

***N*–nitrosamines in surface and drinking waters: An African status report**

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Highlights

- Nitrosamines are carcinogenic disinfection byproducts in water.
- Solid phase extraction is preferred for nitrosamines in water.
- Analysis of nitrosamines is mainly based on GC-MS or LC-MS.
- Nitrosamine research in water matrices in Africa is very limited.
- Highly sensitive but facile analytical methods for nitrosamines in water are required.

Abstract

N-Nitrosamines are considered highly carcinogenic and genotoxic compounds, which are formed in water largely due to chloramination or chlorination disinfection in the presence of ammonia. *N*-nitrosodimethylamine has particularly attracted interest due to its high carcinogenicity. This review seeks to provide a synopsis of the present state of knowledge on the occurrence, toxicity, and analysis of *N*-nitrosamines in African surface and drinking water and highlights limitations and future directions. Solid phase extraction is preferred for nitrosamines in water, whilst analysis is mainly based on GC-MS or LC-MS. Extensive research into the distribution and potential impacts of *N*-nitrosamines in water has not yet been achieved on the African continent. There is a need for comprehensive research towards the development of sensitive but facile analytical methods for *N*-nitrosamines, and the monitoring thereof in African water matrices, particularly in drinking water, in order to better assess potential human health implications.

Keywords: *nitrosamine; disinfection byproducts; N-nitrosodimethylamine; water quality; Africa*

1. Introduction

The ever-increasing human population and the production rate of industrial chemicals have contributed to increased demand for clean and potable water in Africa and globally [1,2]. Countries across Africa employ water reuse and treatment strategies to meet the water demands within their communities. Potable water is of paramount importance and needs to be readily available to humans to curb the spread of water-borne diseases [3–5]. Water treatment plants (WTPs) exploit natural sources of water such as rivers, lakes, springs, groundwater, and municipal wastewater effluents to provide potable drinking water to communities [6,7].

Chlorination and chloramination are the most widely used water disinfection treatments [4,8,9]. Some WTPs employ chloramination due to its ability to reduce levels of ubiquitous disinfection byproducts (DBPs) such as trihalomethanes (THMs) and haloacetic acids (HAAs) [10]. Chloramination is the process of adding chloramines, usually monochloramine, to untreated water to destroy pathogenic microbes and it can also be achieved indirectly by chlorination in the presence of ammonia [11,12]. However, this disinfection treatment produces high levels of nitrogenous DBPs, in particular nitrosamines (NAs) such as *N*-nitrosodimethylamine (NDMA) [13,14].

Existing reports on NAs suggest that these compounds are carcinogenic and genotoxic [15–18]. They possess a nitroso group (NO^+) and their occurrence in water is attributed to numerous factors but mainly chloramination or chlorination in the presence of ammonia or amine species [2,19]. The leaching of dimethylamine (DMA) from ion exchange resins and the use of nitrogen-containing polymers at WTPs has also been associated with the occurrence of NAs in water [11]. Special attention has been given to NDMA as a prevalent member of this class of pollutants in water, especially in drinking water [12]. It has been assigned a drinking water unit risk (DWUR) in the United States (U.S.) of 1.4×10^{-3} per $\mu\text{g/L}$ from oral exposure, where a DWUR is defined as the risk associated with a drinking water concentration of $1 \mu\text{g/L}$, assuming that an adult weighs 70 kg and drinks two liters of water per day [20]. The DWUR for NDMA is a value that is about 1000 times greater than that of dichloroacetic acid (1.4×10^{-6} per $\mu\text{g/L}$), a HAA, and bromodichloromethane (1.8×10^{-6} per $\mu\text{g/L}$), a THM that are commonly detected in waters disinfected with chlorine [19,20].

An extensive literature search revealed that there is very limited research that has been conducted on NAs in African surface and drinking waters, which is a concern due to the health effects these pollutants may pose to humans. This review seeks to provide a synopsis of the current state of knowledge concerning the occurrence, toxicity, and analysis of NAs in African surface and portable water. The literature scope of this review is based on SCOPUS and Web of Science published articles and books, and Google Scholar was also used to search for relevant journal papers. Key limitations in the current state of knowledge and future perspectives are provided, whilst the need to address these research gaps is highlighted. In order to address the paucity of monitoring data for Africa, analytical methods would need to be implemented in African laboratories, therefore the sampling, sample pre-concentration, and analytical approaches which have been reported for NAs in water globally are discussed in this review. The formation, toxicity, and global legal limits for NAs in water are also described to provide context as to the importance of expanding the monitoring of NAs in water in Africa. This is the first composite status report of NAs in Africa.

2. Rationale behind the need for extensive *N*-nitrosamines research in water in Africa

Based on literature and internet searches that were conducted, it was found that most African countries employ chlorination for water disinfection. The African continent consists of developing countries, and the paucity of appropriate infrastructure in some parts of these countries makes it impossible for some of their citizens to receive piped-treated drinking water. Populations in these regions have thus been made to resort to household water treatment practices. The countries with names in a purple font in **Fig 1** were found to have populations that perform household water treatment practices using a variety of chlorine-based products such as sodium dichloroisocyanurate, dilute hypochlorite solution, and sodium hypochlorite [21–23]. The countries whose names are indicated in blue font were found to have WTPs that use chlorination as a disinfection step, whilst South Africa was the only country that has WTPs that use both chlorination and chloramination. For the countries with names in black font, there was no information available due to an inadequate internet presence on water treatment practices.

The formation of NAs in water has been predominantly associated with the disinfection process of chloramination or the addition of chlorine in the presence of ammonia [8,10,24]. However, chlorination alone has also been reported to produce NAs in treated water in other parts of the

world [25,26]. A study that was conducted in China by Luo and coworkers in three different cities (Beijing, Shanghai, and Xuzhou) that have WTPs that employ different water disinfection processes including chlorination and chloramination showed that, out of the seven WTPs that were investigated, three used chlorination as their disinfection process and some nitrosamines were detected in their finished water (NDMA, *N*-nitrosomorpholine (NMor), *N*-nitrosopiperidine (NPip), *N*-nitrosopyrrolidine (NPyr), *N*-nitrosodiphenylamine (NDPhA)) [25]. NDMA was the most frequently detected nitrosamine with concentrations ranging from 0.70 –3.45 ng/L. NMor, NPip, NPyr, and NDPhA were all detected once in the finished water at one of the WTPs in Beijing with concentrations of 14.55, 2.90, 3.75, and 0.30 ng/L, respectively [25].

