Published in final edited form as:
J Food Compost Anal. 2009 December 1; 22(Suppl 1): S42–S47. doi:10.1016/j.jfca.2009.01.008.

Construction of an N-nitroso database for assessing dietary intake

Janice E. Stuff, Ph.D., R.D.*,
Assistant Professor, Baylor College of Medicine, USDA/ARS Children's Nutrition Research Center, 1100 Bates, Houston, TX 77030

Eugenia T. Goh, M.S., R.D.,
Research Coordinator, Baylor College of Medicine, USDA/ARS Children's Nutrition Research Center, 1100 Bates, Houston, TX 77030, 713-798-7098(fax)

Stephanie L. Barrera, M.S., R.D.,
Research Dietitian, Dept. of Epidemiology Department of Epidemiology, Unit 1340, The University of Texas M. D. Anderson Cancer Center, P. O. Box 301439, (713) 745-3983(Phone), 713-792-9568 (Fax)

Melissa L. Bondy, Ph.D., and
Professor, Dept. of Epidemiology, University of Texas M.D. Anderson Cancer Center, P. O. Box 301439, 713-794-5264 (Phone), 713-792-9568 (Fax)

Michele R. Forman, Ph.D.
Professor, Dept. of Epidemiology, University of Texas M.D. Anderson Cancer Center, P. O. Box 301439, Tel: 713-792-1860 (Phone), 713-792-9568 (Fax)

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 twenty-four hour 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 <0.01μg/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.

*Corresponding author. 713-798-7066, 713-798-7098(fax), E-mail address: jstuff@bcm.tmc.edu (Dr J. Stuff).

Keywords

N-nitroso compounds; Dietary carcinogens; Food data; Food safety; Food composition database; Food analysis; Food composition

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;Reed, 1996b). 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-nitrosoamides. 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 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., 2000b). Although the amounts of NMU formed with no added nitritie 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 their 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 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 1970's (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; Mirvish et al., 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; Sen, 1991; Sen et al., 1997; Sen et al., 2000b; Sen et al., 2000a; Sen et al., 2001; Zhou et al., 2006). Several reviews have made substantial contributions to information on N-nitroso perspective of foods (Hecht, 1998; Lijinsky, 1988; Lijinsky, 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 an 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.).

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).

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 the Appendix Table). 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 to 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 to 4 N-nitroso compounds were found in soy, beans and pulses, wine liquor, dairy, roots, vegetables, and fats. Compounds with the highest concentrations (μg/100g) 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 3 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.

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., 2009).

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 are 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 carcinogenity 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.

Acknowledgments

This work was supported by grants from the National Cancer Institute RO3 CA103515 and R01CA070917. We would like to acknowledge following individuals and their contributions who are from the Dept. of Epidemiology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas: Patricia Pillow for consultation on database development, Kalli Schentel and Ladia Hernandez for nutritional analysis, and Phyllis Adatto and Karen Benedict for subject recruitment.

Appendix Table: 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-hydroxymethylthiazolidine-4-carboxylic acid
NHPRO	N-nitroso-4-hydroxyproline
NMAMBA	N-nitroso-N-(1-methylacetonyl)-3-methylbutylamine
NMEA	N-Methyl-N-ethylnitrosamine
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

Abbreviation	Compound Name
NTHZ	N-nitrosothiazolidine
NTHZCA	N-nitrosothiazolidine carboxylic acid and related homologues
NO_3	Nitrate
NO_2	Nitrite

References

Blitz CL, Murphy SP, Au DL. Adding lignan values to a food composition database. Journal of Food Composition and Analysis 2007;20:99–105.

