RESEARCH ARTICLE

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Development of a Food Composition Database for Assessing Nitrate and Nitrite Intake from Animal-based Foods

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Scope: Nitrate and nitrite are approved food additives in some animal-based food products. However, nitrate and nitrite in foods are strictly regulated due to health concerns over methaemoglobinaemia and the potential formation of carcinogenic nitrosamines. In contrast, plants (like leafy vegetables) naturally accumulate nitrate ions; a growing body of research reveals beneficial metabolic effects of nitrate via its endogenous conversion to nitric oxide. To refine the association of dietary nitrate and nitrite intake with health outcomes, reliable measures of nitrate and nitrite intake from dietary food records are required. While a vegetable nitrate content database has been developed, there is a need for a comprehensive up-to-date nitrate and nitrite content database of animal-based foods.

Methods and Results: A systematic literature search (1980–September 2020) on the nitrate and nitrite content of animal-based foods is carried out. Nitrate and nitrite concentration data and other relevant information are extracted and compiled into a database. The database contains 1921 entries for nitrate and 2077 for nitrite, extracted from 193 publications. The highest median nitrate content is observed in chorizo (median [IQR]; 101.61 [60.05–105.93] mg kg^{-1}). Canned fish products have the highest median nitrite level (median [IQR]; 20.32 [6.16–30.16] mg kg^{-1}). By subgroup, the median nitrate value in industrial processed meat products (e.g., uncured burger, patties and sausages), whole milk powder and in particular red meat are higher than cured meat products. Processed meat products from high-income regions have lower median nitrate and nitrite content than those of middle-income regions.

Conclusion: This database can now be used to investigate the associations between nitrate and nitrite dietary intake and health outcomes in clinical trials and observational studies.

1. Introduction

The benefits and risks of nitrate and nitrite intake on human health are yet to be fully determined. While evidence for the beneficial effects of dietary nitrate on human health is strengthening,[1] questions remain around the potential link between dietary nitrate and nitrite intake and cancer.[2,3] Dietary nitrate, through the endogenous nitrate–nitrite–nitric oxide (NO) pathway, is a precursor of NO, a bioactive signaling molecule involved in multiple physiological processes including cardiovascular regulation, endothelial function, cellular metabolic homeostasis and nerve transmission.[3] A large number of clinical studies have demonstrated that dietary vegetable nitrate, via conversion to nitrite and subsequently NO, has multiple physiological functions, in particular beneficial effects on validated markers of cardiovascular disease (CVD) risk such as lowering blood pressure.[2–7]

Vegetables, water, and animal-based foods are the major sources of dietary nitrate and nitrite.[7] More than 80% of dietary nitrate intake is derived from vegetables, particularly leafy green vegetables and beets, which are recognized as protective against cancers, CVD,

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and type 2 diabetes (T2D).[7] While animal-based foods products such as bacon and ham are the main source of dietary nitrite, more than 80% of human nitrite exposure is derived from the reduction of nitrate in the mouth by oral bacteria.[7,8] Sodium and potassium nitrites (E249, E250) and nitrates (E251, E252) have historically been used in the preservation of animal-based foods products (processed meat products in particular).[9,10] However, they are speculated to contribute to the negative health outcomes of processed meat consumption.[11] Nitrite, and nitrate after reduction to nitrite, can potentially react with amines or amides to form genotoxic and carcinogenic *N*-nitroso compounds (NOCs) under high temperature and low pH conditions (similar to those observed in the stomach).[9,10] The potential increased cancer risk, along with the concerns related to methaemoglobinaemia, have driven strict regulations worldwide on both nitrate and nitrite as food additives.[3,12,13]

The conflicting health implications of nitrate and nitrite intake have motivated long-term scientific debate on their potential risks and benefits.[12] Re-evaluations of the use of nitrite and nitrate as food additives in human foods are performed regularly.[12,13–19] However, the lack of a comprehensive food composition database with nitrite and nitrate reference values presents a challenge in accurately assessing dietary exposure.[20,21] Considerable variations are often reported for nitrate and nitrite content data in both epidemiological and clinical studies, potentially contributing to the inconsistency in their dietary exposure assessment.[2] For example, the reported contribution of cured meat consumption to dietary nitrite intake varied greatly, from 10%[22] up to 65%.[23] In recognition of this difficulty, a nitrate database on vegetables, herbs, and spices has been now developed.[21] However, a reliable nitrate and nitrite composition database for foods of animal origin has yet to be developed.

To address this, we performed a systematic, comprehensive collation of available data on the nitrate and nitrite amount in animal-based foods. Second, we conducted comparisons within and between animal-based food groups. In addition, since nitrate intake is suggested to be inversely associated with economic development,[2] ecological analyses were performed to determine associations between nitrate and nitrite content of animal-based foods and geographical region and economic status.

2. Experimental Section

2.1. Literature Search and Selection

Relevant literature on the nitrate and nitrite concentration in animal-based foods (1980–September 2020) was identified using a systematic literature search performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 Statement (**Figure 1**).[7] A primary search was conducted in May 2020 with the last update performed on September 3, 2020. Three subject databases, Medline, Scopus and Web of Science, were searched. The following key search terms were used: nitrite/nitrate, (including molecular formulas of their ions and sodium/potassium salts), main animal-based foods, and infant foods (including human breast milk). Search fields were optimized for each database: for Medline, MeSH terms were used; for Web of Science and Scopus, [Topic] and [Title-Abstract-Keywords] were employed. Additional searches included reports from government agencies and institutions, online databases, and references of relevant review articles. Only papers published in English were included.

All search records were imported into Endnote X9.0 (Thomson Reuters). After removal of the duplicates, two rounds of literature screening were performed. Firstly, the titles and abstracts of all the records were screened. Studies were excluded if (a) they did not report nitrite and nitrate concentration data in animal source human food products; b) their food samples were prepared under experimental conditions and were not commercially available; c) they reported the development of nitrite and/or nitrate analytic methods, but the results were not validated using reference methods; d) the data were compiled as part of a review; and (e) the data was cited or adapted from other sources, and the articles containing the primary data were already included. For the second round of screening, full texts of the eligible papers from the first screening were obtained. Full papers were critically examined to exclude any ineligible articles based on the above criteria. Any uncertainties and discrepancies during the screening procedure were rigorously discussed by at least two reviewers through online meetings to reach consensus.