In another study by Zhao and coworkers, source waters with varying qualities were disinfected using eleven different disinfection techniques that included chlorination and chloramination to investigate the formation of NAs from disinfection treatments [26]. No known nitrosamine precursors were added to the source water to allow for the comparison of the formation of NAs due to the different disinfection methods. Chlorination alone was noted to be capable of producing NAs, as NDMA was frequently detected at concentrations ranging from 10 –63 ng/L when chlorination was employed to treat source waters obtained from six different locations. NMor, NDPhA, *N*-nitrosomethylethylamine (NMEA) were also detected when chlorination was employed as a disinfection method [26].

Therefore, albeit that most of Africa employs chlorination as their disinfection method or uses chlorine-based products as household treatment practices, there is still a great deal of research that needs to be conducted to monitor the occurrence of NAs in African waters as chlorination is clearly also capable of producing NAs. In South Africa especially, rigorous methods are required to monitor NAs in water as both chlorination and chloramination are employed. **Table 1** shows some of the regions of African countries that employ the different disinfection treatments represented by the different colours in **Fig 1**.

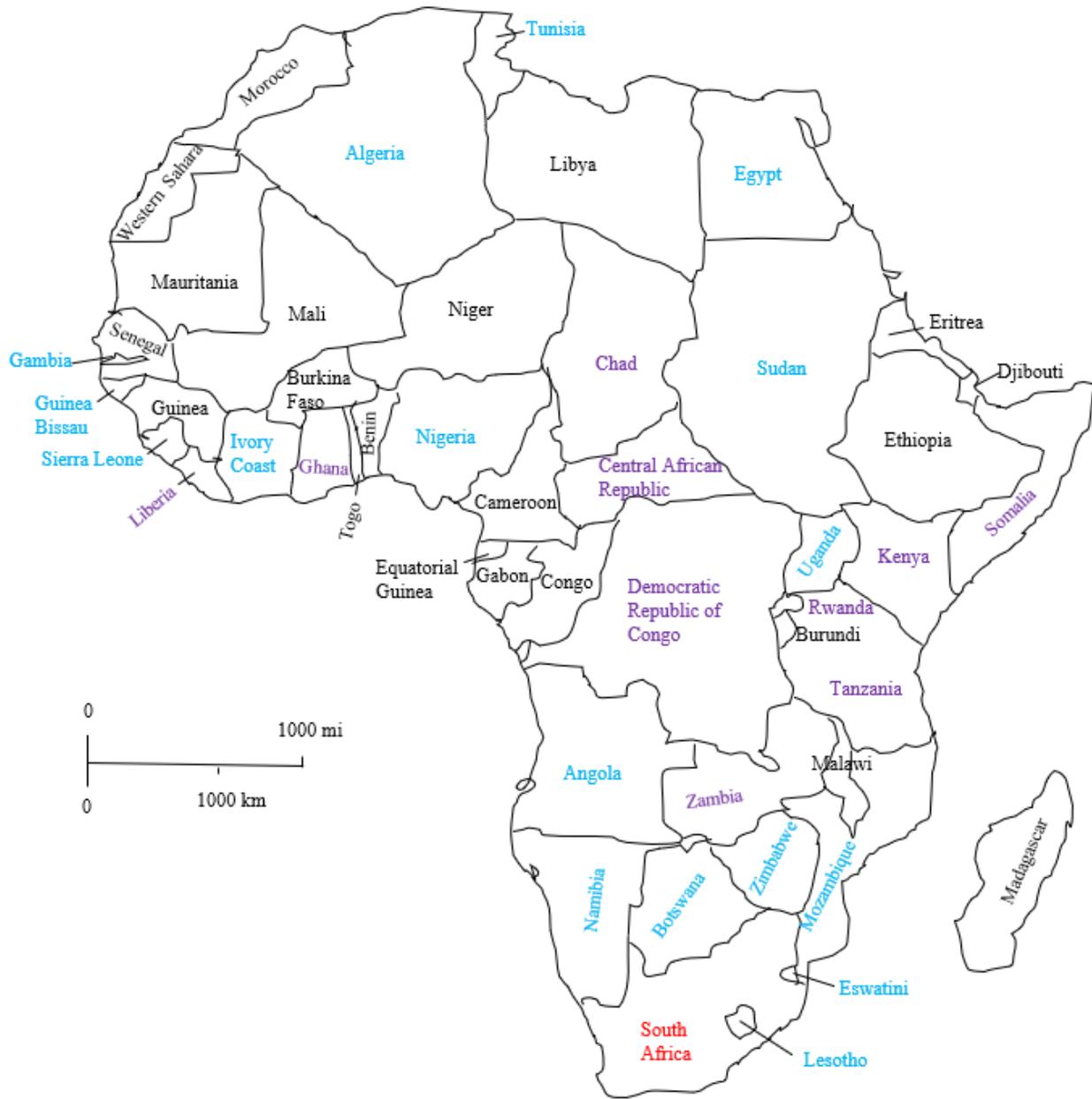


Fig 1: The African map showing country names in different colours to represent the disinfection treatments they employ. Red represents chloramination and chlorination, blue represents chlorination, purple represents household disinfection treatment using chlorine-based products, and black represents no information available.

Table 1: Some of the regions of African countries that employ the different disinfection treatments represented by the different colors in **Fig 1**.

