg/L CN^- in NaOH solution, analytical standard). $K_4[Fe(CN)_6]$, $K_3[Fe(CN)_6]$, $[^{147}Pr_4N]Br$, $CuSO_4 \cdot 5H_2O$, $SnCl_2 \cdot 2H_2O$, $Na_2B_4O_7 \cdot 10H_2O$, 85% H_3PO_4 (Fluka, *TraceSELECT®*), 2,3,4,5,6-pentafluorobenzyl bromide (F_5Bn-Br , analytical standard grade), 30% NaOH solution (Fluka, *TraceSELECT®*), acetone and hexane (HPLC grade), Certified Reference Materials SQC011 (sandy soil) and CRM022-020 (sandy loam) were obtained from Sigma Aldrich. For the evaluation of the recovery a cyanide-free soil (SQC024) provided by Sigma Aldrich was employed. Preparation of samples and solutions was performed gravimetrically using ultrapure water (18.2 M Ω ·cm at $25^\circ C$). Solutions of $K_3[Fe(CN)_6]$ and $K_4[Fe(CN)_6]$ – containing 1000 mg/L CN^- – were prepared in 0.1% NaOH and stored in the dark. A stock solution of 1000 $\mu g/g$ $^{13}C^{15}N^-$ was prepared in 7.5% NaOH. Standard solutions of CN^- and $^{13}C^{15}N^-$ were prepared by dilution in 0.1% or 7.5% NaOH and stored at $4^\circ C$. For isotope dilution analysis, a standard solution of $^{13}C^{15}N^-$ containing 50 $\mu g/g$ of $^{13}C^{15}N^-$ was prepared in 7.5% NaOH.

Safety Considerations. Cyanide is a toxic agent that can be released in the environment as gaseous HCN at $pH < 9$. All cyanide solutions should be prepared in 0.1% NaOH in a vented fumehood. Pentafluorobenzyl bromide is a corrosive alkylating agent and should be handled in a vented fumehood while wearing adequate PPEs.

2.2. Extraction of total cyanide from soil

A 5 g aliquot of homogeneous soil was suspended in 35 mL of 7.5% NaOH. At this point a suitable amount of the isotopically enriched internal standard (50 $\mu g/g$ $^{13}C^{15}N^-$ in 7.5% NaOH) was added

to the sample. The quantity of $^{13}\text{C}^{15}\text{N}^-$ was chosen to match the expected amount of natural cyanide in the soil sample (1:1 ratio between analyte and internal standard, see Supplementary content for sample preparation data). The suspension was left stirring for 16 hours at room temperature and filtered on membrane at $0.45\ \mu\text{m}$.

For the determination of total cyanide, a $250\ \mu\text{L}$ aliquot of undiluted alkaline extract (in NaOH 7.5%) was transferred to a 4 mL vial following the addition of 1.75 mL of water, $25\ \mu\text{L}$ of 1.48 mol/L SnCl_2 (freshly prepared in 0.7 mol/L HCl) and $125\ \mu\text{L}$ of 0.8 mol/L CuSO_4 (prepared in water). Dilution and addition of Sn^{2+} and Cu^{2+} were performed under magnetic stirring using a pipet to transfer the reagents. Despite the acid nature of the Sn^{2+} solution, the pH of the sample, after its addition, remained alkaline due to excess NaOH. This mixture was frozen followed by the addition of $250\ \mu\text{L}$ of 85% H_3PO_4 . The vial was rapidly sealed with a gas-tight screwcap with Teflon/silicon septum and digested under magnetic stirring at $110\ ^\circ\text{C}$ for two hours. After digestion the sample was frozen at -80°C . The vial hosting the frozen digested mixture was then opened under a fumehood and rapidly transferred to a 40 mL vial containing 2 mL of 0.1% NaOH. As shown in Figure 1, the external vial was tightly closed and the system was held at 110°C for 30 minutes to promote migration of gaseous HCN from the acidic digested sample to the 0.1% NaOH solution.

After cooling to room temperature, the alkaline trapping solution was reacted with pentafluorobenzyl bromide and analysed by GC/MS as described in the following paragraphs.

