OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Proposition 65

Evidence on the Carcinogenicity of Nitrite in Combination with Amines or Amides

August 2016

Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

The Office of Environmental Health Hazard Assessment's (OEHHA) Reproductive and Cancer Hazard Assessment Branch was responsible for the preparation of this document.

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PREFACE

Proposition 65[1] requires the publication of a list of chemicals "known to the state" to cause cancer or reproductive toxicity. The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency maintains this list in its role as lead agency for implementing Proposition 65[2]. The Carcinogen Identification Committee (CIC) advises and assists OEHHA in compiling the list of chemicals that cause cancer as required by Health and Safety Code section 25249.8. The Committee serves as the state's qualified experts for determining whether a chemical has been clearly shown to cause cancer.

On February 7, 2014, OEHHA published a public notice in the *California Regulatory Notice Register* announcing its intent to list "nitrite in combination with amines or amides" as causing cancer under Proposition 65 via the authoritative bodies mechanism[3]. After consideration of comments received on the Notice of Intent to List and further evaluation of the scientific evidence supporting the listing, OEHHA determined that the regulatory criteria in Section 25306(e)[4] had not been met for the spectrum of chemicals covered by the broad class "nitrite in combination with amines and amides". Pursuant to Section 25306(i)[5], OEHHA announced on May 6, 2015[6] that the CIC would consider at a future meeting whether "nitrite in combination with amines or amides" or a subset of chemicals of this class, have been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

OEHHA developed this document with information on the evidence on the carcinogenicity of "nitrite in combination with amines or amides" to assist the CIC in its deliberations. The original papers discussed in the document will also be provided to the CIC as part of the hazard identification materials. Comments on this hazard identification document received during the public comment period also form part of the hazard identification materials, and are provided to the CIC members prior to their formal deliberations.

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986 (California Health and Safety Code 25249.5 *et seq*.)
[2] Health and Safety Code section 25249.12, Title 27, Cal. Code of Regs., section 25102(o)
[3] See the February 7, 2014 Notice of Intent to List: Nitrite in Combination with Amines or Amides, available at: http://oehha.ca.gov/proposition-65/crnr/notice-intent-list-nitrite-combination-amines-or-amides
[4] Title 27, Cal. Code of Regs., section 25306(e)
[5] Title 27, Cal. Code of Regs., section 25306(i)
[6] See the public notice posted May 6, 2015 on the OEHHA web site and published May 8, 2015 in the *California Regulatory Notice Register*, available at: http://oehha.ca.gov/proposition-65/crnr/nitrite-combination-amines-or-amides-be-considered-carcinogen-identification

On November 15, 2016, the CIC is scheduled to deliberate on the carcinogenicity of "nitrite in combination with amines or amides". The CIC may also consider whether a subset (or multiple subsets) of chemicals of this broad class should be added to the Proposition 65 list as carcinogens. A transcript of the meeting will be available at www.oehha.ca.gov after the meeting.

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Acronyms and abbreviations

A	adenoma
AC	adenocarcinoma
AML	acute myeloid leukemia
AS	angiosarcoma
BA	bile duct adenoma
BCL	B-cell lymphoma
BCLL	B-cell chronic lymphatic leukemia
BMI	body mass index
C	carcinoma
CAC	cholangiocarcinoma
CI	confidence interval
CIC	Carcinogen Identification Committee
CLL	chronic lymphoid leukemia
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
CML	chronic myeloid leukemia
CONCeRN	Colorectal Neoplasia screening with Colonoscopy in asymptomatic women at Regional Navy/army medical centers
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
EAC	esophageal adenocarcinoma
EPIC	European Prospective Investigation into Cancer and Nutrition
ESCC	esophageal squamous cell carcinoma
EURGAST	Gastric and Esophageal project of European Prospective Investigation into Cancer and Nutrition
FFQ	food frequency questionnaire
FL	follicular lymphoma
g	gram
GC	gastric cancer
GCA	gastric cardia adenocarcinoma
GNCA	gastric noncardia adenocarcinoma
H. pylori	*Helicobacter pylori*
HA	hemangioma
HAES	hemangioendothelial sarcoma
HAS	hemangiosarcoma
HCC	hepatocellular carcinoma
HL	Hodgkin's lymphoma
hMLH1	human mut-L homologue 1
HPFS	Health Professionals Follow-Up Study
HR	hazard ratio
IARC	International Agency for Research on Cancer
IWHS	Iowa Women's Health Study
kcal	kilocalorie
LS	lymphosarcoma
mg	milligram
ML	malignant lymphoma
MM	multiple myeloma
MNCL	mononuclear cell leukemia
MPED	MyPyramid Equivalents Database
MZBL	marginal zone B-cell lymphoma
$NaNO_2$	sodium nitrite
NCI	National Cancer Institute

ND	not-detected
NFS	neurofibrosarcoma
NHL	Non-Hodgkin lymphoma
NHS	Nurses' Health Study (I or II)
NIH	National Institutes of Health
NO_2	nitrite
NSAID	non-steroidal anti-inflammatory drug
NT	not tested
OC	esophageal cancer
OR	odds ratio
P	papilloma
PAH	polycyclic aromatic hydrocarbon
PCE	polychromatic erythrocyte
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
Q	quartiles or quintiles
r	rare tumor type (<1% incidence in historical controls)
r, f	rare tumor type only in females
r, m	rare tumor type only in males
RR	relative risk
S.*typhimurium*	*Salmonella typhimurium*
s.c.	subcutaneous
SCC	squamous cell carcinoma
SCP	squamous cell papilloma
SCS	spindle cell sarcoma
SD	standard deviation
SEER	Surveillance, Epidemiology and End Results
SWHS	Shanghai Women's Health Study
T	tertiles
TCL	T/NK-cell lymphoma
μg	microgram

1. EXECUTIVE SUMMARY

In February 2014, the Office of Environmental Health Hazard Assessment (OEHHA) announced its intent to list “nitrite in combination with amines or amides” as carcinogens under Proposition 65 via the authoritative bodies mechanism[7]. This was based on the finding by the International Agency for Research on Cancer (IARC) in a 2010 Monograph that there was “sufficient evidence of carcinogenicity in experimental animals” for “nitrite in combination with amines or amides”. Amines and amines are large classes of chemicals with thousands of individual members in each class. Because the animal studies cited by IARC as supporting the listing were based on a comparatively small number of chemicals, OEHHA determined in May 2015 that the regulatory criteria for listing via the authoritative bodies mechanism had not been met for the spectrum of chemicals covered by the broad class “nitrite in combination with amines or amides”. Pursuant to Section 25306(i)[8], “nitrite in combination with amines or amides” have been referred to the Carcinogen Identification Committee (CIC) for consideration for listing under Proposition 65. This document summarizes the evidence of carcinogenicity on nitrite in combination with amines or amides: It updates the evidence considered by IARC, including the results from studies examining cancer in humans in relation to nitrite intake, studies of individual amines and amides tested in combination with nitrite in animal cancer bioassays, and genotoxicity assays.

Nitrite (NO_2^-) is a negatively charged ion, which can form salts with positively charged ions such as sodium (Na^+) and potassium (K^+).

Amines are organic compounds that contain a basic nitrogen atom with a lone electron pair; examples include amino acids and biogenic amines like histamine. Depending on the degree of carbon substitution on the nitrogen atom, amines can be classified as "primary", "secondary" or "tertiary”. Positively charged “quaternary” amines can be formed by sharing a lone electron pair with either an alkyl group or aryl group.

Amides are organic compounds that have a nitrogen atom which is directly attached to a carbonyl group. Amides can be formed from amines, and can be classified as "primary", "secondary" or "tertiary" amides, depending on the degree of carbon substitution on the nitrogen atom.

Nitrite or its salts, when present in combination with amines or amides in acidic conditions, may react with the amine or amide to form nitrosated compounds. Amines

[7] See Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs., section 25306.
[8] Title 27, Cal. Code of Regs., section 25306(i)

can undergo various reactions to form nitrosamines, whereas amides react to form nitrosamides.

Nitrite may occur in combination with amines or amides in occupational settings, such as those associated with azo dye production. Relatively high levels of nitrite sometimes occur in combination with amines and amides in foods such as cured and/or processed red meats, poultry, and fish.

In its 2010 Monograph, IARC reviewed the evidence on ingested nitrite. Many studies are available examining cancer in humans in relation to nitrite intake. Some studies report positive associations, and some do not. Evidence of carcinogenicity comes primarily from cohort and case-control studies of colorectal, esophageal and stomach cancer. IARC (2010) evaluated the evidence from studies in humans and concluded: "There is *limited evidence* in humans for the carcinogenicity of nitrite in food. Nitrite in food is associated with increased incidence of stomach cancer." Studies published since IARC's (2010) review add to the evidence on a number of cancers, including colorectal, esophageal, stomach, lymphoma, brain, and thyroid cancer. Various processed meats are sources of relatively high levels of nitrite in combination with amines or amides. An IARC 2015 Working Group classified consumption of processed meat as "carcinogenic to humans" based on sufficient human evidence for colorectal cancer (Bouvard *et al.,* 2015). The IARC Monograph describing the evidence and basis for that finding has not yet been published.

IARC evaluated 55 animal bioassays of nitrite in combination with amines or amides, and concluded "there is sufficient evidence in experimental animals for the carcinogenicity of nitrite in combination with amines or amides" (IARC, 2010).

The animal studies reviewed by IARC plus an additional 35 bioassays identified by OEHHA provide evidence on the carcinogenicity of nitrite in combination with amines or amides in experimental animals. For amines in combination with nitrite some of the animal bioassays report positive tumor findings, while others do not. Different classes of amines have been tested in combination with nitrite to various extents. Primary amines represent a large class of hundreds of chemicals. Two primary amines were tested. 2-Amino-3-methylimidazo[4,5-*f*]quinolone (IQ), a chemical on the Proposition 65 list, tested positive. 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), also on the Proposition 65 list, did not. There are also numerous secondary amines, of which eleven were tested in combination with nitrite in animals. Four tested positive [bis(2-hydroxypropyl)amine; morpholine; N-methylaniline; piperazine], four tested negative and studies on three were inconclusive. Thirteen tertiary amines were tested, with three having some positive results [IQ (also a primary amine); aminopyrine;

chlorpheniramine], seven with negative results and three with inconclusive results. There are no animal studies for the quarternary amines. Cyclic aromatic amines also is a large class of chemicals, of which five were tested, two showing positive results [IQ (also a primary amine and a tertiary amine); chlorpheniramine (also a tertiary amine)], one with negative results and two with inconclusive results.

Similarly, different classes of amides have been tested in combination with nitrite to various extents. Primary and tertiary amides represent large classes of chemicals. No chemicals in these classes were tested. Two secondary amides were tested in combination with nitrite: allantoin tested positive, and 2-acetamidofluorene, a chemical on the Proposition 65 list, did not. Allantoin is also a urea. Of the seven ureas tested in combination with nitrite, in addition to allantoin, butylurea, ethylene thiourea (on the Proposition 65 list), ethylurea and methylurea all had positive studies. Two others did not. Of the three carbamates tested, carbendazim in combination with nitrite tested positive, the Proposition 65 carcinogen ethyl carbamate was negative and disulfiram was inconclusive. None of the sulfonamides were tested. Of the four guanidines tested, one (dodine) tested positive.

For chemicals with positive results, tumors were often observed at multiple sites, sometimes in multiple animal species and strains. Tumors observed in animals treated with nitrite in combination with *amines* include lung and liver tumors, reticular cell sarcoma, rare Zymbal's gland and nasal tumors, and rare chloangiocarcinoma in rats; lung tumors in mice; and liver tumors and rare cholangiocarcinoma in hamsters. Tumors observed in animals treated with nitrite in combination with *amides* include lung tumors, mononuclear cell leukemia, rare forestomach and Zymbal's gland tumors, and rare malignant lymphoma in rats; and lung and Harderian gland tumors, lymphosarcoma, malignant lymphoma, and rare skin, forestomach, intestine, and uterine tumors in mice.

Overall, increased tumor incidences have been observed for seven amines and seven amides, when administered to animals in combination with nitrite. Of the seven amines, one is a primary amine, four are secondary amines, three are tertiary amines, and two are cyclic aromatic amines. Of the seven amides, one is a secondary amide, five are ureas, one is a carbamate, and one is a guanidine.

Additional evidence on the carcinogenicity of nitrite in combination with a number of different amines or amides comes from positive genotoxicity studies conducted in bacteria, yeast, cultured mammalian cells, and in rats and mice following exposure *in vivo*. One hundred and eleven amines and 39 amides have been tested in combination with nitrite for genotoxicity.

For the amines, some of the genotoxicity assays of nitrite in combination with amines report positive findings, while others do not. Different classes of amines have been tested in combination with nitrite for genotoxicity to various extents. Fourteen primary amines were tested for genotoxicity: four tested positive, three tested negative, and studies on seven were inconclusive. Forty-eight secondary amines were tested in combination with nitrite for genotoxicity: 38 tested positive, three tested negative, and studies on seven were inconclusive. Fifty-two tertiary amines were tested: 24 tested positive, 9 tested negative, and findings for 19 were inconclusive. One quarternary amine was tested for genotoxicity, with negative results. Thirty-four cyclic aromatic amines were tested: 16 tested positive, 10 tested negative, and findings for 8 were inconclusive.

For the amides, some of the genotoxicity assays of nitrite in combination with amides report positive findings, while others do not. Different classes of amides have been tested in combination with nitrite for genotoxicity to various extents. Five primary amides were tested for genotoxicity: four tested positive and one was inconclusive. Ten secondary amides were tested in combination with nitrite for genotoxicity: one tested positive, one tested negative, and studies on eight were inconclusive. Seven tertiary amides were tested: two tested positive and studies on five were inconclusive. Six ureas were tested: three tested positive, two tested negative, and the finding for one was inconclusive. Seven carbamates were tested: one tested positive, two tested negative, and studies on four were inconclusive. Five sulfonamides were tested: three tested positive and studies on two were inconclusive. Four guanidines were tested: two with positive results and two with inconclusive results.

Overall, positive genotoxicity findings have been observed in at least one assay for 59 amines and 15 amides, when tested in combination with nitrite. For 36 amines and 20 amides, increases in genotoxic effect were observed in combination with nitrite; however, definitive conclusions could not be reached, since the studies lacked one or two of the three necessary comparator groups.

Of the 59 amines with positive genotoxic findings, four are primary amines (three of these are also secondary amines, and two are also cyclic aromatic amines), 38 are secondary amines (three of these are also primary amines, six are also tertiary amines, nine are also cyclic aromatic amines, and 5 are also amides), 24 are tertiary amines (7 of these are also secondary amines, one is also a cyclic aromatic amine, and three are also amides), and 16 are cyclic aromatic amines (two of these are also primary amines, 10 are also secondary amines, one is also a tertiary amine, and three are also amides).

Of the 15 amides with positive genotoxic findings, four are primary amides (all of these are also amines), one is a secondary amide (and also an amine), two are tertiary amides (one of these is also an amine), three are ureas, one is a carbamate (and also an amine), three are sulfonamides (all of these are also amines, and one is also a guanidine), and two are guanidines (both of these are also amines, and one is also a sulfonamide).

2. INTRODUCTION

In 2006, the International Agency for Research on Cancer (IARC) evaluated the carcinogenicity of nitrite and nitrate. The results of this evaluation were published in volume 94 of the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, which is entitled "Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins" (IARC, 2010). IARC (2010) reached several conclusions regarding the evidence of carcinogenicity of these substances, including the following conclusions specific to either nitrite or nitrite in combination with amines or amides:

- "There is *limited evidence* in humans for the carcinogenicity of nitrite in food. Nitrite in food is associated with an increased incidence of stomach cancer."
- "There is *sufficient evidence* in experimental animals for the carcinogenicity of nitrite in combination with amines or amides."
- "There is *limited evidence* in experimental animals for the carcinogenicity of nitrite *per se*."

IARC's overall evaluation is the following:

- "Ingested nitrate or nitrite under conditions that result in endogenous nitrosation is *probably carcinogenic to* humans (Group 2A).

  There is an active endogenous nitrogen cycle in humans that involves nitrate and nitrite, which are interconvertible *in vivo*. Nitrosating agents that arise from nitrite under acidic gastric conditions react readily with nitrosatable compounds, especially secondary amines and amides, to generate N-nitroso compounds. These nitrosating conditions are enhanced following ingestion of additional nitrate, nitrite, or nitrosatable compounds. Some of the N-nitroso compounds that could be formed in humans under these conditions are known carcinogens."

IARC is one of several institutions designated as authoritative for the identification of chemicals as causing cancer under Proposition 65 (Title 27, California Code of Regs., section 25306(m)).

On February 7, 2014, the Office of Environmental Health Hazard Assessment (OEHHA) published a public notice in the California Regulatory Notice Register announcing its intent to list "nitrite in combination with amines or amides" as known to the state to cause cancer under Proposition 65 via the authoritative bodies mechanism, based on the findings of sufficient evidence of carcinogenicity in experimental animals by IARC (2010).

In the February 7, 2014 Notice of Intent to List[9], OEHHA briefly summarized IARC's discussion of the evidence of carcinogenicity from studies of experimental animals for "nitrite in combination with amines or amides" as follows:

> "Evidence described in the report includes studies showing that nitrite in combination with amines or amides increased the incidences of malignant and combined malignant and benign tumors in multiple studies in rats:
>
> "In many studies in rats, when sodium nitrite and specific secondary or tertiary amines or amides (*e.g.* morpholine, butylurea, disulfiram, aminopyrine, diphenhydramine, chlorpheniramine maleate, heptamethyleneimine hydrochloride, N,N-dimethyldodecylamine- N-oxide or bis(2-hydroxypropyl)-amine) were mixed in the diet or given in the drinking-water or by gastric intubation, an increased incidence of tumours, including benign and malignant oesophageal tumours, haemangiosarcomas, hepatocellular adenomas and carcinomas, lung squamous-cell carcinomas or benign and malignant nasal cavity tumours was observed. In some of these studies, at a constant level of sodium nitrite, the tumour incidence induced was directly related to the levels of amine. When the level of amine was kept constant, tumour yield was also directly related to the level of sodium nitrite. When pregnant rats were given ethylurea *[an amide]* and sodium nitrite in the drinking-water, neurogenic tumours developed in the offspring." [IARC, p. 321]
>
> "A dose-related increase in the incidence of renal-cell carcinoma was observed when rats were administered nitrite in the drinking-water in combination with varying amounts of fishmeal *[a source of amines and amides]* in the diet. Levels of N-nitrosodimethylamine in the stomach contents also showed a dose-related increase." [IARC, p. 321] [10]

On May 6, 2015, after consideration of comments received on the notice and further evaluation of the scientific evidence upon which IARC based its finding (*i.e.*, "There is *sufficient evidence* in experimental animals for the carcinogenicity of nitrite in combination with amines or amides."), OEHHA announced its determination that the regulatory criteria in section 25306(e)[11] (*i.e.*, sufficiency of evidence criteria) for listing via the authoritative bodies mechanism had not been met for the spectrum of chemicals covered by the broad class "nitrite in combination with amines or amides". Pursuant to

[9] February 7, 2014 Notice of Intent to List: Nitrite in Combination with Amines or Amides, available at: http://oehha.ca.gov/proposition-65/crnr/notice-intent-list-nitrite-combination-amines-or-amides
[10] *Ibid.*
[11] All referenced sections are from Title 27 of the Cal. Code of Regulations.

Section 25306(i), “nitrite in combination with amines or amides” is referred to the CIC for consideration for listing as causing cancer under Proposition 65.

OEHHA developed this document with information on the evidence on the carcinogenicity of “nitrite in combination with amines or amides” to assist the CIC in its deliberations. On November 15, 2016, the CIC is scheduled to deliberate on the carcinogenicity of “nitrite in combination with amines or amides”. The CIC may also consider whether a subset (or multiple subsets) of chemicals of this broad class have been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.

Information presented in this document includes the following:

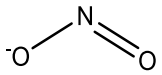
- General chemical structure information on the spectrum of chemicals covered by the broad class “nitrite in combination with amines or amides”.
- General information on occurrence and use of the spectrum of chemicals covered by the broad class “nitrite in combination with amines or amides”.
- The 2010 IARC monograph on ingested nitrate and nitrite is included as Attachment 1.
    - All references cited in the 2010 IARC monograph that are relevant to the carcinogenicity of “nitrite in combination with amines or amides” will be provided to the CIC as part of these hazard identification materials, and are available to the public upon request.
- Information on cancer epidemiology studies, animal bioassays, and genotoxicity studies relevant to the carcinogenicity of “nitrite in combination with amines or amides” which were not included in the IARC review (IARC, 2010).
    - OEHHA conducted a search of the scientific literature to identify additional relevant scientific publications which were not included in IARC’s review, which covered studies through early 2006 (IARC, 2010). The literature search was performed using “nitrite”, “nitrite ion”, “sodium nitrite”, and “potassium nitrite” as the “chemical name” search terms. The search strategy was designed to identify cancer epidemiology studies, animal cancer bioassays, and genotoxicity studies. (See Appendix A for details of the search strategy.)
    - OEHHA’s literature search identified several studies of nitrite in combination with amines or amides that were not included in the IARC (2010) review, including:
        - 35 epidemiology studies of nitrite intake and cancer
        - 35 animal cancer bioassays of nitrite in combination with an amine or amide, and

        - 180 genotoxicity assays of nitrite in combination with an amine or amide
    - In the case of the additional epidemiology studies of nitrite intake and cancer risk that were not included in the IARC (2010) review, study findings are presented graphically in forest plots and information on study design and study findings is summarized here in a series of tables, in Section 3.1.3. Specifically, studies assessing colon and rectal cancers are presented in Figures 2A, 2B, 3A, 3B, 4A, and 4B and Table 3, studies assessing esophageal and stomach cancer are presented in Figures 5A, 5B, 5C, 5D, 6A, 6B, 6C and 6D, and Table 4, studies assessing lymphoma are presented in Figures 7A and 7B and Table 5, and studies assessing other cancers are presented in Table 6. Findings from these additional epideimology studies should be considered together with the findings from the epidemiology studies included in the IARC 2010 review.
    - In the case of animal cancer bioassays, information on study design and study findings has been summarized for all relevant bioassays of nitrite in combination with amines or amides, including the 35 additional studies identified in the literature search and those studies reviewed in IARC (2010), in Section 3.2, Tables 7 – 9.
    - In the case of genotoxicity studies, information on study design and study findings has been summarized for all relevant genotoxicity assays of nitrite in combination with amines or amides, including the 156 additional studies identified in the literature search and those studies reviewed in IARC (2010), in Section 3.3.2, Tables 10 –11.
    - Copies of the additional relevant articles identified in the literature search (*i.e.*, those not included in IARC (2010)) will be provided to the CIC as part of these hazard identification materials, and are available to the public upon request.
- Published findings from a 2015 IARC Working Group evaluation of processed meat (Bouvard *et al*., 2015, provided here as Attachment 2). The 2010 IARC monograph, which focused on ingested nitrite and nitrate, specifically did not include studies that only evaluated consumption of cured meat and risk for cancer, since such investigations “do not represent complete dietary nitrite intake”. Nevertheless, many processed meats contain nitrite in combination with amines or amides, and thus this publication is provided for the CIC’s consideration.

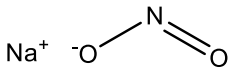
2.1 Chemical Identity

Nitrite

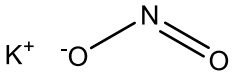
Nitrite (NO_2^-) is a negatively charged ion. Nitrite can form salts with positively charged ions such as sodium (Na^+) and potassium (K^+). Nitrite salts disassociate in water to form nitrite ions. The chemical structures of nitrite ion, sodium nitrite, and potassium nitrite are shown below:



Nitrite ion



Sodium nitrite

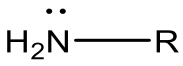


Potassium nitrite

Amines

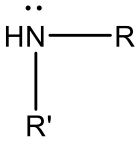
Amines are organic compounds that contain a basic nitrogen atom with a lone electron pair; examples include amino acids and biogenic amines like histamine. Amines can be classified as "primary", "secondary" or "tertiary" depending on the degree of carbon substitution on the nitrogen atom. Additionally, positively charged “quaternary” amines can be formed by sharing a lone electron pair with either an alkyl group or aryl group.

- Primary amines: Primary amines have two hydrogen atoms (H) and one alkyl or aryl group (R) bound to a nitrogen atom (N).



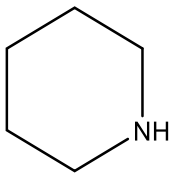
Primary amine

- Secondary amines: Secondary amines have one H atom and two R groups bound to a N atom.

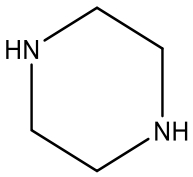


Linear secondary amine

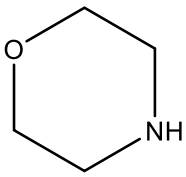
  - Examples of cyclic secondary amines:



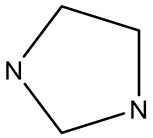
piperidine



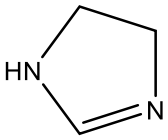
piperazine



morpholine

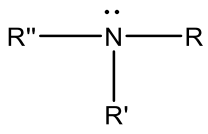


Imidazolidine



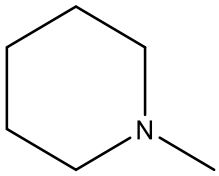
4,5-dihydro-1*H*-imidazole

- Tertiary amines: Tertiary amines have three R groups bound to a N atom.

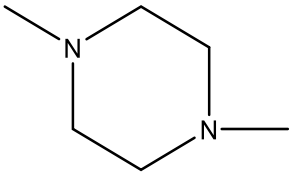


Linear tertiary amine

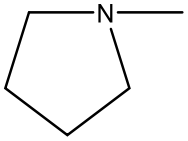
  - Examples of cyclic tertiary amines:



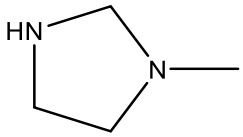
1-methylpiperidine



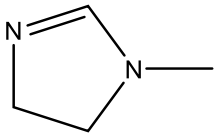
1,4-dimethylpiperazine



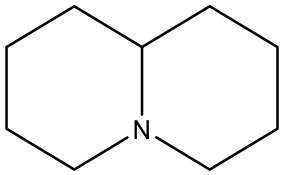
1-methylpyrrolidine



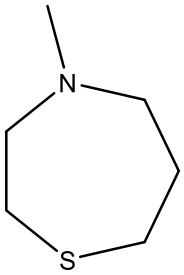
1-methylimidazolidine



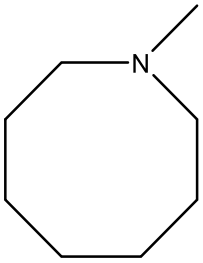
1-methyl-4,5-dihydro-1*H*-imidazole



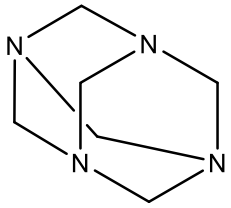
octahydro-2*H*-quinolizine



4-methyl-1,4-thiazepane

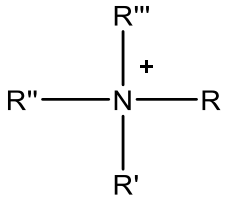


1-methylazocane



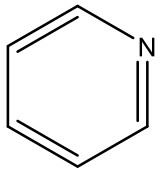
Hexamethylenetetramine

- Quaternary amines (also known as quaternary ammonium cations or quats): Quaternary amines are positively charged polyatomic ions of the structure NR_4^+.

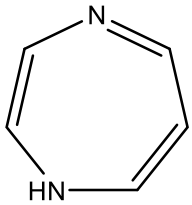


- Cyclic aromatic amines, also known as heterocyclic aromatic amines: Cyclic aromatic amines have at least one N in an aromatic ring.

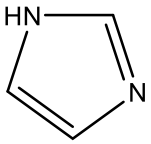
Examples:



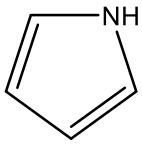
pyridine



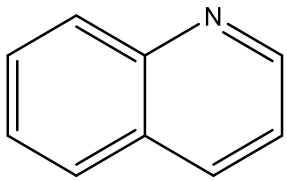
1,4-diazepine



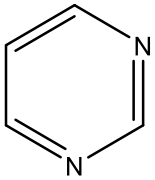
imidazole



pyrrole



quinoline

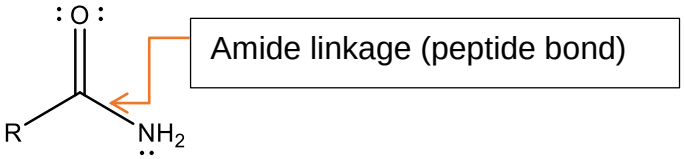


pyrimidine

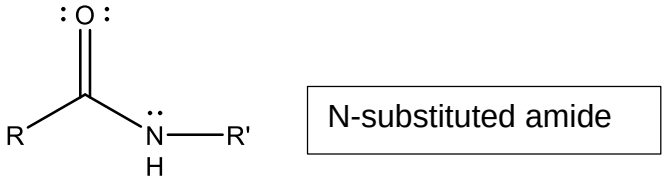
Amides

Amides are organic compounds that have a nitrogen atom which is directly attached to a carbonyl group. Amides can be formed from amines. Like amines, amides can be classified as "primary", "secondary" or "tertiary" amides, depending on the degree of carbon substitution on the nitrogen atom.

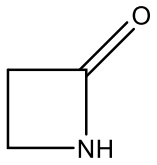
- Primary amides



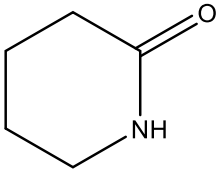
- Secondary amides



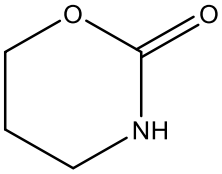
- Examples of cyclic secondary amides:



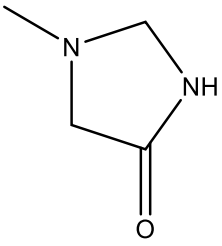
azetidin-2-one



piperidin-2-one

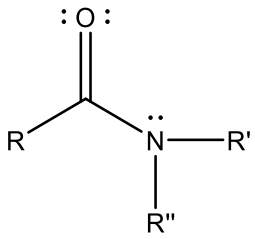


1,3-oxazinan-2-one



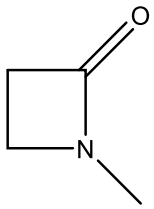
1-methylimidazolidin-4-one

- Tertiary amides

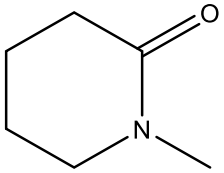


N, N-di-substituted amide

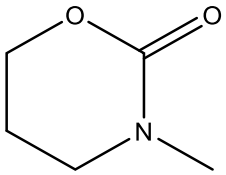
- Examples of cyclic tertiary amides:



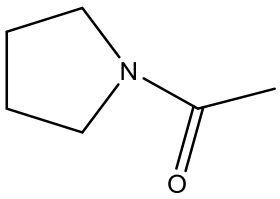
1-methylazetidin-2-one



1-methylpiperidin-2-one

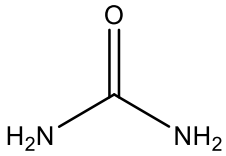


3-methyl-1,3-oxazinan-2-one

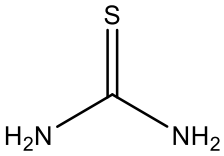


1-(pyrrolidin-1-yl)ethan-1-one

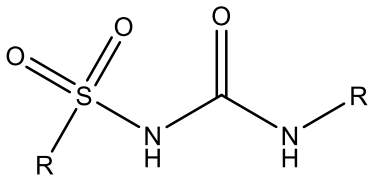
- Ureas (diamides), examples:



urea

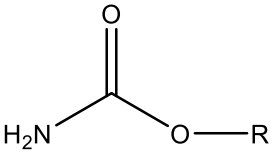


thiourea

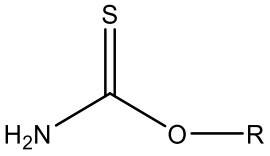


sulfonyl urea

- Carbamates (ester-amides), examples:

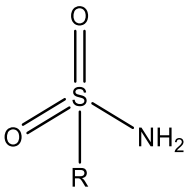


Carbamate

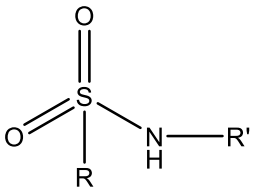


thiocarbamate

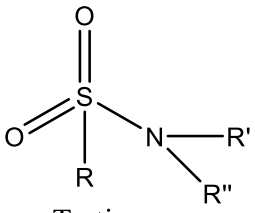
- Sulfonamides (amide analogs with an isosteric SO_2 group):



Primary Sulfonamide

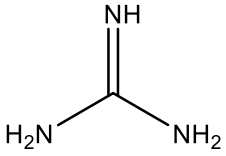


Secondary Sulfonamide



Tertiary Sulfonamide

- Guanidine (also called carbamidine, iminourea):



guanidine

Nitrite in combination with amines or amides

Nitrite or its salts, when present in combination with amines or amides in acidic conditions, may react with the amine or amide to form nitrosated compounds. Amines

can undergo various reactions to form nitrosamines, whereas amides react to form nitrosamides (Mirvish, 1975, Brambilla, 2007).

Primary amines can react with nitrite or its salts in acidic environments to form alkyldiazohydroxides or alkyldiazonium ions. If this reaction occurs in close proximity to DNA, it can lead to alkylation of DNA, or deamination of DNA bases (IARC, 2010).

Secondary and tertiary amines can also react with nitrite or its salts in acidic environments to form nitrosamines, though reactions for tertiary amines are usually slower than those with primary or secondary amines (Brambilla *et al*., 2007).

N-alkylureas, N-alkylcarbamates, guanidines, and simple N-alkylamides can react with nitrite or its salts in acidic environments to form nitrosamides (Brambilla *et al*., 2007).

2.2 Occurrence and Use

Nitrite

Nitrite (NO_2^-) is part of the nitrogen cycle and is common in the environment (Figure 1). It is a product of the oxidation of nitrogen by microorganisms present in soil and water, and often closely associated with the roots of plants. Through microbial action, nitrite can be formed from nitrate (NO_3^-) (IARC, 2010).

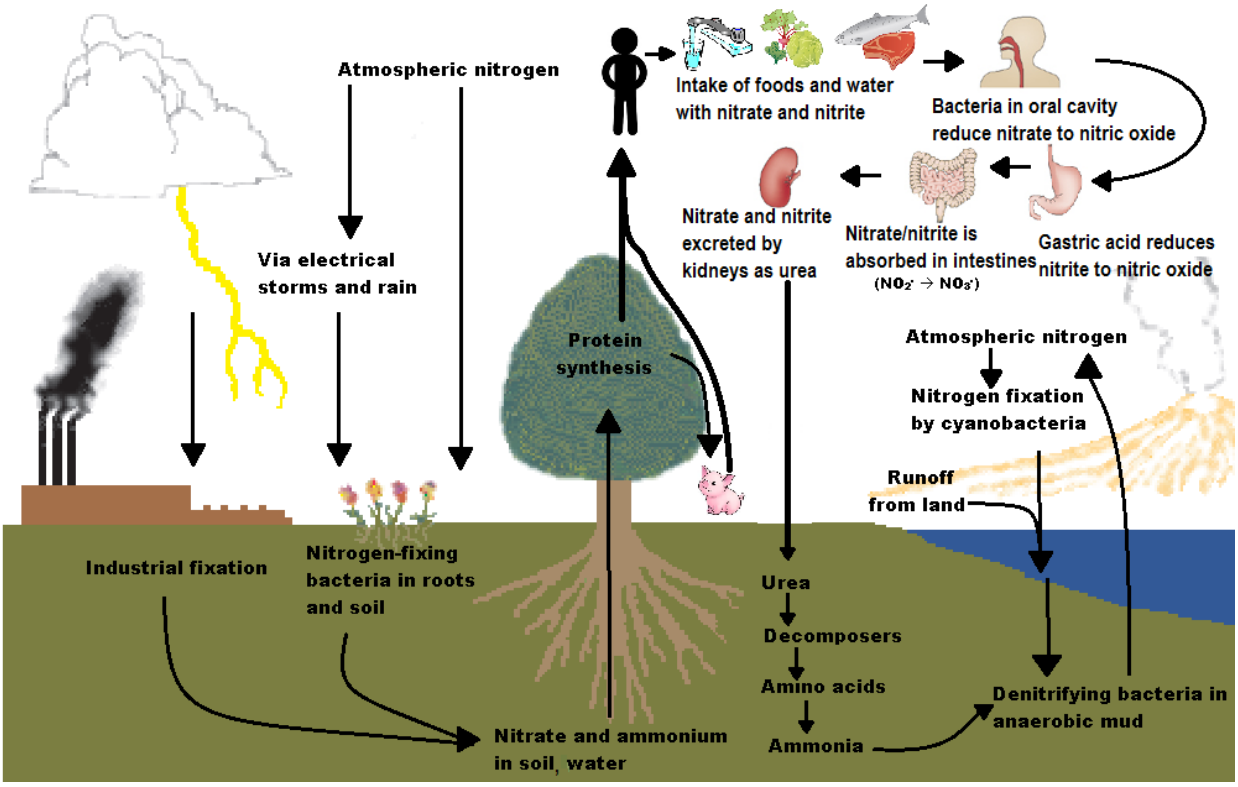


Figure 1. **Simplified diagram of the nitrogen cycle.** Adapted from Vitousek *et al*., 1997 and modified by OEHHA to incoporate the human nitrogen cycle, in which nitrate and nitrite participate in a dynamic interchange.

As shown in Figure 1, nitrite can be present in water and soil. Nitrite has been detected in rainwater, groundwater, surface water, and drinking water. While the concentration of nitrite in groundwater and surface water is generally negligible, nitrite concentrations can increase under anaerobic conditions in the presence of bacteria capable of converting nitrate to nitrite. Other sources of nitrite in water include ammonia, which may be present as a contaminant of chloramine, a drinking-water disinfectant. Oxidation of ammonia can form nitrite (IARC, 2010).

Plants and fish take up nitrite from the environment. As a result, vegetables, grains, and fish all contain very low levels of nitrite (IARC, 2010). Conversion of nitrate to nitrite may also occur during storage of vegetables and other home-prepared foods. For example, higher levels of nitrite have been detected in vegetables that are damaged, poorly stored, stored for extended periods of time, pickled, or fermented (IARC, 2010).

Nitrite salts (*e.g.*, sodium nitrite, potassium nitrite) have been used as food preservatives, especially to cure meats. Sodium nitrite in particular has been used extensively as a curing agent for a variety of meats and meat products, such as ham, bacon and frankfurters. It is also commonly used in brines for certain fish and poultry products. There are several different types of curing processes, including dry curing, immersion curing, and direct addition or injection of the curing ingredients into the meats. Curing mixtures are typically composed of salt (sodium chloride), sodium or potassium salts of nitrite and seasonings. Sodium nitrite acts as a color fixative and inhibits the growth of bacteria, including *Clostridium botulinum*, which is the bacterium that produces botulism toxin (IARC, 2010).

Nitrite salts also have industrial, non-food uses. Most of the industrial uses of nitrite salts (*e.g.*, sodium nitrite) are based on the oxidizing properties of nitrite or on the ability of the salts to form nitrous acid (HNO_2) in acidic solutions. Sodium nitrite is a convenient source of nitrous acid in the nitrosation and diazotation of aromatic amines and the production of azo dyes. Other applications of sodium nitrite include the synthesis of saccharin, synthetic caffeine, fluoroaromatics and other pharmaceuticals, pesticides, and other organic substances; as an inhibitor of polymerization; in the production of foam blowing agents; in the removal of hydrogen sulfide from natural gas; in textile dyeing; and as an analytical reagent. Sodium and potassium nitrites are listed in the European and US Pharmacopeia, which would indicate that they can be used in pharmaceutical preparations. Therapeutic uses of sodium nitrite include as an antidote for cyanide poisoning and as a vasodilator (IARC, 2010).

Amines

Amines are present in many forms in all plants and animals, and include amino acids and biogenic amines like histamine and dopamine (Rodriguez *et al*., 2014). Thus amino acids and biogenic amines are present in raw and processed plant- and animal-based foods (Silla Santos, 1995). Various amines have been reported in fish and other seafood products (*e.g*., cadaverine, diethylamine, dimethylamine, dipropylamine, methylguanidine, morpholine, phenylethylamine, putrescine, spermidine, spermine, trimethylamine-*N*-oxide, tryptamine, tyramine); cereal grains and cereal products (*e.g*., diethylamine, dimethylamine); dairy products including milk and evaporated milk (*e.g.,* dimethylamine,methyl-n-butyl-amine, piperidine) and aged cheese (e.g., cadaverine,

piperidine, phenylethylamine, putrescine, spermidine, spermine, tyramine, tryptamine); and fermented soybean products (*e.g*., dimethylamine, methylamine). Amines are also present in beverages such as wine and beer (*e.g.,* dimethylamine, methylamine, morpholine) and coffee and teas (*e.g.,* diethylamine, dimethylamine, methylethylamine, morpholine, piperidine) (Lin, 1986; Silla Santos, 1996; Maga and Katz, 1978; National Research Council, 1981). Frankfurters, sausages, and other pork and beef products contain biogenic amines, including cadaverine, dimethylamine, ethanolamine, histamine, putrescine, spermidine, spermine, tryptamine, and tyramine (Maga and Katz, 1978). Additionally, heterocyclic amines are formed in meats cooked at high temperatures during the browning reaction (e.g., 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), 2-amino-3-methylimidazo[4,5-*f*]quinolone (IQ), 2-amino-3,4-dimethyl-3H-imidazo[4,5-f]quinolone (MeIQ), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx)). Amines are also present in tobacco smoke and in many pharmaceuticals (Hoffmann *et al*., 1974; Talaska, 2003).

Amines are also used as industrial chemicals, including in the rubber (Ward *et al.*, 1996) and dye industries (van der Zee and Villaverde, 2005). For example, cyclic aromatic amines are used as starting materials for the manufacture of azo dyes (van der Zee and Villaverde, 2005). Amines are used in the manufacture of nylon (Klobukowski *et al*., 2011). Amines are also used as pesticides and drugs (Lee *et al.*, 2005; Andrews *et al.* 1980).

Many amines from common dietary sources have not been experimentally tested in combination with nitrite for genotoxicity or carcinogenicity. Common uses of individual amines that have been tested in combination with nitrite for genotoxicity or carcinogenicity are presented in Table 1.

Table 1. Common Uses of Amines Tested in Combination with Nitrite for Genotoxicity or Carcinogenicity

Chemical	Use	Chemical	Use
Primary Amines			
2-amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine (PhIP)§,a,b	food constituent (formed during cooking)	Dopamine	pharmaceutical
2-amino-3-methylimidazo [4,5-*f*]quinolone (IQ)§,a,b		Methyldopa	
2-Aminopyridineb	pharmaceutical	Metoclopramidea,d	
Ambroxolc		Primaquineb,c	
Amlodipinec		Procainamidea,d	
Cefadroxild,e		Pyrimethamineb	
Cefalexind,e		Sulfanilamidef	pharmaceutical; pesticide
Diaveridineb		Trimethoprimb	pharmaceutical
Secondary Amines			
2-(2-Pyridylamino)ethyldimethyl-amine[a,b]	metabolite of methapyrilene, a pharmaceutical	Morpholine	solvent, food constituent (*e.g.,* fish, pork, beer, wine, coffee)
Alprenolol	pharmaceutical	Myosmineb	food constituent (e.g., meats)
		Nadolol	pharmaceutical
Ambroxolg		Nicardipinea	
Amineptine		Nifedipine	
Amlodipineg		Nimodipine	
Astemizole[a,b]		Nitrendipine	
Atenololh		N-methylaniline	coloring/filling agent
Bamethan		Pamaquine[a,b]	pharmaceutical
Betahistineb		Paroxetine	
Bis(2-hydroxy-propyl)amine	industrial chemical	Pentaquineb	
Chlordiazepoxideb	pharmaceutical	Piperazine	pesticide
Chloroquine[a,b]		Piperidine	food constituent (*e.g.,* cheese, ground pepper, milk, cooked meat and fish)
Cimetidinei		Prenylamine	pharmaceutical
Clonidine		Primaquine[b,g]	
Dehydroemetinea		Propranolol	
Dibutylamine	industrial chemical	Propylhexedrine	
Dimethylamine	pesticide; food constituent (*e.g.*, meats, milk and cheese, wine)	Pseudoephedrine	
Dimetofrine	pharmaceutical	Quinacrine[a,b]	
Enalaprile		Ritodrine	
Ephedrine		Salbutamol	
Ethambutol		Sertraline	
Fluoxetine		Sotalolf	
Heptamethyleneimine		Terbutaline	
Hydrochlorothiazidef		Tizanidineb	
Isoxsuprine		Tolazoline	
Lucanthonea		Trimetazidinea	
Metoprolol			
Tertiary Amines			
2-(2-Pyridylamino)ethyldimethyl-amine[b,c]	metabolite of methapyrilene, a pharmaceutical	Aminopyrine	pharmaceutical
2-amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine (PhIP)§,b,g	food constituent (formed during cooking)	Astemizole[b,c]	
2-amino-3-methylimidazo [4,5-*f*]quinolone (IQ)§,b,g		Carpipramineh	
Ajmaline	pharmaceutical	Chloroquine[b,c]	

Table 1. Common Uses of Amines Tested in Combination with Nitrite for Genotoxicity or Carcinogenicity (continued)

Chemical	Use	Chemical	Use
Tertiary Amines (continued)			
Chlorothen	pharmaceutical	Metoclopramide[d,g]	pharmaceutical
Chlorpheniramine[b]		Nicardipine[c]	
Chlorpromazine		Nitrilotriacetic acid[§]	additive
Chlorprothixene		Opipramol	pharmaceutical
Cinnarizine		Oxytetracycline[h]	
Cyclizine		Pamaquine[b,c]	
Dehydroemetine[c]		Pipamperone[h]	
Dextropropoxyphene		Piromidic acid[b]	
Dilazep		Procainamide[c,g]	
Diltiazem		Prochlorperazine	
Dimethyldodecylamine	pesticide	Pyrantel pamoate	
Diphenhydramine	pharmaceutical	Pyribenzamine[b]	
Dipyridamole[b]		Pyrilamine[b]	
Dipyrone		Quinacrine[b,c]	
Flupentixol		Ranitidine	
Gallopamil		Spiperone[d]	
Guanethidine[i]		Tetracycline[h]	
Hexamethylenetetramine		Thenyldiamine[b]	
Hydroxyzine		Thiothixene[f]	
Imipramine		Tiaramide[e]	
Lucanthone[c]		Trapidil[b]	
Methadone		Trimetazidine[c]	
Methafurylene[b]		Trimethylamine	attractant; reactant; food constituent (e.g., pork, fish, seafood)
Methaphenilene		Verapamil	pharmaceutical
Methapyrilene[b]			
Quaternary Amines			
Bephenium hydroxynaphthoate	pharmaceutical		
Cyclic Aromatic Amines			
2-(2-Pyridylamino)ethyldimethyl-amine[a,c]	metabolite of methapyrilene, a pharmaceutical	Mebendazole[j]	pharmaceutical
2-amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine (PhIP)[§,a,g]	food constituent (formed during cooking)	Methafurylene[a]	
2-amino-3-methylimidazo[4,5-*f*]quinolone (IQ)[§,a,g]		Methapyrilene[a]	
2-Aminopyridine[g]	pharmaceutical	Morsydomine[j]	
Astemizole[a,c]		Myosmine[c]	food constituent (e.g., meats)
Betahistine[c]		Pamaquine[a,c]	pharmaceutical
Bromazepam[c]		Pentaquine[c]	
Cefazolin[d,e]		Piromidic acid[a]	
Chlordiazepoxide[c]		Primaquine[c,g]	
Chloroquine[a,c]		Pyribenzamine[a]	
Chlorpheniramine[a]		Pyridinol carbamate[j]	
Diaveridine[g]		Pyrilamine[a]	
Dipyridamole[a]		Pyrimethamine[g]	
Ecarazine		Quinacrine[a,c]	
Famotidine[f,i]		Thenyldiamine[a]	
Hydralazine		Tizanidine[c]	
Iodochlorhydroxyquin		Trapidil[a]	
Isoniazid		Trimethoprim[g]	

[§] Proposition 65 carcinogen; [a] Also a tertiary amine; [b] Also a cyclic aromatic amine; [c] Also a secondary amine; [d] Also a secondary amide; [e] Also a tertiary amide; [f] Also a sulfonamide (amide); [g] Also a primary amine; [h] Also a primary amide; [i] Also a guanidine (amide); [j] Also a carbamate (amide)

Amides

Amides are present in all plants and animals, as amides are the key linking moiety present in proteins. Thus amides are present in plant- and animal-based foods. In addition to peptides and proteins, miscellaneous amides have also been detected in fish and meat products (*e.g.*, methylguanidine, agmatine, creatinine) (National Research Council, 1981). Amides are also formed during high-temperature cooking (*e.g.*, acrylamide is formed during high-temperature roasting, grilling or frying of plant-based foods through the reaction of amino acids such as arginine with reducing sugars) (Mucci *et al.* 2005; Tareke *et al.* 2002). Amide functional groups are present in peptide drug products, as well as a number of non-peptide drugs (*e.g.*, local anesthetics, antiarrhythmics) (Boonen *et al*. 2012).

Amides are used as industrial chemicals, including in the manufacture of synthetic fibers and nylon (Klobukowski *et al*., 2011). Amides are also used as pesticides and drugs (Lee *et al.*, 2005).

Many amides from common dietary sources have not been experimentally tested in combination with nitrite for genotoxicity or carcinogenicity. Common uses of individual amides that have been tested in combination with nitrite for genotoxicity or carcinogenicity are presented in Table 2.

Table 2. Common Uses of Amides Tested in Combination with Nitrite for Genotoxicity or Carcinogenicity

Chemical	Use	Chemical	Use
Primary Amides		Ureas (continued)	
Atenolol[a]	pharmaceutical	Ethylene thiourea[§]	pesticide (degradant)
Carpipramine[b]		Ethylurea	research chemical
Oxytetracycline[b]		Methylurea	research chemical
Pipamperone[b]		Tolazamide	pharmaceutical
Tetracycline[b]		Tolbutamide	pharmaceutical
Secondary Amides		Carbamates	
2-Acetamidofluorene[§]	research chemical	Carbendazim	pesticide
Acetaminophen	pharmaceutical	Chlorzoxazone	pharmaceutical
Allantoin[c]		Disulfiram	
Bromazepam[d]		Ethyl carbamate[§]	
Cefadroxil[e,f]		Mebendazole[d]	
Cefalexin[e,f]		Meprobamate	
Cefazolin[e,f]		Morsydomine[b]	
Metoclopramide[b,f]		Pyridinol carbamate[d]	
Primidone[§]		Thiram	pesticide
Procainamide[b,f]		Sulfonamides	
Spiperone[b]		Famotidine[d,h]	pharmaceutical
Tertiary Amides		Hydrochlorothiazide[a]	
Cefadroxil[f,g]	pharmaceutical	Sotalol[a]	
Cefalexin[f,g]		Sulfanilamide[f]	pharmaceutical; pesticide
Cefazolin[d,g]		Thiothixene[b]	pharmaceutical
Diazepam		Guanidines	
Enalapril[a]		Arginine	amino acid (present in plant-based and animal-based foods)
Piperine	pesticide	Bethanidine	pharmaceutical
Tiaramide[b]	pharmaceutical	Cimetidine[a]	
Ureas		Dodine	pesticide
Acetohexamide	pharmaceutical	Famotidine[d,i]	pharmaceutical
Allantoin[g]		Guanethidine[b]	
Butylurea	research chemical	Methylguanidine	human metabolite, produced endogenously; food constituent (*e.g.,* fish, beef, evaporated milk)
Dimethylphenylurea	pesticide		

[§] Proposition 65 carcinogen; [a] Also a secondary amine; [b] Also a tertiary amine; [c] Also a urea (amide); [d] Also a cyclic aromatic amine; [e] Also a tertiary amide; [f] Also a primary amine; [g] Also a secondary amide [h] Also a guanidine (amide); [i] Also a sulfonamide (amide)

Nitrite in combination with amines or amides

Nitrite may occur in combination with amines or amides in occupational settings, such as those associated with azo dye production.