Block G, Coyle LM, Hartman AM, Scoppa SM. Revision of dietary analysis software for the Health Habits and History Questionnaire. American Journal of Epidemiology 1994;139:1190–1196. [PubMed: 8209877]

Bos JL. ras oncogenes in human cancer: a review. Cancer Research 1989;49:4682–4689. [PubMed: 2547513]

Chun OK, Chung SJ, Song WO. Estimated dietary flavonoid intake and major food sources of U.S. adults. Journal of Nutrition 2007;137:1244–1252. [PubMed: 17449588]

Dietrich M, Block G, Pogoda JM, Buffler P, Hecht S, Preston-Martin S. A review: dietary and endogenously formed N-nitroso compounds and risk of childhood brain tumors. Cancer Causes Control 2005;16:619–635. [PubMed: 16049800]

Eichholzer M, Gutzwiller F. Dietary nitrates, nitrites, and N-nitroso compounds and cancer risk: a review of the epidemiologic evidence. Nutrition Reviews 1998;56:95–105. [PubMed: 9584494]

Fink BN, Steck SE, Wolff MS, Kabat GC, Gammon MD. Construction of a flavonoid database for assessing intake in a population-based sample of women on Long Island, New York. Nutrition and Cancer 2006;56:57–66. [PubMed: 17176218]

Forman D. Dietary exposure to N-nitroso compounds and the risk of human cancer. Cancer Surveillance 1987;6:719–738.

Gao YT, McLaµghlin JK, Gridley G, Blot WJ, Ji BT, Dai Q, Fraumeni JF Jr. Risk factors for esophageal cancer in Shanghai, China. II. Role of diet and nutrients. International Journal of Cancer 1994;58:197–202.

Groves FD, Issaq H, Fox S, Jeffrey AM, Whysner J, Zhang L, You WC, Fraumeni JF Jr. N-nitroso compounds and mutagens in Chinese fermented (sour) corn pancakes. J Association of Analytical Chemists 2002;85:1052–1056.

Hecht, SS. N-Nitrosamines. In: Rom, WN., editor. Environmental and Occupational Medicine. Philadelphia: Lippincott-Raven; 1998. p. 1227-1238.

Jakszyn P, Agudo A, Ibanez R, Garcia-Closas R, Pera G, Amiano P, Gonzalez CA. Development of a food database of nitrosamines, heterocyclic amines, and polycyclic aromatic hydrocarbons. Journal of Nutrition 2004;134:2011–2014. [PubMed: 15284391]

La Vecchia C, D'Avanzo B, Airoldi L, Braga C, Decarli A. Nitrosamine intake and gastric cancer risk. European Journal of Cancer Prevention 1995;4:469–474. [PubMed: 8580782]

Lijinsky, W. The role of N-nitroso compounds in human cancer. In: Feo, F.; Pani, P.; Columbano, A.; Garcea, R., editors. Chemical Carcinogenesis: Models and Mechanisms. New York: Plenum Press; 1988. p. 639-647.

Lijinsky, W. In vivo testing for carcinogenicity. In: Grover, PL.; Cooper, CS., editors. Chemical Carcinogenesis and Mutagenesis. Berlin: Springer-Verlag; 1990. p. 179-209.

Lijinsky, W. Chemistry and Biology of N-nitroso Compounds. New York: Cambridge University Press; 1992.

Magee PN, Barnes JN. The production of malignant primary hepatic tumours in the rat by feeding dimethylnitrosamine. British Journal of Cancer 1956;10:114–122. [PubMed: 13342328]

Michaud DS, Feskanich D, Rimm EB, Colditz GA, Speizer FE, Willett WC, Giovannucci E. Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts. American Journal of Clinical Nutrition 2000;72:990–997. [PubMed: 11010942]

Mirvish SS, Haorah J, Zhou L, Clapper ML, Harrison KL, Povey AC. Total N-nitroso compounds and their precursors in hot dogs and in the gastrointestinal tract and feces of rats and mice: possible etiologic agents for colon cancer. Journal of Nutrition 2002;132:3526S–3529S. [PubMed: 12421882]

Mirvish SS, Haorah J, Zhou L, Hartman M, Morris CR, Clapper ML. N-nitroso compounds in the gastrointestinal tract of rats and in the feces of mice with induced colitis or fed hot dogs or beef. Carcinogenesis 2003;24:595–603. [PubMed: 12663523]

Palli D, Saieva C, Coppi C, Del Giudice G, Magagnotti C, Nesi G, Orsi F, Airoldi L. O6-alkylguanines, dietary N-nitroso compounds, and their precursors in gastric cancer. Nutrition and Cancer 2001;39:42–49. [PubMed: 11588901]

Pennington JAT. Applications of food composition data: Data sources and considerations for use. Journal of Food Composition and Analysis 2008;21:S3–S12.

