Mini-review article / *http://doi.org/10.15446/rcciquifa.v50n1.95460*

Food nitrates and nitrites as possible causes of cancer: A review

Francisco Patricio de Andrade Júnior[1], Ana Laura Sobreira de Cabral[1], Januse Míllia Dantas de Araújo[2]*, Laísa Vilar Cordeiro[1], Marília de Barros Cândido[2], Alison Pontes da Silva[2], Brenda Tamires de Medeiros Lima[2], Bruna Braga Dantas[3]

[1] Federal University of Paraíba, Health Sciences Center, João Pessoa, Paraíba, Brazil.

[2] Federal University of Campina Grande (UFCG), Education and Health Center (CES), Cuité, Paraíba, Brazil.

[3] Ph. D. Professor at Federal University of Campina Grande (UFCG), Education and Health Center (CES), Cuité, Paraíba, Brazil.

*Corresponding author: janusemillia96@gmail.com

Received: 2 October 2020

Revised: 14 December 2020

Accepted: 18 December 2020

Summary

Introduction: Nitrates and nitrites can be found in meat and dairy products, vegetables, and fruits. The consumption of these preservatives has been associated with the emergence of gastric, colorectal cancer and non-Hodgkin's lymphoma, although studies are still inconclusive. **Methodology:** It is a review of literature of the narrative type, in which there was a recovery of articles published in English and Portuguese, in the databases SciELO, Lilacs, Science Direct and Capes journals. Articles related to nitrates and nitrites in foods were included, as well as articles that correlated the consumption of these preservatives with the appearance of cancers, regardless of the year of publication, although articles published between the years 2009 to 2019 were prioritized. **Results:** Nitrates and nitrites are generally associated with industrialized food products; therefore, it is possible to observe the presence of these salts in a wide variety of foods. The excessive consumption of nitrates and nitrites, whether through water or food, has been associated with a great diversity of diseases, stimulating the development of several studies investigating, including, the correlation between the consumption of these preservatives and the appearance of cancers. **Conclusion:** it is observed that nitrates and nitrites form compounds with a carcinogenic potential, making them interesting to avoid excessive consumption of these preservatives.

Key words: Preservative, carcinogenesis, nitrate, nitrite.

Resumen

Nitratos y nitratos alimentarios como posibles causas de cáncer: una revisión

Introducción: los nitratos y nitritos pueden ser encontrados en carnes y productos lácteos, verduras y frutas. El consumo de estos conservantes ha sido asociado con la aparición de cáncer gástrico, colorrectal y linfoma no Hodgkin, aunque los estudios aún no son concluyentes. **Metodología:** se hizo una revisión de tipo narrativo de la literatura, en la que se recuperaron artículos publicados en inglés y portugués, en las bases de datos SciELO, Lilacs, Science Direct y revistas Capes. Se incluyeron artículos relacionados con nitratos y nitritos en alimentos, así como artículos que correlacionaban el consumo de estos conservantes con la aparición de cánceres, independientemente del año de publicación, aunque se priorizaron artículos publicados entre los años 2009 a 2019. **Resultados:** los nitratos y nitritos se asocian generalmente con productos alimenticios industrializados; por tanto, es posible observar la presencia de estas sales en una amplia variedad de alimentos. El consumo excesivo de nitratos y nitritos, ya sea a través del agua o de los alimentos, se ha asociado a una gran diversidad de enfermedades, estimulando el desarrollo de varios estudios que investigan, entre ellos, la correlación entre el consumo de estos conservantes y la aparición de cánceres. **Conclusión:** así, se observa que los nitratos y nitritos, forman compuestos con potencial carcinogénico, por lo que resulta interesante evitar el consumo excesivo de estos conservantes.

Palabras clave: Conservantes, carcinogénesis, nitratos, nitritos.

Resumo

Nitratos e nitratos dietéticos como possíveis causas de câncer: uma revisão

Introdução: nitratos e nitritos podem ser encontrados em carnes e laticínios, vegetais e frutas. O consumo desses conservantes tem sido associado ao desenvolvimento de câncer gástrico e colorretal e linfoma não Hodgkin, embora os estudos ainda não sejam conclusivos. **Metodologia:** trata-se de uma revisão de literatura do tipo narrativa, na qual houve a recuperação de artigos publicados em inglês e português, nas bases de dados SciELO, Lilacs, Science Direct e Periódicos Capes. Foram incluídos artigos relacionados a nitratos e nitritos em alimentos, bem como artigos que correlacionassem o consumo desses conservantes com o aparecimento de cânceres, independentemente do ano de publicação, embora tenham sido priorizados os artigos publicados entre os anos de 2009 a 2019. **Resultados:** nitratos e nitritos são geralmente associados a produtos alimentícios industrializados; portanto, é possível observar a presença desses sais em uma grande variedade de alimentos. O consumo excessivo de nitratos e nitritos, seja pela água ou pelos alimentos, tem sido associado a uma grande diversidade de doenças, estimulando o desenvolvimento de diversos estudos que investiguem, inclusive, a correlação entre o consumo desses conservantes e o aparecimento de cânceres. **Conclusão:** assim, observa-se que nitratos e nitritos formam compostos com potencial carcinogênico, por isso é interessante evitar o consumo excessivo desses conservantes.

Palavras-chave: Conservantes, carcinogênese, nitratos, nitritos.

Introduction

Food additives can be defined as substances, such as dyes, antioxidants, thickeners, stabilizers, and preservatives, intentionally added to industrial products in order to provide greater safety and validity to them [1].

Among the innumerable preservatives, nitrates and nitrites are curing salts, used in the preservation of industrial foods, whose intention is to maintain the integrity of the product, that is, to act to delay or inhibit microbial degradation and/or enzymatic degradation of food. These substances also have functionality in terms of color fixing and influencing flavor and aroma, characteristic of cured foods [2].