Relatively high levels of nitrite in combination with amines and amides are sometimes found in foods such as cured and/or processed red meats, poultry, and fish. IARC (2010) reports:

> *"In a survey from 1981, sausages (e.g. hot dogs) had a mean content of about 100 mg/kg nitrite and fried bacon and fried ham contained about 35 mg/kg nitrite (National Research Council, 1981). In a report that compiled 85 studies conducted between 1970 and 1991 in Canada and the USA of nitrite levels in cured meat, modelization of the results suggested some reduction in nitrite levels during the study period in most types of meat studied, except for frankfurters (Pogoda & Preston-Martin, 2001)."*

There are six categories of processed meats: fresh processed meat products, cured meat cuts, raw-cooked meat products, precooked-cooked meat products, raw-fermented sausages, and dried meat sausages (Heinz, 2007). However, not all of these processed meat categories contain nitrites. Fresh processed meat products do not contain nitrites, while cured meat cuts and raw-fermented sausages do contain nitrites. Raw-cooked meat products (*e.g.*, frankfurters), precooked-cooked meat products (*e.g.*, liver sausages), and dried meat sausages may or may not contain nitrites, depending on the product.

IARC (2010) notes that for some meats preserved with sodium or potassium nitrite: "Ascorbate is often added to inhibit the formation of N-nitrosamines before the cured meat is eaten. N-nitrosamines can also form in the stomach unless inhibited by vitamin C or other antioxidants."

Lower levels of nitrite (2-5 mg/kg, IARC, 2010) in combination with amines or amides occur naturally in many plant-based foods (some vegetables, grains, and fruits) and fish. IARC (2010) notes that "Many vegetables contain vitamin C and other compounds such as polyphenols that inhibit endogenous nitrosation."

Nitrite from water and fertilizer may be present in tobacco. Nicotine, an amide, is also present in tobacco. Thus, tobacco can be a source of nitrite in combination with amines or amides. N-nitroso compounds, such as nitrosonornicotine, have long been recognized as constituents of tobacco smoke (Hoffmann *et al.*, 1974).

3. DATA ON CARCINOGENICITY

3.1 Carcinogenicity Studies in Humans

IARC (2010) determined that cancer epidemiology studies of dietary nitrite ingestion are the most relevant to evaluation of the carcinogenicity of nitrite in combination with amines and amides:

> "Studies that only evaluated consumption of cured meat and risk for cancer were not reviewed specifically [by IARC] since they do not represent complete dietary nitrite intake. This is because many, but not all, cured meats contain nitrite and because other foods can also be important sources of nitrite." (IARC, 2010, p. 112)

As discussed in Section 2.2, the human diet is rich in sources of nitrite present in combination with amines and amides, including cereals, vegetables, fish, cured meats, and preserved vegetables.

A large number of epidemiology studies have investigated the relationship between ingestion exposure to nitrite and the risk of cancer. Studies published through early 2006 were reviewed by IARC (2010) (see Section 3.1.1).

A number of reviews have been published by authors other than IARC. Summarized briefly in Section 3.1.2 are five reviews/meta-analyses of nitrite exposure and cancer.

Studies published since IARC (2010) investigating the relationship between ingestion exposure to nitrite and the risk of cancer are summarized in Section 3.1.3.

Findings from a 2015 IARC evaluation of the carcinogenicity of processed meat are provided (Bouvard *et al*. 2015, Attachment 2) in Section 3.1.4.

3.1.1 IARC (2010) Review

IARC (2010) reviewed 73 cancer epidemiology studies of ingested nitrite, published through early 2006. See Attachment 1 for relevant sections of the IARC (2010) monograph that discuss and present the findings from these studies.

In evaluating the evidence from studies in humans, IARC concluded:

> "There is *limited evidence* in humans for the carcinogenicity of nitrite in food. Nitrite in food is associated with increased incidence of stomach cancer." (IARC, 2010, p. 325)

3.1.2 Reviews other than IARC

Jakszyn and Gonzalez (2006) reviewed studies published from 1985-2005 to assess the relationship between dietary nitrosamine and nitrite intake and gastric or esophageal cancer risk. They found "the available epidemiological evidence from case-control studies on nitrite and nitrosamine intake supports a positive association with GC [gastric cancer] risk [5 of 7 studies on nitrite intake]. The evidence in relation to OC [esophageal cancer] is insufficient [one of two studies of nitrite intake]."

Reviewing publications examining dietary factors in thyroid cancer including three large US cohort studies with dietary nitrate or nitrite consumption, Choi and Kim (2014) concluded that "…dietary nitrate and nitrite…showed a positive association with thyroid cancer risk," but noted that for these and other dietary factors, "results are inconsistent and investigations into the mechanism for how dietary factors change thyroid hormone levels and influence thyroid function are required."

Bahadoran *et al*. (2015) conducted a meta-analysis of studies investigating nitrate and/or nitrite exposure and thyroid function. They reported that "findings from three cohort studies… showed a significant association between higher exposure to nitrite and the risk of thyroid cancer (risk = 1.48, 95% confidence interval = 1.09 – 2.02, P = 0.012)."

Based on a meta-analysis of 18 studies (8 cohort and 10 case-control) of gastric cancer and nitrite intake, Song *et al*. (2015) report: "The summary relative risk of stomach cancer for the highest categories, compared with the lowest [of nitrite], was 1.31 (95% CI, 1.13–1.52)." Authors report that "…the association was detected in both population-based case-control studies (RR, 1.72; 95% CI, 1.47–2.02) and hospital-based case-control studies (RR, 1.25; 95% CI, 1.09–1.44) with no heterogeneity…. The risk effect of nitrites was also found in subgroups (publication year, before and after 2000; sample size < 2000; quality score < 7 stars…)."

Xie *et al*. (2016) published a meta-analysis of 51 studies of dietary nitrite intake and cancer risk. "Comparing the highest vs. lowest levels dietary nitrite intake was positively associated with adult glioma and thyroid cancer risk with pooled RR of 1.21 (95% CI = 1.03-1.42) and 1.52 (95% CI = 1.12-2.05), respectively." Xie *et al*. note that "a borderline significant association [sic] were found in gastric cancer (RR = 1.21, 95%CI =

0.99-1.47)" "No significant associations were found between dietary nitrate/nitrite and cancers of the breast, bladder, colorectal, esophagus, renal cell, non-Hodgkin lymphoma, ovarian, and pancreas."

3.1.3 Human studies of the carcinogenicity of nitrite published since IARC (2010)

In the ten years since IARC (2010) conducted its review of ingested nitrite, additional epidemiology studies investigating the relationship between exposure to nitrite and the risk of cancer have been published, including the results of several large prospective cohort studies. OEHHA conducted a literature review, using "nitrite", "nitrite ion", "sodium nitrite", and "potassium nitrite" as search terms, to identify epidemiology studies not included in IARC (2010), and identified a total of 35 additional studies that are relevant to the carcinogenicity of nitrite in combination with amines or amides. (See Appendix A for details of OEHHA's literature search strategy.)

The tables and figures in this section include the relevant epidemiological studies of nitrite intake and cancer published since the IARC (2010) review. Values reported in tables and plotted in figures come from the most-adjusted models for each of the studies.

For each group of endpoints, we present figures plotting results of studies of nitrite intake in relation to an endpoint (*e.g.*, colorectal cancer, including colon and rectal cancer analyzed individually). After the figures, we provide tables with information on study design and findings for each of the studies that looked at that group of endpoints.

Specifically, study information is presented as follows:

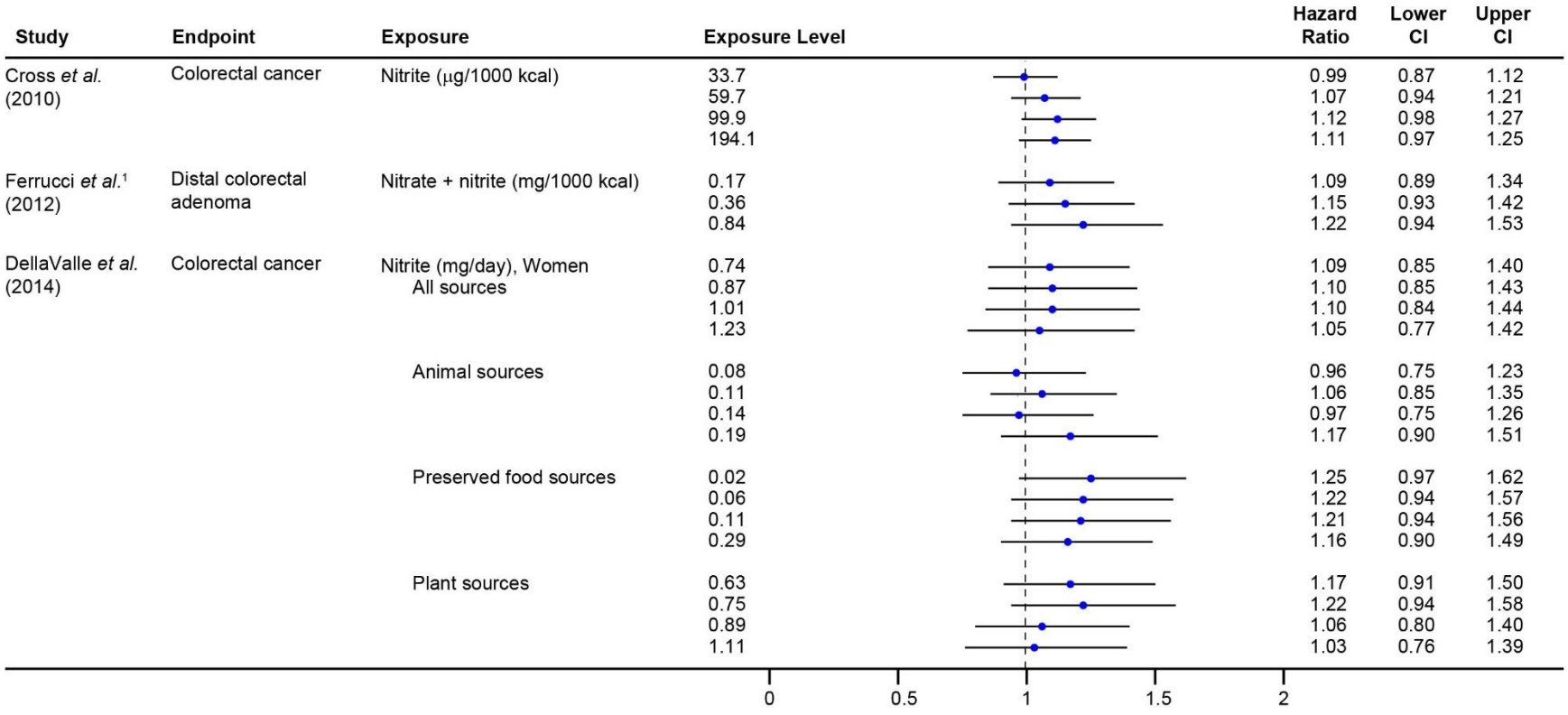
- Colon and rectal cancers
    - Figures 2A, 2B, 3A, 3B, 4A, and 4B
    - Table 3
- Esophageal and stomach cancers
    - Figures 5A, 5B, 5C, 5D, 6A, 6B, 6C, and 6D
    - Table 4
- Lymphoma
    - Figures 7A and 7B
    - Table 5
- Other cancers

    Table 6.

The information presented in the above tables must be considered together with the information presented in IARC (2010), in order to get a complete picture of the available

epidemiologic data investigating the relationship between ingestion exposure to nitrite and cancer.

Figure 2A. Colorectal cancer – cohort studies. Forest plot of the association between dietary nitrite intake and colorectal cancer. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year. Results represent hazard ratios unless otherwise noted.



[1] Ferrucci *et al.* (2012) reported risk estimates as odds ratios.

Figure 2B. Colorectal cancer – case-control studies. Forest plot of the association between dietary nitrite intake and colorectal cancer. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.

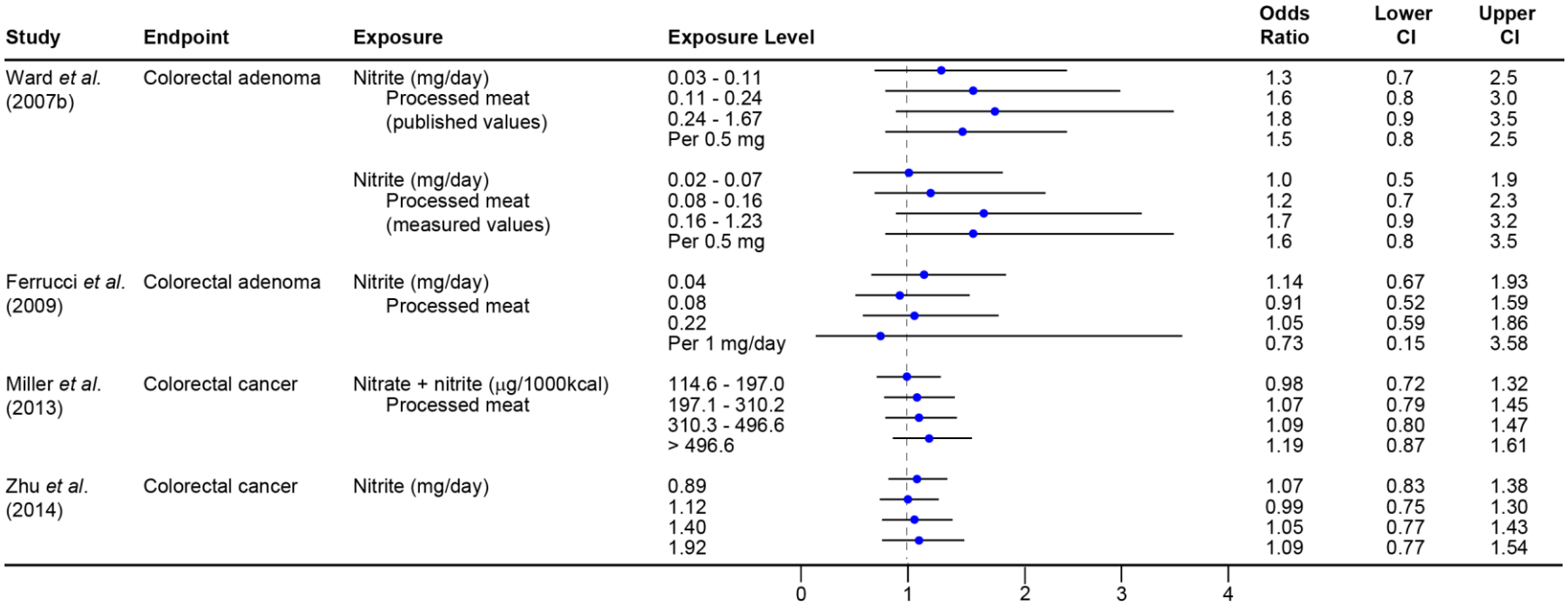
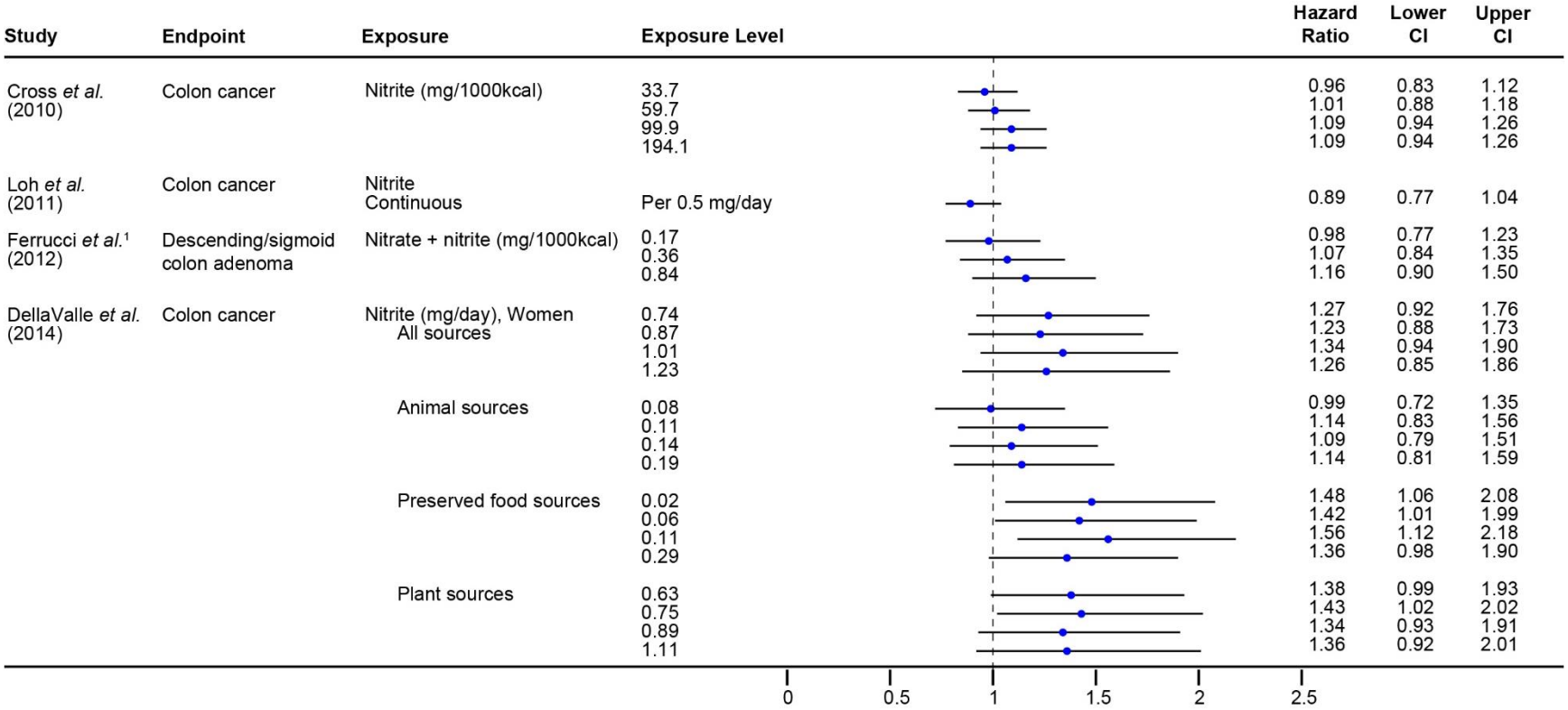


Figure 3A. Colon cancer – cohort studies. Forest plot of the association between dietary nitrite intake and colon cancer. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year. Results represent hazard ratios unless otherwise noted.



[1] Ferrucci *et al.* (2012) reported risk estimates as odds ratios.

Figure 3B. Colon cancer – case-control studies. Forest plot of the association between dietary nitrite intake and colon cancer. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.

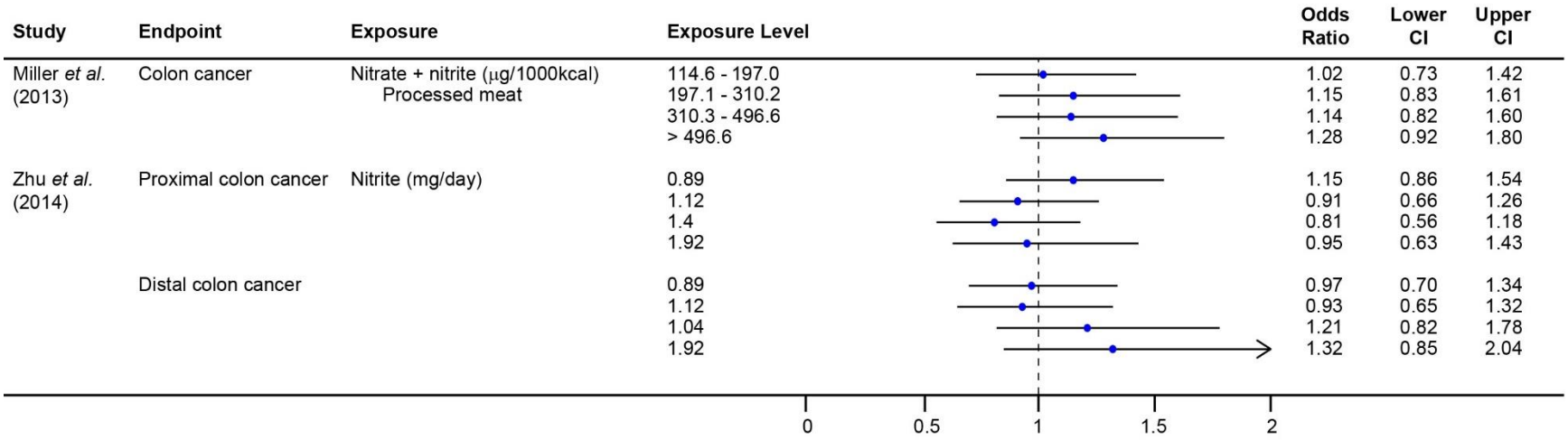
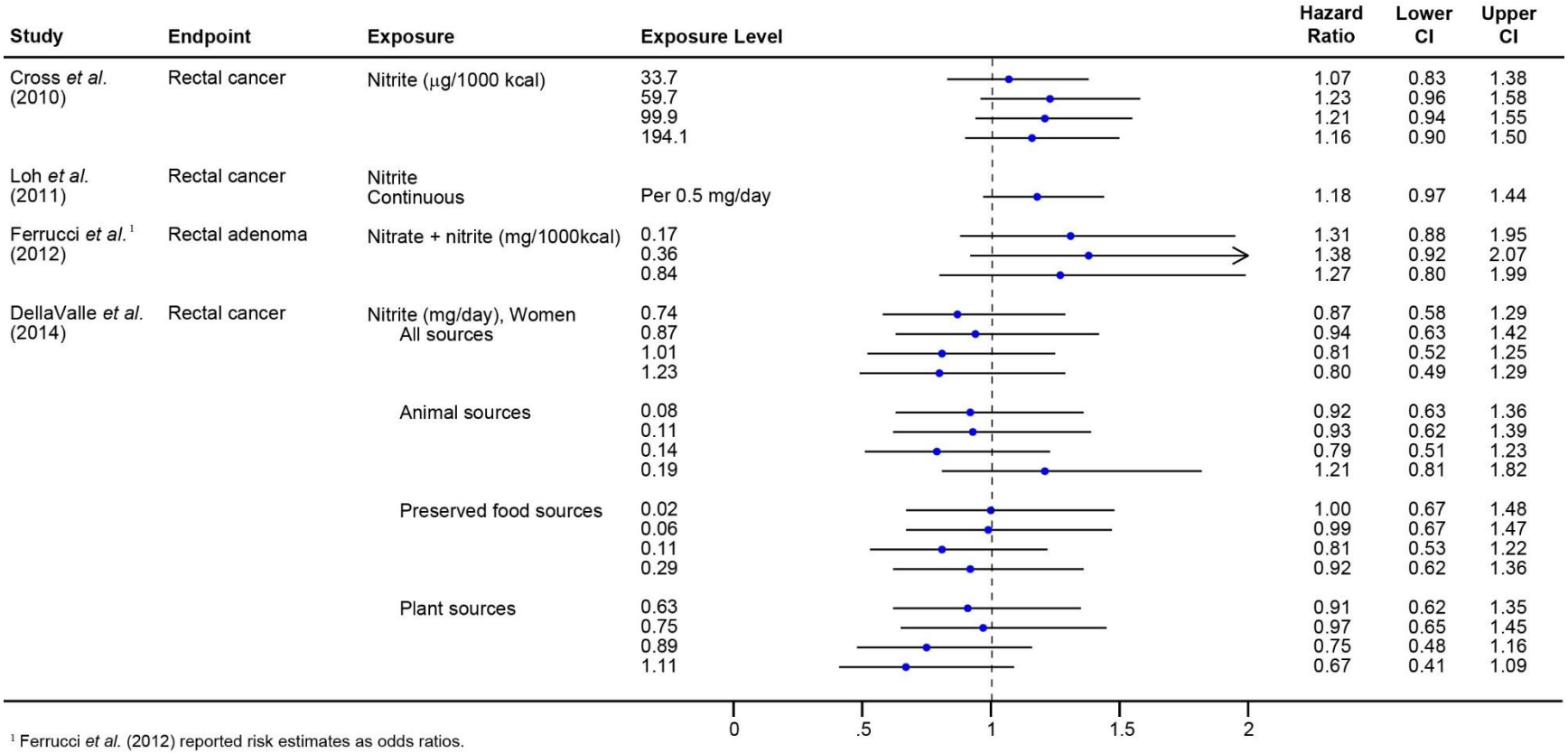


Figure 4A. Rectal cancer – cohort studies. Forest plot of the association between dietary nitrite intake and rectal cancer. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year. Results represent hazard ratios unless otherwise noted.



[1] Ferrucci *et al.* (2012) reported risk estimates as odds ratios.

Figure 4B. Rectal cancer – case-control studies. Forest plot of the association between dietary nitrite intake and rectal cancer. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.

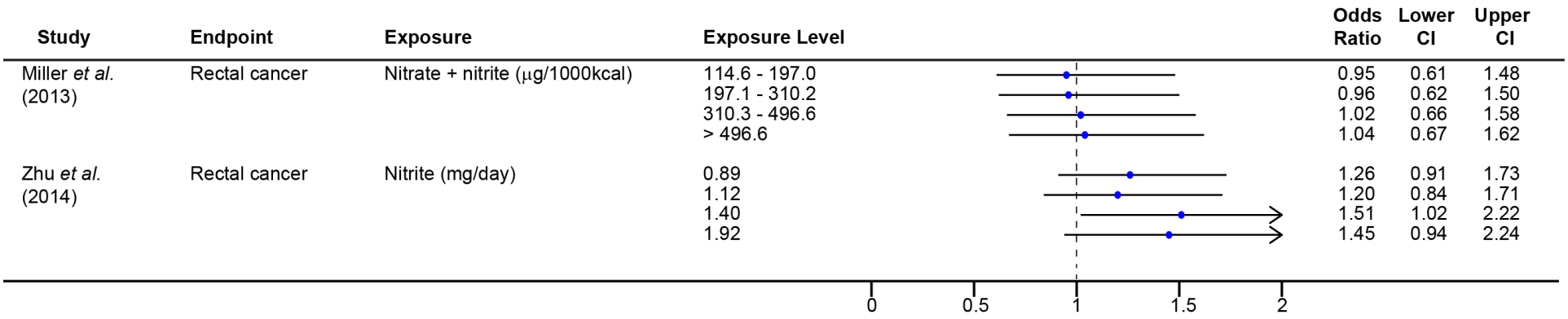


Table 3. Colorectal Cancer – Studies of Nitrite Exposure

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
Cohort Studies							
Cross *et al.* (2010) National Institutes of Health (NIH)-AARP Diet and Health Study US	Prospective cohort 300,948 participants (175,369 men, 125,579 women) 7.2 year follow-up <u>Cases</u> 2,719 Colorectal 1,995 Colon 724 Rectal	Colorectal cancer Colon cancer Rectal cancer	Dietary intake of processed meat intake was estimated using a validated 124-item food frequency questionnaire (FFQ). Nitrite intake was estimated using a National Cancer Institute (NCI) database containing measured values of nitrite in processed meat.	Dietary nitrite intake from processed meats (median) (ug/1000 kcal) Q1= 11.9 Q2= 33.7 Q3= 59.7 Q4= 99.9 Q5= 194.1	<u>Colorectal cancer</u> Q2 HR= 0.99 (0.87-1.12) Q3 HR= 1.07 (0.94-1.21) Q4 HR= 1.12 (0.98-1.27) Q5 HR= 1.11 (0.97-1.25) p-trend = 0.055	<u>Colon cancer</u> Q2 HR= 0.96 (0.83-1.12) Q3 HR= 1.01 (0.88-1.18) Q4 HR= 1.09 (0.94-1.26) Q5 HR= 1.09 (0.94-1.26) p-trend = 0.089 <u>Rectal cancer</u> Q2 HR= 1.07 (0.83-1.38) Q3 HR= 1.23 (0.96-1.58) Q4 HR= 1.21 (0.94-1.55) Q5 HR= 1.16 (0.90-1.50) p-trend = 0.369	Multivariable model adjusted for gender, education, body mass index (BMI), smoking, and intake of total energy, fiber, and dietary calcium. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hotdogs, and low-fat hotdogs made from poultry.
Loh *et al.* (2011) EPIC-Norfolk Study Norfolk, United Kingdom	Prospective cohort 23,363 participants (10,783 men, 12,580 women) 11.4 year follow-up <u>Cancer Cases</u> 276 Colon 137 Rectum	Colon cancer Rectal cancer	Dietary intake was reported using a validated, country-specific FFQ. Nitrite concentrations were estimated using the EPIC-EURGAST study, which determined values from the published literature.	Per 0.5 mg/day nitrite intake (SD) (continuous)	<u>Colon cancer</u> HR= 0.89 (0.77 – 1.04) p-trend= 0.15 <u>Rectal cancer</u> HR= 1.18 (0.97 – 1.44) p-trend= 0.10		Multivariate model adjusted for age, sex, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity status, educational level, and menopausal status (in women).

Table 3. Colorectal Cancer – Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Cohort Studies (continued)						
Ferrucci *et al.* (2012) Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial US	Prospective cohort 17,072 participants (9,453 men, 7,619 women) 3 - 5 year follow-up <u>Cases</u> 1,008 Distal colorectal adenoma 772 Descending/ sigmoid colon adenoma 263 Rectal adenoma	Distal colorectal adenoma Descending/ sigmoid colon adenoma Rectal adenoma	Dietary intake of all sources was estimated using a 137-item FFQ. Combined nitrate and nitrite intake was estimated using a NCI database containing measured values of both compounds.	Dietary nitrate and nitrite intake (median) (mg/1000 kcal) Q1= 0.06 Q2= 0.17 Q3= 0.36 Q4= 0.84	*Combined nitrate and nitrite* <u>Distal colorectal adenoma</u> Q2 OR= 1.09 (0.89-1.34) Q3 OR= 1.15 (0.93-1.42) Q4 OR= 1.22 (0.94-1.53) p-trend = 0.14 <u>Descending/sigmoid colon adenoma</u> Q2 OR= 0.98 (0.77-1.23) Q3 OR= 1.07 (0.84-1.35) Q4 OR= 1.16 (0.90-1.50) p-trend = 0.15 <u>Rectal adenoma</u> Q2 OR= 1.31 (0.88-1.95) Q3 OR= 1.38 (0.92-2.07) Q4 OR= 1.27 (0.80-1.99) p-trend = 0.72	Exposure assessment included nitrate and nitrite, but did not evaluate nitrite only. Adjusted for age at baseline, study center, gender, ethnicity, education, family history of colorectal cancer, BMI, NSAID (non-steroidal anti-inflammatory drug) use, physical activity, smoking status, alcohol intake, dietary calcium, supplemental calcium, dietary fiber, and total energy intake.

Table 3. Colorectal Cancer – Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
Cohort Studies (continued)							
DellaValle *et al.* (2014) Shanghai Women's Health Study (SWHS) Shanghai, China	Prospective cohort 73,188 women 11 year follow-up (mean) <u>Cases</u> 619 Colorectal 383 Colon 236 Rectal	Colorectal cancer Colon cancer Rectal cancer	Dietary intake of all sources was estimated using a validated 77-item FFQ. Nitrite content was determined using values from the published literature.	Total nitrite (All sources)			Adjusted for age, energy intake, education, physical activity, dietary vitamin C intake, carotene, and folate.
				Dietary nitrite intake (median) (mg/day) Q1= 0.56 Q2= 0.74 Q3= 0.87 Q4= 1.01 Q5= 1.23	*Women* <u>Colorectal cancer</u> Q2 HR= 1.09 (0.85-1.40) Q3 HR= 1.10 (0.85-1.43) Q4 HR= 1.10 (0.84-1.44) Q5 HR= 1.05 (0.77-1.42) p-trend = 0.78	<u>Colon cancer</u> Q2 HR= 1.27 (0.92-1.76) Q3 HR= 1.23 (0.88-1.73) Q4 HR= 1.34 (0.94-1.90) Q5 HR= 1.26 (0.85-1.86) p-trend = 0.27 <u>Rectal cancer</u> Q2 HR= 0.87 (0.58-1.29) Q3 HR= 0.94 (0.63-1.42) Q4 HR= 0.81 (0.52-1.25) Q5 HR= 0.80 (0.49-1.29) p-trend = 0.35	
				Animal sources			Adjusted for age, energy intake, education, physical activity, dietary vitamin C intake, carotene, and folate.
				Dietary nitrite intake from animal sources (median) (mg/day) Q1= 0.05 Q2= 0.08 Q3= 0.11 Q4= 0.14 Q5= 0.19	*Women* <u>Colorectal cancer</u> Q2 HR= 0.96 (0.75-1.23) Q3 HR= 1.06 (0.82-1.35) Q4 HR= 0.97 (0.75-1.26) Q5 HR= 1.17 (0.90-1.51) p-trend = 0.27	<u>Colon cancer</u> Q2 HR= 0.99 (0.72-1.35) Q3 HR= 1.14 (0.83-1.56) Q4 HR= 1.09 (0.79-1.51) Q5 HR= 1.14 (0.81-1.59) p-trend = 0.38 <u>Rectal cancer</u> Q2 HR= 0.92 (0.63-1.36) Q3 HR= 0.93 (0.62-1.39) Q4 HR= 0.79 (0.51-1.23) Q5 HR= 1.21 (0.81-1.82) p-trend = 0.49	

Table 3. Colorectal Cancer – Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Cohort Studies (continued)						
DellaValle *et al.* (2014) (continued) Shanghai Women's Health Study (SWHS) Shanghai, China	Prospective cohort 73,188 women 11 year follow-up (mean) <u>Cases</u> 619 Colorectal 383 Colon 236 Rectal	Colorectal cancer Colon cancer Rectal cancer	Dietary intake of all sources was estimated using a validated 77-item FFQ. Nitrite content was determined using values from the published literature.	**Preserved food sources**		Adjusted for age, energy intake, education, physical activity, dietary vitamin C intake, carotene, and folate. Preserved food included salted vegetables, salted eggs, salted fish, salted meat, sausage and smoked meat. Authors state: "And we did not observe an association between nitrate or nitrite from preserved meats (results not shown) and risk of colorectal cancer overall in the SWHS. "
				Dietary nitrite intake from preserved foods (median) (mg/day) Q1= 0.01 Q2= 0.02 Q3= 0.06 Q4= 0.11 Q5= 0.29	*Women* <u>Colorectal cancer</u> Q2 HR= 1.25 (0.97-1.62) Q3 HR= 1.22 (0.94-1.57) Q4 HR= 1.21 (0.94-1.56) Q5 HR= 1.16 (0.90-1.49) p-trend = 0.78 <u>Colon cancer</u> Q2 HR= **1.48 (1.06-2.08) *** Q3 HR= **1.42 (1.01-1.99) *** Q4 HR= **1.56 (1.12-2.18) *** Q5 HR= 1.36 (0.98-1.90) p-trend = 0.44 <u>Rectal cancer</u> Q2 HR= 1.00 (0.67-1.48) Q3 HR= 0.99 (0.67-1.47) Q4 HR= 0.81 (0.53-1.22) Q5 HR= 0.92 (0.62-1.36) p-trend = 0.59	
				Plant sources		
				Dietary nitrite intake from plant sources (median) (mg/day) Q1= 0.47 Q2= 0.63 Q3= 0.75 Q4= 0.89 Q5= 1.11	*Women* <u>Colorectal cancer</u> Q2 HR= 1.17 (0.91-1.50) Q3 HR= 1.22 (0.94-1.58) Q4 HR= 1.06 (0.80-1.40) Q5 HR= 1.03 (0.76-1.39) p-trend = 0.88 <u>Colon cancer</u> Q2 HR= 1.38 (0.99-1.93) Q3 HR= **1.43 (1.02-2.02) *** Q4 HR= 1.34 (0.93-1.91) Q5 HR= 1.36 (0.92-2.01) p-trend = 0.23 <u>Rectal cancer</u> Q2 HR= 0.91 (0.62-1.35) Q3 HR= 0.97 (0.65-1.45) Q4 HR= 0.75 (0.48-1.16) Q5 HR= 0.67 (0.41-1.09) p-trend = 0.08	Adjusted for age, energy intake, education, physical activity, dietary vitamin C intake, carotene, and folate.

Table 3. Colorectal Cancer – Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Case-Control Studies						
Ward *et al.* (2007b) National Naval Medical Center in Bethesda, Maryland	Case-control 146 cases, 228 controls <u>Cases</u> Identified from colonoscopy register. 24% female <u>Controls</u> Recruited from sigmoidoscopy clinic. Age and gender-matched to cases. 37% female	Colorectal adenoma	Dietary intake was estimated using a self-administered food frequency questionnaire (FFQ). Nitrite intake from processed meat was estimated using two methods: 1. Authors used **published** values from previous studies to estimate nitrite levels in processed meat. 2. Authors used **measured** values from a National Cancer Institute (NCI) database containing values of nitrite in processed meat.	Dietary intake of nitrite from processed meat (mg/day) <u>Published values</u> Q1 <0.03 Q2 0.03 – 0.11 Q3 0.11 – 0.24 Q4 0.24 – 1.67 <u>Measured values</u> Q1 <0.02 Q2 0.02 – 0.07 Q3 0.08 – 0.16 Q4 0.16 – 1.23	<u>Colorectal adenoma</u> *Published values of nitrite in processed meats* Q2 OR= 1.3 (0.7 – 2.5) Q3 OR= 1.6 (0.8 – 3.0) Q4 OR= 1.8 (0.9 – 3.5) *Measured values of nitrite in processed meats* Q2 OR= 1.0 (0.5 – 1.9) Q3 OR= 1.2 (0.7 – 2.3) Q4 OR= 1.7 (0.9– 3.2)	Models adjusted for age, gender, calories and pack-years of smoking. Processed meats in published studies included bacon, fried pork sausage, hot dogs, luncheon meat, and other sausages. Processed meats in NCI database included bacon, breakfast sausage, hot dogs/other sausage, ham steaks/pork chops, ham, bologna, luncheon meats including salami, and liverwurst.
				Per 0.5mg nitrite (continuous)	<u>Colorectal adenoma</u> *Published values of nitrite in processed meats* Continuous OR= 1.5 (0.8 – 2.5) *Measured values of nitrite in processed meats* Continuous OR= 1.6 (0.8 – 3.5)	

Table 3. Colorectal Cancer – Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Case-Control Studies (continued)						
Ferrucci *et al*. (2009) COlorectal Neoplasia screening with Colonoscopy in asymptomatic women at Regional Navy/army medical centers (CONCeRN) study	Case-control within multi-center cross-sectional screening 158 cases, 649 controls (All women) <u>Cases</u> (prevalent) Colorectal adenoma <u>Controls</u> Sampled from larger cross-sectional study	Colorectal adenoma	Dietary intake was estimated using a FFQ, sent to participants prior to cancer screening. Nitrite intake was estimated using a NCI database containing measured values of nitrite in processed meat.	Dietary intake of nitrite from processed meat (mg/day) Q1= 0.02 Q2= 0.04 Q3= 0.08 Q4= 0.22	*Women* <u>Colorectal adenoma</u> Q2 OR= 1.14 (0.67 - 1.93) Q3 OR= 0.91 (0.52 - 1.59) Q4 OR= 1.05 (0.59 - 1.86) p-trend= 0.99	Models adjusted for age, education, race, smoking status, physical activity, body mass index (BMI), study center, current hormone replacement therapy use, family history of colorectal polyps or cancer, regular non-steroidal anti-inflammatory drug (NSAID) use, alcohol intake, fiber, dietary calcium, calcium from supplements, and total caloric intake. Processed meat included bacon, cold cuts, ham, hot dogs, and sausage.
				Per 1 mg/day (continuous)	*Women* <u>Colorectal adenoma</u> OR= 0.73 (0.15–3.58)	

Table 3. Colorectal Cancer – Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Case-Control Studies (continued)						
Miller *et al.* (2013) 19 counties, Pennsylvania	Population-based case-control 989 cases, 1033 controls (50% men) <u>Cases</u> 416 proximal colon[3] 253 distal colon[3] 24 overlapping colon sites 289 rectal 7 lacking anatomical subsite data <u>Controls</u> Controls from the same region were identified by random digit dialing	Colorectal cancer: Proximal colon[3] Distal colon[3] Rectal	Dietary intake was estimated using a FFQ. Nitrite plus nitrate intake was estimated using a NCI database containing measured values of nitrite and nitrate in processed meat.	Dietary intake of nitrite plus nitrate from processed meat (µg/1,000 kcal) Q1 <114.6 Q2 114.6 – 197.0 Q3 197.1 – 310.2 Q4 310.3 – 496.6 Q5 >496.6	*Combined nitrate and nitrite* <u>Total colorectal cancer</u> Q2 OR= 0.98 (0.72 – 1.32) Q3 OR= 1.07 (0.79 – 1.45) Q4 OR= 1.09 (0.80 – 1.47) Q5 OR= 1.19 (0.87 – 1.61) p-trend= 0.189 <u>Total colon cancer</u> Q2 OR= 1.02 (0.73 – 1.42) Q3 OR= 1.15 (0.83 – 1.61) Q4 OR= 1.14 (0.82 – 1.60) Q5 OR= 1.28 (0.92 – 1.80) p-trend= 0.115 <u>Proximal colon cancer</u> Q2 OR= 1.05 (0.71 – 1.56) Q3 OR= 1.25 (0.85 – 1.86) Q4 OR= 1.06 (0.71 – 1.58) Q5 OR= **1.57 (1.06 – 2.34) *** **p-trend= 0.023*** <u>Distal colon cancer</u> Q2 OR= 0.99 (0.62 – 1.59) Q3 OR= 1.06 (0.67 – 1.70) Q4 OR= 1.28 (0.81 – 2.01) Q5 OR= 0.98 (0.61 – 1.58) p-trend= 0.952 <u>Rectal cancer</u> Q2 OR= 0.95 (0.61 – 1.48) Q3 OR= 0.96 (0.62 – 1.50) Q4 OR= 1.02 (0.66 – 1.58) Q5 OR= 1.04 (0.67 – 1.62) p-trend= 0.722	Exposure assessment included nitrate and nitrite, but did not evaluate nitrite only. Models adjusted for age, sex, BMI, past regular NSAID use, and intake of total energy and fruits and vegetables. Processed meats included bacon, sausage, cold cuts (ham, bologna, salami, pepperoni, beef luncheon meat, dried or chipped beef, turkey or chicken lunch meat), beef jerky, corned beef, hot dogs, ham, and bacon or sausages made from turkey or chicken.

Table 3. Colorectal Cancer – Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
Case-Control Studies (continued)							
Zhu *et al.* (2014) Newfound-land and Ontario (Canada) colorectal cancer study	Case-control 1760 cases, 2481 controls <u>Cases</u> Recruited from colorectal registries. <u>Controls</u> Selected using random digit dialing. Frequency matched on sex and 5-year age strata.	Colorectal cancer: Proximal colon[3] Distal colon[3] Rectum	Nitrite intake was estimated using a FFQ of foods that contributed the highest amount of N-nitroso compounds, and then linked to the Canadian NCI nutrient databank.	Dietary nitrite intake (mg/day) Q1= 0.65 Q2= 0.89 Q3= 1.12 Q4= 1.40 Q5= 1.92	<u>Total colorectal cancer</u> Q2 OR= 1.07 (0.83-1.38) Q3 OR= 0.99 (0.75-1.30) Q4 OR= 1.05 (0.77-1.43) Q5 OR= 1.09 (0.77-1.54) p-trend= 0.66 <u>Proximal colon cancer</u> Q2 OR= 1.15 (0.86 – 1.54) Q3 OR= 0.91 (0.66-1.26) Q4 OR= 0.81 (0.56 – 1.18) Q5 OR= 0.95 (0.63 – 1.43) p-trend= 0.43	<u>Distal colon cancer</u> Q2 OR= 0.97 (0.70 – 1.34) Q3 OR= 0.93 (0.65 – 1.32) Q4 OR= 1.21 (0.82 – 1.78) Q5 OR= 1.32 (0.85 -2.04) p-trend= 0.06 <u>Rectal cancer</u> Q2 OR= 1.26 (0.91 – 1.73) Q3 OR= 1.20 (0.84 – 1.71) Q4 OR= **1.51 (1.02 – 2.22) *** Q5 OR= 1.45 (0.94 – 2.24) p-trend= 0.08	Models adjusted for age, sex, energy intake, BMI, cigarette smoking status, education attainment, reported colon screening procedure, NSAID use, multivitamin supplement use, folate supplement use, vegetable intake and province.

[1] Exposure assessment methods primarily include food frequency questionnaires (FFQ)—a checklist of foods and beverages with a frequency response section for subjects to report how often each item was consumed over a specified period of time.

[2] Data include both genders unless otherwise specified.

***** Findings are statistically significant. 95% confidence interval excludes 1.0, p-value < 0.05

BMI—Body mass index; **CI**—Confidence interval; **EPIC**—European Prospective Investigation into Cancer & Nutrition; **FFQ**—Food frequency questionnaire; **HR**—Hazard ratio; **NCI**—National Cancer Institute; **NIH**—National Institutes of Health; **NSAID**--Non-steroidal anti-inflammatory drug; **OR**—Odds ratio; **PLCO**--Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; **Q**—Quartiles or quintiles; **SD**—Standard Deviation; **SWHS**—Shanghai Women's Health Study; **T**—Tertiles

Figure 5A. Esophageal cancer – cohort studies. Forest plot of the association between dietary nitrite intake and esophageal cancer. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.

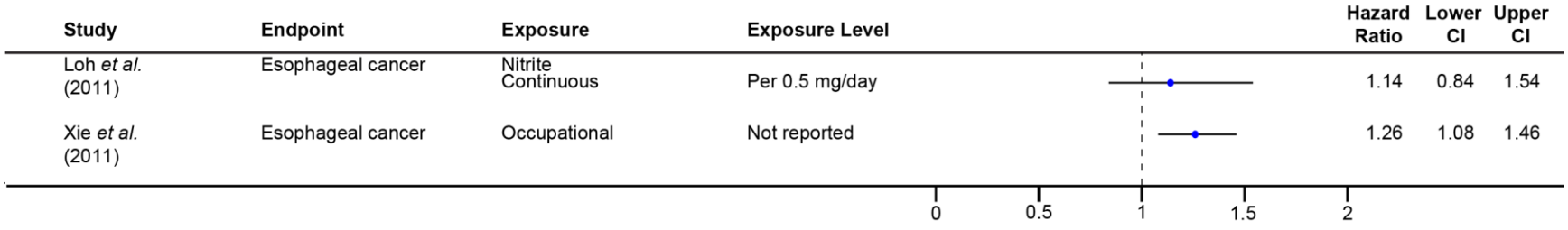


Figure 5B. Esophageal cancer – case-control studies. Forest plot of the association between dietary nitrate and nitrite intake and esophageal cancer. Confidence intervals (95%) are denoted by "CI".

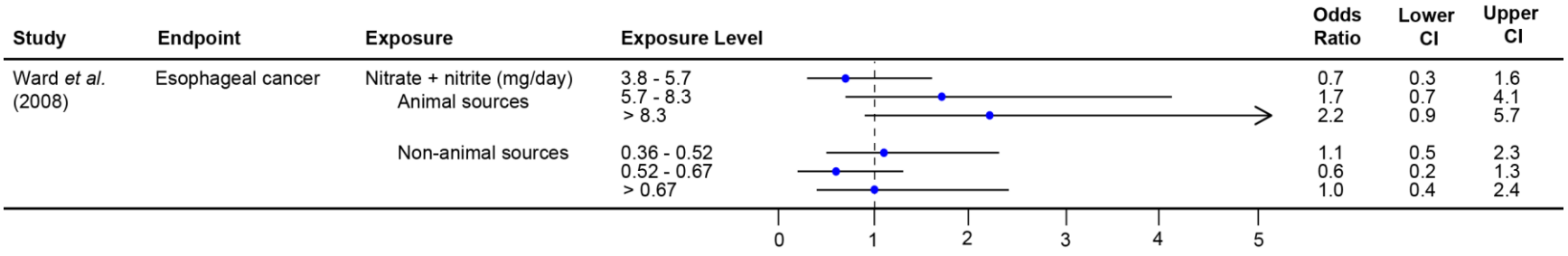
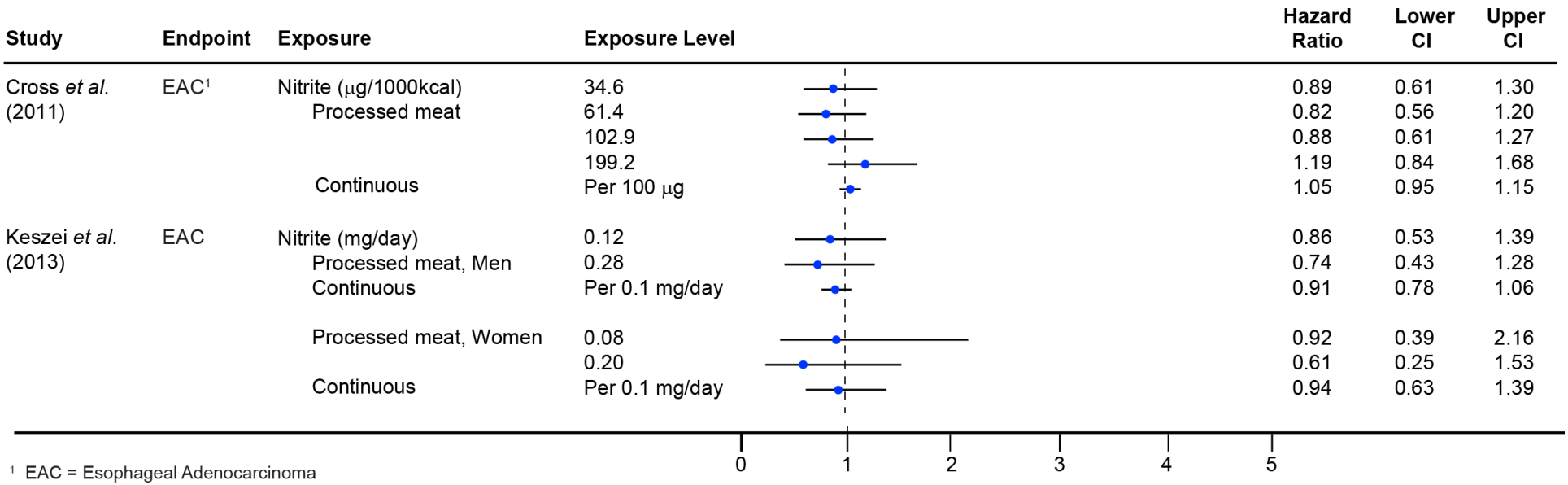


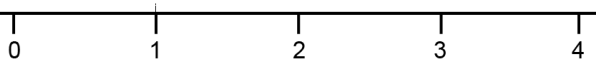
Figure 5C. Esophageal adenocarcinoma (EAC) – cohort studies. Forest plot of the association between dietary nitrite intake and esophageal adenocarcinoma (EAC). Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.



[1] EAC = Esophageal Adenocarcinoma

Figure 5D. Esophageal squamous cell carcinoma (ESCC) – cohort studies. Forest plot of the association between dietary nitrite exposure intake and esophageal squamous cell carcinoma (ESCC). Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.

Study	Endpoint	Exposure	Exposure Level	Hazard Ratio	Lower CI	Upper CI
Cross *et al.* (2011)	ESCC[1]	Nitrite (μg/1000kcal)	34.6	1.36	0.76	2.43
		Processed meat	61.4	0.82	0.43	1.57
			102.9	1.15	0.63	2.11
			199.2	1.21	0.67	2.20
		Continuous	Per 100 μg	1.00	0.83	1.21
Keszei *et al.* (2013)	ESCC	Nitrite (mg/day)	0.12	1.27	0.62	2.62
		Processed meat, Men	0.28	1.92	0.94	3.89
		Continuous	Per 0.1 mg/day	1.19	1.05	1.36
		Processed meat, Women	0.08	0.99	0.48	2.03
			0.02	0.85	0.39	1.88
		Continuous	Per 0.1 mg/day	0.83	0.61	1.12



[1] ESCC= Esophageal squamous cell carcinoma

Figure 6A. Gastric cancer – cohort study. Forest plot of the association between dietary nitrite intake and gastric cancer. Confidence intervals (95%) are denoted by "CI".

Study	Endpoint	Exposure	Exposure Level	Hazard Ratio	Lower CI	Upper CI
Loh *et al.* (2011)	Gastric cancer	Nitrite (mg/day)				
		Continuous	Per 0.5 mg/day	0.86	0.63	1.19

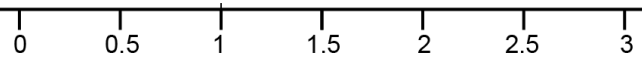


Figure 6B. Gastric cancer – case-control studies. Forest plot of the association between dietary nitrite intake and gastric cancer. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.