2.2. Animal-based Foods Categories

Conventional animal-based foods mainly include red meat, processed meat, offal, dairy products, eggs, fish, and other seafood products.[11] The current database aimed to cover the majority of animal-based foods products widely consumed at a detailed level. The classification system used was adapted from the Australian Health Survey Classification System,[24] meat processing technology and production manual from the Food and Agriculture Organization (FAO)[25] and Part D of Annex II to Regulation (EU) No 1129/2011[26] (**Table 1**). The FAO manual covers a wide range of meat products worldwide and their processing methods.[25] Animal sources (e.g., mammals, poultry, fish) and processing methods (e.g., raw, curing, fermentation, comminuting) were the main considerations for grouping.[25]

In the current study, red meat is defined as: *"The whole or part of unprocessed (but including mincing, boning, slicing, dicing, or freezing meat) mammalian muscle meat."*[27] Processed meat products are *"meat which has, either singly or in combination with other foods, undergone a method of processing other than boning, slicing, dicing, mincing or freezing."*[27] Miscellaneous group includes ambiguous food names such as "Livestock meat," "Meat and meat products (including edible offal)," and "Other processed games." Categories of processed meat products were sub-divided as described by FAO[25] and the International Agency for Research on

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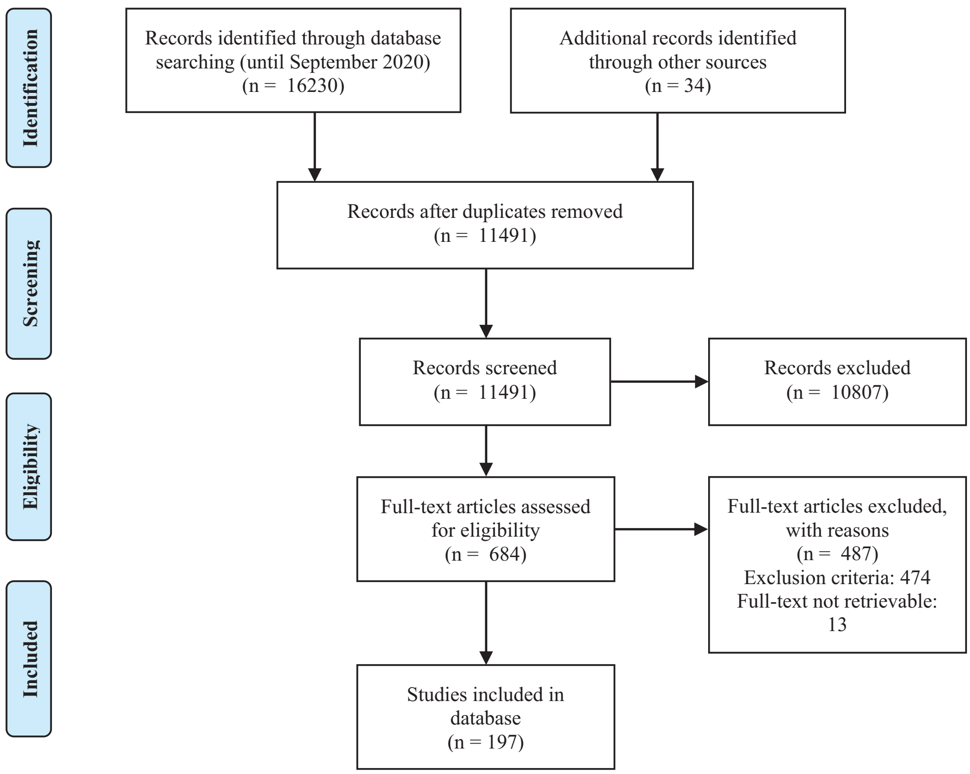

Figure 1. PRISMA flowchart.

Cancer.[11] Fresh uncured industrial processed meat products (including fresh sausages) are home and industry-prepared meat (both pieces and comminuted) in which other food ingredients (common salt for example) may be added but do not undergo curing.[25] Offal are *"the internal organs and entrails of a butchered animal."*[11] Food examples of each subgroups are presented in Table 1. The most common processed meat products, such as salami, frankfurter, bacon, and ham, were listed in the database independently. Those foods which could be considered under two or more subgroups, or for which the processing methods (sausages, in particular) were not clear, were discussed among the authors. Data on "Food name in source" and "Processing method" were collected when available.

2.3. Database Structure, Data Extraction, and Processing

The database contains information on six aspects of each food, namely sample information (including the food groups, names, and processing method), details of the sampling (sampling season and year, sampling country and point, sample size), analytical aspects (including extraction and analytic method, limit of detection (LOD) and limit of quantification (LOQ), nitrate and nitrite concentration values [expression of results (namely nitrate/nitrite ions or their salts), mean and standard deviation, minimum, maximum, the median and interquartile range (IQR), lower/middle/upper bounds], the source of data and additional information.[7] Data extraction criteria applies: a) the Griess reaction-based spectrophotometric method was used as the reference method, and the reliability and applicability of methods ranked as Griess assay (e.g., Association of Official Analytical Chemists method 993.03) > chromatographic methods (ion chromatography and other reversed-phase liquid chromatography (LC), LC-MS, gas chromatography (GC), GC-MS) > spectrofluorimetric methods > capillary electrophoresis > chemiluminescence.[28] Results obtained from methods with the higher reliability were used when multiple analytic methods were used; b) nitrate and nitrite ions (NO_3^-/NO_2^-) were treated as default result expressions if the original publications did not clearly indicate; c) the number of samples with <LOD were extracted. Samples with "ND (not-detected)" or "0" or "<LOD" or "<LOQ" were entered as "< numerical values of LOD/LOQ." Results were entered as "ND" if the papers did not present the LOD and/or LOQ value and were not included in data analysis. Countries were classified into four income groups (namely high, upper-middle, lower-middle, and low-income).[29]

2.4. Statistics

The units and result expressions were unified to be mg kg^{-1} (mg L^{-1} where appropriate) and nitrate/nitrite ions before data aggregation. In addition, only sub-categories of data that included more than two references were included in all analyses. Moreover, the lower, middle, and upper bound of samples with "ND" or "<LOD/LOQ" were entered as 0, LOD/2, and LOD respectively, and the upper bound mean values were used for analyses.[30,31] Comparisons between economic regions were performed using a non-parametric statistical test (Mann-Whitney *U*) because of the non-normally distributions and unequal sample sizes.[32] All data

Table 1. Animal-based foods classification system.

