# Attachment 46g

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



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**LC control no.:** sh 94005142
**LCCN Permalink:** https://lccn.loc.gov/sh94005142
**HEADING:** Protein drugs Dosage forms

**000** 00613cz a2200205n 450
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**005** 20120330081705.0
**008** 940711i| anannbabn |a ana
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**040** __ |**a** DLC |**c** DLC
**150** __ |**a** Protein drugs |**x** Dosage forms
**450** __ |**a** Dosage forms of protein drugs
**550** __ |**w** g |**a** Drug delivery systems
**670** __ |**a** Work cat.: 94-3789: Formulation and delivery of proteins and peptides, 1994.
**906** __ |**t** 9430 |**u** te04 |**v** 1
**952** __ |**a** 0 bib. record(s) to be changed
**952** __ |**a** LC pattern: Drugs--Dosage forms
**953** __ |**a** jc02

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**Library of Congress Online Catalog**
*URL:* https://catalog.loc.gov/

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# Attachment 47a

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041    ##$aeng
050    #4$aTX769 $b.F56 2011
082    00$a613.2 $a664.72272
245    00$aFlour and breads and their fortification in health and
disease prevention $h[electronic resource] / $cedited by Victor R.
Preedy, Ronald Ross Watson, Vinood B. Patel.
250    ##$a1st ed.
260    ##$aLondon : $bElsevier Science, $c2011.
300    ##$a1 online resource (543 p.)
336    ##$atext $btxt
337    ##$acomputer $bc
338    ##$aonline resource $bcr
500    ##$aDescription based upon print version of record.
520    ##$a Bread and flour-based foods are an important part of the
diet for millions of people worldwide. Their complex nature
provides energy, protein, minerals and many other macro- and
micronutrients. However, consideration must be taken of three major
aspects related to flour and bread. The first is that not all
cultures consume bread made from wheat flour. There are literally
dozens of flour types, each with their distinctive heritage,
cultural roles and nutritive contents. Second, not all flours are
used to make leavened bread in the traditional (i.e., Western) loaf
form. There are many differe
546    ##$aEnglish
504    ##$aIncludes bibliographical references and index.
505    0#$asection 1. Flour and breads -- section 2. Fortification
of flour and breads and their metabolic effects.
650    #0$aFlour $xAdditives.
```

```
650    #0$aFlour $xHealth aspects.
650    #0$aBread $xAdditives.
655    #4$aElectronic books.
776    ##$z0-12-380886-3
700    1#$aPreedy, Victor R.
700    1#$aWatson, Ronald R. $q(Ronald Ross)
700    1#$aPatel, Vinood B.
906    ##$aBOOK
```

# Attachment 47b

**OCLC** 700701869 **No holdings in XXX - 506 other holdings**

Books

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| **Type** | a | **ELvl** | M | **Srce** | d | **Audn** | | **Ctrl** | | **Lang** | eng |
| **BLvl** | m | **Form** | o | **Conf** | 0 | **Biog** | | **MRec** | | **Ctry** | vtu |
| | | **Cont** | | **GPub** | | **LitF** | 0 | **Indx** | 0 | | |
| **Desc** | u | **Ills** | | **Fest** | 0 | **DtSt** | s | **Dates** | 2011, | | |

007 c $b r $e n $g ---
040 MERUC $b eng $e pn $c MERUC $d EBLCP $d OCLCQ $d IDEBK $d OCLCQ $d UKDOC $d OCLCQ $d DEBSZ $d OCLCQ $d Z5A $d OCLCO $d ZCU $d OCLCQ $d MERUC $d OCLCQ $d OCLCO $d U3W $d OCLCF $d ICG $d AU@ $d OCLCO $d OCLCQ $d OCLCO $d OCLCA $d DKC $d OCLCQ $d OCLCO $d OCL
020 9780123808875
020 0123808871
050 4 TX558.W5
060 4 2011 C-160
060 4 QU 145.5
082 04 664.72272
090 $b
100 1 Preedy, Victor.
245 10 Flour and Breads and their Fortification in Health and Disease Prevention.
260 Burlington : $b Elsevier Science, $c 2011.
300 1 online resource (543 pages)
336 text $b txt $2 rdacontent
337 computer $b c $2 rdamedia
338 online resource $b cr $2 rdacarrier
505 0 Front Cover; Flour and Breads and their Fortification in Health and Disease Prevention; Copyright; Contents; LIST OF CONTRIBUTORS; PREFACE; Section 1 -Flour and Breads; Section 2 -Fortification of Flour and Breads and their Metabolic Effects; INDEX.
520 Bread and flour-based foods are an important part of the diet for millions of people worldwide. Their complex nature provides energy, protein, minerals and many other macro- and micronutrients. However, consideration must be taken of three major aspects related to flour and bread. The first is that not all cultures consume bread made from wheat flour. There are literally dozens of flour types, each with their distinctive heritage, cultural roles and nutritive contents. Secondly, not all flours are used to make leavened bread in the traditional (i.e., Western) loaf form.
588 0 Print version record.
650 0 Flour $x Additives.
650 0 Flour $x Health aspects.
650 0 Bread $x Additives.
650 0 Bread $x Health aspects.
650 0 Medicine, Preventive.
650 0 Enriched foods.
650 22 Food, Fortified $0 (DNLM)D005527
650 22 Nutritive Value $0 (DNLM)D009753
650 2 Preventive Medicine $0 (DNLM)D011315

650 6 Farine $0 (CaQQLa)201-0004136 $x Adjuvants. $0 (CaQQLa)201-0373850
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650 6 Médecine préventive. $0 (CaQQLa)201-0001925
650 6 Aliments enrichis. $0 (CaQQLa)201-0062846
650 6 Valeur nutritive. $0 (CaQQLa)201-0198561
650 7 TECHNOLOGY & ENGINEERING $x Food Science. $2 bisacsh
650 7 Enriched foods. $2 fast $0 (OCoLC)fst00912556
650 7 Medicine, Preventive. $2 fast $0 (OCoLC)fst01015324
655 4 Electronic books.
700 1 Watson, Ronald Ross.
700 1 Patel, Vinood B.
776 08 $i Print version: $a Preedy, Victor. $t Flour and Breads and their Fortification in Health and Disease Prevention. $d Burlington : Elsevier Science, ©2011 $z 9780123808868
856 40 $3 123Library $u http://www.123library.org/book_details/?id=46263
856 40 $3 MyiLibrary $u http://www.myilibrary.com?id=295479
856 40 $3 ProQuest Ebook Central $u https://public.ebookcentral.proquest.com/choice/publicfullrecord.aspx?p=625340
856 41 $3 MyiLibrary, Table of contents $u http://www.myilibrary.com?id=295479&ref=toc

# Attachment 47c

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



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**LC control no.:** sh 85049267

**LCCN Permalink:** https://lccn.loc.gov/sh85049267

**HEADING:** Flour

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**001** 4700948
**005** 20211113060007.0
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**010** __ |**a** sh 85049267
**035** __ |**a** (DLC)sh 85049267
**035** __ |**a** (DLC)47633
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**053** _0 |**a** TS2120 |**b** TS2159 |**c** Manufacture
**053** _0 |**a** TX393 |**c** Food supply
**053** _0 |**a** TX558.W5 |**c** Food values
**053** _0 |**a** TX595.F6 |**c** Adulteration
**150** __ |**a** Flour
**450** __ |**a** Flours
**450** __ |**a** Wheat flour
**550** __ |**w** g |**a** Plant products
**670** __ |**a** Merriam-Webster dictionary, viewed online Sept. 3, 2021 |**b** (flour: noun, 1. a product consisting of finely milled wheat; also : a similar product made from another grain or food product (such as dried potatoes or fish) 2 : a fine soft powder)
**906** __ |**t** 8824 |**u** fk05 |**v** 0
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**910** __ |**a** Record saved by jr02 on 09/03/2021 at 08:31:26
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**953** __ |**a** xx00 |**b** ff05

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# Attachment 47d

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**LC control no.:** sh 85000820
**LCCN Permalink:** https://lccn.loc.gov/sh85000820
**HEADING:** Additives

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**005** 20110729100611.0
**008** 860211n| bnannbbbn |n ann
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**260** __ |**i** subdivision |**a** Additives |**i** under individual materials and types of materials, e.g. |**a** Concrete--Additives
**906** __ |**t** 8836 |**u** fk05 |**v** 0
**953** __ |**a** xx00 |**b** ta25

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# Attachment 47e

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**LC control no.:** sh 85016646
**LCCN Permalink:** https://lccn.loc.gov/sh85016646
**HEADING:** Bread

**000** 00487cz a2200205n 450
**001** 4669350
**005** 20120322075746.0
**008** 860211i| anannbabn |a ana
**010** __ |**a** sh 85016646
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**035** __ |**a** (DLC)16035
**040** __ |**a** DLC |**c** DLC |**d** DLC
**053** _0 |**a** TX769 |**c** Bread making
**150** __ |**a** Bread
**450** __ |**a** Breads
**550** __ |**w** g |**a** Baked products
**550** __ |**a** Cooking (Bread)
**681** __ |**i** Example under |**a** Food
**906** __ |**t** 9910 |**u** te07 |**v** 0
**953** __ |**a** xx00 |**b** td04

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# Attachment 47f

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U.S. Patent No. 9,943,096



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**LC control no.:** sh 85083162

**LCCN Permalink:** https://lccn.loc.gov/sh85083162

**HEADING:** Medicine, Preventive

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**001** 4733664

**005** 20120327093529.0

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**053** _0 |**a** RA421 |**b** RA790

**150** __ |**a** Medicine, Preventive

**360** __ |**i** subdivision |**a** Prevention |**i** under individual diseases and types of diseases, e.g. |**a** Cancer--Prevention; |**i** and subdivision |**a** Diseases--Prevention |**i** under organs and regions of the body, e.g. |**a** Heart--Diseases--Prevention

**450** __ |**a** Disease prevention

**450** __ |**a** Diseases |**x** Prevention

**450** __ |**a** Prevention of disease

**450** __ |**a** Preventive medicine

**550** __ |**a** Pathology

**550** __ |**a** Preventive health services

**550** __ |**a** Preventive medicine physicians

**550** __ |**a** Public health

**670** __ |**a** LC database, June 2, 1998 |**b** (disease prevention)

**670** __ |**a** Report of the 1980 Invitational Conference on Disease Prevention and Health Promotion in Communities, 1980.

**906** __ |**t** 0251 |**u** te04 |**v** 0

**953** __ |**a** xx00 |**b** ta25

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**LC control no.:** sh 85050240
**LCCN Permalink:** https://lccn.loc.gov/sh85050240
**HEADING:** Enriched foods

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**550** __ |**a** Food additives
**906** __ |**t** 8847 |**u** fk07 |**v** 0
**952** __ |**a** 7 bib. records to be changed
**953** __ |**a** xx00 |**b** fj21

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# Attachment 48a

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245    10$aInnovations in food packaging / $cedited by Jung H. Han.
260    ##$aSan Diego, Calif. : $bElsevier Academic ; $aOxford :
$bElsevier Science [distributor], $c©2005.
263    ##$a2005
300    ##$axiii, 517 pages : $billustrations (some color) ; $c25 cm.
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504    ##$aIncludes bibliographical references and index.
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700    1#$aHan, Jung H.
830    #0$aFood science and technology international series.
948    ##$aLTI 02/04/2016
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# Attachment 48b

**OCLC** 58828180 **No holdings in XXX - 119 other holdings**

Books

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| **BLvl** | m | **Form** | | **Conf** | 0 | **Biog** | | **MRec** | | **Ctry** | cau |
| | | **Cont** | b | **GPub** | | **LitF** | 0 | **Indx** | 1 | | |
| **Desc** | a | **Ills** | a | **Fest** | 0 | **DtSt** | s | **Dates** | 2005, | | |

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015 bA525009
016 7 013146928 $2 Uk
019 1252159901
020 0123116325
020 9780123116321
020 $z 0080455174 (electronic bk.)
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050 14 TP374 $b .I55 2005eb
070 0 TP374 $b .I66 2005
082 04 664.09 $2 22
084 58.34 $2 bcl
090 $b
100 1 Han, Jung H.