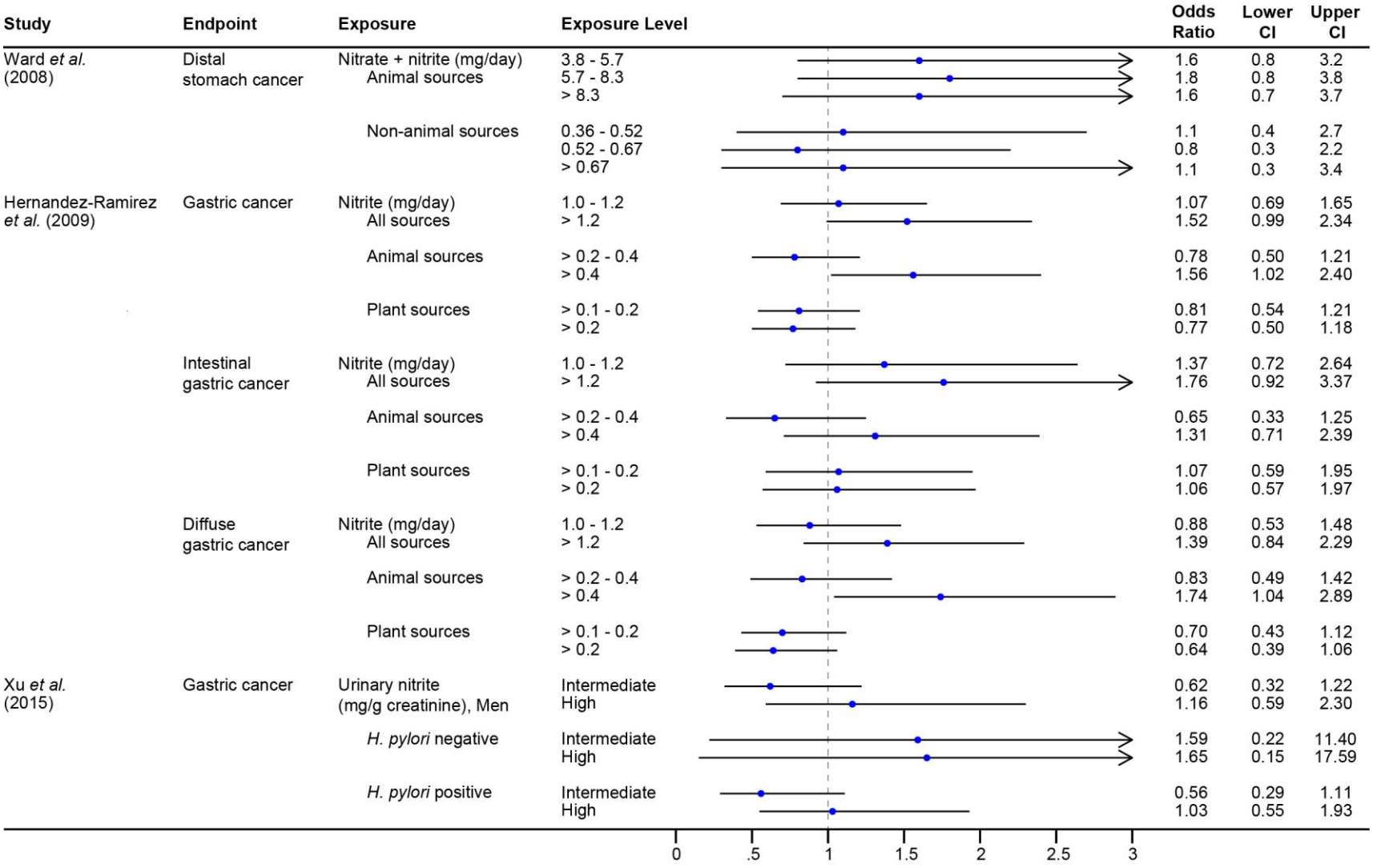
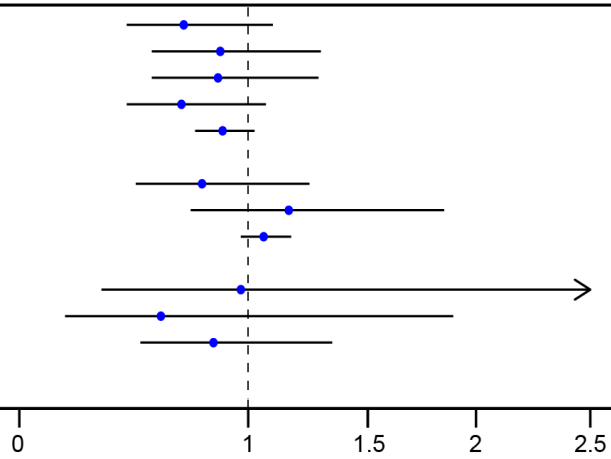


Figure 6C. Gastric cardia adenocarcinoma. Forest plot of the association between dietary nitrite intake and gastric cardia adenocarcinoma. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.

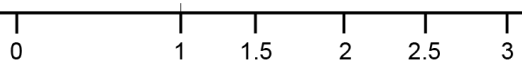
Study	Endpoint	Exposure	Exposure Level	Hazard Ratio	Lower CI	Upper CI
Cross *et al.* (2011)	GCA[1]	Nitrite (μg/1000kcal)	34.6	0.72	0.47	1.11
		Processed meat	61.4	0.88	0.58	1.32
			102.9	0.87	0.58	1.31
			199.2	0.71	0.47	1.08
		Continuous	Per 100 μg/day	0.89	0.77	1.03
Keszei *et al.* (2013)	GCA	Nitrite (mg/day)	0.12	0.80	0.51	1.27
		Processed meat, Men	0.28	1.18	0.75	1.86
		Continuous	Per 0.1 mg/day	1.07	0.97	1.19
		Processed meat, Women	0.08	0.97	0.36	2.58
			0.2	0.62	0.20	1.90
		Continuous	Per 0.1 mg/day	0.85	0.53	1.37



[1] GCA = Gastric cardia adenocarcinoma

Figure 6D. Gastric non-cardia adenocarcinoma. Forest plot of the association between dietary nitrite intake and gastric non-cardia adenocarcinoma. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.

Study	Endpoint	Exposure	Exposure Level	Hazard Ratio	Lower CI	Upper CI
Cross *et al.* (2011)	GNCA[1]	Nitrite (μg/1000kcal)	34.6	0.77	0.51	1.15
		Processed meat	61.4	0.79	0.53	1.18
			102.9	1.04	0.71	1.52
			199.2	0.93	0.63	1.37
		Continuous	Per 100 μg/day	1.02	0.91	1.15
Keszei *et al.* (2013)	GNCA	Nitrite (mg/day)	0.12	1.10	0.80	1.50
		Processed meat, Men	0.28	1.23	0.89	1.70
		Continuous	Per 0.1 mg/day	1.04	0.97	1.12
		Processed meat, Women	0.08	0.94	0.62	1.41
			0.2	1.08	0.71	1.63
		Continuous	Per 0.1 mg/day	0.96	0.83	1.12



[1] GNCA = Gastric noncardia adenocarcinoma

Table 4. Esophageal and Stomach Cancer—Studies of Nitrite Exposure

Study / Location	Study Design / Sample sizes	Outcomes of interest[1]	Exposure assessment[2]	Exposure levels	Results[3] Risk ratio (95% CI)		Confounders / Covariates / Comments
Cohort Studies							
Cross *et al.* (2011) National Institutes of Health (NIH)-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 303,156 participants (176,842 men and 126,314 women) 10-year follow-up (mean) <u>Cancer cases[1]</u> 215 ESCC 630 EAC 454 GCA 501 GNCA	Esophageal cancer: ESCC EAC Gastric cancer: GCA GNCA	Dietary intake of processed meat was estimated using a validated food frequency questionnaire (FFQ). Nitrite intake was estimated using a National Cancer Institute (NCI) database containing measured values of nitrite in processed meat.	Dietary intake of nitrite (median) (µg /1000 kcal) Q1= 12.1 Q2= 34.6 Q3= 61.4 Q4= 102.9 Q5= 199.2	<u>EAC</u> Q2 HR=0.89 (0.61-1.30) Q3 HR=0.82 (0.56-1.20) Q4 HR=0.88 (0.61-1.27) Q5 HR=1.19 (0.84-1.68) **p-trend=0.029 *** <u>ESCC</u> Q2 HR = 1.36 (0.76–2.43) Q3 HR = 0.82 (0.43–1.57) Q4 HR = 1.15 (0.63–2.11) Q5 HR = 1.21 (0.67–2.20) p-trend =0.651	<u>GCA</u> Q2 HR =0.72 (0.47–1.11) Q3 HR = 0.88 (0.58–1.32) Q4 HR = 0.87 (0.58–1.31) Q5 HR = 0.71 (0.47–1.08) p-trend = 0.250 <u>GNCA</u> Q2 HR=0.77 (0.51–1.15) Q3 HR=0.79 (0.53–1.18) Q4 HR=1.04 (0.71–1.52) Q5 HR=0.93 (0.63–1.37) p-trend = 0.615	Models adjusted for age, gender, body mass index (BMI), education, ethnicity, tobacco smoking, alcohol drinking, physical activity, daily intake of fruit, vegetables, saturated fat, and calories Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham and hotdogs (regular and poultry)
				Per 100 µg nitrite (continuous)	<u>EAC</u> HR= 1.05 (0.95-1.15) <u>ESCC</u> HR= 1.00 (0.83–1.21)	<u>GCA</u> HR= 0.89 (0.77–1.03) <u>GNCA</u> HR = 1.02 (0.91–1.15)	
Loh *et al.* (2011) EPIC-Norfolk Study Norfolk, United Kingdom	Prospective cohort 23,363 participants (10,783 men, 12,580 women) 11.4 year follow-up (mean) <u>Cancer Cases</u> 55 Esophageal 64 Stomach	Esophageal cancer Stomach cancer	Dietary intake was reported using a validated, country-specific FFQ. Nitrite concentrations were estimated using the EPIC-EURGAST study, which determined values from the published literature.	Per 0.5 mg/day nitrite intake (SD) (continuous)	<u>Esophageal cancer</u> HR= 1.14 (0.84 – 1.54) p-trend= 0.39 <u>Stomach cancer</u> HR= 0.86 (0.63 – 1.19) p-trend= 0.37		Multivariate model adjusted for age, sex, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity status, educational level, and menopausal status (in women).

Table 4. Esophageal and Stomach Cancer—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1]	Exposure assessment[2]	Exposure levels	Results[3] Risk ratio (95% CI)	Confounders / Covariates / Comments
Cohort Studies (continued)						
Xie *et al.* (2011) Chengdu, Sichuan Province, China	Retrospective cohort Workforce from a wood screw manufacturing facility 30-year follow-up, average 22.1 years exposure 158 exposed 249 unexposed	Esophageal cancer	Exposure inherent in manufacturing process: A worker held a screw that had been immersed in a sodium nitrite solution and blew this solution away from the screw, using his or her mouth Investigators reported that workers had direct exposure to the face, hands, and alimentary and respiratory tract. Hands were soaked in sodium nitrite solution 8 hours/day. Individuals from exposed workshop were compared to individuals from non-exposed workshops in the same facility	Unknown As the facility was no longer in operation, no measurements could be made	RR = **1.26 (1.08–1.46) *** Difference in cumulative incidence in exposed compared to unexposed workers: Chi-square = **116.83, P <0.001 ***	Information on age, gender, smoking, alcohol consumption and family history of esophageal cancer was collected but not directly used in estimating relative risk. The two groups differed significantly by gender (p=0.012) but not by other factors that were examined. The article describing this study provides information about the number of males / females in the exposed / unexposed groups in text and table form, but one provides the reverse information found in the other. It is unclear which information on male/female percentage is correct .

Table 4. Esophageal and Stomach Cancer—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1]	Exposure assessment[2]	Exposure levels	Results[3] Risk ratio (95% CI)		Confounders / Covariates / Comments
Cohort Studies (continued)							
Keszei *et al.* (2013) Netherlands Cohort Study	Prospective cohort with nested case-cohort 120,852 participants (58,279 men, 62,573 women) 16.3-year follow-up 4032 subcohort members <u>Cancer cases[1]</u> 110 ESCC 151 EAC 166 GC 497 GNCA	Esophageal cancer: ESCC EAC Gastric cancer: GCA GNCA	Dietary intake was estimated using a self-reported FFQ. Nitrite intake from processed meat was estimated using measured values available from the Dutch National Institute for Public Health.	Dietary intake of nitrite (median) (mg/d) Men T1= 0.03 T2= 0.12 T3= 0.28	<u>ESCC</u> T2 HR= 1.27 (0.62, 2.62) T3 HR= 1.92 (0.94, 3.89) p-trend= 0.06 <u>EAC</u> T2 HR= 0.86 (0.53, 1.39) T3 HR= 0.74 (0.43, 1.28) p-trend= 0.30	<u>GCA</u> T2 HR= 0.80 (0.51, 1.27) T3 HR= 1.18 (0.75, 1.86) p-trend= 0.34 <u>GNCA</u> T2 HR= 1.10 (0.80, 1.50) T3 HR= 1.23 (0.89, 1.70) p-trend= 0.20	Models adjusted for age, smoking status, number of cigarettes per day and years of smoking, total energy intake, BMI, alcohol intake, vegetable intake, fruit intake, level of education, and non-occupational physical activity Low vitamin C intake and high nitrite intake compared with high vitamin C and low nitrite intake showed positive trend with ESCC, although not significant. Overall tests of interaction between vitamin C intake and nitrite intake were not significant
				Dietary intake of nitrite (median) (mg/d) Women T1= 0.02 T2= 0.08 T3= 0.20	<u>ESCC</u> T2 HR= 0.99 (0.48, 2.03) T3 HR= 0.85 (0.39, 1.88) p-trend= 0.67 <u>EAC</u> T2 HR= 0.92 (0.39, 2.16) T3 HR= 0.61 (0.25, 1.53) p-trend= 0.27	<u>GCA</u> T2 HR= 0.97 (0.36, 2.58) T3 HR= 0.62 (0.20, 1.90) p-trend= 0.37 <u>GNCA</u> T2 HR= 0.94 (0.62, 1.41) T3 HR= 1.08 (0.71, 1.63) p-trend= 0.65	
				Per 0.1-mg/d nitrite (continuous)	*Men* <u>ESCC</u> HR= **1.19 (1.05, 1.36) *** <u>EAC</u> HR= 0.91 (0.78, 1.06) <u>GCA</u> HR= 1.07 (0.97, 1.19) <u>GNCA</u> HR= 1.04 (0.97, 1.12)	*Women* <u>ESCC</u> HR = 0.83 (0.61, 1.12) <u>EAC</u> HR= 0.94 (0.63, 1.39) <u>GCA</u> HR= 0.85 (0.53, 1.37) <u>GNCA</u> HR= 0.96 (0.83, 1.12)	

Table 4. Esophageal and Stomach Cancer—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1]	Exposure assessment[2]	Exposure levels	Results[3] Risk ratio (95% CI)	Confounders / Covariates / Comments
Case-Control studies						
Ward *et al*. (2008) Nebraska USA	Population-based case-control study 98 Esophageal cancer cases 104 Distal stomach cancer cases 397 controls	Esophageal cancer Distal stomach cancer	Dietary intake of all foods was estimated using a FFQ by participant or by proxy. Nitrate plus nitrite concentrations were estimated from the literature.	**Animal sources** Dietary intake of nitrate plus nitrite from animal sources (mg/day) Q1 <3.8 Q2 3.8 - 5.7 Q3 5.7 - 8.3 Q4 8.3+	*Combined nitrate and nitrite* Esophageal Q2 OR=0.7 (0.3-1.6) Q3 OR=1.7 (0.7-4.1) Q4 OR=2.2 (0.9-5.7) **p-trend=0.015 *** Distal Stomach Q2 OR=1.6 (0.8-3.2) Q3 OR=1.8 (0.8-3.8) Q4 OR=1.6 (0.7-3.7) p-trend=0.352	Exposure assessment included nitrate and nitrite, but did not evaluate nitrite only Models adjusted for birth year, BMI, smoking, alcohol, total calories, vitamin A, folate, riboflavin, zinc, protein, carbohydrate Non-animal sources of nitrate plus nitrite were mainly breads and cereals. Proxy interviews were conducted for 80% of stomach cancer cases, 76% of esophagus cancer cases, and 61% of controls
				Non-animal sources Dietary intake of nitrate plus nitrite from non-animal sources (mg/day) Q1 <3.6 Q2 0.36 - 0.52 Q3 0.52 - 0.67 Q4 0.67+	*Combined nitrate and nitrite* Esophageal Q2 OR= 1.1 (0.5-2.3) Q3 OR= 0.6 (0.2-1.3) Q4 OR= 1.0 (0.4-2.4) p–trend= 0.438 Distal Stomach Q2 OR= 1.1 (0.4 – 2.7) Q3 OR= 0.8 (0.3 – 2.2) Q4 OR= 1.1 (0.3 – 3.4) p-trend= 0.275	
Hernandez-Ramırez *et al*. (2009) Mexico City, Mexico	Population-based case-control study 257 cases 478 controls 54% male (Both cases and controls)	Gastric cancer, including intestinal and diffuse gastric cancer	Dietary intake of all foods using a validated FFQ Nitrite levels in foods were estimated from the literature.	**Total Nitrite (All sources)** Dietary nitrite intake from all sources (mg/day) T1 ≤1.0 T2 >1.0 - 1.2 T3 >1.2	<u>All gastric cancer</u> T2 OR= 1.07 (069-1.65) T3 OR= 1.52 (0.99–2.34) p-trend = 0.052 <u>Intestinal gastric cancer</u> T2 OR= 1.37 (0.72-2.64) T3 OR= 1.76 (0.92–3.37) p-trend = 0.087 <u>Diffuse gastric cancer</u> T2 OR= 0.88 (0.53-1.48) T3 OR= 1.39 (0.84–2.29) p-trend = 0.186	Models adjusted by total energy intake, age, gender, *H. pylori* status, education, and consumption of salt, chili and alcohol. Controls resided in the same geographic area as cases and were selected and matched to cases (up to 2 per case) by age (±5 years) and gender.

Table 4. Esophageal and Stomach Cancer—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1]	Exposure assessment[2]	Exposure levels	Results[3] Risk ratio (95% CI)	Confounders / Covariates / Comments
Case-Control studies (continued)						
Hernandez-Ramırez *et al.* (2009) (continued) Mexico City, Mexico	Population-based case-control study 257 cases 478 controls 54% male (Both cases and controls)	Gastric cancer, including intestinal and diffuse gastric cancer	Dietary intake of all foods using a validated FFQ Nitrite levels in foods were estimated from the literature.	**Animal sources** Dietary nitrite intake from animal sources (mg/day) T1 ≤0.2 T2 >0.2 - 0.4 T3 >0.4	<u>All gastric cancer</u> T2 OR= 0.78 (0.50-1.21) T3 OR= **1.56 (1.02-2.40)** **p-trend = 0.03 *** <u>Diffuse gastric cancer</u> T2 OR= 0.83 (0.49-1.42) T3 OR= **1.74 (1.04-2.89)** **p-trend = 0.026 *** <u>Intestinal gastric cancer</u> T2 OR=0.65 (0.33-1.25) T3 OR=1.31 (0.71-2.39) p-trend = 0.334	Models adjusted by total energy intake, age, gender, *H. pylori* status, education, and consumption of salt, chili and alcohol. Controls resided in the same geographic area as cases and were selected and matched to cases (up to 2 per case) by age (±5 years) and gender.
				Plant sources Dietary nitrite intake from plant sources (mg/day) T1 ≤0.1 T2 >0.1 - 0.2 T3 >0.2	<u>All gastric cancer</u> T2 OR= 0.81 (0.54 – 1.21) T3 OR= 0.77 (0.50 – 1.18) p-trend = 0.216 <u>Intestinal gastric cancer</u> T2 OR= 1.07 (0.59 – 1.95) T3 OR= 1.06 (0.57 – 1.97) p-trend = 0.850 <u>Diffuse gastric cancer</u> T2 OR= 0.70 (0.43 – 1.12) T3 OR= 0.64 (0.39 – 1.06) p-trend = 0.069	
Xu *et al.* (2015) Shanghai, China	Case-control nested within prospective cohort <u>Case-control (all men)</u> 104 cases 308 controls	Gastric cancer	Urinary nitrite measured in samples obtained at study entry	Urinary nitrite levels (mg/g creatinine) Low ≤5.3 Intermediate 5.31 – 11.87 High >11.87	*Men* <u>All subjects</u> Intermediate OR= 0.62 (0.32 – 1.22) High OR= 1.16 (0.59-2.30) p-trend=0.642 <u>*H. pylori* negative subjects</u> Intermediate OR= 1.59 (0.22 – 11.40) High OR= 1.65 (0.15-17.59) p-trend = 0.633 <u>*H. pylori* positive subjects</u> Intermediate OR= 0.56 (0.29 – 1.11) High OR= 1.03 (0.55-1.93) p-trend = 0.939	Models adjusted for education level, alcohol consumption, smoking status, levels of serum vitamin C, serum beta-carotene, urinary epigallocatechin, and *H. pylori* status. Geometric mean levels of urinary nitrite levels differed significantly by *H. pylori* status (2 sided p value = 0.048) In those for whom urinary nitrite values were available, only a small number of cases (9) were *H. pylori* negative.

Table 4. Esophageal and Stomach Cancer—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1]	Exposure assessment[2]	Exposure levels	Results[3] Risk ratio (95% CI)	Confounders / Covariates / Comments
Ecologic Studies						
Mitacek *et al.* (2008) Thailand	Ecologic study Geographic distribution of cancer by region in relation to estimated dietary intake in these regions Exposure assessment: 212 males 255 females	Stomach cancer	Dietary intake assessed using 97-item FFQ. Used colorimetric assay to measure levels of nitrite in foods.	Dietary intake of nitrite by geographic area (mean) (mg/day) North 9.5 ±0.38 Northeast 8.8 ±0.35 Central 6.2 ±0.25 South 4.5 ±0.18	Stomach cancer: Age standardized incidence rate per 100,000 by region (e.g., 1995-1997) North: Male 6.45, Female 4.35 Northeast: Male 3.2, Female 1.9 Central: Male 4.9, Female 3.7 South: Male 1.9, Female 1.4	Nitrite intake estimates were based on current diet of people from each region, while cancer incidence data came from earlier time periods. Mean daily intake of nitrite varied by region ($p<0.0001$), based on individuals who completed exposure assessment portion of study. Stomach cancer incidence rates also varied by region. However, authors did not present any analysis of nitrite intake in relation to reported cancer incidence rates.

Table 4. Esophageal and Stomach Cancer—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1]	Exposure assessment[2]	Exposure levels	Results[3] Risk ratio (95% CI)	Confounders / Covariates / Comments
Ecologic Studies (continued)						
Zhang *et al*. (2012) Shexian, China	Ecologic study Geographic distribution of cancer by region in relation to nitrite in drinking water 661 ESCC cases 54,716 total population in 48 villages	ESCC	Water was sampled (twice per village) from locations where villagers obtained daily drinking water. "Nitrite nitrogen" was measured within 24 hours of sampling.	Nitrite (mg/L) in drinking water ≤0.001 0.002-0.004 0.005-0.008 0.009-0.060 0.061-0.195	No analyses are presented of ESCC in relation to nitrite level categories OR=0.29 (0.05-1.68)	Nitrite concentration was low overall in the study area, with only a small cluster of villages in the northwest region with high nitrite. Odds ratio calculated in a logistic regression analysis that included elevation (altitude) (a factor significantly associated with cancer incidence and potentially related to regional variations in drinking water quality), nitrite, nitrate and ammonia. Nitrate levels were reported as significantly related to ESCC, although no data was show in relation to nitrite level categories.

[1] **ESCC**--Esophageal squamous cell carcinoma; **EAC**--Esophageal adenocarcinoma; **GCA**--Gastric cardia adenocarcinoma; **GNCA**--Gastric noncardia adenocarcinoma

[2] Exposure assessment methods primarily include food frequency questionnaires (FFQ)—a checklist of foods and beverages with a frequency response section for subjects to report how often each item was consumed over a specified period of time.

[3] Data include both genders unless otherwise specified.

***** Findings are statistically significant. 95% confidence interval excludes 1.0, p-value < 0.05

BMI—Body mass index; **CI**—Confidence Interval; **EPIC**—European Prospective Investigation into Cancer & Nutrition; **FFQ**—Food frequency questionnaire; **HR**—Hazard Ratio; **NCI**—National Cancer Institute; **OR**—Odds ratio; **Q**—Quartiles or quintiles; **RR**—Risk Ratio; **T**—Tertiles

Figure 7A. Lymphoma – case-control studies, Part A. Forest plot of the association between dietary nitrite intake and lymphoma. Confidence intervals (95%) are denoted by "CI". Studies are ordered by study year.

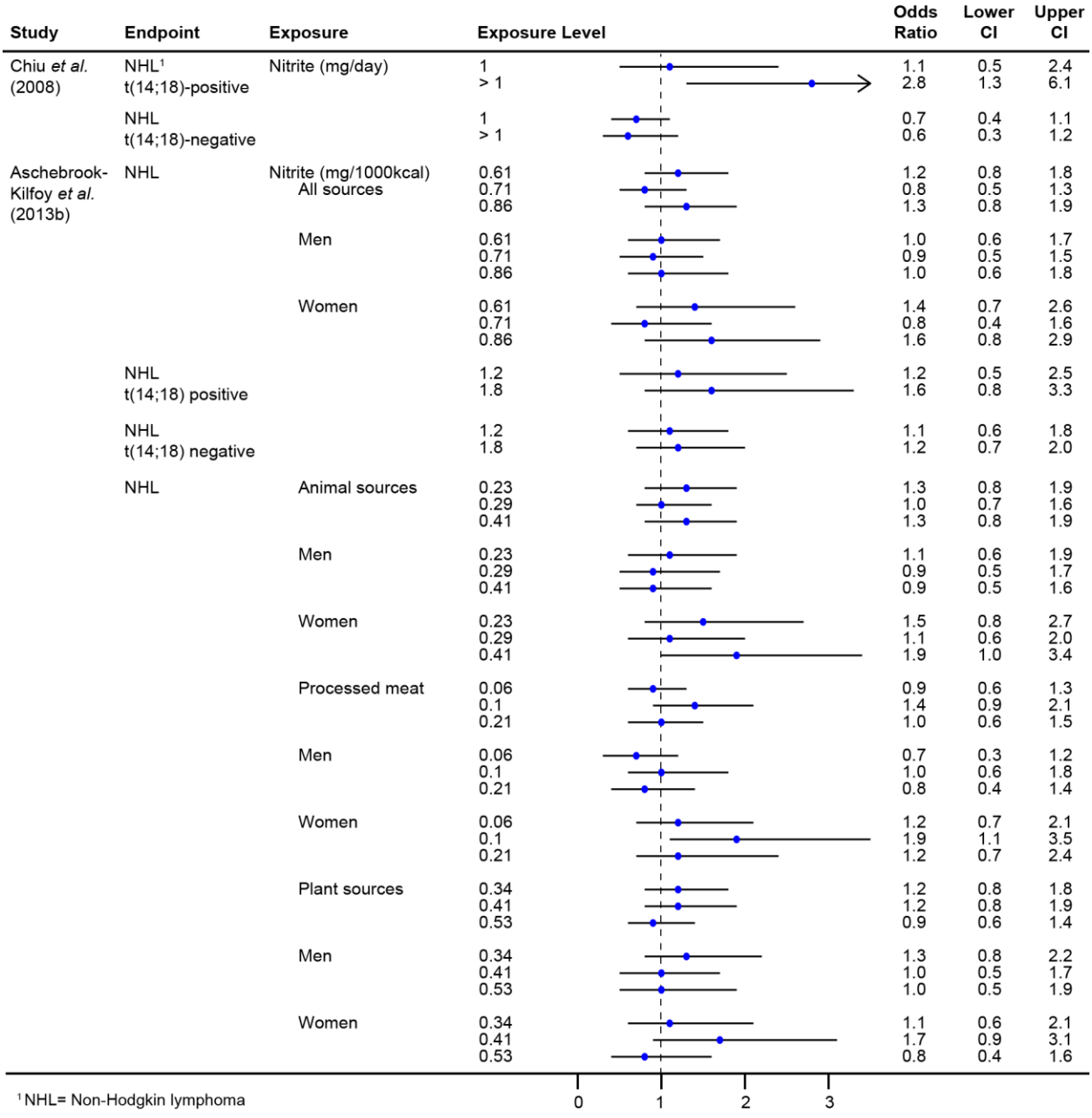
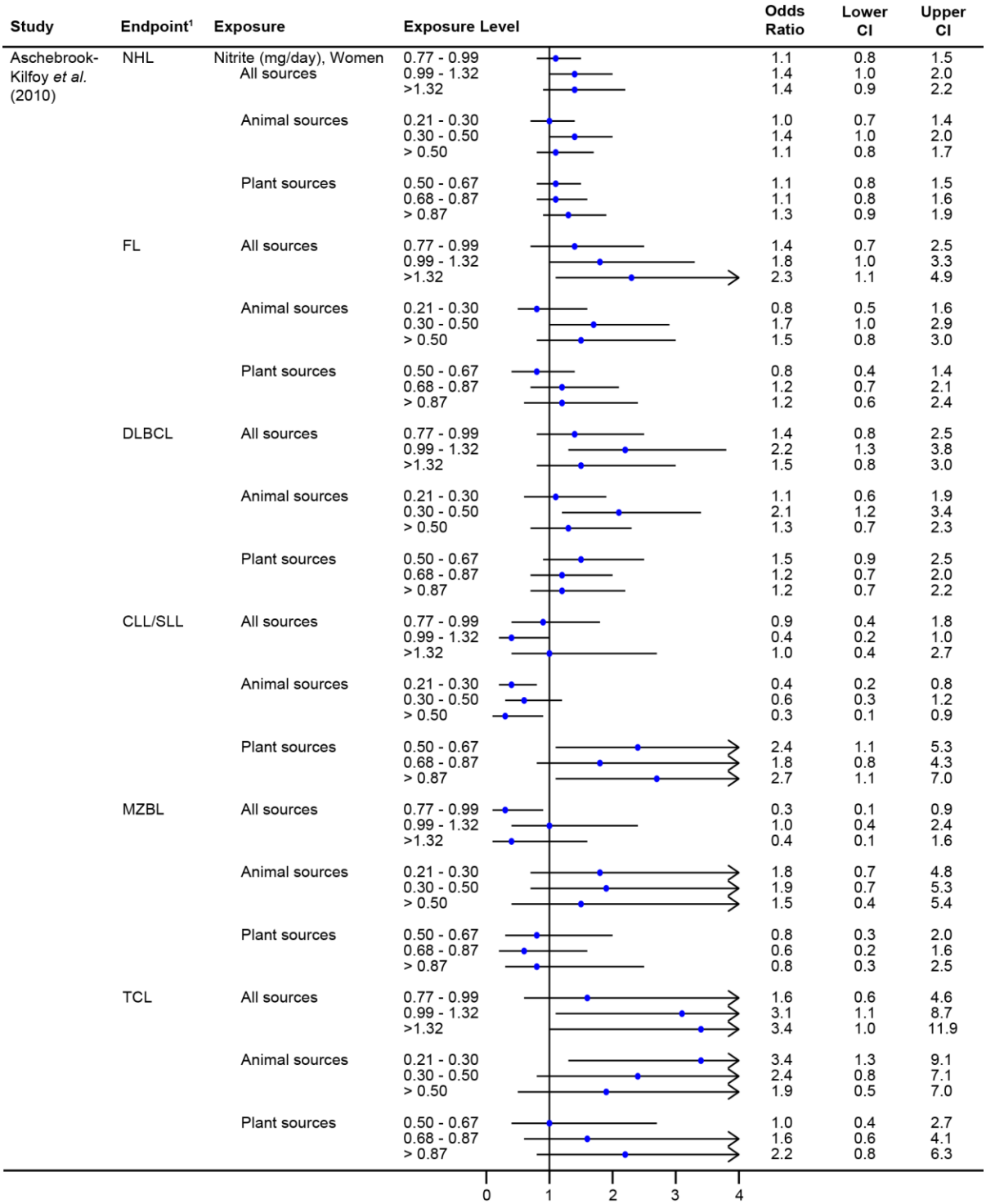


Figure 7B. Lymphoma – case-control studies, Part B. Forest plot of the association between dietary nitrite intake and lymphoma. Confidence intervals (95%) are denoted by "CI".



[1] NHL= Non-Hodgkin lymphoma; FL= Follicular lymphoma; DLBCL= Diffuse large B-cell lymphoma; CLL/SLL= Chronic lymphocytic leukemia/small lymphocytic lymphoma; MZBL= Marginal zone B-cell lymphoma; TCL= T-cell lymphoma

Table 5. Lymphoma—Studies of Nitrite Exposure

Study / Location	Study Design / Sample sizes	Outcomes of interest[1,2]	Exposure assessment[3]	Exposure levels	Results[4] Risk ratio (95% CI)	Confounders / Covariates / Comments
Cohort Studies						
Daniel *et al.* (2012) National Institutes of Health (NIH)-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 302,162 participants (176,179 men, 125,983 women) 9 year follow-up (mean) <u>Cases[1]</u> 2,155 Total NHL 509 DLBCL 368 FL 586 CLL/SLL	NHL <u>NHL subtypes</u> DLBCL FL CLL/SLL	Dietary intake of processed meat was estimated using a validated 124-item food frequency questionnaire (FFQ). Combined nitrate and nitrite concentrations were estimated using a National Cancer Institute (NCI) database of measured values of both compounds in processed meat.	Dietary nitrate + nitrite intake from processed meat (median) (mg/1000 kcal) Q1= 0.04 Q2= 0.10 Q3= 0.18 Q4= 0.27 Q5= 0.47	*Combined nitrate and nitrite* <u>Total NHL</u> Q2 HR= 1.07 (0.94-1.23) Q3 HR= 1.06 (0.92-1.22) Q4 HR= 0.99 (0.85-1.14) Q5 HR= 1.02 (0.88-1.18) p-trend= 0.68 <u>DLBCL</u> Q2 HR= 0.86 (0.65-1.13) Q3 HR= 0.87 (0.66-1.16) Q4 HR= 0.91 (0.68-1.21) Q5 HR= 0.93 (0.70-1.24) p-trend = 0.95 <u>FL</u> Q2 HR= 1.26 (0.91-1.74) Q3 HR= 0.93 (0.66-1.32) Q4 HR= 1.15 (0.82-1.61) Q5 HR= 0.96 (0.67-1.37) p-trend= 0.50 <u>CLL/SLL</u> Q2 HR= 1.25 (0.95-1.63) Q3 HR= **1.36 (1.04-1.78)*** Q4 HR= 1.02 (0.77-1.36) Q5 HR= 1.08 (0.81-1.44) p-trend= 0.50	Exposure assessment included nitrate and nitrite, but did not evaluate nitrite only. Multivariable model adjusted for age, gender, education, family history of any cancer, race, body mass index (BMI), smoking status, physical activity, and intake of alcohol, fruit, vegetables, and total energy. Processed meat included red meat (bacon, cold cuts, ham, hot dogs, and sausage) and poultry (poultry cold cuts, low-fat sausages, and low-fat hot dogs).
Case-Control Studies						
Chiu *et al.* (2008) Nebraska	Population-based case-control 147 cases NHL, 1075 controls <u>Cases</u> 60 t(14;18) positive cases 87 t(14;18) negative cases <u>Controls</u> Controls in Nebraska were recruited using random digit dialing. Controls were 3:1 frequency matched by race, gender, vital status, and age.	NHL t(14;18) positive t(14;18) negative	Dietary intake of all foods was estimated using a 30-item FFQ by participant or next-of-kin. Nitrite concentrations were determined from the literature.	Dietary nitrite intake (mg/day) T1 < 1 T2 1 T3 > 1	<u>t(14;18) positive</u> T2 OR= 1.1 (0.5-2.4) T3 OR= **2.8 (1.3-6.1)*** <u>t(14;18) negative</u> T2 OR= 0.7 (0.4-1.1) T3 OR= 0.6 (0.3-1.2)	Adjusted for age, gender, type of respondent (direct or proxy interview), family history of cancer, and body mass index. Approximate tertiles of intake were based on the frequency of consumption among controls.

Table 5. Lymphoma—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1,2]	Exposure assessment[3]	Exposure levels	Results[4] Risk ratio (95% CI)	Confounders / Covariates / Comments
Case-Control Studies (continued)						
Richardson *et al.* (2008) Northern Germany	Population-based case-control 858 cases, 1821 controls <u>Cases</u> (occupationally exposed to nitrate, nitrite, nitrosamine) 56 High-malignancy NHL 81 Low-malignancy NHL 40 CLL <u>Controls</u> Controls were identified from population registries.	High-malignancy NHL Low-malignancy NHL CLL	In-person interviews were used to assess occupational exposure from longest-held job. Job titles were classified using the International Standard Classification of Occupations of the International Labor Office. Estimates of exposure to 50 chemical, physical, and biological agents were derived by a job exposure matrix.	Ever-exposed vs. Never-exposed occupationally to nitrate, nitrite, or nitrosamine	*Combined nitrate, nitrite, and nitrosamines* <u>High-malignancy NHL</u> OR = **2.22 (1.48-3.35)*** <u>CLL</u> OR = 1.07 (0.70-1.63) <u>Low-malignancy NHL</u> OR = **1.45 (1.05-2.01)***	Exposure assessment included nitrate, nitrite, and nitrosamines, but did not evaluate nitrite only. Conditional logistic regression adjusted for smoking status.
				Cumulative occupational exposure (hours) to nitrate, nitrite, or nitrosamine Q1 0 Q2 > 0 - 26,084 Q3 26,085 - 112,799 Q4 112,800 - 593,610	*Combined nitrate, nitrite, and nitrosamines* <u>High-malignancy NHL</u> Q2 OR = **3.13 (1.64-5.97)*** Q3 OR = 1.19 (0.55-2.59) Q4 OR = **2.39 (1.29-4.42)*** **p-trend = 0.031*** <u>CLL</u> Q2 OR = 0.97 (0.42-2.20) Q3 OR = 1.44 (0.76-2.72) Q4 OR = 0.91 (0.47-1.73) p-trend = 0.884 <u>Low-malignancy NHL</u> Q2 OR = 1.47 (0.91-2.40) Q3 OR = 1.26 (0.72-2.21) Q4 OR = 1.65 (0.99-2.74) **p-trend = 0.046***	

Table 5. Lymphoma—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1,2]	Exposure assessment[3]	Exposure levels	Results[4] Risk ratio (95% CI)	Confounders / Covariates / Comments
Case-Control Studies (continued)						
Aschebrook-Kilfoy *et al.* (2010) Connecticut	Population-based case-control 1304 female participants 594 cases, 710 controls <u>Cases</u> 594 Total NHL DLBCL 187 134 FL 66 CLL/SLL 40 MZBL 44 TCL 123 Other <u>Controls</u> Controls from Connecticut were recruited using random digit dialing.	NHL <u>NHL subtypes</u> DLBCL FL CLL/SLL MZBL TCL	Dietary intake of all sources was estimated using a validated 120 item FFQ. Nitrite concentrations were determined from the literature.	**Total Nitrite (All Sources)** Dietary nitrite intake (median) (mg/day) Q1 < 0.77 Q2 0.77- <0.99 Q3 0.99 - <1.32 Q4 ≥ 1.32	<u>Total NHL</u> Q2 OR= 1.1 (0.8-1.5) Q3 OR= 1.4 (1.0-2.0) Q4 OR= 1.4 (0.9-2.2) p-trend= 0.20 <u>DLBCL</u> Q2 OR= 1.4 (0.8-2.5) Q3 OR= **2.2 (1.3-3.8)*** Q4 OR= 1.5 (0.8-3.0) p-trend= 0.70 <u>FL</u> Q2 OR= 1.4 (0.7-2.5) Q3 OR= 1.8 (1.0-3.3) Q4 OR= **2.3 (1.1-4.9)*** **p-trend= 0.008*** <u>CLL/SLL</u> Q2 OR= 0.9 (0.4-1.8) Q3 OR= 0.4 (0.2-1.0) Q4 OR= 1.0 (0.4-2.7) p-trend= 0.7 <u>MZBL</u> Q2 OR= 0.3 (0.1-0.9) Q3 OR= 1.0 (0.4-2.4) Q4 OR= 0.4 (0.1-1.6) p-trend= 0.50 <u>TCL</u> Q2 OR= 1.6 (0.6-4.6) Q3 OR= **3.1 (1.1-8.7)*** Q4 OR= 3.4 (1.0-11.9) p-trend= 0.3	Multivariable model adjusted for age, family history of cancer, vitamin C intake, vitamin E intake, protein intake, and calories.
				Animal Sources Dietary nitrite intake from animal sources (median) (mg/day) Q1 < 0.21 Q2 0.21 - 0.30 Q3 0.30 - 0.50 Q4 > 0.50	*Women* <u>Total NHL</u> Q2 OR= 1.0 (0.7-1.4) Q3 OR= 1.4 (1.0-2.0) Q4 OR= 1.1 (0.8-1.7) p-trend= 0.9 <u>DLBCL</u> Q2 OR= 1.1 (0.6-1.9) Q3 OR= **2.1 (1.2-3.4)*** Q4 OR= 1.3 (0.7-2.3) p-trend= 0.8 <u>FL</u> Q2 OR= 0.8 (0.5-1.6) Q3 OR= 1.7 (1.0-2.9) Q4 OR= 1.5 (0.8-3.0) **p-trend= 0.04*** <u>CLL/SLL</u> Q2 OR= 0.4 (0.2-0.8) Q3 OR= 0.6 (0.3-1.2) Q4 OR= 0.3 (0.1-0.9) **p-trend= 0.003*** <u>MZBL</u> Q2 OR= 1.8 (0.7-4.8) Q3 OR= 1.9 (0.7-5.3) Q4 OR= 1.5 (0.4-5.4) p-trend= 0.9 <u>TCL</u> Q2 OR= **3.4 (1.3-9.1)*** Q3 OR= 2.4 (0.8-7.1) Q4 OR= 1.9 (0.5-7.0) p-trend= 0.9	Multivariable model adjusted for age, family history of cancer, vitamin C intake, vitamin E intake, protein intake, and calories.

Table 5. Lymphoma—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1,2]	Exposure assessment[3]	Exposure levels	Results[4] Risk ratio (95% CI)	Confounders / Covariates / Comments
Case-Control Studies (continued)						
Aschebrook-Kilfoy *et al.* (2010) (continued) Connecticut	Population-based case-control 1304 female participants 594 cases, 710 controls <u>Cases</u> 594 Total NHL DLBCL 187 134 FL 66 CLL/SLL 40 MZBL 44 TCL 123 Other <u>Controls</u> Controls from Connecticut were recruited using random digit dialing.	NHL <u>NHL subtypes</u> DLBCL FL CLL/SLL MZBL TCL	Dietary intake of all sources was estimated using a validated 120 item FFQ. Nitrite concentrations were determined from the literature.	Processed meat		Multivariable model adjusted for age, family history of cancer, vitamin C intake, vitamin E intake, protein intake, and calories. Processed meats include both red and white meat sources of sausage, luncheon meats, cold cuts, ham, and hotdogs.
				Dietary nitrite intake from processed meat (median) (mg/day)	No significant trend observed (data not provided by authors).	
				Plant sources		Multivariable model adjusted for age, family history of cancer, vitamin C intake, vitamin E intake, protein intake, and calories.
				Dietary nitrite intake from plants (median) (mg/day) Q1 < 0.50 Q2 0.50 – 0.67 Q3 0.68 – 0.87 Q4 > 0.87	*Women* <u>Total NHL</u> Q2 OR= 1.1 (0.8-1.5) Q3 OR= 1.1 (0.8-1.6) Q4 OR= 1.3 (0.9-1.9) p-trend= 0.1 <u>CLL/SLL</u> Q2 OR= **2.4 (1.1-5.3)*** Q3 OR= 1.8 (0.8-4.3) Q4 OR= **2.7 (1.1-7.0)*** p-trend= 0.09 <u>DLBCL</u> Q2 OR= 1.5 (0.9-2.5) Q3 OR= 1.2 (0.7-2.0) Q4 OR= 1.2 (0.7-2.2) p-trend= 0.8 <u>MZBL</u> Q2 OR= 0.8 (0.3-2.0) Q3 OR= 0.6 (0.2-1.6) Q4 OR= 0.8 (0.3-2.5) p-trend= 0.4 <u>FL</u> Q2 OR= 0.8 (0.4-1.4) Q3 OR= 1.2 (0.7-2.1) Q4 OR= 1.2 (0.6-2.4) p-trend= 0.07 <u>TCL</u> Q2 OR= 1.0 (0.4-2.7) Q3 OR= 1.6 (0.6-4.1) Q4 OR= 2.2 (0.8-6.3) p-trend= 0.2	

Table 5. Lymphoma—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1,2]	Exposure assessment[3]	Exposure levels	Results[4] Risk ratio (95% CI)		Confounders / Covariates / Comments
Case-Control Studies (continued)							
Aschebrook-Kilfoy *et al.* (2013b) Nebraska	Population-based case-control 348 cases, 470 controls <u>Cases</u>[2] 348 NHL 106 FL 87 DLBCL 52 t(14;18) positive 104 t(14;18) negative <u>Controls</u> Controls in Nebraska were recruited through random digit dialing. Controls were frequency matched by gender and 5-year age groups.	NHL <u>NHL subtypes</u> DLBCL FL t(14;18) positive t(14;18) negative	Dietary intake of all sources was estimated using a validated FFQ. Nitrite concentrations were determined from the literature.	Total Nitrite (All Sources)			Models adjusted for age, gender, marital status, BMI, education, family history of cancer, vitamin C, E, and total energy intake. Farming status, physical activity, and use of hair dyes were examined but did not change risk estimates.
				Dietary nitrite intake from all sources (median) (mg/1000 kcal) <u>Total NHL</u> Q1= 0.49 Q2= 0.61 Q3= 0.71 Q4= 0.86	<u>Total NHL</u> Q2 OR= 1.2 (0.8-1.8) Q3 OR= 0.8 (0.5-1.3) Q4 OR= 1.3 (0.8-1.9) p-trend= 0.4	<u>Total NHL (Men)</u> Q2 OR= 1.0 (0.6-1.7) Q3 OR= 0.9 (0.5-1.5) Q4 OR= 1.0 (0.6-1.8) p-trend= 0.9 <u>Total NHL (Women)</u> Q2 OR= 1.4 (0.7-2.6) Q3 OR= 0.8 (0.4-1.6) Q4 OR= 1.6 (0.8-2.9) p-trend= 0.2	
				<u>NHL Subtype</u> T1= 0.8 T2= 1.2 T3= 1.8	<u>DLBCL</u> T2 OR= 1.0 (0.6-1.8) T3 OR= 1.1 (0.6-1.9) p-trend= 0.2	<u>FL</u> T2 OR= 0.8 (0.5-1.4) T3 OR= 0.9 (0.5-1.5) p-trend= 0.7	
				<u>t(14;18) status</u> T1= 0.8 T2= 1.2 T3= 1.8	<u>t(14;18) positive</u> T2 OR= 1.2 (0.5-2.5) T3 OR= 1.6 (0.8-3.3) p-trend= 0.2	<u>t(14;18) negative</u> T2 OR= 1.1 (0.6-1.8) T3 OR= 1.2 (0.7-2.0) p-trend= 0.2	
				Animal sources			
				Dietary nitrite intake from animal sources (median) (mg/1000 kcal) <u>Total NHL</u> Q1= 0.16 Q2= 0.23 Q3= 0.29 Q4= 0.41	<u>Total NHL</u> Q2 OR= 1.3 (0.8-1.9) Q3 OR= 1.0 (0.7-1.6) Q4 OR= 1.3 (0.8-1.9) p-trend= 0.3	<u>Total NHL (Men)</u> Q2 OR= 1.1 (0.6-1.9) Q3 OR= 0.9 (0.5-1.7) Q4 OR= 0.9 (0.5-1.6) p-trend= 0.9 <u>Total NHL (Women)</u> Q2 OR= 1.5 (0.8-2.7) Q3 OR= 1.1 (0.6-2.0) Q4 OR= 1.9 (1.0-3.4) p-trend= 0.1	
				<u>NHL Subtype</u> T1= 0.3 T2= 0.5 T3= 0.8	<u>DLBCL</u> T2 OR= 0.9 (0.5-1.7) T3 OR= 1.5 (0.8-2.7) p-trend= 0.2	<u>FL</u> T2 OR= 0.8 (0.5-1.3) T3 OR= 0.8 (0.5-1.4) p-trend= 0.9	
				<u>t(14;18) status</u> T1= 0.3 T2= 0.5 T3= 0.8	<u>t(14;18) positive</u> T2 OR= 1.5 (0.8-3.1) T3 OR= 1.1 (0.5-2.4) p-trend= 0.8	<u>t(14;18) negative</u> T2 OR= 0.9 (0.5-1.5) T3 OR= 1.0 (0.6-1.8) p-trend= 1.0	

Table 5. Lymphoma—Studies of Nitrite Exposure (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest[1,2]	Exposure assessment[3]	Exposure levels	Results[4] Risk ratio (95% CI)		Confounders / Covariates / Comments
Case-Control Studies (continued)							
Aschebrook-Kilfoy *et al.* (2013b) (continued) Nebraska	Population-based case-control 348 cases, 470 controls <u>Cases</u>[2] 348 NHL 106 FL 87 DLBCL 52 t(14;18) positive 104 t(14;18) negative <u>Controls</u> Controls in Nebraska were recruited through random digit dialing. Controls were frequency matched by gender and 5-year age groups.	NHL <u>NHL subtypes</u> DLBCL FL t(14;18) positive t(14;18) negative	Dietary intake of all sources was estimated using a validated FFQ. Nitrite concentrations were determined from the literature.	**Processed meat**			Models adjusted for age, gender, marital status, BMI, education, family history of cancer, vitamin C, E, and total energy intake. Farming status, physical activity, and use of hair dyes were examined but did not change risk estimates. Processed meats include baked ham (not including on sandwiches); bacon; sausage (including Italian, German, Polish, and breakfast); hot dogs; ham; bologna; and other lunch meats.
				Dietary nitrite intake from processed meat (median) (mg/1000 kcal) <u>Total NHL</u> Q1= 0.02 Q2= 0.06 Q3= 0.1 Q4= 0.21	<u>Total NHL</u> Q2 OR= 0.9 (0.6-1.3) Q3 OR= 1.4 (0.9-2.1) Q4 OR= 1.0 (0.6-1.5) p-trend= 0.9	<u>Total NHL(Men)</u> Q2 OR= 0.7 (0.3-1.2) Q3 OR= 1.0 (0.6-1.8) Q4 OR= 0.8 (0.4-1.4) p-trend= 0.3 <u>Total NHL (Women)</u> Q2 OR= 1.2 (0.7-2.1) Q3 OR= **1.9 (1.1-3.5)*** Q4 OR= 1.2 (0.7-2.4) p-trend= 0.2	
				<u>NHL Subtype</u> T1= 0 T2= 0.1 T3= 0.4	<u>DLBCL</u> T2 OR= 1.1 (0.6-2.0) T3 OR= 1.0 (0.5-1.8) p-trend= 0.6	<u>FL</u> T2 OR= 1.1 (0.7-1.9) T3 OR= 0.7 (0.4-1.3) p-trend= 0.3	
				t(14;18) status T1= 0 T2= 0.1 T3= 0.4	<u>t(14;18) positive</u> T2 OR= 1.4 (0.7-2.8) T3 OR= 0.7 (0.3-1.7) p-trend = 0.4	<u>t(14;18) negative</u> T2 OR= **1.9 (1.1-3.4)*** T3 OR= 0.9 (0.5-1.7) p-trend = 0.3	
				Plant sources			Models adjusted for age, gender, marital status, BMI, education, family history of cancer, vitamin C, E, and total energy intake. Farming status, physical activity, and use of hair dyes were examined but did not change risk estimates.
				Dietary nitrite intake from plant sources (median) (mg/1000 kcal) <u>Total NHL</u> Q1= 0.26 Q2= 0.34 Q3= 0.41 Q4= 0.53	<u>Total NHL</u> Q2 OR= 1.2 (0.8-1.8) Q3 OR= 1.2 (0.8-1.9) Q4 OR= 0.9 (0.6-1.4) p-trend= 0.9	<u>Total NHL(Men)</u> Q2 OR= 1.3 (0.8-2.2) Q3 OR= 1.0 (0.5-1.7) Q4 OR= 1.0 (0.5-1.9) p-trend= 0.9 <u>Total NHL (Women)</u> Q2 OR= 1.1 (0.6-2.1) Q3 OR= 1.7 (0.9-3.1) Q4 OR= 0.8 (0.4-1.6) p-trend= 0.8	
				<u>NHL Subtype</u> T1= 0.4 T2= 0.7 T3= 0.1	<u>DLBCL</u> T2 OR= 0.9 (0.5-1.6) T3 OR= 0.9 (0.5-1.7) p-trend= 0.7	<u>FL</u> T2 OR= 1.2 (0.7-1.9) T3 OR= 0.8 (0.5-1.4) p-trend= 0.8	
				<u>t(14;18) status</u> T1 = 0.4 T2 = 0.7 T3 = 0.1	<u>t(14;18) positive</u> T2 OR= 1.8 (0.9-3.8) T3 OR= 1.3 (0.6-3.0) p-trend = 0.2	<u>t(14;18) negative</u> T2 OR= 1.0 (0.6-1.8) T3 OR= 1.4 (0.8-2.4) p-trend = 0.1	

[1] **CLL/SLL**--Chronic lymphocytic leukemia/small lymphocytic lymphoma; **DLBCL**--Diffuse large B-cell lymphoma; **FL**--Follicular lymphoma; **MZBL**--Marginal zone B-cell lymphoma; **NHL**--Non-Hodgkin lymphoma; **TCL**--T/NK-cell lymphoma

[2] t(14;18) refers to one of the most common chromosomal translocations in NHL. Presence of the translocation, denoted as "t(14:18) positive," might characterize a more homogenous group than NHL cases as a whole.