Nitrates and nitrites are preservatives whose primary activity is the inhibitory action of *Clostridium botulinum*, a pathogenic bacterium with a high toxic content, capable of inducing foodborne infections in humans, through the production of neurotoxins related to botulism. However, it is important to emphasize that nitrate directly do not have a potential blocker of this bacterium and its reduction to nitrite is essential for this activity [3].

In terms of conservation, these compounds are of great importance for the technological area of food. On the other hand, their intake is controversial as to their harmful effects on human health, especially in relation to the development and progression of cancers [4].

Cancer is the term used to refer to a complex set of distinct and non-communicable diseases, which is characterized by the uncontrolled growth of cells in the most diverse tissues of the body. Once these cancer cells move from one tissue to another, there is the formation of metastasis [5].

It is believed that the carcinogenic potential of nitrates, nitrites, and their derivatives, is related to the ability to damage molecules of deoxyribunucleic acid (DNA) and may contribute to the process of illness with the emergence of diseases such as cancer [6]. However, it is complicated to talk about reducing the levels of preservatives at an industrial level, since the shelf life of food products and their acceptable storage time are also reduced proportionally [7].

Although preservatives have indisputable benefits, the routine use of nitrite and nitrate salts is questionable and worrisome. Thus, the present study aimed to investigate the relationship between the consumption of nitrates and nitrites and the appearance of cancers.

Methodology

It is a review of literature of the narrative type, in which there was a recovery of articles published in English and Portuguese, in the databases SciELO, Lilacs, Science Direct and Capes journals. Articles related to nitrates and nitrites in foods were included, as well as articles that correlated the consumption of these preservatives with the appearance of cancers, regardless of the year of publication, although articles published between the years 2009 to 2019 were prioritized. In addition, works that could not be accessed in full were immediately excluded from the study.

Results

Nitrates and nitrites are generally associated with industrialized food products; therefore, it is possible to observe the presence of these salts in a wide variety of foods (table 1).

In view of the information described in the table above, it is possible to observe that both meat and processed foods, as well as fruits and vegetables have nitrates and nitrites in their composition, in the most different countries.

It is important to highlight that the concentration of nitrite and nitrate can vary between the samples analyzed, according to the origin (country/region/factory).

Table 1. Concentration of nitrates and nitrites in different foods.

Author (s) and Year	Country	Food (s)	Source of legislation	Range of found concentration/Detection limit
Chetty and Prasad [8]	Fiji	Foods based on fruits, vegetables, dairy, and food processed.	These figures are below the level recommended by European Union legislation (≤150 mg/mL).	The average content of nitrates and nitrites measured was 48.66 and 1.28 mg/kg, respectively. Limit of detection: Nitrate 1.0-20.0 µg/mL. Nitrite 0.025-2.0 µg/mL.
Abdulkair, Elzupir and Alamer [9]	Saudi Arabia	Processed meats	With the exception of one sample, the results obtained are within the limits established in the Saudi Arabian legislation, which recommends maximum concentrations of nitrates and nitrites equivalent to 125 mg/kg.	Nitrite concentrations ranged from 1.78 to 129.69 mg/kg. The concentrations of nitrates found ranged from 0.76 to 96.64 mg/kg. Limit of detection: Nitrate 27.4 ng/mL - 91.4 ng/mL. Nitrite 0.0006 ng/mL - 0.002 ng/mL.
Genualdi *et al.* [10]	United States	Cheese	The results are lower than that recommended by the general standard for food additives (GSFA).	64 samples of cheese, concentrations ranged from below the method detection limit (MDL) to 26 mg/kg for nitrates and no concentrations of nitrites were found in any of the cheese samples above the MDL of 0.1 mg/kg.

Table 1. *(Continuation)*.

Author (s) and Year	Country	Food (s)	Source of legislation	Range of found concentration/Detection limit
Dos Santos Baião *et al.* [11]	Brazil	Beetroot	*	The nitrate content of Brazilian samples ranged from 5.74 mmol/L to 17.1 mmol/L, which was lower than that obtained in North American samples, which had a content of 31.2 mmol/L. As for the nitrite content, the North American samples again had higher concentrations, with a value of 0.45 mmol/L, while the content in the Brazilian samples varied from 0.04 to 0.13 mmol/L. Among the beets purchased in Brazil, samples from Rio de Janeiro and Rio Grande do Norte obtained the highest concentrations of nitrates and nitrites, respectively. The limit of detection for NO_2^- and NO_3^- was of 1.0×10^5 μmol/L.
Silalahi *et al.* [12]	Indonesia	Vegetables	*	The influence of temperature and storage time on the levels of nitrates and nitrites in lettuce was evaluated. At room temperature, the initial concentrations of nitrates and nitrites, which were 6.07 and 22.63 mg/kg, respectively, increased after 48 hours to 70.83 and 48.14 mg/kg, respectively. At a temperature of 10 °C, the initial levels of nitrates and nitrites, which were equivalent to 3.06 and 21.89 mg/kg, respectively, increased after 48 hours to 64.42 and 40.08 mg/kg. Thus, the study showed that higher temperatures and longer storage periods favor increased levels of nitrates and nitrites. Detection limits are not specified.
Adami *et al.* [13]	Brazil	Processed meats	Brazilian legislation	A total of 33 samples were analyzed, sending that 30.3% had nitrite values above the allowable by Brazilian legislation (150 mg/kg), while 69.7% had nitrate values higher than those acceptable in Brazil (300 mg/kg). Detection limits are not specified