Pillow PC, Duphorne CM, Chang S, Contois JH, Strom SS, Spitz MR, Hursting SD. Development of a database for assessing dietary phytoestrogen intake. Nutrition and Cancer 1999;33:3–19. [PubMed: 10227038]

Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles County. Cancer Research 1989;49:6137–6143. [PubMed: 2790826]

Preston-Martin S, Yu MC, Benton B, Henderson BE. N-nitroso compounds and childhood brain tumors: a case-control study. Cancer Research 1982;42:5240–5245. [PubMed: 7139628]

Reed PI. N-nitroso compounds, their relevance to human cancer and further prospects for prevention. European Journal of Cancer Prevention 1996a;5:137–147. [PubMed: 8972309]

Reed, PI. Proceedings of the 13th annual European Cancer Prevention symposium. N-nitroso compounds in human cancer: current status and future trends; London, England. 16-17 October 1995; 1996b. European Journal of Cancer Prevention 5:1–163.

Risch HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. Journal of the National Cancer Institute 2003;95:948–960. [PubMed: 12837831]

Sanches Filho PJ, Rios A, Valcarcel M, Zanin KD, Bastos Caramao E. Determination of nitrosamines in preserved sausages by solid-phase extraction-micellar electrokinetic chromatography. Journal of Chromatography A 2003;985:503–512. [PubMed: 12580519]

Scanlan RA. Formation and occurrence of nitrosamines in food. Cancer Research 1983;43:2435s–2440s. [PubMed: 6831466]

Sen NP. Recent studies in Canada on the occurrence and formation of N-nitroso compounds in foods and food contact materials. International Agency for Research on Cancer Scientific Publication 1991;105:232–234.

Sen NP, Baddoo PA, Weber D, Helgason T. Detection of a new nitrosamine, N-nitroso-N-methylaniline, and other nitrosamines in icelandic smoked mutton. Journal of Agriculture and Food Chemistry 1990;38:1007–1111.

Sen NP, Seaman SW, Baddoo PA, Burgess C, Weber D. Formation of *N*-nitroso-*N*-methylurea in various samples of smoked/dried fish, fish sauce, seafoods, and ethnic fermented/pickled vegetables following incubation with nitrite under acidic conditions. Journal of Agricultural and Food Chemistry 2001;49:2096–2103. [PubMed: 11308373]

Sen NP, Seaman SW, Burgess C, Baddoo PA, Weber D. Investigation on the possible formation of *N*-nitroso-*N*-methylureaby nitrosation of creatinine in model systems and in cured meats at gastric pH. Journal of Agriculture and Food Chemistry 2000a;48:5088–5096.

Sen NP, Seaman SW, Burgess C, Baddoo PA, Weber D. Investigation on the possible formation of *N*-nitroso-*N*-methylureaby nitrosation of creatinine in model systems and in cured meats at gastric pH. Journal of Agriculture and Food Chemistry 2000b;48:5088–5096.

Sen NP, Seaman SW, Page BD. Rapid semi-quantitative estimation of N-nitrosodibutylamine and N-nitrosodibenzylamine in smoked hams by solid-phase microextraction followed by gas chromatography-thermal energy analysis. J Chromatography Analysis 1997;788:131–140.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Silber JR, Blank A, Bobola MS, Mueller BA, Kolstoe DD, Ojemann GA, Berger MS. Lack of the DNA repair protein O6-methylguanine-DNA methyltransferase in histologically normal brain adjacent to primary human brain tumors. Proceedings of the National Academy of Science 1996;93:6941–6946.