Country	City/Province/Town concerned with the type of disinfection used	Reference
Angola	Cunene	[27]
Botswana	Gaborone, Lobatse, Mahalapye, Selebi Phikwe, Francistown	[28]
Lesotho	Maseru, Mapoteng, Roma, Morija, Peka and Maputsoe.	[29,30]
Namibia	Windhoek	[31]
South Africa	Gauteng, KwaZulu-Natal	[32,33]
Eswatini	Manzini, Lubombo, Mbabane	[34]
Zimbabwe	Harare, Ruwa, Chitungwiza, Norton, and Epworth	[35]
Zambia	Lusaka	[36]
Mozambique	Moamba	[37]
Tanzania	Arusha	[38]
Ghana	Tamale	[39]
Egypt	El-Beheira Governorate	[40]
Nigeria	Lagos and Ogun	[41]
Algeria	Ksir Beni Zid, Guelma, Oran	[42]
Kenya	Nyanza, Kisumu	[21]
Sudan	Maban county	[43]
Central African Republic	Bangui	[23]
Uganda	Palorinya	[44]
Rwanda	Nyagatare, Rubavu, Karongi	[45]
Chad	Lake Chad basin	[22]
Çote d'Ivoire	Abidjan	[46]
Gambia	Brikama	[47]
Tunisia	Entire Tunisia	[48]
South Sudan	Wau	[49]
Serria Leone	Mokonde and Njala University	[50]
Guinea-Bissau	Guinea-Bissau	[51]
Liberia	Monrovia	[52]
Democratic Republic of Congo	Kinshasa	[53]
Somalia	Mogadishu	[54]

With Scopus and the Web of Science being the two biggest academic research databases, an attempt was made to search for nitrosamine research that is available on these databases between the years 2000–2022. The following search terms were used:

{nitrosamines in water} OR {nitrosamines in drinking water} OR {nitrogenous disinfection byproducts in water} OR {nitrogenous disinfection byproducts in drinking water} OR {N-nitrosodimethylamine} OR {N-nitrosopyrrolidine} OR {N-nitrosopiperidine} OR {N-nitrosodiphenylamine} OR {N-nitrosodiethylamine} OR {N-nitrosomethylethylamine} OR {N-nitrosodipropylamine} OR {N-nitrosomorpholine} OR {N-nitrosodibutylamine}. Note that quotation marks were used for the Web of Science search instead of brackets.

Documents that had exactly one of either of the phrases in the brackets or any of the words of the nine commonly analyzed NAs in water (as determined from initial review of the literature on which NAs are most frequently analysed in water) publications in their titles, abstracts, or keywords appeared. A total of 2245 and 2667 documents were found on Scopus and the Web of Science, respectively, and these were limited to papers that were published between 2000–2022. The bar graphs in **Fig 2** provide evidence that on both Scopus and Web of Science, Asia has produced the most papers on NAs followed by Europe and North America. The African continent and South America have the least number of papers produced on NAs, with each of these continents having produced less than 100 papers between the years 2000–2022. With the primary focus of this review being Africa, the pie charts in **Fig 2** provide an elucidation of which of the African countries have produced published nitrosamine research in the last two decades. It is noted that a few African countries have made contributions; Egypt has the highest number of papers on NAs on Scopus or the Web of Science followed by Nigeria and South Africa. More than 70% of these papers that are found from the African continent fall predominantly under the fields of medicine, pharmacology, biochemistry, oncology, toxicology, and food sciences. The research produced in Africa on NAs is minuscule when compared to what the rest of the world has published, additionally, most of it does not entail NAs in water including drinking water.

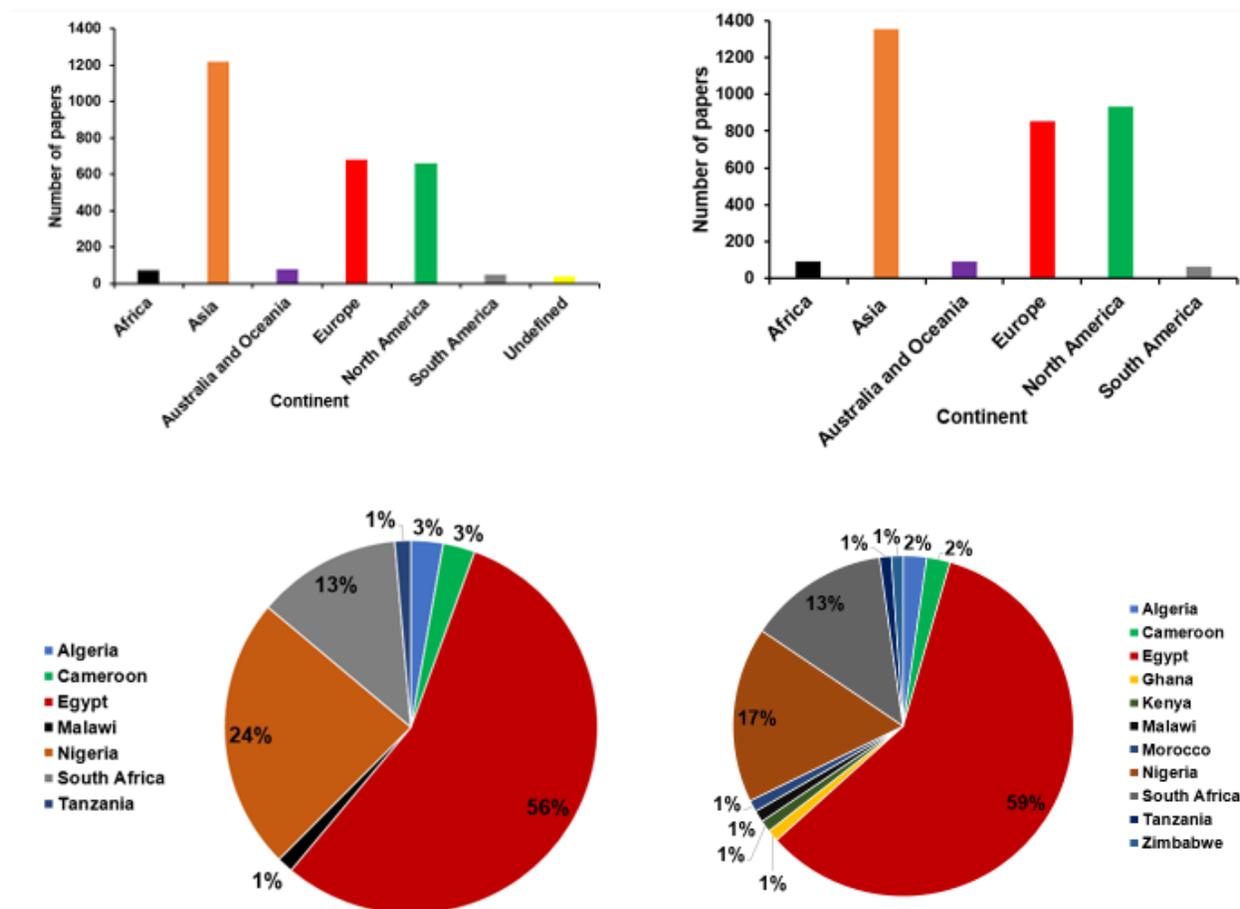


Fig 2: Nitrosamine research on Scopus (left) and Web of Science (right) per continent between the years 2000–2022 (top) and per African country (bottom).

