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Intake and food sources of nitrites and *N*-nitrosodimethylamine in Spain

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Abstract

Objective: To conduct a comprehensive assessment of dietary intakes of nitrites and *N*-nitrosodimethylamine (NDMA).

Subjects and setting: A study was conducted within the Spanish cohort of the European Prospective Investigation in Cancer and Nutrition (EPIC) to assess the intake and food sources of these compounds in Spanish adults. The study included 41 446 health volunteers, aged 29–69 years, from Northern and Southern regions. Usual food intake was estimated by in-person interviews using a computerised dietary questionnaire.

Results: The estimated geometric mean was 0.994 mg day^{-1} for nitrites and 0.114 μg day^{-1} for NDMA. For both compounds a positive trend in consumption with increasing energy intake was observed. Dietary NDMA was related to age and sex after energy adjustment, while nitrite consumption increased with higher intakes of vitamin C ($P < 0.001$). The food groups that contributed most to intakes were meat products, cereals, vegetables and fruits for nitrites, and processed meat, beer, cheese and broiled fish for NDMA. Current and past smokers, who had high levels of NDMA from tobacco exposure, were also identified as the highest consumers of dietary NDMA. Furthermore, smokers had low intakes of vitamin C (an inhibitor of endogenous nitrosation).

Conclusions: Intake levels of NDMA and nitrites in a Mediterranean cohort are currently relatively lower than those previously reported, although processed meat, beer and cured cheese still are the most important contributors to NDMA intake.

Keywords
Nitrites
Nitrosamines
Dietary intake
N-Nitrosodimethylamine
Cancer risk

Humans are exposed to *N*-nitroso compounds (NOC) from diet, tobacco smoke and other environmental sources, as well as from endogenous synthesis[1]. Diet has been identified as the major source of exogenous exposure[2]. Of the various NOC, nitrosamines (NA) have been studied the most extensively in foods. These compounds are formed through the reaction of a nitrosating agent (nitrogen oxides) with amino compounds. Nitrogen oxides are derived from two main sources: (1) the addition of nitrate and/or nitrite to foods and (2) the process of heating and/or drying of foods using combustion gas, during which molecular nitrogen can be oxidised. The highest concentrations of NA are found in cured meat and cheese, smoked preserved foods, foods preserved by drying, pickling and salting, and foods stored under humid conditions[3]. The major NA in the diet are *N*-nitrosodimethlyamine (NDMA), *N*-nitrosopyrrolidine and *N*-nitrosopiperidine.

In vitro and *in vivo* studies have shown that nitrates can be reduced to nitrites by bacterial or mammalian metabolic pathways. Thus, both nitrites and nitrates reduced to nitrites may react endogenously with amines and amides derived from proteins to form carcinogenic NOC[3]. Several studies have reported that endogenous synthesis could contribute 45–75% of total human exposure[4]. This process could be modified by several factors; for instance, vitamin C has been identified as an effective inhibitor of endogenous synthesis[5]. Nitrites are widely used as food preservatives and colouring agents by the food industry. They are mainly found in cured meat

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products, fish and cheeses. Nitrites may also be found in cereal products and vegetables as a result of formation during storage and/or cooking. Although nitrates can be reduced to nitrites, there is not much evidence about their relation to cancer risk.

Various NOC have been found to be carcinogenic in multiple organs in at least 40 animal species, including higher primates[6]. Many studies have reported that a high intake of NA may increase the incidence of nasopharyngeal, oesophageal, pancreatic, gastric, brain and colorectal cancers[7,8]; however, their health effects in humans still have not been clearly established. NDMA and *N*-nitrosodiethylamine are classified by the International Agency for Research on Cancer as probable carcinogens for humans[9].

In the majority of studies carried out to date, the estimation of dietary exposure to NA and NA precursors has focused only on those foods in which the content is high. The advantage of an assessment with a complete list of food items is that all dietary sources of the compound of interest are included. Foods with modest content consumed frequently by a substantial part of the population can be as important as infrequently consumed foods with higher content. In summary, more comprehensive assessment of intake from a wide array of potential dietary sources is needed in order to evaluate the health effects of these compounds in epidemiological research[10].