[3] Exposure assessment methods primarily include food frequency questionnaires (FFQ)—a checklist of foods and beverages with a frequency response section for subjects to report how often each item was consumed over a specified period of time.

[4] Results for both genders unless otherwise specified.

***** Findings are statistically significant. 95% confidence interval excludes 1.0, p-value < 0.05

BMI—Body mass index; **CI**—Confidence Interval; **HR**—Hazard ratio; **NCI**—National Cancer Institute; **NIH**—National Institutes of Health; **OR**—Odds ratio; **Q**—Quartiles or quintiles; **T**—Tertiles

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Central Nervous System Cancers – Cohort Studies						
Michaud *et al.* (2009) Nurses' Health Study (NHS) I & II, Health Professionals Follow-Up Study (HPFS) US	Prospective cohort 230,655 participants (47,897 men in HPFS, 88,795 women in NHS I, 93,963 women in NHS II) ≤ 24 year follow-up (HPFS ≤ 18 y, NHS I ≤ 24 y, NHS II ≤ 14 y) 335 cases	Brain cancer -Glioma	Dietary intake estimated using food frequency questionnaires (FFQ) and published values of nitrite in foods adjusted over different time periods. Dietary information was collected at baseline and updated every four years. NHS I used a 61-item FFQ; NHS II and HPFS used a 131-item FFQ. Authors note that questions on meat intake were very similar on the two FFQs.	Dietary nitrite intake (mg/day) HPFS (Men) Q1 <1.4 Q2 1.4-<1.6 Q3 1.6- <1.8 Q4 1.8- <2.0 Q5 2.0+ NHS I (Women) Q1 <1.1 Q2 1.1-<1.3 Q3 1.3- <1.5 Q4 1.5- <1.7 Q5 1.7+ NHS II (Women) Q1 <1.7 Q2 1.7-<1.9 Q3 1.9- <2.1 Q4 2.1- <2.4 Q5 2.4+	Total nitrite Q2 RR=1.11 (0.72-1.71) Q3 RR=1.20 (0.84-1.71) Q4 RR=1.14 (0.73-1.78) Q5 RR=1.26 (0.89-1.79) p-trend=0.23	Adjusted for age and caloric intake.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
Central Nervous System Cancers – Cohort Studies (continued)							
Dubrow *et al.* (2010) National Institutes of Health (NIH)-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 545,770 participants (322,347 men, 223,423 women) 7.2 year follow-up (mean) 585 cases	Brain cancer -Glioma	Dietary intake reported using a 124-item FFQ and a follow-up questionnaire on meat intake. Nitrite concentrations were estimated using a National Cancer Institute (NCI) database of measured values of nitrite.	Dietary nitrite intake (median) (mg/1000 kcal/day) <u>Total nitrite</u> Q1= 0.45 Q2= 0.57 Q3= 0.65 Q4= 0.74 Q5= 0.90 <u>Animal sources</u> Q1= 0.10 Q2= 0.15 Q3= 0.20 Q4= 0.25 Q5= 0.36 <u>Plant sources</u> Q1=0.25 Q2= 0.34 Q3= 0.42 Q4= 0.51 Q5= 0.68	<u>Total nitrite</u> Q2 HR= 1.25 (0.96-1.63) Q3 HR= 1.03 (0.79-1.36) Q4 HR= 1.16 (0.89 -1.52) Q5 HR= **1.32 (1.01-1.71)*** p-trend= 0.089 <u>Animal sources</u> Q2 HR= 0.87 (0.68-1.13) Q3 HR= 0.91 (0.71-1.17) Q4 HR= 0.80 (0.62-1.04) Q5 HR = 0.90 (0.70–1.16) p-trend =0.45	<u>Plant sources</u> Q2 HR= **1.62 (1.24-2.12)*** Q3 HR= **1.36 (1.03-1.80)*** Q4 HR= **1.35 (1.01-1.79)*** Q5 HR= **1.59 (1.20-2.10)*** **p-trend= 0.028*** *Men* Q2 HR= **2.02 (1.47-2.77)*** Q3 HR= **1.61 (1.15-2.25)*** Q4 HR= **1.63 (1.16-2.30)*** Q5 HR= **2.04 (1.46-2.87)*** **p-trend= 0.0026*** *Women* Q2 HR= 0.84 (0.50-1.41) Q3 HR= 0.84 (0.51-1.40) Q4 HR= 0.79 (0.48-1.30) Q5 HR = 0.84 (0.51-1.36) p-trend = 0.57	Adjusted for gender, age, race, energy intake, education, height, and history of cancer at baseline.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Central Nervous System Cancers – Cohort Studies (continued)						
Dubrow *et al.* (2010) (continued) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 545,770 participants (322,347 men, 223,423 women) 7.2 year follow-up (mean) 585 cases	Brain cancer -Glioma	Dietary intake reported using a 124-item FFQ and a follow-up questionnaire on meat intake. Nitrite concentrations were estimated using a NCI database of measured values of nitrite.	Dietary nitrate and nitrite intake from processed meat (median) (mg/1000 kcal/day) <u>Processed meat</u> Q1= 0.11 Q2= 0.29 Q3= 0.49 Q4= 0.77 Q5= 1.43	*Combined nitrate and nitrite* <u>Processed meat sources</u> Q2 HR= 1.15 (0.88-1.50) Q3 HR= 1.24 (0.95-1.61) Q4 HR= 0.97 (0.74-1.28) Q5 HR= 1.04 (0.79-1.36) p-trend= 0.56	Exposure assessment included nitrate and nitrite, but did not evaluate nitrite only for processed meat. Adjusted for gender, age, race, energy intake, education, height, and history of cancer at baseline. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham and hotdogs (regular and poultry).
	Retrospective cohort 322,178 participants 318 cases	Brain cancer -Glioma	Dietary intake at ages 12 and 13 reported retrospectively using an abbreviated questionnaire focusing on meat intake. Nitrite concentrations were estimated using the 1965-1966 Household Food Consumption survey.	Dietary nitrate and nitrite intake from processed meat at age 12 and 13 (median) (mg/1000kcal/day) <u>Processed meat</u> Q1= 0.37 Q2= 0.99 Q3= 1.70 Q4= 2.51 Q5= 3.94	*Combined nitrate and nitrite* <u>Processed meat sources</u> Q2 HR= 1.05 (0.72-1.52) Q3 HR= 0.86 (0.58-1.28) Q4 HR= **1.47 (1.03-2.08)*** Q5 HR= 1.16 (0.80-1.67) p-trend= 0.16	Exposure assessment included nitrate and nitrite, but did not evaluate nitrite only for processed meat. Adjusted for gender, age, race, energy intake at baseline, education, height, history of cancer at baseline, energy intake at ages 12 – 13 years, body mass index (BMI) at age 18, and physical activity at ages 15 – 18. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham and hotdogs (regular and poultry). Authors examined exposures at ages 12-13 because early life exposures may affect cancer risk later in life.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
Thyroid Cancer – Cohort Studies							
Aschebrook-Kilfoy *et al.* (2011b) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 490,194 participants (292,125 men, 198,069 women) 7 year follow-up (mean) 370 cases	Thyroid cancer	Dietary intake reported using a 124-item, validated FFQ and a follow-up questionnaire on meat intake. Nitrite intake was estimated using the Pyramid Servings Database, a database of measured values of nitrite	Dietary nitrite intake (median) (mg/d) <u>Total Thyroid</u> Q1= 0.5 Q2= 0.6 Q3= 0.7 Q4= 0.7 Q5= 0.9	<u>Total Thyroid Cancer</u> Q2 RR= 1.28 (0.91-1.80) Q3 RR= 1.16 (0.81-1.65) Q4 RR= 1.17 (0.82 -1.67) Q5 RR= 1.32 (0.92-1.91) p-trend=0.26	*Men* Q2 RR= 1.36 (0.83-2.24) Q3 RR= 1.26 (0.75-2.12) Q4 RR= 0.86 (0.48-1.53) Q5 RR= 1.36 (0.78-2.37) p-trend= 0.26 *Women* Q2 RR= 1.09 (0.67-1.78) Q3 RR= 0.95 (0.58-1.58) Q4 RR= 1.28 (0.79-2.06) Q5 RR= 1.19 (0.71-1.98) p-trend= 0.40	Adjusted for entry age, gender, smoking status, calories, race, family history, education, BMI, physical activity, alcohol use, vitamin C, beta-carotene and folate. Dietary nitrite intake for total thyroid is reported here as provided by the authors. Authors appear to have rounded quintiles.
				<u>Thyroid subtypes</u> Q1= 0.5 Q2= 0.6 Q3= 0.7 Q4= 0.9	<u>Papillary thyroid cancer</u> *Men* Q2 RR= 1.12 (0.67-1.88) Q3 RR= 0.86 (0.49-1.51) Q4 RR= 0.81 (0.44-1.48) p-trend= 0.35 *Women* Q2 RR= 0.73 (0.43-1.23) Q3 RR= 0.88 (0.53-1.46) Q4 RR= 1.20 (0.73-1.98) p-trend= 0.35	<u>Follicular thyroid cancer</u> *Men* Q2 RR= 0.80 (0.22-2.95) Q3 RR= 1.75 (0.55-5.57) Q4 RR= 2.74 (0.86-8.77) **p-trend= 0.04*** *Women* Q2 RR= 0.82 (0.31-2.20) Q3 RR= 0.97 (0.37-2.55) Q4 RR= 0.63 (0.21 -1.95) p-trend= 0.49	Adjusted for entry age, gender, smoking status, calories, race, family history, education, BMI, physical activity, alcohol use, vitamin C, beta-carotene and folate.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Thyroid Cancer – Cohort Studies (continued)						
Aschebrook-Kilfoy *et al.* (2013a) Shanghai Women's Health Study Shanghai, China	Prospective cohort 73,317 women 9 year follow-up (mean) 164 cases	Thyroid cancer	Dietary intake of all sources was estimated using a validated FFQ. Nitrite concentrations were determined from the literature.	Dietary nitrite intake (median) (mg/1000 kcal) All sources Q1= 0.6 Q2= 0.8 Q3= 0.9 Q4= 1.1 Animal sources Q1= 0.1 Q2= 0.1 Q3= 0.1 Q4= 0.2 Processed meat sources Q1= 0.0 Q2= 0.0 Q3= 0.0 Q4= 0.1 Plant sources Q1= 0.5 Q2= 0.7 Q3= 0.8 Q4= 1.0	*Women* All sources Q2 RR= 1.64 (1.04-2.58) Q3 RR= 1.09 (0.65-1.85) Q4 RR= **2.05 (1.20-3.51)*** p-trend= 0.36 Animal sources Q2 RR= 1.03 (0.63-1.68) Q3 RR= 1.35 (0.84-2.16) Q4 RR= 1.59 (1.00-2.52) **p-trend= 0.02*** Processed meat sources Q2 RR= 0.77 (0.46-1.31) Q3 RR= 1.20 (0.81-1.75) Q4 RR= **1.96 (1.28-2.99)*** **p-trend <0.01*** Plant sources Q2 RR= 1.30 (0.83-2.02) Q3 RR= 1.15 (0.71-1.87) Q4 RR= 1.30 (0.76-2.4) p-trend= 0.70	Adjusted for age, total energy intake, education, history of thyroid disease, vitamin C, carotene and folate intake Processed meat included salted preserved meat and smoked meat/bacon. According to the authors, preserved meat sources (salted preserved meat and smoked meat/bacon) contributed approximately 1.2% of total nitrite intake. Dietary nitrite intake for animal and processed sources is reported here as provided by the authors. Authors appear to have rounded quartiles.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Lung Cancer – Cohort Studies						
Loh *et al.* (2011) European Prospective Investigation into Cancer and Nutrition (EPIC)– Norfolk Study Norfolk, United Kingdom	Prospective cohort 23,363 participants (10,783 men, 12,580 women) 11.4 year follow-up (mean) 235 cases	Lung cancer	Dietary intake was reported using a validated, country-specific FFQ. Nitrite concentrations were estimated using the EPIC-EURGAST (Gastric and Esophageal) study, which determined values from the published literature.	Per 0.5 mg/day nitrite intake (SD) (continuous)	HR= 0.97 (0.83-1.14) p-trend= 0.74	Multivariate model adjusted for age, gender, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity status, educational level, and menopausal status (in women).
Lung Cancer – Case-Control Studies						
Karimzadeh *et al.* (2012) Mazandaran province of Iran	Population-based case-control 40 cases, 40 controls <u>Cases</u> Cases were recruited from pulmonary wards of hospitals in three Iranian cities. <u>Controls</u> Controls were randomly selected from population registries in hospitals in three Iranian cities. Controls were frequency matched to cases by gender and five-year age groups.	Lung cancer	Dietary intake was estimated over previous 12 months using a FFQ and 10 year history of vitamin supplementation.	Dietary nitrate and nitrite intake (g/day) <u>Animal sources</u> Q1 ≤54.9 Q2 55 - 96.8 Q3 96.9 - 191 Q4 ≥191.1 <u>Plant sources</u> Q1 ≤ 113.35 Q2 113 - 206.2 Q3 206.3 - 396.6 Q4 ≥ 396.7	*Combined nitrate and nitrite* <u>Animal sources</u> Unadjusted Q2 OR= **7.8 (1.8- 32)*** Q3 OR= **9.9 (2.3- 42)*** Q4 OR= 3.8 (0.93- 15.7) Adjusted OR= 2.7 (0.13-0.96) <u>Plant sources</u> Unadjusted Q2 OR= 0.29 (0.07-1.06) Q3 OR= 0.53 (0.15-1.91) Q4 OR= 0.53 (0.15-1.91) Adjusted OR= 0.6 (0.41-2.6)	Exposure assessment includes nitrate and nitrite, but does not evaluate nitrite alone. Adjusted for education, residential area, length of smoking, daily cigarette smoking amount, traditional oven baking of bread, consumption of traditional bread, family history of cancer, vitamin C, A and E supplement intake. Unadjusted ORs included due to error of CI reported for animal source adjusted OR. The study's CIs may not have been correctly calculated and/or reported.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Breast Cancer – Cohort Studies						
Loh *et al.* (2011) EPIC– Norfolk Study Norfolk, United Kingdom	Prospective cohort 23,363 participants (10,783 men, 12,580 women) (Age: 40 - 79 years) 11.4 year follow-up (mean) 423 cases	Breast cancer	Dietary intake was reported using a validated, country-specific FFQ. Nitrite concentrations were estimated using the EPIC-EURGAST study, which determined values from the published literature.	Per 0.5 mg/day nitrite intake (SD) (continuous)	HR= 1.08 (0.96-1.22) p-trend= 0.22	Multivariate model adjusted for age, gender, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity status, educational level, and menopausal status (in women).
Inoue-Choi *et al.* (2012) Iowa Women's Health Study (IWHS) Iowa	Prospective cohort 34,388 women (Age: 52–71 years) ≤ 19 years 2,875 cases	Breast cancer	Dietary intake of all foods was estimated using the Harvard FFQ. Nitrite concentrations were determined from the literature.	Dietary nitrite intake (mg/day) (median) Q1= 0.6 Q2= 0.9 Q3= 1.1 Q4= 1.4 Q5= 1.8	*Women* Q2 HR= 1.12 (0.98-1.28) Q3 HR= 1.06 (0.92-1.22) Q4 HR= 1.10 (0.94-1.28) Q5 HR= 1.05 (0.86-1.29) p-trend= 0.28	Adjusted for age, BMI, waist-hip-ratio, education, smoking, alcohol intake, family history of breast cancer, age at menopause, age at first live birth, estrogen use, total energy intake, total intake of folate, vitamin C, vitamin E, flavonoids, and cruciferous vegetable and red meat intake. Approximately 63% of dietary nitrite intake was from plant sources.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
Pancreatic Cancer – Cohort Studies							
Aschebrook-Kilfoy *et al.* (2011a) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 303,156 participants (176,842 men, 126,314 women) 10 year follow-up (mean) 1,728 cases	Pancreatic cancer	Dietary intake reported using a 124-item FFQ and a follow-up questionnaire on meat intake. Nitrite concentrations were determined from the literature.	Dietary intake of nitrite (median) (mg/1000 kcal) <u>Total nitrite</u> Q1= 0.45 Q2= 0.57 Q3= 0.65 Q4= 0.74 Q5= 0.9	<u>Total nitrite</u> Q2 HR= 0.99 (0.86-1.16) Q3 HR= 0.92 (0.79-1.08) Q4 HR= 0.97 (0.83-1.14) Q5 HR= 0.92 (0.78-1.08) p-trend= 0.31	*Men* Q2 HR= 1.03 (0.86-1.24) Q3 HR= 1.00 (0.82-1.21) Q4 HR= 0.99 (0.81-1.20) Q5 HR= 0.97 (0.79-1.20) p-trend= 0.67 *Women* Q2 HR= 0.93 (0.72-1.19) Q3 HR= 0.78 (0.60-1.02) Q4 HR= 0.92 (0.72-1.19) Q5 HR= 0.81 (0.61-1.06) p-trend= 0.18	Adjusted for age, race, total energy intake, smoking status, family history of cancer, family history of diabetes, BMI, and intakes of saturated fat, folate, and vitamin C.
				<u>Animal sources</u> Q1= 0.1 Q2= 0.15 Q3= 0.2 Q4= 0.25 Q5= 0.36	<u>Animal sources</u> Q2 HR= 1.07 (0.92-1.25) Q3 HR= 1.11 (0.95-1.30) Q4 HR= 1.11 (0.95-1.30) Q5 HR= 0.96 (0.82-1.13) p-trend= 0.41	*Men* Q2 HR= 1.16 (0.94-1.44) Q3 HR= 1.16 (0.94-1.43) Q4 HR= 1.21 (0.98-1.48) Q5 HR= 0.99 (0.80-.123) p-trend= 0.41 *Women* Q2 HR= 0.97 (0.76-1.23) Q3 HR= 1.06 (0.83-1.34) Q4 HR= 0.99 (0.77-1.27) Q5 HR= 0.94 (0.72-1.22) p-trend= 0.69	

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
Pancreatic Cancer – Cohort Studies (continued)							
Aschebrook-Kilfoy *et al.* (2011a) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 303,156 participants (176,842 men, 126,314 women) 10 year follow-up (mean) 1,728 cases	Pancreatic cancer	Dietary intake reported using a 124-item FFQ and a follow-up questionnaire on meat intake. Nitrite concentrations were determined from the literature.	<u>Plant sources</u> Q1= 0.25 Q2= 0.34 Q3= 0.42 Q4= 0.51 Q5= 0.68	<u>Plant sources</u> Q2 HR= 1.02 (0.88-1.18) Q3 HR= 0.87 (0.74-1.01) Q4 HR= 0.99 (0.84-1.16) Q5 HR= 0.91 (0.76-1.09) p-trend= 0.32	*Men* Q2 HR= 0.98 (0.82-1.16) Q3 HR= 0.85 (0.70-1.03) Q4 HR= 0.95 (0.78-1.17) Q5 HR= 0.94 (0.75-1.18) p-trend= 0.61 *Women* Q2 HR= 1.12 (0.86-1.47) Q3 HR= 0.91 (0.69-1.21) Q4 HR= 1.06 (0.80-1.39) Q5 HR= 0.89 (0.65-1.20) p-trend= 0.29	Adjusted for age, race, total energy intake, smoking status, family history of cancer, family history of diabetes, BMI, and intakes of saturated fat, folate, and vitamin C.
				Dietary intake of nitrate and nitrite from processed meat (median) (mg/1000 kcal) Q1= 0.04 Q2= 0.10 Q3= 0.18 Q4= 0.28 Q5= 0.48	*Combined nitrate and nitrite* <u>Processed meat</u> Q2 HR= 1.13 (0.97-1.32) Q3 HR= 1.00 (0.85-1.18) Q4 HR= 1.07 (0.91-1.26) Q5 HR= 1.05 (0.89-1.23) p-trend= 0.96	*Men* Q2 HR= 1.08 (0.86-1.35) Q3 HR= 1.05 (0.84-1.31) Q4 HR= 1.16 (0.94-1.44) Q5 HR= 1.13 (0.91-1.41) p-trend= 0.26 *Women* Q2 HR= 1.23 (0.99-1.52) Q3 HR= 0.93 (0.76-1.24) Q4 HR= 0.90 (0.72-1.21) Q5 HR= 1.09 (0.68-1.20) p-trend= 0.63	Exposure assessment includes nitrate and nitrite, but does not evaluate nitrite only for processed meat. Adjusted for age, race, total energy intake, smoking status, family history of cancer, family history of diabetes, BMI, and intakes of saturated fat, folate, and vitamin C. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham and hotdogs (regular and poultry).

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Pancreatic Cancer – Cohort Studies						
Aschebrook-Kilfoy *et al.* (2011a) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Retrospective cohort 303,156 participants (176,842 men, 126,314 women) 1,055 cases	Pancreatic cancer	Dietary intake at ages 12 and 13 was reported retrospectively using a 37-item abbreviated FFQ and a follow-up questionnaire on meat intake Nitrite concentrations were determined from the literature.	Dietary intake at ages 12 and 13 of nitrate and nitrite from processed meat (median) (mg/1000kcal) Q1= 0.21 Q2= 0.65 Q3= 1.19 Q4= 1.91 Q5= 3.33	*Combined nitrate and nitrite* <u>Processed meat</u> Q2 HR= 1.16 (0.96-1.41) Q3 HR= 1.09 (0.89-1.32) Q4 HR= 1.18 (0.97-1.44) Q5 HR= 1.11 (0.91-1.36) p-trend= 0.46 *Men* Q2 HR= 1.39 (1.10-1.76) Q3 HR= 1.25 (0.97-1.60) Q4 HR= **1.46 (1.13-1.87)*** Q5 HR= 1.32 (0.99-1.76) p-trend= 0.11 *Women* Q2 HR= 1.01 (0.77-1.33) Q3 HR= 0.89 (0.66-1.20) Q4 HR= 1.06 (0.78-1.44) Q5 HR= 0.94 (0.67-1.32) p-trend= 0.83	Exposure assessment includes nitrate and nitrite, but does not evaluate nitrite only for processed meat. Adjusted for age, race, total energy intake, smoking status, family history of cancer, family history of diabetes, BMI, and intakes of saturated fat, folate, and vitamin C. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham and hotdogs (regular and poultry). Authors examined exposures at ages 12-13 because early life exposures may affect cancer risk later in life.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Liver Cancer – Cohort Studies						
Freedman *et al.* (2010) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 495,006 participants (295,332 men, 199,674 women) 7-8 year follow-up 338 cases	Liver cancer (Hepatocellular carcinoma)	Dietary intake reported using a 124-item FFQ and a follow-up questionnaire on meat intake. Nitrite intake from processed meats was estimated using a NCI database of measured values of nitrite.	Dietary intake of nitrite (mg/1000 kcal) Q1 0 - 0.02 Q2 0.02 - 0.05 Q3 0.05 - 0.08 Q4 0.08 - 0.14 Q5 ≥ 0.14	Q2 HR= 1.31 (0.79-2.16) Q3 HR= 1.61 (0.99-2.61) Q4 HR= 1.23 (0.74-2.03) Q5 HR= 0.93 (0.55-1.57) p-trend= 0.15	Adjusted for age, gender, alcohol, cigarette smoking, diabetes, education, fruit intake, vegetable intake, marital status, race and/or ethnicity, total energy from nonalcoholic sources, and usual physical activity throughout the day.
				Per 0.1 mg (continuous)	HR= 0.90 (0.77-1.06)	
Liver Cancer – Ecologic Studies						
Mitacek *et al.* (2008) Thailand	Ecologic study Geographic distribution of cancer by region in relation to estimated dietary intake in these regions Exposure assessment: 212 males 255 females	Liver cancer	Dietary intake assessed using 97-item FFQ. Used colorimetric assay to measure levels of nitrite in foods.	Mean nitrite intake (mg/day) by geographic area: North 9.5 ± 0.38 Northeast 8.8 ± 0.35 Central 6.2 ± 0.25 South 4.5 ± 0.18	Liver cancer: Age standardized incidence rate per 100,000 by region (e.g., 1995-1997) North: Male 23.55, Female 11.55 Northeast: Male 88.0, Female 35.4 Central: Male 14.4, Female 3.9 South: Male 6.6, Female 1.5	Nitrite intake estimates were based on current diet of people from each region, while cancer incidence data came from earlier time periods. Mean daily intake of nitrite varied by region ($p<0.0001$), based on individuals who completed exposure assessment portion of study. Liver cancer incidence rates also varied by region. However, authors did not present any analysis of nitrite intake in relation to reported cancer incidence rates.
Ovarian Cancer – Cohort Studies						
Loh *et al.* (2011) EPIC– Norfolk Study Norfolk, United Kingdom	Prospective cohort 12,580 women (Age: 40 - 79 years) 11.4 year follow-up (mean) 80 cases	Ovarian cancer	Dietary intake was reported using a validated, country-specific FFQ. Nitrite concentrations were estimated using the EPIC-EURGAST study, which determined values from the published literature.	Per 0.5 mg/day nitrite intake (SD) (continuous)	HR= 0.79 (0.58-1.07) p-trend= 0.12	Multivariate model adjusted for age, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity status, educational level, and menopausal status.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
Ovarian Cancer – Cohort Studies (continued)							
Aschebrook-Kilfoy *et al.* (2012) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 151,316 women (50 – 71 years) 10 year follow-up (mean) <u>Cases</u> 709 Epithelial ovarian cancer 374 Serous 66 Endometriod 35 Mucinous 234 Other	Epithelial ovarian cancer Epithelial ovarian cancer subtypes (Serous, Endometriod, Mucinous)	Dietary intake reported using a validated, 124-item FFQ. Nitrite concentrations were estimated from the literature.	Dietary intake of nitrite (median) (mg/1000 kcal) <u>Total nitrite</u> Q1= 0.47 Q2= 0.59 Q3= 0.67 Q4= 0.76 Q5= 0.93 <u>Animal sources</u> Q1= 0.09 Q2= 0.14 Q3= 0.18 Q4= 0.24 Q5= 0.33 <u>Processed meat</u> Q1= 0.01 Q2= 0.03 Q3= 0.05 Q4= 0.07 Q5= 0.14 <u>Plant sources</u> Q1= 0.27 Q2= 0.37 Q3= 0.45 Q4= 0.54 Q5= 0.73	*Women* All Epithelial Ovarian <u>Total nitrite</u> Q2 HR= 1.07 (0.84-1.36) Q3 HR= 1.18 (0.93-1.49) Q4 HR= 0.99 (0.77-1.26) Q5 HR= 1.18 (0.93-1.50) p-trend= 0.31 <u>Animal sources</u> Q2 HR= 1.13 (0.89-1.44) Q3 HR= 1.11 (0.87-1.41) Q4 HR= 1.1 (0.86-1.41) Q5 HR= **1.34 (1.05-1.69)*** **p-trend= 0.02*** <u>Processed meat</u> Q2 HR= 0.85 (0.67-1.08) Q3 HR= 0.93 (0.74-1.18) Q4 HR= 1.06 (0.84-1.34) Q5 HR= 0.97 (0.76-1.23) p-trend= 0.63 <u>Plant sources</u> Q2 HR= 1.06 (0.84-1.34) Q3 HR= 1.1 (0.87-1.39) Q4 HR= 0.96 (0.75-1.22) Q5 HR= 1.03 (0.81-1.32) p-trend= 0.93	Endometriod <u>Total nitrite</u> Q2 HR= 1.47 (0.69-3.15) Q3 HR= 1.03 (0.45-2.33) Q4 HR= 1.01 (0.45-2.31) Q5 HR= 1.15 (0.51-2.56) p-trend= 0.93 <u>Animal sources</u> Q2 HR= 1.49 (0.64-3.51) Q3 HR=1.86 (0.81-4.25) Q4 HR= 2.02 (0.89-4.59) Q5 HR= 1.33 (0.54-3.26) p-trend= 0.59 <u>Processed meat</u> Q2 HR= 0.66 (0.29-1.54) Q3 HR= 0.82 (0.37-1.83) Q4 HR= 1.52 (0.75-3.07) Q5 HR= 0.93 (0.42-2.07) p-trend= 0.61 <u>Plant sources</u> Q2 HR= 1.18 (0.55-2.54) Q3 HR=1.00 (0.45-2.21) Q4 HR= 0.91 (0.40-2.04) Q5 HR= 1.02 (0.46-2.26) p-trend= 0.84	Adjusted for age, race, total energy intake, family history of cancer, BMI, education, smoking status, menopausal status, parity, age at menarche, and total daily dietary vitamin C intake. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham and hotdogs (regular and poultry)

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
Ovarian Cancer – Cohort Studies (continued)							
Aschebrook-Kilfoy *et al.* (2012) (continued) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 151,316 women (50 – 71 years) 10 year follow-up (mean) <u>Cases</u> 709 Epithelial ovarian cancer 374 Serous 66 Endometriod 35 Mucinous 234 Other	Epithelial ovarian cancer Epithelial ovarian cancer subtypes (Serous, Endometriod, Mucinous)	Dietary intake reported using a validated, 124-item FFQ. Nitrite concentrations were estimated from the literature.	Dietary intake of nitrite (median) (mg/1000 kcal) <u>Total nitrite</u> Q1= 0.47 Q2= 0.59 Q3= 0.67 Q4= 0.76 Q5= 0.93 <u>Animal sources</u> Q1= 0.09 Q2= 0.14 Q3= 0.18 Q4= 0.24 Q5= 0.33 <u>Processed meat</u> Q1= 0.01 Q2= 0.03 Q3= 0.05 Q4= 0.07 Q5= 0.14 <u>Plant sources</u> Q1= 0.27 Q2= 0.37 Q3= 0.45 Q4= 0.54 Q5= 0.73	*Women* Serous <u>Total nitrite</u> Q2 HR= 1.04 (0.74-1.46) Q3 HR= 1.35 (0.98-1.86) Q4 HR= 0.96 (0.68-1.37) Q5 HR= 1.22 (0.88-1.71) p-trend= 0.36 <u>Animal sources</u> Q2 HR= 0.79 (0.57-1.12) Q3 HR= 0.92 (0.66-1.27) Q4 HR= 1.00 (0.73-1.38) Q5 HR= 1.05 (0.77-1.44) p-trend= 0.34 <u>Processed meat</u> Q2 HR= 0.75 (0.54-1.05) Q3 HR= 0.97 (0.71-1.32) Q4 HR= 0.98 (0.71-1.34) Q5 HR= 0.82 (0.59-1.15) p-trend= 0.57 <u>Plant sources</u> Q2 HR= 1.06 (0.76-1.47) Q3 HR= 1.03 (0.74-1.44) Q4 HR= 1.04 (0.75-1.45) Q5 HR= 1.00 (0.71-1.40) p-trend= 0.89	Mucinous <u>Total nitrite</u> Q2 HR= 0.76 (0.30-1.94) Q3 HR= 0.48 (0.16-1.40) Q4 HR= 0.86 (0.35-2.14) Q5 HR= 0.29 (0.08-1.09) p-trend= 0.1 <u>Animal sources</u> Q2 HR= 1.66 (0.48-5.68) Q3 HR= 1.83 (0.55-6.15) Q4 HR= 1.6 (0.46-5.52) Q5 HR= 1.99 (0.60-6.58) p-trend= 0.37 <u>Processed meat</u> Q2 HR= 0.59 (0.14-2.47) Q3 HR= 1.55 (0.50-4.80) Q4 HR= 1.34 (0.44-4.32) Q5 HR= 2.24 (0.76-6.61) **p-trend= 0.04*** <u>Plant sources</u> Q2 HR= 0.77 (0.30-1.96) Q3 HR= 0.58 (0.21-1.62) Q4 HR= 0.69 (0.26-1.85) Q5 HR= 0.41 (0.12-1.36) p-trend= 0.15	Adjusted for age, race, total energy intake, family history of cancer, BMI, education, smoking status, menopausal status, parity, age at menarche, and total daily dietary vitamin C intake. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham and hotdogs (regular and poultry)

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Ovarian Cancer – Cohort Studies (continued)						
Inoue-Choi *et al.* (2015) Iowa Women's Health Study (IWHS) Iowa	Prospective cohort 28,555 women (55 – 69 years) ≥ 24 year follow-up 315 cases	Epithelial ovarian cancer	Dietary intake was estimated using a 126-item FFQ. Nitrite levels were determined from the literature.	Dietary nitrite intake (median) (mg/day) <u>Total nitrite</u> Q1 0.11 - 0.80 Q2 0.81 - 1.02 Q3 1.021 - 1.23 Q4 1.239 - 1.53 Q5 1.537 - 7.13 <u>Animal sources</u> Q1 0 - 0.26 Q2 0.26 - 0.36 Q3 0.36 - 0.47 Q4 0.47 - 0.61 Q5 0.61 - 3.47 <u>Processed meat sources</u> Q1 0 Q2 > 0 - 0.09 Q3 0.1 - 0.19 Q4 ≥ 0.2 <u>Plant sources</u> Q1 0.04 - 0.47 Q2 0.47 - 0.61 Q3 0.61 - 0.76 Q4 0.76 - 0.98 Q5 0.98 - 6.39	*Women* <u>Total nitrite</u> Q2 HR= 0.80 (0.53-1.21) Q3 HR= 1.04 (0.68-1.59) Q4 HR= 1.14 (0.71-1.82) Q5 HR= 1.03 (0.58-1.84) p-trend= 0.50 <u>Animal sources</u> Q2 HR= 0.72 (0.48-1.08) Q3 HR= 1.39 (0.96-2.02) Q4 HR= 0.98 (0.64-1.50) Q5 HR= 1.18 (0.72-1.91) p-trend= 0.25 <u>Processed meat sources</u> Q2 HR= 1.01 (0.74-1.38) Q3 HR= 1.27 (0.80-2.01) Q4 HR= 1.65 (0.93-2.94) **p-trend= 0.04*** <u>Plant sources</u> Q2 HR= 0.82 (0.56-1.19) Q3 HR= 0.77 (0.52-1.14) Q4 HR=0.86 (0.57-1.29) Q5 HR= 0.77 (0.48-1.24) p-trend= 0.54	Adjusted for age, BMI, family history of ovarian cancer, number of live births, age at menarche, age at menopause, age at first live birth, oral contraceptive use, estrogen use, history of unilateral oophorectomy and total energy intake. Additionally, adjusted for logarithmically transformed values of cruciferous vegetable and red meat intake. Authors did not define processed meats in their analysis.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Ovarian Cancer – Cohort Studies (continued)						
Inoue-Choi *et al.* (2015) (continued) IWHS Iowa	Prospective cohort 28,555 women (55 – 69 years) ≥ 24 year follow-up 315 cases	Epithelial ovarian cancer	Dietary intake was estimated using a 126-item FFQ. Nitrite levels were determined from the literature.	Per 0.1 mg/day nitrite intake (continuous)	Total intake HR= 0.99 (0.95-1.03) Animal sources HR= 1.06 (1.00-1.13) Processed meats sources HR= **1.12 (1.04-1.20)*** Plant sources HR= 0.97 (0.92-1.01)	Adjusted for age, BMI, family history of ovarian cancer, number of live births, age at menarche, age at menopause, age at first live birth, oral contraceptive use, estrogen use, history of unilateral oophorectomy and total energy intake. Additionally, adjusted for logarithmically transformed values of cruciferous vegetable and red meat intake. Authors did not define processed meats in their analysis.
Urinary Tract Cancer – Cohort Studies						
Ferrucci *et al.* (2010) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 300,933 participants 7 year follow-up 854 cases	Transitional cell bladder cancer	Dietary intake was estimated using a validated, 124-item FFQ and a follow-up questionnaire on meat intake. Nitrite intake from processed meat was estimated using a database of measured values.	Dietary nitrite intake (median) (mg/1000 kcal) Total nitrite Q1= 0.46 Q2= 0.57 Q3= 0.65 Q4= 0.74 Q5= 0.91 Animal sources Q1= 0.10 Q2= 0.15 Q3= 0.20 Q4= 0.25 Q5= 0.36	Total nitrite Q2 HR= 1.17 (0.90-1.45) Q3 HR= 1.10 (0.89-1.37) Q4 HR=1.14 (0.91-1.44) Q5 HR= **1.28 (1.02-1.61)*** p-trend= 0.06 Animal sources Q2 HR= 0.85 (0.67-1.07) Q3 HR= 1.15 (0.92-1.43) Q4 HR=1.04 (0.83-1.31) Q5 HR= 1.09 (0.87-1.36) p-trend= 0.21	Adjusted for age, gender, smoking, intake of fruit, vegetables, beverages, and total energy.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Urinary Tract Cancer – Cohort Studies (continued)						
Ferrucci *et al.* (2010) (continued) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 300,933 participants 7 year follow-up 854 cases	Transitional cell bladder cancer	Dietary intake was estimated using a validated, 124-item food frequency questionnaire and a follow-up questionnaire on meat intake. Nitrite intake from processed meat was estimated using a database of measured values.	Dietary nitrite intake (median) (mg/1000 kcal) <u>Processed meat sources</u> Q1= 0.01 Q2= 0.03 Q3= 0.06 Q4= 0.10 Q5= 0.19 <u>Plant sources</u> Q1= 0.25 Q2= 0.35 Q3= 0.42 Q4= 0.51 Q5= 0.69	<u>Processed meat sources</u> Q2 HR= 1.15 (0.90–1.46) Q3 HR= 1.08 (0.85–1.37) Q4 HR= **1.39 (1.11–1.74)*** Q5 HR= 1.07 (0.85-1.36) p-trend= 0.79 <u>Plant sources</u> Q2 HR= 0.97 (0.79-1.19) Q3 HR= 0.97 (0.78-1.21) Q4 HR= 1.05 (0.84-1.33) Q5 HR= 1.16 (0.90-1.50) p-trend= 0.18	Adjusted for age, gender, smoking, intake of fruit, vegetables, beverages, and total energy. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham and hotdogs (regular and poultry)
Urinary Tract Cancer – Case-Control Studies						
Ward *et al.* (2007a) Iowa Cancer Registry Iowa	Population-based case-control 2,840 participants 406 cases 2,434 controls <u>Cases</u> Cases were ascertained through the Iowa Cancer Registry <u>Controls</u> Controls were frequency matched by gender, race, and 5-year age groups.	Renal cell carcinoma	Dietary intake was estimated using a 55-item FFQ completed by proxy or participant. Nitrite concentrations were determined from the literature.	Dietary nitrite intake (mg/day) <u>Total nitrite</u> Q1 <0.70 Q2 0.70-0.93 Q3 0.94-1.25 Q4 ≥1.26 <u>Animal sources</u> Q1 <0.18 Q2 0.18-0.28 Q3 0.29-0.47 Q4 ≥0.48	<u>Total nitrite</u> Q2 OR= 0.82 (0.58-1.17) Q3 OR= 0.84 (0.57-1.22) Q4 OR= 0.82 (0.50-1.33) <u>Animal sources</u> Q2 OR= 1.37 (0.95-1.95) Q3 OR= 1.24 (0.85-1.83) Q4 OR= 1.00 (0.63-1.59)	Total nitrite adjusted for age, gender, sodium, and total calories. Animal sources adjusted for age, gender, sodium, total fat, and total calories.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Urinary Tract Cancer – Case-Control Studies (continued)						
Catsburg *et al.* (2014) Los Angeles Bladder Cancer Study Los Angeles County, California	Population-based case-control 1,660 cases, 1,586 controls <u>Cases</u> Identified through the Surveillance, Epidemiology and End Results (SEER) cancer registry of Los Angeles County <u>Controls</u> Controls were recruited from neighborhood of case. Controls were matched by age, gender, and race/ethnicity.	Transitional cell carcinoma of the bladder	Dietary intake was estimated using a 40-item FFQ. Nitrite concentrations were estimated using a database of measured values from the US Department of Agriculture.	Dietary nitrite intake (μg/day) Q1 ≤ 234 Q2 253 - 311 Q3 312 - 400 Q4 401 - 532 Q5 ≥ 533	<u>All subjects</u> Q2 OR= 0.75 (0.59-0.94) Q3 OR= 0.81 (0.63-1.03) Q4 OR= 0.82 (0.64-1.07) Q5 OR= 0.89 (0.66-1.20) p-trend= 0.921 <u>Never smokers</u> Q2 OR= 0.81 (0.52-1.27) Q3 OR= 1.03 (0.65-1.62) Q4 OR= 1.19 (0.71-1.99) Q5 OR= 1.56 (0.85-2.87) p-trend= 0.063 <u>Ever smokers</u> Q2 OR= 0.72 (0.54-0.95) Q3 OR= 0.74 (0.55-0.99) Q4 OR= 0.73 (0.54-0.98) Q5 OR= 0.77 (0.54-1.08) p-trend=0.341	Adjusted for BMI, race/ethnicity, education, total vegetable intake, vitamin A intake, vitamin C intake, carotenoid intake, and total servings of food per day. All and Ever smokers further adjusted for smoking duration and smoking intensity (cigarettes per day). Processed meats include fried bacon, ham, salami, pastrami, corned beef, bologna, other lunch meats, hot dogs and Polish sausage.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)	Confounders / Covariates / Comments
Prostate Cancer – Cohort Studies						
Sinha *et al.* (2009) NIH-AARP Diet and Health Study Six states and two metropolitan areas in the United States	Prospective cohort 175,343 men 9 year follow-up 10,313 Incident cases 1,102 Advanced cases 419 Fatal cases	Prostate cancer Advanced prostate cancer Fatal prostate cancer	Dietary intake was estimated using a 124-item FFQ and a follow-up questionnaire on meat intake. Nitrite intake from meat was estimated using a database of measured values.	Dietary intake of nitrite from meat (median) (mg/1000 kcal) Q1= 0.017 Q2= 0.043 Q3= 0.073 Q4= 0.117 Q5= 0.215	*Men* <u>Total incident cases</u> Q2 HR= 1.02 (0.96-1.08) Q3 HR= 1.01 (0.95-1.08) Q4 HR= 1.00 (0.94-1.07) Q5 HR= 1.05 (0.99-1.12) p-trend= 0.14 <u>Advanced prostate cancer</u> Q2 HR= 1.07 (0.89-1.30) Q3 HR= 1.04 (0.86-1.27) Q4 HR= 1.02 (0.84-1.25) Q5 HR= **1.24 (1.02-1.51)*** **p-trend= 0.03*** <u>Fatal prostate cancer</u> Q2 HR= 0.92 (0.67-1.25) Q3 HR= 0.92 (0.67-1.25) Q4 HR= 0.95 (0.70-1.30) Q5 HR= 0.96 (0.70-1.32) p-trend= 0.97	Multivariate model adjusted for age, total energy intake, race/ethnicity, education, marital status, family history of prostate cancer, undergoing prostate-specific antigen testing in the past 3 years, history of diabetes, BMI, smoking history, frequency of vigorous physical activity, and intakes of alcohol, calcium, tomatoes, α-linolenic acid, vitamin E, zinc, and selenium. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham and hotdogs (regular and poultry)
Loh *et al.* (2011) EPIC– Norfolk Study Norfolk, United Kingdom	Prospective cohort 10,783 men (Age: 40 - 79 years) 11.4 year follow-up (mean) 461 cases	Prostate cancer	Dietary intake was reported using a validated, country-specific FFQ. Nitrite concentrations were estimated using the EPIC-EURGAST study, which determined values from the published literature.	Per 0.5 mg/day nitrite intake (SD) (continuous)	HR= 0.90 (0.81-1.01) p-trend= 0.08	Multivariate model adjusted for age, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity status, and educational level.

Table 6. Studies of Nitrite Exposure and Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer (continued)

Study / Location	Study Design / Sample sizes	Outcomes of interest	Exposure assessment[1]	Exposure levels	Results[2] Risk ratio (95% CI)		Confounders / Covariates / Comments
All Cancer – Cohort Studies							
Loh *et al.* (2011) EPIC—Norfolk Study Norfolk, United Kingdom	Prospective cohort 23,363 participants (10,783 men, 12,580 women) 11.4 year follow-up (mean) 3,268 cases	All cancer	Dietary intake was reported using a validated, country-specific FFQ. Nitrite concentrations were estimated using the EPIC-EURGAST study, which determined values from the published literature.	Dietary nitrite intake (mean) (mg/day) Q1= 1.17 Q2= 1.41 Q3= 1.63 Q4= 1.69	<u>All cancer</u> Q2 HR= 1.02 (0.92-1.13) Q3 HR= 0.96 (0.86-1.07) Q4 HR= 1.02 (0.90-1.14) p-trend= 0.91	*Men* Q2 HR= 0.98 (0.85-1.14) Q3 HR=0.93 (0.80-1.09) Q4 HR= 0.98 (0.83-1.16) p-trend= 0.75 *Women* Q2 HR= 1.06 (0.92-1.22) Q3 HR= 0.98 (0.84-1.14) Q4 HR= 1.05 (0.89-1.25) p-trend= 0.83	Multivariate model adjusted for age, gender, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity status, educational level, and menopausal status (in women).

[1] Exposure assessment methods primarily include food frequency questionnaires (FFQ)—a checklist of foods and beverages with a frequency response section for subjects to report how often each item was consumed over a specified period of time.

[2] Results for both genders unless otherwise specified.

***** Findings are statistically significant. 95% confidence interval excludes 1.0, p-value < 0.05

BMI—Body mass index; **CI**—Confidence interval; **EPIC**—European Prospective Investigation into Cancer and Nutrition; **EURGAST—**Gastric and Esophageal project of European Prospective Investigation into Cancer and Nutrition; **HPFS**—Health Professionals Follow-Up Study; **IWHS**—Iowa Women's Health Study; **HR**—Hazard ratio; **NCI**- National Cancer Institute; **NHS**—Nurses' Health Study (I or II); **NIH**—National Institutes of Health; **OR**—Odds ratio; **Q**—Quartile/quintile; **RR**—Risk ratio; **SD**—Standard deviation; **SEER**--Surveillance, Epidemiology and End Results

3.1.4 2015 IARC Review of Processed Meat

As noted above, the 2010 IARC monograph specifically did not include studies that only evaluated consumption of cured meat and risk for cancer, since such investigations "do not represent complete dietary nitrite intake". A 2015 IARC Working Group (Bouvard *et al*. (2015) (Attachment 2) concluded:

> "Consumption of processed meat" is " 'carcinogenic to humans' (Group 1) on the basis of sufficient evidence for colorectal cancer. Additionally, a positive association with the consumption of processed meat was found for stomach cancer." (Bouvard *et al*., 2015)

The IARC Monograph describing the evidence and basis for those findings has not been published, as of August 2016.

For purposes of the IARC 2015 review, processed meat was defined as "meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavor or improve preservation."

With regard to processed meat, Bouvard *et al*. (2015) notes that "processing, such as curing and smoking, can result in formation of carcinogenic chemicals, including N-nitroso-compounds (NOC) and polycyclic aromatic hydrocarbons (PAH)."

3.2 Carcinogenicity Studies in Animals

IARC (2010) reviewed 53 studies in experimental animals of the carcinogenicity of nitrite in combination with amines or amides and two studies of nitrite in combination with fish meal, a complex mixture of amines and amides.

Thirteen different amines were tested in combination with nitrite in the set of studies reviewed by IARC. Positive tumor findings, defined here as statistically significant increases (or biologically significant increases for rare tumors) as compared to (i) untreated or vehicle controls, and (ii) animals treated with nitrite alone, and (iii) animals treated with the amine alone, were reported in at least one study for six of the thirteen amines. For three other amines, increases in tumor incidence were observed when the amine was administered in combination with nitrite; however, definitive conclusions could not be reached, since the studies lacked one or two of the three necessary comparator groups. Of the six amines with positive tumor findings, four are secondary amines [bis(2-hydroxypropyl)amine; morpholine; N-methylaniline; piperazine], one is both a tertiary amine and a cyclic aromatic amine [chlorpheniramine], and one is both a tertiary amine and an amide [aminopyrine].

Twelve amides were tested in combination with nitrite in the set of studies reviewed by IARC. Positive tumor findings were reported in at least one study for seven of the amides. For one other amide, increases in tumor incidence were observed when the amide was administered in combination with nitrite; however, definitive conclusions could not be reached, since the studies lacked one or two of the three necessary comparator groups. Of the seven amides with positive tumor findings, five are ureas [allantoin; butylurea; ethylene thiourea; ethylurea; methylurea] (one of these is also a secondary amide [allantoin]), one is a carbamate [carbendazim], and one is a guanidine [dodine].

Positive tumor findings were reported for the studies reviewed by IARC of the complex mixture of amines and amides present in fish meal and administered in combination with nitrite.

In evaluating the evidence from the above set of studies, IARC concluded:

> "There is *sufficient evidence* in experimental animals for the carcinogenicity of nitrite in combination with amines or amides." (IARC, 2010, p. 325)

Relevant sections of the 2010 IARC monograph on ingested nitrate and nitrite are appended here as Attachment 1.

OEHHA conducted a literature review to identify additional animal cancer bioassays of nitrite in combination with amines or amides not included in IARC (2010). (See Appendix A for details of OEHHA's literature search strategy.) OEHHA identified a total of 35 additional animal studies.

Fifteen amines were tested in combination with nitrite in the set of additional studies identified by OEHHA. Five of the 15 amines had also been tested in the set of studies reviewed by IARC (aminopyrine; chlordiazepoxide; hexamethyleneimine; methapyriline; piperazine). Of the 10 amines unique to the set of additional studies identified by OEHHA, positive tumor findings were reported for one, IQ. This compound is both a primary amine, a cyclic tertiary amine, and a cyclic aromatic amine. For 3 of the 10 unique amines, increases in tumor incidence were observed when the amines were administered in combination with nitrite; however, definitive conclusions could not be reached, since the studies lacked one or two of the three necessary comparator groups.

Four amides were tested in combination with nitrite in the set of additional studies identified by OEHHA. One of these amides, methylguanidine, had also been tested in

the set of studies reviewed by IARC. While the study of methylguanidine reviewed by IARC did not report positive tumor findings, one study in the additional set identified by OEHHA reported an increase in tumor incidence; however, definitive conclusions could not be reached, since the study lacked two of the three necessary comparator groups. Positive tumor findings were not reported for any of the 3 amides unique to the set of additional studies identified by OEHHA.

Information on study design and study findings from all experimental animal studies of nitrite in combination with amines or amides included in IARC (2010) and all additional studies identified by OEHHA is tabulated in Table 7 (Amines tested in combination with nitrite in animal tumor studies), Table 8 (Amides tested in combination with nitrite in animal tumor studies), and Table 9 (Fish meal, a complex mixture of amines and amides, tested in combination with nitrite in animal tumor studies) below.

