Original Article

Construction of an N-nitroso database for assessing dietary intake

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ABSTRACT

Dietary N-nitroso compounds are carcinogens synthesized during food processing from two main classes of precursors, oxides of nitrogen and amines or amides. Quantification of the dietary intake of N-nitroso compounds is significant to human cancers, including those of the stomach and upper gastro-intestinal tract, colon, and brain. Previous studies investigating these cancers primarily used proxy estimates of N-nitroso intake and not a full and complete database. In this report, we describe the development of a database to be used in conjunction with a food frequency questionnaire (FFQ) or 24 h dietary records. Published analytical data for N-nitroso compounds were compiled and evaluated for inclusion in the database. The final database consisted of 23 different N-nitroso compounds for 500 foods from 39 different food subgroups. Next, database foods were matched to foods in a standard FFQ by imputation, or calculated value, or assumed zero. Using the FFQ modified with N-nitroso values, we evaluated the ability to compute N-nitroso intakes for a sample of healthy control subjects of cancer epidemiological studies. N-nitroso content of food items ranged from <0.01 μg/100 g to 142 μg/100 g and the richest sources were sausage, smoked meats, bacon, and luncheon meats. The database is useful to quantify N-nitroso intake for observational and epidemiological studies.

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1. Introduction

The mutagenic properties of N-nitroso compounds, recognized for many years, were first described in 1956 (Magee and Barnes, 1956) when rats fed N-nitroso compounds were observed to develop high rates of cancer. Approximately 300 N-nitroso compounds have been tested for carcinogenicity, 90% of those stimulated carcinogenesis in 40 animal species including higher primates, and at a variety of sites and organs (Forman, 1987; Lijinsky, 1990; Tricker and Preussmann, 1991). As a result, it was concluded that N-nitroso compounds are among the most potent dietary carcinogenic agents or chemicals.

Following the discovery of the carcinogenic potential of N-nitroso compounds in animals, analyses confirmed human exposure to N-nitroso compounds by identifying food sources with high concentrations in cured meats, bacon, smoked fish, and beer, summarized in Table 1. Processing conditions that promote formation of N-nitroso compounds include foods pickled, stored under humid conditions, smoked in air saturated with nitrogen, dried at high temperatures (i.e. protein-containing foods as beer ingredients, nonfat dry milk, cooked bacon, or dried meats), and cured with nitrate and/or nitrite (cured meat). Collectively, a wide array of foods and nearly all Western foods have since been assayed and shown to contain N-nitroso compounds. Currently, a growing interest in N-nitroso compounds and cancer is supported by scientifically sound reports that underscore the need for continuing surveillance and analysis of food products. For, example a comprehensive review on the advances of N-nitroso compounds within each scientific discipline was compiled by the European Cancer Prevention Organization (Reed, 1996a,b). Further, the possible role for N-nitroso compounds specific to pancreatic cancer risk (Risch, 2003), and the role of maternal intake of N-nitroso foods to pediatric brain cancer including a detailed background of N-nitroso compound chemistry and characteristics have been published (Dietrich et al., 2005).

The chemistry for the formation of N-nitroso compounds in foods is a complex process. In brief, the two main precursors of N-nitroso compounds are (1) oxides of nitrogen and (2) amino groups (either secondary amines or amides), together that react and form two major subgroups of N-nitroso compounds, N-nitrosamines and N-nitrosamides. The chemical properties and characteristics of N-nitroso compounds according to the two major subgroups have been described (Dietrich et al., 2005). Although efforts to reduce the amount of nitrite used to cure meat and other food sources has been instituted in the past two to three decades in most meats, naturally occurring precursors for N-nitroso compounds are present in foods and under appropriate conditions the precursors

Table 1
N-nitroso compounds, examples of high food sources.