Recently, we have compiled the information available on the content of nitrates, nitrites and NA in foods[11]. In the present study we used the data to estimate the dietary intake of nitrites and NDMA in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC). We also explored associations between intakes and several variables that might affect NDMA exposure.

Material and methods

Study population

Dietary data and other lifestyle factors from 25 812 women and 15 634 men aged 29–69 years, participants of the EPIC–Spain cohort, were obtained between October 1992 and July 1996. Participants were healthy volunteers recruited in five Spanish regions: three from the North (Asturias, Navarra and Guipúzcoa) and two from the South (Murcia and Granada). Most of the selected subjects were active bloods donors. The mean age at recruitment was 50.8 and 48.4 years for men and women, respectively. The final participation rate was 55–60% across centres.

Dietary information

Usual food intake during the preceding year, taking into account seasonal variations, was estimated by an in-person interview using a computerised dietary history questionnaire which was developed and validated specifically for the EPIC study in Spain[12]. The questionnaire was structured according to occasions of food intake. Trained interviewers gathered data on preparation methods, average frequency of consumption, and usual portion sizes for each food consumed at least twice per month (or once per month for seasonal foods). Portion sizes were reported in natural units, household measures or with the aid of 35 sets of photographs prepared specifically for the study. The questionnaire included a list of 600 foods and beverages, and about 150 regional recipes. Data on vitamin C in foods were obtained from a computerised database of more than 700 food items compiled for the EPIC study in Spain[13]. We took only food sources into account because less than 4% of participants in the study took mineral or vitamin supplements during the previous week[14].

Estimation of nitrite and NDMA intakes

Dietary intakes of nitrites and NDMA were estimated based on information compiled recently in a food database (FDB)[11]. The FDB includes information about 278 and 313 food items for nitrites and NA, respectively. Since considerably more information is available for NDMA than for other NA found in foods, we decided to estimate only dietary intakes of NDMA. Since the food item could have several different source of information, we selected Spanish or European values when they were available. For food items for which content was not available, the value of the nearest comparable food was assigned. When we found several matches for a food item we assigned the mean of all the suitable values ($<5\%$ of the food items).

Statistical analysis

Means for nitrites and NDMA are reported as $\mathrm{mg\,day^{-1}}$ and $\mu\mathrm{g\,day^{-1}}$, respectively. As nitrite and NDMA distributions were strongly right-skewed, we used the natural logarithm ($\log_e$) transformation to improve normality. Arithmetic means for the log-transformed intakes were later exponentiated to obtain the geometric means. Analysis of variance was used to assess differences in nitrite and NDMA intakes across categories of different variables, adjusting for sex, age, energy intake, centre and body mass index (BMI)[15]. The average estimates of dietary intakes of nitrites and NDMA for the whole cohort were age- and sex-standardised based on the structure of the Spanish population (aged 35–64 years)[16].

In order to identify food sources of these compounds in our population, the individual contribution of each food item to the total compound intake was computed. Additionally, to identify which foods better explain the variability in intakes of NDMA, foods were ranked based on the proportion of variance in NDMA they explained (R^2), using linear regression analysis with stepwise selection[15]. Data were analysed using software from the R Foundation for Statistical Computing[17].

Results

The number of food items from the diet history linked to the FDB was 149 for nitrites and 257 for NDMA. The estimated geometric mean was 0.994 mg day^{-1} for nitrites and 0.114 μg day^{-1} for NDMA (age- and sex-standardised based on the Spanish population structure)[16].