245 10 Innovations in food packaging / $c edited by Jung H. Han.
260 San Diego, Calif. : $b Elsevier Academic ; $a Oxford : $b Elsevier Science [distributor], $c ©2005.
300 xiii, 517 pages : $b illustrations (some color) ; $c 25 cm.
336 text $b txt $2 rdacontent
337 unmediated $b n $2 rdamedia
338 volume $b nc $2 rdacarrier
490 1 Food science and technology international series
504 Includes bibliographical references and index.
520 Packaging performs a number of functions in the containment, protection, shipment and selling of goods. Innovations in Food Packaging recognizes that food packaging is a fast-growing area that impacts upon the important areas of product shelf-life and food safety. Each chapter provides information on the scientific background, new material development and utilization, and case studies of the use of new system for perishable food products. Covers four major food packaging topics: * Theories in food packaging * Active packaging * Modified atmosphere packaging * Edible films and coatings.
505 00 $g 1. $t New technologies in food packaging : overview / $r Jung H. Han -- $g 2. $t Mass transfer of gas and solute through packaging materials / $r Jung H. Han and Martin G. Scanlon -- $g 3. $t Quality of packaged foods / $r Rakesh K. Singh and Nepal Singh -- $g 4. $t Surface chemistry of food, packaging and biopolymer materials / $r Jung H. Han, Yachuan Zhang and Roberto A. Buffo -- $g 5. $t Introduction to active food packaging technologies / $r Michael L. Rooney -- $g 6. $t Antimicrobial packaging systems

/ $r Jung H. Han -- $g 7. $t Packaging containing natural antimicrobial or antioxidative agents / $r Dong Sun Lee -- $g 8. $t Oxygen-scavenging packaging / $r Michael L. Rooney -- $g 9. $t Intelligent packaging / $r Jung H. Han, Colin H. L. Ho and Evangelina T. Rodrigues -- $g 10. $t Introduction to modified atmosphere packaging / $r John D. Floros and Konstantinos I. Matsos -- $g 11. $t Internal modified atmospheres of coated fresh fruits and vegetables : understanding relative humidity effects / $r Luis Cisneros-Zevallos and John M. Krochta -- $g 12. $t Modified atmosphere packaging of ready-to-eat foods / $r Kevin C. Spencer -- $g 13. $t Preservative packaging for fresh meats, poultry, and fin fish / $r Alexander O. Gill and Colin O. Gill -- $g 14. $t Centralized packaging systems for meats / $r Roberto A. Buffo and Richard A. Holley -- $g 15. $t Edible films and coatings : a review / $r Jung H. Han and Aristippos Gennadios -- $g 16. $t Agro-polymers for edible and biodegradable films : review of agricultural polymeric materials, physical and mechanical characteristics / $r Stephane Guilbert and Nathalie Gontard -- $g 17. $t Edible films and coatings from plant origin proteins / $r Roberto A. Buffo and Jung H. Han -- $g 18. $t Edible films and coatings from animal-origin proteins / $r Monique Lacroix and Kay Cooksey -- $g 19. $t Edible films and coatings from starches / $r Zhiqiang Liu -- $g 20. $t Edible films and coatings from non-starch polysaccharides / $r Monique Lacroix and Canh Le Tien -- $g 21. $t Lipid-based edible films and coatings / $r Jong Whan Rhim and Thomas H. Shellhammer -- $g 22. $t Emulsion and bi-layer edible films / $r Maria B. Perez-Gago and John M. Krochta -- $g 23. $t Plasticizers in edible films and coatings / $r Rungsinee Sothornvit and John M. Krochta -- $g 24. $t Sensory quality of foods associated with edible film and coating systems and shelf-life extension / $r Yanyun Zhao and Mina McDaniel -- $g 25. $t Commercial uses of active food packaging and modified atmosphere packaging systems / $r Aaron L. Brody -- $g 26. $t US Food and Drug Administration approach to regulating intelligent and active packaging components / $r Yoon S. Song and Mark A. Hepp -- $g 27. $t Packaging for non-thermal food processing / $r Seacheol Min and Q. Howard Zhang.
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650  7 Food $x Packaging $x Technological innovations. $2 fast $0 (OCoLC)fst00930561
650 17 Verpakking. $2 gtt
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653 00 voedselverpakking
653 00 food packaging
653 10 Food Packaging
653 10 Verpakking van levensmiddelen
655  4 Electronic books.
700 1  Han, Jung H.
830  0 Food science and technology international series.

# Attachment 48c

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



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# Attachment 49a

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245    10$aFood processing technology : $bprinciples and practice /
$cP. J. Fellows.
250    ##$aThird edition.
264    #1$aCambridge, England ; $aBoca Raton, Florida : $bWoodhead
Publishing : $bCRC Press, $c2009.
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505    0#$aCover; Food processing technology:Principles and
practice; Copyright; Contents; Acknowledgements; Dedication;
Introduction; A brief history of food processing; The food industry
today; About this book; References; Part I Basic principles; 1
Properties of food and processing; 1.1 Properties of foods; 1.2
Food spoilage, safety and shelf-life; 1.3 Types of processing; 1.4
Effects of processing; 1.5 Control of processing; References; Part
II Ambient-temperature processing; 2 Raw material preparation; 2.1
Cooling crops and carcasses; 2.2 Cleaning; 2.3 Sorting and grading;
2.4 Peeling; References
505    8#$a3 Size reduction 3.1 Size reduction of solid foods; 3.2
Size reduction in liquid foods; References; 4 Mixing and forming;
4.1 Mixing; 4.2 Forming; References; 5 Separation and concentration
of food components; 5.1 Centrifugation; 5.2 Filtration; 5.3
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Expression; 5.4 Extraction using solvents; 5.5 Membrane concentration; References; 6 Food biotechnology; 6.1 Genetic modification; 6.2 Nutritional genomics; 6.3 Functional foods; 6.4 Fermentation technology; 6.5 Microbial enzymes; 6.6 Microencapsulation and controlled release technologies; 6.7 Bacteriocins and antimicrobial ingredients; References
505 8#$a7 Irradiation 7.1 Theory; 7.2 Equipment; 7.3 Applications; 7.4 Effect on Foods; 7.5 Effect on micro-organisms; 7.6 Effect on packaging; 7.7 Detection of irradiated foods; References; 8 High-pressure processing; 8.1 Theory; 8.2 Equipment; 8.3 Effect on parasites and micro-organisms; 8.4 Effect on enzymes; 8.5 Effects on foods; 8.6 Combinations of high pressure and other minimal processing technologies; References; 9 Minimal processing methods under development; 9.1 Pulsed electric field processing; 9.2 Processing using electric arc discharges; 9.3 Processing using oscillating magnetic fields
505 8#$a9.4 Processing using pulsed light and UV light 9.5 Processing using pulsed X-rays; 9.6 Processing using ultrasound; References; Part III Processing by application of heat; 10 Heat processing; 10.1 Theory; 10.2 Sources of heat and methods of application to foods; 10.3 Effect of heat on micro-organisms and enzymes; 10.4 Effect of heat on nutritional and sensory characteristics of foods; References; III.A Heat processing using steam or water; 11 Blanching; 11.1 Theory; 11.2 Equipment; 11.3 Effect on foods; 11.4 Effect on micro-organisms; References; 12 Pasteurisation; 12.1 Theory; 12.2 Equipment
505 8#$a12.3 Effect on foods References; 13 Heat sterilisation; 13.1 In-container sterilisation; 13.2 Ultra-high-temperature (UHT)/aseptic processes; 13.3 Effect on foods; References; 14 Evaporation and distillation; 14.1 Evaporation; 14.2 Distillation; References; 15 Extrusion; 15.1 Extrusion cooking theory; 15.2 Equipment; 15.3 Applications; 15.4 Effect on foods and micro-organisms; References; III.B Heat processing using hot air; 16 Dehydration; 16.1 Theory; 16.2 Equipment; 16.3 Control of dryers; 16.4 Rehydration; 16.5 Effect on foods and micro-organisms; References; 17 Smoking; 17.1 Theory
505 8#$a17.2 Processing
520 ##$aThe first edition of Food processing technology was quickly adopted as the standard text by many food science and technology courses. This completely revised and updated third edition consolidates the position of this textbook as the best single-volume introduction to food manufacturing technologies available. This edition has been updated and extended to include the many developments that have taken place since the second edition was published. In particular, advances in microprocessor control of equipment, 'minimal' processing technologies, functional foods, developments in 'active'
546 ##$aEnglish
500 ##$a"Reprinted in 2008"--T. p. verso.

504 ##$aIncludes bibliographical references at the end of each chapters and index.
588 ##$aDescription based on online resource; title from PDF title page (ebrary, viewed February 8, 2014).
650 #0$aFood industry and trade.
655 #4$aElectronic books.
710 2#$aScienceDirect (Servicio en línea)
776 ##$z1-84569-216-0
830 #0$aWoodhead Publishing Series in Food Science, Technology and Nutrition
906 ##$aBOOK

# Attachment 49b

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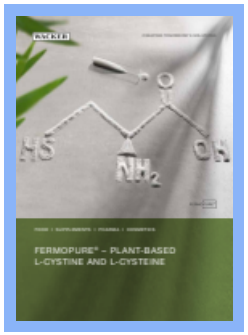
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100 1 Fellows, P. $q (Peter), $d 1953-
245 10 Food processing technology : $b Principles and practice / $c P.J. Fellows.
250 3rd rev. ed.
260 Cambridge : $b Woodhead Publishing Ltd, $c 2009.
300 1 online resource (928 pages).
336 text $b txt $2 rdacontent
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490 1 Woodhead Publishing series in food science, technology and nutrition ; $v 174
505 0 Part 1 Basic principles: Properties of foods. Part 2 Ambient-temperature processing: Raw material preparation-- Size reduction-- Mixing and forming-- Separation and concentration of food components-- Food biotechnology-- Irradiation-- High-pressure processing-- Minimal processing methods under development. Part 3 Processing by application of heat: Heat processing-- Heat processing using steam or water-- Pasteurisation-- Heat sterilisation-- Evaporation and distillation-- Extrusion-- Heat processing using hot air-- Smoking-- Baking and roasting-- Frying-- Heat processing by direct and radiated energy. Part 4 Processing by removal of heat: Chilling and modified atmospheres-- Freezing-- Freeze drying and freeze concentration. Part 5 Post-processing operations: Coating-- Packaging-- Filling and sealing of containers-- Materials handling and process control.
520 The first edition of Food processing technology was quickly adopted as the standard text by many food science and technology courses. This completely revised and updated third edition consolidates the position of this textbook as the best single-volume introduction to food manufacturing technologies available. $b ' ... a well-written and authoritative review of food processing technology - the essential reference for food technologists and students alike.' Food Trade Review (of a previous edition) 'Interesting, logical and concise. A good introduction for students of nutrition, food science and technology, catering or agriculture.' Food Manufacture (of a previous edition) Widely regarded as a

standard work in its field, this book introduces the range of processing techniques that are used in food manufacturing. It explains the principles of each process, the processing equipment used, operating conditions and the effects of processing on micro-organisms that contaminate foods, the biochemical properties of foods and their sensory and nutritional qualities. The third edition is divided into five parts. Part one describes some important basic concepts. Part two describes unit operations that take place at ambient temperature or involve minimum heating of foods. Part three includes operations that heat foods to preserve them or to alter their eating quality. Part four describes operations that remove heat from foods to extend their shelf life with minimal changes in nutritional quality or sensory characteristics. Part five describes post-processing operations, including packaging and distribution logistics. The third edition has been substantially rewritten, updated and extended to include the many developments in food technology that have taken place since the second edition was published in 2000. Nearly all unit operations have undergone significant developments, and these are reflected in the large amount of additional material in each chapter. In particular, advances in microprocessor control of equipment, 'minimal' processing technologies, genetic modification of foods, functional foods, developments in 'active' or 'intelligent' packaging, and storage and distribution logistics are described. Developments in technologies that relate to cost savings, environmental improvement or enhanced product quality are highlighted. Additionally, sections in each chapter on the impact of processing on food-borne micro-organisms are included for the first time. The third edition consolidates the position of Food processing technology as the best single-volume introduction to food manufacturing technologies. It is an essential text for undergraduate and postgraduate students in food technology, food science, food marketing and distribution, agriculture, nutrition, and hospitality management/catering. It is also an ideal reference for all professionals in the food industry.