Compound abbreviation	Chemical nomenclature	High source foods
NDMA	N-nitrosodimethylamine	Beer, sausage, cured meats
NDEA	N-nitrosodiethylamine	Sausage, cheese
NPYR	N-nitrosopyrrolidine	Fried bacon, sausage, ham
NPIP	N-nitrosopiperidine	Bologna, sausages
NSAR	N-nitrosarcosine	Cured meats
NPRO	N-nitrosoproline	Fried bacon, cured meats
NTCA	N-nitrosotioazolidine-4-carboxylic acid	Smoked meats
NHMTCA	N-nitroso-2-hydroxymethylthiazolidine-4-carboxylic acid	Smoked meats
Nitrosating agents	Nitrate nitrite	Vegetables grains, additive to meats, other foods
Become nitrosated	Amines, amides	Protein foods

are synthesized to form N-nitroso compounds. Moreover, regulatory efforts to curtail nitrite and nitrosamines have not reduced the incidence of cancers related to their intake. Recent experiments investigated chemical conditions enhancing formation of N-nitroso-N-methylurea (NMU). In these experiments, a more sensitive assay was used including a specific analytical HPLC technique and a GC–MS confirmation technique, Results showed that 3 of twenty-four samples of meat with no added nitrites, formed 2–26 ng of NMU/10 g of meat, and later samples with added nitrite increased detection (Sen et al., 2000). Although the amounts of NMU formed with no added nitrite were extremely small, this report demonstrates the formation of NMU from cured meats with and without additional nitrite. From an international perspective it is important for food scientists and nutritional database specialists to maintain surveillance and awareness of N-nitroso compounds. For example, in parts of Asia, a very high incidence of esophageal, stomach and gastro-esophageal cancer occurs. Because of the frequent consumption in these cultures of aged and smoked fish sauces, smoked and aged vegetables, and vegetable sauces that are sources of high levels of N-nitroso compounds, these compounds are suspected to be related to these cancers.

Coinciding with the carcinogenic potential of the N-nitroso compounds, biologically plausible mechanisms responsible for their action have been identified. These investigations pinpoint three mechanisms for a genotoxic role of N-nitroso compounds in the promotion of cancer that include: (1) the formation of N-nitroso-DNA adducts, (2) loss of the ability to repair DNA damage and (3) base exchange of the K-ras oncogene (Bos, 1989; Palli et al., 2001; Silber et al., 1996; Souliotis et al., 2002). The first epidemiological study investigating the N-nitroso hypothesis was conducted for brain cancer in children in the late 1970s (Preston-Martin et al., 1982). Subsequent epidemiological studies examined the risk of N-nitroso compounds based on a proxy exposure (i.e. estimates of selected high food sources) to brain (Preston-Martin et al., 1989), stomach (La Vecchia et al., 1995), esophageal (Gao et al., 1994), and nasopharynx cancers. In a review on findings from 50 case control studies on the N-nitroso hypothesis and specific cancers (Eichholzer and Gutzwiller, 1998) one-third of the studies had statistical significance for detecting an association between a food group and cancer, with odds ratios ranging from 1.3 to 7.0. Despite these studies, human risk assessment of N-nitroso compounds for epidemiological studies or among racial/ethnic groups has been severely impeded by lack of a reliable N-nitroso database, lack of clarity in N-nitroso compounds in foods, and confusion in relation to the two classes of compounds, nitrosamines and nitrosamides (Dietrich et al., 2005). Accordingly, to address these gaps we report our research that created a comprehensive database of N-nitroso values in foods that can be used in conjunction with an existing food frequency questionnaire or with dietary food records.

2. Methods

2.1. Sources of N-nitroso database information

N-nitroso compounds constitute a family of compounds formed by the reaction of nitrogen oxides with secondary or tertiary amines or amides. Assays reported for N-nitroso compounds were identified by Medline and internet searches. The search terms most often used were N-nitroso, nitrates, nitrosamines, nitrosamides, nitrites, cured meats, ham, bacon, and combinations of these terms. Other publications on food composition and food assays were thoroughly searched including data of N-nitroso compound content of foodstuffs reported in epidemiological studies. Finally, reports from government agencies that investigated the N-nitroso compounds were incorporated in the database.