3. Formation of *N*-nitrosamines

Urine, human and animal waste possess constituents such as dimethylamine and trimethylamine-*N*-oxide which both bear amine groups [55]. The natural degradation of urine and human and animal waste in water could leach these constituents and they may undergo nitrosylation in the presence of nitrites and nitrates to yield NAs. Wastewater produced by companies that use or manufacture unsymmetrical dimethylhydrazine (UDMH) has also been found to contain NAs. UDMH is a known nitrosamine precursor which produces NAs by oxidation [12,56].

Persistent artificial sweeteners that occur in a specific wastewater source that can resist removal by waste WTPs, such as sucralose and acesulfame, can be used to study the impact that

wastewater poses to environmental compartments [57]. NA concentrations have been found to increase in water impacted by wastewater [57]. Prescott and coworkers evaluated the relationship between NDMA formation potential and sucralose occurrence in the source water [58]. They found that source water with high sucralose concentration typically had high NDMA precursor concentrations. In cases where results were anomalous, in which NDMA precursor concentrations were high but with low sucralose concentrations, this was attributed to the source water being impacted by industrial wastewater rather than domestic wastewater in which sucralose occurs [58].

Research conducted by Mitch and Sedlak suggests that the formation of NDMA from chloramination or chlorination of water in the presence of amine species occurs via the UDMH pathway [8]. Regional and seasonal distributions of NDMA in chlorinated drinking water found that higher concentrations of NDMA form in winter than in summer [19]. This was attributed to less effective pre-chlorination at lower temperatures or low microbial activity and less photodegradation of NDMA because of low sunlight conditions in winter [19]. Higher concentrations of NDMA were also detected in tap water than in the finished water at WTPs, which was attributed to the fact that residual disinfectant remained in the water for a prolonged time and reacted with NDMA precursors as the water was being distributed over long distances resulting in elevated NDMA concentrations at the point of use [19].

NAs in water distribution systems can leach from the rubber sealing rings used to connect pipes [59]. In support of this, monitoring conducted in water that was supplied through a new pipeline in Australia that uses rubber rings showed high levels of NDMA, which surpassed the World Health Organization (WHO) guideline value of 100 ng/L [60]. An old pipeline showed no elevated NDMA levels from the same water, corroborating that NDMA leached from the materials used in the new pipeline [59]. Moreover, NAs have been detected in effluents from rubber manufacturing plants and there have been studies that showed high mortality rates from cancer in rubber manufacturing workers [61,62].

4. Potential toxic effects of NAs

Numerous studies have affirmed the carcinogenicity and genotoxicity of NAs [63–65]. NAs are among the most potent carcinogens known to date, and existing reports suggest that NDMA is the most toxic nitroso compound [66–69]. It has been reported that NAs induce carcinogenetic and mutagenic effects by causing oxidative stress, DNA damage, and lipid degradation.

Carcinogenesis may affect various organs, such as the gastrointestinal tract, liver, prostate, uterus, lungs, bladder, and kidneys [67].

NAs are said to function as alkylating agents which cause disruptions in the DNA. These agents add an alkyl group to the guanine base of DNA and hence prohibit it from forming the normal double helix, leading to DNA damage and incorrect gene expression [64,70]. Activated NAs may cause oxidative stress by promoting an imbalance between reactive oxygen species such as superoxide (O_2^-) or hydrogen peroxide (H_2O_2) and antioxidants and may also lead to lipid peroxidation [71]. DNA damage, oxidative stress, and lipid degradation are important factors in the development of type 2 diabetes mellitus and neurodegeneration [66,67]. The cellular and molecular destructions produced by NAs are similar to those that occur during the pathogenesis of diseases such as Alzheimer's disease, type 2 diabetes mellitus, non-alcoholic steatohepatitis, and the process of aging [72–75].

Berger and coworkers reported the adverse effect of the addition of small amounts of NDMA (0.1 mg/kg/day), NPyr (0.4 mg/kg/day), and *N*-nitrosodiethanolamine (0.2 mg/kg/day) to the drinking water of rats, as these disinfection byproducts caused the growth of liver tumors [76]. A related study examined esophageal and liver tumors caused by *N*-nitrosodiethylamine (NDEA) or NDMA in rats, and findings showed that exposures to concentrations as low as 1 ppm of either NDEA or NDMA in drinking water given to rats resulted in 25% of the animals developing liver tumors [77].

5. *N*-nitrosamine guideline levels

Most of the research that has been conducted to date on NAs in water mainly focuses on NDMA because it is the commonly detected NA in water matrices and has been assigned a high DWUR as discussed in Section 1 [78, 19]. NDMA concentrations in most reported cases tend to be higher than the concentrations of other NAs in water [79]. There are a few regulatory agencies that have guidelines set out for NAs in water, and the majority of the available guideline levels for NAs in water are for NDMA [78, 82, 12].

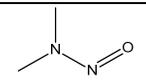
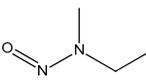
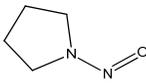
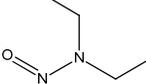
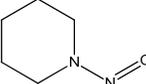
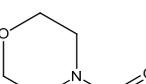
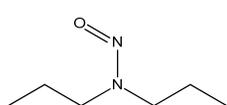
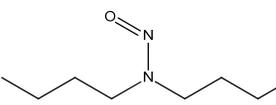
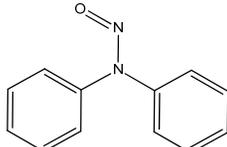
The Ontario Ministry of the Environment in Canada has set a maximum allowable concentration for NDMA of 9 ng/L in drinking water, while the California Department of Public Health has set NDMA and NDEA permissible levels at 10 ng/L in drinking water [80–82]. 12 ng/L and 10 ng/L

were set as nitrosamine guidelines in the Netherlands and Germany, respectively, in drinking water [83]. The World Health Organization (WHO) has a guideline value for NDMA of 100 ng/L in drinking water [60]. To date, African countries do not have guidelines set out for NAs in water. Sufficient research still needs to be conducted to provide the necessary information required by established governing bodies to set these guidelines, as these are pivotal to environmental health and safety, as well as the well-being of humans.