545 0  Dr Peter Fellows is a senior consultant in food processing, working mostly in Africa and Asia. Over the last 30 years, he has worked extensively as a food technologist in over twenty countries, supporting institutions that promote small-scale agro-industrial development programmes. He is a Visiting Fellow at Oxford Brookes University in the UK, and has held the UNESCO Chair in Post-Harvest Technology at Makerere University, Uganda. In addition to Food processing technology, he has written 22 books and numerous articles on different aspects of food processing.
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650  7 Food industry and trade. $2 fast $0 (OCoLC)fst00930843
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776 08 $i Print version: $a Fellows, P J. $t Food Processing Technology : Principles and Practice. $d Burlington : Elsevier Science, ©2009 $z 9781845692162
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856 40 $3 Ebook Library $u http://public.eblib.com/choice/publicfullrecord.aspx?p=1639821
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# Attachment 50a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096
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3

FERMENTATION FOR UTMOST PURITY, SAFETY AND EFFICIENCY

# Attachment 51a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

Cambridge Core



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English | **Français**

# Public health implications of meat production and consumption

Published online by Cambridge University Press: **02 January 2007**

Polly Walker, Pamela Rhubart-Berg, Shawn McKenzie, Kristin Kelling and Robert S Lawrence

Article contents

## Abstract

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The high level of meat and saturated fat consumption in the USA and other high-income countries exceeds nutritional needs and contributes to high rates of chronic diseases such as cardiovascular disease, diabetes mellitus and some cancers. Affluent citizens in middle- and low-income countries are adopting similar high-meat diets and experiencing increased rates of these same chronic diseases. The industrial agricultural system, now the predominant form of agriculture in the USA and increasingly world-wide, has consequences for public health owing to its extensive use of fertilisers and pesticides, unsustainable use of resources and environmental pollution. In industrial animal production there are public health concerns surrounding feed formulations that include animal tissues, arsenic and antibiotics as well as occupational health risks and risks for nearby communities. It is of paramount importance for public health professionals to become aware of and involved in how our food is produced.

## Keywords

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

Diet Environment Health Nutrition Industrial agriculture Industrial animal production Sustainability Sustainable agriculture Aquaculture Meat

**Type**

Invited Paper

**Information**

Public Health Nutrition, Volume 8, Issue 4, June 2005, pp. 348 - 356
DOI: https://doi.org/10.1079/PHN2005727

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**Regulation of Food Systems**

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| 060 | 00 \| **‡a** W1**‡b** PU535 |
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| 245 | 00 \| **‡a** Public health nutrition. |
| 246 | 1_ \| **‡a** PHN |
| 260 | __ \| **‡a** Wallingford, Oxon, UK :**‡b** Published on behalf of the Nutrition Society by CAB International,**‡c** c1998- |
| 260 | 3_ \| **‡3** <2007- > :**‡a** Oxford :**‡b** Cambridge University Press |
| 300 | __ \| **‡a** v. :**‡b** ill. |
| 310 | __ \| **‡a** Eighteen issues a year,**‡b** 2015- |

321 __ | ‡**a** Quarterly,‡**b** -2001
321 __ | ‡**a** 6 times per year,‡**b** 2002
321 __ | ‡**a** 8 times per year,‡**b** 2003-2006
321 __ | ‡**a** Monthly,‡**b** 2007-2014
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338 __ | ‡**a** volume‡**b** nc‡**2** rdacarrier
362 0_ | ‡**a** Vol. 1, no. 1 (Mar. 1998)-
500 __ | ‡**a** Contents page and abstracts available on the Internet before publication.
500 __ | ‡**a** Title from cover.
510 1_ | ‡**9** 1‡**a** MEDLINE‡**b** v1n1, Mar. 1998-
510 0_ | ‡**9** 1‡**a** PubMed‡**b** v1n1, Mar. 1998-
510 1_ | ‡**a** Index medicus
510 0_ | ‡**a** PMC Forthcoming
530 __ | ‡**a** Also issued online.
583 __ | ‡**3** v.1, no. 1 (March 1998)‡**c** 19990728‡**f** Notice published‡**l** Printed on acid-free paper
650 02 | ‡**a** Diet
650 02 | ‡**a** Health Promotion
650 02 | ‡**a** Nutritional Physiological Phenomena
650 02 | ‡**a** Public Health
655 _2 | ‡**a** Periodical
710 2_ | ‡**a** Nutrition Society (Great Britain)
856 4_ | ‡**u** https://www.cambridge.org/core/journals/public-health-nutrition
911 __ | ‡**a** Electronic and print, print canceled 2018
914 __ | ‡**a** Portico‡**b** Current to 2022 as of 20220627‡**c** ISSN_13689800
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995 __ | ‡**a** AUTH‡**b** 19980611‡**c** REV‡**d** 20220629
996 __ | ‡**a** CONSER‡**b** 19980617
998 __ | ‡**a** ERMSOA 120673‡**b** 20090619
999 __ | ‡**a** AUTH
035 __ | ‡**a** (DNLM)SR0092240(s)
035 __ | ‡**a** (OCoLC)39319725

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# Attachment 51c

# Health Promotion MeSH Descriptor Data 2022

Details | Qualifiers | MeSH Tree Structures | Concepts

| | |
|---|---|
| **MeSH Heading** | Health Promotion |
| **Tree Number(s)** | I02.233.332.445<br>N02.421.726.407.579 |
| **Unique ID** | D006293 |
| **RDF Unique Identifier** | http://id.nlm.nih.gov/mesh/D006293 |
| **Annotation** | IM |
| **Scope Note** | Encouraging consumer behaviors most likely to optimize health potentials (physical and psychosocial) through health information, preventive programs, and access to medical care. |
| **Entry Term(s)** | Health Campaigns<br>Promotion of Health<br>Promotional Items<br>Wellness Programs |
| **See Also** | Health Behavior |
| **Public MeSH Note** | 80 |
| **History Note** | 80 |
| **Date Established** | 1980/01/01 |
| **Date of Entry** | 1979/06/01 |
| **Revision Date** | 2017/07/11 |

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# Attachment 51d

# Public Health MeSH Descriptor Data 2022

Details | Qualifiers | MeSH Tree Structures | Concepts

| | |
|---|---|
| **MeSH Heading** | Public Health |
| **Tree Number(s)** | H02.403.720<br>N01.400.550<br>N06.850 |
| **Unique ID** | D011634 |
| **RDF Unique Identifier** | http://id.nlm.nih.gov/mesh/D011634 |
| **Annotation** | specialty; do not confuse with NATIONAL HEALTH PROGRAMS |
| **Scope Note** | Branch of medicine concerned with the prevention and control of disease and disability, and the promotion of physical and mental health of the population on the international, national, state, or municipal level. |
| **Entry Term(s)** | Community Health<br>Environment, Preventive Medicine & Public Health<br>Environment, Preventive Medicine and Public Health |
| **See Also** | Preventive Medicine<br>Social Medicine<br>Zoonoses |
| **Entry Combination** | organization & administration:Public Health Administration |
| **Date Established** | 1966/01/01 |
| **Date of Entry** | 1999/01/01 |
| **Revision Date** | 2018/02/28 |

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# Attachment 51e

**OCLC** 39319725 **No holdings in XXX - 90 other holdings**

Continuing Resources

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210 10 Public Health Nutr $2 dnlm
245 00 Public health nutrition.
260 Wallingford, Oxon, UK : $b Published on behalf of the Nutrition Society by CAB International, $c ©1998-
260 3 $3 <2007- : $a Oxford : $b Cambridge University Press
300 volumes : $b illustrations ; $c 28 cm
310 Eighteen issues a year, $b 2015-
321 Quarterly, $b -2001
321 6 times per year, $b 2002
321 8 times per year, $b 2003-2006
321 Monthly, $b 2007-2014
336 text $b txt $2 rdacontent
337 unmediated $b n $2 rdamedia
338 volume $b nc $2 rdacarrier
362 0 Vol. 1, no. 1 (Mar. 1998)-
500 Contents page and abstracts available on the Internet before publication.
500 Title from cover.

500 Published by: Oxford :Cambridge University Press, <2007-
588 Latest issue consulted: Vol. 11, no. 3 (Mar. 2008).
650 0 Nutrition $v Periodicals.
650 0 Diseases $x Nutritional aspects $v Periodicals.
650 0 Public health $v Periodicals.
650 0 Diet in disease.
650 0 Health promotion.
650 0 Nutrition.
650 0 Public health.
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650 7 Public health. $2 fast $0 (OCoLC)fst01082238
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653 HUMAN NUTRITION
653 PUBLIC HEALTH
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655 3 Internet resource.
655 7 Periodicals. $2 fast $0 (OCoLC)fst01411641
710 2 Nutrition Society (Great Britain)
776 08 $i Online version: $t Public health nutrition (Online) $x 1475-2727 $w (DLC) 2005233018 $w (OCoLC)41948583
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856 42 $z Scope $u http://firstsearch.oclc.org/journal=1368-9800;screen=info;ECOIP $z Address for accessing the journal from an authorized IP address through OCLC FirstSearch Electronic Collections Online

# Attachment 51f

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



**LC control no.:** sh 85038411

**LCCN Permalink:** https://lccn.loc.gov/sh85038411

**HEADING:** Diseases

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**035** __ |**a** (DLC)264694
**040** __ |**a** DLC |**c** DLC |**d** DLC
**150** __ |**a** Diseases
**360** __ |**i** individual diseases, e.g. |**a** Cancer; |**i** and subdivision |**a** Diseases |**i** under individual organs and regions of the body, individual animals and groups of animals, classes of persons and ethnic groups, e.g. |**a** Heart--Diseases; Fishes--Diseases; Infants--Diseases; African Americans--Diseases
**450** __ |**a** Human beings |**x** Diseases
**450** __ |**a** Illness
**450** __ |**a** Illnesses
**450** __ |**a** Morbidity
**450** __ |**a** Sickness
**450** __ |**a** Sicknesses
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**550** __ |**a** Sick
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# Attachment 51g

Case No.: IPR2023-00206
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**LC control no.:** sh2008110201
**LCCN Permalink:** https://lccn.loc.gov/sh2008110201
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**150** __ |**a** Public health |**v** Periodicals
**667** __ |**a** Record generated for validation purposes.
**670** __ |**a** Work cat.: Kyōto-shi Eisei Kōgai Kenkyūjo nenpō =, Heisei 3-nen [1991]-
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# Attachment 51h

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



**LC control no.:** sh 85037854
**LCCN Permalink:** https://lccn.loc.gov/sh85037854
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**953** __ |**a** xx00 |**b** ta25

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# Attachment 51i

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**LC control no.:** sh 85059591

**LCCN Permalink:** https://lccn.loc.gov/sh85059591

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**053** _0 |**a** RA427.8
**150** __ |**a** Health promotion
**360** __ |**i** subdivision |**a** Health promotion services |**i** under types of educational institutions, e.g. |**a** Universities and colleges--Health promotion services
**450** __ |**a** Health promotion programs
**450** __ |**a** Health promotion services
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**550** __ |**w** g |**a** Preventive health services
**550** __ |**a** Health education
**906** __ |**t** 9436 |**u** te03 |**v** 1
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Nutrition & Dietetics / Volume 64, Issue s4 / p. S113-S119

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# Nutritional composition of red meat

Peter WILLIAMS

First published: 15 August 2007
https://doi.org/10.1111/j.1747-0080.2007.00197.x
Citations: 330

This section begins with the nutritional composition of red meat, and then focuses on the key nutrients delivered through the consumption of red meat in the context of the Australian diet. The reviews draw on the scientific literature to provide an overview of the metabolism and associations with clinical conditions of each of these nutrients. They then provide a perspective on the contributions of red meat in the diet to meet nutritional requirements. Williams provides up-to-date nutritional composition information; Truswell outlines the clinical conditions associated with vitamin B12 deficiency; Samman focuses on metabolism, food sources and requirements for iron and zinc; and Howe and colleagues provide an update on the nutritional implications of the long-chain omega-3 fatty acids. To conclude this section, Baghurst provides a perspective on food guides and the implications for red meat as a core food in the diet



## KEY POINTS

The lean component of red meat is:

- An excellent source of high biological value protein, vitamin B12, niacin, vitamin B6, iron, zinc and phosphorus
- A source of long-chain omega-3 polyunsaturated fats, riboflavin, pantothenic acid, selenium and, possibly, also vitamin D
- Relatively low in fat and sodium

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- A source of a range of endogenous antioxidants and other bioactive substances, including taurine, carnitine, carnosine, ubiquinone, glutathione and creatine

# INTRODUCTION

The Food Standards Australia New Zealand (FSANZ) Food Standards Code defines meat as 'the whole or part of the carcass of any buffalo, camel, cattle, deer, goat, hare, pig, poultry, rabbit or sheep, slaughtered other than in a wild state, but does not include eggs, or foetuses'.[1] This definition does not include kangaroo meat, which is now widely available for purchase in Australia and is likely to be considered as meat.