2.3. Cyanide derivatization with pentafluorobenzyl bromide

In a 2 mL amber vial, a $100\ \mu\text{L}$ volume of alkaline sample extract (0.1% NaOH medium) was diluted with $700\ \mu\text{L}$ of acetone and derivatized with $10\ \mu\text{L}$ of pentafluorobenzyl bromide. The reaction mixture was held at 22°C for 10 min. After cooling to room temperature, the mixture was taken to dryness under a nitrogen flow, redissolved with $500\ \mu\text{L}$ of n-hexane, transferred in a clean vial and analysed by GC/MS. Such extract were analysed after one, two and four weeks without any

detectable change in the response, thus trialkylated cyanide is stable for over a month in the n-hexane solution kept at 4 °C.

2.4. GC-MS analysis

An Agilent 5973 GC/MS system equipped with a CombiPAL autosampler (CTC Analytics, Switzerland) was used for all measurements. The GC was fitted with a (50%-cyanopropylphenyl)-dimethylpolysiloxane fused silica capillary column (Agilent J&W DB 225 MS, 30 m × 250 µm i.d., 0.25 µm film thickness). The injector was heated at 220 °C and the injection volume was 1 µL in split mode (5:1 ratio). Helium was used as carrier gas at a constant flow rate of 1.0 mL/min. The temperature program was the following: 80°C for 5 min then 20°C/min up to 220 °C held for 15 min (total run time 27.00 min). The mass spectrometer transfer line was kept at 300°C. Negative chemical ionization mass spectrometry was performed at 202 eV, with 50 µA emission current, 150°C ion source temperature, and 150°C quadrupole temperature. Methane was used as reagent gas (CI gas flow: 40%).

The acquisition for quantitative measurement was performed in SIM mode by monitoring negative ions (F₅Bn)(F₅Ph)C–¹²C¹⁴N[−] at $m/z = 386$ Da and (F₅Bn)(F₅Ph)C–¹³C¹⁵N[−] at $m/z = 388$ Da with a 75 ms of dwell time.

2.5. Quantitation and blank correction

The isotope dilution method was adopted for quantitation.[44] A calibration graph was established in the 5 – 80 ng/g CN[−] range. Calibration standards were prepared by diluting a suitable amount of CN[−] up to 35 mL with 7.5% NaOH, and adding a suitable amount of 50 µg/g ¹³C¹⁵N[−] as internal standard. Thus, the same solution of ¹³C¹⁵N[−] was used for all sample/calibration blends. The concentration of CN[−] standard solution and the amount of ¹³C¹⁵N[−] were chosen to match the expected cyanide concentration in the soil sample. Each standard was then diluted to obtain a final concentration in the range of 5 – 80 ng/g.

In order to compensate for procedural blank, the method of blank-matching was applied.[45] The only reagent that provides a contribution to the blank is the sodium hydroxide. In order to compensate for its effect, the same batch of sodium hydroxide was used for sample preparation and for dilution of the primary standards. By ensuring an identical level of reagent blank for all sample/calibration mixtures, the results produced by applying the calibration plot do not require further corrections for blank. An example of sample preparation and calibration are reported in the Supplementary content.

After derivatization and GC/MS analysis of the calibration solutions, the calibration plot was constructed by reporting the mass fraction of cyanide on the x -axis and the respective isotope amount ratio on the y -axis. The isotope ratio was calculated by dividing the peak area of the signal at $m/z = 386$ Da ((F₅Bn)(F₅Ph)C-¹²C¹⁴N⁻) with the one at $m/z = 388$ Da ((F₅Bn)(F₅Ph)C-¹³C¹⁵N⁻).