Analyses on N-nitroso compounds in foods had a peak of research conducted during 1970–1980. In most cases each reference reported analyses devoted to a specific food component and one or more N-nitroso compounds. More recent assays and reports were conducted in the 2000s (Groves et al., 2002; Mirvish et al., 2002, 2003; Sanches Filho et al., 2003; Zhou et al., 2006). Sen et al. have focused on N-nitroso food analyses, advancing our understanding with improvements in methodology and experimental procedures (Sen et al., 1990, 1997, 2000, 2001; Sen, 1991; Zhou et al., 2006). Several reviews have made substantial contributions to information on N-nitroso perspective of foods (Hecht, 1998; Lijinsky, 1988, 1992; Tricker, 1997; Walker, 1990).

2.2. Database product

Values for N-nitroso compounds in foods reported from references in tables or text were entered into a Microsoft Office Access 2003 database. Sources were documented with information on their sampling and handling plans for foods and beverages, the laboratory methods used to determine N-nitroso content, analytical quality control, cooking method, food descriptor and name, country of assay, number of samples used in the assay determination, unit of assay, and reference citation.

Because of the complexities of assays for the vast number of N-nitroso compounds, analysis by one laboratory (reference) on a food product was usually restricted to a few N-nitroso compounds, many foods did not have values reported for all compounds, as shown in Table 2. The final research core database consisted of 4301 entries for 23 N-nitroso compounds, for 500 foods, from 47 references. When similar foods were aggregated on the basis of common usage and nutrient composition 39 food subgroups were formed. Food subgroups consisted of those with high concentrations of N-nitroso compounds (sausage, ham, bacon, cured lunch meat, hotdog, organ meats, and beer), and foods with lower concentrations (vegetables, grains, fresh dairy, etc.).

Table 2
Summary of N-nitroso compounds and foods in the N-nitroso database.[a]

Food group	N-nitroso compound											Other N-nitroso compounds
	NDMA	NPYR	NPIP	NO3	NO2	NDEA	NDBA	NMOR	NPRO	NTCA	NTHZ	
Sausage	x	x	x	x	x	x		x	x	x	x	NMTCA, NHPRO, NPIP, NTHZ
Ham	x	x	x	x	x	x	x	x	x	x	x	NDBA, NDBZA, NMOCA, NMTCA, NHPRO, NTHZ
Bacon	x	x	x	x	x	x	x		x	x	x	NDBA, NHMT, NMTCA, NHPRO, NTHZ, NHMTCA
Cured Lunch meat	x	x	x	x	x	x	x	x	x	x	x	NAA, NDBZA, NDBA, NMTCA, NHPRO, NMOCA, NSAR, NTHZ
Hotdog	x				x	x				x	x	NTHZCA
Organ meats	x	x										
Beer	x			x								NAA
Fresh seafood	x	x-			x	x			x	x	x	NDBA, NAA, NDPA, NTHZ,
Dairy dry	x	x	x	x	x							
Beef	x			x	x		x			x	x	NDBA, NTCA, NTHZ
Cooked meats	x	x	x			x			x			NDPA
Spices	x	x	x									NAA, NTCA
Liquor	x	x										NAA,
Cheese	x	x	x	x	x	x				x		NAA, NDPA, NMTCA, NTCA
Chicken	x	x		x								
Smoked seafood	x									x		NAA, NMTCA, NTHZ
Egg	x	x										
Grain	x	x				x						NAA, NMAMBA, NMEA
Beans and pulses	x				x							
Smoked meat	x	x	x	x	x	x			x	x	x	NMTCA, NHMTCA, NTHZ
Solid fat	x							x				NAA
Wine	x	x										
Roots	x	x			x							
Oil	x											
Fresh dairy	x	x	x									NAA, NPIP
Dried meats					x					x		NTHZ
Green leafy					x						x	
Fruit												

[a] Heavily-shaded area represent N-nitroso compounds and foods typically reported in previous epidemiological studies; all rows and columns are represented in the database.

2.3. Assignment of database values to FFQ

The traditional construction of a database for analysis in association studies involves linking values from the research core database to the FFQ food item. For an initial estimation, in our collaboration with M.D. Anderson Cancer Center (MDACC) we linked the research core database to a modified Block Food Frequency Questionnaire (FFQ) (Block et al., 1994) used by MDACC researchers for dietary assessment of brain and other cancer studies. Recommended procedures previously reported were followed to compile food composition data sources and to assign N-nitroso values to the foods on the FFQ questionnaire (Blitz et al., 2007; Chun et al., 2007; Fink et al., 2006; Pennington, 2008; Pillow et al., 1999).

