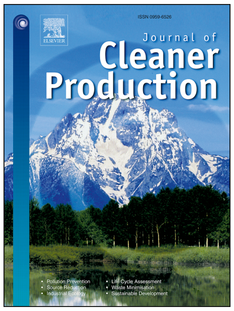

A non-threshold model to estimate carcinogenic risk of nitrate-nitrite in drinking water

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I have appended the modified the "Credit Author Statement" below for your consideration:

CRediT authorship contribution statement

R.N. and C.J conceived the study conceptually. Data collection and analysis were carried out by F.F., S.A (Fourth author), and M.M. The health risk models were driven by R.N., F.F. and S.A (Fourth author). The first draft of the manuscript was prepared by R.N., F.F. and S.A (Fourth author). The funding acquisition was made by R.N. and F.F. The analyses and results were supervised and validated by R.N., C.J., F.G., M.H., M.R.V.N., S.M.B. and S.A (Last author). All figures were drawn by R.N., S.M.B., and M.M. All authors read and approved the final version of the manuscript.

A non-threshold model to estimate carcinogenic risk of nitrate-nitrite in drinking water

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Abstract

Understanding nitrate–nitrite (NO_3^-–NO_2^-) levels in drinking water and associated non-carcinogenic and carcinogenic health risks are essential to protect public health safety. The non-carcinogenic risk assessment of NO_3^-–NO_2^- in drinking water has been well documented, however, there remains a knowledge gap in understanding and quantification of the carcinogenic risk of NO_3^-–NO_2^-. This study develops a non-threshold–based model for estimation of carcinogenic risk of NO_3^-–NO_2^- ingested through drinking water for a densely populated urban area with a case study of Tehran's potable water (TPW). In this regard, 200 tap water samples from different parts of the city were taken in wet (May 2018) and dry (October 2018) periods to determine NO_3^-–NO_2^- concentration in the TPW and the associated health risks across different grounds of end-users. Sampling results reveal higher concentrations of NO_3^-–NO_2^- during the dry period, which can be associated to the significant contribution of nitrogen–rich groundwater in supplying the city's water demands during the dry period. Findings suggest concerns associated with the non-carcinogenic risk of NO_3^-–NO_2^- in the TPW, especially for children. More than 55% of the samples taken during the dry period show a positive carcinogenic risk for different groups of end-users (68% for men, 72% for women, and 56% for children) whilst just 8% of the samples are deemed unsafe with regards to the permissible NO_3^- level in drinking water, i.e. 50 mg/L. Approximately, 45% of the samples taken during the wet period show a positive carcinogenic risk for adults whilst the maximum concentration of NO_3^- was about 23 mg/L, i.e. two times less than the permissible level in drinking water. The findings emphasize on the necessity of reducing the permissible level of NO_3^- in drinking water, set out by the existing water quality standards, to safeguard public health against the carcinogenic risks. The model developed within this study recommends the urgent need for reduction of NO_3^- level in Tehran's water resources to protect public health of over 13 M population who incessantly use the TPW.

Keywords: Carcinogenic risk; Nitrogen–rich groundwater resources; Potable water; Water quality; Tehran.

1. Introduction

Nitrate (NO_3^-) contamination is one of the main concerns threatening clean water production for during the Anthropocene (Fewtrell, 2004; Burow et al., 2010; Gu et al., 2013; Sarkar et al., 2021; Zhang et al., 2021). The maximum permissible level of NO_3^- in drinking water, i.e. 50 mg/L (WHO, 2008), was specified to safeguard against the Blue baby syndrome (also known as methemoglobinemia) in the early 1960s (Ward et al., 2018). Epidemiological studies have found the presence of NO_3^- in drinking water can be associated with elevated carcinogenic risks and adverse birth consequences (Brender et al., 2004; Ward et al., 2005; Brender et al., 2013; Villanueva et al., 2014; Jones et al., 2016 and 2019; Stayner et al., 2017 and 2021; Ward et al., 2018; Temkin et al., 2019). NO_3^- ingested through drinking water can react with dietary amides/amines to create nitrosamines with carcinogenic potency (IARC, 2010), even in concentrations less than the permissible level of NO_3^- (Temkin et al., 2019). This value has been reported to be ~22 mg/L (De Roos et al., 2003) and even ~3 to ~9 mg/L of NO_3^- in drinking water (Schullehner et al., 2018; Espejo-Herrera et al., 2019).

Although epidemiological evidence suggesting the elevated concentration of NO_3^- in drinking water is associated with the carcinogenic risks (IARC, 2010), there is no a global consensus on this issue due to the complex conversion processes of NO_3^- to nitrosamines (Powlson et al., 2008; Ward et al., 2018 and 2021). This viewpoint is reflected in modelingbased studies associated with health risk assessment of NO_3^- in drinking water, where almost all of the non-epidemiologic publications aimed to only determine the non-carcinogenic risks induced by this pollutant (e.g., Hu et al., 2005; Proca et al., 2009; Su et al., 2013; Chen et al., 2016; Sadler et al., 2016; Su et al., 2018; Adimalla and Li, 2019; Adimalla, 2020; Liu et al., 2021; Xiao et al., 2021; Zhang et al., 2021). For estimation of carcinogenic risk of NO_3^-, Shephard et al. (1987) suggested a non-threshold model that determines the worst-case dose-response at low dosages. Shepard's model supposes the health risk is linearly correlated with nitrosamines that are carcinogenic. Although Shephard's model provides good information on the possible carcinogenic risk of NO_3^- in drinking water, quantification of endogenous nitrosamines is poorly understood. This study aims to develop an exposure-based model for estimation of carcinogenic risk of NO_3^- ingested though drinking water. The proposed model is tested for the case study of Tehran's potable water (TPW), the densely populated capital of Iran with over 13 M population.

Two sampling campaigns were conducted during both dry and wet periods, to determine nitrate–nitrite (NO_3^-–NO_2^-) concentration in the TPW. Following the sampling campaigns, a non-threshold model based on the methodology suggested by Shephard et al. (1987) was developed to estimate the spatial and temporal carcinogenic risk of NO_3^-–NO_2^- for different groups of end-users who incessantly use the TPW. To better describe the estimated carcinogenic risks of NO_3^-–NO_2^- in TPW, the corresponding non-carcinogenic risks were also determined at different sampling points across the case study location using the model suggested by the U. S. Environmental Protection Agency (U. S. EPA, 1989). Given the current debate on the carcinogenic risks of NO_3^- ingested through drinking water (Ward et al., 2005; Van Grinsven et al., 2006; Powlson et al., 2008), this study provides strong evidence to support the idea of further tightening the permissible level of NO_3^-, to better safeguard the public health against the possible risks.

2. Materials and methods

2.1. Study area

Tehran, the capital of Iran, with an area of about 750 km^2, and constant and variable population of approximately 9 and 13 M, respectively, is located at the southern slope of Alborz Mountain. This city has an annual average precipitation and temperature of about 250 mm and 17 °C, respectively. Tehran's elevation varies from 1026 m in the south to 1846 m above sea level in the north (Fig. 1).

Tehran's water demand is supplied through Mamlo, Taleghan, Latyan, Lar, and Karaj dams with the total capacity of around 1.95 km^3 annually (Fig. 1), as well as groundwater sources that mainly located in the south of the city. Share of the surface water varies between 30% and 70% of the total water demand in Tehran during dry and wet periods, respectively. Surface water is transferred from the dams to seven water treatment plants to purify the TPW. For many years, the TPW was separately supplied through nitrogen–poor surface water and nitrogen–rich groundwater sources. To dilute the concentration of NO_3^- in TPW for the end-users, a water loop have been established that first mixes both surface and ground waters, and then the mixed water gets injected to the water distribution network. Nitrogen–rich groundwater sources are stored in the 151 reservoir tanks in Tehran and then added to the water distribution network after a simple pretreatment process (often disinfection).