Main category	Subgroup (*abbreviation*)	Food examples
Eggs	Eggs, chicken	
	Eggs, others	
	Processed eggs	Salted egg; Century egg
Red meat	Beef and veal	
	Lamb and mutton	
	Pork	
	Horse	
	Minced mixed meat, unspecified red meat (*Red meat, others*)	
	Mammalian game meats (*MGM*)	Kangaroo; Buffalo; Antelope; Camel; Yak; Rabbit; Reindeer; Boar; Hare
Processed meat	Fresh sausages	Bratwurst; Longaniza; Chorizo criollo; Merguez; Breakfast sausage; Boerwors; Chipolata; Diot; Boudin noir; Boudin blanc
	Fresh industrial processed meat products, other than fresh sausages (*FPM (except fresh sausage)*)	Hamburgers; Burger; Kebab; Patties; Souflaki; Shashlik;
	Bacon	
	Ham	Parma Ham; San Daniele Ham; Jinhua Ham; Jamon Serrano; Jambon Savoie; Virginia Ham; Cured/smoked pork loin and breakfast ham; Prosciutto
	Cured meat in whole cut or pieces (non- comminuted) other than bacon and ham (*Cured meat cuts (except bacon and ham)*)	Cold cut; Raw cured beef; Cooked beef; Pastrami; Silverside
	Frankfurter	
	Cured and cooked comminuted products other than frankfurter (*CCM (except frankfurter)*)	Hotdogs; Viennas; Saveloy; Luncheon; Mortadella; Kielbasa; Meatloaf; Meatball; Kofta; Bologna (baloney); Lyoner; Liver sausage; Blood sausage (Blood pudding); Canned corned beef; Liver pâté; Liverwurst; Ham sausage; White sausages; Kielbasa; Wiejska; Krakowska; Andouille; Andouillette; Boterhamworst; Strasbourg sausage; Other cooked comminuted fermented meat products and smoked sausages which do need any further cooking before consumption[25–28]
	Salami	Saucisson (French salami)
	Chorizo	
	Uncooked comminuted fermented meat products other than salami and chorizo (*UCFM (except salami and chorizo)*)	Pepperoni; Cervelats; Mettwurst; Summer sausage; Naem; Droë wors; Sucuk; Dry sausages and semi-dry sausages (Summer sausage)
	Dried meat	Dried meat strips or flat pieces (Biltong; Beef jerkey); Kabano; Meat floss
	Sausage, unspecified	
	Animal fat	Lard; Cattle fat; Buffalo fat; Goat fat; Sheep fat; Horse fat. Exclude milk fat[26]
	Meat spread	Meat spread
	Processed mammalian game meats (*Processed MGM*)	
	Processed meat products, pooled, unspecified	
Poultry and feathered game meat products	Chicken meat	
	Other poultry meat	Turkey; Broiler
	Feathered game meat	
	Processed poultry	Processed duck/turkey; Chicken nugget; Chicken sausage; Dried/pressed duck
	Poultry *and* feathered game products, others	Bird nest

(*Continued*)

Table 1. (Continued).

Main category	Subgroup (*abbreviation*)	Food examples
Offal	Offal	Animal blood; Brain cheese; Scrotum; Small intestine; Heart; Kidney; Liver; Testicle; Tongue; Stomach; Spleen; Foie gras[27]
Fish and seafood products	Finfish, fresh or frozen	
	Canned fish	
	Cured, fermented, smoked, dried fish (except canned fish) (*Processed fish (except canned fish)*)	
	Crustacea	Shrimp; Crab
	Molluscs	Shellfish
	Roe	
	Other sea and freshwater foods, pooled, unspecified (*Fish and seafood products, others*)	
Dairy products	Milk, cow, fluid, whole	
	Milk, cow, fluid, skim	
	Milk, cow, powder, whole	
	Milk, cow, powder, skim	
	Milk, other, fluid	
	Yoghurt	
	Cheese and cheese products	
	Butter	
	Other milk-based products, pooled, unspecified (*Dairy products, others*)	Buttermilk; Whey protein; Casein powder
Infant formulae and foods	Infant formula, prepared	
	Human breast milk	
	Toddler formula, prepared	
	Infant meat-based foods	
Mixed dishes	Mixed dishes	Pie; Pizza; Sandwiches; Lasagne; Soup; Cassoulet; Galantine
Reptiles, amphibia and insects	Honey	
	Reptiles	
	Insects	
	Amphibia	
	Land molluscs	Snail
Miscellaneous	Miscellaneous	

analyses and visualizations were performed on the Jupyter Notebook using Python packages (pandas, numpy, scipy, matplotlib, and seaborn).

3. Results and Discussion

3.1. Overview of the Database

A total of 16 230 publications were identified by the literature search (Figure 1). Of these, 193 publications were eligible for data extraction (Full list of references see Supporting information), and 122 eligible studies were published after 2005. The database has a total of 3998 entries (nitrate = 1921, nitrite = 2077) from 51 countries. Of the 197 studies, 119 of the included studies were from World Bank assigned high-income countries,[29] 67 from upper-middle income countries and 10 from lower-middle income countries, and only one paper was from low-income country (i.e., Sudan). The most commonly reported on foods were processed meat products, followed by dairy products, fish and seafood products, poultry and feathered game, and red meat. A small variation in nitrate content across main-categories was observed, with processed meat products showing the highest median nitrate content (median [IQR]; 29.20 [13.13–62.30] mg kg^{-1}) and eggs showing the lowest (median [IQR]; 3.34 [1.87–5.87] mg kg^{-1}; **Figure 2**A). In contrast, the miscellaneous group had the highest median nitrite value (median [IQR]; 16.53 [5.87–24.57] mg kg^{-1}), followed by poultry and feathered game meat products (median [IQR]; 11.92 [2.60–27.13] mg kg^{-1}) and processed meat (median [IQR]; 9.67 [4.20–20.64] mg kg^{-1}; Figure 2B).

The median concentrations of nitrate varied substantially across the food subgroups, from a low of 0.40 [IQR: 0.36–4.19] mg kg^{-1} in skimmed milk to a high of 101.61 [IQR: 60.05–105.93] mg kg^{-1} in chorizo and 77.43 [IQR: 40.40–160.20] mg kg^{-1} in fresh sausages (**Table 2** and **Figure 3**). However, the median nitrate val-