The term 'meat' may refer only to meat flesh (skeletal muscle plus any attached connective tissue or fat), but the FSANZ definition also includes offal (i.e. meat other than meat flesh, including brain, heart, kidney, liver, pancreas, spleen, thymus, tongue and tripe) although it excludes bone and bone marrow.

In Australia, the term 'red meat' is used by the meat industry to refer to meat from cattle, sheep and goat (i.e. beef, veal, lamb, mutton and goat meat). It does not include meat from pigs (e.g. pork, bacon, ham) or kangaroo, nor less common game meats like buffalo and camel, although nutrient composition of some of these products is now becoming available.[2] Purchased red meat usually consists of both lean tissue (muscle) and fat tissue, which can be either distributed throughout the muscle as marbling (internal fat) or surrounding the muscle meat as selvage or external fat. In trimmed lean meat, it is usually the external fat only that is removed.[3] Processed meat means a product containing no less than 30% meat, that has undergone a method of preservation other than freezing, and includes manufactured meat and cured and/or dried meat flesh (e.g. sausages, salami, canned meats).[1] This paper outlines the key nutrients for which red meat could be considered a significant dietary source based on data of relative composition.

# NUTRIENT COMPOSITION OF RED MEAT

Red meat contains high biological value protein and important micronutrients that are needed for good health throughout life. It also contains a range of fats, including essential omega-3 polyunsaturated fats. Recent analyses have shown that there has been a significant trend to leaner cuts of meat over the past two decades.[4] While the nutritional composition will vary somewhat according to breed, feeding regimen, season and meat cut, the following discussion will show that, in general, lean red meat has a relatively low fat content, is moderate in cholesterol, and is rich in protein and many essential vitamins and minerals.

Table 1 presents the typical nutrient composition of samples of fat-trimmed Australian red meat (beef, veal, lamb and mutton), based on recent analyses of national retail samples,[5-7] and compares this with the new Australian recommended dietary intakes (RDI).[8] While there are

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some differences between the four meats, in general lean red meat is a particularly good source of protein, niacin, vitamin B6, vitamin B12, phosphorus, zinc and iron, with 100 gproviding more than 25% RDI of these nutrients. It also provides more than 10% RDI of riboflavin, pantothenic acid and selenium. Of the four meats, mutton is particularly nutrient-dense, and the richest source of thiamin, vitamins B6 and B12, phosphorus, iron and copper.

**Table 1.** Average nutrient composition (per 100 g) of the lean component of Australian red meat[5-7]

| | *Beef* [(a)] | *Veal* [(b)] | *Lamb* [(c)] | *Mutton* [(d)] | *Adult Australian RDI* |
|---|---|---|---|---|---|
| Moisture (g) | 73.1 | 74.8 | 72.9 | 73.2 | |
| Protein (g) | 23.2 | 24.8 | 21.9 | 21.5 | 46–64 |
| Fat (g) | 2.8 | 1.5 | 4.7 | 4.0 | – |
| Energy (kJ) | 498 | 477 | 546 | 514 | 6.5–15.8 MJ |
| Cholesterol (mg) | 50 | 51 | 66 | 66 | – |
| Thiamin (mg) | 0.04 | 0.06 | 0.12 | 0.16 | 1.1–1.2 |
| Riboflavin (mg) | 0.18 | 0.20 | 0.23 | 0.25 | 1.1–1.6 |
| Niacin (mg) | 5.0 | 16.0 | 5.2 | 8.0 | 14–16 |
| Vitamin B6 (mg) | 0.52 | 0.8 | 0.10 | 0.8 | 1.3–1.7 |
| Vitamin B12 (μg) | 2.5 | 1.6 | 0.96 | 2.8 | 2.4 |
| Pantothenic acid (mg) | 0.35 | 1.50 | 0.74 | 1.33 | 4–6 |
| Vitamin A (μg) | <5 | <5 | 8.6 | 7.8 | 700–900 μg RE[(e)] |
| Beta-carotene (μg) | 10 | <5 | <5 | <5 | 700–900 μg RE[(e)] |
| Alpha-tocopherol (mg) | 0.63 | 0.50 | 0.44 | 0.20 | 7–10 |
| Sodium (mg) | 51 | 51 | 69 | 71 | 460–920 |

[(a)] Mean values for diced, stir-fry, round, rump, topside, silverside, fillet, sirloin, scotch fillet, T-bone, blade and chuck steak.

[(b)] Mean values for stir-fry, diced, leg steak and culet.

[(c)] Mean values for diced, stir-fry, leg roast, easy-carve roast, mini-roast, chump chop, loin chop, cutlet and easy-carve shoulder.

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(d) Mean values for leg roast and casserole mutton.

(e) RE = retinol equivalents (=1 μg retinol or 6 μg or beta-carotene).

RDI = recommended dietary intake.

## Protein and amino acids

Raw red muscle meat contains around 20–25 g protein/100 g. Cooked red meat contains 28–36 g/100 g, because the water content decreases and nutrients become more concentrated during cooking. The protein is highly digestible, around 94% compared with the digestibility of 78% in beans and 86% in whole wheat.[9] Protein from meat provides all essential amino acids (lysine, threonine, methionine, phenylalanine, tryptophan, leucine, isoleucine, valine) and has no limiting amino acids. Protein Digestibility Corrected Amino Acid Score is a method of evaluating the protein quality, with a maximum possible score of 1.0. Animal meats like beef have a score of approximately 0.9, compared with values of 0.5–0.7 for most plant foods.[10] The amino acid glutamic acid/glutamine is present in meat in the highest amounts (16.5%), followed by arginine, alanine and aspartic acid.

## Fat

Table 2 shows examples of the amount of separable fat found on typical retail cuts of red meat available for sale in Australia.[4, 11] There is a wide variation in the amount of total separable fat between the different beef and lamb cuts, ranging from 37% in loin lamb chops to only 1% in veal steak.

**Table 2.** Lean and separable fat from untrimmed raw boneless Australian red meat (mean weight)[4, 11]

| *Meat cut* | *% Lean* | *% External fat* | *% Internal fat* |
|---|---|---|---|
| Beef | | | |
| Topside roast | 91 | 6 | 3 |
| Silverside roast | 89 | 7 | 4 |
| Blade steak | 88 | 6 | 6 |
| Porterhouse steak | 77 | 18 | 5 |
| Stir-fry | 98 | 2 | 0 |
| Scotch fillet | 81 | 8 | 11 |
| Veal | | | |

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| | | | |
|---|---|---|---|
| Leg steak | 99 | 0 | 1 |
| Diced | 98 | 2 | 0 |
| Cutlet | 93 | 1 | 6 |
| Lamb | | | |
| Leg roast | 83 | 11 | 6 |
| Chump chop | 75 | 15 | 10 |
| Diced | 98 | 2 | 0 |

The gross composition values show that there generally appears to be less separable fat in the untrimmed raw retail samples collected in 2002 compared with those reported from 1983 to 1986.[12, 13] For example, the percentage separable fat has declined from 18% to 12% in rump steak and from 10% to 6.6% in fillet steak. This trend to lower-fat cuts has been due to three factors: selective breeding and feeding practices designed to increase the carcase lean-to-fat ratio; meat classification and marketing systems designed to favour leaner products; and modern butchery techniques such as seaming out whole muscles and trimming away intermuscular fat.[14]

Given the trend to prepare and consume meat after trimming external fat, the most recent nutritional analyses show that all trimmed lean red meats are relatively low in fat (<7%) and have moderate cholesterol content, with the exception of mince meats (Table 3). An important contributor to the leanness of muscle meat in Australian beef and lamb is that almost all animals are pasture (grass) fed for most of their lives, although some are given short periods of grain finishing before slaughter (D Thomason, MLA, personal communication).

**Table 3.** Fat and cholesterol content of trimmed raw and cooked Australian red meat (per 100 g)[5]

| *Meat cut* | *Total fat (g)* | *Cholesterol (mg)* |
|---|---|---|
| Beef | | |
| Diced, raw | 2.7 | 54 |
| Diced, cooked | 3.0 | 77 |
| Round steak, raw | 1.7 | 62 |
| Round steak, cooked | 2.0 | 75 |
| Topside roast, raw | 4.7 | 35 |

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| | | |
|---|---|---|
| Topside roast, cooked | 2.8 | 62 |
| Sirloin steak, raw | 1.9 | 58 |
| Sirloin steak, cooked | 3.8 | 70 |
| Scotch fillet, raw | 2.8 | 58 |
| Scotch fillet, cooked | 4.5 | 70 |
| Regular mince, raw | 10.8 | 76 |
| Regular mince, cooked | 12.7 | 99 |
| Low-fat mince, raw | 6.8 | 61 |
| Low-fat mince, cooked | 9.0 | 81 |

## Fatty acids

While discussion on the fat content of red meat may focus on the saturated fat content, the amount of saturated fat in Australian beef and lamb is actually lower than the total amount of unsaturated fats on a per edible portion basis.

Table 4 shows the average fatty acid profiles of beef, veal, lamb and mutton compared with other white meats and fish. Saturated fatty acids comprise, on average, 40% of total fatty acids in the lean component and 48% in the fat component of red meat. In beef and veal, approximately half of the saturated fatty acid in both the lean and fat component of red meat is palmitic acid (16:0), and about a third is stearic acid (18:0). In lamb and mutton, the proportions of these two fatty acids are more similar. There is little variation between cuts in the proportion of fatty acids.

**Table 4.** Fatty acid profile of raw lean meats (g/100 g edible portion)

| *Fatty acid* | *Beef* [a] | *Veal* [a] | *Lamb* [a] | *Mutton* [a] | *Skinless chicken* [b] | *Lean pork* [c] | *White fish* [d] | *Oily fish* [e] |
|---|---|---|---|---|---|---|---|---|
| C14:0 | 0.096 | 0.034 | 0.101 | 0.060 | 0.020 | 0.010 | 0.020 | 0.680 |
| C15:0 | 0.012 | 0.006 | 0.016 | 0.011 | 0.000 | 0.000 | 0.000 | 0.070 |
| C16:0 | 0.607 | 0.215 | 0.842 | 0.667 | 0.340 | 0.250 | 0.180 | 2.170 |
| C17:0 | 0.028 | 0.009 | 0.051 | 0.036 | 0.010 | 0.000 | 0.000 | 0.050 |
| C18:0 | 0.356 | 0.119 | 0.644 | 0.609 | 0.120 | 0.130 | 0.050 | 0.350 |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Total saturated | 1.149 | 0.409 | 1.730 | 1.464 | 0.500 | 0.400 | 0.300 | 3.320 |
| C14:1 | 0.025 | 0.007 | 0.004 | 0.003 | 0.000 | 0.000 | 0.000 | 0.000 |
| C16:1 | 0.082 | 0.033 | 0.066 | 0.039 | 0.004 | 0.030 | 0.060 | 0.590 |
| C18:1 | 1.103 | 0.356 | 1.995 | 1.370 | 0.620 | 0.390 | 0.110 | 2.190 |
| C20:1 | 0.015 | 0.048 | 0.010 | 0.011 | 0.010 | 0.010 | 0.010 | 1.340 |
| Total monounsaturated | 1.205 | 0.399 | 2.066 | 1.413 | 0.700 | 0.430 | 0.200 | 5.390 |
| C18:2 ω-6 | 0.204 | 0.090 | 0.321 | 0.339 | 0.210 | 0.120 | 0.010 | 0.250 |
| C18:3 ω-3 | 0.048 | 0.022 | 0.072 | 0.107 | 0.010 | 0.010 | 0.000 | 0.130 |
| C20:3 ω-6 | 0.020 | 0.012 | 0.009 | 0.009 | 0.008 | 0.003 | 0.000 | 0.000 |
| C20:4 ω-6 | 0.076 | 0.056 | 0.094 | 0.101 | 0.030 | 0.019 | 0.040 | 0.050 |

(a) Average values from 2002 analyses of Australian red meat.[15]

(b) Values for raw lean chicken breast from NUTTAB 2006.[16]

(c) Values for raw lean pork fillet from NUTTAB 2006.[16]

(d) Values for raw flathead from NUTTAB 2006.[16]

(e) Values for canned red salmon from NUTTAB 2006.[16]

DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid.