6. Water sampling, detection, and analysis of *N*-nitrosamines

The major challenge in the analysis of NAs is the development of efficient methods for extraction of NAs from water samples and concentration thereof to detectable levels prior to instrumental analysis. The differences in polarities and structures between these compounds continue to pose analytical challenges, particularly with respect to NDMA. NDMA is the most hydrophilic of the nine NAs listed in **Table 2** and has proven to be very difficult to extract from water [10,84].

Table 2: Nine commonly analyzed NAs in water, their CAS (Chemical Abstracts Service) numbers, chemical formulae, and molecular weights (MW), log K_{ow} (octanol-water partition coefficients which provide a measure of hydrophilicity/lipophilicity), and chemical structures [10,84].

Name	Acronym	CAS number	Chemical formula	MW (g/mol)	Log K_{ow}	Structure
<i>N</i> -nitrosodimethylamine	NDMA	62-75-9	C ₂ H ₆ N ₂ O	74	-0.57	
<i>N</i> -nitrosomethylethylamine	NMEA	10595-95-6	C ₃ H ₈ N ₂ O	88	0.08	
<i>N</i> -nitrosopyrrolidine	NPyr	930-55-2	C ₄ H ₈ N ₂ O	100	-0.19	
<i>N</i> -nitrosodiethylamine	NDEA	55-18-5	C ₄ H ₁₀ N ₂ O	102	0.48	
<i>N</i> -nitrosopiperidine	NPip	100-75-4	C ₅ H ₁₀ N ₂ O	114	0.63	
<i>N</i> -nitrosomorpholine	NMor	59-89-2	C ₄ H ₈ N ₂ O ₂	116	-0.44	
<i>N</i> -nitrosodi- <i>n</i> -propylamine	NDPA	621-64-7	C ₆ H ₁₄ N ₂ O	130	1.36	
<i>N</i> -nitrosodi- <i>n</i> -butylamine	NDBA	924-16-3	C ₈ H ₁₈ N ₂ O	158	1.92	
<i>N</i> -nitrosodiphenylamine	NPhA	86-30-6	C ₁₂ H ₁₀ N ₂ O	198	3.13	

6.1 Water sampling

Water samples for the analysis of NAs are typically collected in amber glass bottles with PTFE-lined caps [10,11,85,86]. It is of paramount importance that the bottles are amber or covered with aluminum foil, as NAs are susceptible to degradation when exposed to ultraviolet radiation or sunlight [85]. The caps of the bottles should not be lined with rubber products because NAs can

be found in rubber products as contaminants. After sampling, sodium thiosulfate or ascorbic acid is added to the water samples to preserve the integrity of the samples by neutralizing residual chlorine and chloramine that may be present and thereby reduce the chance of further formation of NAs in water samples during transport and storage [82,87]. Water samples should be stored at 4 °C and analyzed within a week [10,88]. The basic steps involved in the monitoring of NAs in water samples are shown in **Fig 3**.

6. 2 Extraction and enrichment

Preconcentration and clean-up steps are required prior to the analysis of NAs as these contaminants are found at very low concentrations (ng/L) in water [13,89]. Preconcentration also plays a pivotal role in the elimination of matrix effects and enhances the sensitivity of the chromatographic technique to be employed [82,84,90–92]. Different clean-up techniques such as liquid-liquid extraction (LLE), solid-phase microextraction (SPME), and solid-phase extraction (SPE) have been used by different researchers for this application.

LLE methods for NAs have been shown to have low recoveries and require large volumes of organic solvent to extract NAs [2,84,93–95]. LLE is a laborious technique, inefficient for the analysis of NAs, and not eco-friendly [26,95].

SPME has the potential to be an efficient method for the extraction of NAs prior to GC analysis, as it eliminates the use of organic solvents and contains fewer steps compared to LLE and SPE [84,96,97]. However, difficulties in providing the necessary sensitivity and capability of analyzing a range of NAs simultaneously still need to be addressed. Grebel and coworkers compared four SPME fibers (carboxen/polydimethylsiloxane (CAR/PDMS), carbowax/divinylbenzene (CW/DVB), polydimethylsiloxane/divinylbenzene (PDMS/DVB), and polyacrylate (PA)) to determine which one was best suited for extraction of NAs from water [96]. Each fiber was tested for both headspace and direct immersion extraction, and it was found that headspace extraction yielded better recoveries for NDMA. Three fibers (CAR/PDMS, PA, CW/DVB) had increased NDMA extraction in the headspace versus direct immersion extraction, whilst PDMS/DVB was the only fiber with decreased efficacy in the headspace [96]. CAR/PDMS was chosen as the best fiber for NAs extraction as it had better NDMA recoveries than the other fibers. In another study by Hung and coworkers, CAR/PDMS was again shown to have better NAs extraction efficiencies from water than the other two fibers tested (PDMS and (DVB/CAR/PDMS)). The area response of

NDMA for CAR/PDMS was almost four-fold higher than that for DVB/CAR/PDMS, whilst there was no NDMA extracted with the PDMS fiber [97].

SPE has been the preferred extraction method for the analysis of NAs in water [82]. Different SPE sorbents have been evaluated which have shown that activated carbon (AC) sorbents can provide the required efficacy for the analysis of all nine NAs commonly analyzed, namely NDMA, NMEA, NPyr, NDEA, NPip, NMor, *N*-nitrosodi-*n*-propylamine (NDPA), *N*-nitrosodi-*n*-butylamine (NDBA), and NDPhA [84,98]. Cheng and coworkers used NDMA recoveries alone to determine which sorbent and conditions to use for the analysis of NAs [85]. Two reversed-phase sorbents based on ion exchange (Oasis MAX and MCX), two activated carbons (Supelclean ENVI-carb and Ambersorb 572), and two reversed-phase sorbents (LC-18 and Oasis HLB) were investigated. Ambersorb 572 was the sorbent of choice due to better NDMA recoveries, whilst the ionic sorbents had poor NDMA recoveries. ENVI-carb retained NDMA but did not release this analyte, thus a combination of the two activated carbon sorbents (Supelclean ENVI-carb and Ambersorb 572) was employed to obtain satisfactory recoveries of eight NAs (76–95%) [85].