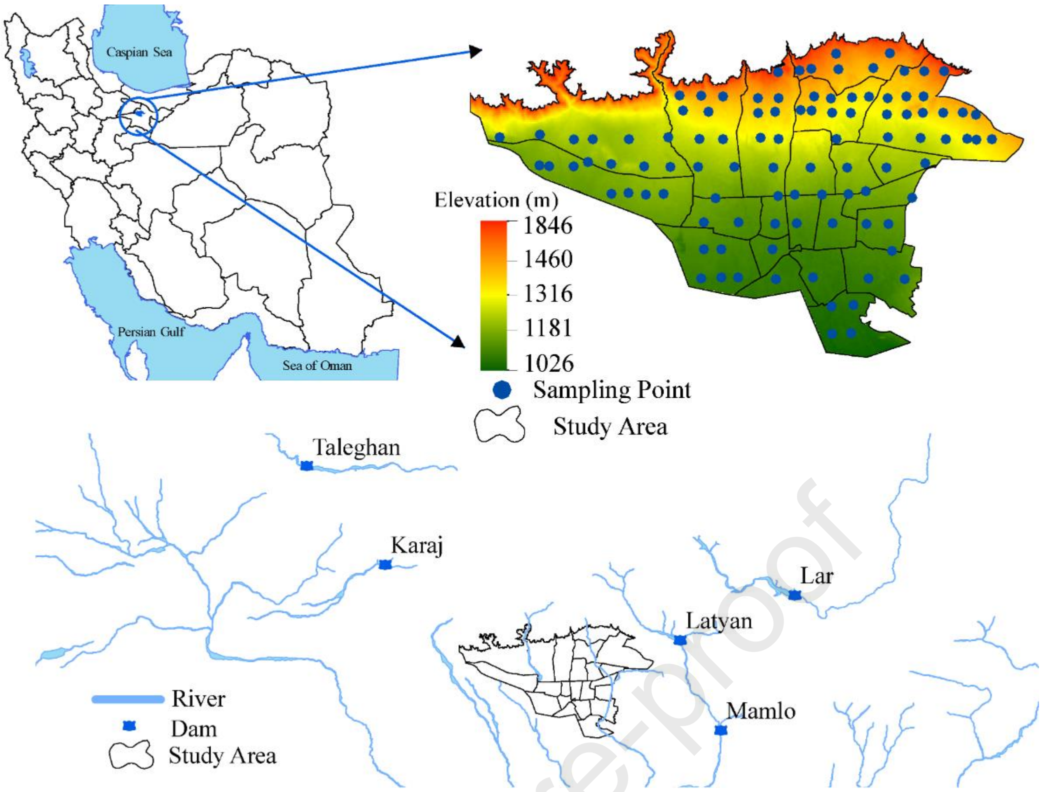


Figure 1: The study area, sampling locations and the geographical position of the main surface water reservoirs that contribute to the supply of Tehran's potable water (TPW).

2.2. Sampling

Analysis of drinking water quality analysis through sampling campaigns can provide the information required for detailed assessment of the NO_3^-–NO_2^- contamination risks in TPW. Previous studies examined the quality of water resources with a direct focus on waterworks (i.e. wells, rivers, and dam reservoirs), that partially supply drinking water for Tehran metropolis (Imandel et al., 2000; Torabian et al., 2000; Joekar-Niasar and Ataie-Ashtiani, 2009; Mohseni-Bandpei et al., 2018; Nejatijahromi et al., 2019). Although taking samples from the waterworks can provide useful information to determine the degree of exposure for end-users (Schullehner et al., 2017), they are not entirely representative of supplied water, given that the TPW comes from a mixture of both surface- and ground- waters. Another alternative is to take water samples directly from the outlet of water treatment plants (WTPs) to evaluate the suitability of drinking water and its related human health risk (Karavoltsos et al., 2008; Ward et al., 2010; Lautenschlager et al., 2013; Schullehner and Hansen, 2014). WTP's samples also cannot fully represent the water quality consumed by end-users in Tehran, given that:

(i) Nitrogen–rich groundwater sources are usually stored in reservoir tanks and later added to Tehran's water distribution network after a simple pretreatment (often disinfection) at different points of the network,

(ii) Tehran's water distribution network is relatively old which presumably results in the intake of NO_3^- at breaking points once pressure on the network is equal or less than zero at the time of water partitioning. Note that, due to the lack of centralized sewage collection systems, most areas in the city use pit latrines, resulting in soil pollution and leachate of contaminants to the groundwater. The bacterial communities in the soil can decompose the nitrogen–rich sewage into NO_3^- and NO_2^- (Jensen et al., 2014; Yin et al., 2019), which increases the possibility of leaking NO_3^- to Tehran's water distribution network at breaking points.

To ensure exact similarity between the samples taken and the water used by the end-users, samples were directly taken from tap water in homes across the city. The sampling was performed in both wet (May 2018) and dry (October 2018) periods, as the inter-seasonal variations in the share of nitrogen–rich groundwater and relatively nitrogen–poor surface water in supplying TPW are not the same. 100 samples were collected for each sampling period to cover the large geographical extent of the city (approximately 750 km^2) (Fig. 1). Sampling locations were selected in such a way to uniformly cover the entire city. For this purpose, the city was divided into 100 equal-sized square grids. Further, each grid was divided to eight sub-grids. Then, a tap water sample consisted of the mixed samples taken from eight sub-grids was selected as the representative of that grid. This process repeated for all the 100 grids to take the representative samples covering the entire area of Tehran megacity, during both dry and wet periods.

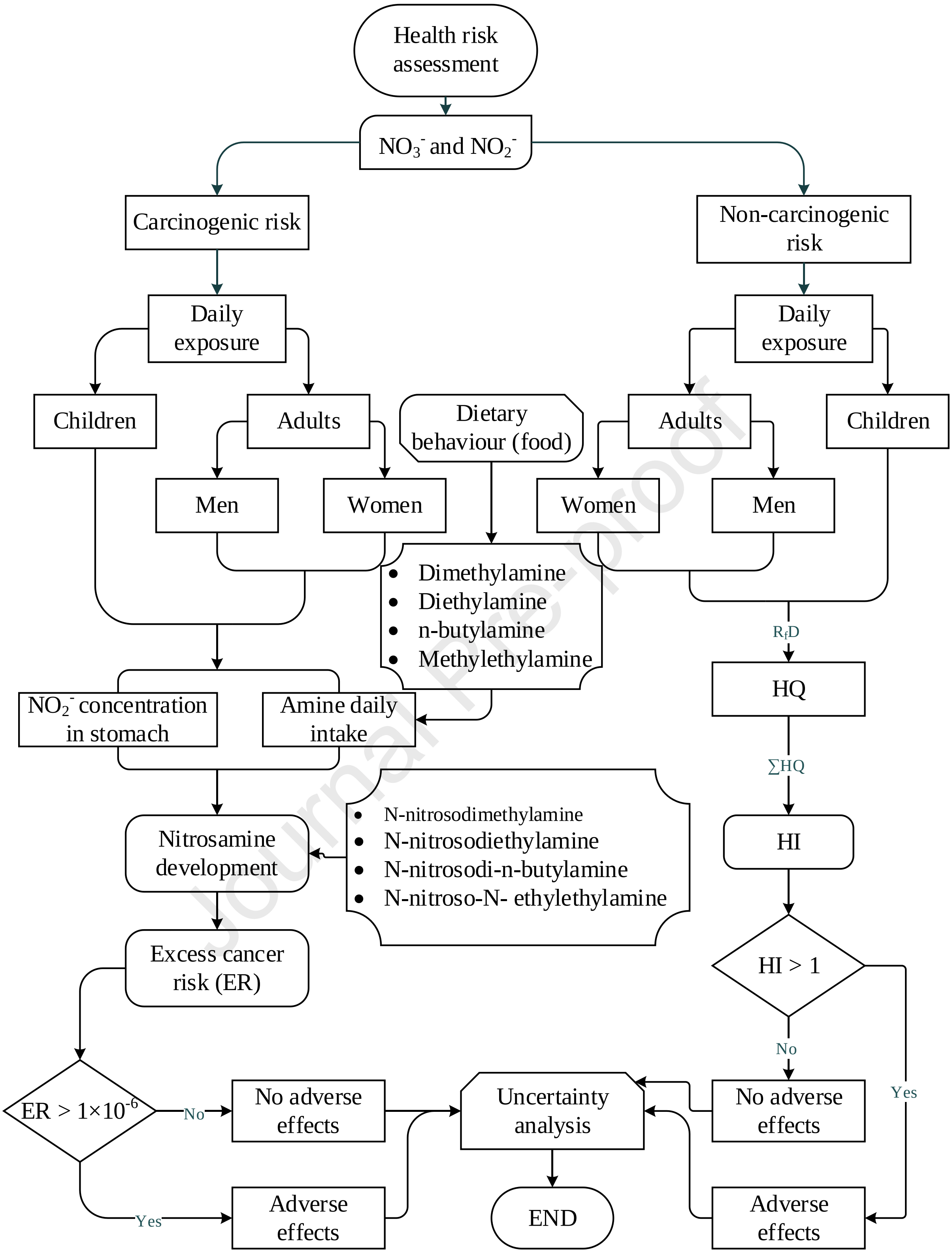
2.3. Sample analysis

Polyethylene bottles with the capacity of 1L were used for sampling and the samples taken were stored at 4 °C in a dark chamber and transferred to the laboratory for further analyses. Samples were then analyzed up to 48 h after the sampling collection. NO_3^- and NO_2^- concentration in the samples were measured using Hach DR 5000^{TM} UV-Vis Spectrophotometer with Hach method 10020 and 807 nm wavelength and Hach method 8507 with the wavelength of 410 nm, respectively. The detection limits of Hach methods 10020 and 8507 are 0.3 and 0.002 mg/L for NO_3^- and NO_2^-, respectively.