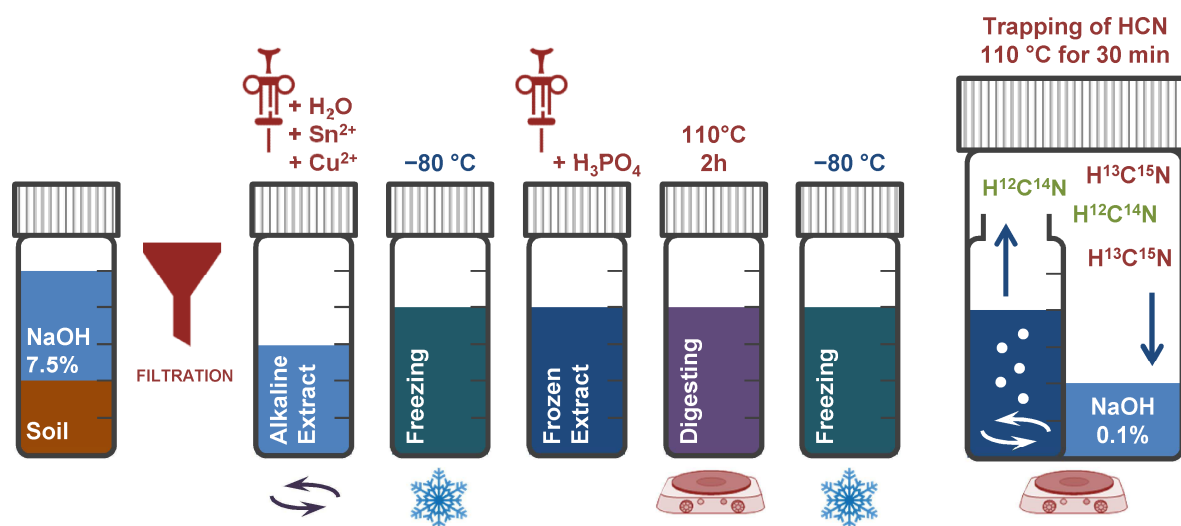


Figure 1. Extraction/digestion procedure for the determination of total cyanide in soil.

3. Results and discussion

3.1. The reactivity of F₅Bn–Br with cyanide

Pentafluorobenzyl bromide is a commercially available alkylating agent commonly employed for derivatization of inorganic anions, thiols, phenols and carboxylic acids.[46-52]

Despite F₅Bn–Br having been used for the determination of cyanide by gas chromatography, the reactivity of CN[−] with F₅Bn–Br, has not been fully investigated. Starting from CN[−] and F₅Bn–Br, one would expect a simple nucleophilic substitution resulting in the formation of F₅Bn–CN:



The above reaction however, is not sufficient to describe this chemistry. 2-(pentafluorophenyl)acetonitrile (F₅Bn–CN) is the major product formed from the reaction of cyanide with F₅Bn–Br in water : EtOH or water : THF mixtures.[53-55] However, depending on the experimental conditions, F₅Bn–CN can undergo further alkylations:



The two electron withdrawing groups (–C₆F₅ and –CN) allow the deprotonation of the CH₂ unit and electrophilic attack by a second F₅Bn–Br molecule, yielding the di-alkylated derivative (F₅Bn)(F₅Ph)CH–CN.[56] For the same reasons, the latter compound is also prone to F₅Bn–Br electrophilic attack, leading to the formation of the tri-alkylated nitrile, (F₅Bn)₂(F₅Ph)C–CN. To the best of our knowledge, (F₅Bn)₂(F₅Ph)C–CN (Figure 2) has never been reported in the literature; while its non-fluorinated analogue is known.[57]

All three alkyl derivatives were identified by GC/MS in positive (CI⁺) and negative (CI[−]) chemical ionization and in electron impact ionization (EI). The mass spectra are reported in the Supplementary content and the main fragmentations containing the –CN moiety are listed in Table 2. In EI, the molecular ion was the only –CN containing ion that was observed. In CI⁺ the protonated molecular ion appeared as the most intense signal for all derivatives. In CI[−] the molecular ion was observed only for the F₅Bn–CN whereas the loss of the –F₅Bn moiety was

observed for the Cl^- mass spectrum of the di-, and tri- alkylated derivatives. For quantitation of these polyfluorinated compounds, Cl^- mode was preferred because it allowed for 10 and 50 times higher S/N ratios compared to EI and Cl^+ respectively. Furthermore, the tri-alkylated derivative provided the best instrumental response in terms of detection limits and chromatographic separation, and therefore was chosen as the molecular target for quantitation.

The Cl^- mass spectrum of the tri-alkylated derivative generated from a cyanide standard of natural isotopic composition revealed one main signal at $m/z = 386$ Da $(\text{F}_5\text{Bn})(\text{F}_5\text{Ph})\text{C}-^{12}\text{C}^{14}\text{N}^-$. The isotopically enriched internal standard ($^{13}\text{C}^{15}\text{N}^-$) was detected at $m/z = 388$ Da $(\text{F}_5\text{Bn})(\text{F}_5\text{Ph})\text{C}-^{13}\text{C}^{15}\text{N}^-$ (Figure 3).

In order to enhance selectivity, tandem mass spectrometry was attempted on the signal at 386 Da (Figure 3) using an Agilent 7000 GC TripleQuad. However, the reactions observed in the collision cell (5, 10, 20, and 30 eV) resulted in a fragment (F_5Bn^- at m/z 181 Da) that did not contain the $-\text{CN}$ moiety. This detection option was therefore discarded because it was unsuitable for isotope dilution quantitation.