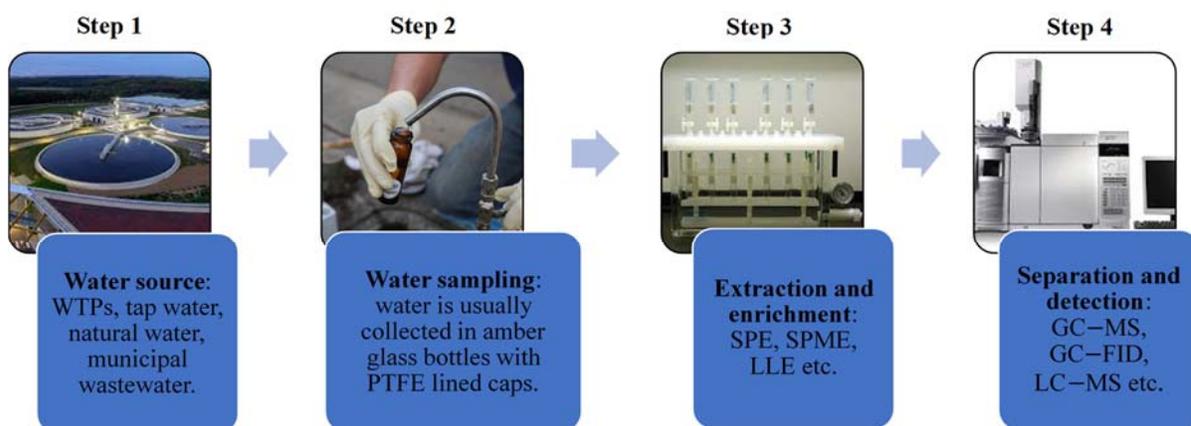


Fig 3: Flowchart showing the steps involved in the monitoring of NAs in water (*Water treatment plants (WTPs), polytetrafluoroethylene (PTFE), solid-phase extraction (SPE), solid-phase microextraction (SPME), liquid-liquid extraction (LLE), gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), gas chromatography- flame ionization detection (GC-FID)*).

6.3 GC-MS analysis

The most prevalent means to analyze NAs in water is SPE coupled with gas chromatography-mass spectrometry (GC-MS) [2,99–102]. The analysis of NAs such as NDMA in water has proven very challenging due to its high polarity and the low detection limits required, which are below the detection limits achievable with many instruments (low ppt or ng/L) [2,104,105].

Grebel and coworkers compared three GC detection systems for NA analysis: nitrogen-phosphorous detection (NPD), nitrogen-chemiluminescence detection (NCD), and chemical ionization-MS (CI-MS). The method detection limits (MDLs) achieved when utilizing SPME preconcentration ranged from 30–890 ng/L across all three detectors [96]. NCD produced the most trustworthy results and was chosen as the best detection system for SPME whilst CI-MS produced the lowest detection limits but the variability of NAs spike recoveries in real water samples still needed addressing and NPD showed the least reliability and sensitivity [96]. This method was later modified by Hung and coworkers to improve the MDLs by using GC tandem MS (GC-MS/MS). The MDLs achieved ranged from 3.2 –3.5 ng/L for NDMA, NDEA, and NDPA, respectively, whilst for NMor it was 15.2 ng/L [97]. Charrois and coworkers developed a method that could detect NAs at relevant drinking water concentrations (low ppt) by using SPE with GC-MS, incorporating positive chemical ionization mode with ammonia [106]. CI has proven to be a better alternative than electron ionization (EI) for analysis of NAs in water [101,102]. With EI, analytes are highly fragmented, and for some molecules, this may lead to problems as fragment ions could be obscured compromising sensitivity. CI, on the other hand, offers softer ionization and reduced fragmentation [101]. Pozzi and coworkers compared methods for the determination of NAs in water. EI and CI with methanol were compared with three modes of ion analysis namely, selected ion storage, full scan, and tandem ion trap mass spectrometry. The results showed that CI and selected ion storage were better suited to provide low limits of detection in the range of 0.8 to 2.7 ng/L [101]. However, the use of GC precludes the analysis of non-volatile or thermally unstable NAs (such as NDPhA) which decompose in the GC injector [2,84]. **Table 3** lists some of the different GC-MS methods that were produced from countries outside the African continent between 2010–2020.

Table 3: Analysis of nitrosamines in various water matrices by gas chromatography coupled with mass spectrometry (between 2010–2020).

DBPs	Water sample type	Extraction method	Method for analysis	Ionization mode	GC column	Detection limits (ng/L)	Recoveries (%)	Country	Reference
NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip	Drinking water	SPME	GC/CI–MS	CI	DB-624 column (30 m x 0.25 mm I. D. x 1.4 mm film thickness)	0.1–0.8	77–114	Taiwan	[102]
NDMA, NDPA, NDEA, NMor	Surface and drinking water	SPME	GC/CI–MS/MS	CI	FactorFour VF-624 ms capillary column (60 m long×0.25 mm inner diameter with 1.4- μ m film thickness)	3.2–3.5	92.5–129	Taiwan	[97]
NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip, NMor, NDPhA	Surface, ground, ad pool water	SPE	GC/CI–MS	CI	PTA-5 column (30m×0.25mm I. D.×0.5 μ m film thickness)	1– 2	71–96	Italy	[101]
NDMA, NMEA, NDEA, NDPA, NPyr, NMor, NPip, NDBA	Drinking water and wastewater	SPE	GC/EI–MS/MS	EI	Agilent DB-1701P (30 m x 0.25 mm, 0.25 mm film thickness)	0.4–4	51–93	Australia	[100]
NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip, NMor	Drinking, fishpond, ground, and surface waters.	SPE	GC/EI–MS/MS	EI	HP-5 MS, 5% diphenyl 95% dimethylpolysiloxane (15 m, 0.25 mm i.d., and 0.25 mm film)	1.1–3.1	78–127	China	[108]
NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip, NMor, NDPhA	Drinking water and wastewater	SPE	GC–QToF–MS	CI	DB-WAXetr (extended temperature range high polarity polyethylene glycol, 30 m × 0.25 mm, 0.50 μ m film thickness)	0.2–1.3	90–120	Spain	[102]