Distilled water samples (blanks) with zero concentration of NO_3^- and NO_2^- were used to control the quality of the results. Measurements were randomly repeated for 100 out of 200 samples taken in wet and dry periods. Acceptable recovery rate from 95% to 106% was observed for the duplicate analysis of the samples and blanks with a maximum standard deviation of 4.7%.

2.4. Health risk assessment

Human health is threatened by the existence of NO_3^- and NO_2^- ingested through drinking water. In this study, both non-carcinogenic risk (HI) and carcinogenic risk (ER) induced by NO_3^- and NO_2^- in the TPW are investigated. The process of determining the carcinogenic and non-carcinogenic human health risks is described by Fig. 2.



149

150 **Figure 2:** The process developed for determining the carcinogenic and non-carcinogenic

151 human health risks of NO_3^- and NO_2^- in Tehran's potable water (TPW).

152 *2.4.1. Non-carcinogenic risk of* NO_3^- *and* NO_2^-

In this study, the daily ingestion dose (DID) of NO_3^- and NO_2^- were determined using Eq. (1).

$$\mathrm{DID} = \frac{C \times DI}{BW} \tag{1}$$

where, *C* is the concentration of NO_3^- or NO_2^- (mg/L), *DI* denotes the water consumed by each person (L), and *BW* is the bodyweight of end-users (kg) (Aradpour et al., 2021).

Due to the lack of detailed information on *DI* and *BW* values for the case of Tehran, the reference values suggested by the U. S. EPA were adopted in this study (U. S. EPA, 1989). According to the U. S. EPA, *DI* value was chosen as 2 and 1 L/d for adults and children, respectively. The *BW* was chosen to be 78, 65, and 14.5 kg for men, women, and children, respectively. Duration of exposure to NO_3^- and NO_2^- was selected to be 365 d due to the circadian use of potable water by individuals (U. S. EPA, 1989). Then, the value of hazard quotient (HQ) was determined using Eq. (2):

$$\mathrm{HQ} = \frac{DID}{R_f D} \tag{2}$$

where, R_fD is the reference dose suggested to be 1.6 and 0.1 for NO_3^- and NO_2^-, respectively (U.S. EPA, 1989).

Total non-carcinogenic risk of NO_3^- and NO_2^- (HI) in the TPW was estimated by Eq. (3):

$$\mathrm{HI} = \mathrm{HQ}_{NO_3^-} + \mathrm{HQ}_{NO_2^-} \tag{3}$$

The $0 \leq$ HI ≤ 1 denotes the safe conditions whereas HI >1 represents dangerous conditions (U. S. EPA, 1989).

Due to the lack of information needed to assess the health risk of NO_3^- and NO_2^- in the TPW and consequential use of reference values recommended by the U.S. EPA (1989), the results of this study may contain some uncertainty for the people who live in Tehran. To account for the uncertainty, the risk levels were also recalculated for two different conditions (scenarios). Then, they were compared with the risk level calculated for the baseline condition (reference scenario). The first scenario includes 25% and 5% decrease and increase, in *DI* and *BW*, respectively. This scenario is optimistic since *DI* and *BW* are positively and negatively proportional to HQ. On the contrary, the second scenario (pessimistic scenario) introduces 25% and 5% increase and decrease, in *DI* and *BW*, respectively. Table 1 shows detailed information the *DI* and *BW* for the reference, optimistic, and pessimistic scenarios.

Table 1: Modified variables for determining the non-carcinogenic and carcinogenic risks for the reference, optimistic and pessimistic scenarios.

Risk	Variable	End-user	Reference scenario	Optimistic scenario		Pessimistic scenario	
				Change (%)	New value	Change (%)	New value
Non-carcinogenic	*DI* (L)	Man	2	-25%	1.5	+25%	2.5
		Woman	2		1.5		2.5
		Children	1		0.75		1.25
	BW (kg)	Man	78	+5%	81.9	-5%	74.1
		Woman	65		68.25		61.75
		Children	14.5		15.225		13.775
Carcinogenic risk	*TR*	Man	20%	+15%	23%	+30%	26%
		Woman	20%	+15%	23%	+30%	26%
		Children	10%	+5%	10.5%	+20%	12%
	DD_{am}	Dimethylamine	2.03	-20%	1.624	+20%	2.436
		Diethylamine	0.85	-20%	0.68	+20%	1.02
		n-butylamine	11.34	-20%	9.072	+20%	13.608
		Methylethylamine	0.15	-20%	0.12	+20%	0.18

2.4.2. Carcinogenic risk of $NO_3^-–NO_2^-$

NO_3^- ingested through drinking water is converted into NO_2^- in the stomach, that engages in the production of nitrosamines with carcinogenic potency for different digestive system organs (Ward et a., 2010). In fact, NO_2^- by chemical reaction or absorption quickly disappears in the stomach content. This reaction in healthy individuals will often occur at the esophageal/cardia junction, where gastric juices first encounter saliva (Chébékoué, 2009). As a result, NO_2^- is typically first transformed to nitrous acid by gastric acidity. Since nitrous acid is transient, it transforms into active nitrosating species, which nitrous anhydride is the most important product of this reaction. The result of nitrosating species with nitrosatable compounds are nitrosamines (Chébékoué, 2009). Nitrosamines are responsible for the development of certain type of cancers, i.e. esophagus, stomach, colon, nasopharynx, and urinary bladder (Ward et al., 2005; Krasner et al., 2013).

It is noteworthy to mention that, ingested NO_3^- through foods (vegetables mostly that contribute to dietary NO_3^- intake) does not usually pose any threats, since they are accompanied by antioxidants such as vitamin C, which are the inhibitors of endogenous nitrosation (Bartsch et al., 1988; Bartsch and Frank, 1996; Chébékoué, 2009). Given that tap water does not contain any antioxidants, ingestion of water contaminated by NO_3^- can increase the carcinogenic risk of the exposed population (Ward et al., 2005). Since NO_3^- is not directly related to the development of carcinogenic risks in human, the existing standards for NO_3^- concentration in drinking water are only based on methemoglobinemia (Chébékoué, 2009). Therefore, it is urgently needed to robustly evaluate the secondary effects of NO_3^- on human health as a result of water consumption, i.e. the carcinogenic risk of nitrosamine compounds which are the results of chemical reactions of NO_3^- in human body.

In this study, to estimate the carcinogenic risk of NO_3^-–NO_2^- in the TPW, the non-threshold model suggested by Shephard et al. (1987), i.e. Eq. (4), was adopted.

$$\mathrm{ER} = DD_{nitros} \times R \qquad (4)$$

where, ER is the carcinogenic risk of exposure to a certain nitrosamine, DD_{nitros} is the daily dose of nitrosamines in mg/kg.d, and *R* (kg.d/mg) is carcinogenic potency factor of each nitrosamine which defines carcinogenic risk of exposure to 1 mg of a specific nitrosamine for 1 kg of body weight. Each nitrosamine has a specific carcinogenic potency as shown in Table S1.