Table 1. *(Continuation).*

Author (s) and Year	Country	Food (s)	Source of legislation	Range of found concentration/Detection limit
Sousa *et al.* [14]	Brazil	Processed meats	Brazilian legislation.	Calabrian sausages from four different manufacturers (A, B, C, D) were evaluated and it can be seen that the sample concentrations ranged from 105.0 mg/kg to 122.0 mg/kg and 234.0 mg/kg to 245.0 mg/kg for nitrite and nitrate, respectively. Analyzing the levels of nitrite and nitrate separately, it was noted that in all brands evaluated the quantities obtained obeyed the levels proposed by the legislation (150 mg/kg for nitrite and 300 mg/kg for nitrate). Detection limits are not specified.
Oliveira *et al.* [15]	Brazil	Processed meats	Brazilian legislation	A total of 270 sausage samples from three different manufacturers each were analyzed. The presence of nitrite was in all samples of the meat products analyzed, whose average concentrations ranged from 29.25 ppm to 249.80 ppm. Sausages from manufacturers A and C had a nitrite content higher than that allowed by Brazilian legislation (maximum 150 ppm). Among the sausages and mortadella, all the samples analyzed showed nitrite levels within the parameters recommended by legislation. Detection limits are not specified.
Makki and Ziarati, [16]	Iran	Tomato products	World Health Organization legislation	The nitrate level analyzed in fresh tomato fruits showed an average of 12.55 ± 0.002 (mg/kg ± S.E). Tomato juice obtained the lowest average in the level of nitrate with 6.77 ± 0.002 (mg/kg ± S.E). Ketchup showed the highest average nitrate concentration, with 65.73 ± 0.007 (mg/kg ± S.E). The results of nitrite in the studied samples showed different trend, the tomato fruit had an average nitrite concentration of 0.21 ± 0.001 (mg/kg ± S.E), and the highest average level of nitrite was found in tomato juice with 0.28 ± 0.001 (mg/kg ± S.E), while ketchup sauce had the lowest average nitrite content with 0.10 ± 0.001 (mg/kg ± S.E). Detection limits are not specified.

Table 1. *(Continuation)*.

Author (s) and Year	Country	Food (s)	Source of legislation	Range of found concentration/Detection limit
Alexander *et al*., [17]	Nigeria	Vegetables	World Health Organization legislation	The average level of nitrates was higher in spinach (52.50 ± 4.00 mg/kg at 53.50 ± 4.50 mg/kg), amaranth (43.50 ± 3.50 mg/kg at 47.50 ± 2.50 mg/kg), okra (39.00 ± 2.10 mg/kg at 40.50 ± 0.90 mg/kg) and onion (37.50 ± 0.40 mg/kg at 39.00 ± 1.60 mg/kg), intermediate in tomato (34.50 ± 2.40 mg/kg at 36.50 ± 2.40 mg/kg) and lower in cabbage (15.00 ± 1.60 mg/kg at 20.50 ± 1.50 mg/kg), with nitrate levels in these vegetables being below the WHO standard limit. The nitrite concentration in the different vegetables studied exceeded 1.0 mg/kg, but it is within the limit allowed by the WHO standard limit, and the values do not show a significant difference between most vegetables. Detection limits are not specified.
Perufo and Hoehne [18]	Brazil	Processed meat	World Health Organization legislation	A total of 5 legalized agribusinesses were evaluated and all samples of colonial type salami showed residual levels of sodium nitrite (<5.0 ppm) and sodium nitrate (71.70 ppm at 146.00 ppm), below the recommended by current legislation. Still, of the 5 irregular manufacturers evaluated, only 1 (20%), was inadequate with residual sodium nitrate value (336 ppm), above the values established by current legislation. Detection limits are not specified.
Hentges *et al*. [19]	Brazil	Processed meat	Brazilian legislation	The study aimed to determine the levels of nitrite and nitrate in sausages sold in a region of southern Brazil, comparing the levels between different brands. The results of the study indicated that a value less than half of the samples (29), represented by the percentage of 40.3%, presented nitrite concentrations above the content established by the legislation, while half of the samples (36), represented by the percentage of 50%, and presented nitrate concentrations above the established content. Detection limits are not specified.

Table 1. *(Continuation).*

Author (s) and Year	Country	Food (s)	Source of legislation	Range of found concentration/Detection limit
Faria *et al.* [20]	Brazil	Processed meat	Brazilian legislation	In the results of the study, it was observed that the analyzed samples had an average concentration of nitrite of 140.48 ± 0.77 mg/kg after manufacture, therefore being in compliance with the maximum limit established and allowed by Brazilian legislation (150 mg/kg). Detection limits are not specified.
Bahadoran *et al.* [21]	Iran	Vegetables, fruits, grains, dairy, meat and processed foods	*	Relatively high levels of nitrate were observed in breads (0.50 mg/g). The averages of nitrate and nitrite in fruits ranged from 0.07 to 0.47 mg/gand 0.15-0.71 mg/100 g, respectively. The vegetables that had the highest nitrate concentrations were included radish (6.3 mg/g), beet (4.9 mg/g), tarragon (4.2 mg/g), lettuce (3.6 mg/g), mint (2.8 mg/g) and celery (2.6 mg/g). Nitrite concentrations in vegetables ranged from 0.21 to 0.74 mg/100 g. In dairy products, the average nitrite and nitrate content ranged from 0.14-0.45 mg/100 gto 0.01-0.06 mg/g. The average concentrations of nitrate and nitrite in meat and processed products ranged from 0.05 to 0.19 mg/gand 2.93-13.9 mg/100 g, respectively. Limit of detection was 0.006 mg/g and 0.10 mg/100 g, for nitrate and nitrite.
Laia *et al.* [22]	Portugal	Vegetables and fruits	Portuguese legislation	In the referred study, the nitrate content in 17 samples was analyzed. The nitrate concentration of the analyzed samples varied between the values of 11 and 2369 mg/kg of product. The horticultural product that showed a higher level than the maximum level established by the legislation was lettuce. The nitrate content in all samples was below the maximum allowed limits (2500 to 4500 mg/kg).

Table 1. *(Continuation)*.

Author (s) and Year	Country	Food (s)	Source of legislation	Range of found concentration/Detection limit
Ding *et al.* [23]	United States	Fruits and vegetables	*	131 samples of fermented and acidified vegetable products were analyzed from batches of 46 products available for sale. In the analyzes, nitrite was detected in low concentrations (<1.5 mg/100 g) in four acidified products, including pickled green beans, red cabbage, pickled beets and pickled mushrooms and in two fermented products, in Greek olives and kimchi. Nitrate concentrations showed variations from an average value of 122 mg/100 g for kimchi to levels not detectable in acidified Brussels sprouts. The limit of detection for nitrite was 0.5 mg/L.
Scheibler, Marchi and Souza [24]	Brazil	Processed meat	Brazilian legislation	Nitrate and nitrite concentrations were higher than allowed (80 mg/kg). Detection limits are not specified.