Polyunsaturated fatty acids (PUFA) range from 11% to 29% of total fatty acids. Pasture fed beef is a better source of omega-3 fats than grain feed beef, and this explains the better fatty acid ratio in Australian red meat compared with that in the USA, where there is extensive grain feeding.[17, 18] Beef and lamb also have more omega-3 fatty acids than either chicken or pork, although fish is still a significantly better source than any of the red meats.

The recent development of Nutrient Reference Values for Australians recommended a daily adequate intake of long-chain omega-3 fats (docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and docosapentaenoic acid) of 160 mg for men and 90 mg for women, with higher targets of 610 mg and 430 mg respectively to reduce the risk of long-term chronic disease.[8] As the levels of long-chain PUFA found in Australian beef, veal and lamb muscle meat are greater than 30 mg per serving (135 g) of red meat, they are considered a source of long-chain omega-3 PUFA according to Australian food regulations (Food Standards Australia New Zealand 2002)[1]. Mutton muscle meat, which has more than 60 mg EPA + DHA per serving of red meat, can be described as a good source of long-chain omega-3 polyunsaturated fats. Red meat is frequently consumed by Australians and makes the second greatest contribution to intake of long-chain omega-3 PUFA, after fish, in the Australian diet.[19]

## *Trans*-fatty acids

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*Trans*-fatty acids are found in ruminant fat as a result of biohydrogenation by rumen bacteria. *Trans*-fatty acids (18:1 *trans*) in raw muscle meat vary from as little as 22 mg/100 g in veal to 123 mg/100 g in lamb, but is generally less than 3% of the total fatty acid content.[15] Levels in both raw and cooked muscle meat are higher in lamb and mutton than in beef and veal.

## Choline

Choline is a precursor of a number of compounds, including neurotransmitters and membrane phospholipids. Although choline can be made in the body, dietary essentiality has been demonstrated, and the new Australian Nutrient Reference Values recommend an adequate intake of 550 mg/day for men and 425 mg/day for women.[8] The best dietary sources are milk, liver and eggs, but meat is also a significant source and beef contains 78 mg/100 g.[20]

## Vitamins

As with other animal foods, red meat is an excellent source of bioavailable vitamin B12, providing over two-thirds of the daily requirement in a 100 g serve (Table 1). Up to 25% RDI of riboflavin, niacin, vitamin B6 and pantothenic acid can also be provided by 100 g of red meat, but compared with pork, it is a relatively poor source of thiamin. Liver is an excellent source of vitamin A and folate, but the levels in lean muscle meat tissue are low. For all these vitamins, older animals tend to have higher concentrations, so the levels in beef are generally higher than those in veal, and mutton has more than lamb. Levels of vitamin D in meat are low and difficult to measure and have often not been included in food composition data previously. However, recent assays of meat in New Zealand have reported levels of 0.10 μg vitamin D3 and 0.45 μg 25-OH D3 per 100 g in beef and levels of 0.04 and 0.93 μg/100 g respectively in lamb.[21] Given the higher biological activity of the 25-OH vitamin D, this means that 100 g of cooked beef could provide 12% of the estimated adequate intake of 10 μg/day for a 51- to 70-year-old individual,[8] and cooked lamb could provide more than 25%, and hence be an important source of this nutrient, especially for housebound elderly people.

## Minerals

Beef and lamb meat are among the richest sources of the minerals iron and zinc, with 100 g providing at least one-quarter of daily adult requirements (Table 1). The iron in meat is mostly haem iron, which is well absorbed, and meat protein also appears to enhance the absorption of iron from meat. Similarly, absorption of zinc from a diet high in animal protein is greater than from plant foods, and the requirements for zinc may be as much as 50% higher for vegetarians.[8] Red meats are also good sources of selenium, providing over 20% RDI per 100 g serve, although it is likely that selenium values in meat will be significantly affected by where animals feed and the time of the year of sampling. Lean meat is low in sodium, with a potassium–sodium ratio of >5. The copper content in raw lean cuts range from 0.055 to

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0.190 mg/100 g in beef and veal, 0.090 to 0.140 mg/100 g in lamb, and 0.190 to 0.240 mg/100 g in mutton, all significantly higher than values reported in British meat.[22]

# MEAT-BASED BIOACTIVE COMPOUNDS

In addition to the traditional essential nutrients with defined requirements, there are a number of meat-based bioactive substances that have been studied for their potential beneficial effects.[23]

## Taurine

An amino acid in meat of particular interest is taurine. Meat is rich in taurine (110 mg/100 g in lamb and 77 mg/100 g in beef),[24] and is the most abundant dietary source. While taurine can be derived from methionine and cysteine metabolism, there have been suggestions that it should be considered a conditionally essential amino acid during lactation, during times of immune challenge, and may offer protection against oxidative stress.[25, 26]

## Carnitine

L-carnitine (beta-hydroxy-gamma-trimethyl amino butyric acid) transports long-chain fatty acids across the inner mitochondrial membranes to produce energy during exercise. Although not an essential nutrient, needs appear to be increased during pregnancy and after strenuous exercise, and a recommended intake of 24–81 mg/day has been proposed.[27] It is found in skeletal muscle and is particularly abundant in sheep muscle at up to 209 mg/100 g[28] and in beef at around 60 mg/100 g.[29]

## Conjugated linoleic acid

Conjugated linoleic acid (CLA) has antioxidant and immunomodulatory properties and may also play a role in the control of obesity.[30] As rumen bacteria convert linoleic acid to CLA, it is most abundant in the fat of ruminant animals, although CLA is also present in partially hydrogenated vegetable oils. The CLA content of meat is affected by several factors, including breed, age and food composition.[31] It is mostly present in the fat component of red meat (approximately 1 g/100 g) but is also found in the muscle meat: 10–46 mg/100 g in raw meat and 30–100 mg/100 g in cooked red meat.[15]

## Endogenous antioxidants

Several endogenous compounds (including ubiquinone, glutathione, lipoic acid, spermine, carnosine, anserine) have been studied in skeletal muscle.[32] Both carnosine and anserine are antioxidative histidyl dipeptides and the most abundant antioxidants in meat. Carnosine is present at around 365 mg/100 g in beef[33] and 400 mg/100 g in lamb.[24] Because carnosine is absorbed into the plasma intact, it is a potentially important dietary antioxidant.[34]

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Coenzyme Q10 (ubiquinone) also has antioxidant properties, and supplements have shown beneficial effects in some studies.[35] Levels in meat are estimated to be around 2 mg/100 g in both beef and sheep meat.[33] Glutathione is a component of glutathione peroxidase enzymes, which have an important antioxidant role in the body. It may also play a role in immune response and enhancing iron absorption by contributing to the 'meat factor'. Glutathione levels in red meat are estimated to be 12–26 mg/100 g in beef,[36] and most meats contain approximately twice the level of glutathione of poultry and up to 10 times the content found in fish.

### Creatine

Creatine and its phosphorylated derivative creatine phosphate play an important role in muscle energy metabolism and, under some circumstances, creatine supplements can enhance muscle performance.[37] Red meat contains approximately 350 mg/100 g[33] and is the principal dietary source for humans. Creatine in meat is readily absorbed,[38] but typical intakes are unlikely to provide the levels of creatine used for supplementation of sports performance (up to 15 g/day).

## NUTRIENT COMPOSITION OF ORGAN MEATS

Table 5 provides a comparison of the nutrient content of liver, kidney, heart, brains and tripe from beef and lamb. From this table, the following general statements can be made:

**Table 5.** Selected nutrients (per 100 g) in raw liver, kidney, heart, brain and tripe [(a)]

| | *Liver* | | *Kidney* | | *Heart* | | *Brain* | *Tripe* |
|---|---|---|---|---|---|---|---|---|
| | *Beef* | *Lamb* | *Beef* | *Lamb* | *Beef* | *Lamb* | *Lamb* | *Beef* |
| Protein (g) | 20.0 | 21.4 | 18.2 | 17.1 | 18.2 | 17.8 | 12.3 | 13.2 |
| Fat (g) | 8.6 | 7.5 | 1.6 | 2.5 | 3.0 | 5.6 | 8.0 | 2.1 |
| Saturated fat (g) | 2.8 | 2.2 | 0.6 | 0.9 | 1.2 | 2.3 | 2.2 | 0.9 |
| Long-chain omega-3 fat (mg) | 561 | 361 | 47 | 103 | 54 | 102 | 574 | 20 |
| Cholesterol (mg) | 271 | 433 | 313 | 338 | 103 | 129 | 1352 | 82 |
| Thiamin (mg) | 0.23 | 0.24 | 0.40 | 0.56 | 0.50 | 0.61 | 0.14 | 0 |
| Riboflavin (mg) | 4.80 | 2.80 | 3.60 | 2.10 | 1.50 | 1.10 | 0.40 | 0.10 |
| Niacin (mg) | 9.4 | 10.9 | 6.5 | 7.6 | 6.9 | 5.9 | 5.1 | 0.2 |
| Folate (μg) | 290 | 230 | 98 | 28 | 3 | 2 | 3 | 5 |

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| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Vitamin B12 (μg) | 59 | 90 | 28 | 52 | 9 | 10 | 11 | 1 |
| Retinol equivalents (μg) | 13 877 | 31 400 | 155 | 93 | 10 | 0 | 0 | 0 |
| Zinc (mg) | 3.6 | 4.3 | 1.8 | 2.6 | 1.6 | 1.6 | 1.1 | 1.2 |
| Iron (mg) | 5.8 | 9.5 | 5.4 | 9.8 | 5.0 | 3.9 | 1.7 | 0.4 |
| Magnesium (mg) | 15 | 19 | 15 | 16 | 17 | 17 | 12 | 6 |

(a) Folate values from US data;[39] all other values from NUTTAB 2006.[16]

- All organ meats (except tripe) are extremely rich in vitamin B12, with much more than 100% of the RDI in 100 g
- Liver is a rich source of protein, iron, zinc, riboflavin, niacin, vitamin A and folate
- Kidney is rich in protein, thiamin, riboflavin, iron and a source of folate
- Heart is a good source of iron and zinc, but not as good as liver and kidney
- Brains and tripe are not particularly good sources of vitamins or minerals
- All organ meats are high in cholesterol, especially brains, and mostly low in sodium
- Liver is such a rich source of retinol that consumption of large amounts is not recommended in pregnancy.[40]

## SUMMARY

The Australian Guide to Healthy Eating recommends that a healthy diet include 1–2 serves per day of meat or equivalents such as eggs, nuts or legumes.[41] However, the vegetarian alternatives that are used as protein sources have very different nutritional profiles from red meat, as shown in Table 6, which compares the percentage of an adult male daily requirement provided by 100 g of food. Lean beef and lamb are better protein sources than all the options except cheese, and are mostly lower in sodium. The meats are higher in zinc and niacin than all the alternatives, and also higher in omega-3 fats than the vegetable sources; a better source of vitamin B6 (except for the walnuts); richer in selenium (except in comparison to eggs); and are the best source of vitamin B12, which is absent entirely from the vegetable products. Egg, cheese and nuts are also much higher sources of total fat than lean beef or lamb. Thus, data on the nutritional composition of lean red meat highlight the relative value of this food category in delivering essential nutrients in a reasonably balanced form.