NDPA, NDBA, NPip	Drinking water and groundwater	DLLME	GC-MS	EI	DB-5 fused-silica capillary column (30 m × 0.25 mm id; 0.25 μm film thickness)	5.7–124	93.9–103.7	Saudi Arabia	[93]
NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip, NMor, NDPhA	Drinking water, seawater, and wastewater	Micro-SPE	GC-MS	EI	19091J-413 MS column (with thickness of 0.25 μm, length of 30.0 m, and diameter of 0.32 mm)	800– 3 300	85–104.2	Saudi Arabia	[104]
NDMA, NMEA, NDEA, NDPA, NPyr, NMor, NPip, NDBA, NDPhA	Drinking and surface water	SPE	GC-MS	EI	PTA-5 column (30 m×0.25 mm internal diameter×0.5 μm film thickness)	0.8–4.3	75–103 and 62–101	China	[98]
NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip	Drinking water	SPE	GC-MS/MS	AEI	TraceGOLD TG-1701MS (30 m × 0.25 mm × 0.5 μm)	0.1–0.5	80.7–111.1	Spain	[99]

Advanced electron ionization (AEI), dispersive liquid–liquid microextraction (DLLME), gas chromatography– quadrupole– time of flight–mass spectrometry (GC–QToF–MS).

6.4 LC-MS analysis

While GC–MS is the most commonly reported method for NAs separation and determination in water, some studies have devised liquid chromatography–mass spectrometry (LC–MS) methods, which can analyze thermally unstable NAs and/or higher molecular weight NAs that may be formed during the disinfection process that cannot be analyzed by GC–MS [84]. This renders LC–MS a good alternative for the identification of NAs that are not yet known.

Zhao and coworkers were the first researchers to develop an LC-MS method to analyze NAs in water [109]. The method they developed used high performance liquid chromatography (HPLC) with triple-quadrupole mass spectrometry to determine NAs at relevant drinking water concentrations (low ng/L). In this method, NDPhA was measured directly for the first time at m/z 199, which obviated the need to depend on the fragment ion diphenylamine (m/z 177) and the method detection limits were estimated to be 0.1–10.6 ng/L [109]. The separation and identification of NAs using LC-MS or LC-MS/MS using either electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) have been reported by various researchers [10,86,110–113]. **Table 4** lists some of the different LC–MS methods that were produced from countries outside the African continent between 2010–2020.

Table 4: Analysis of nitrosamines in various water matrices by liquid chromatography coupled with mass spectrometry (between 2010–2020)

DBP	Water sample type	Extraction method	Method for analysis	Ionization mode	LC column	Mobile phase	Detection limits (ng/L)	Recoveries (%)	Country	Reference
NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip, NMor, NDPhA, NNN, NAT, NAB, NNAL	Drinking water, wastewater- impacted drinking water, water in which tobacco leached	SPE	HPLC–MS/MS	ESI+	Kinetex C8 column (100 × 3.0 mm i.d., 2.6 μm)	Solvent A (10 mM ammonium acetate and 0.01% acetic acid in water) and solvent B (100% methanol)	0.01–2.7	53–93	Canada and United States	[10]
NDMA	Drinking and surface water	SPE	UPLC–MS/MS	ESI+	BEH C18 column (2.1 mm × 150 mm i.d., 1.7 μm)	10 mmol/L ammonium bicarbonate aqueous solution and acetonitrile	1.2	61– 65 and 96– 108	China	[5]
NDMA, NDEA, NMor	Surface water	SPE	UHPLC–MS/MS	APCI+	Acquity BEH (Ethylene Bridged Hybrid) C18column (100 mm × 2.1 mm, 1.7 μm)	Acetonitrile, ultrapure water, and formic acid (60:40:0.1, v/v/v)	0.04– 0.16	98–101	France	[82]
NDMA, NDEA, NDPA, NMor	Drinking and surface water	SPE	UHPLC–MS/MS	APCI+	Ethylene Bridged Hybrid C18 column (100 mm × 2.1 mm, 1.7 μm)	Acetonitrile, ultrapure water, and formic acid (60:40:0.1, v/v/v)	0.04–0.4	98–100	France	[87]
NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip, NMor	Drinking, surface, and wastewater	SPE	UHPLC–MS/MS	APCI+	Atlantis T3 C18 (100 mm × 4.6 mm, 5 μm)	Water/acetonitrile gradient	1–8	90–120	Spain	[113]

NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip, NMor, NDPhA,	Drinking and wastewater	SPE	HPLC-Q-ExactiveMS	HESI+	Hypersil Gold C18	Water/methanol+ formic acid	0.4–12	68–83 and 22–31	Canada	[86]
NDBA, NDPA NDEA, NDPhA, NPip	Drinking and surface water.	MIP-SPE	HPLC-MS/MS	ESI+	Eclipse Plus C18 column (2.1×100 mm, 3.5 μm)	Water/methanol+ 0.1 % formic acid	0.2–0.7 and 0.6–2.1	93–107	China	[114]

N-nitrosornicotine (NNN), *N*-nitrosoanatabine (NAT), *N*-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), Heated electrospray ionization (HESI), Molecularly imprinted polymer (MIP), Ultra high performance liquid chromatography (UHPLC), Ultra performance liquid chromatography (UPLC).

6.5 Alternative analytical approaches

Research reports that are based on the use of SPE-LC/MS/MS or SPE-LC/MS for the determination of NAs in water differ mostly in the ionization modes used [86,109,111,113]. A new method was reported by Kodamatani and coworkers that obviated the need for clean-up and enrichment steps when determining NAs in water samples at ng/L levels (parts per trillion). The method entailed the use of HPLC with online ultraviolet radiation followed by chemiluminescence detection with no oxidant added [115]. Under neutral conditions, the N–NO bond of NAs when irradiated by UV light can undergo homolytic cleavage to yield amine radicals and nitric oxide [116]. In basic aqueous solution, water irradiated by UV generates superoxide which subsequently reacts with the nitric oxide to form peroxyxynitrite. This compound further reacts with luminol and produces strong chemiluminescence in a luminol-hydrogen peroxide chemiluminescence system [2,115]. The limits of detection for this method ranged from 1.5 – 3.0 ng/L [115].