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies

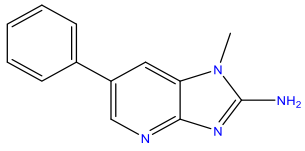
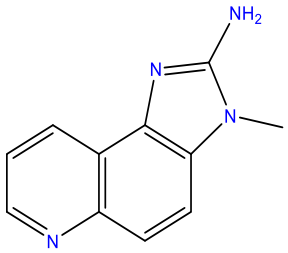
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]					↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Primary Amines										
2-Amino-1-methyl- 6-phenylimidazo [4,5-*b*]pyridine (PhIP) § (primary amine, cyclic tertiary amine and cyclic aromatic amine)		Kitamura *et al.*, 2006b†; Hirose *et al.*, 2002	Female Sprague-Dawley rats		Mammary gland					**No**
					Carcinoma			Fibroadenoma		
				Control	0/10			0/10		
				$NaNO_2$	0/10			0/10		
				PhIP	11/20			3/20		
				PhIP + $NaNO_2$	6/10++			2/10		
2-Amino-3-methylimidazo [4,5-*f*]quinolone (IQ)§ (primary amine, cyclic tertiary amine and cyclic aromatic amine)		Kitamura *et al.*, 2006a†	Male F344/Du Crj SPF rats		Zymbal's gland (r)	Lung		Liver	Colon	**Yes** (Zymbal's gland)
						A	C			
				Control	0/18	0/18	0/18	7/18	7/18	
				$NaNO_2$ (0.1%)	0/18	0/18	0/18	2/18	6/18	
				$NaNO_2$ (0.2%)	0/20	1/20	1/20	4/20	6/20	
				IQ	2/15	7/15	11/15	12/15	11/12	
				IQ + $NaNO_2$ (0.1%)	6/16++	5/16+	8/16 +++	16/16 +++	15/15 +++	
				IQ + $NaNO_2$ (0.2%)	14/19 ***,+++	4/19	8/19 ++	16/19 +++	14/15 +++	

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

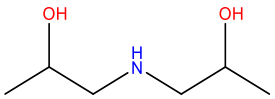
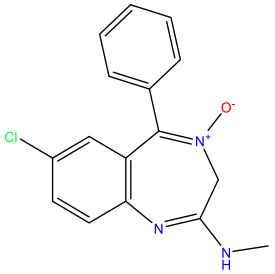
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]							↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines												
Bis(2-hydroxy-propyl)amine		Konishi *et al.*, 1991; Yamamoto *et al.*, 1989	Male Wistar rats		Nasal (r)		Esophagus (r)	Lung (bronchial) P	Lung (bronchioalveolar)			**Yes** (multiple sites)
					C (r)	P (r)			A	AC (r)	SCC (r)	
				Control	0/19	0/19	0/19	0/19	0/19	0/19	0/19	
				$NaNO_2$ (0.15%)	0/18	0/18	0/18	0/18	0/18	0/18	0/18	
				$NaNO_2$ (0.3%)	0/16	0/16	0/16	0/16	0/16	0/16	0/16	
				Bis(2-hydroxy-propyl)amine (1%)	0/16	0/16	0/16	0/16	0/16	0/16	0/16	
				Bis(2-hydroxy-propyl)amine (1%) + $NaNO_2$ (0.15%)	0/19	0/19	0/19	3/19	0/19	0/19	0/19	
				Bis(2-hydroxy-propyl)amine (1%) + $NaNO_2$ (0.3%)	10/19 ***,+++	11/19 ***,+++	2/19	10/19 ***,+++	2/19	1/19	2/19	
Chlordiazepoxide (secondary amine and cyclic aromatic amine; benzodiazepine-4-oxide)		Lijinsky and Taylor, 1977a	Male Sprague-Dawley rats		Liver		Pancreatic AC	Neurogenic (r)	Skin Kerato-acanthoma (r, f)	Mandibular Lymphangio-sarcoma	Vertebral osteosarcoma (r)	**?** (Slight increase observed with NO_2 + amine compared to NO_2 alone at multiple rare sites; no untreated control; no amine alone)
					Hepatoma	Cholangio-carcinoma (r)						
				$NaNO_2$	0/26	0/26	0/26	1/26	0/26	0/26	0/26	
				Chlorodiazepoxide + $NaNO_2$	0/15	1/15	0/15	3/15	1/15	1/15	1/15	
			Female Sprague-Dawley rats	$NaNO_2$	0/30	0/30	0/30	0/30	0/30	0/30	0/30	**?** (Slight increase observed with NO_2 + amine compared to NO_2 tumors at multiple rare sites; no untreated control; no amine alone)
				Chlorodiazepoxide + $NaNO_2$	1/15	1/15	1/15	1/15	0/15	0/15	0/15	

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

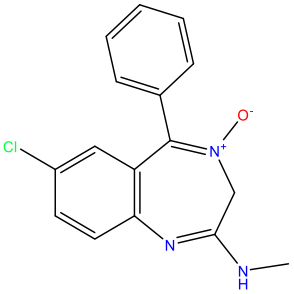
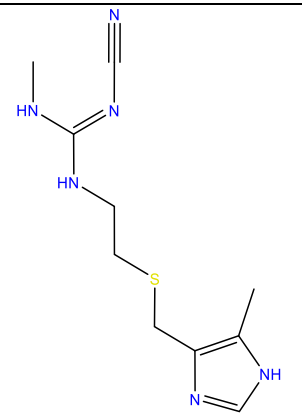
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)													
Chlordiazepoxide (secondary amine and cyclic aromatic amine; benzodiazepine-4-oxide) (continued)		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Liver[2]	Pancreas[2]	Adrenal	Mammary (r, m)	Uterus (r)	Neurogenic[2] (r)	**?** (Slight increase observed with NO_2 + amine compared to NO_2 alone for neurogenic tumors; no untreated control; no amine alone)
				$NaNO_2$	6/26	4/26	1/26	4/26	10/26	3/26	---	1/26	
				Chlorodiazepoxide + $NaNO_2$	0/15	0/15	1/15	0/15	3/15	4/15	---	3/15	
			Female rats	$NaNO_2$	20/30	4/30	0/30	1/30	7/30	18/30	9/30	0/30	**?** (Slight increase observed with NO_2 + amine compared to NO_2 alone for tumors at multiple sites; no untreated control; no amine alone)
				Chlorodiazepoxide + $NaNO_2$	3/15	0/15	2/15	1/15	0/15	11/15	2/15	1/15	
Cimetidine (cyclic secondary amine and guanidine)		Anderson *et al.*, 1985	Male BALB/c mice		Lung C	Liver	Fore-stomach P (r)	Lymphoid	Fibro-sarcoma	Angio-sarcoma			**No**
				Control	6/52	4/52	9/37	7/52	4/52	3/52			
				Cimetidine (low)	14/61	3/61	8/55	6/61	6/61	6/61			
				Cimetidine (high)	10/56	3/56	12/45	10/56	2/56	3/56			
				$NaNO_2$ (low)	13/52	3/52	8/45	16/52	1/52	6/52			
				$NaNO_2$ (high)	15/54	2/54	13/42	6/54	4/54	4/54			
				Cimetidine + $NaNO_2$ (low)	6/50	0/50	12/46	9/50	2/50	5/50			
				Cimetidine + $NaNO_2$ (high)	19/79	2/79	22/72	7/79	6/79	6/79			

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

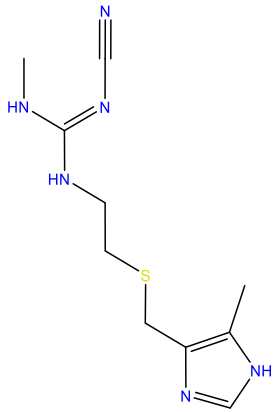
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]							↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)												
Cimetidine (cyclic secondary amine and guanidine) (continued)		Anderson *et al.*, 1985 (continued)	Female C57BL/6 mice		Pituitary	Lung C	Fore- stomach P (r)	Mammary C	Lymphoid	Fibro- sarcoma	Angio- sarcoma	**No**
				Control	13/66	4/66	19/62	4/66	31/66	4/66	5/66	
				Cimetidine (low)	8/65	4/66	19/62	3/65	30/65	5/65	8/65	
				Cimetidine (high)	14/59	6/59	12/59	7/59	41/59	3/59	6/59	
				$NaNO_2$ (low)	6/39	5/39	13/38	2/39	15/39	5/39	1/39	
				$NaNO_2$ (high)	4/65	7/65	19/64	5/65	26/65	9/65	7/65	
				Cimetidine + $NaNO_2$ (low)	7/51	5/51	11/47	7/51	23/51	2/51	4/51	
				Cimetidine + $NaNO_2$ (high)	3/58	7/58	12/55	3/58	33/58+	2/58	3/58	
Dibutylamine		Rijhsinghani *et al.*, 1982	Male newborn $C_{57}BL$ X C_3HF_1 mice		Liver							**No**
					Adenomatous (benign)		Trabecular (benign)		Hemangioma (r)			
				Control	0/17		2/17		0/17			
				$NaNO_2$	1/11		0/11		1/11			
				Dibutylamine	3/15		2/15		0/15			
				Dibutylamine + $NaNO_2$	10/23+		4/23		0/23			

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

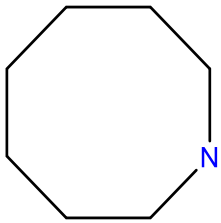
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]									↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)														
Hepta-methyleneimine		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Esophagus (r)	Lung C	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone at multiple sites; no untreated control)
				$NaNO_2$	6/26	4/26	0/26	0/26	1/26	4/26	10/26	3/26	---	
				Heptamethyleneimine	1/15	1/15	0/15	0/15	0/15	0/15	5/15	2/15	---	
				Heptamethyleneimine + $NaNO_2$	0/15	0/15	9/15 ***, +++	5/15 *,++	0/15	0/15	1/15	0/15	---	
			Female rats	$NaNO_2$	20/30	4/30	0/30	0/30	0/30	1/30	7/30	18/30	9/30	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone at multiple sites; no untreated control)
				Heptamethyleneimine	7/15	0/15	0/15	0/15	0/15	0/15	1/15	8/15	0/15	
				Heptamethyleneimine + $NaNO_2$	1/15	0/15	14/15 ***, +++	11/15 ***, +++	0/15	0/15	0/15	0/15	0/15	
		Lijinsky *et al.*, 1973			Esophagus (r)			Lung				Liver		**?** (Slight increase observed with NO_2 + amine compared to NO_2 alone and amine alone at multiple sites; no untreated control)
			Male Sprague-Dawley rats	$NaNO_2$	0/15[3]			0/15[3]				0/15[3]		
				Heptamethyleneimine	0/15[3]			0/15[3]				0/15[3]		
				Heptamethyleneimine + $NaNO_2$	3/15			2/15				0/15		
			Female Sprague-Dawley rats	$NaNO_2$	0/15[3]			0/15[3]				0/15[3]		**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone at multiple sites; no untreated control)
				Heptamethyleneimine	0/15[3]			0/15[3]				0/15[3]		
				Heptamethyleneimine + $NaNO_2$	14/15***,+++			11/15***,+++				0/15		

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

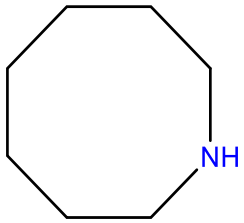
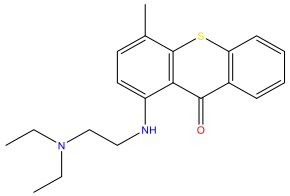
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)													
Hepta-methyleneimine (continued)		Taylor and Lijinsky, 1975a	Male Sprague-Dawley rats		Nasal cavity SCC (r)		Larynx and trachea (r)		Forestomach, esophagus, tongue, oropharynx SCC (r)		Lung		? (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone at multiple sites; no untreated control)
				$NaNO_2$	0/27		0/27		0/27		0/27		
				Heptamethyleneimine	0/15		0/15		0/15		0/15		
				Heptamethyleneimine + $NaNO_2$	4/15*,+		1/15		11/15***,+++		5/15*,++		
			Female Sprague-Dawley rats	$NaNO_2$	0/26		0/26		0/26		0/26		? (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone at multiple sites; no untreated control)
				Heptamethyleneimine	0/15		0/15		0/15		0/15		
				Heptamethyleneimine + $NaNO_2$	4/15*,+		3/15+		14/15***,+++		11/15***,+++		
Lucanthone		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	Lymphosarcoma	**No**
				$NaNO_2$	6/26	4/26	1/26	4/26	10/26	3/26	---	0/26	
				Lucanthone	0/15	0/15	1/15	2/15	1/15	0/15	---	0/15	
				Lucanthone + $NaNO_2$	1/15	0/15	1/15	0/15	2/15	2/15	---	1/15	

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

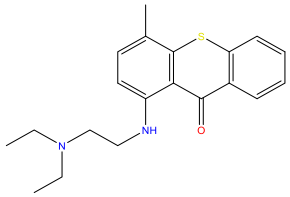
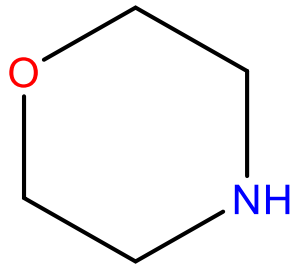
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)													
Lucanthone (continued)		Lijinsky and Taylor, 1977b† (continued)	Female rats		Pituitary	Thyroid	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	Lympho-sarcoma	**No**
				$NaNO_2$	20/30	4/30	0/30	1/30	7/30	18/30	9/30	0/30	
				Lucanthone	2/15	1/15	5/15	0/15	0/15	10/15	1/15	0/15	
				Lucanthone + $NaNO_2$	7/15	1/15	1/15	0/15	1/15	9/15	2/15	3/15+	
Morpholine (heterocyclic secondary amine)		Greenblatt *et al.*, 1971	Swiss mice		Lung adenoma					Malignant lymphoma			**Yes** (lung adenoma)
				Control	20/144					10/144			
				$NaNO_2$	14/74					1/74			
				Morpholine	5/38					5/38			
				Morpholine + $NaNO_2$	20/35***,+++					2/35			
		Shank and Newberne, 1976	Sprague-Dawley rats	F1 + F2 populations exposed *in utero* and via diet	Lung AS		Liver			Other AS			**Yes** (multiple sites)
							C		AS				
				Control	0/156		0/156		0/156	0/156			
				$NaNO_2$	0/96		1/96		0/96	1/96			
				Morpholine	2/104		3/104		0/104	1/104			
				Morpholine + $NaNO_2$	23/159 ***,+++		97/159 ***,+++		14/159 ***,+++	1/159			
			Syrian golden hamsters		Lung adenoma				Liver carcinoma				**Yes** (liver carcinoma)
				Control	0/23				1/23				
				$NaNO_2$	0/30				0/30				
				Morpholine	0/22				0/22				
				Morpholine + $NaNO_2$	1/16				5/16**,++				

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

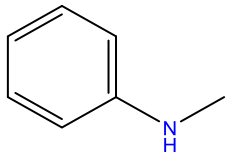
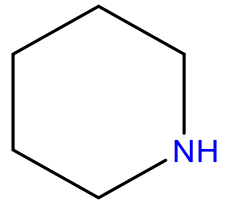
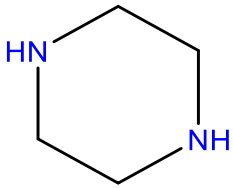
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)													
N-Methylaniline		Greenblatt *et al.,* 1971	Swiss mice		Lung adenoma					Malignant lymphoma			**Yes** (lung adenoma)
				Control	20/144					10/144			
				$NaNO_2$	14/74					1/74			
				Methylaniline	6/36					5/36			
				Methylaniline + $NaNO_2$	23/38***,+++					5/38+			
Piperidine (cyclic secondary amine)		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Lung A	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	**No**
				$NaNO_2$	6/26	4/26	0/26	1/26	4/26	10/26	3/26	---	
				Piperidine	0/15	1/15	0/15	0/15	1/15	3/15	1/15	---	
				Piperidine + $NaNO_2$	6/15**	3/15	0/15	1/15	0/15	5/15	1/15	---	
			Female rats	$NaNO_2$	20/30	4/30	0/26	0/30	1/30	7/30	18/30	9/30	**No**
				Piperidine	8/15	0/15	0/15	0/15	1/15	4/15	9/15	5/15	
				Piperidine + $NaNO_2$	9/15	0/15	1/15	1/15	0/15	3/15	8/15	3/15	
Piperazine (cyclic secondary amine)		Greenblatt *et al*., 1971	Swiss mice		Malignant lymphoma					Lung adenoma			**Yes** (lung adenoma)
				Control	10/144					20/144			
				$NaNO_2$	1/74					14/74			
				Piperazine	2/68					10/68			
				Piperazine + NaNO2	4/75					48/75***,+++			
		Greenblatt and Mirvish, 1973	Male Strain A mice (Series 1)		Lung adenoma								**Yes** (lung adenoma)
				Control	12/37								
				$NaNO_2$	11/37								
				Piperazine	7/33								
				Piperazine + $NaNO_2$	35/40***,+++								
			Male Strain A mice (Series 2)	Control	5/39								**Yes** (lung adenoma)
				Piperazine	11/39								
				$NaNO_2$	7/39								
				Piperazine + $NaNO_2$	39/40***,+++								

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

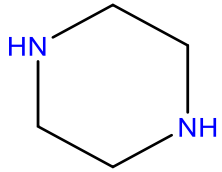
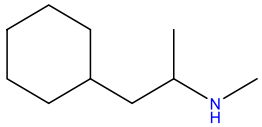
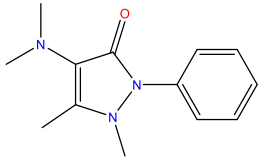
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]					↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)										
Piperazine (cyclic secondary amine) (continued)		Schneider *et al.*, 1977†	Hooded rats		Nasal cavity (r)	Esophagus (r)	Leukoses	Paracoecal Reticular cell sarcoma	Soft Tissue Sarcoma	**No**
				Piperazine	0/5	0/5	0/5	1/5	0/5	
				Piperazine + $NaNO_2$	1/14	1/14	2/14	0/14	1/14	
Propylhexedrine		Schneider *et al.*, 1977†	Hooded rats		Leukoses			Paracoecal Reticular cell sarcoma		**?** (Slight increase observed with NO_2 + amine compared to NO_2 *and* amine alone for multiple sites; no untreated control)
				Propylhexedrine	0/5			0/5		
				$NaNO_2$	0/5			1/5		
				Propylhexedrine + $NaNO_2$	3/18			7/18		
Tertiary Amines										
2-Amino-1-methyl- 6-phenylimidazo [4,5-*b*]pyridine (PhIP) §	See primary amines									**No** (1 of 1 studies)
2-Amino-3-methylimidazo [4,5-*f*]quinolone (IQ)§	See primary amines									**Yes** (1 of 1 studies)
Aminopyrine (Amidopyrine) (tertiary amine)		Lijinsky *et al.*, 1973	Male Sprague-Dawley rats		Esophagus (r)		Lung		Liver	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone for liver; no untreated control)
				$NaNO_2$	0/15[3]		0/15[3]		0/15[3]	
				Aminopyrine	0/15[3]		0/15[3]		0/15[3]	
				Aminopyrine + $NaNO_2$ (250 ppm)	0/15		0/15		4/15*,+	
				Aminopyrine + $NaNO_2$ (1000 ppm)	0/15		0/15		14/15***,+++	

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

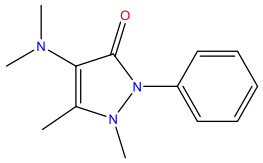
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)													
Aminopyrine (Amidopyrine) (tertiary amine) (continued)		Lijinsky *et al.*, 1973 (continued)	Female Sprague-Dawley rats		Esophagus (r)			Lung		Liver			**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone for liver; no untreated control)
				$NaNO_2$	0/15[3]			0/15[3]		0/15[3]			
				Aminopyrine	0/15[3]			0/15[3]		0/15[3]			
				Aminopyrine + $NaNO_2$ (250 ppm)	0/15			0/15		8/15***,+++			
				Aminopyrine + $NaNO_2$ (1000 ppm)	0/15			1/15		15/15***,+++			
		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Zymbal's gland (r)	Thyroid	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone for liver; no untreated control)
				$NaNO_2$	6/26	1/26	4/26	1/26	4/26	10/26	3/26	---	
				Aminopyrine	0/15	0/15	1/15	0/15	1/15	6/15	2/15	---	
				Aminopyrine + $NaNO_2$	0/15	0/15	0/15	14/15 ***, +++	0/15	0/15	0/15	---	
			Female rats	$NaNO_2$	20/30	1/30	4/30	0/30	1/30	7/30	18/30	9/30	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone for liver; no untreated control)
				Aminopyrine	3/15	0/15	0/15	1/15	0/15	2/15	8/15	2/15	
				Aminopyrine + $NaNO_2$	0/15	0/15	0/15	15/15 ***, +++	0/15	0/15	0/15	0/15	
		Thamavit *et al.*, 1988†	Male Syrian golden hamsters		Cholangiocarcinoma (r)								**Yes** (CAC)
				Control	0/15								
				$NaNO_2$	0/15								
				Aminopyrine	0/15								
				Aminopyrine + $NaNO_2$	3/17								

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

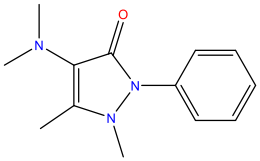
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]							↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)												
					Lung		Liver					
					A	AC (r)	Hepatoma	Hepato-cellular C	Chol-angioma	Cholangio-carcinoma (r)	Reticular cell sarcoma	
Aminopyrine (Amidopyrine) (tertiary amine and amide) (continued)		Scheunig *et al.*, 1979	Male Wistar rats	Control	0/40	1/40	4/48	2/48	0/48	1/48	3/48	**Yes** (multiple sites)
				$NaNO_2$	1/36	1/36	2/44	2/44	14/44	1/44	4/44	
				Aminopyrine	1/32	1/32	1/44	1/44	0/44	0/44	4/44	
				Aminopyrine + $NaNO_2$	0/31	3/31	9/45	16/45 **,+	5/45*	3/45	11/45 *,+	
			Female Wistar rats	Control	0/44	0/44	0/41	1/41	0/41	0/41	1/41	**Yes** (multiple sites)
				$NaNO_2$	0/34	0/34	1/44	0/44	1/44	1/44	1/44	
				Aminopyrine	0/44	1/44	2/46	1/46	0/46	0/46	3/45	
				Aminopyrine + $NaNO_2$	0/7	2/7	1/42	10/42 **,+++	4/42*	7/42**,+	3/39	
		Taylor and Lijinsky, 1975b	Male Wistar rats		Hemangio-endothelial tumors in liver (r)							**?** (Increased effect observed with NO_2 + amine compared to amine alone; no untreated control; no NO_2 alone)
				Aminopyrine	0/15							
				Aminopyrine + $NaNO_2$	14/15***							
			Female Wistar rats	Aminopyrine	0/15							**?** (Increased effect observed with NO_2 + amine compared to amine alone; no untreated control; no NO_2 alone)
				Aminopyrine + $NaNO_2$	15/15***							

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

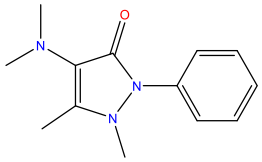
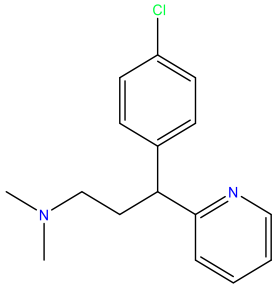
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]							↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)												
Aminopyrine (tertiary amine) (continued)		Yada *et al.*, 2002	Male F344 rats		Lung adenocarcinoma (r)				Liver hemangiosarcoma (r)			**No**
				Control	0/5				0/5			
				$NaNO_2$	0/5				0/5			
				Aminopyrine	0/5				0/5			
				Aminopyrine + $NaNO_2$	0/5				0/5			
Chlorpheniramine (tertiary amine and cyclic aromatic amine)		Lijinsky, 1984	Male F344 rats		Pituitary	Liver	Forestomach (r)	Pancreas	Adrenal medulla	Mammary (r, m)	Leukemia	**Yes** (liver)
				Control	14/24	5/24	0/24	6/24	7/24	3/24	12/24	
				$NaNO_2$	14/24	3/24	1/24	6/24	9/24	1/24	4/24	
				Chlorpheniramine maleate	12/24	3/24	0/24	3/24	5/24	2/24	9/24	
				Chlorpheniramine maleate + $NaNO_2$	10/24	14/24 ***,+++	1/24	3/24	3/24	3/24	4/24	
			Female F344 rats	Control	22/24	4/24	1/24	5/24	1/24	15/24	7/24	**No**
				$NaNO_2$	22/24	13/24	0/24	2/24	4/24	13/24	3/24	
				Chlorpheniramine maleate	15/24	3/24	1/24	0/24	0/24	3/24	7/24	
				Chlorpheniramine maleate + $NaNO_2$	15/24	8/24	0/24	2/24	2/24	2/24	6/24	

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

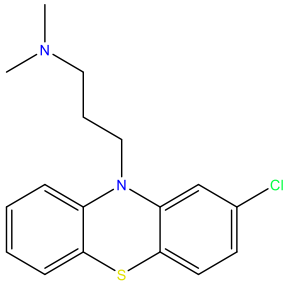
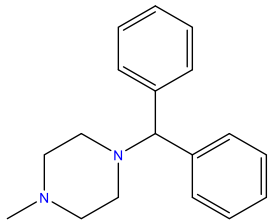
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)													
Chlorpromazine (tertiary amine and cyclic tertiary amine)		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	Lympho-sarcoma	**No**
				$NaNO_2$	6/26	4/26	1/26	4/26	10/26	3/26	----	0/26	
				Chlorpromazine	1/15	2/15	0/15	1/15	1/15	1/15	---	2/15	
				Chlorpromazine + $NaNO_2$	1/15	0/15	0/15	0/15	2/15	1/15	---	0/15	
			Female rats	$NaNO_2$	20/30	4/30	0/30	1/30	7/30	18/30	9/30	0/30	**No**
				Chlorpromazine	4/15	0/15	0/15	1/15	1/15	8/15	0/15	1/15	
				Chlorpromazine + $NaNO_2$	6/15	2/15	1/15	0/15	4/15	4/15	1/15	0/15	
Cyclizine (cyclic tertiary amine)		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Lung AC (r)	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	**No**
				$NaNO_2$	6/26	4/26	0/26	1/26	4/26	10/26	3/26	---	
				Cyclizine + $NaNO_2$	1/15	0/15	0/15	0/15	0/15	5/15	2/15	---	
			Female rats	$NaNO_2$	20/30	4/30	0/30	0/30	1/30	7/30	18/30	9/30	**?** (Slight increase observed with NO_2 + amine compared to NO_2 alone for lung AC; no untreated control; no amine alone)
				Cyclizine + $NaNO_2$	1/15	1/15	1/15	0/15	0/15	0/15	7/15	2/15	

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

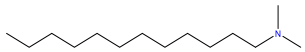
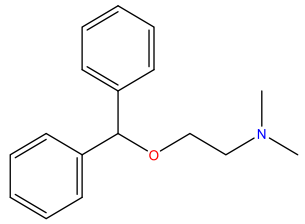
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)													
Dimethyl-dodecylamine		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Liver	Pancreas	Adrenal	Bladder (r)	Mammary	Uterus	**?** (Slight increase observed with NO_2 + amine compared to NO_2 alone for bladder; no untreated control; no amine alone)
				$NaNO_2$	6/26	4/26	1/26	4/26	10/26	0/26	3/26	---	
				Dimethyl-dodecylamine +$NaNO_2$	0/15	0/15	1/15	0/15	2/15	2/15	3/15	---	
			Female rats	$NaNO_2$	20/30	4/30	0/30	1/30	7/30	0/30	18/30	9/30	**?** (Slight increase observed with NO_2 + amine compared to NO_2 alone for bladder; no untreated control; no amine alone)
				Dimethyl-dodecylamine + $NaNO_2$	3/9	0/9	0/9	1/9	0/9	1/9	4/9	0/9	
Diphen-hydramine		Lijinsky, 1984	Male F344 rats		Pituitary	Liver (r)		Fore-stomach	Pancreas	Adrenal medulla	Mammary (r, m)	Leukemia	**No**
				Control	14/24	5/24		0/24	6/24	7/24	3/24	12/24	
				$NaNO_2$	14/24	3/24		1/24	6/24	9/24	1/24	4/24	
				Diphenhydramine	11/24	4/24		0/24	3/24	2/24	2/24	11/24	
				Diphenhydramine + $NaNO_2$	13/24	11/24*,+ not significant compared to control (p = 0.062)		4/24	4/24	4/24	0/24	9/24	
			Female F344 rats	Control	22/24	4/24		1/24	5/24	1/24	15/24	7/24	**No**
				$NaNO_2$	22/24	13/24		0/24	2/24	4/24	13/24	3/24	
				Diphenhydramine	11/24	3/24		1/24	1/24	2/24	2/24	6/24	
				Diphenhydramine + $NaNO_2$	19/24*	6/24		0/24	0/24	1/24	1/24	4/24	

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

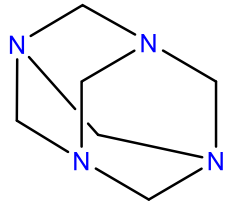
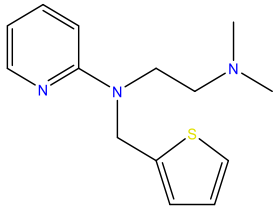
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)													
Hexamethylene-tetramine (cyclic tertiary amine)		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Lung AC (r)	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	**No**
				$NaNO_2$	6/26	4/26	0/26	1/26	4/26	10/26	3/26	---	
				Hexamethylene-tetramine	0/15	0/15	0/15	0/15	2/15	3/15	2/15	---	
				Hexamethylene-tetramine + $NaNO_2$	1/15	2/15	1/15	0/15	0/15	4/15	2/15	---	
			Female rats	$NaNO_2$	20/30	4/30	0/30	0/30	1/30	7/30	18/30	9/30	**No**
				Hexamethylene-tetramine	10/15	0/15	0/15	0/15	0/15	2/15	9/15	4/15	
				Hexamethylene-tetramine + $NaNO_2$	6/15	0/15	0/15	0/15	1/15	3/15	10/15	1/15	
Lucanthone	See secondary amines												**No** (1 of 1 studies)
Methapyrilene (tertiary amine and cyclic aromatic amine)		Lijinsky and Taylor, 1977a	Male Sprague-Dawley rats		Liver			Spinal cord	**?** (Slight increase observed with NO_2 + amine compared to NO_2 alone for liver CAC; no untreated control; no amine alone)				
					CAC (r)	HCC	HAES (r)	NFS					
				$NaNO_2$	0/26	1/26	0/26	0/26					
				Methapyrilene + $NaNO_2$	1/15	2/15	0/15	1/15					
			Female Sprague-Dawley rats	$NaNO_2$	0/30	0/30	0/30	0/30	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone for liver CAC; no untreated control; no amine alone)				
				Methapyrilene + $NaNO_2$	4/14++	1/14	1/14	0/14					

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

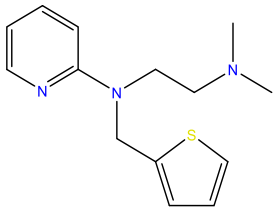
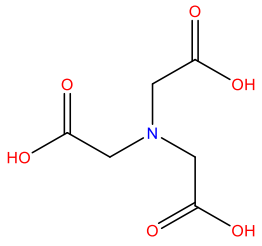
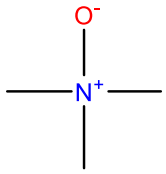
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)													
Methapyrilene (tertiary amine and cyclic aromatic amine) (continued)		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	Lympho-sarcoma	**No**
				$NaNO_2$	6/26	4/26	1/26	4/26	10/26	3/26	---	0/26	
				Methapyrilene + $NaNO_2$	1/15	0/15	3/15	1/15	2/15	3/15	---	0/15	
			Female rats	$NaNO_2$	20/30	4/30	0/30	1/30	7/30	18/30	9/30	0/30	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone at multiple sites; no untreated control; no amine alone)
				Methapyrilene + $NaNO_2$	1/14	0/14	6/14 +++	0/14	0/14	13/14 +	1/14	1/14	
Nitrilotriacetic acid§		Greenblatt and Lijinsky, 1974	Male Swiss mice		Lung adenoma		Forestomach SCP (r)			Malignant lymphoma			**No**
				Control	7/38		0/38			2/38			
				$NaNO_2$	4/36		1/36			2/36			
				Nitrilotriacetic acid	0/39		2/39			3/39			
				Nitrilotriacetic acid + $NaNO_2$	12/37***,+ not significant compared to control (p = 0.129)		1/37			3/37			
			Female Swiss mice	Control	4/38		0/38			18/38			**No**
				$NaNO_2$	6/39		1/39			11/39			
				Nitrilotriacetic acid	4/35		0/35			9/35			
				Nitrilotriacetic acid + $NaNO_2$	6/39		1/39			11/39			

Table 7. Amines Tested in Combination with Nitrite in Animal Tumor Studies (continued)

Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
					Pituitary	Thyroid	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	Lympho-sarcoma	
Tertiary Amines (continued)													
Trimethylamine (precursor of Trimethylamine oxide)		Lijinsky and Taylor, 1977b†	Male rats	$NaNO_2$	6/26	4/26	1/26	4/26	10/26	3/26	---	0/26	**No**
				Trimethylamine oxide	2/15	0/15	0/15	0/15	9/15	0/15	---	0/15	
				Trimethylamine oxide + $NaNO_2$	1/15	0/15	0/15	0/15	3/15	0/15	---	1/15	
			Female rats	$NaNO_2$	20/30	4/30	0/30	1/30	7/30	18/30	9/30	0/30	**No**
				Trimethylamine oxide	7/15	0/15	0/15	0/15	3/15	11/15	0/15	2/15	
				Trimethylamine oxide + $NaNO_2$	6/15	2/15	0/15	0/15	1/15	8/15	4/15 *	0/15	
Cyclic Aromatic Amines													
2-Amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine (PhIP) §	See primary amines												**No** (1 of 1 studies)
2-Amino-3-methylimidazo [4,5-*f*]quinolone (IQ)§	See primary amines												**Yes** (1 of 1 studies)
Chlordiazepoxide	See secondary amines												**?** (4 of 4 studies)
Chlorpheniramine	See tertiary amines												**Yes** (1 of 2 studies)
Methapyrilene	See tertiary amines												**?** (3 of 4 studies)

All studies were reviewed in IARC (2010), unless the reference is marked with "†".

§ Proposition 65 carcinogen

[1] **A**: adenoma; **C**: carcinoma; **AC**: adenocarcinoma; **P**: papilloma; **SCC**: squamous cell carcinoma; **LS**: lymphosarcoma; **AS**: angiosarcoma; **HCC**: hepatocellular carcinoma; **CAC**: cholangiocarcinoma; **HAES**: hemangioendothelial sarcoma; **NFS**: neurofibrosarcoma; **SCP**: squamous cell papilloma

[2] Findings also reported in Lijinsky and Taylor, 1977a

[3] Data not shown. Authors stated, “None of the controls fed nitrite, aminopyrine, or heptamethyleneimine alone died, with the exception of one accidental death and one animal that died with a large mammary tumor.”

(r) Indicates rare tumor type (<1% incidence in historical controls); (r, m) Indicate rare tumor type only in males; (r, f) Indicate rare tumor type only in females

* p<0.05; ** p<0.01; *** p < 0.001 [Treatment (Amide + Nitrite) group as compared to treatment (Amide) group]

+ p<0.05; ++ p<0.01; +++ p < 0.001 [Treatment (Amide+ Nitrite) group as compared to treatment (Nitrite) group]

Table 8. Amides Tested in Combination with Nitrite in Animal Tumor Studies

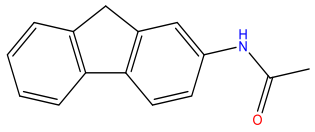
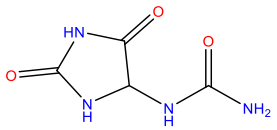
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]							↑effect observed with NO_2 + amide, compared to NO_2 alone *and* amide alone?
Secondary Amides												
2-Acetamido-fluorene§		Commoner *et al.*, 1970	Male Holtzman rats		Zymbal's gland[2] (r)			Liver				
				Control	0/26			0/26				**No**
				$NaNO_2$	1/24			0/24				
				2-Acetamidofluorene	10/19			25/26				
				$NaNO_2$ + 2-Acetamidofluorene	6/29			24/38+++				
Allantoin		Lijinsky 1984	Male F344 rats		Pituitary	Liver	Forestomach (r)	Pancreas	Adrenal medulla	Mammary (r, m)	Leukemia	
				Control	14/24	5/24	0/24	6/24	7/24	3/24	12/24	**Yes** (forestomach)
				$NaNO_2$	14/24	3/24	1/24	6/24	9/24	1/24	4/24	
				Allantoin	10/24	2/24	0/24	7/24	2/24	1/24	6/24	
				Allantoin + $NaNO_2$	8/20	3/20	5/20*	8/20	4/20	3/20	6/20	
			Female F344 rats	Control	22/24	4/24	1/24	5/24	1/24	15/24	7/24	**Equivocal** (forestomach)
				$NaNO_2$	22/24	13/24	0/24	2/24	4/24	13/24	3/24	
				Allantoin	13/24	3/24	0/24	0/24	8/24	8/24	9/24	
				Allantoin + $NaNO_2$	8/20	6/20	3/20	3/20	0/20	11/20	7/20	

Table 8. Amides Tested in Combination with Nitrite in Animal Tumor Studies (continued)

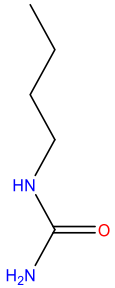
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]							↑effect observed with NO_2 + amide, compared to NO_2 alone *and* amide alone?
Urea, including Sulfonyl urea and Thiourea												
Allantoin	**See Secondary Amides**											**Yes** (1 of 2 studies)
Butylurea (urea)		Murthy *et al.*, 1979 (rats)	Male F344 rats		Zymbal's gland SCC (r)	Lung A	Forestomach		Intestine AC	Hemato-poietic		**Yes** (multiple sites)
							SCP (r)	SCC (r)		MNCL	ML (r)	
				Control	0/50	1/50	0/50	0/50	0/50	0/50	0/50	
				Butylurea	1/16	0/16	0/16	0/16	0/16	0/16	0/16	
				$NaNO_2$	0/16	0/16	0/16	0/16	0/16	0/16	0/16	
				Butylurea + $NaNO_2$	10/46 [+]	11/46*,[+]	16/46 **,[++]	12/46 *,[+]	6/46	5/46	3/46	
			Female F344 rats	Control	0/44	0/44	0/44	0/44	0/44	1/44	0/44	**Yes** (multiple sites)
				Butylurea	0/16	0/16	0/16	0/16	0/16	0/16	1/16	
				$NaNO_2$	1/16	0/16	0/16	0/16	0/16	0/16	0/16	
				Butylurea + $NaNO_2$	8/45	4/45	16/45 **,[++]	9/45	2/45	11/45 *,[+]	6/45	
		Murthy *et al.*, 1979 (mice)	Male C57BL6 mice		Lung A	Forestomach		Intestine AC (r)	Skin SCC (r)	Malignant lymphoma		**Yes** (multiple sites)
						SCP (r)	SCC (r)					
				Control	1/95	0/95	0/95	0/95	0/95	0/95		
				Butylurea	1/26	0/26	0/26	0/26	0/26	3/26		
				$NaNO_2$	1/11	0/11	0/11	0/11	0/11	0/11		
				Butylurea + $NaNO_2$	10/39*	1/39	2/39	2/39	2/39	24/39 ***,[+++]		

Table 8. Amides Tested in Combination with Nitrite in Animal Tumor Studies (continued)

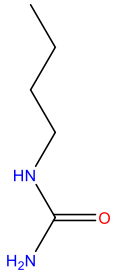
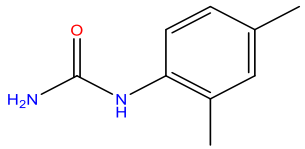
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]							↑effect observed with NO_2 + amide, compared to NO_2 alone *and* amide alone?
Urea, including Sulfonyl urea and Thiourea (continued)												
Butylurea (urea) (continued)		Murthy *et al.*, 1979 (mice) (continued)	Female C57BL6 mice		Lung A	Forestomach SCP (r)	Forestomach SCC (r)	Intestine AC (r)	Skin SCC (r)	Malignant lymphoma		**Yes** (Forestomach SCC)
				Control	2/92	0/92	0/92	0/92	0/92	6/92		
				Butylurea	0/24	0/24	0/24	0/24	0/24	2/24		
				$NaNO_2$	0/12	0/12	0/12	0/12	0/12	2/12		
				Butylurea + $NaNO_2$	7/40*	0/40	2/40	1/40	0/40	19/40***		
		Maekawa *et al.*, 1977	ACI/N rats (F_1)		Pituitary gland	Colon	Bladder	Uterus	Testis	Nervous system		**?** (Increased effect observed with NO_2 + amide compared to amide alone for nervous system tumors; no untreated control; no NO_2 alone)
				Butylurea (*in utero*)	1/23	0/23	0/23	2/23	4/23	0/23		
				Butylurea + $NaNO_2$ (*in utero*)	2/36	1/36	3/36	0/36	4/36	23/36***		
Dimethyl-phenylurea (urea)		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Liver	Pancreas	Adrenal	Mammary (r, m)	Uterus (r)	**No**
				$NaNO_2$	6/26	4/26	1/26	4/26	10/26	3/26	---	
				Dimethylphenylurea	0/15	2/15	0/15	0/15	3/15	2/15	---	
				Dimethylphenylurea + $NaNO_2$	2/15	0/15	1/15	2/15	6/15	3/15	---	
			Female rats	$NaNO_2$	20/30	4/30	0/30	1/30	7/30	18/30	9/30	**No**
				Dimethylphenylurea	8/14	0/14	0/14	1/14	2/14	12/14	2/14	
				Dimethylphenylurea + $NaNO_2$	6/15	0/15	1/15	0/15	2/15	13/15	2/15	

Table 8. Amides Tested in Combination with Nitrite in Animal Tumor Studies (continued)

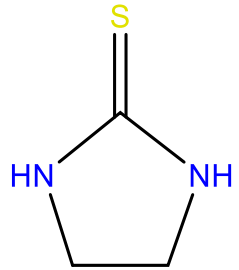
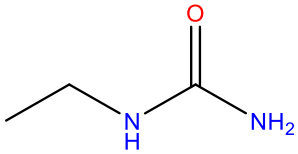
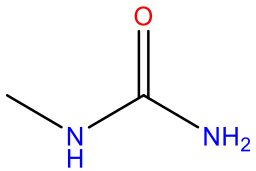
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]					↑effect observed with NO_2 + amide, compared to NO_2 alone *and* amide alone?
Urea, including Sulfonyl urea and Thiourea (continued)										
Ethylene thiourea[§] (thiourea)		Yoshida *et al.*, 1993	Male ICR mice		Harderian gland A	Lung	Fore-stomach (r)	Uterus AC (r)	Malignant lymphoma	**Yes** (multiple sites)
				Control	3/30	9/30	0/30	---	3/30	
				ETU	1/30	9/30	0/30	---	3/30	
				$NaNO_2$	1/30	11/30	0/30	---	4/30	
				ETU +$NaNO_2$	9/30 **,++	25/30 ***,+++	12/30 ***,+++	---	13/30 **,++	
			Female ICR mice	Control	0/30	3/30	0/30	0/30	6/30	**Yes** (multiple sites)
				ETU	2/30	4/30	0/30	0/30	7/30	
				$NaNO_2$	4/30	5/30	0/30	0/30	12/30	
				ETU +$NaNO_2$	7/30	21/30 ***,+++	8/30**,++	6/30 *,+	19/30 **	
Ethylurea (EU, urea)		Mirvish *et al.*, 1972	Swiss mice		Lung		Malignant lymphoma			**Yes** (lung adenoma)
					A	AC				
				Control	20/144	0/144	10/154			
				$NaNO_2$	14/74	0/74	1/75			
				Ethylurea	9/37	1/37	2/39			
				Ethylurea + $NaNO_2$	25/31***,+++	1/31	6/37++			
Methylurea (MU, urea)		Mirvish *et al.*, 1972	Swiss mice		Lung		Malignant lymphoma			**Yes** (lung adenoma)
					A	AC				
				Control	20/144	0/144	10/154			
				$NaNO_2$	14/74	0/74	1/75			
				Methylurea	7/36	1/36	2/38			
				Methylurea + $NaNO_2$	16/26***,+++	2/26	4/30+			

Table 8. Amides Tested in Combination with Nitrite in Animal Tumor Studies (continued)

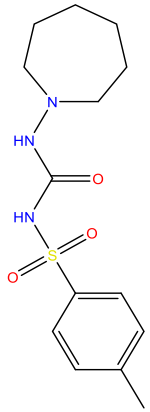
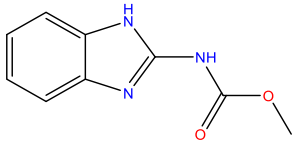
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amide, compared to NO_2 alone *and* amide alone?
Urea, including Sulfonyl urea and Thiourea (continued)													
Tolazamide (sulfonyl urea)		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Zymbal's gland (r)	Thyroid	Liver	Pancreas	Adrenal	Mammary (r,m)	Uterus (r)	**No**
				$NaNO_2$	6/26	1/26	4/26	1/26	4/26	10/26	3/26	---	
				Tolazamide	2/15	1/15	0/15	0/15	1/15	3/15	1/15	---	
				Tolazamide + $NaNO_2$	2/15	1/15	1/15	0/15	2/15	2/15	0/15	---	
			Female rats	$NaNO_2$	20/30	1/30	4/30	0/30	1/30	7/30	18/30	9/30	**No**
				Tolazamide	7/15	1/15	0/15	0/15	0/15	1/15	11/15	2/15	
				Tolazamide + $NaNO_2$	2/15	0/15	1/15	0/15	2/15	1/15	7/15	1/15	
Carbamates, including Thiocarbamates													
Carbendazim (carbamate)		Borzsonyi *et al.*, 1976	Male Swiss mice (F_1)		Lymphosarcoma								**Yes** (lympho-sarcoma)
				Control	0/118								
				$NaNO_2$ (*in utero*)	0/40								
				Carbendazim (*in utero*)	0/42								
				Carbendazim + $NaNO_2$ (*in utero*)	13/30***,+++								
			Female Swiss mice (F_1)	Control	1/138								**Yes** (lympho-sarcoma)
				$NaNO_2$ (*in utero*)	0/42								
				Carbendazim (*in utero*)	0/43								
				Carbendazim + $NaNO_2$ (*in utero*)	18/40***,+++								

Table 8. Amides Tested in Combination with Nitrite in Animal Tumor Studies (continued)

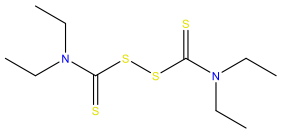
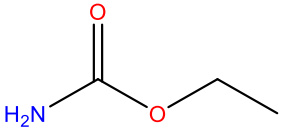
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]				↑effect observed with NO_2 + amide, compared to NO_2 alone *and* amide alone?
Carbamates, including Thiocarbamates (continued)									
Disulfiram (thiocarbamate)		Lijinsky and Reuber, 1980	Male Fischer rats		Nasal cavity (r)	Tongue (r)	Esophagus (r)	Forestomach (r)	**?** (Increased effect observed with NO_2 + amide compared to amide alone and NO_2 alone at multiple rare sites; no untreated control)
				$NaNO_2$	0/20	0/20	0/20	0/20	
				Disulfiram	0/50	0/50	0/50	0/50	
				Disulfiram + $NaNO_2$	2/20	0/20	7/20**, +++	3/20+	
			Female Fischer rats	$NaNO_2$	0/20	0/20	0/20	0/20	**?** (Increased effect observed with NO_2 + amide compared to amide alone and NO_2 alone for esophagus; no untreated control)
				Disulfiram	0/50	0/50	0/50	0/50	
				Disulfiram + $NaNO_2$	2/20	2/20	11/20***, +++	0/20	
Ethyl carbamate[§] (urethane)		Koohdani *et al.*, 2009	BALB/c mice		Lung				**No**
				Control	0/10				
				$NaNO_2$	1/9				
				Urethane	7/10				
				Urethane + $NaNO_2$	7/9++				

Table 8. Amides Tested in Combination with Nitrite in Animal Tumor Studies (continued)

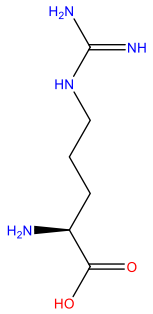
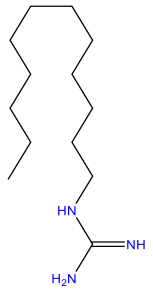
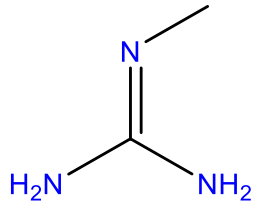
Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amide, compared to NO_2 alone *and* amide alone?
Guanidines													
Arginine		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Liver	Pancreas	Adrenal	Mammary (r,m)	Uterus (r)	Lympho-sarcoma	**No**
				$NaNO_2$	6/26	4/26	1/26	4/26	10/26	3/26	---	0/26	
				Arginine + $NaNO_2$	3/15	0/15	1/15	0/15	5/15	1/15	---	1/15	
			Female rats	$NaNO_2$	20/30	4/30	0/30	1/30	7/30	18/30	9/30	0/30	**?** (Slight increase observed with NO_2 + amide compared to NO_2 alone for LS; no untreated control; no amide alone)
				Arginine + $NaNO_2$	7/15	0/15	0/15	0/15	1/15	7/15	3/15	2/15	
Cimetidine	See secondary amines in amine table												**No** (2 of 2 studies)
Dodine		Borzsonyi *et al.*, 1978	Female Swiss/ Leiden mice (F_0)		Lung adenoma				Lymphosarcoma				**Yes** (Lympho-sarcoma)
				Control	0/18				1/18				
				$NaNO_2$	0/19				1/19				
				Dodine	0/10				0/10				
				Dodine + $NaNO_2$	1/17				9/17**,++				
			Male Swiss/ Leiden mice (F_1)	Control	1/70				2/70				**Yes** (Lympho-sarcoma)
				$NaNO_2$ (*in utero*)	1/62				2/62				
				Dodine (*in utero*)	0/39				1/39				
				Dodine + $NaNO_2$ (*in utero*)	0/28				14/28***,+++				
			Female Swiss/ Leiden mice (F_1)	Control	3/62				2/62				**Yes** (Lympho-sarcoma)
				$NaNO_2$ (*in utero*)	1/71				4/71				
				Dodine (*in utero*)	0/29				3/29				
				Dodine + $NaNO_2$ (*in utero*)	3/48				21/48**,+++				

Table 8. Amides Tested in Combination with Nitrite in Animal Tumor Studies (continued)

Chemical	Structure	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type[1]								↑effect observed with NO_2 + amide, compared to NO_2 alone *and* amide alone?
Guanidines (continued)													
Methylguanidine		Matsukura *et al.*, 1977	Male Wistar rats		Liver								**No**
					BA		HA (r)		HAS (r)		HCC		SCS
				Control	0/10		0/10		0/10		0/10		0/10
				$NaNO_2$	3/4		2/4		0/4		0/4		0/4
				Methylguanidine	0/5		1/5		0/5		0/5		0/5
				Methylguanidine + $NaNO_2$	8/15		6/15		1/15		1/15		1/15
		Lijinsky and Taylor, 1977b†	Male rats		Pituitary	Thyroid	Liver	Pancreas	Adrenal	Mammary (r,m)	Uterus (r)	Lympho-sarcoma	**?** (Increased effect observed with NO2 + amide compared to NO_2 alone for LS; no untreated control; no amide alone)
				$NaNO_2$	6/26	4/26	1/26	4/26	10/26	3/26	---	0/26	
				Methylguanidine + $NaNO_2$	2/15	0/15	0/15	1/15	0/15	2/15	---	3/15+	
			Female rats	$NaNO_2$	20/30	4/30	0/30	1/30	7/30	18/30	9/30	0/30	**No**
				Methylguanidine + $NaNO_2$	8/15	1/15	0/15	1/15	1/15	9/15	1/15	1/15	

All studies were reviewed in IARC (2010), unless the reference is marked with "†".

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[1] **C:** carcinoma; **A:** adenoma; **AC:** adenocarcinoma; **SCP:** squamous cell papilloma; **SCC:** squamous cell carcinoma; **LS:** lymphosarcoma; **ML:** malignant lymphoma; **MNCL:** mononuclear cell leukemia; **HA:** hemangioma; **BA:** bile duct adenoma; **HCC:** hepatocellular carcinoma; **HAS:** hemangiosarcoma; **SCS:** spindle cell sarcoma

[2] Authors reported as tumor of the ear canal

(r) Indicates rare tumor type (<1% incidence in historical controls); (r, m) Indicates rare tumor type only in males

* p<0.05; ** p<0.01; *** p < 0.001 [Treatment (Amide + Nitrite) group as compared to treatment (Amide) group]

+ p<0.05; ++ p<0.01; +++ p < 0.001 [Treatment (Amide+ Nitrite) group as compared to treatment (Nitrite) group]

Table 9. Fish Meal, a Complex Mixture of Amines and Amides,Tested in Combination with Nitrite in Animal Tumor Studies

Chemical	Reference	Gender/ Strain/ Species	Treatment	Tumor Incidence by Site/Type				↑effect observed with NO_2 + fish meal compared to fish meal alone?
				Kidney (r)		Uterus (r)		
				Adenoma (r)	Adeno-carcinoma (r)	Adenoma (r)	Adeno-carcinoma (r)	
Fish meal, a complex mixture of various amines and amides	Furukawa *et al.*, 2000	Male F344 rats	Fish meal (8%)	0/47	0/47	---	---	**Yes** Increased incidence of rare kidney adenoma and kidney adenocarcinoma with increasing doses of nitrite plus fish meal. (No tumors observed in animals treated with increasing doses of fish meal.)
			Fish meal (8%) + $NaNO_2$ (16.7 g total /2 yrs)	1/49	0/49	---	---	
			Fish meal (32%)	0/49	0/49	---	---	
			Fish meal (32%) + $NaNO_2$ (24.2 g total /2yrs)	12/47***	7/47**	---	---	
			Fish meal (64%)	1/47	0/47	---	---	
			Fish meal (64%) + $NaNO_2$ (37.6 g total /2 yrs)	33/49***	28/49***	---	---	
		Female F344 rats	Fish meal (8%)	0/45	0/45	0/45	0/45	**Yes** Increased incidence of rare kidney adenoma, kidney adenocarcinoma, uterine adenoma, and uterine adenocarcinoma with increasing doses of nitrite plus fish meal. (No tumors observed in animals treated with increasing doses of fish meal.)
			Fish meal (8%) + $NaNO_2$ (12.0 g total /2 yrs)	1/47	0/47	0/47	0/47	
			Fish meal (32%)	0/50	0/50	0/50	0/50	
			Fish meal (32%) + $NaNO_2$ (16.9 g total /2 yrs)	1/43	0/43	3/43	1/43	
			Fish meal (64%)	0/49	0/49	0/49	0/49	
			Fish meal (64%) + $NaNO_2$ (24.5 g total /2 yrs)	8/48**	1/48	0/48	2/48	

3.3 Mechanistic Evidence and Other Relevant Data

3.3.1 IARC 2010 Review

The 2010 IARC review discusses a wide range of other relevant data, including data on the absorption, distribution, metabolism and excretion of nitrite, and data on genetic and related effects. Possible carcinogenic pathways involving nitrite are also reviewed. Relevant sections of the 2010 IARC monograph on ingested nitrate and nitrite are appended here as Attachment 1.