Although the model suggested by Shephard et al. (1987) gives some information on the possible carcinogenic risk of $\mathrm{NO_3^-}$–$\mathrm{NO_2^-}$ in drinking water, our understanding of quantification of DD_{nitros} is still poor. The main obstacle to use this model is the calculation of DD_{nitros}, led to rare application of Eq. (4) for estimation of carcinogenic risk of $\mathrm{NO_3^-}$–$\mathrm{NO_2^-}$ in drinking water. This study develops an exposure-based model for estimation of carcinogenic risk of $\mathrm{NO_3^-}$–$\mathrm{NO_2^-}$ in the TPW by proposing a robust method for determination of DD_{nitros}. The DD_{nitros} of four relevant nitrosamines in the stomach was estimated in this study. These nitrosamines include N–nitrosodi–n–butylamine, Nnitrosodimethylamine, N–nitroso–N–methylethylamine, and N–nitrosodiethylamine (Chébékoué, 2009). The DD_{nitros} is a function of two important factors: (i) $\mathrm{NO_2^-}$ concentration in stomach because of daily intake of $\mathrm{NO_2^-}$ and transformation of ingested $\mathrm{NO_3^-}$ to $\mathrm{NO_2^-}$, and (ii) daily intake of dietary amines. Note that amines are not carcinogen. But, they can convert to nitrosamines, under specific environmental conditions, that have carcinogenic potency. To estimate the gastric $\mathrm{NO_2^-}$ concentration in mol/L from $\mathrm{NO_3^-}$ ingestion in the TPW, i.e. $[\mathrm{NO_2^-}]_i$, the *DI*, volume of stomach in liter (V_s), and the rate of transformation of $\mathrm{NO_3^-}$ into $\mathrm{NO_2^-}$ (*TR*) were used as Eq. (5):

$$[\mathrm{NO_2^-}]_i = \frac{[\mathrm{NO_3^-}]\times TR\times DI}{V_s} \tag{5}$$

Similar to Section 2.4.1, *DI* taken as 2 and 1 L/d for adults and children, respectively. The *TR* varies from 5% to 30%. In our study, *TR* values about 10% and 20%, respectively, were selected for children and adults because this parameter increases with the age (Chébékoué, 2009; Ward et al., 2018). The stomach volume (V_s) was assumed to be the same as esophago/cardia region equal to 0.5 L (Chébékoué, 2009) for both adults and children, given that esophago/cardia region plays an important role in the luminal nitrosation (Ward et al., 2005). In addition, Eq. (5) was further modified to better estimate gastric $\mathrm{NO_2^-}$ concentration resulting from direct exposure of this contaminant, i.e. $[\mathrm{NO_2^-}]_{ii}$, in the TPW as:

$$[\mathrm{NO_2^-}]_{ii} = \frac{[\mathrm{NO_2^-}]_{\mathrm{obs}} \times DI}{V_s} \qquad (6)$$

where, $[\mathrm{NO_2^-}]_{\mathrm{obs}}$ is the $\mathrm{NO_2^-}$ concentration in mol/L in the TPW, measured during the sampling campaigns.

Considering both Eqs. (5) and (6), the total gastric $\mathrm{NO_2^-}$ concentration in mol/L was calculated as:

$$[\mathrm{NO_2^-}] = [\mathrm{NO_2^-}]_i + [\mathrm{NO_2^-}]_{ii} \qquad (7)$$

The daily intake of dietary amines also influences the DD_{nitros}. In this study, the calculated results by Chébékoué (2009) for daily amine intake (DD_{am}) were used based on Canadian food consumption data as given in Table S2. Four most relevant amines were considered in the analysis: (i) Dimethylamine, (ii) Diethylamine, (iii) n-butylamine, and (iv) Methylethylamine. Then, the DD_{nitros} transformed from amines for each sub-group under study (i.e., men, women, and children) was estimated by Eq. (8).

$$DD_{nitros} = \frac{[\mathrm{NO_2^-}]^2 \times DD_{am} \times K \times 3600 \times MW_{nitros}}{BW} \qquad (8)$$

where, K denotes the constant rate of nitrosatability ($\mathrm{L^2/mol.s}$), representing the speed of nitrosation of a specific amine; 3600 is the conversion of 1 h to seconds; MW_{nitros} is the molecular weight of a specific nitrosamine (g/mol); and BW describes the average body weight of men (78 kg), women (65 kg), and children (14.5 kg).

Having the detailed information calculated in the above, the model suggested by Shephard et al. (1987) was further modified as Eq. (9).

$$\mathrm{ER} = \frac{[\mathrm{NO_2^-}]^2 \times DD_{am} \times K \times 3600 \times MW_{nitros}}{BW} \times R \qquad (9)$$

where, ER $\leq 1\times10^{-6}$ and ER $>1\times10^{-6}$ represent the safe and carcinogenic conditions, respectively (IARC, 2010).

We used the reference values suggested by the U. S. EPA (1987) and Canadian food consumption data to estimate the carcinogenic risk of NO_3^-–NO_2^- ingested through drinking water in Tehran, Iran. Using these reference values could introduce some uncertainty in our results since they are not localized for our case study region, i.e. the TPW. To account for the potential uncertainties due to our assumptions, the carcinogenic risk of exposure to a certain nitrosamine were recalculated under two optimistic and pessimistic scenarios. In these scenarios, suitable ranges for the reference values were used to best represent the local conditions in our case study. In optimistic scenario, we decreased (increased) the values of variables that positively (negatively) influence ER value. These variables are DI, BW, TR, and DD_{am}. In this regard, DI and DD_{am} were reduced about 25% and 20%, respectively, and BW, TR for adult, and TR for children were increased about 5%, 15%, and 5%, respectively. For the pessimistic scenario, we increased (decreased) the values of these variables that influence ER value, resulting in an increase of about 25%, 20%, 30%, and 20%, in DI, DD_{am}, TR for adult, and TR for children, respectively, and a decrease of about 5% in BW. Detailed information is given in Table 1.

3. Results and discussion

3.1. NO_3^- and NO_2^- concentration in Tehran's potable water

The analysis of the sampling campaigns conducted during wet period, i.e. May 2018, indicated that NO_3^- and NO_2^- concentrations were lower than the device detection limits (ND) in 18 and 29 out of 100 samples, respectively (Table S3). Whereas, for the dry period, i.e. October 2018, these numbers were 10 and 8 out of 100 samples for NO_3^- and NO_2^-, respectively (Table S4). In the studied samples, NO_3^-–NO_2^- concentrations varied from lower than the device detection limits, i.e. <0.3 and <0.002 mg/L, respectively, to 102.6–1.3 mg/L and 23.5–0.215 mg/L, respectively, for both dry and wet periods. The mean NO_3^- (NO_2^-) concentrations were 7.03 (0.038) mg/L and 20.07 (0.154) mg/L, in wet and dry periods, respectively.

Spatial distribution of NO_3^- and NO_2^- in the TPW is shown in Figs. 3 and 4, respectively. In some areas of the city (urban districts #03, #09 and #21), the highest NO_3^- concentration was observed in dry period. Also, the highest NO_2^- concentration was observed in the dry period in some areas of the west, north, and south of Tehran (i.e. urban districts #02, #15, and #21). Considering the permissible concentrations of 50 and 1 mg/L for NO_3^- and NO_2^- in drinking water, respectively (WHO, 2008), no concerning data for TPW was observed in the wet period. However, 8 and 3 out of the 100 samples taken in dry period showed values greater than the permissible limit concentrations for NO_3^- and NO_2^- in the TPW, respectively. Furthermore, NO_3^- >100 mg/L was observed in two sampling locations in the TPW in dry period, which is far greater than the permissible level in drinking water. Previous studies also reported high concentration of NO_3^- in Tehran's water resources, especially for the groundwater resources that mainly located in the southern regions of this city (Imandel et al., 2000; Torabian et al., 2000; Joekar-Niasar and Ataie-Ashtiani, 2009; Ghahremanzadeh et al., 2018; Noori et al., 2019; Nejatijahromi et al., 2019). However, contamination of water resources by NO_3^- is a global concern, especially in highly populated area with dense agricultural lands. Using NO_3^- concentrations sampled at 5101 wells across the USA from 1991 to 2003, Burow et al. (2010) concluded that some groundwater samples taken from 8% (437) of wells were polluted by higher NO_3^- concentration than the permissible level. A similar study was conducted for 628 groundwater samples across China (2000-2012) showed higher NO_3^- concentration than the permissible level at 28% of groundwater samples (Gu et al., 2013). Zhou et al. (2019) data highlighted concern regarding NO_3^- at the Jinhua region of Zhejiang Province, China. Another study conducted by collecting around 3 M samples taken from wells across 7038 administrative blocks in India (2010-2017) revealed that about 8% of the blocks were impacted by higher than permissible level of NO_3^- (Sarkar et al., 2021).

