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Endocrine disruptors concentrations in drinking water samples from México and their health implications

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Research Article

Keywords: drinking water, nonylphenol, surfactant, emerging pollutant, Mexico, gas chromatography-mass spectrometry

Posted Date: January 18th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2394953/v1

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Abstract

Nonylphenol ethoxylate, used mainly in detergent production, is transformed under environmental conditions into the endocrine disruptor, Nonylphenol (NP). 4-Nonylphenol (4-NP) was identified in drinking water samples from a developing country without regulations (Mexico) to establish exposure and environmental concentrations. The extraction and quantification of 4-NP were performed using solid phase microextraction (SPME) combined with gas chromatography-mass spectrometry (GC-MS). A derivatization process was carried out to increase sensitivity in the method. Eighty percent of the samples showed concentrations above the detection limit, and 57% of the samples presented concentrations above the Directive on the Quality of Water intended for human consumption (0.3 µg L-1). Our data gives an overview of the exposure levels and the environmental and health risks that these may represent. According to the results, continuous monitoring and regulations of this pollutant are highly recommended to prevent exposure and ecological and health effects.

1. Introduction

Water quality research has focused on nutrients, microbial contaminants, heavy metals, and priority pollutants. Recently, a new type of pollutants (emerging pollutants) has been recognized (EPA 2005). Currently, more than 1036 emerging pollutants are listed in the European Aquatic Environment NORMAN Network (www.norman-network.net) significantly affecting water quality and causing potential public health and security problems (Bilal et al. 2019). However, due to its recent detection and low concentrations (µg L^{-1}, ng L^{-1}), there is a gap in the knowledge about its occurrence, fate, behavior, risk assessment, and ecological and human effects (Vargas-Berrones et al. 2020a). In addition, population growth has resulted in major environmental impacts, being water bodies the most affected in terms of availability and quality (Peña-Guzmán et al. 2019). One of the most reported organic pollutants in wastewater, effluents, rivers, drinking water, sediments, and soil are the Alkylphenol Ethoxylates (APEs) (Belmont et al. 2006, Chen et al. 2013, Dong et al. 2015, Jie et al. 2017, Van Zijl et al. 2017). APEs are non-ionic surfactants widely used in detergent manufacturing, plastic additives, emulsifiers, and pesticides (Ferrara et al. 2011). Above 95% of APEs are removed from wastewaters with conventional treatment plants processes; however, the main problem is the formation of resistant metabolites classified as endocrine disruptors (Petrović et al. 2003). The most used APE is the nonylphenol ethoxylated (NPE) due to its capacity to form micelles in solution (Araujo et al. 2018). After their disposal, NPE is degraded by microorganisms or ultraviolet light under environmental conditions transforming them into nonylphenol (NP), including mainly 4-nonylphenol (4-NP) (Cheng et al. 2017). NP is classified as an endocrine disruptor which are external agents that interfere with the formation, elimination, transport, attachment, activity, or displacement of natural hormones that maintain homeostasis development, reproduction, and behavior (EPA 1997). Endocrine disruptors are hardly reviewed and regulated, so there is scarce information regarding their occurrence, fate, and health impacts (Gavrilescu et al. 2015). Therefore, NP has been included as a priority pollutant by some authorities. The Water Framework Directive of the European Union allows maximum concentrations in surface water of 2 µg L^{-1}

(European Union 2013), and the Environmental Protection Agency (EPA) of the United States establishes a maximum concentration of 6.6 μg L^{-1} in surface water (EPA 2005). Also, regulations to restrict the use of NPE in industries have been introduced. For example, the European Union (EU) with the Directive 2003/53/EC establishes that NPE "…may not be placed on the market or used as a substance or constituent of preparations in concentrations equal or higher than 0,1 % by mass…" (Union 2003), and Directive 775/2004(02/2076) prohibits the use of NPE in pesticides formulations (Union 2006). On the other hand, the EPA added NPE to the Toxics Release Inventory (TRI) list and meets the toxicity listing criteria of the EPA´s Emergency Planning and Community Right-to-know Act (EPCRA) section 313(d)(2)(C) indicating that NPE is highly toxic to aquatic organisms (EPA 2018). However, regulations in developing countries that restrict levels of NP in water are null, and their health and environmental effects are not well understood (Shannon et al. 2008).