Ideally, a direct match is preferred when assigning values from the database to another food on a FFQ or other comprehensive database. A direct match may be a food for which the description in the literature matched exactly the FFQ food. Alternatively, imputed values are estimated levels of components in a food when laboratory data are not available (Pennington, 2008), and is an acceptable practice for the development of food composition tables if appropriate guidelines are followed. Accordingly, in the present study a determination was made whether or not a direct match could be applied. Because of the specialized objective of assays for N-nitroso compounds of a particular food reported by literature references, and the limitation in variety of foods assayed, imputation methods were used in the current study.

The first type of calculation used in assigning N-nitroso values was an average of values where multiple values were provided in the literature, thus a representative value for N-nitroso compounds was derived. We computed a mean value of the compounds (when more than 2 per compound) from the foods assigned to the FFQ line item (Subar et al., 2000). Examples are multiple references reported assayed NDMA and NTCA compounds for bacon. The need for this calculation was infrequent, but was used for the N-nitroso compounds of NDMA, NTCA, or nitrates.

The next type of calculation was to aggregate similar foods to derive the imputation for the corresponding FFQ food item. In this instance, each equivalent food contributed a value for one or more N-nitroso compounds to collectively profile several N-nitroso compounds for the food. For example, eight ham products collectively profiled 12 different N-nitroso compound values for ham. Because the hierarchical structure of the database and identity of foods with their detailed food descriptions is maintained, this first effort to aggregate food sources to derive an imputed match can be modified in the future for these or other foods. Future planned collaborations with other researchers will enhance the quality, interpretation and use of this database. Detailed documentation allows users to make informed decisions regarding imputation of values and enhances the ability to match foods carried on a particular database.

Other recommended database procedures were followed. We used standard recipes published by the USDA (U.S. Department of Agriculture, 2004) for the following items: stew, pizza, vegetable soup, mixed chicken, and MDACC recipes for nachos, and enchiladas. When this N-nitroso database is applied to match foods and recipes reported in food records, most nutritional analysis programs disentangle the components of recipes and identify the grams of components foods going in to the product, N-nitroso values may be assigned directly to the individual foods. Next, when articles reported values for dry ingredients or uncooked forms, we made adjustments for conversion to cooked forms, if needed (U.S. Department of Agriculture, 2007).

Table 3
N-nitroso compound list.

Abbreviation	Compound name
NAA	N-nitrosoamino acids
NDBA	N-nitrosodibutylamine
NDBZA	N-nitrosodibenzylamine
NDEA	N-nitrosodiethylamine
NDMA	N-nitrosodimethylamine
NDPA	N-nitrosodipropylamine
NHMT	N-nitroso-2-(hydroxymethyl)thiazolidine
NHMTCA	N-nitroso-2-(hydroxymethyl)thiazolidine-4-carboxylic acid
NHPRO	N-nitroso-4-hydroxyproline
NMAMBA	N-nitroso-N-(1-methylacetonyl)-3-methylbutylamine
NMEA	N-nitroso-methylethylamine
NMOCA	N-nitroso-5-methyloxazolidine-4-carboxylic acid
NMOR	N-nitrosomorpholine
NMTCA	N-nitroso-2-methylthiazolidine-4-carboxylic acid
NPIP	N-nitrosopiperidine
NPYR	N-nitrosopyrrolidine
NPRO	N-nitrosoproline
NSAR	N-nitrososarcosine
NTCA	N-nitrosothiazolidine-4-carboxylic acid
NTHZ	N-nitrosothiazolidine
NTHZCA	N-nitrosothiazolidine-4-carboxylic acid and related homologues
NO$_3$	Nitrate
NO$_2$	Nitrite

Of the 205 food items on the modified FFQ, 137 items were matched to foods in the N-nitroso database and thus received N-nitroso values. After representative values were identified, data values of the N-nitroso compounds were entered into DietSys, the software designed to perform the nutrient analysis for the FFQ.