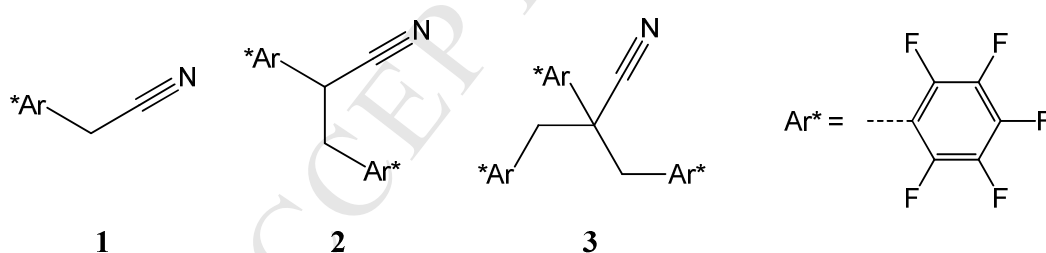


Figure 2. Chemical structure of the (1) mono-, (2) di- and (3) tri- alkylated derivatives.

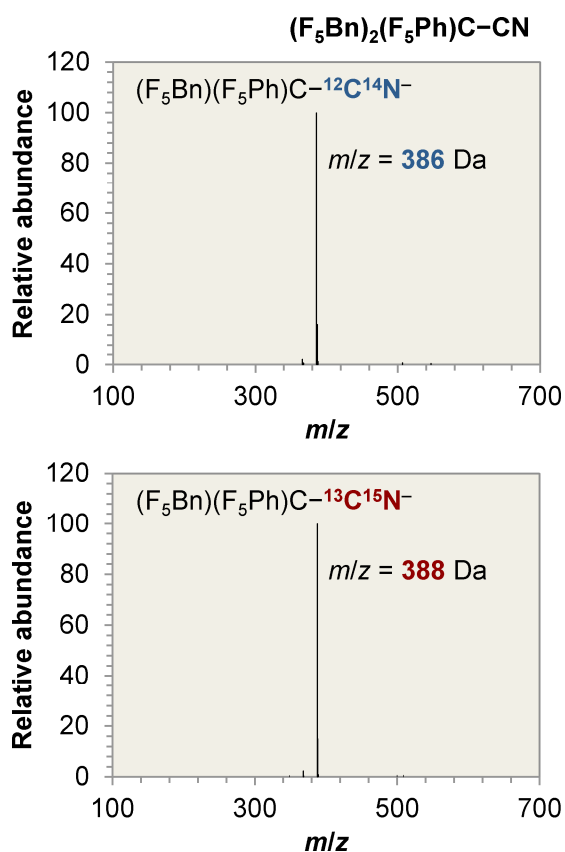


Figure 3. Experimental CI^- mass spectra of the tri-alkylated derivative generated from cyanide of natural (top) and enriched (bottom) isotopic composition.

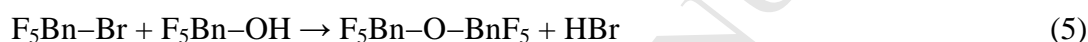
Table 2. EI, CI^+ , CI^- mass spectra of the three main derivatization products: $\text{F}_5\text{Bn-CN}$, $(\text{F}_5\text{Bn})(\text{F}_5\text{Ph})\text{CH-CN}$ and $(\text{F}_5\text{Bn})_2(\text{F}_5\text{Ph})\text{C-CN}$.