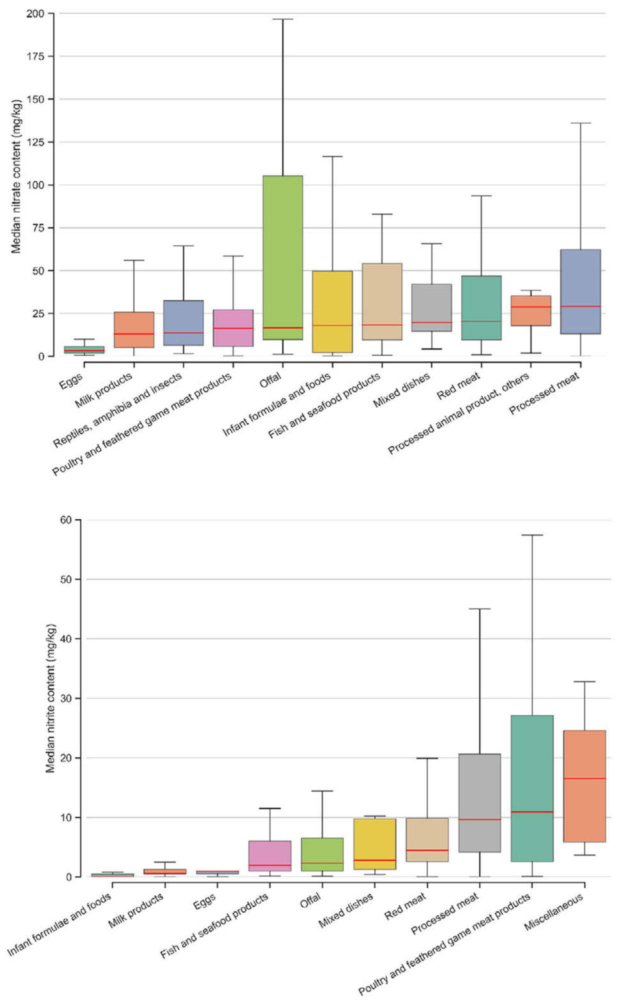

Figure 2. The median nitrate (A) and nitrite (B) content in selected animal-based foods grouped by main category.

ues of most subgroups were lower than 50 mg kg^{-1}. With respect to nitrite content, median values were much lower, with the highest being 6.53 [IQR: 2.60–27.13] mg kg^{-1} in poultry and feathered game meat products and 9.67 [IQR: 4.20–20.63] mg kg^{-1} in processed meat; nitrite values were less variable across all subcategories (**Table 3** and Figure 3).

3.2. Nitrate and Nitrite Content of Processed Meat Products

In total, 2026 records (nitrate = 871, nitrite = 1155) were compiled for processed meat products from 135 references and 41 countries. Cooked and cured comminuted meat products other than frankfurter (CCM except frankfurter) were the most frequently measured (nitrate = 285, nitrite = 368), followed by ham (nitrate = 146, nitrite = 176), cured meat cuts (except bacon and ham; nitrate = 132, nitrite = 152) and bacon (nitrate = 90, nitrite = 123). Fresh sausages and chorizo had median nitrate values > 50 mg kg^{-1}, with the remaining subgroups ranging from 19.31 [IQR: 10.07–48.10] mg kg^{-1} in ham to 49.00 [IQR: 43.91–59.02] mg/kg in dried meats (Table 2 and Figure 3). The mean and median nitrite content in all processed meat subgroups was lower and less variable than that of nitrate, with the highest median nitrite content being found in fresh prepared meat products except fresh sausage (i.e., FPM except fresh sausage; median [IQR]; 21.65 [7.06–58.77] mg kg^{-1}) and fresh sausage (median [IQR]; 16.28 [6.29–24.55] mg kg^{-1}), which were higher than those of frankfurter (median [IQR]; 13.90 [7.07–32.80] mg kg^{-1}), bacon (median [IQR]; 12.25 [6.55–23.04] mg kg^{-1}) and ham (median [IQR]; 11.24 [5.69–19.65] mg kg^{-1}) (Table 3).

Curing with small amounts of nitrite contributes to the development of the characteristic bright red color and flavor of many processed meat products such as bacon and ham.[9,10] Nitrate can be reduced to nitrite by nitrate-reducing bacteria, therefore, it can act as a precursor of nitrite and be used in products, which need long time ripening and/or drying process, such as chorizo and dry-cured ham.[9,33] Up to 500 mg kg^{-1} of nitrate and 200 mg kg^{-1} of nitrite are currently authorized by U.S. Food and Drug Administration (FDA) for cured meat products.[34] Likewise, 30–500 kg are permitted for particular types of cured meat products by EFSA 2011.[26] On the other hand, nitrate and nitrite as food additives, are not allowed for fresh meat preparations (i.e., uncured fresh sausages and other industrial processed meat products such as hamburgers) and red meat in most countries.[26,34,35] As presented in Tables 2 and 3, there was quantifiable amounts nitrate and nitrite in fresh prepared meat products, with values being higher than those of bacon and ham, suggesting that raw meat could be a natural source of both nitrate and nitrite. Moreover, non-meat ingredients in sausages such as soy concentrate, herbs and spices, chili, garlic, and onions can also be natural sources of nitrate and nitrite.[21,25]

3.3. Nitrate and Nitrite Content of Red Meat

In total, the present database collected 140 records (nitrate = 70, nitrite = 70) of red meat nitrate and nitrite concentration data, which were extracted from 39 publications. Despite there being no approval for the addition of nitrite and nitrate to red meat products, the median nitrate value in lamb and mutton (median [IQR]; 45.56 [12.00–61.34] mg kg^{-1}) was higher than that for ham, bacon, and salami (Table 2). Beef and veal, lamb, pork and horse meat also had considerable amounts of nitrate, ranging from 1.75 to 7.85 mg kg^{-1}. With respect to nitrite, the median values of all subgroups were lower than 10 mg kg^{-1} (Table 2). Iammarino and di Taranto[35] investigated the nitrate and nitrite concentration of 150 red meat samples (pork, beef and equine); the authors detected nitrate in 19 red meat samples, but nitrite was not detected in any sample (< 4.50 mg kg^{-1}). The authors suggest that the identified nitrate is derived from natural endogenous sources instead of food additives addition.[35] Likewise, the European Food Safety Authority (EFSA)[13] collected 144 fresh pork, two beef and six lamb meat samples from European countries; nitrate was detected in 125 pork samples, one beef sample, and four lamb samples.

High red and processed meat consumption has been linked to a higher risk of CVD, T2D, cancers, and all-cause mortality.[11,36,37] Processed meat products are considered to be carcinogenic to humans due to the reported associations with colorectal cancer (CRC), while red meat has been recognized as a probable carcinogen.[11,36,37] However, the association of dietary

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Table 2. Nitrate content [mg kg^{-1}] of selected animal-based foods products.