3.3.2 Genotoxicity

IARC (2010) reviewed several genotoxicity studies of nitrite, and many of these studies included treatments with nitrite in combination with an amine or an amide. However, IARC did not present detailed findings observed in the treatment groups receiving nitrite plus an amine or amide in those genotoxicity studies. In order to better understand the scope of the available genotoxicity evidence for this broad class of compounds, OEHHA conducted a literature review to identify additional genotoxicity studies of nitrite in combination with amines or amides. (See Appendix A for details of OEHHA's literature search strategy.) A total of 180 genotoxicity assays of nitrite in combination with an amine or amide were identified from the 2010 IARC review and OEHHA's literature search.

More amines and amides have been tested in combination with nitrite for genotoxicity than have been tested in animal cancer bioassays. Specifically, 111 amines and 39 amides have been tested for genotoxicity.

Among these studies, positive findings were found in several different *in vitro* and *in vivo* genotoxicity assays, including bacterial reverse mutation assays, comet assays of DNA strand breaks, micronucleus tests, unscheduled DNA synthesis assays, and assays for DNA adduct formation.

Positive findings of genotoxicity, defined as the observation of increased genotoxic effect with nitrite in combination with an amine or amide, as compared to (i) untreated or vehicle controls, and (ii) nitrite alone, and (iii) amine or amide alone, were reported in at least one assay for 59 amines and 15 amides. For 36 amines and 20 amides, increases in genotoxic effect were observed in combination with nitrite; however, definitive conclusions could not be reached, since the studies lacked one or two of the three necessary comparator groups.

Of the 59 amines with positive genotoxic findings, four are primary amines (three of these are also secondary amines, and two are also cyclic aromatic amines), 38 are secondary amines (three of these are also primary amines, six are also tertiary amines, nine are also cyclic aromatic amines, and 5 are also amides), 24 are tertiary amines (7 of these are also secondary amines, one is also a cyclic aromatic amine, and three are also amides), and 16 are cyclic aromatic amines (two of these are also primary amines, 10 are also secondary amines, one is also a tertiary amine, and three are also amides).

Of the 15 amides with positive genotoxic findings, four are primary amides (all of these are also amines), one is a secondary amide (and also an amine), two are tertiary amides (one of these is also an amine), three are ureas, one is a carbamate (and also an amine), three are sulfonamides (all of these are also amines, and one is also a guanidine), and two are guanidines (both of these are also amines, and one is also a sulfonamide).

Information on study design and study findings from these genotoxicity studies is tabulated in Table 10 (Amines tested in combination with nitrite for genotoxicity) and Table 11 (Amides tested in combination with nitrite for genotoxicity) below.

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity

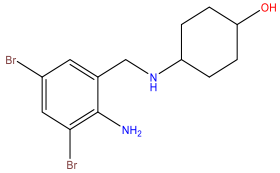
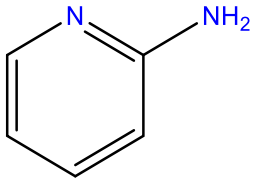
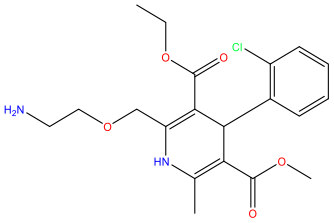
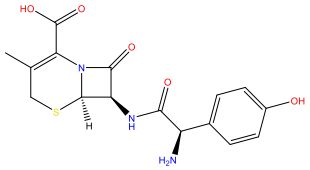
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results				↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Primary Amines									
Ambroxol (primary amine and secondary amine)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)				**Yes**
					-S9		+S9		
				Control	139		102		
				$NaNO_2$	139		82		
				Ambroxol	N (Non-mutagenic)[4]		N[4]		
				Ambroxol/nitrite[3]	320		180		
2-Aminopyridine (primary amine and cyclic aromatic amine)		Kammerer *et al.*, 1986[1]†	*S. typhimurium*, TA98 and TA100 reverse mutation		No. of Revertants				**Yes** (in TA98 without S9)
					TA 98		TA 100		
					-S9	+S9	-S9	+S9	
				Control	18	23	116	126	
				$NaNO_2$	18	23	115	123	
				2-Aminopyridine	12	20	108	105	
				2-Aminopyridine/ nitrite[3]	35	29	127	117	
Amlodipine (primary amine and cyclic secondary amine)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)				**Yes**
					-S9		+S9		
				Control	139		102		
				$NaNO_2$	139		82		
				Amlodipine	N[4]		N[4]		
				Amlodipine/nitrite[3] (Amlodipine mg/mL) 0.06	223		171		
				0.12	182		223		
Cefadroxil (primary amine, secondary amide, cyclic tertiary amide)		Brambilla *et al.*, 1985†	DNA strand breaks in Chinese hamster ovary (CHO) cells *in vitro*		DNA-damage (single strand breaks) potency[5]				**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	0				
				Cefadroxil	N[4]				
				Cefadroxil/nitrite[3] (Yield: 18 – 19%)	12.6				

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

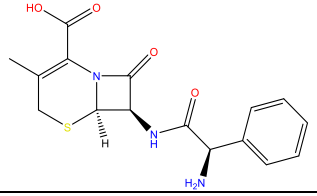
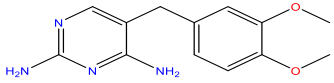
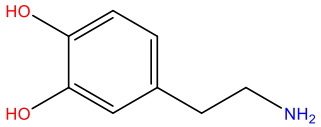
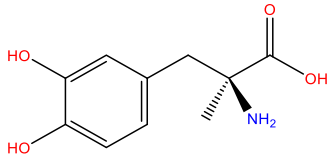
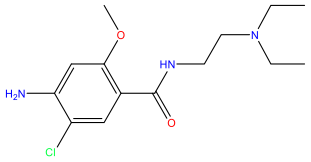
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Primary Amines (continued)						
Cefalexin (primary amine, secondary amide, cyclic tertiary amide)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	0	
				Cefalexin	N[4]	
				Cefalexin/nitrite[3] (Yield: 0.5 – 1.5%)	14.8	
Diaveridine (primary amine and cyclic aromatic amine)		Ono-Ogata *et al.*, 2002[1]†	*E. coli* WP2*uvr*A/pKM 101 reverse mutation		No. of Revertants	**No**
				Control	118	
				$NaNO_2$	117	
				Diaveridine	118	
				Diaveridine/nitrite[3]	134	
Dopamine		Changhao *et al.*, 1995[1]†	*S. typhimurium* TA98, TA100 and E. *coli* WP2uvrA reverse mutation		Revertants/plate: TA 100 / TA 98 / WP2uvrA	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	116 / 14 / 16	
				Dopamine	123 / 11 / 18	
				Dopamine/nitrite[3]	571 / 181 / 96	
Methyldopa		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Methyldopa: TA98 / TA100	**?** (Increased effect observed with NO_2 + amine compared to amine alone; no NO_2 alone)
				Control	16 / 66	
				Methyldopa	N[4] / N[4]	
				Methyldopa/nitrite[3] (Yield: 5%)	38 / 206	
Metoclo-pramide (primary amine, secondary amide and tertiary amine)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	0	
				Metoclopramide	N[4]	
				Metoclopramide/nitrite[3] (Yield: 5 – 9%)	64.9	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

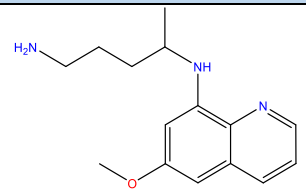
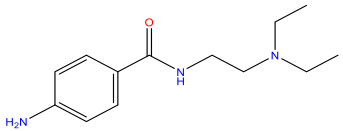
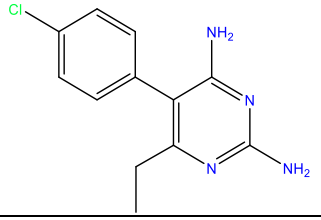
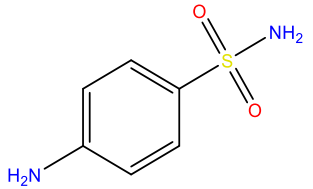
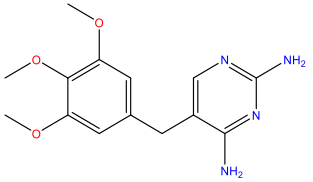
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Primary Amines (continued)						
Primaquine (primary amine, secondary amine and cyclic aromatic amine)		Ono-Ogata *et al.*, 2002[1]†	*E. coli* WP2*uvr*A/pKM 101 reverse mutation		No. of Revertants	**Yes**
				Control	118	
				$NaNO_2$	117	
				Primaquine	112	
				Primaquine/nitrite[3]	271	
Procainamide (primary amine, secondary amide and tertiary amine)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damaging potency[5]	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	0	
				Procainamide	N[4]	
				Procainamide/nitrite[3] (Yield: 75 – 100%)	6.9	
Pyrimethamine (primary amine and cyclic aromatic amine)		Ono-Ogata *et al.*, 2002[1]†	*E. coli* WP2*uvr*A/ pKM101 reverse mutation		No. of Revertants	**No**
				Control	118	
				$NaNO_2$	117	
				Pyrimethamine	102	
				Pyrimethamine/nitrite[3]	79	
Sulfanilamide (primary amine and sulfonamide)		Endo *et al.*, 1980†	Mutation induction in Syrian golden hamster embryos by injection of sulfanilamide *in vivo*		Mutant colonies/10^7 cells	**?** (Increased effect observed with NO_2 + amine compared to amine alone; no NO_2 alone)
				Control	7.5	
				Sulfanilamide	9.7	
				Sulfanilamide/nitrite[3]	426.6	
Trimethoprim (primary amine and cyclic aromatic amine)		Ono-Ogata *et al.*, 2002[1]†	*E. coli* WP2*uvr*A /pKM101 reverse mutation		No. of Revertants	**No**
				Control	118	
				$NaNO_2$	117	
				Trimethoprim	130	
				Trimethoprim/nitrite[3]	115	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

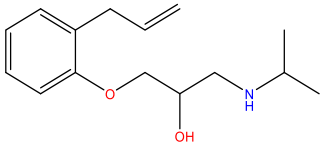
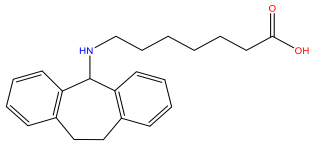
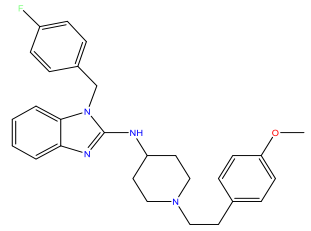
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines							
Alprenolol		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Alprenolol		**No**
					TA98	TA100	
				Control	16	66	
				Alprenolol	N[4]	N[4]	
				Alprenolol/nitrite[3] (Yield: 91%)	N[4]	N[4]	
Ambroxol	See primary amines						**Yes** (1 of 1 studies)
Amineptine		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)		**Yes**
					-S9	+S9	
				Control	139	102	
				$NaNO_2$	139	82	
				Amineptine	N[4]	N[4]	
				Amineptine/nitrite[3] (mg/mL) 1.4	270	128	
				2.8	267	226	
Amlodipine	See primary amines						**Yes** (1 of 1 studies)
Astemizole (secondary amine, cyclic tertiary amine and cyclic aromatic amine)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)		**Yes**
					-S9	+S9	
				Control	139	102	
				$NaNO_2$	139	82	
				Astemizole	N[4]	N[4]	
				Astemizole/nitrite[3] (mg/mL) 0.14	301	190	
				0.28	305	201	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

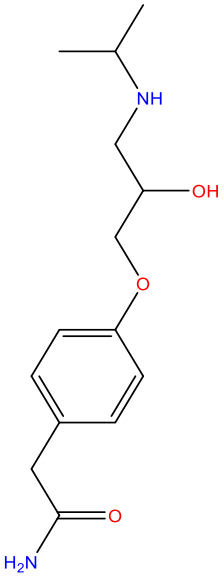
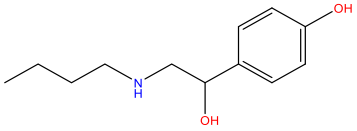
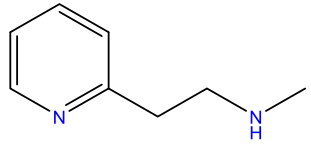
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)						
Atenolol (secondary amine and primary amide)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)	**Yes**
					-S9 / +S9	
				Control	139 / 102	
				$NaNO_2$	139 / 82	
				Atenolol	N[4] / N[4]	
				Atenolol/nitrite[3] (mg/mL) 0.7	209 / 275	
				1.4	292 / 337	
				2.1	320 / 245	
				2.8	500 / 214	
				3.5	403 / 204	
		Martelli *et al.*, 1994[1]†	Micronucleus tests in rat hepatocytes, rat polychromatic erythrocytes (PCEs) in bone marrow and spleen *in vivo*		Frequency of micronucleated cells (%)	**?** (Increased effect observed with NO_2 + amine compared to amine alone for rat hepatocytes; no NO_2 alone)
					Hepatocytes / PCEs in bone marrow / PCEs in spleen	
				Control	1.66 / 64.9 / 13.1	
				Atenolol	1.98 / 54.6 / 8.7	
				Atenolol/nitrite[3]	4.96 / 54.0 / 12.3	
Bamethan		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Bamethan	**?** (Increased effect observed with NO_2 + amine compared to amine alone; no NO_2 alone)
					TA98 / TA100	
				Control	16 / 66	
				Bamethan	N[4] / N[4]	
				Bamethan/nitrite[3] (Yield: 80%)	5816 / 5366	
Betahistine (secondary amine and cyclic aromatic amine)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)	**Yes**
					-S9 / +S9	
				Control	139 / 102	
				$NaNO_2$	139 / 82	
				Betahistine	N[4] / N[4]	
				Betahistine/nitrite[3]	292 / 286	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

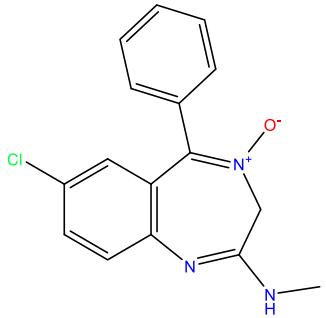
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)						
Chlordiaz-epoxide (secondary amine and cyclic aromatic amine)		Takeda and Kanaya, 1981†	*S. typhimurium* TA98 and TA100 reverse mutation	Revertants	TA98: -S9 / +S9; TA100: -S9 / +S9	**?** (Increased effect observed with NO_2 + amine compared to amine alone; no NO_2 alone)
				Control	15 / 30 / 110 / 120	
				Chlordiazepoxide	N[4] / N[4] / N[4] / N[4]	
				Chlordiazepoxide/nitrite[3] (Yield: 57.4%)	44 / 29 / 12000 / 3500	
		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 reverse mutation		TA 1535 / TA 1537 / TA 1538 / TA 98 / TA 100	**Yes**
				Control	13 / 16 / 15 / 34 / 169	
				$NaNO_2$	19 / 5 / 10 / 30 / 172	
				Chlordiazepoxide	13 / 12 / 9 / 27 / 158	
				Chlordiazepoxide/nitrite[3]	42 / 28 / 39 / 112 / 360	
		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U): -S9 / +S9	**Yes**
				Control	139 / 102	
				$NaNO_2$	139 / 82	
				Chlordiazepoxide	N[4] / N[4]	
				Chlordiazepoxide/nitrite[3]	297 / 310	
		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	0	
				Chlordiazepoxide	N[4]	
				Chlordiazepoxide/nitrite[3] (Yield: 69-70%)	323	
		Robbiano *et al.*, 1990†	DNA strand breaks in liver of male SD rats *in vivo*		DNA fragmentation (%)	**Yes**
				Control	14.5	
				$NaNO_2$	15.2	
				Chlordiazepoxide	14.0	
				Chlordiazepoxide + $NaNO_2$	26.2	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

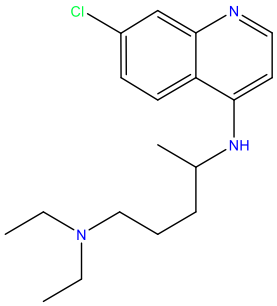
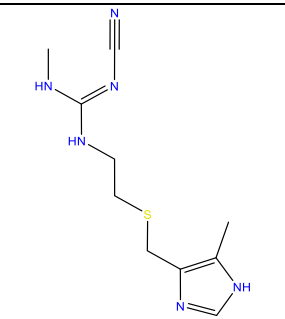
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)						
Chloroquine (secondary amine, tertiary amine and cyclic aromatic amine)		Arriaga Alba *et al.*, 1988†	*S. typhimurium* TA1535 reverse mutation		Revertants/plate +S9 / -S9	**Yes**
				Control	29.00 / 33.50	
				$NaNO_2$	32.16 / 36.50	
				Chloroquine	25.00 / 28.60	
				Chloroquine/nitrite[3] (Yield: 12%)	164.35 / 44.00	
		Arriaga Alba *et al.*, 1989[1]†	*S. typhimurium* TA1535 reverse mutations induced by urine from exposed male CD-1 mice		Revertants/plate +β-glucuronidase / -β-glucuronidase	**Yes**
				Control	37.3 / 25.3	
				$NaNO_2$	42.0 / 43.3	
				Chloroquine	48.0 / 50.0	
				Chloroquine + $NaNO_2$	101.6 / 67.3	
		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	0	
				Chloroquine	N[4]	
				Chloroquine/nitrite[3] (Yield: 15%)	14.7	
Cimetidine (cyclic secondary amine and guanidine)		De Flora and Picciotto, 1980[1]†	*S. typhimurium* TA100, TA98, TA1535, TA1537, TA1538 reverse mutations induced by human gastric juice + treatment		Revertants/plate TA 1535: - S9 / + S9; TA 1537: - S9 / + S9; TA 1538: - S9 / + S9; TA98: - S9 / + S9; TA100: - S9 / + S9	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amine alone, no control)
				$NaNO_2$	14 / 11 / 10 / 47 / 19 / 28 / 28 / 39 / 179 / 162	
				Cimetidine/nitrite[3]	389 / 324 / 8 / 34 / 59 / 71 / 72 / 93 / 849 / 811	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

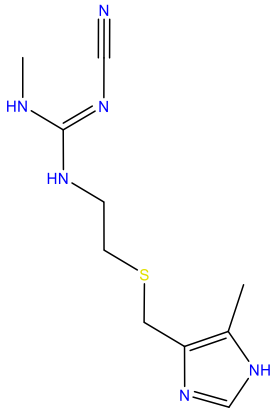
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results			↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)								
Cimetidine (cyclic secondary amine and guanidine) (continued)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)			**Yes**
					-S9	+S9		
				Control	139	102		
				$NaNO_2$	139	82		
				Cimetidine	N[4]	N[4]		
				Cimetidine/nitrite[3] (mg/mL) 3.20	125	Not tested (NT)		
				6.40	195	214		
				9.60	236	NT		
				12.80	292	224		
				16.00	209	224		
		Brambilla *et al.*, 1982†	DNA strand breaks in liver of male SD rats *in vivo*		% DNA Eluted from Filter (Mean)			**No**
				Control	21.9			
				$NaNO_2$	23.5			
				Cimetidine	23.9			
				Cimetidine + $NaNO_2$	27.2			
		Pino and Robbiano, 1983†	DNA strand breaks in gastric mucosa of male SD albino rats *in vivo*		% DNA Eluted from Filter (Mean)			**No**
				Control	24.6			
				$NaNO_2$	26.5			
				Cimetidine	24.3			
				Cimetidine + $NaNO_2$	25.8			
		Kyrtopoulos *et al.*,1982†	Covalent binding to DNA in male Wistar rats *in vivo*		µmol *O*-methylguanine/mol guanine			**No**
					Stomach	Liver	Intestines	
				Citrate buffer (control)	Not detected (ND)	ND	ND	
				Cimetidine	ND	ND	ND	
				Cimetidine + $NaNO_2$	ND	ND	ND	
				N-methyl-N'-nitro-N-nitrosoguanidine (positive control)	10	8	5	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

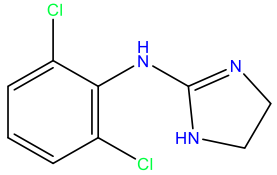
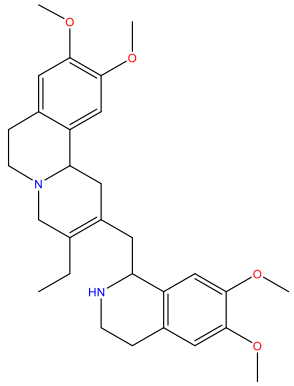
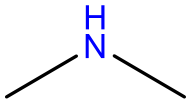
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)							
Clonidine (secondary amine and cyclic secondary amine)		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Clonidine		**?** (Increased effect observed with NO_2 + amine compared to amine alone; no NO_2 alone)
					TA98	TA100	
				Control	16	66	
				Clonidine	N[4]	N[4]	
				Clonidine/nitrite[3] (Yield: 75%)	830	1400	
Dehydroemetine (cyclic secondary amine and cyclic tertiary amine)		Arriaga Alba *et al.*, 1988†	*S. typhimurium* TA1535 reverse mutation		Revertants/plate		**Yes**
					+S9	-S9	
				Control	29.00	33.50	
				$NaNO_2$	32.16	36.50	
				Dehydroemetine	32.16	38.16	
				Dehydroemetine/nitrite[3] (Yield: 17%)	176.50	52.80	
		Arriaga Alba *et al.*, 1989[1]†	*S. typhimurium* TA1535 reverse mutations induced by urine from exposed male CD-1 mice		Revertants/plate		**Yes**
					+β-glucuronidase	-β-glucuronidase	
				Control	37.3	25.3	
				$NaNO_2$	42.0	43.3	
				Dehydroemetine	34.6	31.6	
				Dehydroemetine + $NaNO_2$	74.0	67.5	
Dimethylamine (DMA)		Whong *et al.*,1979	*S. typhimurium* G46, host-mediated assay in female CD-1 mice		No. of Revertants		**Yes**
				Control	0.6		
				$NaNO_2$	0.5		
				DMA	0.6		
				$NaNO_2$+DMA	99		
			S. typhimurium G46, host-mediated assay in female CD rats		No. of Revertants		**Yes**
				Control	0.4		
				$NaNO_2$	0.9		
				DMA	0.7		
				$NaNO_2$+DMA	164		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

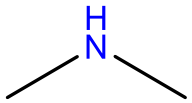
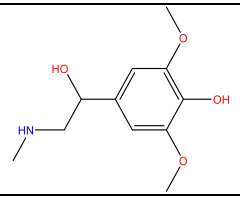
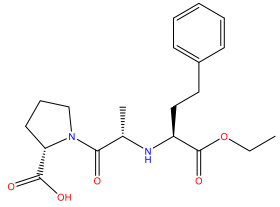
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)							
Dimethylamine (DMA) (continued)		Couch and Friedman, 1975	*S. typhimurium* G46, host-mediated assay in male ICR mice		Mutant Frequency (mutant cells/total cells)		**Yes**
				Control	0.007		
				$NaNO_2$	0.004		
				DMA	0.005		
				$NaNO_2$+DMA	0.026		
		Rubenchik *et al.*, 1990[1]	*S. typhimurium* reverse mutation assay in strains TA1950 and TA100		No. of Revertants		**No**
					TA100	TA1950	
				Control	85	9	
				$NaNO_2$	1354	580	
				DMA	101	14	
				$NaNO_2$+DMA	1232	480	
			DNA single-strand breaks in liver of male rats *in vivo*		DNA damage (%)		**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	5		
				DMA	2.5		
				$NaNO_2$+DMA	10		
Dimetofrine (dimethophrine)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]		**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	0		
				Dimetofrine	N[4]		
				Dimetofrine/nitrite[3] (Yield: 68-73%)	305		
Enalapril (secondary amine and cyclic tertiary amide)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)		**Yes**
					-S9	+S9	
				Control	139	102	
				$NaNO_2$	139	82	
				Enalapril	N[4]	N[4]	
				Enalapril/nitrite[3] (mg/mL) 0.56	168	130	
				1.12	402	361	
				1.66	291	278	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

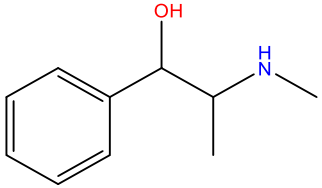
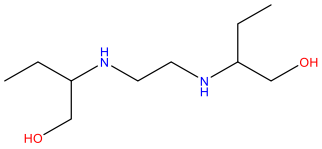
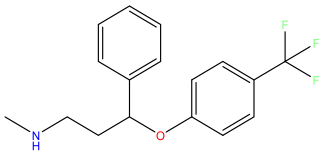
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results				↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)									
Ephedrine		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)				**Yes**
					-S9		+S9		
				Control	139		102		
				$NaNO_2$	139		82		
				Ephedrine	N[4]		N[4]		
				Ephedrine/nitrite[3] (mg/mL) 1.00	358		237		
				2.00	718		510		
Ethambutol		Takeda and Kanaya, 1982[1]†	*S. typhimurium* TA98 and TA100 reverse mutation	Revertants	TA98		TA100		**?** (Less than two-fold increase above control observed with NO_2 + amine; no NO_2 alone)
					-S9	+S9	-S9	+S9	
				Control	20	22	117	126	
				Ethambutol	N[4]	N[4]	N[4]	N[4]	
				Ethambutol/nitrite[3]	±[7]	±[7]	±[7]	±[7]	
		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)				**Yes**
					-S9		+S9		
				Control	139		102		
				$NaNO_2$	139		82		
				Ethambutol	N[4]		N[4]		
				Ethambutol/nitrite[3] (mg/mL) 25.00	213		115		
				50.00	190		131		
				75.00	199		149		
Fluoxetine		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)				**Yes**
					-S9		+S9		
				Control	139		102		
				$NaNO_2$	139		82		
				Fluoxetine	N[4]		N[4]		
				Fluoxetine/nitrite[3] (mg/mL) 0.06	351		337		
				0.09	506		441		
				0.12	318		306		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

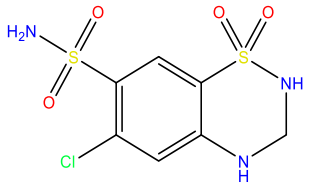
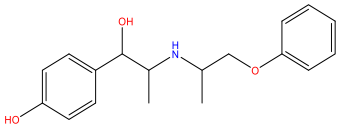
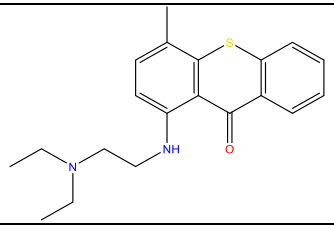
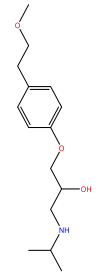
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)						
Hydrochloro-thiazide (cyclic secondary amine and sulfonamide)		Andrews *et al.*, 1984[1]†	*S. typhimurium* TA98 and TA100 reverse mutation		TA1535 -S9 / TA1535 +S9 / TA1538 -S9 / TA1538 +S9 / TA98 -S9 / TA98 +S9 / TA100 -S9 / TA100 +S9	**Yes** (TA98)
				Control	12 / 15 / 11 / 21 / 17 / 37 / 103 / 113	
				$NaNO_2$	7 / 12 / 6 / 21 / 16 / 32 / 87 / 104	
				Hydrochlorothiazide	9 / 6 / 6 / 16 / 18 / 36 / 110 / 122	
				Hydrochlorothiazide/ nitrite[3]	3 / 19 / 9 / 10 / 67 / 94 / 67 / 144	
Isoxsuprine		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Isoxsuprine: TA98 / TA100	**?** (Increased effect observed with NO_2 + amine compared to amine alone; no NO_2 alone)
				Control	16 / 66	
				Isoxsuprine	N[4] / N[4]	
				Isoxsuprine/nitrite[3] (Yield: 31%)	450 / 610	
Lucanthone (secondary and tertiary amine)		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98, TA100, TA1535, TA1538 reverse mutation		TA1535 -S9 / TA1535 +S9 / TA1538 -S9 / TA1538 +S9 / TA98 -S9 / TA98 +S9 / TA100 -S9 / TA100 +S9	**No**
				Control	21 / 22 / 9 / 18 / 35 / 44 / 236 / 136	
				$NaNO_2$	19 / 18 / 10 / 20 / 30 / 36 / 172 / 117	
				Lucanthone	17 / 24 / 17 / 120 / 29 / 188 / 126 / 189	
				Lucanthone/nitrite[3]	34 / 31 / 16 / 75 / 38 / 121 / 254 / 196	
Metoprolol		Ozhan and Alpertunga, 2003[1]†	*umu*-test with S. typhimurium TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U): -S9 / +S9	**Yes**
				Control	139 / 102	
				$NaNO_2$	139 / 82	
				Metoprolol	N[4] / N[4]	
				Metoprolol/nitrite[3] (mg/mL) 0.60	299 / 207	
				1.20	271 / 171	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

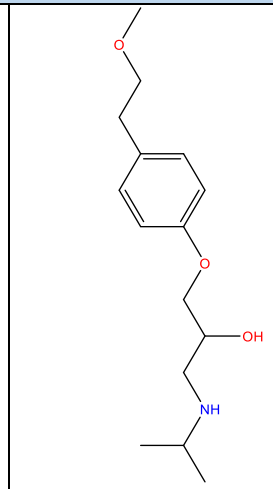
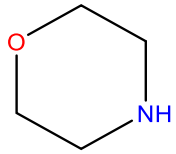
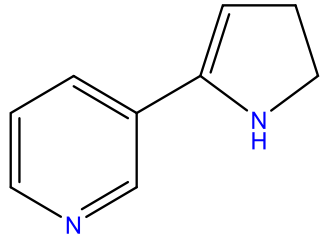
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results				↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)									
Metoprolol (continued)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damaging potency[5]				**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone and amine alone; no untreated control)
				$NaNO_2$	0				
				Metoprolol	N[4]				
				Metoprolol/nitrite[3] (Yield: 34-57%)	11.3				
		Martelli *et al.*,1994[1]†	Micronucleus tests in rat hepatocytes, rat PCEs in bone marrow and spleen *in vivo*		Frequency of micronucleated cells (%)				**?** (Increased effect observed with NO_2 + amine compared to amine alone for rat hepatocytes; no NO_2 alone)
					Hepatocytes	PCEs in bone marrow	PCEs in spleen		
				Control	1.66	64.9	13.1		
				Metoprolol	1.74	59.7	9.9		
				Metoprolol/nitrite[3]	6.92	58.1	12.5		
Morpholine (MOR) (heterocyclic secondary amine)		Edwards *et al.*, 1979	*S. typhimurium* 1530, host-mediated assay in female CD-1 mice		No. of Revertants				**Yes**
				Control	2.3				
				$NaNO_2$	2.3				
				MOR	2.9				
				$NaNO_2$+MOR	43.9				
Myosmine (cyclic aromatic amine and cyclic secondary amine)		Hecht *et al.*, 2007[3]†	Hemoglobin (Hb) and DNA adducts in liver, lung and esophagus in male F-344 rats *in vivo*		Hb adducts (mmol/mg Hb)	DNA adducts			**Yes** (Hb adducts)
						Liver	Lung	Esophagus	
				Control	0.007	ND	ND	ND	
				$NaNO_2$	0.11	ND	ND	ND	
				Myosmine	0.33	ND	ND	ND	
				Myosmine/nitrite[3]	0.30	ND	ND	ND	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

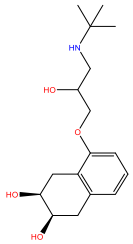
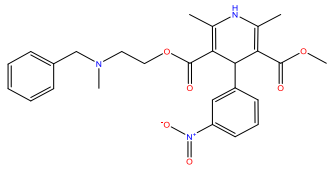
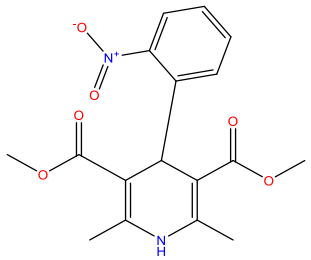
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results			↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)								
Nadolol		Martelli *et al.*,1994[1]†	Micronucleus tests in rat hepatocytes, rat PCEs in bone marrow and spleen *in vivo*		Frequency of micronucleated cells (%)			**?** (Increased dose response effect observed with NO_2 + amine compared to amine for rat hepatocytes; no NO_2 alone)
					Hepatocytes	PCEs in bone marrow	PCEs in spleen	
				Control	1.66	64.9	13.1	
				Nadolol	1.24	54.3	5.7	
				Nadolol/nitrite[3]	6.21	62.8	11.6	
Nicardipine (cyclic secondary amine and tertiary amine)		Martelli *et al.*, 2007†	DNA strand breaks in liver of male SD rats *in vivo*		Comet assay metric			**Yes**
					Tail length (µm)		Tail moment	
				Control	1.83		170	
				$NaNO_2$	2.16		210	
				Nicardipine	2.11		191	
				Nicardipine + $NaNO_2$	3.36		301	
Nifedipine (cyclic secondary amine)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with S. typhimurium TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)			**Yes**
					-S9		+S9	
				Control	139		102	
				$NaNO_2$	139		82	
				Nifedipine	N[4]		N[4]	
				Nifedipine/nitrite[3] (mg/mL) 0.07	360		289	
				0.15	521		373	
		Martelli *et al.*, 2007†	DNA strand breaks in liver of male SD rats *in vivo*		Comet assay metric			**Yes**
					Tail length (µm)		Tail moment	
				Control	1.83		170	
				$NaNO_2$	2.16		210	
				Nifedipine	1.87		212	
				Nicardipine + $NaNO_2$	4.14		363	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

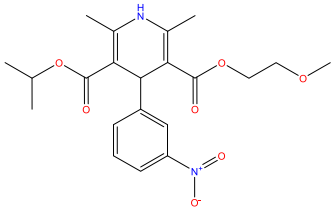
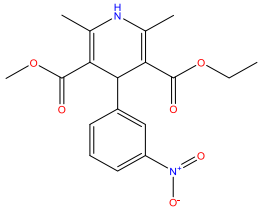
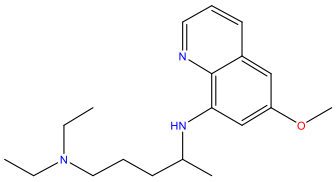
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)							
Nimodipine (cyclic secondary amine)		Martelli *et al.*, 2007†	DNA strand breaks in liver of male SD rats *in vivo*		Comet assay metric		**Yes**
					Tail length (µm)	Tail moment	
				Control	1.83	170	
				$NaNO_2$	2.16	210	
				Nimodipine	1.05	101	
				Nicardipine + $NaNO_2$	3.31	301	
Nitrendipine (cyclic secondary amine)		Martelli *et al.*, 2007†	DNA strand breaks in liver of male SD rats *in vivo*		Comet assay metric		**Yes**
					Tail length (µm)	Tail moment	
				Control	1.83	170	
				$NaNO_2$	2.16	210	
				Nitrendipine	1.59	186	
				Nicardipine + $NaNO_2$	3.36	313	
Pamaquine (secondary, tertiary and cyclic aromatic amine)		Ono-Ogata *et al.*, 2002[1]†	*E.* coli WP2*uvr*A /pKM101 reverse mutation		No. of Revertants/plate		**Yes**
					-S9	+S9	
				Control	100	141	
				$NaNO_2$	72	139	
				Pamaquine 200 (µg/plate)	93	167	
				300	107	156	
				400	98	174	
				Pamaquine/nitrite[3] 100 (µg/plate)	204	301	
				200	321	370	
				300	358	545	
				400	440	676	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

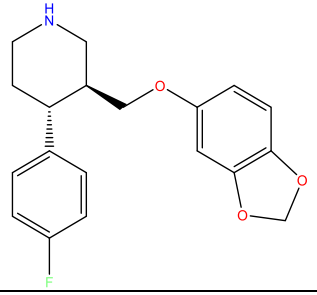
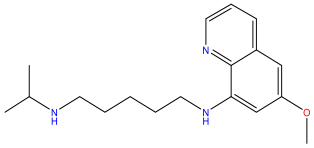
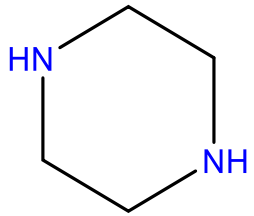
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)							
Paroxetine (cyclic secondary amine)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)		**Yes**
					-S9	+S9	
				Control	139	102	
				$NaNO_2$	139	82	
				Paroxetine	N[4]	N[4]	
				Paroxetine/nitrite[3] (mg/mL) 0.7	304	309	
				1.4	391	358	
				2.1	450	309	
Pentaquine (secondary amine and cyclic aromatic amine)		Ono-Ogata *et al.*, 2002[1]†	*E. coli* WP2*uvr*A/ pKM101 reverse mutation		No. of Revertants/plate		**Yes**
					-S9	+S9	
				Control	111	147	
				$NaNO_2$	75	144	
				Pentaquine	130	128	
				Pentaquine/nitrite[3]	266	394	
Piperazine (cyclic secondary amine)		Arriaga Alba *et al.*, 1988†	*S. typhimurium* TA1535 reverse mutation		Revertants/plate		**Yes**
					+S9	-S9	
				Control	29.00	33.50	
				$NaNO_2$	32.16	36.50	
				Piperazine	27.82	26.30	
				Piperazine/nitrite[3] (Yield: 38%)	165.25	72.25	
		Arriaga Alba *et al.*, 1989[1]†	*S. typhimurium* TA1535 reverse mutations induced by urine from exposed male CD-1 mice		Revertants/plate		**Yes**
					+ β-galactosidase	- β-galactosidase	
				Control	37.3	25.3	
				$NaNO_2$	42.0	43.3	
				Piperazine	47.6	51.6	
				Piperazine + $NaNO_2$	105.6	47.6	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

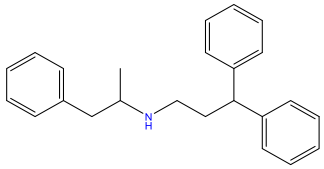
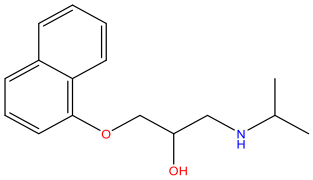
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)							
Prenylamine		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Prenylamine		**No**
					TA98	TA100	
				Control	16	66	
				Prenylamine	N[4]	N[4]	
				Prenylamine/nitrite[3] (Yield: 10%)	N[4]	N[4]	
Primaquine	See primary amines						**Yes** (1 of 1 studies)
Propranolol		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Propanolol		**?** (Increased effect observed with NO_2 + amine compared to amine alone in TA98; no NO_2 alone)
					TA98	TA100	
				Control	16	66	
				Propanolol	N[4]	N[4]	
				Propanolol/nitrite[3] (Yield: 94%)	53	N[4]	
		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)		**Yes**
					-S9	+S9	
				Control	139	102	
				$NaNO_2$	139	82	
				Propranolol	N[4]	N[4]	
				Propranolol/nitrite[3](mg/mL) 0.08	431	255	
				0.16	473	377	
				0.32	639	469	
				0.48	473	347	
				0.64	320	326	
				0.72	236	265	
		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]		**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amine alone, no untreated control)
				$NaNO_2$	0		
				Propanolol	N[4]		
				Propranolol/nitrite[3] (Yield: 58-71%)	29.6		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

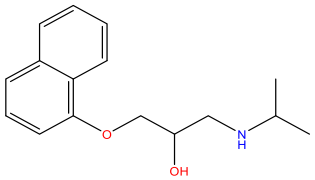
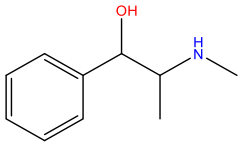
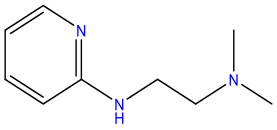
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results				↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)									
Propranolol (continued)		Martelli *et al.*,1994[1]†	Micronucleus tests in rat hepatocytes, rat PCEs in bone marrow and spleen *in vivo*		Frequency of micronucleated cells (%)				**?** (Increased dose response effect observed with NO_2 + amine compared to amine alone for rat hepatocytes; no NO_2 alone)
					Hepatocytes	PCEs in bone marrow	PCEs in spleen		
				Control	1.66	64.9	13.1		
				Propranolol	0.75	53.0	12.1		
				Propranolol/nitrite[3]	6.94	46.9	10.6		
Pseudoephedrine		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)				**Yes**
					-S9		+S9		
				Control	139		102		
				$NaNO_2$	139		82		
				Pseudoephedrine	N[4]		N[4]		
				Pseudoephedrine/nitrite[3] (mg/mL) 0.84	153		122		
				1.68	459		347		
2-Pyridyl-N'-dimethylethylene-diamine (secondary, tertiary and cyclic aromatic amine)		Kammerer *et al*, 1986[1]†	*S. typhimurium* TA100 and TA98 reverse mutation		No. of Revertants				**Yes**
					TA98		TA100		
					+S9	-S9	+S9	-S9	
				Control	23	18	126	116	
				$NaNO_2$	23	18	123	115	
				2-Pyridyl-N'-dimethylethylene-diamine	29	16	106	113	
				N-2-Pyridyl-N'-dimethylethylene-diamine/nitrite[3]	24	35	320	191	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

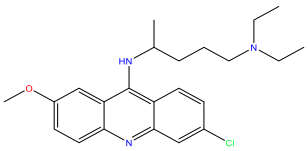
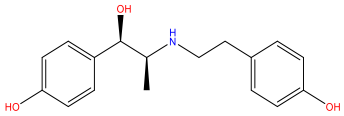
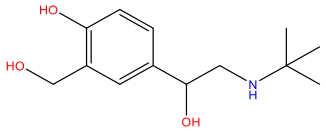
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)													
Quinacrine (secondary, tertiary and cyclic aromatic amine)		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98, TA100, TA1535, TA1538 reverse mutation		TA 1535		TA 1538		TA 98		TA 100		**Yes**
					-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	
				Control	21	22	9	18	35	44	236	136	
				$NaNO_2$	19	18	10	20	30	36	172	117	
				Quinacrine	20	62	34	42	50	84	165	251	
				Quinacrine/nitrite[3]	33	42	40	34	86	96	703	453	
Ritodrine		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)								**Yes**
					-S9						+S9		
				Control	139						102		
				$NaNO_2$	139						82		
				Ritodrine	N[4]						N[4]		
				Ritodrine/nitrite[3] (mg/mL) 0.14	165						143		
				0.28	181						156		
				0.42	131						211		
Salbutamol		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)								**Yes**
					-S9						+S9		
				Control	139						102		
				$NaNO_2$	139						82		
				Salbutamol	N[4]						N[4]		
				Salbutamol/nitrite[3] (mg/mL) 0.16	150						305		
				0.24	320						180		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

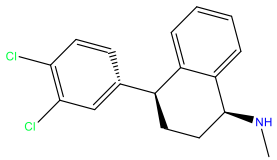
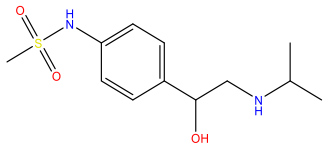
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results			↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)								
Sertraline		Ozhan and Alpertunga, 2003[1]	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)			**Yes**
					-S9	+S9		
				Control	139	102		
				$NaNO_2$	139	82		
				Sertraline	N[4]	N[4]		
				Sertraline/nitrite[3] (mg/mL) 0.07	179	145		
				0.14	222	102		
Sotalol (secondary amine and secondary sulfonamide)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)			**Yes**
					-S9	+S9		
				Control	139	102		
				$NaNO_2$	139	82		
				Sotalol	N[4]	N[4]		
				Sotalol/nitrite[3] (mg/mL) 3.00	253	172		
				6.00	354	250		
				9.00	349	297		
		Martelli *et al.*,1994[1]†	Micronucleus tests in rat hepatocytes, rat PCEs in bone marrow and spleen *in vivo*		Frequency of micronucleated cells (%)			**?** (Increased effect observed with NO_2 + amine compared to amine alone for rat hepatocytes; no NO_2 alone)
					Hepatocytes	PCEs in bone marrow	PCEs in spleen	
				Control	1.66	64.9	13.1	
				Sotalol	1.24	50.3	14.2	
				Sotalol/nitrite[3]	4.95	56.3	12.8	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

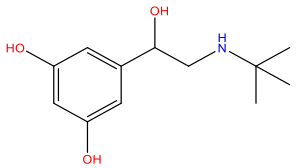
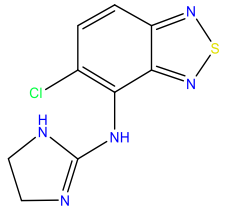
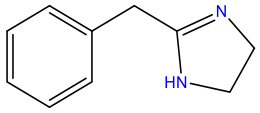
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)							
Terbutaline		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)		**Yes**
					-S9	+S9	
				Control	139	102	
				$NaNO_2$	139	82	
				Terbutaline	N[4]	N[4]	
				Terbutaline/nitrite[3] (mg/mL) 0.04	292	122	
				0.08	570	184	
				0.12	487	214	
Tizanidine (secondary amine, cyclic secondary amine and heterocyclic aromatic amine)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U)		**Yes**
					-S9	+S9	
				Control	139	102	
				$NaNO_2$	139	82	
				Tizanidine	N[4]	N[4]	
				Tizanidine/nitrite[3] (mg/mL) 0.04	292	525	
				0.12	356	611	
				0.16	367	751	
Tolazoline (cyclic secondary amine; 4,5-dihydro-1*H*-imidazole)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damaging potency[5]		**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amine alone, no untreated control)
				$NaNO_2$	0		
				Tolazoline	N[4]		
				Tolazoline/nitrite[3] (Yield: 1-2%)	3192		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

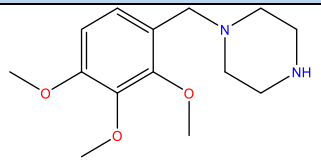
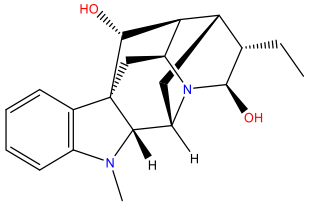
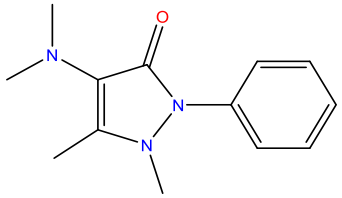
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amines (continued)						
Trimetazidine (cyclic secondary amine and cyclic tertiary amine)		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Trimetazidine: TA98 / TA100	**?** (Increased effect observed with NO_2 + amine compared to amine alone; no NO_2 alone)
				Control	16 / 66	
				Trimetazidine	N[4] / N[4]	
				Trimetazidine/nitrite[3] (Yield: 98%)	73 / 290	
Tertiary Amines						
Ajmaline (cyclic tertiary amine)		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Ajmaline: TA98 / TA100	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
				Control	16 / 66	
				Ajmaline	N[4] / N[4]	
				Ajmaline/nitrite[3] (Yield 80%)	226 / 606	
Aminopyrine (AP, Aminophenazone) (tertiary amine and cyclic tertiary amine)		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98, TA100, TA1535, TA1538 reverse mutation		Revertants/plate: TA1535 (-S9 / +S9), TA1538 (-S9 / +S9), TA98 (-S9 / +S9), TA100 (-S9 / +S9)	**Yes** (TA100 with S9)
				Control	21 / 22 / 9 / 18 / 35 / 44 / 236 / 136	
				$NaNO_2$	19 / 18 / 10 / 20 / 30 / 36 / 172 / 117	
				Aminopyrine	18 / 27 / 6 / 21 / 27 / 31 / 178 / 139	
				Aminopyrine/nitrite[3]	29 / 18 / 14 / 23 / 26 / 49 / 177 / 164	
		Boido *et al.*, 1980[1]†	*S. typhimurium* TA100 reverse mutation		Revertants/plate	**?** (Increased effect observed with NO_2 + amine as compared to nitrite alone; no control alone)
				$NaNO_2$ (2.2µM)	180	
				$NaNO_2$ (36µM)	260	
				Aminopyrine	200	
				Aminopyrine/2.2µM nitrite[3]	320	
				Aminopyrine/36 µM nitrite[3]	1000	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

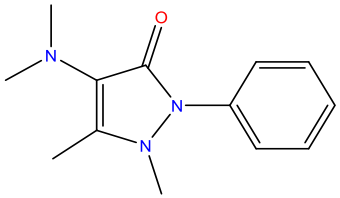
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)							
Aminopyrine (AP, aminophenazone) (tertiary amine and cyclic tertiary amine) (continued)		Braun *et al.*, 1980†	*S. typhimurium* G46, host-mediated assay in mice		Mutation frequency (Mf) x 10^{-9}		**Yes**
					Intraperitoneal	Intravenous	
				Control	3.66	3.96	
				$NaNO_2$	N[4]	N[4]	
				Aminophenazone	N[4]	N[4]	
				Aminophenazone, +$NaNO_2$	9.17	4622.98	
		Parodi *et al.*, 1980[1]†	DNA strand breaks in liver of male SD rats *in vivo*		Average DNA elution rate/ml		**Yes**
					Gavage	Drinking water	
				Control	0.015	0.015	
				$NaNO_2$	0.019	0.022	
				Aminophenazone	0.027	0.015	
				Aminophenazone/ nitrite[3] (mg/kg) 320/80	0.03	NT	
				400/200	NT	0.056	
		Farmer *et al.*,1986[1]†	Covalent binding to rat DNA *in vivo*		µg MeG excreted in urine/day		**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone, no untreated control)
				Aminophenazone	<1		
				Aminophenazone + $NaNO_2$	~7.5		
		Rubenchik *et al.*,1990	*S. typhimurium* reverse mutation assay in strains TA1950 and TA100		No. of Revertants		**No**
					TA100	TA1950	
				Control	85	9	
				$NaNO_2$	1354	580	
				AP	117	6.3	
				$NaNO_2$+AP	57	249	
			DNA single-strand breaks in liver of male rats *in vivo*		DNA damage (%)		**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amine alone)
				Control	5		
				$NaNO_2$	6.6		
				$NaNO_2$+AP	40		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

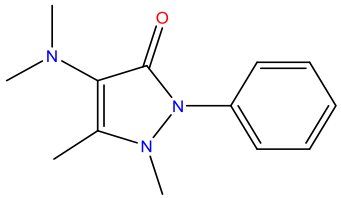
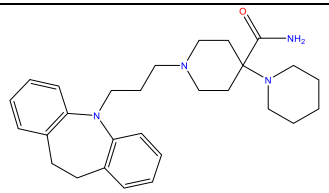
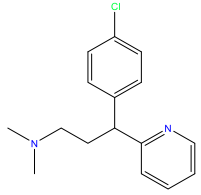
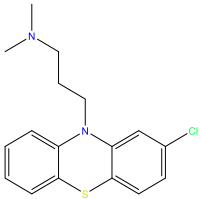
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Aminopyrine (AP, aminophenazone) (tertiary amine and cyclic tertiary amine) (continued)		Gombar *et al.*, 1983[1]†	Covalent binding to rat liver DNA *in vivo*		Amount of MeG Urine (nmol/day) / Liver (µmol/mol G)	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone, no untreated control)
				Aminophenazone (mg/kg) 146	0 / NT	
				Aminophenazone/nitrite[3] 140	114 / 2800	
				Aminophenazone /nitrite[3] 165	248 / 7900	
Astemizole	See secondary amines					**Yes** (1 of 1 studies)
Carpipramine (cyclic tertiary amine and primary amide)		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98: -S9 / +S9; TA 100: -S9 / +S9	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
				Control	15 / 30 / 110 / 120	
				Carpipramine	N[4] / N[4] / N[4] / N[4]	
				Carpipramine/nitrite[3] (Yield 2.9%)	---[9] / 500 / ---[9] / 310	
Chlorpheniramine (tertiary amine and cyclic aromatic amine)		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98, TA100, TA1537, TA1538 reverse mutation		TA 1537: -S9 / +S9; TA 1538: -S9 / +S9; TA 98: -S9 / +S9; TA 100: -S9 / +S9	**No**
				Control	15 / 20 / 9 / 18 / 35 / 44 / 236 / 136	
				$NaNO_2$	5 / 11 / 10 / 20 / 30 / 36 / 172 / 117	
				Chlorpheniramine	8 / 10 / 6 / 17 / 20 / 40 / 108 / 120	
				Chlorpheniramine/nitrite[3]	10 / 10 / 16 / 32 / 33 / 63 / 101 / 88	
Chlorpromazine (tertiary amine and cyclic tertiary amine)		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98: -S9 / +S9; TA 100: -S9 / +S9	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
				Control	15 / 30 / 110 / 120	
				Chlorpromazine	N[4] / N[4] / N[4] / N[4]	
				Chlorpromazine/nitrite[3] (Yield 5.3%)	---[9] / ±[7] / ±[7] / 350	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