*The study does not cite consulted legislation source; Source: Research data, 2019.

In addition, the storage time and temperature itself can contribute to the increase in the content of these preservatives, indicating that the longer the product takes to be consumed, the richer in nitrates and nitrites it can become [12].

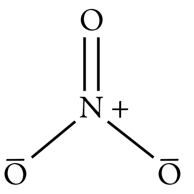
Nitrites are mainly associated with meat products, requiring a minimum of 20 mg $NaNO_2$ /kg of product, while nitrates are mostly found in vegetables, corresponding to 70% of the intake of this ion in the human diet, in which is believed to vary between 100 to 200 mg in a conventional diet [2, 25, 26].

Thus, it is important to note that, especially in meat products, the uses of these preservatives are essential to allow the protection of these products against *C. botulinum*. On the other hand, in fruits and vegetables, their concentrations are influenced by the climate, soil and use of fertilizers. Therefore, there is moderation in the consumption of these foods, especially the industrialized ones that present higher levels of these and other preservatives [2, 12].

Reactions involving nitrates and nitrites after ingestion

The chemical structures of the nitrate and nitrite ions can be seen below (figure 1).

1



2

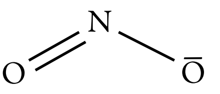


Figure 1. Chemical structure of nitrate (1) and nitrite (2) ions.

These ions can be found in organic and inorganic form. The organic ones are more complex from the structural point of view, being obtained in a synthetic way, while the inorganic ones are structurally simpler and occur naturally [27].

In the human organism, these compounds appear endogenously (biosynthesis process) and exogenously (water and food) [27, 28]. After ingesting the food or water containing these preservatives, regardless of concentration, there is a natural reaction of reduction by bacterial enzymes (nitrates reductases) and there is a biotransformation of nitrate (NO_3) into nitrite (NO_2) (equation 1).

$$NO_3^- + 2H^+ + 2e^- \longleftrightarrow NO_2^- + H_2O$$

Reaction 1. Biotransformation from nitrate to nitrite by reducing bacteria.

Although nitrate is moderately stable, but nitrite is extremely reactive and this characteristic allows an easy formation of N-nitrous compounds (carcinogens), such as N-nitrosodimethylamine and monomethylnitrosamine, which are about ten times more toxic than nitrates [28-30].

Nitrite is converted into nitrous acid, in the presence of favorable reducing conditions for carrying out the reaction, in which the nitrous acid is reduced to nitric oxide. It is possible to observe the reactions that happen (figure 2), which are potentiated by the acidic pH of the stomach [27, 29].

$$NaNO_2 + H_2O \xrightarrow{\text{pH } 5.4-6.0} HNO_2 + NaOH$$

$$3\,NHO_2 \xrightarrow{\text{Reducing substances}} 2NO + HNO_3 + H_2O$$

Figure 2. Formation of nitrous acid (1) and nitric oxide (2).

The consumption of nitrates and nitrites and the appearance of cancers

The excessive consumption of nitrates and nitrites, whether through water or food, has been associated with a great diversity of diseases, stimulating the development of several studies investigating, including, the correlation between the consumption of these preservatives and the appearance of cancers (table 2).

Since 1992, studies have linked the consumption of nitrates and nitrites to cancer. It is known that cancer is a set of several neoplasms that can originate in any part of the body, having a multifactorial cause. In this perspective, the studies analyzed the relationship between the consumption of healing salts and the development of a variety of neoplasms and it was possible to observe that a direct association of the intake of these preservatives and the emergence of non-Hodgkin's lymphoma, gastric cancer, rectal cancer, and prostate cancer. However, some researchers have failed to prove this relationship [31-42]. This contradiction can be influenced by numerous factors, considering that the development of type of cancers can be related to several other population factors, such as age, gender, genetic predisposition, eating habits and lifestyle associated with smoking and consumption of alcohol, disregarding the rules and inspection of each country regarding the presence of these salts in the water and food offered to the population.

In studies in which correlations or an increased likelihood of neoplasms were observed, it was noted that gastric cancer has been the most cited of all, which is a worrying finding, since it is considered the sixth most common cancer in world and the third

Table 2. Conclusions about the consumption of water and foods rich in nitrates and nitrites and the appearance of cancers, from studies published between 1992 and 2017.

Author and year	Food type	Sample size	Article title	Cancer type and conclusions
Gulis, Czompolyova and Cerhan [31]	Water	197 854 individuals. 96341 men and 101513 women.	An ecologic study of nitrate in municipal drinking water and cancer incidence in Trnava District, Slovakia.	Non-Hodgkin's lymphoma and incidence of colorectal cancer was observed among men and women exposed to water containing high concentrations of nitrates (> 20 mg/L).
Jensen [32]	Water	1113 individuals. The study did not differ between the sexes of the participants.	Nitrate in drinking water and cancer in northern Jutland, Denmark, with special reference to stomach cancer.	It was observed that the consumption of nitrate seems to be weakly associated with the development of gastric cancer, believing that nitrate is only one of the several factors associated with gastric cancer.
Knekt *et al.* [33]	Cured meats and sausages, vegetables, and beer	9985 individuals. 5274 men, 4711 women.	Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study.	There was no correlation between nitrite consumption and the incidence of tumors in the stomach and intestine.
Law *et al.* [34]	Water	20702 individuals. The study did not differ between the sexes of the participants.	Non-Hodgkin's lymphoma and nitrate in drinking water: a study in Yorkshire, United Kingdom.	No association was found between the consumption of high concentrations of nitrate and bladder and kidney cancers, however it seemed to contribute to the appearance of non-Hodgkin's lymphoma.