Geometric means of both compounds were computed separately for categories of sex, age, centre, smoking, BMI, energy intake and vitamin C intake (Table 1). Means were adjusted by sex, age, BMI, centre and energy consumption. For nitrites, we found a positive trend across categories of energy intake. The group with the highest energy intake had 46% more nitrites than the group with the lowest energy intake. When comparing intakes of nitrites in relation to intakes of vitamin C, we observed a positive gradient (Fig. 1). We found a 27% difference between the highest and the lowest quartiles of vitamin C consumption. Differences in the intake of nitrites across categories of sex, age, centre, BMI and smoking did not follow a significant pattern.

NDMA intakes were 20% higher in men (0.118 μg day^{-1}) than in women (0.098 μg day^{-1}). Geometric mean NDMA intakes tended to decline with increasing age. The lowest values were observed in older people while the highest were found in young individuals (0.085 vs. 0.117 μg day^{-1}). When comparing NDMA intake across levels of energy intake, the difference between the highest and the lowest energy intake group was 79%. There were no meaningful differences in NDMA intake across categories of centre, BMI, tobacco use and vitamin C.

The association between vitamin C consumption and NDMA intake was also examined after stratifying based on categories of tobacco use, as shown in Fig. 2. Current and past smokers in the bottom two quintiles of vitamin C consumption had substantially higher levels of NDMA than smokers in the top two quintiles of vitamin C intake.

Table 1 Intakes of nitrites and *N*-nitrosodimethylamine (NDMA) in categories of different variables

		Nitrites (mg day^{-1})		NDMA (μg day^{-1})	
	n	Geometric mean*†	Proportion of change‡	Geometric mean*†	Proportion of change‡
Sex§					
Male	15 579	0.96	1.00	0.12	1.00
Female	25 752	0.96	0.99	0.10	0.80
Age (years)§					
28–34	300	0.97	1.00	0.12	1.00
35–44	13 808	0.97	0.99	0.12	0.98
45–54	16 075	0.96	0.98	0.11	0.89
55–64	10 693	0.95	0.97	0.09	0.80
65–74	455	0.94	0.96	0.09	0.72
Energy intake (kcal day^{-1})§					
Q1 (323–1750)	10 321	0.79	1.00	0.08	1.00
Q2 (1750–2180)	10 331	0.93	1.17	0.10	1.26
Q3 (2180–3270)	10 338	1.00	1.26	0.12	1.44
Q4 (2730–3102)	10 341	1.15	1.46	0.14	1.79
Centre§					
North Spain	25 109	1.01	1.00	0.10	1.00
South Spain	16 307	0.91	0.90	0.11	1.05
Body mass index (kg m^{-2})§					
< 25	9195	0.96	1.00	0.11	1.00
25–30	19 674	0.96	1.00	0.11	0.99
> 30	12 462	0.96	1.00	0.104	0.98
Vitamin C intake (mg day^{-1})§					
Q1 (1.45–94)	10 341	0.85	1.00	0.11	1.00
Q2 (94–137)	10 325	0.94	1.10	0.11	1.00
Q3 (137–191)	10 335	0.99	1.16	0.10	0.97
Q4 (191–1263)	10 330	1.08	1.27	0.10	0.95
Smoking§					
Never	22 927	0.96	1.00	0.10	1.00
Past	7285	0.97	1.01	0.11	1.05
Current	10 109	0.92	0.95	0.11	1.04

Q – quartile.
* Adjusted for sex, age, energy intake, body mass index (BMI) and centre.
† The values reported are calculated over the number of subjects with valid information; the numbers of subjects with missing information were as follows: sex, age, energy intake, BMI and vitamin C (115), centre (30) and tobacco smoking (1125).
‡ This value shows the proportional change taking the first category as reference.
§ In all cases *P*-values were < 0.001, except for nitrites in categories of BMI.