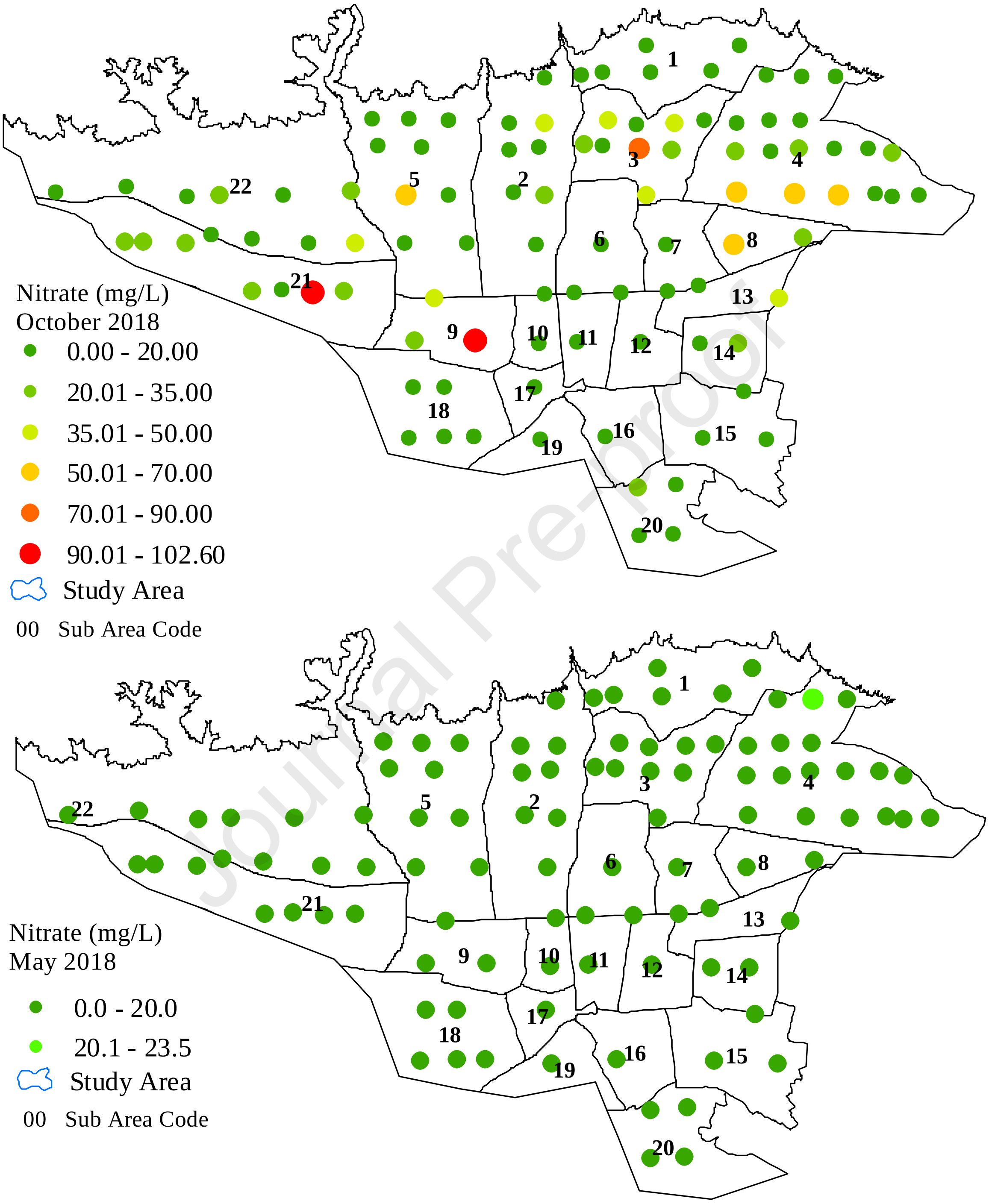


Figure 3: Spatial distribution of nitrate (NO_3^-) in Tehran's potable water (TPW) during dry (October 2018) and wet (May 2018) periods.

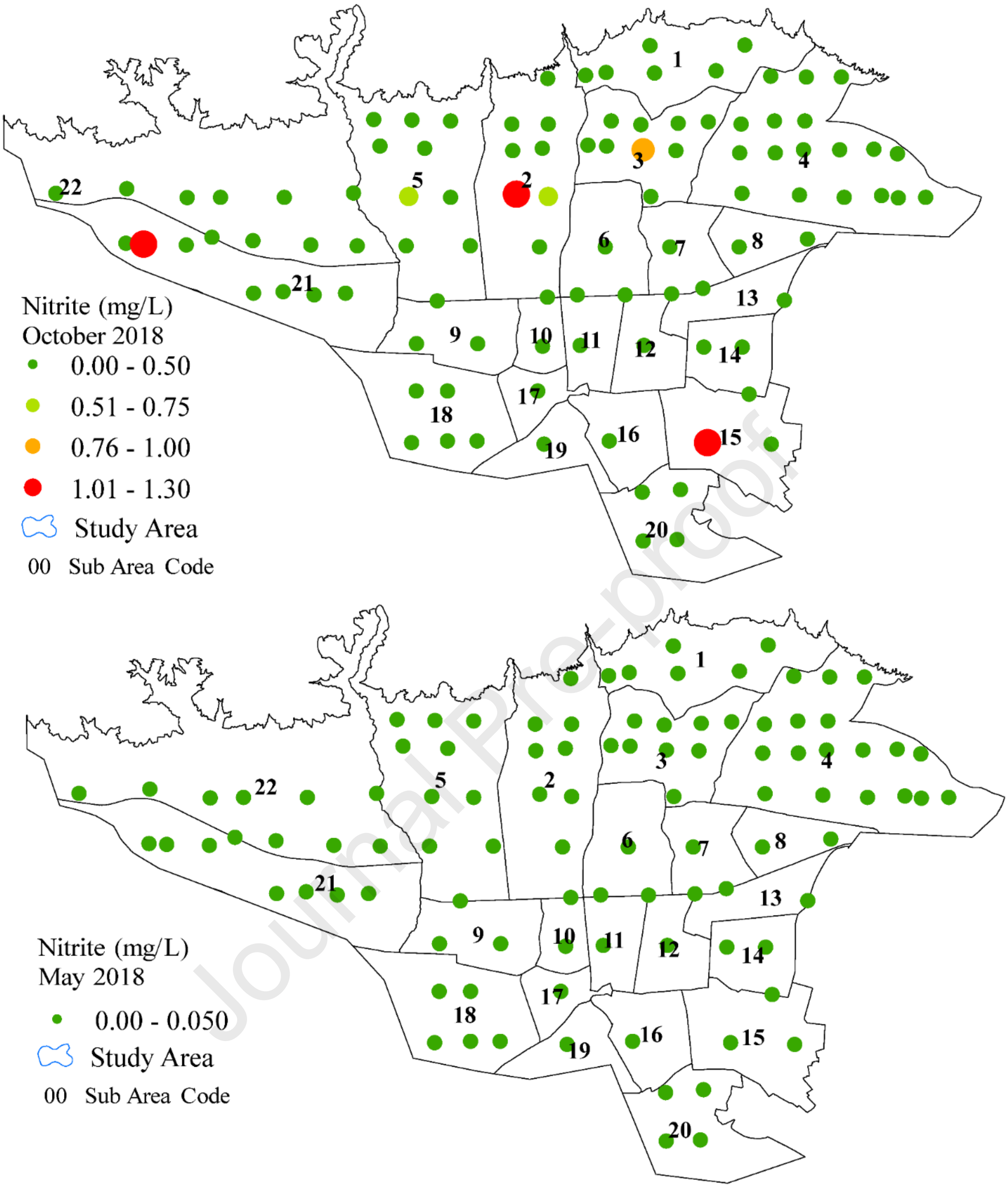
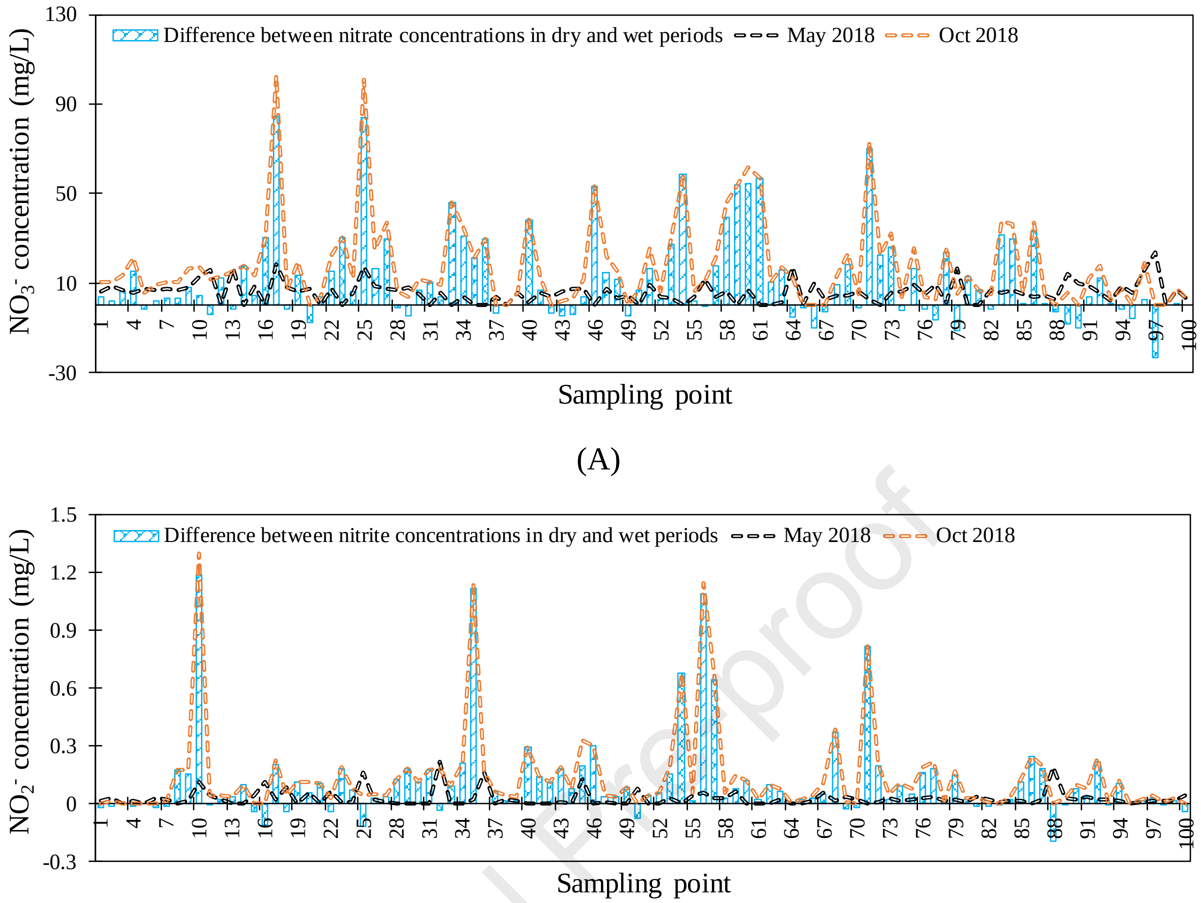