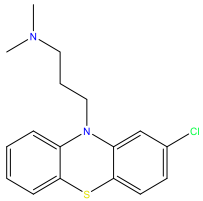
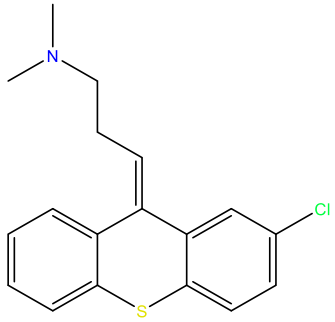
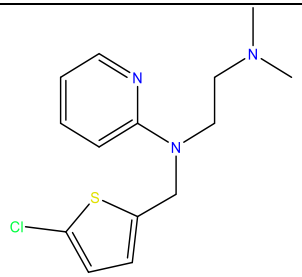
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Chlorpromazine (tertiary amine and cyclic tertiary amine) (continued)		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98, TA100, TA1537, TA1538 reverse mutation		Revertants/plate TA1537 -S9 / TA1537 +S9 / TA1538 -S9 / TA1538 +S9 / TA98 -S9 / TA98 +S9 / TA100 -S9 / TA100 +S9 Control: 15 / 20 / 9 / 18 / 35 / 44 / 236 / 136 $NaNO_2$: 5 / 11 / 10 / 20 / 30 / 36 / 172 / 117 Chlorpromazine: 18 / 14 / 14 / 24 / 27 / 41 / 183 / 142 Chlorpromazine/nitrite[3]: 65 / 39 / 929 / 805 / 1124 / 863 / 276 / 195	**Yes**
Chlorprothixene		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98 -S9: 15; TA 98 +S9: 30; TA 100 -S9: 110; TA 100 +S9: 120 Chlorprothixine: N[4] / N[4] / N[4] / N[4] Chlorprothixine/ nitrite[3] (Yield 43.4%): ---[9] / ±[7] / ---[9] / 81	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5] $NaNO_2$: 0 Chlorprothixine: N[4] Chlorprothixine/nitrite[3] (Yield 14 -21%): 263	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amine alone, no untreated control)
Chloroquine	See secondary amines					**Yes** (2 of 3 studies)
Chlorothen (tertiary and cyclic amine)		Andrews *et al.*, 1984[1]†	*S. typhimurium* TA98, TA100, TA1535, TA1538 reverse mutation		TA1535 -S9 / TA1535 +S9 / TA1538 -S9 / TA1538 +S9 / TA 98 -S9 / TA 98 +S9 / TA 100 -S9 / TA 100 +S9 Control: 12 / 15 / 11 / 21 / 17 / 37 / 103 / 113 $NaNO_2$: 7 / 12 / 6 / 21 / 16 / 32 / 87 / 104 Chlorothen: 17 / 15 / 5 / 26 / 7 / 25 / 21 / 93 Chlorothen/nitrite[3]: 4 / 4 / 16 / 16 / 4 / 18 / 2 / 58	**No**

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

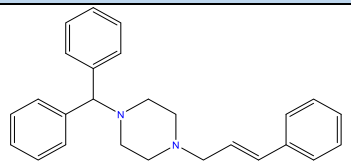
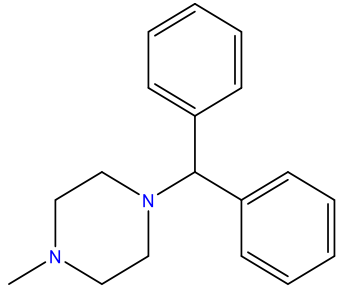
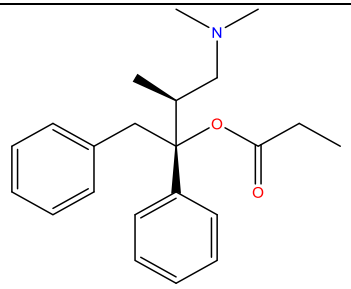
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Cinnarizine (cyclic tertiary amine)		Takeda and Kanaya, 1982†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98: -S9 / +S9; TA 100: -S9 / +S9	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
				Control	20 / 22 / 117 / 126	
				Cinnarizine	N[4] / N[4] / N[4] / N[4]	
				Cinnarizine/nitrite[3] (Yield 42.8%)	110 / 10 / 81 / 140	
Cyclizine (cyclic tertiary amine)		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98, TA100, TA1537, TA1538 reverse mutation		TA 1537: -S9 / +S9; TA 1538: -S9 / +S9; TA 98: -S9 / +S9; TA 100: -S9 / +S9	**Yes** (TA 98)
				Control	15 / 20 / 9 / 18 / 35 / 44 / 236 / 136	
				$NaNO_2$	5 / 11 / 10 / 20 / 30 / 36 / 172 / 117	
				Cyclizine	15 / 21 / 8 / 18 / 34 / 48 / 217 / 220	
				Cyclizine/nitrite[3]	28 / 22 / 15 / 29 / 103 / 61 / 299 / 136	
Dehydroemetine	See secondary amines					**Yes** (2 of 2 studies)
Dextro-propoxyphene		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98 reverse mutation		TA 1537: -S9 / +S9; TA 1538: -S9 / +S9; TA 98: -S9 / +S9; TA 100: -S9 / +S9	**Yes** (TA 98)
				Control	15 / 20 / 9 / 18 / 35 / 44 / 236 / 136	
				$NaNO_2$	5 / 11 / 10 / 20 / 30 / 36 / 172 / 117	
				Dextropropoxyphene	5 / 7 / 5 / 13 / 20 / 28 / 52 / 66	
				Dextropropoxyphene/ nitrite[3]	12 / 17 / 9 / 20 / 78 / 64 / 244 / 119	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

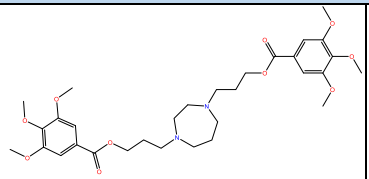
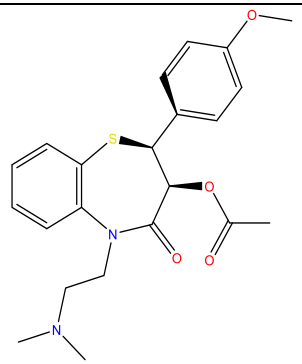
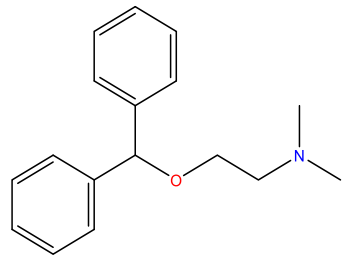
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Dilazep (cyclic tertiary amine)		Kikugawa *et al.*, 1987 †	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Dilazep TA98 / TA100	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
				Control	16 / 66	
				Dilazep	N[4] / N[4]	
				Dilazep/nitrite[3] (Yield 94%)	N[4] / 226	
Diltiazem (tertiary amine and cyclic tertiary amine)		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Diltiazem TA98 / TA100	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
				Control	16 / 66	
				Diltiazem	N[4] / N[4]	
				Diltiazem/nitrite[3] (Yield 15%)	36 / N[4]	
		Martelli *et al.*, 2007†	DNA strand breaks in liver of male SD rats *in vivo*		Comet assay metric Tail length (µm) / Tail moment	**Yes**
				Control	N[4] / N[4]	
				$NaNO_2$	2.16 / 210	
				Diltiazem	2.26 / 265	
				Diltiazem + $NaNO_2$	4.93 / 389	
Diphen-hydramine		Andrews *et al.*, 1984[1]†	*S. typhimurium* TA98, TA100, TA1535 reverse mutation		TA 1535 (-S9 / +S9) / TA 98 (-S9 / +S9) / TA 100 (-S9 / +S9)	**Yes** (TA98)
				Control	12 / 15 / 17 / 37 / 103 / 113	
				$NaNO_2$	7 / 12 / 16 / 32 / 87 / 104	
				Diphenhydramine	8 / 12 / 13 / 32 / 111 / 84	
				Diphenhydramine/ nitrite[3]	14 / 20 / 66 / 78 / 54 / 112	
		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amine alone, no untreated control)
				$NaNO_2$	0	
				Diphenhydramine	N[4]	
				Diphenhydramine/ nitrite[3] (Yield 7-9%)	20.8	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

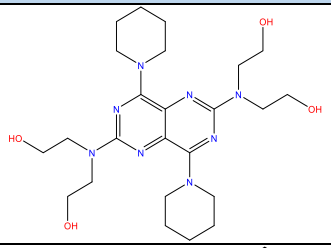
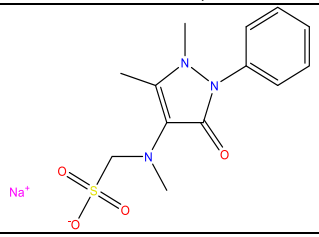
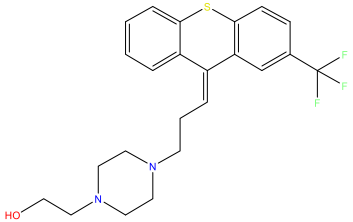
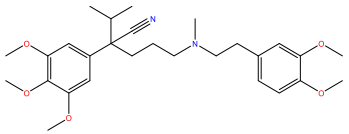
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results				↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)									
Dipyridamole (tertiary amine, cyclic tertiary amine and cyclic aromatic amine)		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 reverse mutation		Revertants/µmole Dipyridamole				**No**
					TA98		TA100		
				Control	16		66		
				Dipyridamole	N[4]		N[4]		
				Dipyridamole/nitrite[3] (Yield 19%)	N[4]		N[4]		
Dipyrone (analgine, sulpyrine) (tertiary amine and cyclic tertiary amine)		Braun *et al.*, 1980[1]†	*S. typhimurium* G49, host mediated assay in mice		Mutation frequency (Mf) x 10^{-9}				**Yes**
					Intraperitoneal		Intrasanguine		
				Control	1.94		3.8		
				$NaNO_2$	N[4]		N[4]		
				Analgine	N[4]		N[4]		
				Analgine+$NaNO_2$	1.8		13.3		
Flupentixol (cyclic tertiary amine)		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation		TA 98		TA 100		**?** (Less than two-fold increase above control observed with NO_2 + amine; no NO_2 alone)
				Revertants	-S9	+S9	-S9	+S9	
				Control	15	30	110	120	
				Flupentixol	N[4]	N[4]	N[4]	N[4]	
				Flupentixol/nitrite[3] (Yield 73.4%)	±[7]	±[7]	±[7]	±[7]	
Gallopamil		Martelli *et al.*, 2007†	DNA strand breaks in liver of male SD rats *in vivo*		Comet assay metric				**Yes**
					Tail length (µm)		Tail moment		
				Control	N[4]		N[4]		
				$NaNO_2$ (80 mg/kg)	2.16		210		
				Gallopamil (54 mg/kg)	1.77		208		
				Gallopamil+$NaNO_2$ (54 + 80 mg/kg)	5.54		403		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

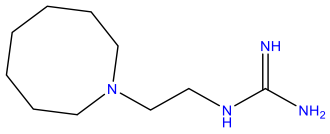
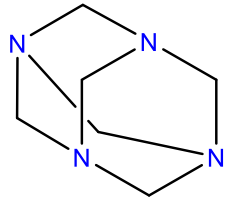
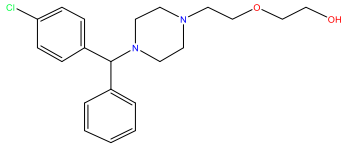
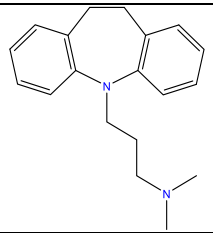
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Guanethidine (cyclic tertiary amine and guanidine)		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Guanethidine TA 98 / TA 100	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
				Control	16 / 66	
				Guanethidine	N[4] / N[4]	
				Guanethidine/nitrite[3] (Yield 63%)	146 / 476	
Hexamethylene-tetramine (cyclic tertiary amine)		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98 reverse mutation		TA 1537 (-S9 / +S9) / TA 1538 (-S9 / +S9) / TA 98 (-S9 / +S9) / TA 100 (-S9 / +S9)	**Yes** (TA 98)
				Control	15 / 20 / 9 / 18 / 35 / 44 / 236 / 136	
				$NaNO_2$	5 / 11 / 10 / 20 / 30 / 36 / 172 / 117	
				Hexamethylene-tetramine	16 / 17 / 10 / 20 / 29 / 38 / 185 / 128	
				Hexamethylene-tetramine/nitrite[3]	12 / 10 / 7 / 11 / 73 / 102 / 138 / 115	
Hydroxyzine (cyclic tertiary amine)		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98 (-S9 / +S9) / TA 100 (-S9 / +S9)	**?** (Less than two-fold increase above control observed with NO_2 + amine; no NO_2 alone)
				Control	15 / 30 / 110 / 120	
				Hydroxyzine	N[4] / N[4] / N[4] / N[4]	
				Hydroxyzine/nitrite[3] (Yield 5.5%)	---[9] / ±[7] / ---[9] / ±[7]	
Imipramine (tertiary amine and cyclic tertiary amine)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amine alone, no untreated control)
				NaNO	0	
				Imipramine	N[4]	
				Imipramine/nitrite[3] (Yield 1-2%)	2202	
Lucanthone	See secondary amines					**No** (1 of 1 studies)

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

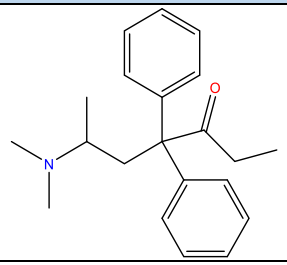
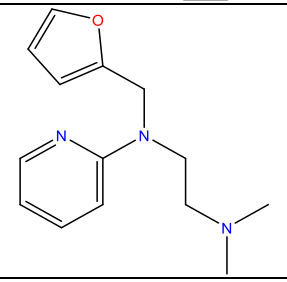
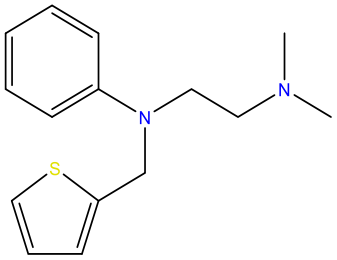
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)													
Methadone		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98, TA100, TA1537, TA1538 reverse mutation		TA 1537		TA 1538		TA 98		TA 100		**No**
					-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	
				Control	15	20	9	18	35	44	236	136	
				$NaNO_2$	5	11	10	20	30	36	172	117	
				Methadone	14	16	11	31	31	46	129	116	
				Methadone/nitrite[3]	7	14	16	21	41	56	130	151	
Methafurylene (tertiary amine and cyclic aromatic amine)		Andrews *et al.*, 1984[1]†	*S. typhimurium* TA98, TA100, TA1535, TA1538 reverse mutation		TA 1537		TA 1538		TA 98		TA 100		**No**
					-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	
				Control	12	15	11	21	17	37	103	113	
				$NaNO_2$	7	12	6	21	16	32	87	104	
				Methafurylene	9	5	11	24	16	34	78	103	
				Methafurylene/nitrite[3]	4	3	7	14	8	16	68	87	
Methaphenilene		Andrews *et al.*, 1984[1]†	*S. typhimurium* TA98, TA100, TA1538 reverse mutation		TA 1537		TA 1538		TA 98		TA 100		**Yes**
					-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	
				Control	12	15	11	21	17	37	103	113	
				$NaNO_2$	7	12	6	21	16	32	87	104	
				Methaphenilene	13	12	16	22	16	45	91	57	
				Methaphenilene/nitrite[3]	0	3	35	25	281	95	331	247	
		Kammerer *et al.*, 1986[1]†	*S. typhimurium*, TA98 and TA100 reverse mutation		No. of Revertants								**Yes**
					TA 98				TA 100				
					-S9		+S9		-S9		+S9		
				Control	18		23		116		126		
				$NaNO_2$	18		23		115		123		
				Methaphenilene	17		18		131		109		
				Methaphenilene/nitrite[3]	147		66		191		323		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

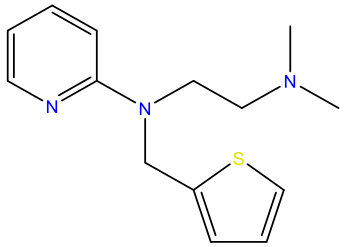
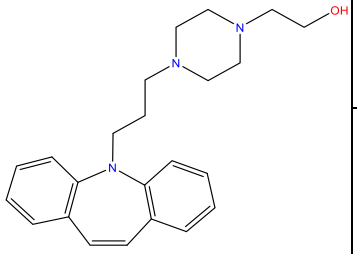
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Methapyrilene (tertiary amine and cyclic aromatic amine)		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA1538 reverse mutation		TA 1535 -S9 / +S9; TA 1538 -S9 / +S9; TA 98 -S9 / +S9; TA 100 -S9 / +S9	**Yes**
				Control	21 / 22; 9 / 18; 35 / 44; 236 / 136	
				$NaNO_2$	19 / 18; 10 / 20; 30 / 36; 172 / 117	
				Methapyrilene	19 / 17; 9 / 13; 17 / 33; 198 / 122	
				Methapyrilene/nitrite[3]	26 / 21; 27 / 29; 39 / 58; 237 / 135	
		Kammerer *et al.*, 1986[1]†	*S. typhimurium* TA98 and TA100 reverse mutation		No. of Revertants; TA 98 -S9 / +S9; TA 100 -S9 / +S9	**No**
				Control	18 / 23; 116 / 126	
				$NaNO_2$	18 / 23; 115 / 123	
				Methapyrilene	10 / 18; 121 / 125	
				Methapyrilene/nitrite[3]	15 / 24; 126 / 137	
Metoclopramide	See primary amines					**?** (1 of 1 studies)
Nicardipine	See secondary amines					**Yes** (1 of 1 studies)
Opipramol (cyclic tertiary amine)		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation		TA 98 -S9 / +S9; TA 100 -S9 / +S9	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
				Revertants: Control	15 / 30; 110 / 120	
				Opipramol	N[4] / N[4]; N[4] / N[4]	
				Opipramol/nitrite[3] (Yield 7.5%)	9600 / 4500; 12000 / 4100	
		Glatt *et al.*, 1987†	*S. typhimurium*, TA98 and TA100 reverse mutation		Revertants/plate; TA 98; TA 100	**?** (Increased effect observed with NO_2 + amine as compared to untreated control; no NO_2 or amine alone)
				Control	27; 95	
				Opipramol/nitrite[3]	132; 175	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

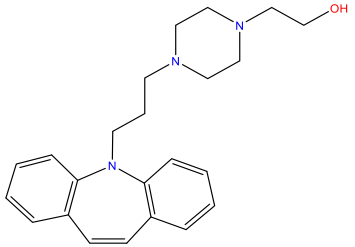
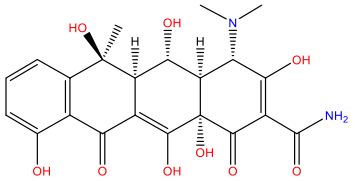
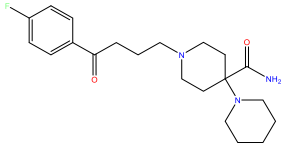
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Opipramol (cyclic tertiary amine) (continued)		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		B-galactosidase activity (U) -S9 / +S9	**Yes**
				Control	139 / 102	
				$NaNO_2$	139 / 82	
				Opipramol	N[4] / N[4]	
				Opipramol/nitrite[3] (mg/ml) 0.05	528 / 191	
				0.10	664 / 215	
Oxytetracycline (tertiary amine and primary amide)		Andrews *et al.*, 1980[1]†	*S. typhimurium* TA98, TA100, TA1537, TA1538 reverse mutation		TA 1537 (-S9 / +S9); TA 1538 (-S9 / +S9); TA 98 (-S9 / +S9); TA 100 (-S9 / +S9)	**Yes**
				Control	15 / 20 / 9 / 18 / 35 / 44 / 236 / 136	
				$NaNO_2$	5 / 11 / 10 / 20 / 30 / 36 / 172 / 117	
				Oxytetracycline	15 / 22 / 6 / 21 / 31 / 48 / 188 / 115	
				Oxytetracycline/nitrite[3]	44 / 46 / 10 / 39 / 72 / 93 / 180 / 226	
Pamaquine	See secondary amines					**Yes** (1 of 1 studies)
Pipamperone (cyclic tertiary amine and primary amide)		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation		TA 98 (-S9 / +S9); TA 100 (-S9 / +S9)	**?** (Less than two-fold increase above control observed with NO_2 + amine; no NO_2 alone)
				Revertants: Control	15 / 30 / 110 / 120	
				Pipamperone	N[4] / N[4] / N[4] / N[4]	
				Pipamperone/ nitrite[3] (Yield 15.3%)	±[7] / ±[7] / ±[7] / ±[7]	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

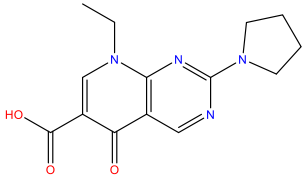
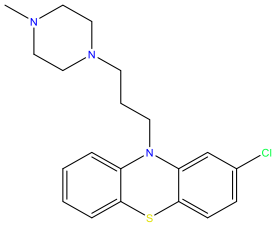
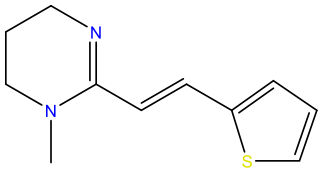
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results				↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)									
Piromidic acid (cyclic tertiary amine and cyclic aromatic amine)		Takeda and Kanaya, 1982†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98		TA 100		**?** (Less than two-fold increase above control observed with NO_2 + amine; no NO_2 alone)
					-S9	+S9	-S9	+S9	
				Control	20	22	117	126	
				Piromidic acid	N[4]	N[4]	N[4]	N[4]	
				Piromidic acid/nitrite[3] (Yield 0.3%)	±[7]	±[7]	±[7]	±[7]	
Procainamide	See primary amines								**?** (1 of 1 studies)
Prochlorperazine (cyclic tertiary amine)		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98		TA 100		**?** (Slight increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
					-S9	+S9	-S9	+S9	
				Control	15	30	110	120	
				Prochlorperazine	N[4]	N[4]	N[4]	N[4]	
				Prochlorperazine/nitrite[3] (Yield 6.5%)	---[9]	38	---[9]	±[7]	
Pyrantel pamoate (cyclic tertiary amine)		Arriaga Alba *et al.*, 1988†	*S. typhimurium* TA1535 reverse mutation		Revertants/plate				**Yes**
					-S9		+S9		
				Control	33.50		29.00		
				$NaNO_2$	36.50		32.16		
				Pyrantel pamoate	28.6		29.16		
				Pyrantel pamoate/nitrite[3] (Yield 65%)	127.4		148.50		
		Arriaga Alba *et al.*, 1989[1]†	*S. typhimurium* TA1535 reverse mutations induced by urine from exposed male CD-1 mice		Revertants/plate				**Yes**
					+ β-galactosidase		- β-galactosidase		
				Control	37.3		25.3		
				$NaNO_2$	42.0		43.3		
				Pyrantel pamoate	44.76		27.3		
				Pyrantel pamoate + $NaNO_2$	60.3		41		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

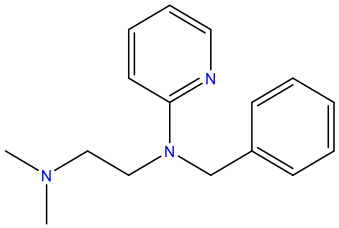
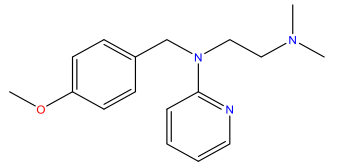
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Pyribenzamine (tripelennamine) (tertiary amine and cyclic aromatic amine)		Brambilla *et al.,* 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amine alone, no untreated control
				$NaNO_2$	0	
				Pyribenzamine	N[4]	
				Pyribenzamine/nitrite[3] (Yield 9-14%)	374	
		Kammerer *et al.,* 1986[1]†	*S. typhimurium* TA98 and TA100 reverse mutation		No. of Revertants: TA 98 (-S9, +S9); TA 100 (-S9, +S9)	**No**
				Control	18, 23, 116, 126	
				$NaNO_2$	18, 23, 115, 123	
				Pyribenzamine	18, 27, 140, 126	
				Pyribenzamine/nitrite[3]	22, 42, 113, 156	
2-Pyridyl-N'-dimethylethylene-diamine	See secondary amines					**Yes** (1 of 1 studies)
Pyrilamine (tertiary amine and cyclic aromatic amine)		Andrews *et al.,* 1984[1]†	*S. typhimurium* TA98, TA100, TA1535, TA1538 reverse mutation		TA 1535 (-S9, +S9); TA 1538 (-S9, +S9); TA 98 (-S9, +S9); TA 100 (-S9, +S9)	**No**
				Control	12, 15, 11, 21, 17, 37, 103, 113	
				$NaNO_2$	7, 12, 6, 21, 16, 32, 87, 104	
				Pyrilamine	7, 6, 15, 35, 11, 36, 72, 117	
				Pyrilamine/nitrite[3]	6, 16, 10, 17, 25, 40, 68, 128	
		Kammerer *et al.,* 1986[1]†	*S. typhimurium*, TA98 and TA100 reverse mutation		No. of Revertants: TA 98 (-S9, +S9); TA 100 (-S9, +S9)	**No**
				Control	18, 23, 116, 126	
				$NaNO_2$	18, 23, 115, 123	
				Pyrilamine	12, 15, 108, 103	
				Pyrilamine/nitrite[3]	14, 19, 100, 107	
		Farmer *et al.,* 1986[1]†	Covalent binding to rat DNA *in vivo*		µg MeG excreted in urine/day	**No**
				Pyrilamine	ND	
				Pyrilamine + $NaNO_2$	ND	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

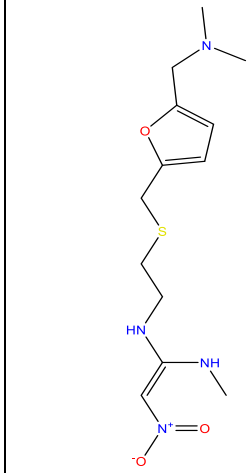
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Quinacrine	See secondary amines					**Yes** (1 of 1 studies)
Ranitidine		De Flora *et al.*, 1983[1]†	*S. typhimurium* TA100 and TA1535 reverse mutation; *E. coli*, WP67 and WP2*uvr*A reverse mutation		*S. typhimurium*: TA100 -S9 / TA100 +S9 / TA 1535 -S9 / TA 1535 +S9; *E. coli*: WP67 -S9 / WP67 +S9 / WP2*uvr*A -S9 / WP2*uvr*A +S9	**?** (Increased effect observed with NO_2 + amine as compared to NO_2 alone; no amine alone, no untreated control)
				Nitrite	171 / 143 / 18 / 18 / 12 / 12 / 18 / 18	
				Ranitidine/nitrite[3]	494 / 555 / 128 / 125 / 90 / 73 / 289 / 344	
		Franekic *et al.*, 1989[1]†	*S. typhimurium* TA98 and TA100 reverse mutation		TA 100: -S9 / +S9; TA 98: -S9 / +S9	**Yes**
				Control	109 / 142 / 17 / 28	
				$NaNO_2$	161 / 174 / 23 / 38	
				Ranitidine	126 / 158 / 24 / 35	
				Ranitidine/nitrite[3]	302 / 357 / 36 / 58	
		Franekic *et al.*, 1989[1]†	*S. cerevisiae*, gene conversion[8]		No. of Convertants/10^5 survivors	**Yes**
				Control	1.07	
				$NaNO_2$	1.65	
				Ranitidine	1.86	
				Ranitidine/nitrite[3]	5.36	
		Ozhan and Alpertunga, 2003[1]†	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		β-galactosidase activity (U): -S9 / +S9	**Yes**
				Control	139 / 102	
				$NaNO_2$	139 / 82	
				Ranitidine	N[4] / N[4]	
				Ranitidine/nitrite[3] (mg/ml) 4.0	164 / 493	
				6.0	146 / 528	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

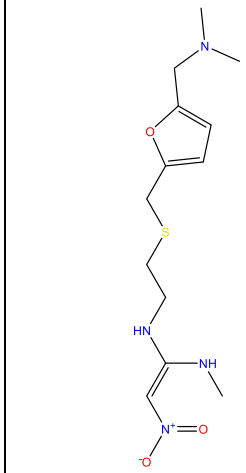
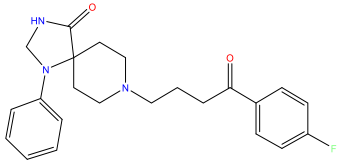
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results				↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)									
Ranitidine (continued)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damaging potency[5]				? (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amine alone, no untreated control)
				$NaNO_2$	0				
				Ranitidine	N[4]				
				Ranitidine/nitrite[3] (Yield 16-22%)	373				
		Maura *et al.*, 1983†	DNA strand breaks in CHO cells *in vitro*		% DNA eluted				**Yes**
				Control	17				
				$NaNO_2$	18.4				
				Ranitidine	19.6				
				Ranitidine/nitrite[3]	29.5				
		Martelli *et al.*, 1983†	Unscheduled DNA synthesis in rat primary hepatocytes *in vitro*		DNA repair synthesis (Grains/nucleus)[6]				**Yes**
					Expt. 1	Expt. 2	Expt. 3		
				Control	0.5	0.6	0.6		
				$NaNO_2$	6.6	2.1	3.2		
				Ranitidine	8.6	3	4.1		
				Ranitidine/nitrite[3] (Yield 16.2 – 21.7%)	52.7	15	29.7		
		Brambilla *et al.*, 1983†	DNA strand breaks in liver and gastric mucosa of male SD rats *in vivo*		% DNA Eluted from Filter (Mean)				**Yes**
				Control	22.3				
				$NaNO_2$	23.1				
				Ranitidine	21.5				
				Ranitidine+$NaNO_2$	31.8				
Spiperone (cyclic tertiary amine and cyclic secondary amide)		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98		TA 100		**?** (Less than two-fold increase above control observed with NO_2 + amine; no NO_2 alone)
					-S9	+S9	-S9	+S9	
				Control	15	30	110	120	
				Spiperone	N[4]	N[4]	N[4]	N[4]	
				Spiperone/nitrite[3] (Yield 50.4%)	±[7]	±[7]	±[7]	±[7]	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

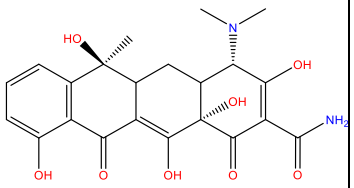
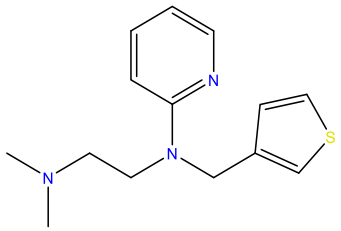
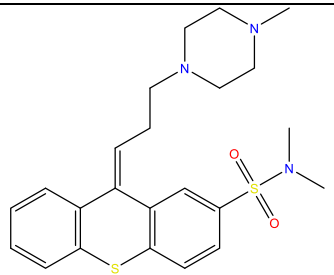
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)						
Tetracycline (tertiary amine and primary amide)		Kasamaki and Urasawa, 1987[1]†	*S. typhimurium*, TA98 and TA100 reverse mutation		No. Revertants/plate TA 98: -S9 / +S9; TA 100: -S9 / +S9	**Yes** (TA 98)
				Control	130 / 130 / 36 / 36	
				$NaNO_2$	65 / 65 / 18 / 18	
				Tetracycline	130 / 130 / 36 / 36	
				Tetracycline/nitrite[3]	258 / 130 / 46 / 18	
Thenyldiamine (tertiary amine and cyclic aromatic amine)		Andrews *et al.*, 1984[1]†	*S. typhimurium* TA98, TA100, TA1535, TA1538 reverse mutation		TA1535 (-S9 / +S9); TA1538 (-S9 / +S9); TA 98 (-S9 / +S9); TA 100 (-S9 / +S9)	**No**
				Control	12 / 15 / 11 / 21 / 17 / 37 / 103 / 113	
				$NaNO_2$	7 / 12 / 6 / 21 / 16 / 32 / 87 / 104	
				Thenyldiamine	10 / 15 / 11 / 19 / 13 / 41 / 80 / 106	
				Thenyldiamine/nitrite[3]	5 / 4 / 11 / 12 / 10 / 30 / 70 / 64	
		Kammerer *et al.*, 1986[1]†	*S. typhimurium*, TA98 and TA100 reverse mutation		No. of Revertants TA 98: -S9 / +S9; TA 100: -S9 / +S9	**No**
				Control	18 / 23 / 116 / 126	
				$NaNO_2$	18 / 23 / 115 / 123	
				Thenyldiamine	15 / 23 / 127 / 123	
				Thenyldiamine/nitrite[3]	17 / 23 / 113 / 122	
Thiothixene (cyclic tertiary amine and sulfonamide)		Takeda and Kanaya, 1981†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98: -S9 / +S9; TA 100: -S9 / +S9	**?** (Increased effect observed with NO_2 + amine as compared to amine alone; no NO_2 alone)
				Control	15 / 30 / 110 / 120	
				Thiothixene	N[4] / N[4] / N[4] / N[4]	
				Thiothixene/nitrite[3] (Yield 48%)	±[7] / 110 / ---[9] / 530	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

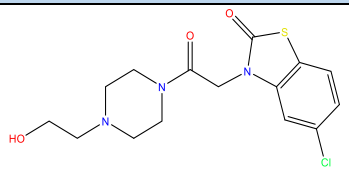
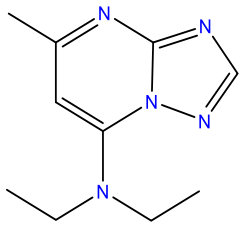
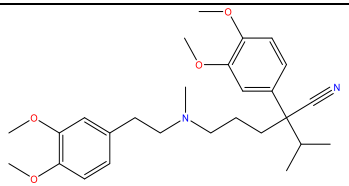
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results				↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amines (continued)									
Tiaramide (cyclic tertiary amine and tertiary amide)		Takeda and Kanaya, 1982†	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA 98		TA 100		**?** (Less than two-fold increase above control observed with NO_2 + amine; no NO_2 alone)
					-S9	+S9	-S9	+S9	
				Control	20	22	117	126	
				Tiaramide	N[4]	N[4]	N[4]	N[4]	
				Tiaramide/nitrite[3] (Yield 1.1%)	±[7]	6	±[7]	±[7]	
Trapidil (tertiary amine and cyclic aromatic amine)		Kikugawa *et al.*, 1987†	*S. typhimurium*, TA98 and TA100 reverse mutation		Revertants/µmole Trapidil				**No**
					TA98		TA100		
				Control	16		66		
				Trapidil	N[4]		N[4]		
				Trapidil/nitrite[3] (Yield 0%)	N[4]		N[4]		
Trimetazidine	See secondary amines								**?** (1 of 1 studies)
Verapamil		Martelli *et al.*, 2007†	DNA strand breaks in liver of male SD rats *in vivo*		Comet assay metric				**Yes**
					Tail length (µm)		Tail moment		
				Control	N[4]		N[4]		
				$NaNO_2$	2.16		210		
				Verapamil	2.51		242		
				Verapamil/nitrite[3]	3.27		278		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

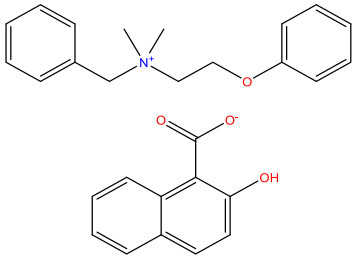
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Quaternary Amines							
Bephenium hydroxyl-naphthoate (quaternary amino salt)		Arriaga Alba *et al.*, 1988†	*S. typhimurium* TA1535 reverse mutation		Revertants/plate		**No**
					-S9	+S9	
				Control	33.50	29.00	
				$NaNO_2$	36.50	32.16	
				Bephenium hydroxynaphthoate	30.5	31.8	
				Bephenium hydroxynaphthoate /nitrite[3] (Yield 0%)	31.16	35.6	
		Arriaga Alba *et al.*, 1989[1]†	*S. typhimurium* TA1535 reverse mutations induced by urine from exposed male CD-1 mice		Revertants/plate		**No**
					+ β-galactosidase	- β-galactosidase	
				Control	37.3	25.3	
				$NaNO_2$	42.0	43.3	
				Bephenium hydroxynaphthoate	32.6	35.3	
				Bephenium hydroxynaphthoate + $NaNO_2$	36.6	33.3	
Cyclic Aromatic Amines							
2-Aminopyridine	See primary amines						**Yes** (1 of 1 studies)
Astemizole	See secondary amines						**Yes** (1 of 1 studies)
Betahistine	See secondary amines						**Yes** (1 of 1 studies)
Bromazepam	See secondary amides in amide table						**Yes** (1 of 2 studies)
Cefazolin	See secondary amides in amide table						**?** (1 of 1 studies)
Chlordi-azepoxide	See secondary amines						**Yes** (3 of 5 studies)
Chloroquine	See secondary amines						**Yes** (2 of 3 studies)
Chlor-pheniramine	See tertiary amines						**No** (1 of 1 studies)

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

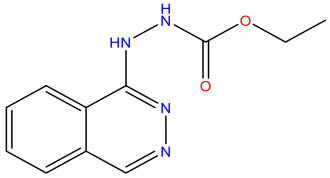
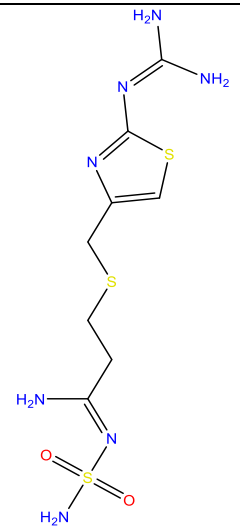
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Cyclic Aromatic Amines (continued)						
Diaveridine	See primary amines					**No** (1 of 1 studies)
Dipyridamole	See tertiary amines					**No** (1 of 1 studies)
Ecarazine		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation	Control	Revertants/µmol Ecarazine: TA98 16; TA100 66	**?** (Increased effect observed with NO_2 + amine compared to amine alone for TA98, no NO_2 alone)
				Ecarazine	TA98 N[4]; TA100 N[4]	
				Ecarazine/nitrite[3] (Yield: 1%)	TA98 46; TA100 N[4]	
Famotidine (cyclic aromatic amine, guanidine and sulfonamide)		De Flora and Picciotto, 1986[1]†	*S. typhimurium* TA97, TA100,TA102, TA1535 reverse mutation		TA1535 - S9 / TA1535 + S9 / TA97 - S9 / TA97 + S9 / TA100 - S9 / TA100 + S9 / TA102 - S9 / TA102 + S9	**Yes**
				Control	15 / 18 / 174 / 193 / 133 / 126 / 245 / 287	
				$NaNO_2$	487 / 454 / 306 / 294 / 372 / 326 / 301 / 319	
				Famotidine	N[4] / N[4] / N[4] / N[4] / N[4] / N[4] / N[4] / N[4]	
				Famotidine/nitrite[3] (5 mg famotidine)	Toxic (T) / 26 / T / 684 / 1494 / 1363 / T / 720	
				Famotidine/nitrite[3] (2.5 mg famotidine)	113 / 118 / 564 / 355 / 853 / 741 / T / 532	
				Famotidine/nitrite[3] (1.25 mg famotidine)	240 / 235 / 298 / 309 / 491 / 369 / 506 / 396	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

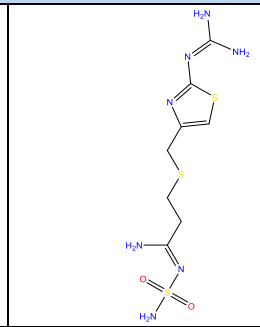
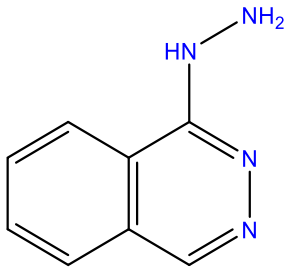
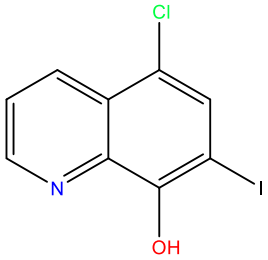
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results				↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Cyclic Aromatic Amines (continued)									
Famotidine (cyclic aromatic amine, guanidine and sulfonamide) (continued)		De Flora and Picciotto, 1986[1]† (continued)	*E. coli* WP2uvrA and WP67 reverse mutation		WP2*uvrA*		WP67		**?** (Increased effect observed with NO_2 + amine compared to NO_2 alone; no amide alone, no untreated control)
					-S9	+S9	-S9	+S9	
				NaNO2	N[4]	N[4]	N[4]	N[4]	
				Famotidine/nitrite[3]	156	1250	156	1250	
Hydralazine		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Hydralazine				**?** (Increased effect observed with NO_2 + amine compared to amine alone; no NO_2 alone)
					TA98		TA100		
				Control	16		66		
				Hydralazine	N[4]		N[4]		
				Hydralazine/nitrite[3] (Yield: 0%)	300		160		
Iodochlor-hydroxyquin (cyclic aromatic amine; pyridine)		Arriaga Alba *et al.*, 1989[1]†	*S. typhimurium* TA1535 reverse mutations induced by urine from exposed male CD-1 mice		Revertants/plate				**No**
					+ β-galactosidase		- β-galactosidase		
				Control	37.3		25.3		
				$NaNO_2$	42.0		43.3		
				Iodochlor-hydroxyquin	48.0		44.6		
				Iodochlor-hydroxyquin + $NaNO_2$	44.6		28.3		

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

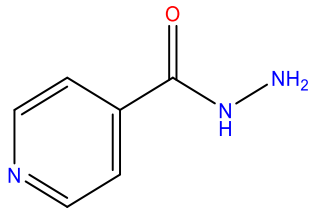
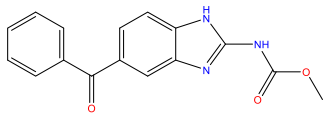
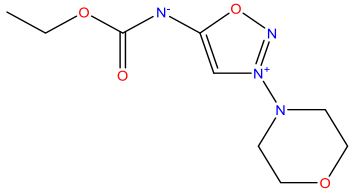
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results		↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Cyclic Aromatic Amines (continued)							
Isoniazid (Pyridine-4-carbohydrazide)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]		**?** (Increased effect observed with NO_2 + amine compared to amine alone and NO_2 alone; no untreated control)
				$NaNO_2$	0		
				Isoniazid	N[4]		
				Isoniazid/nitrite[3] (Yield: 28-30%)	5.6		
Mebendazole (cyclic aromatic amine and secondary carbamate)		Arriaga Alba *et al.*, 1988†	*S. typhimurium* TA1535 reverse mutation		Revertants/plate		**Yes**
					+S9	-S9	
				Control	29.00	33.50	
				$NaNO_2$	57.50	47.00	
				Mebendazole	29.16	19.00	
				Mebendazole/nitrite[3] (Yield: 50%)	378.50	115.00	
Methafurylene	See tertiary amines						**No** (1 of 1 studies)
Methapyrilene	See tertiary amines						**Yes** (1 of 2 studies)
Morsydomine (cyclic aromatic amine and carbamate)		Kikugawa *et al.*, 1987†	S. typhimurium TA98 reverse mutation		Revertants/µmol Morsydomine		**?** (Increased effect observed with NO_2 + amine compared to amine alone for TA98, no NO_2 alone)
					TA98	TA100	
				Control	16	66	
				Morsydomine	N[4]	N[4]	
				Morsydomine/nitrite[3] (Yield: 1%)	46	N[4]	

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

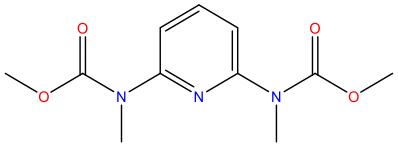
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Cyclic Aromatic Amines (continued)						
Myosmine	See secondary amines					**Yes** (1 of 1 studies)
Pamaquine	See secondary amines					**Yes** (1 of 1 studies)
Pentaquine	See secondary amines					**Yes** (1 of 1 studies)
Piromidic acid	See tertiary amines					**?** (1 of 1 studies)
Primaquine	See primary amines					**Yes** (1 of 1 studies)
Pyribenzamine (Tripelennamine)	See tertiary amines					**?** (1 of 2)
Pyridinol carbamate (secondary carbamate and cyclic aromatic amine)		Takeda and Kanaya, 1982[1] †	*S. typhimurium*, TA98 and TA100 reverse mutation	Revertants	TA98 -S9: 20; TA98 +S9: 22; TA100 -S9: 117; TA100 +S9: 126	**?** (Increased effect observed with NO_2 + amine compared to amine alone; no NO_2 alone)
				Pyridinol carbamate	TA98 -S9: N[4]; TA98 +S9: N[4]; TA100 -S9: N[4]; TA100 +S9: N[4]	
				Pyridinol carbamate/nitrite[3]	TA98 -S9: ±[7]; TA98 +S9: 3; TA100 -S9: 120000; TA100 +S9: 540	
2-Pyridyl-N'-dimethylethylene-diamine	See secondary amines					**Yes** (1 of 1 studies)
Pyrilamine	See tertiary amines					**No** (3 of 3 studies)
Pyrimethamine	See primary amines					**No** (1 of 1 studies)
Quinacrine	See secondary amines					**Yes** (1 of 1 studies)

Table 10. Amines Tested in Combination with Nitrite for Genotoxicity (continued)

Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Cyclic Aromatic Amines (continued)						
Thenyldiamine	See tertiary amines					**No** (2 of 2 studies)
Tizanidine	See secondary amines					**Yes** (1 of 1 studies)
Trapidil	See tertiary amines					**No** (1 of 1 studies)
Trimethoprim	See primary amines					**No** (1 of 1 studies)

All studies were reviewed in IARC (2010), unless the reference is marked with "†".

N: Non-mutagenic; **NT:** Not tested; **ND**: Not-detected; **T:** Toxic

§ Proposition 65 carcinogen

[1] Nitrosation yield not reported.

[2] The *umu*-test is based on the ability of DNA-damaging agents to induce the *umu* operon. DNA-damaging agents are tested in *S. typhimurium* strain TA 1535/pSK 1002, which carries a fused *umuC'-'lacZ* gene. Mutagenicity is monitored by the level of cellular β-galactosidase activity (U) produced by the fusion *umu* operon.

[3] The amine was pre-mixed with nitrite before administration to the test animals or before application in the test system. Nitrosation occurs in the mixture to differing degrees, depending on the amine.

[4] Data not shown.

[5] The number is calculated from the ratio [damaged DNA elution rate per number of nitrite treated cells] : [average concentration (mM) of amine/nitrite].

[6] Mean of net nuclear grain counts of 100 cells from duplicate autoradiographs. Grain counts include cells with no nuclear labeling encountered in the 50 cells counted for each slide. Silver grains over the nucleus minus the grains over an equal area in the cytoplasm were defined as net grains/nucleus. A cell with greater than 5 net nuclear grains was considered in repair for both rat and human hepatocytes. The data are the means of 100 net nuclear counts obtained from two autoradiographs.

[7] Authors reported slight increase in the number of revertants (less than twice the control value).

[8] The test substance was administered by *s.c.* injection into the back of the rats. 1 h later, the animals were killed and their livers were collected. The livers were homogenized and added into yeast cells for mitotic gene conversion tests.

[9] No data obtained because of the bacteriostatic effect of the sample tested.