Main food category	Sub-category[a]	Mean ± SD[b]	Median [IQR][b]	Range[b]	No. of samples[c]	No. of references[d]	No. of countries[d]
Processed meat	Chorizo	88.99 ± 45.56	101.61 [60.05–105.93]	8.24–164.10	137	4	4
	Fresh sausages	98.68 ± 80.67	77.43 [40.40–160.20]	7.29–248.00	1065	7	6
	Dried meat	45.09 ± 21.99	49.00 [43.91–59.02]	8.61–64.90	213	4	4
	Sausage, unspecified	77.06 ± 100.60	43.83 [14.44–86.42]	1.31–502.23	775	22	17
	FPM (except fresh sausage)	44.35 ± 24.99	43.50 [22.60–59.41]	13.21–92.78	280	8	7
	Frankfurter	51.00 ± 47.78	41.50 [28.42–55.62]	4.60–257.00	316	15	10
	UCFM (except salami and chorizo)	58.87 ± 75.11	39.72 [18.61–68.10]	1.00–368.00	2238	12	9
	Bacon	64.47 ± 65.47	38.69 [15.00–88.86]	1.02–324.36	1480	23	16
	Processed meat, others	48.50 ± 43.24	34.00 [22.72–41.80]	14.50–168.30	5006	7	5
	CCM (except frankfurter)	53.53 ± 104.12	32.56 [15.24–57.80]	0.10–1380.00	6285	47	27
	Processed MGM	74.44 ± 77.16	32.40 [28.60–94.55]	18.40–224.00	107	4	3
	Salami	43.09 ± 50.13	29.10 [12.40–51.15]	1.00–299.00	1168	26	16
	Cured meat cuts (except bacon and ham)	37.88 ± 53.56	20.00 [10.71–38.58]	0.73–368.09	1563	27	18
	Ham	46.32 ± 61.88	19.31 [10.07–48.10]	0.08–325.24	2072	37	21
Red meat	Lamb and mutton	54.97 ± 56.93	45.56 [12.00–61.34]	7.51–148.43	25	5	5
	Red meat, others	34.03 ± 24.46	30.00 [14.01–47.80]	2.70–93.70	1144	14	12
	Beef and veal	29.47 ± 39.90	13.10 [4.92–39.25]	0.92–150.89	182	13	11
	Pork	16.09 ± 16.27	10.60 [4.27–22.76]	1.07–49.50	279	11	8
	Horse	45.78 ± 79.17	9.60 [6.11–20.60]	5.60–187.00	118	4	2
Poultry and feathered game meat products	Poultry and feathered game products, others	30.63 ± 13.68	26.24 [21.70–38.91]	16.30–50.00	66	3	3
	Processed poultry	25.25 ± 20.86	20.60 [8.96–28.58]	0.36–75.78	265	10	8
	Chicken meat	16.68 ± 22.63	7.66 [4.52–15.59]	0.15–81.56	235	12	9
	Other poultry meat	9.06 ± 10.66	5.91 [5.15–5.95]	0.58–27.70	37	4	3
Milk products	Milk, cow, powder, whole	129.89 ± 193.41	51.51 [9.18–152.20]	1.54–630.00	56	5	5
	Milk products, others	25.32 ± 21.56	17.50 [9.00–33.75]	1.00–96.00	211	8	7
	Milk, cow, powder, skim	20.61 ± 31.75	13.00 [8.23–23.00]	1.70–395.00	268	3	3
	Cheese and cheese products	21.46 ± 34.98	10.86 [3.17–24.95]	0.00[e]–323.90	1908	27	18
	Milk, other, fluid	11.17 ± 11.90	5.90 [0.47–23.04]	0.25–25.00	9	3	3
	Milk, cow, fluid, whole	26.05 ± 65.57	1.57 [0.73–16.23]	0.05–326.22	848	21	15
	Milk, cow, fluid, skim	3.20 ± 4.98	0.40 [0.36–4.19]	0.29–12.60	26	4	3
Infant formulae and foods	Infant meals	62.42 ± 39.65	45.92 [41.40–72.20]	11.20–157.58	842	5	5
	Infant formula, prepared	24.47 ± 34.71	8.80 [1.28–38.99]	0.15–122.20	205	7	5
	Human breast milk	3.98 ± 6.32	1.39 [0.82–3.03]	0.70–18.10	80	4	4
Fish and seafood products	Canned fish	47.03 ± 27.98	54.22 [17.79–77.20]	11.88–79.04	52	3	3
	Processed fish (except canned fish)	69.15 ± 123.59	19.30 [9.00–72.00]	1.90–565.00	251	7	7
	Finfish, fresh, frozen	18.47 ± 14.38	13.91 [8.73–31.50]	0.70–48.00	145	8	7
Eggs	Eggs, chicken	3.96 ± 3.07	2.86 [1.71–5.01]	0.55–10.00	184	5	5
Offal	Offal	57.27 ± 60.68	16.75 [9.83–105.36]	1.20–196.60	256	10	9

FPM, Fresh industrial processed meat products; CCM, Cured and cooked comminuted products; UCFM, Uncooked comminuted fermented meat products; MGM, Mammalian game meats. [a] Only subgroups with data derived from ≥ 3 references were included. The full subgroup list is available in Table 1. [b] Upper bound mean, samples < LOD, or "ND" were imputed as the actual LOD in the calculations. [c] Sample size was assigned as 1 where publications did not clearly present. [d] Full list of references and sampling countries see Supporting Information Table S1. [e] <0.01 mg kg^{-1}.

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Table 3. Nitrite content [mg kg^{-1}] of selected animal-based foods products.