	$\text{F}_5\text{Bn-CN}$ RT = 10.3 min	$(\text{F}_5\text{Bn})(\text{F}_5\text{Ph})\text{CH-CN}$ RT = 13.2 min	$(\text{F}_5\text{Bn})_2(\text{F}_5\text{Ph})\text{C-CN}$ RT = 20.5 min
EI	$[\text{F}_5\text{Bn-CN}]^+$ (207 Da)	$[(\text{F}_5\text{Bn})(\text{F}_5\text{Ph})\text{CH-CN}]^+$ (387 Da)	$[(\text{F}_5\text{Bn})_2(\text{F}_5\text{Ph})\text{C-CN}]^+$ (567 Da)
CI^+	$[\text{F}_5\text{Bn-CN} + \text{H}]^+$ (208 Da)	$[(\text{F}_5\text{Ph})\text{CH}_2\text{-CN} + \text{H}]^+$ (208 Da) $[(\text{F}_5\text{Bn})(\text{F}_5\text{Ph})\text{CH-CN} + \text{H}]^+$ (388 Da)	$[(\text{F}_5\text{Bn})(\text{F}_5\text{Ph})\text{CH-CN} + \text{H}]^+$ (388 Da) $[(\text{F}_5\text{Bn})_2(\text{F}_5\text{Ph})\text{C-CN} + \text{H}]^+$ (568 Da)
CI^-	$[\text{F}_5\text{Bn-CN} - \text{HF}]^-$ (187 Da) $[\text{F}_5\text{Bn-CN}]^-$ (207 Da)	$[(\text{F}_5\text{Ph})\text{CH-CN}]^-$ (206 Da)	$[(\text{F}_5\text{Bn})(\text{F}_5\text{Ph})\text{C-CN}]^-$ (386 Da)

RT = Retention Time; EI = Electron impact ionization; CI^+ = Positive chemical ionization; CI^- negative chemical ionization.

3.2. Derivatization procedures

Two procedures for the derivatization of anions with F_5Bn-Br are reported: the extractive alkylation and the direct derivatization.[58-60] The principle of extractive alkylation is the transfer of the anion, as an ion pair with a quaternary ammonium cation, from the aqueous solution to a water-immiscible organic phase containing the alkylating reagent. Two different extractive alkylation methods were evaluated, but unsatisfactory derivatization yields were obtained (Supplementary content). This result was likely due to the competitive transport of both CN^- and OH^- ions by the ammonium cation into the organic phase and to the subsequent degradation of F_5Bn-Br to pentafluorobenzyl alcohol and bis(pentafluorobenzyl)ether[61]:



Since the extractive alkylation was not promising for the derivatization of cyanide, the direct derivatization approach was followed. This method is based on the direct dilution of the sample with a water-miscible organic solvent, followed by reaction with F_5Bn-Br . The reaction mixture can be heated to promote the derivatization.

We found that the performance of the direct derivatization approach is dependent on the nature of the solvent and pH of the aqueous sample analysed.

Water-miscible organic solvents have a strong effect on the yield and selectivity of the alkylation. When the derivatization was performed without an organic solvent or in methanol, no formation of cyanide derivatives was observed. In a tetrahydrofuran media the formation of F_5Bn-CN was promoted, whereas in acetone, the formation of di- and tri-alkylated derivatives was favoured. Selective formation of $(F_5Bn)_2(F_5Ph)C-CN$ was obtained when 100 μL of aqueous sample in 0.1% NaOH was reacted with 10 μL of F_5Bn-CN in 700 μL of acetone. Figure 4 shows a chromatogram from the analysis of the reagent blank and 1 ng/g cyanide standard obtained using the optimized derivatization conditions (Supplementary content).

The role of pH is important for the pentafluorobenzoylation of cyanide. The use of a sodium hydroxide media is necessary to ensure cyanide remains in an ionic form and to favour multiple alkylations, since HBr is a byproduct of such reactions. A 0.1% NaOH medium allows for the highest yield of the tri-alkylated derivative along with the best *S/N* ratio. Higher amounts of sodium hydroxide decrease the *S/N* ratio due to the accelerated hydrolysis of F₅Bn–Br.

For the optimization of reaction time and temperature, we performed a central composite design with two factors at five levels (time: 4 – 60 min; temperature: 20 – 60°C) for a total number of 9 experiments. The obtained response surface and contour plot are reported in the Supplementary content. We found that a reaction time of 10 min at 25°C is sufficient to reach the highest yield of trialkylated nitrile.

The procedure was highly reproducible, with a RSD of 1.5% based on five independent measurements of 50 ng/g of cyanide standard in NaOH 0.1 M.

3.3. Cyanide extraction from soil

Cyanide is present in soils and sediments in different chemical forms, i.e., free cyanide, weak-acid dissociable cyanide and strong-acid cyanide. The acid pretreatment described in this work (pH < 2) allows accurate quantitation of total cyanide, with a simple and cost effective approach that can be useful in soil monitoring schemes.