Figure 4: Spatial distribution of nitrite (NO_2^-) in Tehran's potable water (TPW) during dry (October 2018) and wet (May 2018) periods.

Given the similarity of sampling points in both wet and dry periods, the difference in NO_3^- and NO_2^- concentrations between two sampling periods is also shown in Figs. 5A and 5B, respectively. The concentrations of NO_3^- and NO_2^- were lower in the wet period (May 2018) than those samples collected in the dry period (October 2018), across a large area of the sampling points. This is due to more significant contribution of nitrogen–rich groundwater than the surface water in providing the TPW during the dry period. One of the main causes of groundwater contamination in the Tehran aquifer is the widespread use of nitrogen–rich fertilizers in the cultivation season (spring and summer) that increases NO_3^- and NO_2^- concentrations in the TPW with a lag impact in the dry season (October 2018). Also, the widespread use of latrine wells for wastewater disposal and the dominant north-south slope in Tehran, lead to the transport of nitrogen–rich disposed sewages, as well as polluted run-offs, to the alluvial plain in the south of the city, which is the main bed of water wells and groundwater supply for Tehran (Torabian et al., 2000; Ghahremanzadeh et al., 2018; Noori et al., 2019). Therefore, wastewater disposal through latrine wells contributes to the soil pollution and leachate of contaminants to the groundwater. The bacterial communities in the soil can decompose the nitrogen–rich sewage into NO_3^- and NO_2^- (Jensen et al., 2014; Yin et al., 2019), which further increases these nutrients in Tehran's groundwater resources. Unbalanced nitrogen–rich fertilizers use (Maghrebi et al., 2020) for urban green space can also play a role in high concentration of NO_3^- and NO_2^- in the Tehran's groundwater resources (Imandel et al., 2000). About 20% of Tehran area is covered by green space that are annually enriched by about 200 kg of nitrogen–rich fertilizers per hectare during the cultivation season, i.e. spring and summer. Another major contributor to NO_3^- and NO_2^- concentrations in the Tehran's groundwater resources is industrial activities, which are mainly located at the west of this city (Imandel et al., 2000). The absorption of nitrogen–rich compounds through atmosphere to Tehran's groundwater resources is negligible since most of the area in Tehran is covered by permeable surfaces (Joekar-Niasar and Ataie-Ashtiani, 2009).



(A)

(B)

Figure 5: (A) NO_3^- concentration measured in the sampling points during wet (May 2018) and dry (October) periods and difference between the concentrations observed in these periods, and (B) NO_2^- concentration measured in the sampling points during wet (May 2018) and dry (October 2018) periods and difference between the concentrations observed in these periods.

The statistical analysis preformed on the collected dataset revealed no significant relationship between NO_3^- concentrations in wet and dry periods (correlation coefficient = 0.03) and also between NO_2^- concentrations in these periods (correlation coefficient = 0.10). This presumably contributes to different sources of NO_3^- and NO_2^- in the TPW in dry and wet periods. During the wet period, nitrogen–rich groundwater sources have less contribution to the supply of TPW. Therefore, the TPW is safe with respect to NO_3^- and NO_2^- during the wet period. On the contrary, nitrogen–rich groundwater sources mainly contribute to the supply of

TPW during dry period, when the surface water supply is very low, leading to an elevated concentrations of NO_3^- and NO_2^- in the dry period (Fig. 5). In addition, the coefficient of determination between NO_3^- and NO_2^- concentrations in both wet and dry periods were observed to be very small during the study period (correlation coefficients = 0.01 and 0.20). This fact presumably reveals no evidence of denitrification process in Tehran's water distribution network, a process that converts NO_3^- to NO_2^-, and finally to N_2 (Dehestaniathar et al., 2021; Noori et al., 2021). This finding is in line with the results reported by Schullehner et al. (2017) who concluded no occurrence of denitrification in Danish public waterworks.

3.2. Estimation of non-carcinogenic risk of NO_3^-–NO_2^-

The HI values regarding NO_3^-–NO_2^- were determined for all 100 sampling locations for men, women, and children subgroups, and during both wet and dry periods (Table S5). The minimum, mean, maximum, and the standard deviation of HI values across different population groups are given in Table S6.

During the dry period, the non-carcinogenic risk of NO_3^-–NO_2^- (HI >1) for men, women, and children was observed at 5, 8 and 30 sampling locations, respectively (Fig. 6), mainly located in urban districts #04 and #08 (east), #21 and #05 (west), #03 (north), and #09 (center) (Fig. 7). In some parts of Tehran, the HI value calculated for children was four times greater than the safe value with respect to non-carcinogenic risk (2 out of the 100 samples).

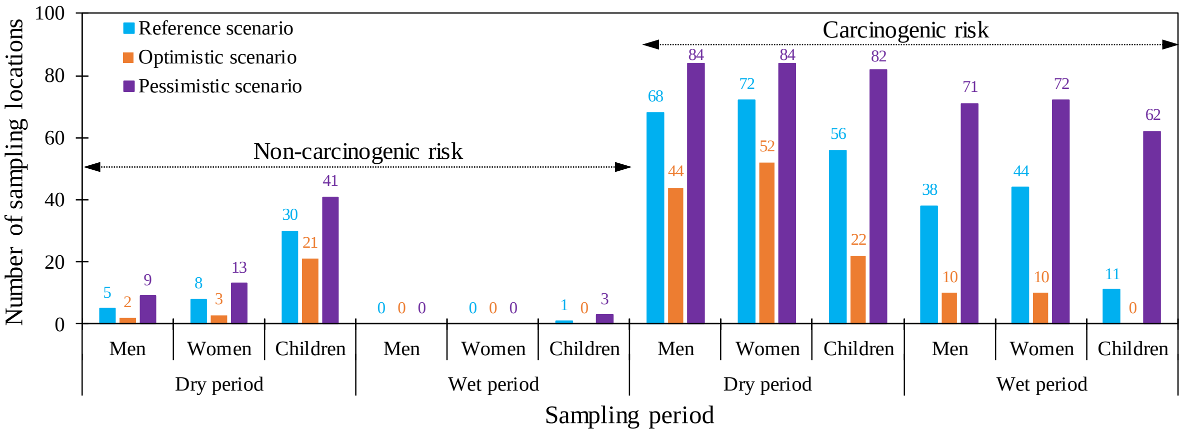


Figure 6: The number of sampling locations exposed to the non-carcinogenic and carcinogenic risks associated with NO_3^-–NO_2^- in Tehran's potable water (TPW) calculated for the reference, optimistic, and pessimistic scenarios, and for different subgroups (men, women, and children).