The main exposure pathway of NP is through food and water intake, which leads to bioaccumulation and biomagnification. Effects of NP exposure in animals have been previously reported in concentrations from 1 to >195 μg L^{-1} (Lussier et al. 2000, Scaia et al. 2019, Tabassum et al. 2017); however, effects in humans are still debated and require more investigation. Some studies have suggested potential health effects like decreased sperm count, reproductive malformations, immune deficiency, an increase in prostate, breast, ovarian and testicular cancer, neurological effects, poor intellect development in children, and psychological effects being the more vulnerable population fetuses and newborns (Bolong et al. 2009, Lussier et al. 2000, Tijani et al. 2016). The predicted no-effect concentration (PNEC) of NP has not been established because there is not enough toxicity data, and the specific mechanism in organisms is still unclear (Bakke 2003). Therefore, the World Health Organization (WHO) suggests a maximum concentration of 0.3 μg L^{-1} in drinking water based on the precautionary values that comply with existing environmental quality standards (WHO 2017). There is a current concern about the future and transport of NP through the environment and humans because of the continuous detection and identification of NP in water sources. Thus, the objective of this study was to monitor the concentrations of 4-NP in drinking water from countries without regulation (Mexico) to demonstrate potential human health risks from water intake (**Figure 1**). It is paramount to implement monitoring strategies in water to contribute to the generation of regulatory framework in developing countries due to the toxicity associated with NP and the extensive use of NPEs.

2. Materials And Methods

2.1 Reagents and chemicals

Stock standard solution of 4-NP (1000 μg L-1) was prepared in acetone and stored in the dark at -40ºC until further analysis. SPME fiber DVB/CAR/PDMS (50/30 μm stableflex divinylbenzene/carboxen/polydimethylsiloxane) was supplied by Supelco (Edo. Mexico) and it was conditioned before its use following the manufacturer´s instructions. A 0.1 M hydrochloric acid (HCl) solution (JT Baker, Edo. Mexico), sodium chloride (NaCl) (JT Baker, Edo Mexico), N-Methyl-bis(trifluoroacetamide) (MBTFA) ≥ 97.0% GC (Sigma Aldrich, Edo. Mexico), and Milli-Q deionized water (18.3 MΩ, Millipore) were used for the derivatization process. Samples were analyzed in a gas chromatograph (GC) (Agilent 6890) coupled to a mass spectrometry detector (MS) (Agilent 5975) in electron impact ionization mode (EI). The injection port was operated in splitless mode with a 0.75 mm liner without glass wool. GC separation was performed on a HP 5MS (60 m x 0.25 mm x 0.25 µm) column (Agilent). Helium, used as carrier gas, was controlled at a flow rate of 1 mL min-1 and 36 psi. The injection port temperature was set at 230ºC, and the oven temperature program used was as follows: 90ºC (2 min), 180ºC (30ºC min-1), 200ºC (1ºC min-1), 230ºC (30ºC min-1) and held for 5 min with a run time of 31 min. The tune parameters were: emission: 34.6; energy: 69.9; repeller: 26.6 and EMVolts: 1341. The SCAN mode (50–500 m/z) was used to identify the compound. The identification and quantification ions were selected for SIM mode (203/316 m/z). Results were obtained and processed with Chemstation Software (Agilent).

2.2 Sampling preparation

Directed monitoring of drinking water samples was performed. Since tap water is not potable in Mexico, water samples were collected from jugs of different water purifiers in Mexico. One-liter plastic bottles previously rinsed with Milli-Q water were used. No detergent was applied to prevent contamination. Immediately after sampling, they were stored in the dark at -20°C until further analysis.

2.3 4-NP quantification

4-NP quantification was performed based on the methodology described by Vargas-Berrones et al (Vargas-Berrones et al. 2020b). The lineal range ($r^2 = 0.99$) of the method was from 0.5 to 50 µg L^{-1}, the detection (LOD) and quantification (LOQ) limits were determined by blank signal and the obtained values were 0.01 µg L^{-1} and 0.15 µg L^{-1}, respectively. One milliliter of water sample, 20 µL of HCl (0.1 M), and NaCl (3%) were added to a 10 mL sealed amber vial with gentle agitation. HCl and NaCl were used to adjust pH and enhance ionic strength, respectively. Solid phase microextraction (SPME) was carried out with a DVB/CAR/PDMS (50/30 µm stable flex divinylbenzene/carboxen/polydimethylsiloxane) sorbent. The fiber was exposed to the headspace at 80°C for 20 min magnetically stirred at 600 rpm. After the extraction of 4-NP, a derivatization process with N-Methyl-bis(trifluoroacetamide) (MBTFA) was carried out to improve the volatility and sensitivity of the method. This consisted of exposing the fiber to the headspace of a solution of acetone (1 mL) with MBTFA (100 µL) at 60°C for 10 min magnetically stirred at 600 rpm. After derivatization, samples were analyzed by gas chromatography (GC) (Agilent 6890) coupled to a mass spectrometry detector (MS) (Agilent 5975) in electron impact ionization mode (EI).