3. Results

Based on an initial review of the literature, thirty-six N-nitroso compounds were expected to have reported assays in foodstuffs (compounds and their abbreviations are shown in Table 3). However, thirteen N-nitroso compounds had no reported assays in foodstuffs, yielding reports for 23 N-nitroso compounds. As shown in Table 2, the N-nitroso compounds retained are displayed according to their occurrence in food subgroups. NDMA, NPYR, NPIP, NTHZ, NDEA, NTCA, NDBA, NMOR, NPRO compounds were the most frequently assayed. Two observations from (Table 2) are that assays for N-nitroso compounds in foods were not available for all foods, and no food had all N-nitroso compounds reported or assayed. In the upper left quadrant of Table 2, foods and N-nitroso compounds used as exposure items in previous epidemiological studies are indicated, and demonstrate that five or fewer N-nitroso compounds and ten food subgroups have been used previously in cancer association studies. In contrast, the present N-nitroso database has 23 N-nitroso compounds in foodstuffs representing sources ranging from foods with high concentrations to commonly eaten foods with low concentrations. The diversity of food items and the comprehensive inclusion of 23 compounds, make possible more complete and representative intake.

The most abundant food sources for NDMA were sausage, fermented pickles, ham, bacon, and cured luncheon meats, and moderate sources were ice cream, salad dressing, wine, margarine, grains, and cheese. The most abundant food sources for NPIP were sauerkraut, bacon, and ham. NSAR was detected and reported only in ham. NTHZ was detected in smoked fish, bacon, beef, and hot dogs. The most abundant sources for NTCA were bacon, ham, lunch meats, and sausage. NMTCA had the highest concentration in cheese, and was moderately high in bacon, ham pork, lunch meats, and sausage. NHPRO was only reported in pork, ham, luncheon meats. Importantly, many foods had concentrations of several N-nitroso compounds, for example, a range of 10–19 N-nitroso compounds were found in cured lunch meats, bacon, sausage, cheese, fresh seafood, and salted seafood; a range of five to nine N-nitroso compounds were found in dried meats, dairy, cooked meat, hot dogs; a range of 1–4 N-nitroso compounds were found in soy, beans and pulses, wine liquor, dairy, roots, vegetables, and fats. Compounds with the highest concentrations (µg/100 g) and source were NTCA 142 µg, bacon; NHMTCA 118 µg, cheese; NDMA 10.9 µg, sausage; NDBA 1.3 µg, bacon; and NDBZA 3.6 µg, cured luncheon meat.

Table 4 presents representative values for 9 N-nitroso compounds for selected items on the Block Modified Food Frequency questionnaire.

4. Discussion

Over 50 studies have examined cancer risk and N-nitroso compound intake primarily based on proxy estimates, i.e. amounts of foods eaten that have high levels of N-nitroso compounds. Accordingly, previous assessment of N-nitroso compounds has been difficult because of lack of compiled data that are linked to dietary questionnaires. Moreover, to date N-nitroso intake and food patterns driving their intake measured by a reliable N-nitroso database across the US population, among racial/ethnic groups and other subgroups are unknown.

Table 4
N-nitroso compound concentration (for 9 compounds) of selected food items on the modified Block Food Frequency Form.

	µg/100 g								
	NDMA	NPYR	NPIP	NDEA	NDBA	NMOR	NPRO	NTCA	NTHZ
Peas		0.025					0.300		
Whole milk	0.014	0.003	0.003						
Margarine	0.026					0.049			
French fries, fried potatoes	0.024	0.041							
White Wine	0.025	0.109							
Butter	0.026					0.049			
Refried beans or pinto beans	0.033								
Rolls, buns, muffins, bagels	0.050	0.009		0.023					
Cottage cheese	0.076	0.004	0.009	0.057				1.500	
Fried fish	0.169	0.003		0.088	0.004		1.200	4.660	0.018
Beer	0.202								
Hot dogs or franks	0.221							8.950	0.372
Bacon	0.454	2.129	0.049	0.067	1.365		1.000	142.742	2.643
Ham	0.490	0.534	0.004	0.149	0.458	0.286	5.752	46.130	0.154
Sauerkraut	0.660	0.555	0.220	0.079			2.095	0.900	
Oysters	1.139	0.038		0.109		0.007	5.416	0.864	
Sausage or chorizo	10.941	0.086	0.001	0.040		0.052	1.720	11.896	0.172