The TPW was safe for both men and women with respect to non-carcinogenic risk during the wet period (Fig. 6). However, one of the sampling locations, i.e. urban district #04 (east), still shows concerning results regarding the non-carcinogenic risk for children in the wet period (Fig. 7).

According to the results determined for the optimistic scenario (Fig. S1 and Table S7), a lower number of sampling locations, compared to the reference scenario, exposed to the non-carcinogenic risk (i.e. HI >1) (Fig. 6). Comparison of the non-carcinogenic risk under pessimistic scenario to the reference scenario (Tables S5 and S8) shows increased risks during the wet period which raise concerns (Fig. S2). The number of sampling locations with HI >1 increased from 5 to 9 for men, 8 to 13 for women, and 30 to 41 for children during the dry period. For the wet period, the HI values recalculated under pessimistic scenario were approximately similar to those determined for the reference scenario (Fig. 6).

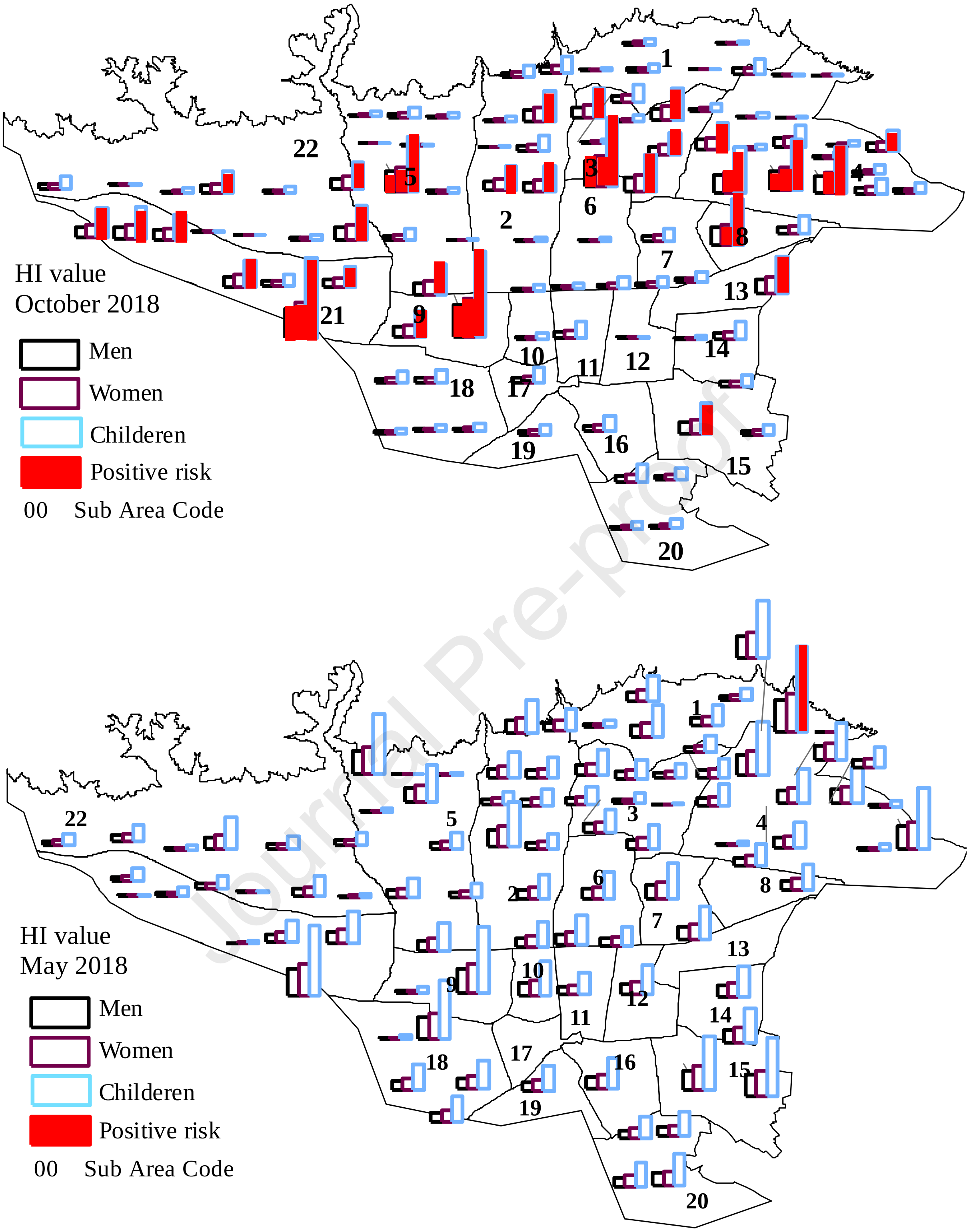


Figure 7: Spatial distribution of HI associated with nitrate–nitrite (NO_3^-–NO_2^-) determined for Tehran' potable water (TPW) for different subgroups (i.e. men, women, and children) in both wet and dry periods. The sampling points with a positive non-carcinogenic risk for each subgroup are shown by red color.

3.3. Estimation of carcinogenic risk of NO_3^-–NO_2^-

The carcinogenic risk (ER) was separately calculated for all the nitrosamines including N–nitrosodimethylamine, N–nitrosodiethylamine, N–nitrosodi–n–butylamine, and N–nitroso–N–ethylethylamine (Tables S9–S12). The carcinogenic risk concerns for men were observed in 16 (0), 40 (3), 69 (38), and 8 (0) sampling locations with respect to N–nitrosodimethylamine, N–nitrosodiethylamine, N–nitrosodi–n–butylamine, and N–nitroso–N–ethylethylamine, respectively, in dry (wet) period (Table 2). The estimated ER values for women and children are also determined and further described in Table 2.

The carcinogenic risk concern in a sampling location exist if ER $>1\times10^{-6}$ with respect to at least one of the nitrosamines. Our results suggest that the TPW is not safe for most of the sampling points taken during dry period (Figs. 6 and 8). The carcinogenic risk concern associated with NO_3^-–NO_2^- in the TPW during the dry period is more than that observed in the wet period, with over 45% of the sampling points show ER $>1\times10^{-6}$, depending on the subgroups.

Table 2: The number of sampling points with excess carcinogenic risk of exposure to different nitrosamines (ER $>1\times10^{-6}$) in the reference, optimistic, and pessimistic scenarios for each subgroup of end-users in Tehran's potable water (The first, second, and third numbers in the format of '*/*/*' are responsible for samplings with ER $>1\times10^{-6}$ in the reference, optimistic, and pessimistic scenarios, respectively).

Nitrosamines	Man		Women		Children	
	May	November	May	November	May	November
N–nitrosodimethylamine	0/0/5	0/0/5	0/0/8	18/4/42	0/0/1	5/0/32
N–nitrosodiethylamine	3/0/23	3/0/23	8/0/27	41/21/63	0/0/11	23/3/57

N–nitrosodi–n–butylamine	38/10/71	38/10/71	44/10/72	70/57/84	11/0/62	56/22/82
N–nitroso–N–methylethylamine	0/0/0	0/0/0	0/0/1	8/2/30	0/0/0	2/0/19

The number of samples with ER >1×10^{-6} for children in both dry and wet periods was less than those calculated for men and women (Fig. 6). This is due to the selected rate of transformation of NO_3^- into NO_2^- (i.e. *TR*) for different subgroups (Table 1), given that *TR* increases with the age (Chébékoué, 2009) and positively influences the estimated ER values.