Sample treatment with 7.5% NaOH is required in order to dissolve ionic and complexed cyanide as well as for the hydrolysis of Prussian Blue. F₅Bn–Br is able to derivatize free CN[–] ions in solution whereas it does not react with metal-cyanide complexes such as [Fe(CN)₆]^{3–} and [Fe(CN)₆]^{4–}. Therefore, for the determination of total cyanide, acid hydrolysis of the alkaline soil extract followed by alkaline trapping of the resulting HCN was adopted.[62] The alkaline extract was placed in a vial with water, CuSO₄ and SnCl₂. Tin(II) and copper(II) salts were added to catalyse the decomposition of cyanide complexes and to suppress the interference from sulfur compounds, according to a known procedure.[62] At this point the solution was frozen and an aliquot of

phosphoric acid was rapidly added to promote hydrolysis of the complexed cyanide. The vial was closed with a gas-tight stopper. This *modus operandi* avoided exposure of the sample to an acidic medium while the vial was kept open for the addition of the reagents. In this manner, all cyanide containing compounds and the labelled internal standard remained in the closed system for digestion and equilibration. The digestion was carried out at 110 °C for two hours resulting in the conversion of all cyanide species to free HCN which promote equilibration of the $^{13}\text{C}^{15}\text{N}^-$ internal standard with the endogenous cyanide. This point is of particular importance for the success of the assay: the correct use of an isotopic internal standard strictly depends upon the physical and chemical homogenization of analyte and internal standard. In this case the cyanide in the soil extracts was present as free or complex cyanide, whereas the internal standard was present only as free $^{13}\text{C}^{15}\text{N}^-$. For this reason, the procedure adopted for the digestion of $[\text{Fe}(\text{CN})_6]^{3-}$ and $[\text{Fe}(\text{CN})_6]^{4-}$ standard solutions was tested for the complete recovery of cyanide as CN^- .

The equilibration between analyte and internal standard was proven experimentally by analyzing $[\text{Fe}(\text{CN})_6]^{3-}$ and $[\text{Fe}(\text{CN})_6]^{4-}$. These compounds were spiked with an equal molar amount of $^{13}\text{C}^{15}\text{N}^-$ and analyzed accordingly to the procedure presented in Figure 1. As shown in Table 3, after a 2 hour digestion at 110°C under magnetic stirring complex cyanide was converted to free cyanide, thus in the same form of the internal standard (free $^{13}\text{C}^{15}\text{N}^-$).

Eventual analyte losses which could occur after equilibration, did not pose a concern because they were fully accounted for by the internal standard. In this regard, it is worth mentioning that the isotope ratio is an *intensive* variable for isotope dilution quantitation which is independent from the size of the sample. After digestion, the sample was kept at -80°C until the solution was completely frozen. At this temperature the HCN gas-liquid equilibrium shifted entirely to the condensed phase. The vial was then rapidly opened and inserted in a larger vial containing 0.1% NaOH, as shown in Figure 1. The external vial was tightly closed and the system was heated to 110°C for 30 min to promote the release of HCN and its subsequent trapping in the NaOH external solution. During the migration of HCN to the NaOH solution, the digested sample was magnetically stirred. The

diffusion of HCN to the NaOH solution was not quantitative (40-60 % of efficiency). At this point however, the loss of HCN during diffusion and trapping was fully accounted for by the internal standard.

This method has important advantages over the classic distillation approach commonly employed for the determination of total cyanide in soil. It is safer because it requires a minimal amount of sample extract (250 μ L) limiting the potential exposure of the analyst to HCN. It is simpler because it avoids assembly of a distillation apparatus, requiring only commercially available glass vials. It is also more efficient as it allows analysis of several samples in parallel. Figure 6 shows representative chromatograms of cyanide extracted from soil. The chromatogram is free from interferences, the baseline is stable and no co-eluting peaks are observed. These results are a direct consequence of the sample preparation step, which separates the analyte in its gaseous form from other possible interferences present in the matrix.