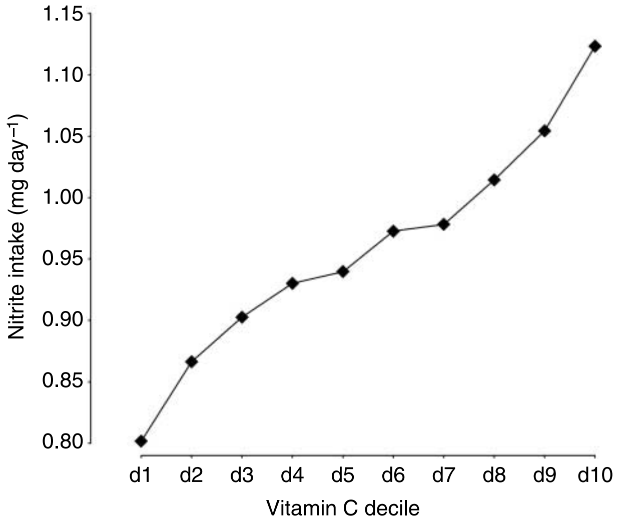

Fig. 1 Intake* of nitrites by vitamin C decile (d). *Geometric means adjusted by age, sex, centre, energy intake and body mass index

Among never smokers, there was no association between NDMA and vitamin C.

The food groups that contributed most to intakes of each compound were also identified (Table 2). For NDMA, we identified the following food items: cured meats (14%), cheese (13%), frankfurters (12%), beer (11%), bacon (11%), broiled fish (5%) and fresh sausage (4%). Overall, processed meat contributed more than 40% to total NDMA intakes. For NDMA we also analysed the contribution of foods to the between-person variance. The major contributors to the variance were frankfurters, beer, bacon and cured meats ($R^2 = 0.71$) (data not shown). The food items selected by the model were the same as the main contributors to total intake, but their relative contribution in terms of explained variance or slopes in intake was not the same. The food items that contributed most to nitrite intakes were meat products (boiled ham, bacon, sausage, hamburger), cereals (bread, spaghetti), vegetables (potato, lettuce, leek, tomato, cucumber) and fruits (orange, apple, pear, peach) (Table 2).

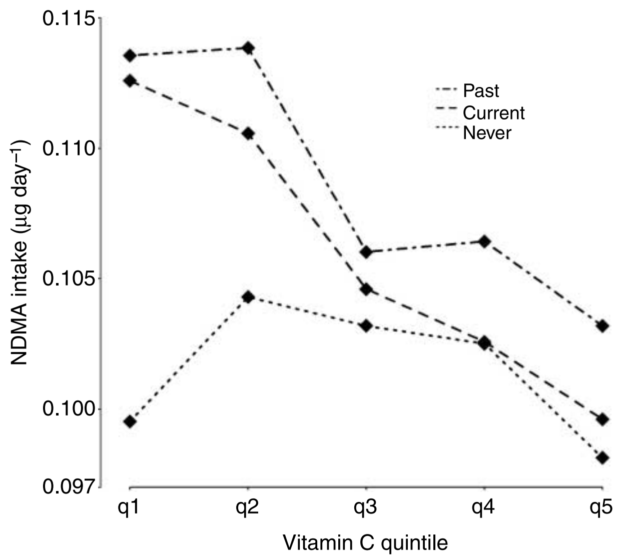

Fig. 2 Intake* of *N*-nitrosodimethylamine (NDMA) by vitamin C quintile (q) in past, current and never smokers. *Geometric means adjusted by age, sex, centre, energy intake and body mass index

Discussion

In the present study we estimated dietary intakes and food sources of nitrites and NDMA in Spanish adults. The geometric mean was $0.994\,\mathrm{mg\,day^{-1}}$ and $0.114\,\mu\mathrm{g\,day^{-1}}$ for nitrites and NDMA, respectively.

Analysis of the NDMA distribution suggests that dietary intakes are 20% higher for men than for women. Several other studies have also shown that intake in men could be up three times higher[18–20]. A possible explanation for sex differences in this study is that men consumed significantly more beer and processed meat than women, given that these foods are strongly related to NDMA intake.