Table 2. *(Continuation)*.

Author and year	Food type	Sample size	Article title	Cancer type and conclusions
Yang, Wu and Chang [35]	Water	2234 individuals. 1310 men and 924 women.	Nitrate in drinking water and risk of death from colon cancer in Taiwan.	There is no correlation between water consumption and colon cancer.
Zhu *et al.* [36]	Beer, pickled vegetables, and meats.	4241 individuals, 2291 men and 1, 950 women.	Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada.	Ingestion of N-nitrous compounds was associated with an increased risk of developing colorectal cancer, specifically for rectal carcinoma.
Loh *et al.* [37]	Meat	3268 individuals with cancer. 1 671 men and 1 597 women.	N-nitroso compounds and cancer incidence: the European prospective investigation into cancer and nutrition (EPIC)-Norfolk study.	The diet rich in N-nitrous compounds is correlated with an increased risk of rectal cancer.
Morales-Suarez-Varela, et al., [38]	Water	*	Impact of nitrates in drinking water on cancer mortality in Valencia, Spain.	There was a correlation between the consumption of water containing nitrates (> 25 mg/L) and the increased mortality from gastric and prostate cancer.
Palli *et al.* [39]	Various foods	24 patients. 15 men and 9 women.	O6-alkylguanines, dietary N-nitroso compounds, and their precursors in gastric cancer.	Association between gastric cancer and elevated dietary nitrate intake.

Table 2. *(Continuation).*

Author and year	Food type	Sample size	Article title	Cancer type and conclusions
Song, Wu and Guan [40]	*	*	Dietary Nitrates, Nitrites, and Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis.	Nitrites have been associated with an increased risk of gastric cancer.
Van Loon *et al.* [41]	Vegetables, water, and meat	282 members of the cohort (219 men and 63 women) and 3123 members of the subcohort (1525 men and 1598 women).	Intake of nitrate and nitrite and the risk of gastric cancer: a prospective cohort study.	There was no correlation between the levels of nitrate ingested and stomach cancer.
Taneja *et al.* [42]	Water and vegetables	234 individuals, of whom 78 had gastric cancer (47 men and 31 women) and 156 were in the control group (110 men and 46 women).	The risk of cancer as a result of elevated levels of nitrate in drinking water and vegetables in Central India.	Indicated that the intake of >45 mg/L nitrate via drinking water produced an additional Gastric Cancer risk.

* No data.

with the highest mortality rate [43, 44]. High mortality is associated with the fact that gastric cancer is usually silent, causing those affected to show signs and symptoms when the tumor is already quite developed. In these stages there is, for example, weight loss, constipation, vomiting and, in more advanced clinical situations, there is the presence of a palpable tumor mass [45]. A systematic review with meta-analysis, carried out on stomach cancer, showed that there is a statistically significant association between the high or moderate consumption of nitrates and the appearance of this type of cancer [46].

Colorectal cancer, in turn, covers tumors in the regions of the large intestine, mainly involving the colon, rectum and anus. Those affected usually have abdominal pain, bleeding in the stools, weight loss, anemia, and abdominal mass (tumor) [47], while non-Hodgkin's lymphoma is a type of cancer that originates in the lymphatic system, arising when a lymphocyte turns into a malignant cell, with the presence of water, fevers, night sweats, pruritus, and weight loss [48].

All cancers evidenced in the studies that are correlated with the consumption of NO_2^- and NO_3^-, can arise due to the excessive consumption of industrialized foods such as sausage, sausage, ham, bologna, salami, among others. In addition, it is important to highlight that, as already mentioned in this study, these foods are rich in nitrates and nitrites and in several studies, they present concentrations above those allowed by the laws of different countries, with the possibility of consuming foods rich in these preservatives, be directly related to the appearance of neoplasms [47].

In studies that observe a high consumption of nitrites and nitrites, there is a higher prevalence for the appearance of cancers when compared to populations where there is no consumption of such compounds. This finding has been proven in the laboratory through the quantification of nitrates in the urine and saliva of individuals affected by different types of cancers [49].

However, even though it is not completely clear, the general concern with prolonged exposure to nitrite and nitrate is due to the formation of nitrosamines, which are extremely carcinogenic nitrogen compounds [50]. In addition, it is important to show that nitrate is naturally eliminated from the body through urine and saliva, however nitrite tends to accumulate and contribute to the formation of N-nitrous compounds [51].

Nitrates are bioconverted to nitrites by reducing bacteria in the oral cavity, leading to increased production of free radicals. In addition, in the stomach, these nitrites are bioconverted to nitrosamines that are widely absorbed by the gastrointestinal tract, which can cause injury to several cells. Nitrosamines, once they come into contact with different cells from different tissues, can react with the DNA molecule, promoting the formation of adducts. But, for this, those compounds that do not undergo bioaccumulation need to be metabolized. Biotransformation starts from the hydroxylation of the carbon of the alkyl group, with the enzyme CYP2E1, as the main catalyst. Thus, there is the formation of an aldehyde or ketone and a primary nitrosamine, which tautomerizes to an alkyldiazohydroxide that can give rise to a diazonic ion, which takes up nucleophilic sites of DNA and RNA, with the formation of adducts and causing possible mutations (figure 3) [26, 51, 52, 53].