3. Results And Discussion

Concentrations in drinking water from different water purifiers are shown in Table 1.

Table 1
Concentrations of 4-NP in different samples of drinking water from water purifiers of countries without regulation (Mexico).

Sample	Concentration	Sample	Concentration	Sample	Concentration
1	1.33	21	0.47	41	3.05
2	<LOD	22	0.89	42	3.42
3	2.32	23	0.19	43	0.79
4	2.64	24	0.10	44	1.50
5	6.08	25	0.12	45	2.48
6	40.29	26	0.40	46	1.42
7	3.99	27	0.13	47	0.85
8	<LOD	28	0.37	48	4.62
9	<LOD	29	3.66	49	0.40
10	<LOD	30	0.14	50	0.09
11	<LOD	31	0.11	51	0.22
12	<LOD	32	2.99	52	2.17
13	<LOD	33	0.91	53	0.84
14	<LOD	34	0.20	54	0.95
15	0.85	35	0.23	55	0.31
16	<LOD	36	0.94	56	4.19
17	<LOD	37	3.34	57	0.25
18	<LOD	38	1.83	58	0.17
19	<LOD	39	6.43	59	0.16
20	15.29	40	1.82	60	0.09

*Units: μg L^{-1}; LOD: 0.01 μg L^{-1}

Values above the LOD were detected in 80% of the collected samples, and 57% of the samples presented concentrations above the Directive on the quality of water intended for human consumption (0.3 μg L^{-1}) (WHO 2017). Reported values are similar to previous studies (Table 2).

Table 2
Concentrations of 4-NP in drinking water from different countries

	Country	n	Min	Median	Max	Reference
Drinking water	Mexico	5	<LOD	2.48	6.08	(Vargas-Berrones et al., 2020b)
	China	15	0.01	0.05	2.7	(Shao et al., 2005)
	Czech Republic	6	0.029	0.0335	0.045	(Pernica et al., 2015)
	China	62	ND	0.027	0.558	(Fan et al., 2013a)
	Italy	35	< 0.0077	0.0149	0.084	(Maggioni et al., 2013)
	China	21	0.108	0.170	0.298	(Li et al., 2010)
	China	6	0.196	0.502	1.073	(Li et al., 2010)
	France	8	<LOQ	0.0159	0.0594	(Dupuis et al., 2012)
	China	8	0.0082	0.577 (media)	0.918	(Jie et al., 2017)
	Taiwan	18	0.017	0.032 (media)	0.195	(Cheng et al., 2016)
	Japan	9	0.016	0.076	0.078	(Toyo et al., 2000)
	Greece	6	NR	NR	0.15	(Amiridou and Voutsa, 2011)
	United States	18	NR	100	93	(Benotti et al., 2009)
	United States	12	NR	NR	1.1	(Stackelberg et al., 2007)
	Germany	10	0.0025	0.0066	0.016	(Kuch and Ballschmiter, 2001)

*Units: µg L^{-1}; LOD: limit of detection; LOQ: limit of quantification; ND: not detected

Occurrence of NP has increased significantly because of its great industrial demand (Silva et al. 2018). It is difficult to determine the source of contamination in water samples; however, the most common use of NPE is in detergents (Kim et al. 2019, Priac et al. 2017). For example, 41% of 90 domestic detergents in Taiwan contained from 0.2 to 21% of NP (Huang et al. 2014). This suggests that the presence of NP in water is mainly due to the use of detergents, tourism, people washing clothes, illegal water discharges in rivers, and inadequacy and lack of maintenance in drainage networks (Fenet et al. 2003, Gambolati et al. 2006). In countries where NP and its ethoxylates are not regulated, like Mexico, it is common to find these compounds in detergents due to their excellent surfactant properties (Merrettig-Bruns &Jelen 2009) and low cost (Perron &Juneau 2011). In this country, water jugs are washed each time before being refilled.