Souliotis VL, Henneman JR, Reed CD, Chhabra SK, Diwan BA, Anderson LM, Kyrtopoulos SA. DNA adducts and liver DNA replication in rats during chronic exposure to N-nitrosodimethylamine (NDMA) and their relationships to the dose- dependence of NDMA hepatocarcinogenesis. Mutation Research 2002;500:75–87. [PubMed: 11890936]

Stuff J, Goh E, Barrera S, Bondy M, Forman M. N-nitroso comound intake and their food patterns: Assessing agreement between food frequency questionnaires and 7-day food records. Journal of the American Dietetic Association. 2009 accepted.

Subar AF, Midthune D, Kulldorff M, Brown CC, Thompson FE, Kipnis V, Schatzkin A. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. American Journal of Epidemiology 2000;152:279–286. [PubMed: 10933275]

Tricker AR. N-nitroso compounds and man: sources of exposure, endogenous formation and occurrence in body fluids. European Journal of Cancer Prevention 1997;6:226–268. [PubMed: 9306073]

Tricker AR, Kubacki SJ. Review of the occurrence and formation of nonvolatile N-nitroso compounds in foods. Food Additives And Contaminants 1992;9:39–69. [PubMed: 1397391]

Tricker AR, Preussmann R. Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. Mutation Research 1991;259:277–289. [PubMed: 2017213]

U.S. Department of Agriculture, Agricultural Research Service, and USDA Nutrient Data Laboratory. USDA National Nutrient Database for Standard Reference, Release 18. 2004

U.S. Department of Agriculture, Agricultural Research Service, and USDA Nutrient Data Laboratory. USDA Table of Nutrient Retention Factors, Release 6. 2007

Walker R. Nitrates, nitrites and N-nitrosocompounds: a review of the occurrence in food and diet and the toxicological implications. Food Additives And Contaminants 1990;7:717–768. [PubMed: 2079111]

Wright ME, Mayne ST, Stolzenberg-Solomon RZ, Li Z, Pietinen P, Taylor PR, Virtamo J, Albanes D. Development of a comprehensive dietary antioxidant index and application to lung cancer risk in a cohort of male smokers. American Journal of Epidemiology 2004;160:68–76. [PubMed: 15229119]

Yong LC, Brown CC, Schatzkin A, Dresser CM, Slesinski MJ, Cox CS, Taylor PR. Intake of vitamins E, C, and A and risk of lung cancer. The NHANES I epidemiologic followup study. First National Health and Nutrition Examination Survey. American Journal of Epidemiology 1997;146:231–243. [PubMed: 9247007]

Zhou L, Haorah J, Perini F, Carmella SG, Shibamoto T, Mirvish SS. Partial purification from hot dogs of N-nitroso compound precursors and their mutagenicity after nitrosation. Journal of Agriculture and Food Chemistry 2006;54:5679–5687.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

N-nitroso compounds, examples of high food sources

Compound Abbreviation	1 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-nitrososo-2-hydroxymethylthiazolidine-4-carboxylic acid	Smoked meats
Nitrosating agents	Nitrate Nitrite	Vegetables grains Additive to meats, other foods
Become Nitrosated	Amines Amides	Protein foods Protein foods

Table 2

Summary of N-nitroso compounds and foods in the N-nitroso database*

Food Group	N-nitroso Compound											
	NDMA	**NPYR**	**NPIP**	**NO_3**	**NO_2**	**NDEA**	**NDBA**	**NMOR**	**NPRO**	**NTCA**	**NTHZ**	**Other N-nitroso Compounds**
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

Food Group	N-nitroso Compound											
	NDMA	NPYR	NPIP	NO_3	NO_2	NDEA	NDBA	NMOR	NPRO	NTCA	NTHZ	Other N-nitroso Compounds
Dried Meats					X					x		NTHZ
Green Leafy				x							x	
Fruit												
Fruit and Vegetables		x		x					x			NTCA

* Shaded area represent N-nitroso compounds and foods typically reported in previous epidemiological studies; All rows and columns are represented in the database.

Table 3

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