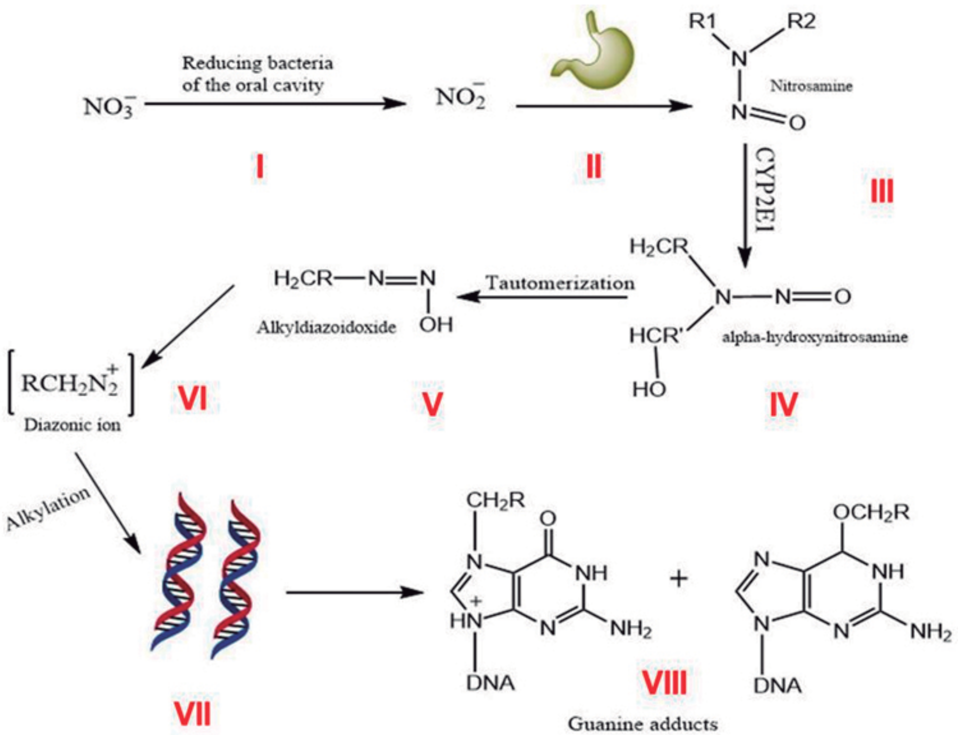


Figure 3. Mechanisms of adduct formation after ingesting nitrates and nitrites. I.Nitrates are bioconverted to nitrites, by reducing bacteria, in the oral cavity. II. In the stomach, nitrites are bioconverted to nitrosamines. III.Nitrosamines undergo hydroxylation of the carbon of the alkyl group, with the enzyme CYP2E1 as the main catalyst. IV. There is formation of an aldehyde or ketone and a primary nitrosamine. V. Occurs tautomerization to an alkyldiazohydroxide. VI. Diazonic ion is formed. VII. The diazonic ion alkylates DNA nucleophilic sites. VIII. Adduct formation and possible mutations.

Another evidence that supports the hypothesis that these compounds are carcinogenic is the appearance of micronuclei in lymphocytes from individuals who excrete these nitrogen compounds in the urine. The presence of a micronucleus, by itself, indicates mutations and an increased risk of cancer [54].

In addition, nitrosamines, which can originate through nitrates and nitrites, have been classified in group 2A for toxic substances, indicating that there is indeed evidence of their carcinogenic potential in humans and rodents. Furthermore, the toxicity of nitrates and nitrites occurs differently for each person, since age, nutritional and immune status, environment, and frequency of ingestion of certain foods, may be associated with the appearance of cancers [2, 26, 53].

Conclusion

Nitrates and nitrites are important for the conservation and improvement of organoleptic characteristics in various foods, and can be found in meat products, dairy products, fruits, and vegetables. For this reason, it is relevant to emphasize that it is already well documented in the literature that these compounds, when biotransformed, have a carcinogenic potential, so that it becomes interesting to avoid excessive consumption of these food inputs.

However, the different studies are still contradictory in relation to the results expressed. Thus, there is a lack of epidemiological studies that can characterize different populations and different neoplasms in relation to the consumption of these healing salts, making the data present in this research can be used to encourage the emergence of new research on this topic.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. M.A. Coimbra, B.B. Oliveira, F. Poças, A. Teixeira, I. Delgadillo, Aditivos e contaminantes da cadeia alimentar: enquadramento legal, progressos relevantes e riscos emergentes (Riscos e Alimentos), *Conselho Científico da ASAE*, **14**, 36-43 (2017).

2. L.Z. Iamarino, M.C. Oliveira, M.M. Antunes, M. Oliveira, R.O. Rodrigues, C.I.C.B. Zanin, M. Schimile, A.A. Lima, Nitritos e nitratos em produtos cárneos enlatados e/ou embutidos, *Gestão Foco*, 7, 246-251 (2015).

3. A. Fratucci, L. Silva, M.D.C.S. Guedes, Nitratos, nitritos e n-nitrosaminas: efeitos no organismo, *Revista Eletrônica FACP*, **6**(11), 41-55 (2017).

4. R. Olivo, L.G.T. Ribeiro, New concepts on nitrates and nitrites, *Braz. J. Surg. Clin. Res.*, **24**, 115-125 (2018).

5. Brasil, Ministério da Saúde, *Câncer: o que é, causas, tipos, sintomas, tratamentos, causas e prevenção*, 2019. URL: http://portalms.saude.gov.br/saude-de-a-z/cancer, consultado em: 20 dez. 2019.

6. F.S. Ferreira, Aditivos alimentares e suas reações adversas no consumo infantil, *Rev. Univ. Vale do Rio Verde*, **13**, 397-407 (2015).

7. L. Rodrigues, *Exigência do consumidor perante a indústria de alimentos: Revisão de literatura*, Trabalho de Conclusão de Curso, Bacharelado em Engenharia de Alimentos, Instituto Federal Goiano, Rio Verde, 2019, pp. 1-25.

8. A.A. Chetty, S. Prasad, Flow injection analysis of nitrate and nitrite in commercial baby foods, *Food Chem.*, **197**, 503-508 (2016).

9. B.Y. Abdulkair, A.O. Elzupir, A.S. Alamer, An ultrasound assessed extraction combined with ion-pair HPLC method and risk assessment of nitrite and nitrate in cured meat, *J. Anal. Methods Chem.*, **2018**, ID 1907151, 1-6 (2018).

10. S. Genualdi, N. Jeong, L. Dejager, Determination of endogenous concentrations of nitrites and nitrates in different types of cheese in the United States: method development and validation using ion chromatography, *Food Addit. Contamin.: Part A*, **35**, 615-623 (2018).