The relationship between NDMA and age was negative, as intakes in younger people were higher than in older individuals. The difference between the oldest and youngest individual was 28%. This pattern was attributable to the higher intakes of processed meat and beer among younger subjects.

For both nitrites and NDMA a positive association with energy intake was observed. This could be a consequence of the substantial contribution of key food sources of nitrites and NDMA to total energy intakes. This link with energy intake was stronger for NDMA than for nitrites, probably because NDMA is concentrated in food groups with high energy density ($\mathrm{kcal\,g^{-1}}$) such as processed meat and beer, while the key sources of nitrites include foods with low energy density, such as vegetables and fruits.

Patterns of intake across other variables analysed were not meaningful in spite of their statistical significance, which is probably due to the large sample size.

Figure 1 shows a direct relationship between intake of nitrites and consumption of vitamin C. Ascorbic acid has been identified as an important factor in the inhibition of NA formation because it reduces nitrites to nitric oxide[5]. In our study, individuals who had higher intakes of nitrites also consumed higher levels of vitamin C, which can help to inhibit their transformation to NA. In order to identify groups of individuals who have higher overall exposure to NA, we explored the relationship between vitamin C consumption and NDMA intakes across categories of tobacco use. These results showed that, among current and past smokers (also exposed to NA from tobacco) in our population, those with low intakes of vitamin C also had high dietary intakes of NDMA. These low intakes of vitamin C in this group could exacerbate the problem of endogenous formation of NA. This pattern of exposure

Table 2 Contributions of food items to total intakes of *N*-nitrosodimethylamine (NDMA) and nitrites

	Contribution to total intake of NDMA			Contribution to total intake of nitrites	
Food item	Percentage	Cumulative percentage	Food item	Percentage	Cumulative percentage
Cured meat	14.26	14.26	Boiled ham	15.08	15.08
Cured cheese	13.16	27.42	Bread	10.17	25.25
Frankfurt sausage	11.17	38.52	Hamburger	7.28	32.53
Beer	11.00	49.59	Bacon	6.70	39.23
Bacon	10.56	60.15	Spaghetti	6.50	45.73
Broiled fish	4.66	64.81	Potato	4.80	50.53
Fresh sausage	4.31	69.12	Sausage	3.87	54.40
Hamburger	2.89	72.12	Lettuce	2.81	57.21
Boiled ham	1.26	73.27	Orange	2.54	59.75
Wine	0.68	73.95	Apple	2.51	62.26
Whisky	0.11	74.06	Leek	2.16	64.42
			Cucumber	2.12	66.63
			Tomato	1.98	68.61
			Spinach	1.91	70.52

reflects the fact that, in our population, smokers had the most unhealthy dietary profile, consuming less vegetables and fruits[21] and more processed meat and alcohol[22] than non-smokers. Similar findings have been reported in other populations. For instance, in a meta-analysis carried out by Dallongeville *et al.*, smokers consumed 16.5% less vitamin C and 9% more saturated fats than non-smokers[23]. Moreover, smoking itself decreases levels of vitamin C in plasma, increasing dietary requirements[24]. This could further exacerbate total NA exposure in this population.

For NDMA our estimated intake value is within the range of 0.08 to 0.55 $\mu g\,day^{-1}$ found in previous studies[25–32]. Although data suggest that mean intakes in our population are relatively low, it is important to note that 10% of the population had consumption levels above 0.40 $\mu g\,day^{-1}$, while 5% had intakes five-fold higher than the estimated mean (0.78 $\mu g\,day^{-1}$). To evaluate differences in estimated intakes across studies, several methodological issues must be taken into account. First, various dietary assessment instruments (food-frequency questionnaire, diet history, 48-hour recall or duplicate sampling) have been utilised. Second, there are large differences between the numbers of food items used to estimate total intakes of NDMA (28 to 474 items). Finally, the results reported in previous studies have been expressed as arithmetic means or medians, while in our study the values are shown as the geometric mean. In the present study, median and arithmetic mean were 0.109 and 0.19 $\mu g\,day^{-1}$, respectively.