Table 3. Conversion of complexed cyanide into free cyanide by acid digestion (Figure 1)

Digestion time (min)	$[\text{Fe}(\text{CN})_6]^{3-}$ Recovery as CN^-	$[\text{Fe}(\text{CN})_6]^{4-}$ Recovery as CN^-
30	84%	70%
60	87%	80%
90	100%	87%
120	99%	99%

All experiment were performed in triplicate with a relative standard deviations of 0.5%

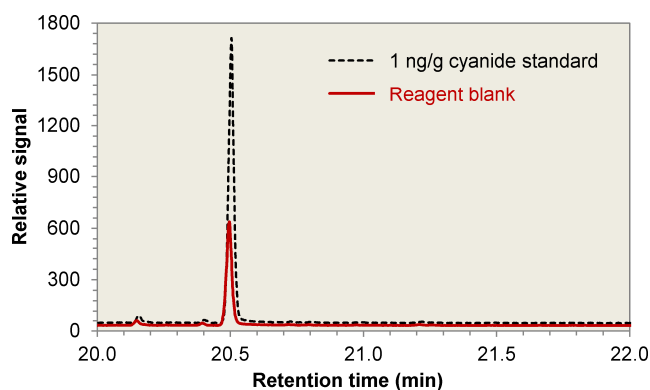


Figure 4. Gas chromatogram-selected ion monitoring ($m/z = 386$ Da) of the tri-alkylated derivative $((F_5Bn)_2(F_5Ph)C-CN$, retention time 20.5 min). The solid red line indicates the chromatogram of the reagent blank while the dotted black line indicates the chromatogram of the 1 ng/g cyanide standard solution.

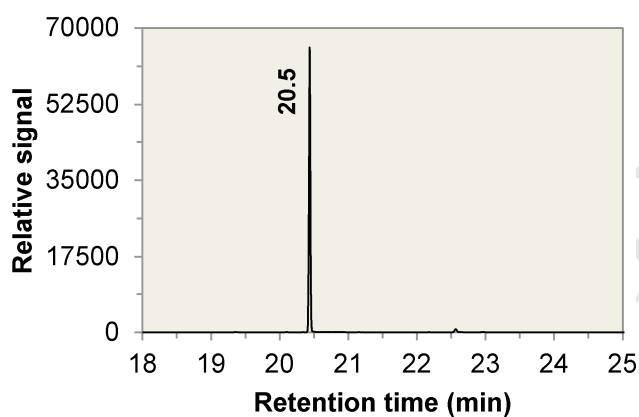


Figure 5. Selected ion monitoring ($m/z = 386$ Da) of CRM-022 soil sample treated for the determination of total cyanide.

3.4. Method validation and figures of merit

An isotope dilution calibration plot was built for quantitation purposes by preparing several calibration blends (A^*B) from various amounts of the primary standard ($m_{A^*(A^*B)}$) mixed with a set amount of isotopic internal standard ($m_{B(A^*B)}$). A legend for the symbols used in this study is reported in the Supplementary content. The isotope ratio r_{A^*B} of the area of the chromatographic peak at $m/z = 386$ Da $[(F_5Bn)_2(F_5Ph)C-^{12}C^{14}N]^-$ and the area of the chromatographic peak at $m/z = 388$ Da $[(F_5Bn)_2(F_5Ph)C-^{13}C^{15}N]^-$ was measured by mass spectrometry, and the calibration line was constructed by plotting the ratio $w_{A^*}[m_{A^*(A^*B)}/m_{B(A^*B)}]$ (x -axis) versus r_{A^*B} , (w_{A^*} is the mass fraction of the analyte in the primary standard used for preparation of the calibration blends; the $m_{A^*(A^*B)}/m_{B(A^*B)}$ factor allows accounting the very-small variations in the amount of internal standard used to prepare sample and calibration blends), as reported in Figure 6.

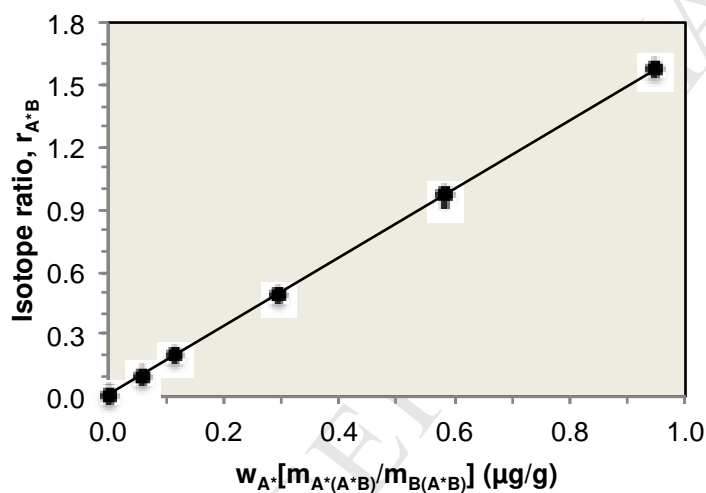


Figure 6. Calibration plot used to quantitate cyanide in the CRM022-020 soil sample.