11. D. dos Santos-Baião, C.A. Conte-Junior, V.M.F. Paschoalin, T.S. Alvares, Quantitative and comparative contents of nitrate and nitrite in *Beta vulgaris* L. by reversed-phase high-performance liquid chromatography-fluorescence, *Food Anal. Methods*, **9**, 1002-1008 (2016).

12. J. Silalahi, A.F. Nasution, N. Ginting, Y.C. Silalahi, The effect of storage condition on nitrite and nitrate content in lettuce (*Lactuca sativa* L.), *Int. J. PharmTech Res.*, **9**, 422-427 (2016).

13. F.S. Adami, L.S. Giovanaz, G. Altenhofen, S.M. dal Bosco, A. Marcadenti, E.C. Oliveira, Análise microbiológica e de nitrito e nitrato em linguiça, *Scientia Plena*, **11**, 1-7 (2015).

14. V.S.C. Sousa, L.H.G.M. Lima, S.A. Teixeira, B.V.S. Cardoso, Quantificação de nitrato e nitrito utilizados em linguiças tipo calabresa comercializadas em Picos-PI, *Rev. Intertox, Toxicol. Risco Amb. Soc.*, **9**, 55-67 (2016).

15. J.F. Oliveira, U.R. Silva, V.A.A. Pastore, E.C. Azevedo, G.M. Campos, F.C.G. Silva, F. Raghiante, O.A. Martins, Determinação espectrofotométrica de nitrito em produtos cárneos embutidos, *Rev. Bras. Hig. Sanid. Animal*, **11**, 19-31 (2017).

16. F.M. Makki, P. Ziariti, Nitrate and nitrite in fresh tomatoes and tomato products, *Biomed. Pharmacol. J.*, **8**, 115-122 (2015).

17. P. Alexander, P. Handawa, U.T. Charles, Determination of nitrate and nitrite contents of some edible vegetables in Guyuk Local Government Area of Adamawa State, Nigeria, *Amer. Chem. Sci. Int. J.*, **13**(3), 1-7 (2016).

18. N.B. Perufo, L. Hoehne, Análise de sais de cura em salames tipo colonial comercializados na Serra do Rio Grande do Sul, *Rev. Destaq. Acadêm.*, 7, 193-201 (2015).

19. D. Hentges, N. Zart, L.G. Marmitt, E.C. Oliveira, F.S. Adami, Concentrações de nitrito e nitrato em salsichas, *Rev. Bras. Promoç. Saúde*, **29**, 27-33 (2016).

20. G.H.F. Faria, A.F. Moreno, M.F.A. Silveira, R.M. Geraldine, D.M. Carvalho, Avaliação do teor de nitrito em apresuntados armazenados em diferentes temperaturas, *Rev. Proc. Quím.*, **10**, 281-285 (2016).

21. Z. Bahadoran, P. Mirmiran, S. Jeddi, F. Azizi, A. Ghasemi, F. Hadaegh, Nitrate and nitrite content of vegetables, fruits, grains, legumes, dairy products, meats and processed meats, *J. Food Comp. Anal.*, **51**, 93-105 (2016).

22. R. Laia, A. Rebelo, C. Serra, E. Vasco, Teor de nitrato em produtos hortícolas e frutos consumidos ao longo do ano em Portugal, *Bol. Epidemiol.*, 7, 21-24 (2018).

23. Z. Ding, S. D. Johanningsmeier, R. Price, R. Reynolds, V.-D. Truong, S.C. Payton, F. Breidt, Evaluation of nitrate and nitrite contents in pickled fruit and vegetable products, *Food Control*, **90**, 304-311 (2018).

24. J.R. Scheibler, M.I. Marchi, C.F.V. Souza, Análise dos teores de nitritos e nitratos de embutidos produzidos em municípios do Vale do Taquari-RS, *Rev. Destaq. Acadêm.*, **5**, 201-207 (2013).

25. F.M.C. Ganhão, *Evolução do teor de nitritos e de nitratos e da concentração de pigmentos no fiambre e na mortadela ao longo do seu processo produtivo e do seu prazo de vida útil*, Dissertação de Mestrado, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2011, p. 1-111.

26. C.M.J. Benevides, M.V. Souza, R.D.B. Souza, M.V. Lopes, Fatores antinutricionais em alimentos: revisão, *Segurança Alimentar e Nutricional*, **18**, 67-79 (2011).

27. ATSDR, *ATSDR Case Studies in environmental Medicine -Nitrate/Nitrite toxicity*, Department of Health and Human Services -Agency for toxic substances and disease registry, 2013, pp. 1-90.

28. S.A. Omar, E. Artime, A.J. Webb, A comparison of organic and inorganic nitrates/nitrites, *Nitric Oxide*, **26**, 229-240 (2012).

29. N.S. Bryan, J.L. Ivy, Inorganic nitrite and nitrate: evidence to support consideration as dietary nutrients, *Nutrit. Res.*, **35**, 643-654 (2015).

30. K.O. Honikel, The use and control of nitrate and nitrite for the processing of meat products, *Meat Sci.*, **78**, 68-76 (2008).

31. G. Gulis, M. Czompolyova, J.R. Cerhan, An ecologic study of nitrate in municipal drinking water and cancer incidence in Trnava District, Slovakia, *Environm. Res.*, **88**, 182-187 (2002).

32. O.M. Jensen, Nitrate in drinking water and cancer in northern Jutland, Denmark, with special reference to stomach cancer, *Ecotoxicol. Environm. Safety*, **6**, 258-267 (1982).

33. P. Knekt, R. Jarvinen, J. Dich, T. Hakulinen, Risk of colorectal and other gastrointestinal cancers after exposure to nitrate, nitrite and Nnitroso compounds: a follow-up study, *Int. J. Cancer*, **80**, 852-856 (1999).