Main food category	Sub-category[a]	Mean ± SD[b]	Median [IQR][b]	Range[b]	No. of samples[c]	No. of references[d]	No. of country of sampling[d]
Processed meat	FPM (except fresh sausage)	37.73 ± 38.97	21.65 [7.06–58.77]	0.50–169.80	505	12	9
	Fresh sausages	28.53 ± 35.43	16.28 [6.29–24.55]	0.88–97.60	832	8	7
	Frankfurter	25.31 ± 24.41	13.90 [7.07–32.80]	0.25–83.90	110	17	9
	Bacon	19.90 ± 22.82	12.25 [6.55–23.04]	0.20–144.42	1027	31	19
	Ham	21.11 ± 45.78	11.24 [5.69–19.65]	0.35–527.36	2443	50	24
	Sausage, unspecified	25.57 ± 37.79	10.71 [6.42–28.85]	0.05–187.00	1013	34	19
	CCM (except frankfurter)	19.00 ± 32.16	9.41 [3.98–21.70]	0.00[f]–332.00	20 063	69	35
	Salami	17.84 ± 24.87	8.20 [3.67–23.72]	0.50–119.00	1176	36	18
	Cured meat cuts (except bacon and ham)	12.82 ± 20.78	7.42 [3.08–13.84]	0.09–163.65	5576	39	23
	UCFM (except salami and chorizo)	21.86 ± 36.09	7.33 [3.65–19.14]	0.10–216.63	1199	16	10
	Processed MGM	6.28 ± 3.49	6.15 [3.25–8.80]	2.50–12.00	165	5	3
	Dried meat	6.78 ± 6.36	5.40 [1.88–11.11]	0.05–18.23	234	6	5
	Chorizo	15.03 ± 35.72	4.35 [2.93–5.80]	0.49–148.98	217	6	4
	Processed meat, others	5.21 ± 6.55	0.01 [0.01–11.27]	0.01–18.19	13 495	9	8
Red meat	Beef and veal	9.15 ± 7.56	7.85 [4.50–11.50]	0.10–25.80	197	12	11
	Horse	7.65 ± 6.58	4.50 [4.50–9.60]	1.47–18.20	109	4	3
	Pork	7.83 ± 10.09	4.50 [2.62–9.00]	0.10–35.00	112	8	7
	Red meat, others	8.36 ± 9.50	4.50 [2.65–11.07]	0.05–42.00	1660	16	13
	Lamb and mutton	9.17 ± 16.00	1.75 [0.15–10.77]	0.10–33.07	23	4	4
Poultry and feathered game meat products	Processed poultry	35.14 ± 42.58	18.60 [6.74–39.08]	0.20–162.40	364	15	11
	Poultry and feathered game products, others	7.34 ± 4.86	6.25 [4.00–12.25]	1.71–12.49	55	3	3
	Chicken meat	30.18 ± 62.44	3.54 [1.20–17.79]	0.10–215.90	224	9	8
Milk products	Cheese and cheese products	2.28 ± 3.13	1.00 [0.58–1.80]	0.00[f]–18.40	2193	29	19
	Milk products, others	1.21 ± 0.93	0.90 [0.50–1.50]	0.01–5.90	213	6	6
	Milk, cow, powder, skim	0.81 ± 0.90	0.50 [0.50–0.60]	0.50–8.10	178	3	3
	Milk, cow, fluid, skim	0.32 ± 0.49	0.14 [0.07–0.25]	0.04–1.40	26	4	3
	Milk, cow, fluid, whole	0.75 ± 1.23	0.12 [0.08–1.05]	0.00[f]–5.30	453	16	11
	Milk, other, fluid	0.23 ± 0.38	0.08 [0.04–0.12]	0.04–1.00	8	3	3
	Milk, cow, powder, whole	1.69 ± 2.73	0.07 [0.06–2.27]	0.02–6.48	44	3	3
Infant formulae and foods	Infant meals	1.60 ± 3.43	0.49 [0.49–0.49]	0.04–14.00	225	5	5
	Infant formula, prepared	3.10 ± 13.72	0.07 [0.01–0.20]	0.00[f]–64.54	187	7	6
	Human breast milk	0.07 ± 0.17	0.01 [0.00–0.01]	0.00[f]–0.53	101	3	3
Fish and seafood products	Canned fish	17.58 ± 13.08	20.32 [6.16–30.16]	0.27–31.04	52	4	4
	Molluscs	4.00 ± 1.32	4.50 [4.50–4.50][d]	1.00–4.50	271	3	2
	Finfish, fresh, frozen	5.60 ± 6.42	4.00 [1.07–7.25]	0.20–22.60	119	7	6
	Roe	2.32 ± 1.19	2.00 [2.00–2.20]	1.20–5.30	1929	4	2
	Processed fish (except canned fish)	3.44 ± 6.38	1.00 [1.00–2.12]	0.14–35.00	508	9	7
Eggs	Eggs, chicken	0.68 ± 0.55	1.00 [0.52–1.00]	0.04–1.00	52	3	3
Offal	Offal	4.64 ± 6.45	2.31 [1.02–6.53]	0.12–38.54	228	12	11

FPM, Fresh industrial processed meat products; CCM, Cured and cooked comminuted products; UCFM, Uncooked comminuted fermented meat products; MGM, Mammalian game meats. [a] Only subgroups with data derived from ≥ 3 references were included. The full subgroup list is available in Table 1. [b] Upper bound mean, samples < LOD, or "ND" were imputed as the LOD in the calculations. [c] Sample size was assigned as 1 where publications did not clearly present. [d] Full list of references and sampling countries see Supporting Information Table S2. [e] Five entries from two of the three references had the same value (4.5 mg kg^{-1}). [f] <0.01 mg kg^{-1}.

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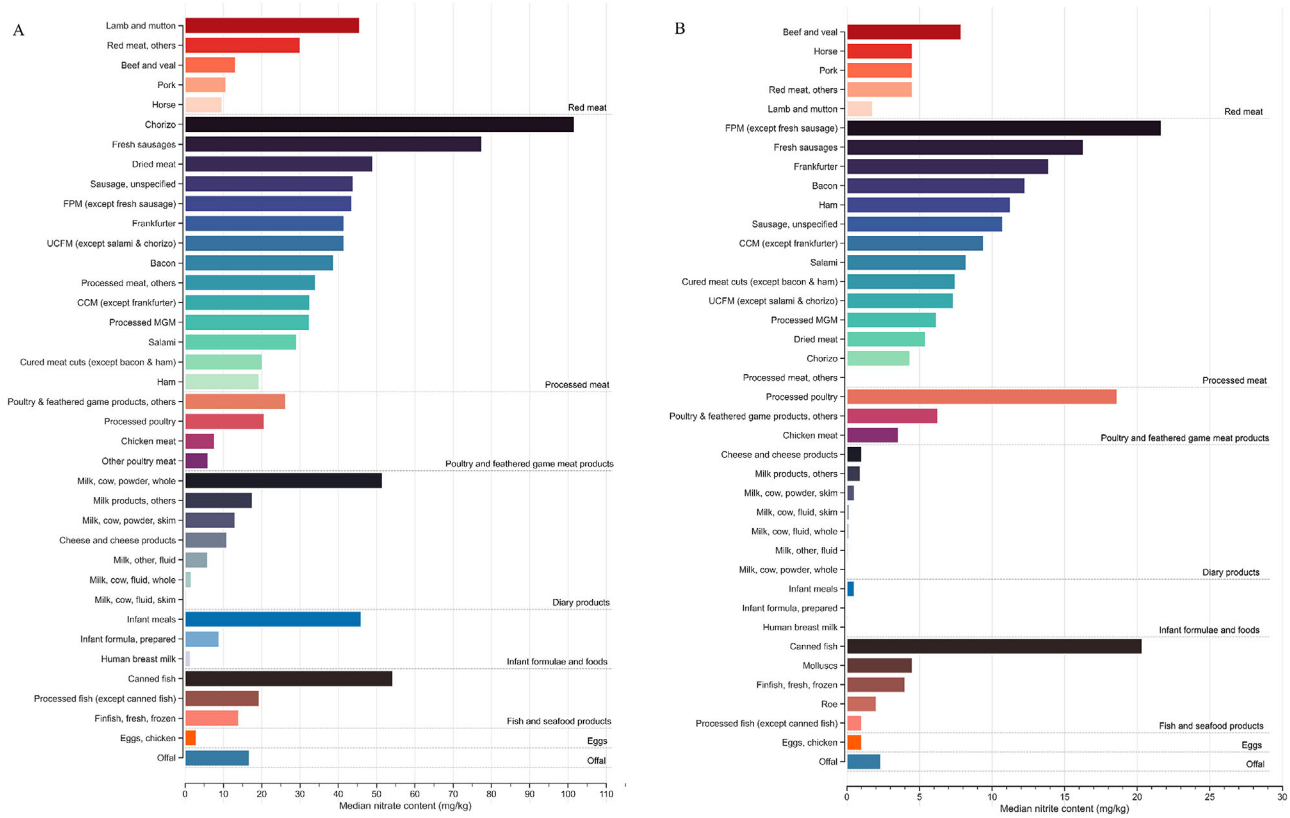