So, a poor rinse may explain the high concentrations of NP found in drinking water. Also, conventional water purification processes do not remove endocrine disruptors like NP (Van Zijl et al. 2017), and NPE may be degraded into shorter ethoxylated chains in the treatment processes (Soares et al. 2008). Furthermore, the chlorination process in water supply systems forms byproducts like monochloro-NP (CNP) and dichloro-NP (DCNP). These compounds have previously demonstrated estrogenic activity (Fan et al. 2013, Takemura et al. 2005).

Previous studies have demonstrated adverse effects in biota (Table 3) and humans (Table 4). However, more research in this regard is paramount to understanding the risks and effects due to the exposure of this xenobiotic. A risk assessment regarding NP exposure through water intake could be performed as future work with these results. The estimation of the non-carcinogenic risk obtained by the hazard quotation (HQ) for water intake would indicate the potential risks of adverse health effects according to the values established by the EPA (0.1 mg kg^{-1} day^{-1}) (Bakke 2003). Risk assessment regarding NP exposure has been previously reported in sludge (González et al. 2010, Kollmann et al. 2003, Roberts et al. 2006), surface water, wastewaters (Chen et al. 2014, Gao et al. 2014, Jin et al. 2014), and aquatic organisms (Lee et al. 2015, Pachura-Bouchet et al. 2006, Servos et al. 2003). Nevertheless, limited information about risk assessment in humans is available because of high analysis costs and the lack of scientific data in this area (Tijani et al. 2016). The United Nations Environment Programme has established that the highest estimated value for human exposure through the environment is 5.31 x 10^{-3} mg $kg^{-1}day^{-1}$ and the maximum intake combined from the air, water, and food exposure is 6.4 mg $kg^{-1}day^{-1}$. However, there is uncertainty in the daily intake estimated making it difficult to determine accurate predictions in this regard (Bontje D. 2002). These values have only been considered in adults though children are more vulnerable to hormone impacts caused by environmental xenobiotics. This vulnerability is associated with physiological differences like constant increase in weight, higher respiration and ventilation range, higher relative consumption of water and food, and faster brain development (Longnecker et al. 2003, McElroy 2008, Mishra &Vankar 2002, Norgil Damgaard et al. 2002, Selevan et al. 2000). Previous studies have shown that NP is ubiquitous in baby food representing a daily intake from 0.23 to 0.65 μg kg^{-1} bw d^{-1} (Raecker et al. 2011). However, low concentrations in humans may have virtually no chance to compete with natural hormones in the unions of free receptors, implying that the health risks of endocrine disruptors may be insignificant (Autrup et al. 2020). Therefore, exposure effects of endocrine disruptors at low doses during the development of humans have been underestimated (Welshons et al. 2006). A greater potential risk for infants and babies is expected due to the higher vulnerability to hormonal effects and their higher relative NP consumption through food and water compared to adults; also, a reference dose for infants has not been established yet.

Table 3
NP and 4-NP concentrations in different species.

Organism	Specie	Compound	Concentration	Effects	Reference
Plants	*Vigna radiata*	NP	1000 mg/kg	Leaf vein necrosis	(Kim 2019)
Fish	*Orechromis niloticus*	NP	16 µg/L	Alterations in the female gonads	(Rivero 2008)
	Bream and black rockfish	4-NP	50 µg /L	Reduced gonadosomatic index	(Saravanan 2019)
	Oncorhynchus mykiss	NP	1 µg /L	Alterations in the immune system	(Hébert 2009)
	Xiphophorus maculatus	NP	> 0.96 mg/L	Negative effects on testicular morphology and male fertility	(Kinnberg 2000)
Oyster	*Crassostrea gigas*	4-NP NP	0.1–10 µg /L	Development of abnormalities	(Nice HE 2000)
Oyster	*Crassostrea gigas*	4-NP NP	1-100 µg /L	Increased incidence of hermaphroditism	(Nice HE 2003)
Crustacean	*Elminus modestus*	4-NP	0.1–10 µg /L	DNA adduct formation, mutations and genomic rearrangements	(Atiezar FA 2002)
Amphibians	*Xenopus laevis*	NP	0.1–10 µg /L	Increased mortality, morphological deformations, and increased apoptosis	(Bevan CL 2003)
Mice	Ratones	NP	50–500 µg /L	Negative effects on spermatogenesis and sperm quality	(Kyselova V 2003)