Despite the intrinsic nonlinearity of the isotope dilution curve, a linear approximation was satisfactory to describe the calibration plot in the interval of concentration investigated for this study. For the utmost precision however, a Padé [1,1] approximant should be employed to fit the calibration data points for an isotope dilution experiment.[63]

A comparison between the results generated by linear calibration and Padé [1,1] is reported in Table 3. As presented previously,[63] the Padé [1,1] describes the true curvature of the isotope dilution

graph, and therefore accounts for the overlap between the signals of the analyte in the sample and in the labelled internal standard. A Padé [1,1] fit can be easily obtained using Microsoft Excel Linest function and an example of this calculation is reported in the Supplementary content.

Isotope dilution is regarded as a primary method for the generation of quantitative data. In our approach the use of the isotopically enriched internal standard – added at the beginning of the analysis – compensates for potential analyte losses due to sample preparation and incomplete derivatization, and to correct for matrix effects.

The method presented also has the advantage of high sensitivity: when a 100 μL volume of 5 ng/g CN^- standard was analysed with the procedure for total cyanide, a S/N ratio of 1600 was observed for the analytical peak. In our experiment, the blank of the 0.1% NaOH limits the detection limit of the method to 0.5 ng/g and the limit of quantification to 1.7 ng/g CN^- . The chromatograms of the reagent blank and of a 1 ng/g cyanide standard solution are reported in Figure 4. Even at the part-per-billion level, the analytical peak for cyanide is the most intense and is resolved from other closely eluting peaks whose area is less than 1% of the cyanide peak at the quantitation limit.

The detection and quantification limits for the determination of total cyanide in soil are 0.04 and 0.14 mg/kg, respectively, evaluated during extraction of 5 g of soil in 35 mL of 7.5% NaOH and treated for the analysis of total cyanide as described in Section 2.2.

Validation of the proposed method was carried out by analysing two certified reference materials and the results (Table 4) are in agreement with the certified property values for total cyanide. The compatibility between certified and measured values was verified accordingly to ISO 10576-1 guideline. Furthermore a spike recovery test was performed on a blank soil matrix with 20 mg/kg $\text{K}_3[\text{Fe}(\text{CN})_6]$ and quantitative recoveries were attained (100.5% and 99.6% with linear and Padé fitting, respectively).

Table 4. Determination of total cyanide in certified soil reference material.

Sample	$w(\text{CN}^-)$ /(mg/kg) – total cyanide		
	Linear fit	Padé fit	Certified
SQC011 ($n = 6$)	69.00 ± 0.91	68.70 ± 0.91	68.7 ± 1.93
CRM022-020 ($n = 3$)	26.13 ± 0.51	26.11 ± 0.51	26.6 ± 0.32

Uncertainties are reported with a coverage factor $k = 1$

4. Conclusions

Over one million metric tons of cyanide are used annually by the chemical industry for mining gold. The monitoring of this toxic analyte in soil is therefore an important environmental task. The novel method presented here for the determination of total cyanide is mass spectrometry-based and takes full advantage of the use of $^{13}\text{C}^{15}\text{N}^-$ internal standard for quantitation and traceability of the results. The method is simple, cost effective and allows for detection at the low part-per-billion level in negative chemical ionization mode. When such sensitivity is not required, the electron impact ionization may be employed. In this study, a novel micro-diffusion apparatus was designed for a single-step matrix removal and sample pre-concentration. Furthermore, derivatization with pentafluorobenzyl bromide has been evaluated for the alkylation of cyanide and the $(\text{F}_5\text{Bn})_2(\text{F}_5\text{Ph})\text{C}-\text{CN}$ derivative has been reported for the first time.

Application of the procedure for the analysis of CRMs produced results with a precision better than 3% and in excellent agreement with the property values. In our opinion, this method is a valid SI traceable alternative to the current methodologies for cyanide measurement and should be embraced when results of high-metrological quality are sought.

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RESEARCH HIGHLIGHTS

- A cost-effective, fast and simple method for determination of total cyanide in soil is presented.
- A new micro-distillation strategy was developed overcoming the problems of a conventional distillation.
- Negative chemical ionization-mass spectrometer has been exploited to obtain a high sensitivity and specificity.
- High accuracy was attained for the analysis of certified reference materials with quadruple isotope dilution technique.