Figure 3. The median nitrate (A) and nitrite (B) content in subgroups of selected animal-based foods.

intake of nitrate and nitrite through processed meat products with the development of CRC or other cancers is yet to be well established.[12,17,36] Currently, cured meat products (bacon and ham in particular) are scrutinized for the presence of nitrate and nitrite over concerns of the formation of NOCs.[38] The potential negative health effects of red meat are generally blamed on its high fat and heme iron content, and compounds linked with increased cancer risk (polycyclic aromatic hydrocarbons and heterocyclic aromatic amines) induced by high temperature.[37,39] Red meat consumption is generally much higher than processed meat in most countries.[11] Globally, mean consumption of red meat and processed meat were 27 and 4 g day^{-1} in 2017, respectively.[40] Our study suggests that uncured fresh prepared meat products and sausages, in particular red meat, could be an under-recognized and under-reported dietary nitrate source, as compared to cured meat products.

3.4. Nitrate and Nitrite Content of Poultry and Feathered Game Meat Products

Global poultry consumption per capita has undergone a rapid increase.[41] However, the availability of data for nitrate and nitrite concentration in poultry products was relatively limited, with 53 records of nitrate data and 58 of nitrite data from 28 publications entered in the database. As illustrated in Table 2, fresh prepared poultry meats were nitrate positive. Processed poultry (including cured turkey, chicken-based ham, chicken luncheon meats, chicken sausages, and chicken nuggets) had the highest median nitrite concentration at 18.60 [IQR: 6.74–39.08] mg kg^{-1}. This contrasts with the findings of Ologhobo et al.[42] who reported a much higher nitrate (range: 1210.00–2170.00 mg kg^{-1}) and nitrite (range: 710.00–1750.00 mg kg^{-1}) content in Nigerian raw chicken meat in comparison with data from 13 other publications (range: nitrate 0.16–81.56 mg kg^{-1}, nitrite 0.11–215.9 mg kg^{-1}). Therefore, the data were excluded from the data aggregation in this publication.

3.5. Nitrate and Nitrite Content of Dairy Products

In the current database, dairy products include cow, buffalo, goat, and other mammalian milk, either fluid or powder, and their related products (e.g., cheese, yoghurt and whey protein), while human breast milk and formula were assigned as "Infant formulae and foods" (Table 1). In total, 56 publications provided 651 entries of nitrate and 519 entries of nitrite content data of 31 countries.

A wide range in nitrate concentration was observed for whole cow milk powder samples (1.54–630 mg kg^{-1}). Moreover, whole milk powder had a higher nitrate content than skimmed milk powder (Table 2). In comparison, both whole and skimmed fluid cow milk had a minimal nitrate content (<2.00 mg L^{-1}). Prolonged heat, fouling, and contaminations could contribute to the high nitrate and nitrite content in milk powder.[43] Some countries allow the use of nitrate as an additive in certain cheese (e.g., European Union (EU) and Japan), which may explain the high interest in monitoring nitrate content in cheese products ($n = 144$ records in the database).[26,44] Nevertheless, the nitrate content in cheese was much lower than that of milk powder (Table 2). In terms of the nitrite content, only a negligible amount of nitrite was found in all dairy products, with all median levels being lower than 1.00 mg kg^{-1} (mg L^{-1}) (Table 3). Indyk and Woollard[45] and Silanikove et al.[46] summarized that the nitrate and nitrite content in typical dairy products was 3.00–36.00 and 0–1.75 mg kg^{-1}, respectively, suggesting a low nitrate and nitrite level in most dairy products. The results are in line with the findings of the current study. Of note, the median nitrate content in whole milk powder was found to be higher than that of bacon and ham (Table 2).

3.6. Nitrate and Nitrite Content of Fish and Seafood Products

In total, 151 records of the nitrate ($n = 72$) and nitrite ($n = 79$) concentration data of fish and seafood products were obtained from 28 publications from 18 countries. The "Finfish, fresh, frozen" and "Processed fish" were the only two subgroups containing enough data (derived from more than three studies) for nitrate data aggregation (Table 2). Regarding nitrite, the highest median value was found in canned fish (median [IQR]; 20.32 [6.16–30.16] mg kg^{-1}). In comparison, the median nitrite content of other processed fish (except canned fish) was much lower (median [IQR]; 1.00 [1.00–2.12] mg kg^{-1}) (Table 3).

Nitrate and nitrite are only permitted as food additives for specific fish and fishery products in certain countries such as Japan (fish-based ham, bacon and sausage, salted/smoked salmon roes) and the USA (smoked and cured tuna, salmon, shad and chub).[34,44] In Japan, a maximum amount of 5 mg kg^{-1} nitrite is allowed for salmon roe, while up to 200 mg kg^{-1} of nitrate is allowed for cod roe in the USA. In the EU, up to 500 mg kg^{-1} of nitrate is permissible in pickled herring and sprat only.[26] The values collated in our database demonstrated that the nitrite content in fish and seafood products were well below the regulation limits around the world (Table 3). However, processed fish products are relatively high in biogenic amines, implying greater concern due to the potential formation of NOCs.[47,48]

3.7. Nitrate and Nitrite Content of Infant Formula and Meat-based Baby Food

There were 16 studies that investigated nitrate and nitrite in breast milk and animal source baby foods such as formulae and meat-based puree, contributing, in total, 63 records to the database. As shown in Tables 2 and **3**, the content of both nitrate and nitrite in infant formulae was much lower than that observed for whole cow milk powder. Moreover, the amount of nitrate and nitrite observed in breast milk was negligible, being below 1.50 and 0.10 mg L^{-1} respectively. Jones et al.[49] indicated that nitrite content in milk of mothers of preterm infants was significantly lower than that of term infants. A high median nitrate value was found in infant meals (45.92 mg kg^{-1}). The meals included in the present database were animal ingredients-based (e.g., meat, milk, or fish) but may also have contained vegetables and/or fruit that could have contributed to the totals.

3.8. Nitrate and Nitrite Content of Other Animal-based Foods Products

Eggs, offal products, mixed meals (e.g., pie, pizza, sandwiches, lasagne, cassoulet, and galantine), and other specific animal products (e.g., lard, honey, snail, and bird nest) were also included in the present database. Currently, considerable ongoing efforts have been taken to commercialize many novel meat products, such as edible insects, cultured meat and plant-based meat analogues.[50] However, no available data for edible insects and plant-based meat analogue products were found. In view of the high nitrate values found in mixed meals which contain plant-based ingredients in the current database (e.g., lamb stewed with okra, vegetable quiche, stuffed escalope, small springs), future analyses are required to monitor nitrate and nitrite concentrations in plant-based meat analogues.