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**Table 6.** Percentage of male adult recommended dietary intake (RDI) or adequate intake (AI) provided by 100 g of lean red meat and some vegetarian protein sources

| | *RDI/AI for men aged 31–50 years* | *Beef* [a] *% of RDI* | *Lamb* [a] *%* | *Egg* [b] *%* | *Cheddar cheese* [b] | *Baked beans salt reduced* [b] | *Walnuts* [b] *%* |
|---|---|---|---|---|---|---|---|
| Protein | 64 g | 36 | 34 | 21 | 40 | 7 | 23 |
| Long-chain omega-3 fat | 160 mg | 50 | 53 | 111 | 55 | 0 | 0 |
| Thiamin | 1.2 mg | 3 | 8 | 8 | 3 | 4 | 28 |
| Riboflavin | 1.3 mg | 25 | 15 | 31 | 39 | 0 | 14 |
| Niacin | 16 mg | 31 | 70 | 0 | <1 | 5 | 9 |
| Vitamin B6 | 1.3 mg | 23 | 43 | 5 | 6 | 8 | 33 |
| Vitamin B12 | 2.4 µg | 79 | 71 | 58 | 35 | 0 | 0 |
| Pantothenic acid | 6 mg | 12 | 13 | 34 | 7 | <1 | 11 |
| Vitamin A | 900 µg | <1 | <1 | 25 | 43 | <1 | <1 |
| Vitamin E | 10 mg | 7 | 5 | 22 | 40 | 1 | 26 |
| Phosphorus | 1000 mg | 22 | 23 | 20 | 47 | 8 | 37 |
| Zinc | 14 mg | 30 | 31 | 9 | 26 | 4 | 18 |
| Iron | 8 mg | 24 | 25 | 26 | 3 | 20 | 31 |

(a) Average values from 2002 analyses of Australian red meat.[5] (b) Values from NUTTAB 2006.[16]

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710 2#$aDietitians Association of Australia, $eissuing body.
710 2#$aDietitians NZ (Organization), $eissuing body.
906 ##$aJOURNAL

# Attachment 52c

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



**LC control no.:** sh 86005508
**LCCN Permalink:** https://lccn.loc.gov/sh86005508
**HEADING:** Dietetics

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**150** __ |**a** Dietetics
**550** __ |**a** Nutrition
**670** __ |**a** Work cat.: Helm, K.K. The entrepreneurial nutritionist, c1987.
**670** __ |**a** Swanson, B. Careers in health care, 1984: pp. 63-69.
**670** __ |**a** Dorland's med. dict. |**b** ("Science or study and regulation of the diet")
**670** __ |**a** Gould's med. dict.
**670** __ |**a** Stedman's med. dict. |**b** (Branch of therapeutics treating of food and drink in relation to health and diseases)
**670** __ |**a** Web. 3 |**b** (Science or art of applying principles of nutrition to the feeding of individuals or groups under different economic conditions or for hygienic or therapeutic purposes)
**670** __ |**a** MESH.
**670** __ |**a** NIH |**b** (Nutrition, Dietetics)
**670** __ |**a** TEST.
**906** __ |**t** 8639 |**u** fk02 |**v** 1
**952** __ |**a** 84 bib. records to be changed
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RESEARCH ARTICLE

# A Prospective Study of Red and Processed Meat Intake in Relation to Cancer Risk

Amanda J Cross, Michael F Leitzmann, Mitchell H Gail, Albert R Hollenbeck, Arthur Schatzkin, Rashmi Sinha

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## Abstract

### Background

Red meat and processed meat have been associated with carcinogenesis at several anatomic sites, but no prospective study has examined meat intake in relation to a range of malignancies. We investigated whether red or processed meat intake increases cancer risk at a variety of sites.

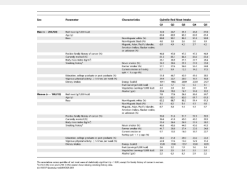
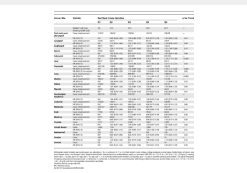
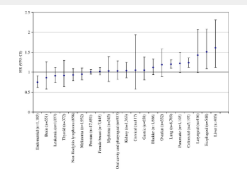
### Methods and Findings

The National Institutes of Health (NIH)-AARP (formerly the American Association for Retired Persons) Diet and Health Study is a cohort of approximately 500,000 people aged 50–71 y at baseline (1995–1996). Meat intake was estimated from a food frequency questionnaire administered at baseline. Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals within quintiles of red and processed meat intake. During up to 8.2 y of follow-up, 53,396 incident cancers were ascertained. Statistically significant elevated risks (ranging from 20% to 60%) were evident for esophageal, colorectal, liver, and lung cancer, comparing individuals in the highest with those in the lowest quintile of red meat intake. Furthermore, individuals in the highest quintile of processed meat intake had a 20% elevated risk for colorectal and a 16% elevated risk for lung cancer.

### Conclusions

Both red and processed meat intakes were positively associated with cancers of the colorectum and lung; furthermore, red meat intake was associated with an elevated risk for cancers of the esophagus and liver.

## Figures

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**Citation:** Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R (2007) A Prospective Study of Red and Processed Meat Intake in Relation to Cancer Risk. PLoS Med 4(12): e325. https://doi.org/10.1371/journal.pmed.0040325

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**Competing interests:** The authors have declared that no competing interests exist.

**Abbreviations:** AARP, formerly known as the American Association for Retired Persons; BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio; HCA, heterocyclic amine; NAT, N-acetyltransferase; NOC, N-nitroso compound; PAH, polycyclic aromatic hydrocarbon; RR, relative risk

## Editors' Summary

### Background.

Every year, there are more than 10 million new cases of cancer around the world. These cases are not spread evenly across the globe. The annual incidence of cancer (the number of new cases divided by the population size) and the type of cancer most commonly diagnosed varies widely among countries. Much of the global variation in cancer incidence and type is thought to be due to environmental influences. These include exposure to agents in the air or water that cause cancer, and lifestyle factors such as smoking and diet. Researchers identify environmental factors that affect cancer risk by measuring the exposure of a large number of individuals to a specific environmental factor and then monitoring these people for several years to see who develops cancer. The hope is that by identifying the environmental factors that cause or prevent cancer, the global burden of cancer can be reduced.

### Why Was This Study Done?

Diet is thought to influence the incidence of several cancers but it is very difficult to unravel which aspects of diet are important. Being overweight, for example, is strongly associated with an increased risk of developing several types of cancer, but the evidence that the intake of red meat (beef, pork, and lamb) and of processed meat (for example, bacon, ham, and sausages) is linked to cancer risk is much weaker. Although several studies have linked a high intake of red meat and processed meat to an increased risk of colorectal cancer (the colon is the large bowel; the rectum is the final few inches of the large bowel before the anus), whether this aspect of diet affects the




Subject Areas

Meat
Lung and intrathoracic t...
Colorectal cancer
Cancer risk factors
Prostate cancer
Breast cancer
Esophageal cancer
Diet

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risk of other types of cancer is unclear. In this prospective study, the researchers have examined the association between meat intake and the incidence of a wide range of cancers.

### What Did the Researchers Do and Find?

In 1995–1996, nearly half a million US men and women aged 50–71 y joined the NIH-AARP Diet and Health Study. The participants in this study—none of whom had had cancer previously—completed a questionnaire about their dietary habits over the previous year and provided other personal information such as their age, weight, and smoking history. The researchers used these data and information from state cancer registries to look for associations between the intake of red and processed meat and the incidence of various cancers. They found that people whose red meat intake was in the top fifth of the range of intakes recorded in the study (the highest quintile of consumption) had an increased risk of developing colorectal, liver, lung, and esophageal cancer when compared with people in the lowest quintile of consumption. People in the highest quintile of processed meat intake had an increased risk of developing colorectal and lung cancer. The incidences of other cancers were largely unaffected by meat intake.

### What Do These Findings Mean?

These findings provide strong evidence that people who eat a lot of red and processed meats have greater risk of developing colorectal and lung cancer than do people who eat small quantities. They also indicate that a high red meat intake is associated with an increased risk of esophageal and liver cancer, and that one in ten colorectal and one in ten lung cancers could be avoided if people reduced their red and processed meat intake to the lowest quintile. However, although the researchers allowed for factors such as smoking history that might have affected cancer incidences, some of the effects they ascribe to meat intake might be caused by other lifestyle factors. Furthermore, because the study's definitions of red meat and processed meat overlapped—bacon and ham, for example, were included in both categories—exactly which type of meat is related to cancer remains unclear. Finally, most of the study participants were non-Hispanic white, so these findings may not apply to people with different genetic backgrounds. Nevertheless, they add to the evidence that suggests that decreased consumption of red and processed meats could reduce the incidence of several types of cancer.

### Additional Information.

Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0040325.

- The American Cancer Society provides answers to common questions about diet and cancer
- Information is available from the charity Cancer Research UK about diet, healthy eating, and cancer
- The American Institute for Cancer Research also provides information on diet and cancer
- The NIH-AARP Diet and Health Study presents information on the impact of diet and lifestyle factors on risk of cancer
- The US National Cancer Institute provides information about the kind of food questionnaire used in this study

## Introduction

Much of the global variation in cancer incidence has been attributed to environmental influences, including dietary preferences. Not only does meat intake vary substantially around the world, but diets high in red or processed meats have been associated with carcinogenesis at a variety of anatomic sites. The evidence to support a positive association between meat intake and carcinogenesis is based on an assortment of research ranging from laboratory studies [1–3] to observational epidemiology [4–8].

Thus far, the majority of epidemiologic meat research has focused on the more prevalent cancers, particularly colorectal cancer. The most recent meta-analysis of prospective studies of meat and colorectal cancer reported significantly elevated summary relative risks (RRs) for both red meat (RR = 1.28; 95% confidence interval (CI) = 1.15–1.42) and processed meat (RR = 1.20; 95% CI = 1.11–1.31) in the highest versus lowest category of intake [9]. To date, findings for other major cancers—such as prostate, breast, lung, and pancreatic cancer—are less consistent. Prospective data for rarer cancers are sparse, and most epidemiologic studies of

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less–commonly occurring cancers are restricted to case-control studies, for which investigations of dietary associations are difficult, because of the potential for recall bias [10].

We prospectively investigated red and processed meat intake in relation to cancer incidence in a cohort of approximately half a million men and women enrolled in the National Institutes of Health (NIH)-AARP (formerly known as the American Association for Retired Persons) Diet and Health Study. This study's large size facilitated the investigation of comparatively rare cancers that have not yet been prospectively investigated.

## Materials and Methods

### Study Population

The NIH-AARP Diet and Health Study is a large prospective cohort of men and women, aged 50–71 y, from six states in the United States (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia; and Detroit, Michigan). Recruitment began in 1995 when a self-administered questionnaire eliciting information on demographic and lifestyle characteristics, including dietary habits, was mailed to 3.5 million members of AARP; further details of the design of the study have been described in detail elsewhere [11,12]. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute, and written informed consent was obtained from all participants by virtue of completing the baseline questionnaire.

### Dietary Assessment

A 124-item food frequency questionnaire (FFQ), based on the Diet History Questionnaire (http://riskfactor.cancer.gov/DHQ/forms/files/shared/dhq1.2002.sample.pdf), developed at the National Cancer Institute, was completed at baseline. The FFQ assessed the usual frequency of consumption and portion size information (based on three categories of <25th, 25th–75th, and >75th percentile of intake from national dietary data) of foods and drinks over the previous 12 mo. Portion sizes and daily nutrient intakes were calculated from the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intake by Individuals [13]. The FFQ compared favorably to other FFQs [14], and was also calibrated within this study population against two 24-h recall diaries [12]. Red meat intake was calculated from the frequency of consumption and portion size information of all types of beef, pork, and lamb; this included bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage, and steak. The processed meat variable included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs, and low-fat hot dogs made from poultry. The meat variables also included meats added to complex food mixtures, such as pizza, chili, lasagna, and stew.