Another important influence on intakes is the fact that, during the 1980s, reductions in the use of nitrates and nitrites for curing meat and modifications in malting techniques in the brewing industry resulted in significant reductions in the levels of NA in foods[3]. For instance, the value used in the present study for beer was 10 times lower than values used in previous studies. Since beer is an important contributor to total intakes, it is not surprising that NDMA exposure in our population is lower than in the majority of the studies published in the past. These results show that, at the present, the contribution from dietary sources to total exposure is lower than in previous decades.

In accordance with other studies, intakes of NDMA were also strongly dependent on the consumption of processed meats, especially frankfurters, sausages, bacon and cured meats, followed by beer and cheese. Moreover, we found that broiled fish was one of 10 main contributors, with 5% of intake. This finding is relevant because despite the fact that broiled fish does not have a high content of NDMA, intakes in Mediterranean countries are very high. On the other hand, foods with a high content of NDMA[11], such as smoked or salted fish, are not important contributors to the total intake because they are consumed by a very low percentage of the EPIC–Spain population (0.30% and 3%, respectively). Different patterns of consumption have been found in studies published in Finland and France, in which smoked fish contributed 22–25% to total intakes of NDMA[18,33]. The highest values of NDMA intake have been reported in Japan, due to high intakes of dried and smoked fish[34].

When the contribution by foods to total intake and to between-person variance of NDMA was analysed, the food items selected were similar but differed in their relative importance. In the present study, only four foods (frankfurters, beer, bacon and salami; $R^2 = 0.71$) explained 70% of the variance in NDMA consumption (data not shown). These same four foods jointly contributed 49% of total NDMA intake. As is generally found in other studies, fewer items are necessary explain a given proportion of between person-variance than the same proportion of total intakes[35,36].

Intakes of nitrites were comparable with previously published values[2,18], which ranged between 0.8 and 5.3 $mg\,day^{-1}$. For nitrites the major contributors to total intake were meat products (32%), cereals and derivatives

(22%), vegetables (16%) and fruits (12%). We found that bread is one of the most important contributors to total intake of nitrites. It is relevant because despite the fact that bread does not have a high content of nitrites, intakes in Spanish adults are very high. The present study indicates that major sources of nitrites in Spanish adults are the same as those reported in previous investigations from other countries[37].

One limitation of our study could be that the Spanish EPIC study is based on a non-representative sample of the general population. However, the number of subjects was very large, the participation rate was relatively high, subjects came from different social levels and different geographical areas, and the pattern of dietary intake and other lifestyle factors was very similar to that observed in population-based surveys carried out in the Spanish regions included in the present study[38–40]. In order to minimise this limitation, the reported geometric means for the whole cohort were standardised using the age and sex distribution of the Spanish population.

The limitations of assigning values to foods based on published reports include the limited availability of data on levels of these compounds in some items, and the variation in levels found in similar items across countries. We addressed this problem by taking the most suitable value for our population taking into account the analytical method, the origin and the year of publication.

Among the strengths of the present study are the large dataset (41 446 subjects), the number of food items included for analysis and the validated methodology used in the dietary assessment[12]. This is important, taking into account that even high-quality food composition tables will produce poor estimates when combined with low-quality data due to deficient validity and/or reliability of a dietary questionnaire. Several studies have reported intakes of these compounds, but in some cases the accuracy of the methods used to assess dietary intakes was limited.

In summary, we have estimated exogenous dietary exposure to nitrites and NDMA in Spanish adults (aged 35–64 years). These findings may contribute to improved ability to classify subjects according to their dietary intake patterns, and, in the future, to better understanding of the role of such compounds in cancer risk. In our study we also found that current and past smokers, groups with low intakes of vitamin C (an inhibitor of endogenous nitrosation), also had high dietary NDMA exposure. Thus, these groups could be considered a high-risk population. Additional research to estimate endogenous synthesis is needed for an accurate assessment of total exposure.

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