3.9. The Occurrence of Nitrate and Nitrite in Processed Meat Products by Region

Comparisons between geographical and economic regions were performed for processed meat products only due to the limited data availability and/or the minor heterogeneity across regions for other animal foods (e.g., dairy products). The collated data contained nitrate and nitrite concentration of meat products from six of the seven world geographical regions designated by World Bank, with no data from South Asia (including Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka).[29] As illustrated in **Figure 4**, the median nitrate levels in all included processed meat products of high-income countries were lower than those of middle-income regions, with the differences in CCM (except frankfurter), cured meat cuts (except bacon and ham), ham, unspecified sausages, and UCFM (except salami and chorizo) being significant ($p < 0.05$). A similar pattern was found in nitrite contents of the included processed meat products. Babateen et al.[2] found that daily nitrate intake was inversely associated with economic development status of the countries. Animal-based food consumption tends to increase as countries get richer, while nitrate-rich vegetables and fruit intake decrease.[2] The similar inverse association between the nitrate and nitrite content in animal-based foods and economic development status observed in this study could further support the explanation for the lower dietary nitrate intake in developed countries.

4. Future Perspectives

For nitrate in vegetable and drinking water, there are several ongoing monitoring programs in European countries and the USA[51]; to the best of our knowledge, no similar programs for animal-based food products exist. As part of our future work, the current database and the vegetable nitrate database will be updated regularly, and a database for other foods (e.g., fruits, grains, nuts, beverages) is under development. In the current study, large variabilities of nitrate and nitrite content for most food groups were observed, indicating that values from study-specific nitrate and nitrite quantifications, or compiled from limited number of

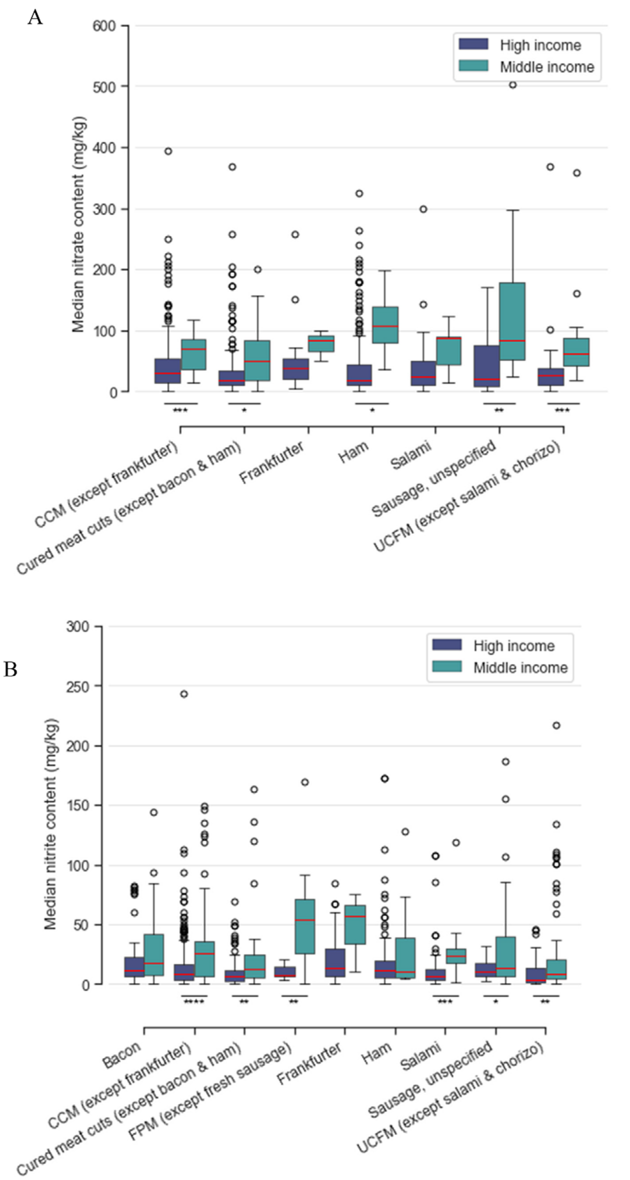

Figure 4. The median nitrate (A) and nitrite (B) content in selected processed meat products in different economic regions.

literatures are likely to be unreliable.[2] A major strength of this study is that the nitrate and nitrite concentration data collected from a large number of references, both mean (upper bound) and median values are presented. There is apparent data skewness in many food groups (non-normal distribution; Figure 4); thus, we recommend using median nitrate and nitrite concentrations rather than mean values when assessing associations between dietary nitrate/nitrite intake and health outcomes.[52] In addition, given that across-region comparisons identified considerable variability in nitrate and nitrite content, region-specific nitrate, and nitrite concentrations should be used.

The current database is not without limitations. Only a limited number of eligible studies in this database detailed the processing methods. Information is insufficient to quantify the impacts of processing/cooking on nitrate and nitrite content, whereas their retention rate after processing should be taken into consideration when calculating their dietary intake.[21] In addition, large heterogeneity in the concentration data among studies was observed, therefore, future work will aim to improve the data quality of the databases and minimize the literature selection bias, as well as improve representativeness of geographical coverage (data from lower-income countries particularly). In this context, we encourage more researchers to share their peer-reviewed data in English, in particular, those previously published in non-English.

5. Conclusion

This database will be useful for assigning nitrate and nitrite concentration values to foods and mixed dishes from food consumption surveys. In conjunction with the vegetable nitrate database,[21] this database facilitates researchers to obtain a robust assessment of plant and animal-based nitrate and nitrite dietary intake in cohort studies, and ultimately more accurately determine the association between nitrate and nitrite dietary exposure and health outcomes. Moreover, the database could be used by nutritionists and dietitians to quantify nitrate and nitrite levels in the diets of clients and patients. The database will also be of use in establishing dietary guidelines and regulations.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

J.M.H. and C.P.B. contributed equally to this work. The responsibilities of authors were: C.P.B., J.M.H., J.R.L., and L.C.B. proposed and designed the research; L.Z.Z., A.L., and C.P.B. conducted the literature search and data extraction; L.Z.Z and C.P.B. analyzed the data and wrote the manuscript in consultation with J.M.H. and L.C.B. All authors provided critical feedback on data analysis, the interpretation of the results, and the final manuscript.

Data Availability Statement

Data available on request from the authors.

Keywords

animal-based foods, database, dietary intake, nitrate, nitrite

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