Table 4
Health effects in human by NP and/or 4-NP exposure

Sample	Analyte	Concentration	Exposure	Effects	Reference
Semen	NP	< 7 pg/mL	Normal food and water intake	No significant exposure	(Katayama et al. 2003)
Urine	4-NP	< 110 ng/mL	Normal food and water intake	Not available	(Inoue et al. 2003)
Human milk	NP	< 56.3 ng/mL	Normal food and water intake	No significant exposure	(Ademollo et al. 2008)
Human breast carcinoma cell line (MCF-7)	NPEOs	NA	100–200 μM	γ-H2AX generation caused by direct chemically induced DNA damage	(Zhao et al. 2015)
Human breast carcinoma cell line (MCF-7)	NPEOs	NA	100–500 μM	Generation of γ-H2AX means the formation of DSBs (DNA damage)	(Toyooka et al. 2012)
CHO-K1 cells	NP	NA	0.025-0.1 μM	DNA damage (sister-chromatid exchange)	(Tayama et al. 2008)
Jurkat cells	4-NP	NA	Not specified	Induced loss of mitochondrial membrane potential, caspase-8 activation, and internucleosomal DNA fragmentation	(Yao et al. 2007)
Jurkat cells	NP	NA	9.72–38.9 μM	Induced DNA damage	(Park &Choi 2007)
Saccharomyces cerevisiae cells	4-NP	NA	50 mg/L	Induced significant cytotoxic effect	(Frassinetti et al. 2011)
Spermatozoa	NP	NA	5 μL	Oxidative stress and DNA damage	(Bennetts et al. 2008)

*NA: Not applicable; NP: Nonylphenol; 4-NP: 4-nonylphenol; NPEOs: Nonylphenol Ethoxylates

Some limitations were considered when interpreting the results of this study. 1) Only 4-NP was considered because of its commercial availability (Calafat et al. 2005). It is also important to acknowledge that NP is a mixture of approximately 20 para-substituted isomers with different branched alkyl chains and with intermediate structures compounds that make the mixture more toxic (Ieda et al.

2005, Ruß et al. 2005, Thiele et al. 2004, Wheeler et al. 1997). Previous studies have reported that 4-NP only represents 2.2% of the total mass in water, and represents only 26% of all the risk (Fenner et al. 2002). Moreover, NP isomers have relevant differences among them regarding their disruptive endocrine activity. Therefore, it is not adequate to take any isomer as a general reference to establish models, activities, structure relations, and/or risk assessments (Preuss et al. 2006). Thus, to achieve a complete analysis, it would be necessary to examine all isomers in the sample. Even though our study only considers 4-NP, it provides a reference point and allows to establish minimum exposure concentrations. 2) Other pollutants classified as endocrine disruptors may be found in drinking water. Consequently, it may be practically impossible to predict health problems caused by each compound since they can act independently or in synergy with others. For example, Bisphenol A (BPA) is a monomer used for polycarbonates and epoxy resin production. This product is used as a coating for food cans, water containers, water pipes, reusable milk containers, food storage vessels, and baby bottles. Its incomplete polymerization during manufacture and the temperature increment through bottling processes may cause the compound to leach into food and beverages (Markey et al. 2001). Accordingly, phthalates (PEs) are endocrine disruptors mainly used as plasticizers and in paints, adhesives, dyes, and cosmetics manufacture. Usually, PEs are incorporated into food and water through packaging and manufacturing processes (Serodio &Nogueira 2006). Good practices and environmental policies are needed to mitigate potential risks to human and ecologic health established on the precautionary principle approach, based on evidence of potential harm without compelling absolute scientific certainty.

4. Conclusions

According to the literature, this is the first monitoring of 4-nonylphenol in Mexico in drinking water samples. This study aimed to provide a reference to establish minimum NP exposure concentrations through water intake. An exposure scenario of 4-NP in drinking water is shown in countries without regulations (Mexico). Our results demonstrate that 4-NP was detected in 80% of the water samples. Fifty seven percent of the samples presented concentrations above the Directive on the quality of water intended for human consumption. Although these results may not represent a significant risk for the consumption of NP through water intake, there is no consensus among the scientific community about this issue. Moreover, it is critical to acknowledge that current parameters are considered only for adults, and water intake in children may represent a greater risk. Efforts in investigation and strategies to promote consciousness of the impact of NP as a pollutant are required. These developments would help to establish a responsible approach regarding the use and handling of NP and its ethoxylates. The search for environmental quality to protect human and ecological health is a compulsory long-term challenge shared by most modern societies and civilizations worldwide.