34. G. Law, R. Parslow, P. McKinney, R. Cartwright, Non-Hodgkin's lymphoma and nitrate in drinking water: a study in Yorkshire, United Kingdom, *J. Epidemiol. Commun. Health*, **53**, 383-384 (1999).

35. C.Y. Yang, D.C Wu, C.C. Chang, Nitrate in drinking water and risk of death from colon cancer in Taiwan, *Environm. Int.*, **33**, 649-653 (2007).

36. Y. Zhu, P.P. Wang, J. Zhao, R. Green, Z. Sun, B. Roebothan, J. Squires, S. Buehler, E. Dicks, J. Zhao, M. Cotterchio, P.T. Campbell, M. Jain, P.S. Parfrey, J.R. Mclaughlin, Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada, *Brit. J. Nutrit.*, **28**, 1109-1117 (2014).

37. Y.H. Loh, P. Jakszyn, R.N. Luben, A.A. Mulligan, P.N. Mitrou, K.T. Khaw, N-Nitroso compounds and cancer incidence: the European prospective investigation into cancer and nutrition (EPIC)-Norfolk study, *Amer. J. Clin. Nutrit.*, **93**, 1053-1061 (2011).

38. M.M. Morales-Suarez-Varela, A. Llopis-Gonzalez, M L. Tejerizo-Perez, Impact of nitrates in drinking water on cancer mortality in Valencia, Spain, *Eur. J. Epidemiol.*, **11**, 15-21 (1995).

39. D. Palli, C. Saieva, C. Coppi, G. del Giudice, C. Magagnotti, G. Nesi, F. Orsi, L. Airoldi, O6-alkylguanines, dietary N-nitroso compounds, and their precursors in gastric cancer, *Nutrit. Cancer*, **39**, 42-49 (2001).

40. P. Song, L. Wu, W. Guan, Dietary nitrates, nitrites and nitrosamines intake and risk of gastric cancer: A meta-analysis, *Nutrients*, 7, 9872-9895 (2015).

41. A.J. Van Loon, A.A. Botterweck, R.A. Goldbohm, H.A. Brants, J.D. Van Klaveren, P.A. Van Den Brandt, Intake of nitrate and nitrite and the risk of gastric cancer: a prospective cohort study, *Brit. J. Cancer*, **78**, 129-135 (1998).

42. P. Taneja, P. Labhasetwar, P. Nagarnaik, J.H. Ensink, The risk of cancer as a result of elevated levels of nitrate in drinking water and vegetables in Central India, *J. Water Health*, **15**, 602-614 (2017).

43. INCA (Instituto Nacional do Câncer), *Câncer de Estômago*, URL: https://www.inca.gov.br/tipos-de-cancer/cancer-de-estomago, consultado en 01 octubre de 2020.

44. INCA (Instituto Nacional do Câncer), *Atlas do INCA*, URL: https://www.inca.gov.br/MortalidadeWeb/pages/Modelo10/consultar.xhtml#panelResultado, consultado en 01 octubre de 2020.

45. M.S. Farias, K.M. Azevedo-Ponte, D.F. Gomes, R.S.P. Menezes, Câncer gástrico e seu dimensionamento nas redes de serviços de saúde: Estudo bibliográfico, *Rev. Saúde em Foco, Teresina*, **4**, 48-57 (2017).

46. F.X. Zhang, Y. Miao, J.G. Ruan, S.P. Meng, J.D. Dong, H. Yin, Y. Huang, F.R. Chen, Z.C. Wang, Y.F. Lai, Association between nitrite and nitrate intake and risk of gastric cancer: A systematic review and meta-analysis, *Med. Sci. Mont*, **9**, 1788-1799 (2019).

47. INCA (Instituto Nacional do Câncer), *Câncer de intestino*, URL: https://www.inca.gov.br/tipos-de-cancer/cancer-de-intestino, consultado en 01 octubre de 2020.

48. INCA (Instituto Nacional do Câncer), *Linfoma não-Hodgkin*, URL: https://www.inca.gov.br/tipos-de-cancer/linfoma-nao-hodgkin, consultado en 01 octubre de 2020.

49. P. Zhang, J. Lee, G. Kang, Y. Li, D. Yang, B. Pang, Y. Zhang, Disparity of nitrate and nitrite in vivo in cancer villages as compared to other areas in Huai River Basin, China, *Sci. Total Environm.*, **612**, 966-974 (2018).

50. M. Parvizishad, A. Dalvand, A. H. Mahvi, F. Goodarzi, A review of adverse effects and benefits of nitrate and nitrite in drinking water and food on human health, *Health Scope Int. Quart. J.*, **6**, e14164, 1-9 (2017).

51. A. Garófolo, C.M. Aversani, K.G. Camargo, M.E. Barros, S.R.J. Silva, J.A.A.C. Taddei, D.M. Sigulem, Dieta e câncer: um enfoque epidemiológico, *Rev. Nutrição*, **17**, 491-505 (2004).

52. A.J. Gushgari, R.U. Halden, Critical review of major sources of human exposure to N-nitrosamines, *Chemosphere*, **210**, 1124-1136 (2018).

53. C.D. Dutra, S. Rath, F.G.R. Reyes, Nitrosaminas voláteis em alimentos, *Alimentos e Nutrição*, **18**, 111-120 (2008).

54. M. Habermeyer, A. Roth, S. Guth, P. Diel, K. H. Engel, B. Epe, G. Eisenbrand, Nitrate and nitrite in the diet: how to assess their benefit and risk for human health, *Mol. Nutr. Food Res.*, **59**, 106-128 (2014).

How to cite this article

F.P. de Andrade Júnior, A.L. Sobreira de Cabral, J.M. Dantas de Araújo, L. Vilar-Cordeiro, M. de Barros-Cândido, A. Pontes da Silva, B. Tamires de Medeiros-Lima, B. Braga-Dantas, Food nitrates and nitrites as possible causes of cancer: A review, *Rev. Colomb. Cienc. Quím. Farm*. **50**(1), 269-291 (2021).