### Cohort Follow-Up and Case Ascertainment

Cohort members are followed annually for change of address using the US Postal Service, and vital status is ascertained by annual linkage to the US Social Security Administration Death Master File. Follow-up for these analyses was calculated from baseline (1995–1996) until censoring at the end of 2003, or when the participant moved out of one of the eight study areas, had a cancer diagnosis, or died, whichever came first. Cancer cases were identified by linkage to state cancer registries and the National Death Index Plus. The eight state cancer registry databases are estimated to be 95% complete within 2 y of cancer incidence and are certified by the North American Association of Central Cancer Registries for meeting the highest standard of data quality [11]. Cancer diagnoses contributed to the incidence of the tumor site of the first diagnosis only and not subsequent diagnoses for additional sites. The cancer endpoints were defined by anatomic site and histologic code of the International Classification of Diseases for Oncology (ICD-0–3) [15]. Advanced prostate cancer may have a distinct etiology; therefore, we used the Tumor-Node-Metastasis classification system [16], and defined those with clinical or pathologic stage T3, T4, or N1 or M1, as well as individuals who died of prostate cancer, to have advanced disease. Results are presented for cancer sites with at least 60 cases within each sex.

### Statistical Analysis

A total of 567,169 persons returned the baseline questionnaire and were available for analysis. We excluded individuals with duplicate records ($n$ = 179), those who died before returning the baseline questionnaire ($n$ = 261), those who had zero person years of follow-up ($n$ = 32), those who moved out of the eight study areas before returning the questionnaire ($n$ = 269), those who requested to be withdrawn from the study ($n$ = 1), those whose questionnaire was filled in by someone else on their behalf ($n$ = 15,765), those who had prevalent cancer (as noted by cancer registry or self-report) at baseline ($n$ = 51,212) or end-stage renal disease ($n$ = 997), and those with extreme daily total energy intake ($n$ = 4,417), defined as more than two inter-quartile ranges above the 75th or below the 25th percentile on the logarithmic scale. After all

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exclusions, our analytic cohort consisted of 494,036 persons (294,724 men and 199,312 women).

Hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards regression with time since entry (person years) as the underlying time metric. Analyses using age as the underlying time metric yielded almost identical HRs. We controlled for age as a continuous variable in the Cox model; inclusion of a quadratic term for age did not improve the fit of the model, nor did it modify the HRs appreciably. Multivariate HRs are reported within quintiles, using the lowest quintile as the referent category, adjusted for the covariates listed in the tables. Missing data were minimal for this study; where appropriate—i.e., for smoking history and body mass index (BMI)—we created "missing" categories, but for others, such as family history of cancer, we set individuals missing this data to zero: no family history. Saturated fat intake and menopausal hormone therapy were investigated as potential confounders of the meat–cancer association, but neither proved to change the HR by greater than 10% and were not, therefore, included in the final models. Extremely fine control for smoking history and dosage was investigated, by constructing a 31-level variable using smoking status (never, former, current), time since quitting for former smokers, and smoking dose.

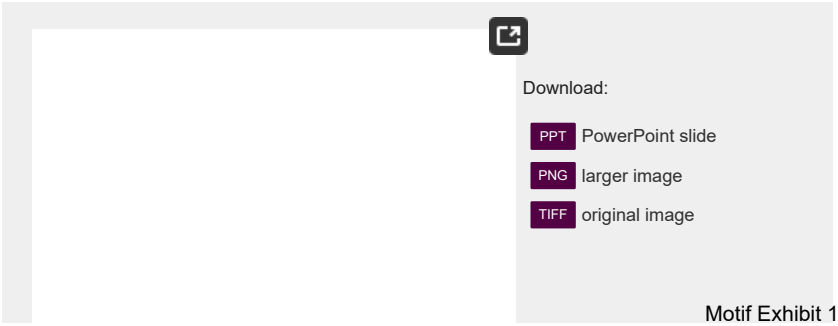
We examined models that were adjusted for energy by two different methods: the multivariate nutrient density method and the residual energy adjustment method [10]. Since both methods of energy adjustment gave similar results in our study, and because the interpretation of the multivariate nutrient density method applies to actual intakes as a percent of energy, which tends to be the units expressed for public health recommendations, we report the results from the multivariate nutrient density adjusted models.

Risks are reported for both sexes combined, unless there was a statistically significant interaction between meat intake and sex. Interactions were evaluated by including cross product terms in multivariate models. Furthermore, we conducted a lag analysis, excluding the first 2 y of follow-up, as well as various subanalyses to verify the stability of our risk estimates within subgroups of race, BMI, education, smoking status, physical activity level, and alcohol intake. The proportional hazards assumption was verified using a time interaction model. Tests for linear trend were calculated using the median value of each quintile. All reported *p*-values are two-sided. To test for heterogeneity, we used a chi-square test. To test for heterogeneity among the 21 cancer sites with 20 degrees of freedom, we first calculated the weighted average of the 21 beta coefficients from the Cox model, with weights being proportional to the inverse of the variances. Then we calculated the following chi-square statistic: $T = \sum_{i=1}^{21} (\hat{\beta}_i - \bar{\beta})^2 / \sigma_i^2$, where $\hat{\beta}_i$ and $\sigma_i^2$ are the coefficient and its variance for each cancer, and $\bar{\beta}$ is the weighted average of the beta coefficients. Likewise, to test for heterogeneity between subsites, such as colon versus rectum, we used the same chi-squared test given above, but using one degree of freedom. We also calculated population-attributable risks as an estimate of the percentage of cases that could be prevented if individuals adopted intake levels within the first quintile, given the assumption of a causal association between red or processed meat intake and cancer. All statistical analyses were carried out using Statistical Analytic Systems (SAS) software (SAS Institute).

## Results

During a mean follow-up of 6.8 y, 53,396 cancer diagnoses (36,907 male cases and 16,489 female cases) were ascertained. The mean energy–adjusted red meat intake in this cohort was 34.6 g/1,000 kcal (38.0 g/1,000 kcal in men and 29.5 g/1,000 kcal in women). The medians of extreme quintiles ranged from 9.8 to 62.7 g/1,000 kcal for red meat and 1.6 to 22.6 g/1,000 kcal for processed meat.

In general, those in the highest quintile of red meat intake tended to be slightly younger, less educated, less physically active, and less likely to consume fruits, vegetables, and alcohol than those in the lowest quintile. In contrast, those in the highest quintile of red meat intake were more likely to have a higher total energy intake, a higher BMI, and more likely to be a current smoker. Women in the highest quintile of red meat intake were also more likely to be married than those in the lowest quintile (Table 1).



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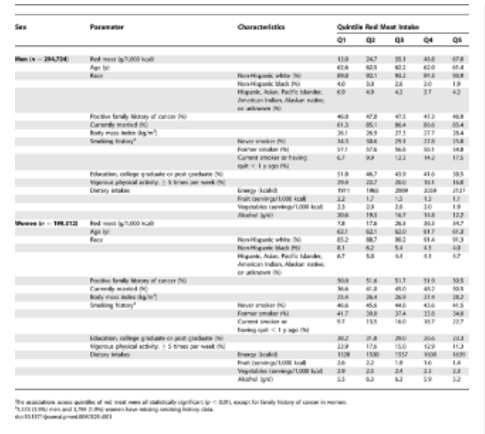
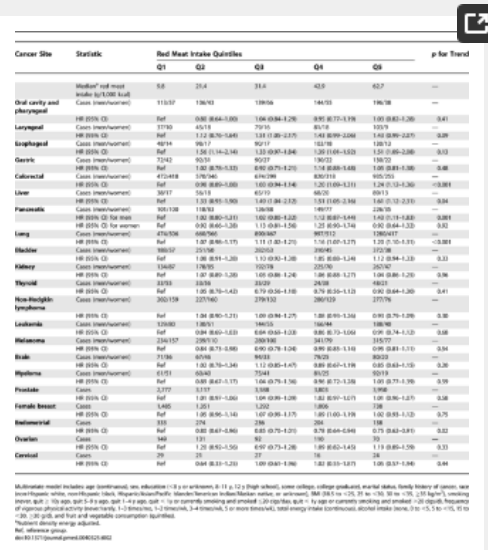


**Table 1.**
Means and Proportions for Baseline Characteristics of the NIH-AARP Diet and Health Study Cohort (*n* = 494,036) by Red Meat Quintile
https://doi.org/10.1371/journal.pmed.0040325.t001

## Red Meat

Individuals in the highest quintile of red meat intake, compared with those in lowest, had a statistically significant elevated risk of several malignancies (Table 2), including esophageal (HR = 1.51; 95% CI = 1.09–2.08; *p* for trend = 0.13), colorectal (HR = 1.24; 95% CI = 1.12–1.36; *p* for trend < 0.001, liver (HR = 1.61; 95% CI = 1.12–2.31; *p* for trend = 0.04), lung (HR = 1.20; 95% CI = 1.10–1.31; *p* for trend < 0.001), and borderline statistical significance for laryngeal cancer (HR = 1.43; 95% CI = 0.99–2.07; *p* for trend = 0.09). The positive association for red meat intake and colorectal cancer was due more to cancer of the rectum (*n* = 1,418; HR = 1.45; 95% CI = 1.20–1.75; *p* for trend < 0.001) than the colon (*n* = 3,689; HR = 1.17; 95% CI = 1.05–1.31; *p* for trend < 0.001), and this difference in risk was marginally statistically significant (*p* for heterogeneity = 0.06). Additional fine control for smoking did not alter the associations for cancers of the esophagus, colorectum, liver, lung, or larynx. In addition, the tests for interaction between smoking and both red meat (*p* interaction = 0.69) and processed meat (*p* interaction = 0.48) intake for lung cancer risk were not statistically significant. The population-attributable risks, representing the percentage of cases that could be prevented if individuals adopted red meat intake levels within the first quintile, were 33%, 9%, 35%, and 10% for esophageal, colorectal, liver, and lung cancer, respectively.



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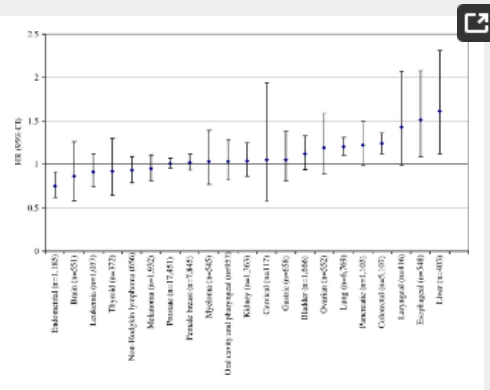
**Table 2.**
Multivariate HRs and 95% CIs (Both Sexes Combined) for Red Meat Intake and Cancer in the NIH-AARP Diet and Health Study
https://doi.org/10.1371/journal.pmed.0040325.t002

Red meat intake was not associated with gastric or bladder cancer, leukemia, lymphoma, or melanoma. The associations between red meat and cancer are summarized in Figure 1, arranged by order of the magnitude of the risk; the figure also shows the null findings for sex

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specific cancers, such as breast, ovarian, cervical, and prostate cancer. Unexpectedly, red meat intake was inversely associated with endometrial cancer (HR = 0.75; 95% CI = 0.62–0.91; *p* for trend = 0.02).



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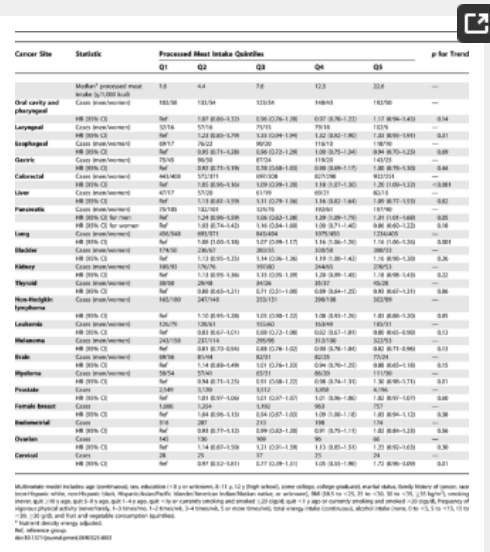
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**Figure 1. HRs and 95% CIs for the 5th Versus 1st Quintile of Red Meat Intake and Cancer Risk for Both Sexes Combined (Except for Sex-Specific Cancers)**
https://doi.org/10.1371/journal.pmed.0040325.g001

In further sex-specific analyses, red meat intake was positively associated with pancreatic cancer among men only (HR = 1.43; 95% CI = 1.11–1.83; *p* for trend = 0.001; *p* interaction by sex = 0.03); this risk was not attenuated by fine control for smoking. We observed no differences in risk by sex for other cancer sites.