Declarations

Acknowledgements

This work was supported by the National Council for Science and Technology – Initial Academic Postdoctoral Research CVU 815662 and CB-CONACYT (#2017-2018- A1-S-28176).

Ethical Approval

The paper reflects the authors' own research and analysis in a truthful and complete manner.

Consent to Participate and Publish

All persons who meet authorship criteria are listed as authors, and all authors consent to participate and publish in the work to take public responsibility for the content

Author Contributions

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Conceptualization, Sampling, Analytical methods, Writing and manuscript editing by Karla Ximena Vargas-Berrones; Analytical methods by Juan Manuel Izar-Landeta, Luis Armando Bernal-Jácome, and Jennifer Iridian Sánchez-García; Analytical methods and Conceptualization, Writing- Reviewing, Editing and Funding by Rogelio Flores-Ramírez.

Funding

The authors acknowledge grants and fellowships from the National Council on Science and Technology-Sectoral Research Fund for Education Basic-Science # A1-S-28176 and Initial Academic Postdoctoral Research CVU 815662.

Disclosure of potential conflicts of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Availability of data and materials

Data available on request from the authors

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Figures

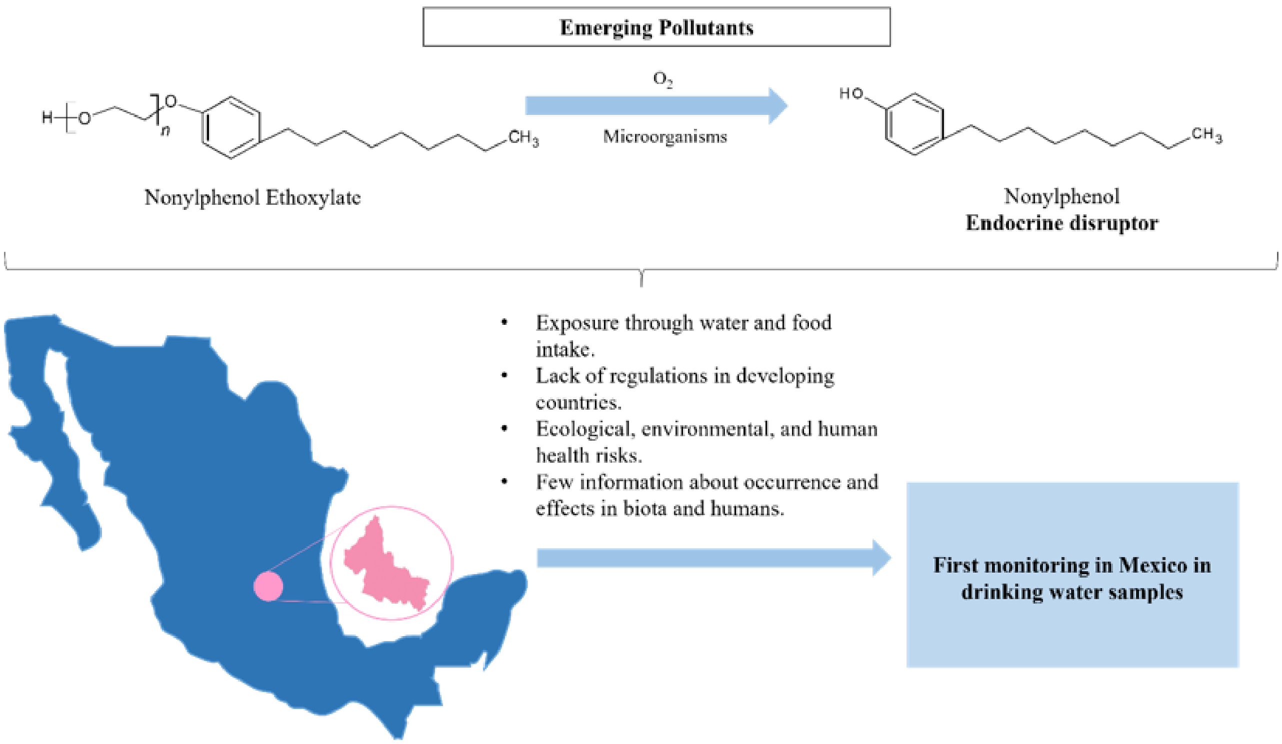

Figure 1

Context of nonylphenol analysis in drinking water samples to determine potential exposure risks through water intake in developing countries.