Various alternative methods have been developed to quantify NAs in water matrices that employ fluorescence detection, chemiluminescence or nitrogen detectors [117–122]. HPLC methods that make use of a photochemical reaction and chemiluminescence for detection (HPLC-PR-CL) and quantification of NAs in water have been developed, with detection limits as low as 0.2–2 ng/L, comparable to those of conventional GC–MS and LC–MS methods [117,119,122]. **Table 5** lists some of the different LC-based methods hyphenated to other detectors besides MS, that were produced from countries outside the African continent between 2010–2020.

Table 5: Analysis of nitrosamines in various water matrices by liquid chromatography coupled to other detectors (between 2010–2020).

DBP	Water sample type	Extraction method	Method for analysis	LC column	Eluent	Detection limits (ng/L)	Recoveries (%)	Country	Reference
NDMA, NMEA, NDEA, NDPA, NDBA, NPyr, NPip, NMor, NDPhA	Drinking and pool water	SPE	HPLC-PCUV	Tosoh Bioscience TSKgel G2500PWxl SEC column (300 x 7.8 mm, 7 µm)	100 % of 25 mM phosphate buffer (pH 6.7) to 65%/35% acetonitrile	4–28	57–83	Switzerland	[121]
NDMA	Drinking water	SPE	HPLC-hv-CL	Capcell Pak C18 MGII column (5 µm, 100 mm + 250 mm length; 4.6 mm i.d)	10 mM phosphate buffer–methanol (99:1, v/v, pH 6.9)	0.2	96–98	Japan	[120]
NDMA	Wastewater	No extraction	HPLC-PR-CL	Octadecylsilyl (ODS) column	10 mM phosphate buffer (pH 7) with 1% methanol	0.2–2	--	Japan	[117]
NDMA, NMEA, NPyr, NMor	Surface water and recycled water	No extraction	HPLC-AEM-PR-CL	C18-AQ column (5 µm, 250 mm length; 4.6 mm i.d)	1 mM phosphate buffer–methanol, 95:5, v/v, (pH 6.9)	0.42–1.4	--	Japan	[119]
NDMA, NMEA, NPyr, NMor	Drinking and wastewater	No extraction	HPLC-PR-CL	InertSustain AQ C18, (5 µm, 250 mm length; 4.6 mm i.d)	1 mM phosphate buffer with 5% methanol	0.4–1.1	--	USA	[122]
DBA, NDEA, NDMA, NMEA, NMor, NPip, NDPA, NPyr	Drinking water	SPE	HPLC-FD	Microsorb-MV Si column (250 mm long, 4.6 mm i.d., 5 µm particle diameter)	Acetonitrile and water (60:40, v/v)	0.5–1.4	95.1–100.9	Korea	[118]

HPLC–anion exchange module–photochemical reactor–chemiluminescence (AEM–PR–CL), HPLC – fluorescence detection (HPLC–FD), HPLC–Post Column UV photolysis/Griess reaction (HPLC–PCUV), HPLC – chemiluminescence detection (HPLC – hv– CL).

7. Occurrence of *N*-nitrosamines in African water bodies

There is a paucity of research conducted that is related to the determination of NAs in drinking water in Africa, as discussed in Section 2. Considering the population distribution on the African continent, most people are predominantly located in rural areas [123]. Rural areas in Africa are typically underdeveloped with minimal or no infrastructure, poor sanitation, and no potable drinking water. The people in these areas drink water from dams, lakes, or river streams that may possess harmful pathogens that could potentially threaten their well-being [124,125]. The water they drink may be impacted by industrial wastewater, runoff from agricultural fields, and by impurities due to anthropogenic activities. In some regions of the African continent, these people are provided with chlorine-based products (CBPs) to disinfect their water [21,23]. The CBPs may react with dissolved organic matter in the water and yield a variety of DBPs. These people may be exposed to carcinogenic chemical water pollutants such as NAs or their precursors.

To the best of our knowledge, Mhlongo and coworkers are the only researchers that have published research on NAs in drinking water across the whole African continent to date. In this work, three South African WTPs were monitored, namely, Rand Water (Gauteng Province), Sedibeng (Free State Province), and Magalies (North-West Province). Qualitative analysis of NAs in the samples collected from these WTPs was done, in which SPME was employed as a sample preparation step prior to analysis by GC–MS. PDMS/DVB coated fibers were used and direct immersion of the fiber in the water samples was performed instead of employing headspace sampling. The disinfection process employed at Sedibeng and Magalies involved chlorination and chloramination whilst at Rand Water, it was mainly chlorination. Detection of trace amounts of NDMA in one of the WTPs (Sedibeng) and its distribution network was noted, whilst there was no NDMA detected in the water samples from the other two WTPs. Cyclodextrin (CD) polymers were synthesized and used to remove NDMA from the water collected at Sedibeng. A decrease in NDMA peak intensities was noted after the water samples were passed through SPE cartridges that contained the synthesized CD polymers. This suggested that CD polymers can be employed at WTPs as means to remove NDMA from water [13].

8. Conclusion and future outlook

In Africa, there is a paucity of information regarding the monitoring and ecotoxicology of NAs in the aquatic environment and drinking water. This can be attributed to a lack of adequate research

facilities, infrastructure, and funding. Considering the potential adverse health effects that may be caused by these pollutants, there is a need for African researchers to focus on the monitoring of nitrosamines in water, especially due to the disinfection treatment methods used including chloramination. There are millions of people across the African continent living in rural areas, with poor sanitation and unsafe drinking water. These people may inadvertently be exposed to NAs and other pollutants that may have adverse health effects. More comprehensive studies will provide data and information required to set permissible limits and advise suitable mitigation steps to avert further pollution of drinking water sources in Africa and exposure to disinfection byproducts. There is also a need to develop methods that are suitable for widespread implementation in developing countries. Advanced analytical instruments are required for the detection and quantification of NAs in water at environmentally relevant concentrations. Therefore, the support of governments and funding bodies is required to allow for the purchase, installation, and maintenance of the instruments required for extensive research in this regard.

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