Previous epidemiological studies investigating the role of N-nitroso compounds and cancer have focused the intake of ham, bacon, cured lunch meats, hot dogs, organ meats, and beer, and limited studies have estimated NDMA, NPYR, NPIP, nitrates and nitrites. The disadvantage of this approach is that foods with low to moderate N-nitroso content, yet consumed much more frequently are not accounted for, missing a substantial intake of these compounds. In contrast, the present study had a broader coverage, both from the standpoint of the list of N-nitroso compounds assessed and their food sources. In addition, although N-nitroso compounds are known to be consumed in small quantities (micrograms) they are known to have potent biological activity.

Findings for this N-nitroso database confirm previous literature (Dietrich et al., 2005; Scanlan, 1983; Tricker and Kubacki, 1992; Tricker, 1997) reporting the richest food sources of N-nitroso compounds were bacon, luncheon meats, sausage, and hot dogs. In these foods, NDMA, NPIP, NPYR, NDEA, and NTCA contributed the highest concentrations. The next highest food source of N-nitroso compounds was from fresh and smoked seafoods. Finally, low to moderate sources of several N-nitroso compounds were observed in grains and dairy, oils, liquor and wine.

Estimates of the total daily intake for each individual N-nitroso compound may be derived by summing values for that compounds from all food sources. Alternatively, this N-nitroso database could be used to investigate whether a cumulative index for all N-nitroso compounds, or groups of compounds that are associated with cancer similar to antioxidant indices (Michaud et al., 2000; Wright et al., 2004; Yong et al., 1997).

Tables of food concentrations of N-nitroso compounds (and two other dietary carcinogens) have been developed and published by European Prospective Investigation of Cancer and Nutrition (EPIC) (Jakszyn et al., 2004). EPIC tables contain values for foods consumed in Europe and Spain; values are presented in ranges accompanied by limited descriptions of foods. In contrast, our N-nitroso database contains more N-nitroso compounds, has a wider coverage of food sources, and is easily modified or adjusted because of the database structure. In addition, the present database was accompanied by procedures linking values from the research core database to a commonly used validated Food Frequency Questionnaire, and the modified Food Frequency Questionnaire has been validated with a large study sample of seven-day food records (Stuff et al., in press).

Our database has several limitations, largely because of the limited N-nitroso values on which it is based. The process of determining appropriate food items and values required interpretation of data from the published literature. To maximize the number of values added to the FFQ, assumptions were made regarding whether foods reported in the literature were similar to and appropriate matches for foods in the FFQ. Concentration of N-nitroso compounds is known to vary by food source and environmental conditions, and food production and processing. Furthermore, values for some foods are based on only one analysis. Recommended procedures previously used for assigning values to the food frequency form were followed (Blitz et al., 2007; Chun et al., 2007; Fink et al., 2006; Pennington, 2008; Pillow et al., 1999) Further, documentation of all descriptors for the foods compiled to form aggregated estimates, decreased the subjectivity and increased the consistency of these evaluations. In the future, the N-nitroso content in a greater variety of foods, foods from different regions, and foods processed under different conditions must be analyzed to increase the comprehensiveness and accuracy of the database.

5. Conclusions

Quantifying the dietary intake of N-nitroso compounds is particularly relevant for research on the relationship of diet and cancer. Despite reports on the carcinogenicity of N-nitroso compounds and on food analysis of N-nitroso compounds, use of a comprehensive N-nitroso database has not been applied to estimate distribution of intakes on a population basis or in cancer epidemiological studies. We created a database of N-nitroso values and systematically assigned N-nitroso values to foods in a commonly used FFQ. Future collaborations will continue to refine and interpret the database. While the addition of N-nitroso values to the FFQ is not without limitations, it will assist future studies that identify the highest consumers and those most susceptible to N-nitroso compounds using etiological study designs that in turn inform interventions implemented to reduce their intake and negative outcomes.

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