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity

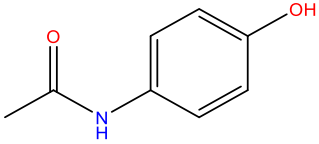
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Primary Amides						
Atenolol (secondary amine and primary amide)	See secondary amines in amine table					**Yes** (1 of 2 studies)
Carpipramine (cyclic tertiary amine and primary amide)	See tertiary amines in amine table					**Yes** (1 of 1 studies)
Oxytetracycline (tertiary amine and primary amide)	See tertiary amines in amine table					**Yes** (1 of 1 studies)
Pipamperone (cyclic tertiary amine and primary amide)	See tertiary amines in amine table					**?** (1 of 1 studies)
Tetracycline (tertiary amine and primary amide)	See tertiary amines in amine table					**Yes** (1 of 1 studies)
Secondary Amides						
Acetaminophen (secondary amide)		Ohta *et al.*, 1988[1] †	*S. typhimurium* TA98 and TA100 reverse mutation		TA 98: -S9 / +S9; TA 100: -S9 / +S9	**?** (Increased effect observed with NO_2 + amide as compared to NO_2 alone; no amide alone)
				Control	33 / 30 / 136 / 144	
				$NaNO_2$	Non-mutagenic (N)[4] / N[4] / N[4] / N[4]	
				Acetaminophen/nitrite[3]	64 / 57 / 326 / 463	

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity (continued)

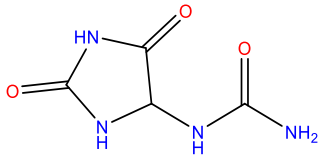
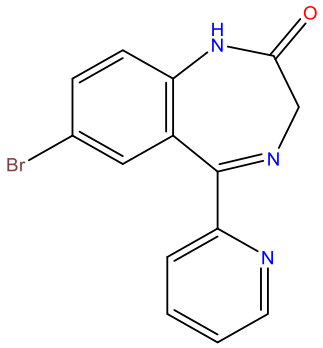
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amides (continued)						
Allantoin (secondary amide and urea)		Andrews *et al.*, 1984[1] †	*S. typhimurium* TA98, TA100, TA1535, TA1538 reverse mutation		TA1535: -S9 / +S9; TA1538: -S9 / +S9; TA 98: -S9 / +S9; TA 100: -S9 / +S9	**No**
				Control	12 / 15; 11 / 21; 17 / 37; 103 / 113	
				$NaNO_2$	7 / 12; 6 / 21; 16 / 32; 87 / 104	
				Allantoin	6 / 29; 10 / 16; 12 / 39; 101 / 162	
				Allantoin/nitrite[3]	12 / 18; 10 / 20; 16 / 36; 133 / 118	
Bromazepam (cyclic secondary amide and cyclic aromatic amine)		Takeda and Kanaya, 1981†	*S. typhimurium* TA98 and TA100 reverse mutation	Revertants	TA 98: -S9 / +S9; TA 100: -S9 / +S9	**?** (Increased effect observed with NO_2 + amide as compared to amide alone; no NO_2 alone)
				Control	15 / 30; 110 / 120	
				Bromazepam	N[4] / N[4]; N[4] / N[4]	
				Bromazepam/nitrite[3] (Yield 25%)	1400 / 850; 970 / 270	
		Ozhan and Alpertunga, 2003[1] †	*umu*-test with *S. typhimurium* TA1535 strain (DNA-damaging test)[2]		B-galactosidase activity (U): -S9 / +S9	**Yes**
				Control	139 / 102	
				$NaNO_2$	139 / 82	
				Bromazepam	N[4] / N[4]	
				Bromazepam/nitrite[3] (mg/ml) 0.75	232 / 192	
				1.5	450 / 213	

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity (continued)

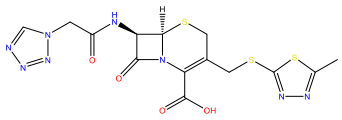
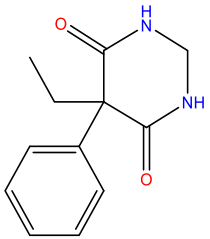
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amides (continued)						
Cefadroxil (primary amine, secondary amide, cyclic tertiary amide)	See primary amines in amine table					**?** (1 of 1 studies)
Cefalexin (primary amine, secondary amide, cyclic tertiary amide)	See primary amines in amine table					**?** (1 of 1 studies)
Cefazolin (cyclic aromatic amine, secondary amide and cyclic tertiary amide)		Brambilla *et al.*, 1985†	DNA strand breaks in Chinese hamster ovary (CHO) cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amide as compared to amide alone and NO_2; no control)
				$NaNO_2$	0	
				Cefazolin	N[4]	
				Cefazolin/nitrite[3] (Yield 5-13%)	50.5	
Metoclopramide (primary amine and secondary amide)	See primary amines in amine table					**?** (1 of 1 studies)
Primidone[§] (cyclic secondary di-amide)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amide as compared to amide alone and NO_2; no control)
				$NaNO_2$	0	
				Primidone	N[4]	
				Primidone/nitrite[3] (Yield 12-18%)	275	

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity (continued)

Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Secondary Amides (continued)						
Procainamide (primary amine, secondary amide and tertiary amine)	See primary amines in amine table					**?** (1 of 1 studies)
Spiperone (cyclic tertiary amine and cyclic secondary amide)	See tertiary amines in amine table					**?** (1 of 1 studies)
Tertiary Amides						
Cefadroxil (primary amine, secondary amide, cyclic tertiary amide)	See primary amines in amine table					**?** (1 of 1 studies)
Cefalexin (primary amine, secondary amide, cyclic tertiary amide)	See primary amines in amine table					**?** (1 of 1 studies)
Cefazolin (primary amine, secondary amide, cyclic tertiary amide)	See secondary amides					**?** (1 of 1 studies)

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity (continued)

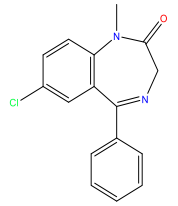
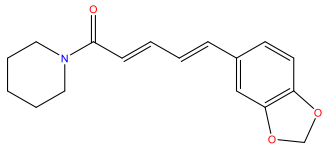
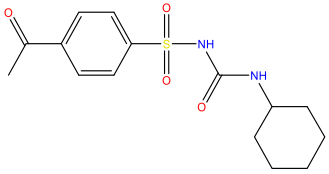
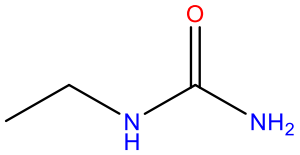
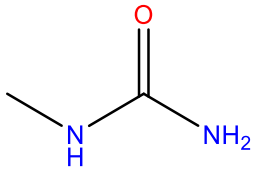
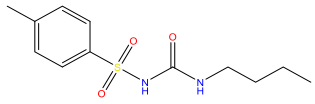
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Tertiary Amides (continued)						
Diazepam (cyclic tertiary amide)		Takeda and Kanaya, 1981†	*S. typhimurium* TA98 and TA100 reverse mutation	Revertants	TA 98: -S9 / +S9; TA 100: -S9 / +S9	**?** (Increased effect observed with NO_2 + amide as compared to amide alone; no NO_2 alone)
				Control	15 / 30 / 110 / 120	
				Diazepam	N[4] / N[4] / N[4] / N[4]	
				Diazepam/nitrite[3] (Yield 7%)	---[9] / 54 / ---[9] / ±[7]	
Enalapril (secondary amine and cyclic tertiary amide)	See secondary amines in amine table					**Yes** (1 of 1 studies)
Piperine (cyclic tertiary amide)		Andrews *et al.,* 1980[1] †	*S. typhimurium* TA98, TA100, TA1538 reverse mutation		Revertants/plate: TA1537 (-S9 / +S9), TA1538 (-S9 / +S9), TA98 (-S9 / +S9), TA100 (-S9 / +S9)	**Yes** (TA1538, TA98)
				Control	15 / 20 / 9 / 18 / 35 / 44 / 236 / 136	
				$NaNO_2$	5 / 11 / 10 / 20 / 30 / 36 / 172 / 117	
				Piperine	10 / 14 / 7 / 18 / 19 / 46 / 76 / 123	
				Piperine/nitrite[3]	19 / 20 / 65 / 59 / 84 / 110 / 423 / 219	
Tiaramide (cyclic tertiary amine and tertiary amide)	See tertiary amines in amine table					**?** (1 of 1 studies)
Ureas, including Sulfonyl Ureas						
Acetohexamide (sulfonyl urea)		Brambilla *et al.,* 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amide as compared to amide alone; no NO_2 alone)
				$NaNO_2$	0	
				Acetohexamide	N[4]	
				Acetohexamide/nitrite[3] (Yield 5-6%)	680	

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity (continued)

Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Ureas, including Sulfonyl Ureas (continued)						
Allantoin (secondary amide and urea)	See secondary amides					**No** (1 of 1 studies)
Ethylurea (EU, urea)		Couch and Friedman 1975[1]	*S. typhimurium* G46, host-mediated assay in male ICR mice *in vivo*		Mutant frequency (mutants/total cells)	**Yes**
				Control	0.01	
				$NaNO_2$	0.004	
				Ethylurea	0.004	
				$NaNO_2$ + Ethylurea	0.102	
Methylurea (MU, urea)		Brambilla *et al.*, 1985†	DNA strand breaks in Chinese hamster ovary cells *in vitro*		DNA-damage (single strand breaks) potency[5]	**?** (Increased effect observed with NO_2 + amide as compared to amide alone; no NO_2 alone)
				$NaNO_2$	0	
				Methylurea	N[4]	
				Methylurea/nitrite[3] (Yield 73-80%)	55.2	
		Couch and Friedman, 1975[1]	*S. typhimurium* G46, host-mediated assay in male ICR mice in *vivo*		Mutant frequency (mutant cells/total cells)	**Yes**
				Control	0.01	
				$NaNO_2$	0.004	
				Methylurea	0.02	
				$NaNO_2$+ Methylurea	8.5	
Tolbutamide (sulfonyl urea)		Andrews *et al.*, 1980[1] †	*S. typhimurium* TA98, TA100, TA1537, TA1538 reverse mutation		Revertants/plate	**No**

	TA1537		TA1538		TA98		TA100	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Control	15	20	9	18	35	44	236	136
$NaNO_2$	5	11	10	20	30	36	172	117
Tolbutamide	18	17	11	19	29	37	175	110
Tolbutamide/nitrite[3]	9	6	9	21	40	44	240	149

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity (continued)

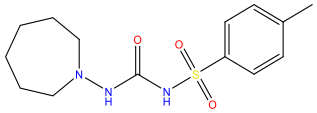
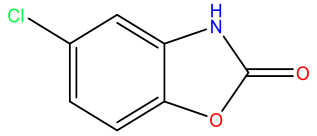
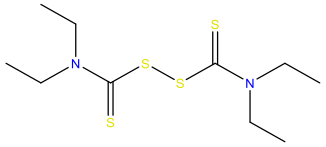
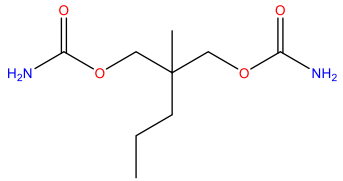
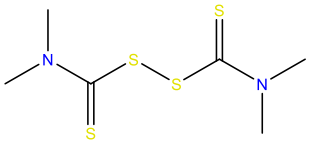
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results								↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Ureas, including Sulfonyl Ureas (continued)													
Tolazamide (sulfonyl urea)		Andrews *et al.*, 1980[1] †	*S. typhimurium* TA 98, TA100, TA1535, TA 1537 reverse mutation		Revertants/plate								**Yes** (TA1535)
					TA1535		TA1537		TA98		TA100		
					-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	
				Control	21	22	15	20	35	44	236	136	
				$NaNO_2$	19	18	5	11	30	36	172	117	
				Tolazamide	19	25	15	19	29	41	170	97	
				Tolazamide/nitrite[3]	721	254	8	12	39	56	427	172	
Carbamates, including Thiocarbamates													
Chlorzoxazone (carbamate)		Brambilla *et al.*, 1985†	DNA strand breaks in CHO cells *in vitro*		DNA-damage (single strand breaks) potency[5]								**?** (Increased effect observed with NO_2 + amide as compared to amide alone and NO_2; no control)
				$NaNO_2$	0								
				Chlorzoxazone	N[4]								
				Chlorzoxazone /nitrite[3] (Yield15%)	80.9								
Disulfiram (thiocarbamate)		Andrews *et al.*, 1980[1] †	*S. typhimurium* TA98, TA100, TA1537, TA1538 reverse mutation		Revertants/plate								**No**
					TA1537		TA1538		TA98		TA100		
					-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	
				Control	15	20	9	18	35	44	236	136	
				$NaNO_2$	5	11	10	20	30	36	172	117	
				Disulfiram	12	7	3	8	23	27	64	139	
				Disulfiram/nitrite[3]	8	10	8	23	39	45	221	152	

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity (continued)

Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Carbamates, including Thiocarbamates (continued)						
Mebendazole (cyclic aromatic amine and secondary carbamate)	See cyclic aromatic amines in amine table					**Yes** (1 of 1 studies)
Meprobamate (primary carbamate)		Takeda and Kanaya, 1981†	*S. typhimurium* TA98 and TA100 reverse mutation	Revertants	TA 98 -S9 / TA 98 +S9 / TA 100 -S9 / TA 100 +S9	**?** (Less than two-fold increase above control observed with NO_2 + amine; no NO_2 alone)
				Control	15 / 30 / 110 / 120	
				Meprobamate	N[4] / N[4] / N[4] / N[4]	
				Meprobamate/nitrite[3] (Yield 0.8%)	±[7] / ±[7] / ±[7] / ±[7]	
Morsydomine	See cyclic aromatic amines in amine table					**?** (1 of 1 studies)
Pyridinol carbamate (secondary carbamate and cyclic aromatic amine)	See cyclic aromatic amines in amine table					**?** (1 of 1 studies)
Thiram (thiocarbamate)		Andrews *et al.*, 1980[1] †	*S. typhimurium* TA98, TA100, TA1535, TA1537 reverse mutation		Revertants/plate	**No**

	TA1535		TA1537		TA98		TA100	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Control	21	22	15	20	35	44	236	136
$NaNO_2$	19	18	5	11	30	36	172	117
Thiram	35	49	24	32	50	66	291	352
Thiram/nitrite[3]	44	44	19	24	64	68	299	258

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity (continued)

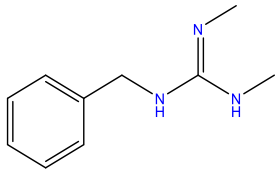
Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Sulfonamides						
Famotidine (cyclic aromatic amine, guanidine and sulfonamide)	See cyclic aromatic amines in amine table					**Yes** (1 of 2 studies)
Hydrochloro-thiazide (cyclic secondary amine and sulfonamide)	See secondary amines in amine table					**Yes** (1 of 1 studies)
Sotalol (secondary amine and secondary sulfonamide)	See secondary amines in amine table					**Yes** (1 of 2 studies)
Sulfanilamide (primary amine and sulfonamide)	See primary amines in amine table					**?** (1 of 1 studies)
Thiothixene (cyclic tertiary amine and sulfonamide)	See tertiary amines in amine table					**?** (1 of 1 studies)
Guanidines						
Bethanidine (quinidine)		Kikugawa *et al.*, 1987†	*S. typhimurium* TA98 and TA100 reverse mutation		Revertants/µmole Bethanidine	**?** (Increased effect observed with NO_2 + amide as compared to amide alone; no NO_2 alone)
					TA98 / TA100	
				Control	16 / 66	
				Bethanidine	N[4] / N[4]	
				Bethanidine/nitrite[3] (Yield 1%)	346 / 956	

Table 11. Amides Tested in Combination with Nitrite for Genotoxicity (continued)

Chemical	Structure	Reference	Assay, Endpoint	Treatment	Results	↑effect observed with NO_2 + amine, compared to NO_2 alone *and* amine alone?
Guanidines (continued)						
Cimetidine (cyclic secondary amine and guanidine)	See secondary amines in amine table					**Yes** (1 of 5 studies)
Famotidine (cyclic aromatic amine, guanidine and sulfonamide)	See cyclic aromatic amines in amine table					**Yes** (1 of 2 studies)
Guanethidine (cyclic tertiary amine and guanidine)	See tertiary amines in amine table					**?** (1 of 1 studies)

All studies were reviewed in IARC (2010), unless the reference is marked with "†".

N: Non-mutagenic; **NT:** Not tested; **ND**: Not-detected

§ Proposition 65 carcinogen

[1] Nitrosation yield not reported.

[2] The *umu*-test is based on the ability of DNA-damaging agents to induce the *umu* operon. DNA-damaging agents are tested in *S. typhimurium* strain TA 1535/pSK 1002, which carries a fused *umuC'-'lacZ* gene. Mutagenicity is monitored by the level of cellular β-galactosidase activity (U) produced by the fusion *umu* operon.

[3] The amine was pre-mixed with nitrite before administration to the test animals or before application in the test system. Nitrosation occurs in the mixture to differing degrees, depending on the amine.

[4] Data not shown.

[5] The number is calculated from the ratio [damaged DNA elution rate per number of nitrite treated cells] : [average concentration (mM) of amide/nitrite].

[6] Mean of net nuclear grain counts of 100 cells from duplicate autoradiographs. Grain counts include cells with no nuclear labeling encountered in the 50 cells counted for each slide. Silver grains over the nucleus minus the grains over an equal area in the cytoplasm were defined as net grains/nucleus. A cell with greater than 5 net nuclear grains was considered in repair for both rat and human hepatocytes. The data are the means of 100 net nuclear counts obtained from two autoradiographs.

[7] Authors reported slight increase in the number of revertants (less than twice the control value).

[8] The test substance was administered by *s.c.* injection into the back of the rats. 1 h later, the animals were killed and their livers were collected. The livers were homogenized and added into yeast cells for mitotic gene conversion tests.

[9] No data obtained because of the bacteriostatic effect of the sample tested

4. SUMMARY

4.1 Evidence from Studies in Humans

Many studies are available examining cancer in humans in relation to nitrite intake. Some studies report positive associations, while some do not. Evidence of carcinogenicity comes primarily from cohort and case-control studies of colorectal, esophageal and stomach cancer. Studies of lymphoma, brain, and thyroid cancer also provide evidence of carcinogenicity.

4.1.1 Colorectal cancer

Several studies on nitrite exposure and colorectal cancer have been published since the IARC 2010 review. Two studies on colorectal cancer and nitrite intake were considered by IARC (2010): "[t]he case – control study found a 50% increased risk for colon cancer and a 70% increased risk for rectal cancer. Dietary intake of nitrite was not associated with risk in the cohort study."

In studies summarized in Table 3 and Figures 2A-2B that looked at colorectal cancer overall, no clear association was seen in the two cohort studies that examined risk in relation to dietary nitrite exposure. Case-control studies of colorectal cancer in relation to nitrite intake found no significantly increased risks. Studies examining the more specific sites, colon and rectal cancers, are discussed below.

IARC (2010) did not consider studies that looked only at processed meat exposure because "many, but not all, cured meats contain nitrite and because other foods can also be important sources of nitrite". [The IARC 2015 Working Group on Red and Processed Meats classified consumption of processed meat as "carcinogenic to humans" (Group 1) on the basis of "sufficient evidence for colorectal cancer" (Bouvard *et al.* 2015). The IARC Monograph describing the evidence and basis for that finding has not been published, as of August 2016.]

Colon cancer - summarized in Table 3 and Figures 3A-3B

One of three cohort studies of colon cancer in relation to nitrite exposure, a study of women in Shanghai (DellaValle *et al.*, 2014), found elevated risks with intake of preserved food sources and plant sources (*e.g.*, third quintile: HR= 1.42, 95% CI, 1.01-1.99; HR= 1.43, 95% CI, 1.02-2.02, respectively) of dietary nitrite but no clear evidence of a trend with increasing intake. In two case-control studies of colon cancer in relation

to nitrite (or nitrate + nitrite) intake, there are some indications of an effect, but risks are not significantly elevated.

Rectal cancer - summarized in Table 3 and Figures 4A-4B

Of four cohort studies of rectal cancer in relation to dietary nitrite or nitrate plus nitrite exposure, three studies showed some indication of an association but risks were not significantly elevated nor were significant trends observed. A case-control study of dietary nitrite (Zhu *et al.*, 2014) found elevated risks of rectal cancer (fourth quintile, OR= 1.51, 95% CI, 1.02 – 2.22) while one that looked at nitrate plus nitrite did not.

4.1.2 Esophageal and stomach cancer

Esophageal cancer

IARC (2010) noted that "…two case‐control studies of oesophageal cancer, both of which were conducted in the USA, assessed the association with nitrite intake. Both were well designed and adjustment was made for the main risk factors for oesophageal cancer. Both studies reported a positive but non-significant association." Jakszyn and Gonzalez (2006), in their review of studies published from 1985-2005 of the relationship between dietary nitrite intake and esophageal cancer risk, found "The evidence in relation to OC [esophageal cancer] is insufficient [one of two studies of nitrite intake]."

In studies of esophageal cancer summarized in Table 4 and Figures 5A-5D, no clear association was seen in the two cohort studies that examined risk of esophageal adenocarcinoma (EAC) in relation to dietary nitrite exposure.

One of the two cohort studies that examined risk of esophageal squamous cell carcinoma (ESCC) in relation to dietary nitrite exposure found indications of increasing risk with increasing exposure in men (Keszei *et al.*, 2013a); the continuous HR was significantly increased (per 0.1-mg/d nitrite: HR= 1.19, 95% CI 1.05, 1.36).

With regard to esophageal cancers more broadly defined, two recent studies were identified. An occupational cohort study (Xie *et al.*, 2011) reported a significantly increased risk of esophageal cancer in relation to nitrite exposure (HR =1.26, 95%CI 1.08-1.46); exposure levels were unknown for workers in this manufacturing facility in China. A case-control study that examined esophageal cancer in relation to combined exposure to nitrate and nitrite (Ward *et al.*, 2008) found no significantly elevated risks.

Stomach cancer

IARC (2010) reviewed the evidence for gastric cancer and ingested nitrite:

> "Six of seven case – control studies found a positive association, which was significant in four…. Two cohort studies were reviewed, one of which was conducted in the Netherlands and the other in Finland. In the Finnish study, no association was found between the risk for stomach cancer and dietary intake of nitrites…. The Dutch cohort reported a significant increase in risk for nitrite that was limited to the highest level of intake and became non-significant after adjustment for potential confounders…. [N]one of the studies that were reviewed had taken into account potential confounding or effect modification by *Helicobacter pylori*, an important risk factor for stomach cancer, when assessing the effect of nitrite."

IARC (2010) concluded: "Nitrite in food is associated with increased incidence of stomach cancer" in classifying the overall human evidence as limited. Bouvard *et al.* (2015), summarizing the findings of the IARC 2015 Working Group on Red and Processed Meats, noted: "a positive association with the consumption of processed meat was found for stomach cancer."

Jakszyn and Gonzalez (2006), in their review of studies published from 1985-2005 of the relationship between dietary nitrite intake and gastric cancer risk, found "the available epidemiological evidence from case-control studies on nitrite and nitrosamine intake supports a positive association with GC [gastric cancer] risk [5 of 7 studies on nitrite intake]." Song *et al.* (2015) provide a summary relative risk from their meta-analysis of 18 studies of gastric cancer and nitrite intake (RR=1.31, 95% CI, 1.13–1.52). Xie *et al.* (2016) provide a pooled relative risk from a meta-analysis of 51 studies of dietary nitrite intake and gastric cancer risk (RR = 1.21, 95% CI, 0.99-1.47).

In studies of gastric cardia adenocarcinoma (GCA) summarized in Table 4 and Figure 6C, no clear pattern and no significantly elevated risks are seen in either of the two cohort studies that analyzed the association between dietary nitrite and risk. There appears to be a difference in the response seen in men as compared to women in the study (Keszei *et al*., 2013) that compared these groups.

In studies of gastric non-cardia adenocarcinoma (GNCA) summarized in Table 4 and Figure 6D, a slight, statistically non-significant pattern of increasing risk with increasing exposure to nitrite appears in the two cohort studies that analyzed the association

between dietary nitrite and risk of GNCA, particularly in the men in the Keszei *et al.* (2013) cohort.

With regard to stomach cancers more broadly defined, recent studies are summarized in Table 4 and Figures 6A-6B. One of two case-control studies of dietary nitrite intake found significantly elevated risks for "all gastric cancer" and "diffuse gastric cancer" for those with the highest levels of intake from animal source foods (all: OR= 1.56 95% CI, 1.02-2.40, p-trend = 0.03; diffuse: OR= 1.74, 95% CI, 1.04-2.89, p-trend = 0.026).

4.1.3 Lymphoma

IARC (2010) reports: "The relationship between ingested nitrite and non-Hodgkin lymphoma was evaluated in two case–control studies in the USA. Dietary nitrite was not associated with risk for non-Hodgkin lymphoma in one study but there was an increase in risk with increasing quartiles of nitrite intake in the second study. When plant and animal sources of dietary nitrite were evaluated separately, the positive association was observed only for plant sources."

Xie *et al.* (2016), in a recent meta-analysis of dietary nitrite intake and cancer risk, notes "No significant associations were found between dietary nitrate/nitrite and…non-Hodgkin lymphoma…."

Of the studies of lymphoma summarized in Table 5 and Figures 7A-7B, one cohort study (Daniel *et al.*, 2012, not shown in figures) looked at nitrate plus nitrite dietary intake in relation to non-Hodgkin lymphoma (NHL) overall and with respect to sub-types; for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) only, there was some indication of elevated risks (third quintile: HR= 1.36, 95% CI, 1.04-1.78), but no trend with increasing exposure.

In three case-control studies analyzing dietary nitrite intake in relation to NHL, some elevated associations are reported, but no clear pattern of increasing risk with increasing exposure is evident. Two case-control studies examined risk by sub-type and by source of nitrite exposure (Aschebrook-Kilfoy *et al*., 2010; Aschebrook-Kilfoy *et al.,* 2013b) and reported some elevated risks; most notably follicular lymphoma with total nitrite intake (fourth quartile: OR= 2.3, 95% CI, 1.1-4.9, p-trend= 0.008) and CLL/SLL with plant source nitrite (fourth quartile: OR= 2.7, 95% CI, 1.1-7.0, p-trend=0.09), both from Aschebrook-Kilfoy *et al.* (2010). Two case-control studies looked at t(14;18), one of the most common chromosomal translocations in NHL; presence of the translocation, denoted as "t(14:18) positive," might characterize a more homogenous group than NHL cases as a whole. One (Chiu *et al.,* 2008) found significantly elevated risks with all

dietary nitrite (t{14:18} positive: OR= 2.8, 95% CI, 1.3-6.1); the other (Aschebrook-Kilfoy *et al.,* 2013b) evaluated risk by source of nitrite and found increased risks only for plant sources, among those without the translocation (t{14;18} negative, second tertile: OR= 1.9, 95% CI, 1.1-3.4). An occupational case-control study in northern Germany (Richardson *et al.,* 2008) that looked at nitrate, nitrite and nitrosamine exposures based on interviews and job classifications found an increased risk of "high malignancy NHL" in relation to hours of exposure (fourth quartile: OR=2.39, 95% CI, 1.29-4.42, p-trend = 0.031).

4.1.4 Other Cancers: Central Nervous System, Thyroid, Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer

Central Nervous System

IARC (2010) reviewed the evidence for brain tumors:

> "The Working Group evaluated 12 case–control studies that focused on nitrite in the diet or in drinking-water, five of which investigated brain tumours in children and four of which examined maternal diet during pregnancy as a possible risk factor for the development of brain tumours in the offspring. The largest case–control study…observed… children born to mothers who had the highest category of intake of nitrite specifically from cured meat (> 1.28 mg per day) had an almost twofold increased risk for brain tumours; nitrite intake from vegetable sources was not associated with the occurrence of brain tumours. "
>
> "Nitrite in the drinking-water was investigated in a study… [in which] [c]urrent levels of nitrite in the tap-water [was measured] in homes in which the pregnancies had occurred… This study reported a twofold increase in risk for brain tumours in the offspring… This association was stronger among women who did not rely on bottled water and was confined to astroglial tumours."
>
> "Seven studies of dietary intake of nitrite and adult brain tumours were conducted…. No significant associations were reported for dietary nitrite intake overall. The largest study in California, USA, observed a twofold increase in risk among men who consumed levels of nitrite above the median and levels of vitamin C below the median; this pattern did not occur among women. Two small studies… observed a positive association with intake of nitrite from cured meat; a larger case–control study… observed no association with nitrite from animal sources but a threefold increase in risk for glioma among persons who had high consumption of nitrite from plant sources."

In a recent meta-analysis of dietary nitrite intake and cancer risk, Xie *et al.* (2016) note: "Comparing the highest vs. lowest levels, …dietary nitrite intake was positively associated with adult glioma… with pooled RR of 1.21 (95% CI = 1.03-1.42) …."

One (Dubrow *et al.*, 2010) of two prospective cohort studies of adult glioma and dietary nitrite intake (see Table 6A) reported increased risks for total nitrite (fifth quintile: HR= 1.32, 95% CI, 1.01-1.71); in this study, intake from plant sources had the highest risks, particularly among men. These authors also examined intake of nitrate and nitrite from processed meats at ages 12-13 (retrospectively) and reported elevated adult glioma risks (fourth quintile: HR= 1.47, 95% CI, 1.03-2.08).

Thyroid

Reviewing publications examining dietary factors in thyroid cancer including three large US cohort studies, Choi and Kim (2014) concluded that "…dietary nitrate and nitrite…showed a positive association with thyroid cancer risk…." A meta-analysis by Bahadoran *et al.* (2015) of studies investigating nitrate and/or nitrite exposure and thyroid function report "a significant association between higher exposure to nitrite and the risk of thyroid cancer (risk = 1.48, 95% confidence interval = 1.09–2.02, P = 0.012)." A meta-analysis by Xie *et al.* (2016) reported "[c]omparing the highest vs. lowest levels,…dietary nitrite intake was positively associated with… thyroid cancer risk with pooled RR of…1.52 (95% CI = 1.12-2.05)…."

Both prospective cohort studies (Table 6) that examined dietary nitrite in relation to thyroid cancer reported some increased risks. In a US cohort (Aschebrook-Kilfoy *et al.*, 2011b), total thyroid cancer was elevated but not significantly, and follicular thyroid cancer in men was elevated with a significant trend (fourth quartile: RR= 2.74, 95% CI, 0.86-8.77, p-trend= 0.04). In a cohort of women in Shanghai, China, thyroid cancer risks were increased for intake of nitrite from all sources (fourth quartile: RR= 2.05, 95% CI, 1.20-3.51) and processed meat sources, with a positive trend for nitrite from processed meat sources (fourth quartile: RR= 1.96, 95% CI,1.28-2.99, p-trend <0.01).

Lung, Breast, Pancreatic, Liver, Ovarian, Urinary Tract, Prostate and 'All' Cancer

IARC (2010) reviewed studies of urinary tract cancers:

> Two well-designed case–control studies of tumours of the urinary tract assessed dietary intake of nitrite; [one] found an increased risk for cancer of the urinary bladder with greater dietary intake of nitrite among Japanese men. There was no association among Japanese women or among Caucasian men or women. In a

study of cancer of the urinary bladder from Iowa (largely Caucasian), dietary intake of nitrite was not associated with risk."

IARC (2010) reviewed studies of cancers at other sites:

> "Dietary nitrite intake was evaluated in case–control or cohort studies in relation to oral, laryngeal, nasopharyngeal, pancreatic and lung cancers. The number of studies of any given cancer site were few: three case–control studies of pancreatic cancer and two or fewer studies of cancers at other sites were available."

The report on a meta-analysis of 51 studies of dietary nitrite intake and cancer risk (Xie *et al.*, 2016) noted: "No significant associations were found between dietary nitrate/nitrite and cancers of the breast, bladder, …renal cell, … ovarian, and pancreas."

Positive associations were seen in some but not all studies (Table 6) for lung, pancreatic, ovarian, urinary tract, and prostate cancer studies in relation to nitrite intake. Studies of breast, liver and 'all' cancer had no positive findings.

4.2 Evidence from Studies in Experimental Animals

In 2006, IARC evaluated 55 animal bioassays of nitrite, and concluded "there is sufficient evidence in experimental animals for the carcinogenicity of nitrite in combination with amines or amides" (IARC, 2010). Section 3.2 of this document summarizes the tumor findings from the experimental animal studies evaluated by IARC, as well as findings from an additional 35 studies identified by OEHHA (see Table 7 (Amines tested in combination with nitrite in animal tumor studies), Table 8 (Amides tested in combination with nitrite in animal tumor studies), and Table 9 (Fish meal, a complex mixture of amines and amides, tested in combination with nitrite in animal tumor studies)). The overall number of amines and amides tested in this set of studies is small; however, compared to the thousands of individual chemicals that exist in each of these large chemical classes.

Evidence on the carcinogenicity of nitrite in combination with amines or amides comes from a number of animal studies. A number of studies show significant increases in tumors, including rare tumors, in animals treated with nitrite plus an amine or amide, as compared to untreated or vehicle controls, animals treated with nitrite alone, and animals treated with the amine or amide alone. A number of other studies do not find tumorigenic effects (See Tables 7 and 8, see also Tables 12 and 13). In addition, there are two studies in which significant increases in tumors, including rare tumors, have

been observed in animals treated with nitrite plus fish meal, a complex mixture of amines and amides, as compared to animals treated with fish meal alone (Table 9).

Inconclusive evidence for the carcinogenicity of nitrite in combination with amines or amides comes from animal studies that included only one or two comparator groups, rather than all three (*i.e.*, untreated or vehicle control, nitrite alone, amine or amide alone).

Species and strains tested and tumor types observed

With regard to the types of animals studied and tumors observed in these studies of exposure to nitrite in combination with amines or amides, increases in tumor incidence have been reported, often at multiple sites, in multiple strains of rats (Sprague-Dawley, F344, and Wistar strains) and mice (Swiss, Swiss/Leiden, Strain A, C57BL6, and ICR strains), and in one strain of hamsters (Syrian golden). Tumors observed in animals treated with nitrite in combination with *amines* include lung and liver tumors, reticular cell sarcoma, rare Zymbal's gland and nasal tumors, and rare cholangiocarcinoma in rats; lung tumors in mice; and liver tumors and rare cholangiocarcinoma in hamsters. Tumors observed in the studies with *amides* include lung tumors, mononuclear cell leukemia, rare forestomach and Zymbal's gland tumors, and rare malignant lymphoma in rats; and lung and Harderian gland tumors, lymphosarcoma, malignant lymphoma, and rare skin, forestomach, intestine, and uterine tumors in mice. Finally, rare kidney and uterine tumors were observed in rats treated with nitrite in combination with fish meal, a complex mixture of amines and amides.

Amines

As summarized in Table 12 below, some of the animal bioassays of nitrite in combination with amines report positive tumor findings, while others do not. Different classes of amines have been tested in combination with nitrite to various extents. Primary amines represent a large class of hundreds of chemicals. Two primary amines were tested. IQ, a chemical on the Proposition 65 list, tested positive. PhIP, also on the Proposition 65 list, did not. There are also numerous secondary amines, of which eleven were tested in combination with nitrite in animals. Four tested positive [bis(2-hydroxypropyl)amine; morpholine; N-methylaniline; piperazine], four tested negative and studies on three were inconclusive. Thirteen tertiary amines were tested, with three having some positive results [IQ (also a primary amine); aminopyrine; chlorpheniramine], seven with negative results and three with inconclusive results. There are no animal studies for the quarternary amines. Cyclic aromatic amines also is a large class of chemicals, of which five were tested, two showing positive results [IQ

(also a primary amine and a tertiary amine); chlorpheniramine (also a tertiary amine)], one with negative results and two with inconsistent results.

Thus across the classes of the amines tested in combination with nitrite, 23 amines were tested in animal bioassays. Positive tumor findings were reported for 7, inconclusive findings were reported for 6, and negative findings were reported for 10 (Tables 7 and 12). Of the 7 amines with positive tumor findings, four are secondary amines [bis(2-hydroxypropyl)amine; morpholine; N-methylaniline; piperazine], one is both a tertiary amine and a cyclic aromatic amine [chlorpheniramine], one is both a tertiary amine and an amide [aminopyrine], and one is both a primary amine, a cyclic tertiary amine, and a cyclic aromatic amine [IQ]. Within each of these subgroups of amines with positive tumor findings, there were other amines with negative tumor tumor findings, or that lacked all necessary comparator groups.

Amides

As summarized in Table 13 below, some of the animal bioassays of nitrite in combination with amides report positive tumor findings, while others do not. Different classes of amides have been tested in combination with nitrite to various extents. Primary and tertiary amides represent large classes of chemicals. No chemicals in these classes were tested in animal studies. Two secondary amides were tested: allantoin tested positive, and 2-acetamidofluorene, a chemical on the Proposition 65 list, did not. Allantoin is also a urea. Of the seven ureas tested in combination with nitrite, in addition to allantoin, butylurea, ethylene thiourea (on the Proposition 65 list), ethyl urea and methyl urea all had positive studies. Two others did not. Of the carbamates tested, carbendazim in combination with nitrite tested positive, the Proposition 65 carcinogen ethyl carbamate was negative and disulfiram was inconclusive. None of the sulfonamides were tested. Of the four guanadines tested, one (dodine) tested positive.

Across the classes of the amides tested in combination with nitrite, 15 amides were tested in animal bioassays. Positive tumor findings were reported for 7, inconclusive findings were reported for 3, and negative findings were reported for 5 (Tables 8 and 13). Of the 7 amides with positive tumor findings, five are ureas [allantoin; butylurea; ethylene thiourea; ethylurea; methylurea] (one of these is also a secondary amide [allantoin]), one is a carbamate [carbendazim], and one is a guanidine [dodine]. Within each of these subgroups of amides with positive tumor findings, there were other amides with negative tumor findings, or that lacked all necessary comparator groups.

4.3 Evidence from Genotoxicity Studies

Additional evidence for the carcinogenicity of nitrite in combination with amines or amides comes from studies in which increases in genotoxicity have been observed in assays of nitrite plus a number of different amines and amides, as compared to untreated or vehicle controls, treatment with nitrite alone, and treatment with the amine or amide alone (see Table 10 [Amines tested in combination with nitrite for genotoxicity] and Table 11 [Amides tested in combination with nitrite for genotoxicity]).

A substantially greater number of amines and amides have been tested in combination with nitrite in at least one genotoxicity assay, as compared to the number of amines and amides than have been tested for carcinogenicity in animal cancer bioassays. Specifically, 111 amines and 39 amides have been tested for genotoxicity, as compared to 23 amines and 15 amides tested in animal cancer bioassays. However, the overall number of amines and amides tested for genotoxicity still represent a small portion of the thousands of individual amines and amides that exist.

Evidence for the genotoxicity of nitrite in combination with amines or amides comes from a number of studies in which increased genotoxic effects were observed following treatment with nitrite in combination with an amine or amide, as compared to (i) untreated or vehicle controls, and (ii) nitrite alone, and (iii) amine or amide alone. Inconclusive evidence for the genotoxicity of nitrite in combination with amines or amides comes from studies that included only one or two comparator groups, rather than all three (*i.e.*, untreated or vehicle control, nitrite alone, amine or amide alone) (See Tables 10 and 11; see also Tables 12 and 13).

Amines

Positive genotoxicity findings have been observed for nitrite in combination with amines in the following test systems:

- *Bacteria*
    - Reverse mutations in one or more *Salmonella* test strains
    - Reverse mutations in *Salmonella* treated with urine from mice exposed *in vivo*
    - Reverse mutations in *E. coli*
    - DNA-damaging effects in the *umu*-test with *Salmonella* strain TA1535
- *Yeast*
    - Gene conversions in *S. cerevisiae*
- *Mammalian cells in vitro*
    - DNA strand breaks in CHO cells (Comet assay)

    - Unscheduled DNA synthesis in rat primary hepatocytes
- *Rodents in vivo*
    - DNA strand breaks in liver and gastric mucosa of rats (Comet assay)
    - Reverse mutations in *Salmonella* strain G46 in the host-mediated assay in mice and rats
    - Hemoglobin adducts in rats

As summarized in Table 12 below, some of the genotoxicity assays of nitrite in combination with amines report positive findings, while others do not. Different classes of amines have been tested in combination with nitrite for genotoxicity to various extents. Fourteen primary amines were tested for genotoxicity: four tested positive, three tested negative, and studies on seven were inconclusive. Forty-eight secondary amines were tested in combination with nitrite for genotoxicity: 38 tested positive, three tested negative, and studies on seven were inconclusive. Fifty-two tertiary amines were tested: 24 tested positive, 9 tested negative, and findings for 19 were inconclusive. One quarternary amine was tested for genotoxicity, with negative results. Thirty-four cyclic aromatic amines were tested: 16 tested positive, 10 tested negative, and findings for 8 were inconclusive.

Thus across the classes of amines tested in combination with nitrite, 111 amines were tested for genotoxicity. Positive genotoxicity findings were reported for 59, inconclusive findings were reported for 36, and negative findings were reported for 16 (Tables 10 and 12). Of the 59 amines with positive genotoxic findings, four are primary amines (three of these are also secondary amines, and two are also cyclic aromatic amines), 38 are secondary amines (three of these are also primary amines, six are also tertiary amines, nine are also cyclic aromatic amines, and 5 are also amides), 24 are tertiary amines (7 of these are also secondary amines, one is also a cyclic aromatic amine, and three are also amides), and 16 are cyclic aromatic amines (two of these are also primary amines, 10 are also secondary amines, one is also a tertiary amine, and three are also amides). Within each of these subgroups of amines with positive genotoxicity findings, there were other amines that were negative, or that lacked all necessary comparator groups.

Amides

Positive genotoxicity findings have been observed for nitrite in combination with *amides* in the following testing systems:

- *Bacteria*
    - Reverse mutations in one or more *Salmonella* test strains
    - DNA-damaging effects in the *umu*-test with *Salmonella* strain TA1535

- *Mammalian cells in vitro*
    - DNA strand breaks in CHO cells (Comet assay)
- *Rodents in vivo*
    - DNA strand breaks in liver and gastric mucosa of rats (Comet assays)
    - Reverse mutations in *Salmonella* strain G46 in the host-mediated assay in mice

As summarized in Table 13 below, some of the genotoxicity assays of nitrite in combination with amides report positive findings, while others do not. Different classes of amides have been tested in combination with nitrite for genotoxicity to various extents. Five primary amides were tested for genotoxicity: four tested positive and one was inconclusive. Ten secondary amides were tested in combination with nitrite for genotoxicity: one tested positive, one tested negative, and studies on eight were inconclusive. Seven tertiary amides were tested: two tested positive and studies on five were inconclusive. Six ureas were tested: three tested positive, two tested negative, and the finding for one was inconclusive. Seven carbamates were tested: one tested positive, two tested negative, and studies on four were inconclusive. Five sulfonamides were tested: three tested positive and studies on two were inconclusive. Four guanidines were tested: two with positive results and two with inconclusive results.

Thus across the classes of amides tested in combination with nitrite, 39 amides were tested for genotoxicity. Positive genotoxicity findings were reported for 15, inconclusive findings were reported for 20, and negative findings were reported for 4 (Tables 11 and 13). Of the 15 amides with positive genotoxic findings, four are primary amides (all of these are also amines), one is a secondary amide (and also an amine), two are tertiary amides (one of these is also an amine), three are ureas, one is a carbamate (and also an amine), three are sulfonamides (all of these are also amines, and one is also a guanidine), and two are guanidines (both of these are also amines, and one is also a sulfonamide). Within each of these subgroups of amides with positive genotoxicity findings, there were other amides that were negative, or that lacked all necessary comparator groups.

Table 12. Summary of Amines Tested in Combination with Nitrite for Genotoxicity or Carcinogenicity

Chemical	↑ Effect observed with NO_2 + amine on		Chemical	↑ Effect observed with NO_2 + amine on	
	Animal tumors	Genotoxicity		Animal tumors	Genotoxicity
Primary Amines					
PhIP[§,a,b]	No		Dopamine		?
IQ[§,a,b]	Yes		Methyldopa		?
2-Aminopyridine[b]		Yes	Metoclopramide[a,d]		?
Ambroxol[c]		Yes	Primaquine[b,c]		Yes
Amlodipine[c]		Yes	Procainamide[a,d]		?
Cefadroxil[d,e]		?	Pyrimethamine[b]		No
Cefalexin[d,e]		?	Sulfanilamide[f]		?
Diaveridine[b]		No	Trimethoprim[b]		No
Secondary Amines					
2-(2-Pyridylamino)-ethyldimethyl-amine[a,b]		Yes	Morpholine	Yes	Yes
Alprenolol		No	Myosmine[b]		Yes
Ambroxol[g]		Yes	Nadolol		?
Amineptine		Yes	Nicardipine		Yes
Amlodipine[g]		Yes	Nifedipine		Yes
Astemizole[a,b]		Yes	Nimodipine		Yes
Atenolol[h]		1 Yes; 1 ?	Nitrendipine		Yes
Bamethan		?	N-methylaniline	Yes	
Betahistine[b]		Yes	Pamaquine[a,b]		Yes
Bis(2-hydroxy-propyl)amine	Yes		Paroxetine		Yes
Chlordiazepoxide[b]	?	3 Yes; 2 ?	Pentaquine[b]		Yes
Chloroquine[a,b]		2 Yes; 1?	Piperazine	3 Yes; 1 No	Yes
Cimetidine[i]	No	1 Yes; 1 ?; 3 No	Piperidine	No	
Clonidine		?	Prenylamine		No
Dehydroemetine[a]		Yes	Primaquine[b,g]		Yes
Dibutylamine	No		Propranolol		1 Yes; 3 ?
Dimethylamine		3 Yes; 1 ?; 1 No	Propylhexedrine	?	
Dimetofrine		?	Pseudoephedrine		Yes
Enalapril[e]		Yes	Quinacrine[a,b]		Yes
Ephedrine		Yes	Ritodrine		Yes
Ethambutol		1 Yes; 1 ?	Salbutamol		Yes
Fluoxetine		Yes	Sertraline		Yes
Heptamethyleneimine	?		Sotalol[f]		Yes; 1 ?
Hydrochlorothiazide[f]		Yes	Terbutaline		Yes
Isoxsuprine		?	Tizanidine[b]		Yes
Lucanthone[a]	No	No	Tolazoline		?
Metoprolol		1 Yes; 2 ?	Trimetazidine[a]		?
Tertiary Amines					
2-(2-Pyridylamino)-ethyldimethyl-amine[b,c]		Yes	Chloroquine[b,c]		2 Yes; 1?
PhIP[§,b,g]	No		Chlorothen		No
IQ[§,b,g]	Yes		Chlorpheniramine[b]	1 Yes; 1 No	No
Ajmaline		?	Chlorpromazine	No	1 Yes; 1 ?
Aminopyrine	3 Yes; 6 ?; 1 No	3 Yes; 4 ?; 1 No	Chlorprothixene		?
Astemizole[b,c]		Yes	Cinnarizine		?
Carpipramine[h]		?	Cyclizine	1 ?; 1 No	Yes

Table 12. Summary of Amines Tested in Combination with Nitrite for Genotoxicity or Carcinogenicity (continued)

Chemical	↑ Effect observed with NO_2 + amine on		Chemical	↑ Effect observed with NO_2 + amine on	
	Animal tumors	Genotoxicity		Animal tumors	Genotoxicity
Tertiary Amines (continued)					
Dehydroemetine[c]		Yes	Opipramol		1 Yes; 2 ?
Dextropropoxyphene		Yes	Oxytetracycline[h]		Yes
Dilazep		?	Pamaquine[b,c]		Yes
Diltiazem		1 Yes; 1 ?			
Dimethyldodecylamine	?		Pipamperone[h]		?
Diphenhydramine	No	1 Yes; 1 ?	Piromidic acid[b]		?
Dipyridamole[b]		No	Procainamide[c,g]		?
Dipyrone		Yes	Prochlorperazine		?
Flupentixol		?	Pyrantel pamoate		Yes
Gallopamil		Yes	Pyribenzamine[b]		1 ?; 1 No
Guanethidine[i]		?	Pyrilamine[b]		No
Hexamethylenetetramine	No	Yes	Quinacrine[b,c]		Yes
Hydroxyzine		?	Ranitidine		6 Yes; 2 ?
Imipramine		?	Spiperone[d]		?
Lucanthone[c]	No	No	Tetracycline[h]		Yes
Methadone		No	Thenyldiamine[b]		No
Methafurylene[b]		No	Thiothixene[f]		?
Methaphenilene		Yes	Tiaramide[e]		?
Methapyrilene[b]	3 ?; 1 No	1 Yes; 1 No	Trapidil[b]		No
Metoclopramide[d,g]		?	Trimetazidine[c]		?
Nicardipine[c]		Yes	Trimethylamine	No	
Nitrilotriacetic acid[§]	No		Verapamil		Yes
Quaternary Amines					
Bephenium hydroxynaphthoate		No			
Cyclic Aromatic Amines					
2-(2-Pyridylamino) ethyldimethyl-amine[a,c]		Yes	Mebendazole[i]		Yes
			Methafurylene[a]		No
PhIP[§,a,g]	No		Methapyrilene[a]	3 ?; 1 No	1 Yes; 1 No
IQ[§,a,g]	Yes		Morsydomine[j]		?
2-Aminopyridine[g]		Yes	Myosmine[c]		Yes
Astemizole[a,c]		Yes	Pamaquine[a,c]		Yes
Betahistine[c]		Yes	Pentaquine[c]		Yes
Bromazepam[c]		Yes	Piromidic acid[a]		?
Cefazolin[d,e]		?	Primaquine[c,g]		Yes
Chlordiazepoxide[c]	?	Yes	Pyribenzamine[a]		?
Chloroquine[a,c]		Yes	Pyridinol carbamate[j]		?
Chlorpheniramine[a]	1 Yes; 1 No	No	Pyrilamine[a]		No
Diaveridine[g]		No	Pyrimethamine[g]		No
Dipyridamole[a]		No	Quinacrine[a,c]		Yes
Ecarazine		?	Thenyldiamine[a]		No
Famotidine[f,i]		1 Yes; 1 ?	Tizanidine[c]		Yes
Hydralazine		?	Trapidil[a]		No
Iodochlorhydroxyquin		No	Trimethoprim[g]		No
Isoniazid		?			

Gray box—Not tested

§ Proposition 65 carcinogen; [a] Also a tertiary amine; [b] Also a cyclic aromatic amine; [c] Also a secondary amine; [d] Also a secondary amide; [e] Also a tertiary amide; [f] Also a sulfonamide; (amide) [g] Also a primary amine; [h] Also a primary amide; [i] Also a guanidine (amide); [j] Also a carbamate (amide)

Table 13. Summary of Amides Tested in Combination with Nitrite for Genotoxicity or Carcinogenicity

Chemical	↑ Effect observed with NO_2 + amide on		Chemical	↑ Effect observed with NO_2 + amide on	
	Animal tumors	Genotoxicity		Animal tumors	Genotoxicity
Primary Amides					
Atenolol[a]		1 Yes; 1 ?	Pipamperone[b]		?
Carpipramine[b]		Yes	Tetracycline[b]		Yes
Oxytetracycline[b]		Yes			
Secondary Amides					
2-Acetamidofluorene[§]	No		Cefazolin[e,f]		?
Acetaminophen		?	Metoclopramide[b,f]		?
Allantoin[c]	1 Yes; 1 Equivocal	No	Primidone[§]		?
Bromazepam[d]		1 Yes; 1 ?	Procainamide[b,f]		?
Cefadroxil[e,f]		?	Spiperone[b]		?
Cefalexin[e,f]		?			
Tertiary Amides					
Cefadroxil[f,g]		?	Enalapril[a]		Yes
Cefalexin[f,g]		?	Piperine		Yes
Cefazolin[d,g]		?	Tiaramide[b]		?
Diazepam		?			
Ureas					
Acetohexamide		?	Ethylurea	Yes	Yes
Allantoin[g]	1 Yes; 1 Equivocal	No	Methylurea	Yes	1 Yes; 1 ?
Butylurea	4 Yes; 1 ?		Tolazamide	No	Yes
Dimethylphenylurea	No		Tolbutamide		No
Ethylene thiourea[§]	Yes				
Carbamates					
Carbendazim	Yes		Meprobamate		?
Chlorzoxazone		?	Morsydomine[b]		?
Disulfiram	?	No	Pyridinol carbamate[d]		?
Ethyl carbamate[§]	No		Thiram		No
Mebendazole[d]		Yes			
Sulfonamides					
Famotidine[d,h]		1 Yes; 1 ?	Sulfanilamide[f]		?
Hydrochlorothiazide[a]		Yes	Thiothixene[b]		?
Sotalol[a]		Yes; 1 ?			
Guanidines					
Arginine	1 ?, 1 No		Famotidine[d,i]		1 Yes; 1 ?
Bethanidine		?	Guanethidine[b]		?
Cimetidine[a]	No	1 Yes; 1 ?; 3 No	Methylguanidine	1 ?, 2 No	
Dodine	Yes				

Gray box—Not tested

[§] Proposition 65 carcinogen; [a] Also a secondary amine; [b] Also a tertiary amine; [c] Also a urea (amide); [d] Also a cyclic aromatic amine; [e] Also a tertiary amide; [f] Also a primary amine; [g] Also a secondary amide; [h] Also a guanidine (amide); [i] Also a sulfonamide (amide)

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APPENDIX A. Parameters for Literature Searches on the Carcinogenicity of Nitrite in Combination with Amines or Amides

General searches of the literature on the carcinogenicity of “nitrite in combination with amines or amides” were conducted under contract by the University of California at Berkeley (Charleen Kubota, M.L.I.S.). The goal was to update peer-reviewed open source and proprietary journal articles, print and digital books, reports and gray literature that potentially reported relevant toxicological and epidemiological information on the carcinogenicity of nitrite in combination with amines or amides since the review by IARC in early 2006 (IARC, 2010). Literature searches were conducted up to July 2016.

Databases

The literature search utilized the following search platforms/database vendors:

- PubMed (National Library of Medicine)
- EMIC (National Library of Medicine)
- SciFinder®: CAS (Chemical Abstracts Service)
- TOXNET (National Library of Medicine): Toxicology Literature Online (TOXLINE), Genetic Toxicology Data Bank (GENE-TOX)
- Web of Knowledge: BIOSIS Previews®, Web of Science® (Thomson-Reuters, Inc.)

Search Process

Relevant subject terms were entered into the PubMed Search Builder to execute a search.

The following is a typical chemical search strategy used to search PubMed:
(“*chemical name*” [MeSH] OR “CAS *registry number”* [RN]) AND ("bioassay"[MeSH] OR "carcinogenicity"[MeSH] OR "cancer"[MeSH] OR "tumor"[MeSH]) OR "neoplasm"[MeSH]) OR "genotoxicity"[MeSH]) OR "mutagenicity"[MeSH]) OR "DNA damage"[MeSH]) OR "DNA adducts"[MeSH]) OR "chromosomal aberrations"[MeSH]) OR "micronucleus tests"[MeSH] OR "cell transformation"[MeSH] OR "chromosomal breakage"[MeSH])

Four chemical names, *i.e.* nitrite, nitrite ion, sodium nitrite and potassium nitrite were searched according to the above search strategy.

In PubMed, MeSH (Medical Subject Headings) terms at the top of hierarchical lists of subject headings are automatically “exploded” in a search to retrieve citations with more

specific MeSH terms. For example, the heading “carcinogenicity” includes broad conditions that are related to cancer induction in animals and humans.

Additional databases listed above were then searched. The search strategies were tailored according to the search features unique to each database. Web of Science, for example, was searched by entering chemical terms and refining the search by applying the following the Web of Science categories: Toxicology and/or Public, Environmental and Occupational Health. The search term used includes either the CAS registry number or the chemical name and its available synonyms. Sometimes other databases not listed here were searched as needed.

Additional update searches and focused searches for Sections 3.1.2, 3.1.3, 3.2, and 3.3.2 were performed by OEHHA and these search strategies are briefly described as follows:

- PubChem Compound (http://www.ncbi.nlm.nih.gov/pccompound) was searched first to gather synonyms, CAS registry number, MeSH terms before searching bibliographic databases. Related chemicals are searched: Sodium nitrite (CAS 7632-00-0), potassium nitrite (CAS 7758-09-0), nitrite ion (CAS 14797-65-0).
- Databases and other resources used: Google search engine, MeSH (Medical Subject Headings) (National Library of Medicine, http://www.ncbi.nlm.nih.gov/mesh/), PubMed (National Library of Medicine, http://www.ncbi.nlm.nih.gov/pubmed), TOXLINE (National Library of Medicine, https://toxnet.nlm.nih.gov/newtoxnet/toxline.htm), iCSS Dashboard v2 (US EPA ToxCast, https://actor.epa.gov/dashboard2/) and CTD (Comparative Toxicogenomics Database, http://ctdbase.org/).
- Search keywords applied were: mutagenicity, mutagenicity tests, mutagen, DNA adducts, DNA damage, chromosomal breakage, chromosomal aberrations, micronucleus tests, DNA repair, genomic instability, cell transformation, neoplasm(s), neoplastic, epigenetic, reactive oxygen species, oxidative stress, inflammation, epithelial mesenchymal transition, cancer, carcinogen, carcinogenicity, tumor, amines, and amides.
- The search timeframe was October 2005 to July 2016.
- Additional relevant literature was identified from citations in individual articles.
- This search strategy is focused on “nitrite in combination of amines or amides”; therefore, the search strings applied here identified studies of cancer associated with nitrite exposure, including some that also reported associations with consumption of processed meats. However, the search strategy was not designed to identify all studies of processed meat consumption and cancer risk.

ATTACHMENT 1 IARC 2010

ATTACHMENT 2 Bouvard *et al.*, 2015