To account for the uncertainties raised from the assumptions made, the ER values separately recalculated for each nitrosamine under two optimistic and pessimistic scenarios (Table 2). Also, the number of sampling points with ER >1×10^{-6} with respect to at least one of the nitrosamines recalculated for the optimistic and pessimistic scenarios are illustrated in Fig. 6. The detailed analysis of re-calculated results under the optimistic and pessimistic scenarios are given in Fig. S3 and S4, respectively. The number of sampling points with the concern of carcinogenic risk in the pessimistic scenario compared to that in the reference scenario show an increase from 68 to 84 (for men), 72 to 84 (for women), and 56 to 82 (for children) during the dry period. Compared to the reference scenario, the maximum increase in the number of sampling points with ER >1×10^{-6} was observed for children in the pessimistic scenario and during the wet period (from 11 to 62 sampling points) (Fig. 6).

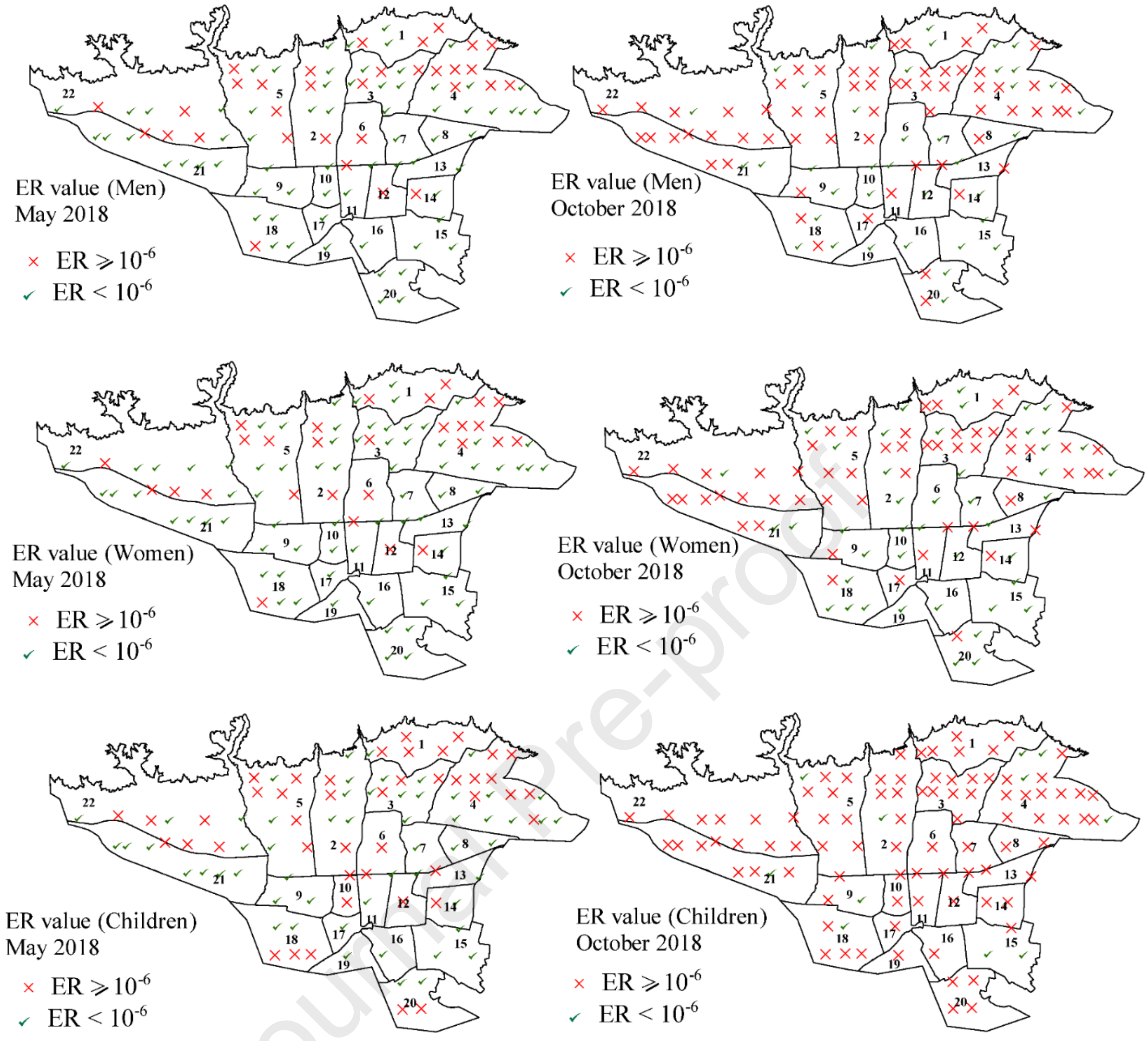


Figure 8: Sampling locations with no estimated carcinogenic risk associated with NO_3^-–NO_2^- in Tehran' potable water, i.e. ER ≤ 1×10^{-6} (check symbol ✓), and with estimated carcinogenic risk, i.e. ER > 1×10^{-6} (multiply symbol ×) for different subgroups in wet and dry periods.

There is an ongoing debate on the human health carcinogenic risks of NO_3^- in drinking water (Ward et al., 2005; Van Grinsven et al., 2006; Powlson et al., 2008). Some previous studies (e.g., Avery, 1999; L'hirondel and L'hirondel, 2002) have emphasized on the importance and the role of NO_3^- in potable water as a risk cause that only contributes to the Blue baby syndrome. These studies have proposed that the permissible level of NO_3^- could be safely doubled with no increase in the Blue baby cases, to reduce the costs associated with NO_3^-

removals for potable water. However, strong epidemiological evidences in recent decades suggest the elevated concentration of NO_3^- in drinking water is associated with the carcinogenic risks (Ward et al., 2005; Jones et al., 2016 and 2019; Ward et al., 2018; Temkin et al., 2019; Stayner et al., 2021), even for those concentrations that are considerably lower than its current permissible level (De Roos et al., 2003; Schullehner et al., 2018; Espejo-Herrera et al., 2019). The results presented in this study recommend that the permissible level of NO_3^- should be lowered, to reduce its potential carcinogenic risks for end-users. Despite the results presented in this study that show most of the sampling points pass the safe condition criteria with respect to the maximum permissible levels of NO_3^- and NO_2^- in dry period (92 and 97 samples for NO_3^- and NO_2^-, respectively) (Figs. 3 and 4), some 68%, 72%, and 56% of samples reveal positive carcinogenic risks for men, women, and children categorizes, respectively. In wet season when NO_3^- and NO_2^- levels are about two times less than the maximum permissible limits, the positive carcinogenic risk are observed in 38%, 44%, and 11% of sampling points for men, women, and children, respectively.

4. Conclusions

Non-carcinogenic risk assessment of $NO_3^- - NO_2^-$ ingested through drinking water is well documented whilst a gap of knowledge exists in robust assessment and quantification of the carcinogenic risk of these contaminants. This study investigated the carcinogenic and non-carcinogenic risks imposed by NO_3^-–NO_2^- ingested through potable water, for a case study of Tehran, Iran. The analysis of the sampling data showed the carcinogenic risk associated with the presence of NO_3^-–NO_2^- in the TPW, which is likely to endanger human health in Tehran. The methodological approach developed in this study to determine the carcinogenic risk associated with $NO_3^- - NO_2^-$ in the TPW represents the worst–case dose–response at low dosages. Therefore, the carcinogenic risk of the TPW described in this study shows the worst scenario induced by NO_3^-–NO_2^- concentration in the TPW. Our findings raise concerns on the health risk imposed by $NO_3^- - NO_2^-$ concentration in TPW and highlight the necessity of developing robust amendatory action plans for the water industry, to protect public health of over 13 M people who incessantly use the TPW. Given the current debate on the human health carcinogenic risks of NO_3^- in drinking water, the results outlined in this study suggest the importance of reducing the permissible level of NO_3^- set out by the current standards for potable water to minimize the potential carcinogenic risks for end-users.

Data availability

All data used in this study are given in Supplementary Materials.

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Compliance with ethical standards

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Ethics approval and consent to participate: Not applicable

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- A model is developed to estimate carcinogenic risk of NO_3^- in drinking water
- Non-carcinogenic risk of NO_3^-–NO_2^- was observed in Tehran's drinking water
- Majority of samples taken in dry period show a positive carcinogenic risk of NO_3^-
- The permissible level of NO_3^- does not safeguard human health vs carcinogenic risks

Declaration 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

A non-threshold model to estimate carcinogenic risk of nitrate-nitrite in drinking water

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