## Processed Meat

Individuals in the highest quintile, compared with those in the lowest quintile, of processed meat intake were at elevated risk for colorectal (HR = 1.20; 95% CI = 1.09–1.32; *p* for trend < 0.001) and lung cancer (HR = 1.16; 95% CI = 1.06–1.26; *p* for trend = 0.001) (Table 3). In concordance with the red meat association, the risk observed for processed meat and colorectal cancer was slightly higher for rectal (HR = 1.24; 95% CI = 1.03–1.49; *p* for trend = 0.03) than colon cancer (HR = 1.18; 95% CI = 1.06–1.32; *p* for trend = 0.001), although this difference in risk was not statistically significant (*p* for heterogeneity = 0.67). Additional fine control for smoking did not alter the risk estimates for cancers of the colorectum or lung. Furthermore, borderline statistically significant increased risks for bladder cancer (HR = 1.16; 95% CI = 0.98–1.38; *p* for trend = 0.26) and myeloma (HR = 1.30; 95% CI = 0.98–1.71; *p* for trend = 0.01) were observed for those in the highest quintile of processed meat intake. The population-attributable risks, representing the proportion of cases potentially preventable if individuals adopted processed meat intake levels within the first quintile, were 10% for colorectal cancer and 9% for lung cancer.



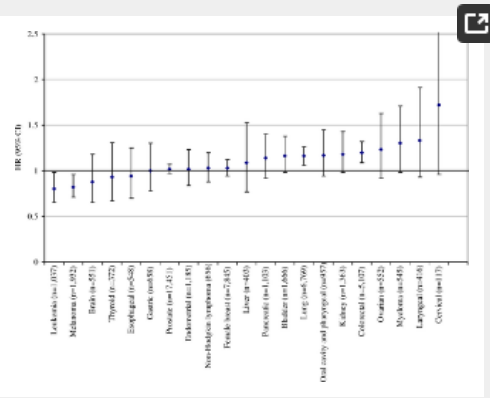
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**Table 3.**
Multivariate HRs and 95% CIs (Both Sexes Combined) for Processed Meat Intake and Cancer in the NIH-AARP Diet and Health Study
https://doi.org/10.1371/journal.pmed.0040325.t003

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Surprisingly, both leukemia and melanoma were inversely associated with processed meat intake; the inverse association for leukemia was mainly for lymphocytic leukemia ($n$ = 534; HR = 0.70; 95% CI = 0.52–0.93; $p$ for trend = 0.05) and not myeloid and monocytic leukemia ($n$ = 457; HR = 0.88; 95% CI = 0.64–1.20; $p$ for trend = 0.73). The associations between processed meat intake and cancer risk are summarized in Figure 2, in order of risk magnitude.



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**Figure 2. HRs and 95% CIs for the 5th Versus 1st Quintile of Processed Meat Intake and Cancer Risk for Both Sexes Combined (Except for Sex-Specific Cancers)**

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Sex-specific analyses revealed a positive association for men in the highest quintile of processed meat consumption for pancreatic cancer (HR = 1.31; 95% CI = 1.01–1.68; $p$ for trend = 0.05; $p$ interaction = 0.01); this association was not attenuated by fine control for smoking. Furthermore, women in the highest quintile of processed meat had a borderline statistically significant elevated risk for cervical cancer (HR = 1.72; 95% CI = 0.96–3.09; $p$ for trend = 0.01).

Further analyses did not reveal differences in risk associated with either red or processed meat intake for squamous versus adenocarcinoma of the esophagus, cardia versus non-cardia gastric cancer, and pre- versus post-menopausal breast cancer (unpublished data). However, we observed a suggestion of an elevated risk for advanced prostate cancer ($n$ = 1,782), for both red meat (HR = 1.15; 95% CI = 0.98–1.36; $p$ for trend = 0.21) and processed meat intake (HR = 1.22; 95% CI = 1.05–1.43; $p$ for trend = 0.08), when comparing those in the highest with those in the lowest quintile of intake.

We conducted sensitivity analyses excluding processed meats from the red meat variable to determine whether the risks associated with red and processed meat are independent of each other. The removal of processed meats from the red meat variable reduced the median intake of red meat from 31.4 g/1,000 kcal to 23.6 g/1,000 kcal. The positive associations for red meat and cancer of the liver, esophagus, colorectum, and lung all remain when processed meats were removed from the red meat variable. Furthermore, the inverse association for red meat and endometrial cancer remained after removing processed meats.

In a lag analysis excluding the first two years of follow-up, both the positive and the inverse associations reported in this study remained. A stepwise addition of the covariates to a simple age- and sex-adjusted model showed that the effects of red and processed meat intake on cancer risk were attenuated the most by the addition of the smoking variable to the models. Subanalyses showed that there was no clear gradient in risk for colorectal or lung cancer across categories of education, BMI, physical activity, or alcohol intake. With regard to race, the increased risk observed for red and processed meat and cancer of the colorectum and lung was not evident for blacks, although this ethnicity only represented 3.8 and 4.0 percent of the cases for each cancer site, respectively, and therefore the confidence intervals were wide. The risks for lung cancer associated with both red and processed meat intake were apparent across all categories of smoking.

## Discussion

In this large, prospective investigation of red and processed meat intake in relation to cancer risk, we found elevated risks for colorectal and lung cancer with both meat types. Red, but not processed, meat intake was also associated with increased risk for cancer of the esophagus and liver. We observed borderline statistically significant elevated risks for advanced prostate

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cancer with both red and processed meat intake, for laryngeal cancer with red meat, and for bladder cancer and myeloma and with processed meat intake.

The cancer site most consistently associated with meat intake has been the colorectum. A recent meta-analysis of 15 prospective studies published through March, 2006, included approximately 7,500 cases, and reported elevated risks in the highest category of consumption of 28% for red meat and 20% for processed meat [9]. Our study included over 5,000 colorectal cancer cases, and it lends strong support to implicate red and processed meat as risk factors for this malignancy. Consistent with previous studies [9], we observed a stronger positive association for rectal than colon cancer.

The positive associations for both red and processed meat that we report for lung cancer were of similar magnitude to the findings for colorectal cancer. To date, our study includes the largest prospective analysis of meat intake and lung cancer risk. Previous case-control studies have reported elevated risks for lung cancer for those in the highest categories of red meat [17–19], fried red meat [8,19], well-done red meat [17], and processed meat intake [20]. Despite conducting analyses to show that very fine control of smoking history, using a 31-level variable, did not attenuate the lung cancer associations, there remains a potential issue of residual confounding by smoking, because it is such a strong risk factor for this disease.

We found a positive association between red meat intake specifically and cancers of the esophagus and liver, and a borderline significant positive association for laryngeal cancer. The first prospective study of meat intake and esophageal cancer was published recently; that study had only 65 cases and found a positive association for processed meat, but not red meat, with esophageal adenocarcinoma [21]. Our study suggests a threshold effect for red meat intake on esophageal cancer risk, beginning at a low level of intake, with no further increase in risk with higher intakes, as reflected in the $p$-trend ($p = 0.13$), although it is possible that the referent group had a smaller-than-expected cancer incidence by chance. Data on meat intake and cancers of the liver and larynx are limited, and our study is the first prospective investigation to report on these associations. Two case-control studies reported elevated risks for laryngeal cancer for those in the highest intake categories of red meat intake [22,23] and fried beef/veal [24].

In our study, those in the highest quintile of processed meat intake had borderline statistically significant elevated risks for myeloma, a malignancy that has not been well-studied for dietary associations, and bladder cancer. A study of two prospective cohorts combined [25], and one case-control study [26], both found elevated risks of bladder cancer for those in the highest categories of processed meat consumption, but another cohort study found no association [27].

Unexpectedly, we found an inverse association between red meat intake and endometrial cancer; this association was not attenuated by adjustment for known risk factors, such as body mass index or menopausal hormone therapy, or by fine control for smoking, which has been inversely associated with this malignancy [28]. Previous studies have reported null [29,30] or positive relations [31] between red meat and endometrial cancer. We also observed inverse associations between processed meat intake and leukemia and melanoma. In contrast to our findings, childhood leukemia has been positively associated with intake of processed meats in a case-control study [32].

Both red and processed meat intake were positively associated with pancreatic cancer in men, but not women. Red meat has been associated with pancreatic cancer in some [33,34], but not all [35–39] previous cohort studies, as has processed meat in one cohort [34] and several case-control studies [40–44]; although a sex-specific association has not been reported before. Although the association between pancreatic cancer and red or processed meat intake in men was unchanged by fine control for smoking, residual confounding by smoking is still possible.

Our study did not reveal an association between red or processed meat intake and gastric, prostate, or breast cancer, or non-Hodgkin lymphoma. In contrast to the positive relation between both red and processed meat intakes and noncardia gastric cancer in a large cohort in Europe [21], we found no differences in risk according to gastric anatomic subsite. The evidence for a positive association between meat intake and gastric cancer has been more consistent for processed meat than red meat, with elevated risks for processed meat in several case-control [45–52] and cohort studies [53–57], whereas red meat has been positively associated in some [45,46], but not all studies [47,58,59].

Previous studies of meat intake and prostate cancer are conflicting. Some studies have reported null findings [5,60–66], and others suggest positive associations [67–74]. Despite finding no association between red or processed meat intake and overall prostate cancer risk, we observed a suggestion of an elevated risk for advanced prostate cancer with both meat types. If the relation of meat intake to prostate cancer is confined to advanced disease, this could explain some of the inconsistencies in the literature as most previous studies have not specifically addressed advanced prostate cancer.

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With regard to breast cancer, a pooled analysis of eight cohort studies found no association with red meat intake [75]; however, the two most recent prospective studies found positive associations for both red and processed meat [76], specifically for estrogen and progesterone receptor–positive breast cancers in premenopausal women [77]. Although breast cancer risk related to meat intake did not appear to differ by menopausal status in our study, we had very few premenopausal cases ($n$ = 94) and lacked information on hormone receptor status for a large number of cases.

In agreement with our findings, the majority of studies of red meat and non-Hodgkin lymphoma have been null [78–85], although elevated risks were reported in some studies [86–88]; similarly, of nine studies investigating processed meat and non-Hodgkin lymphoma [79–82,84,86–89], only two found a positive association [81,89]. In contrast to our null findings, some case-control studies have reported positive associations for red or processed meat intake and cancer of the oral cavity, pharynx [90,91], kidney [92], ovaries [83], thyroid [83], and brain [93], although data for these cancer sites are limited.

Both red meat, regardless of processing procedure, and processed meat can be linked to carcinogenesis by different mechanisms; for example, they are both sources of saturated fat and iron, which have independently been associated with carcinogenesis. Associations between saturated fat and cancer are likely to be related to energy balance in general, whereas iron is thought to contribute to carcinogenesis specifically by generating free radicals and inducing oxidative stress [94]. Most recently, dietary fat was positively associated with breast cancer [95], and iron intake was positively associated with liver [96] and colorectal cancers [97].

Meat is also a source of several known mutagens, including *N*-nitroso compounds (NOCs), heterocyclic amines (HCAs), and polycyclic aromatic hydrocarbons (PAHs). Exposure to NOCs occurs from endogenous formation, which is directly related to red meat intake [98], and from exogenous exposure from nitrite-preserved meats, for example [1]. Red meat is a large source of readily available heme iron, which has been associated with increased endogenous NOC formation [99]. Human exposure to NOCs and subsequent cancer risk has not been studied extensively; although a Finnish cohort reported an increased risk of colorectal cancer with exogenous exposure to *N*-nitrosodimethylamine (from smoked and salted meats) [6]. In addition, NOC intake and excretion were significantly greater in an area within China considered as high-risk for esophageal cancer [100]. HCAs and PAHs, which are formed during high-temperature cooking of meat [101], dose-dependently generate DNA adducts [3] and tumors in rodents [2,102] in a wide variety of tissues and organs, with similarities between experimental animals and humans [103]. Epidemiologic studies with the capacity to estimate HCA and PAH intake from meat cooking information have found elevated risks of colorectal neoplasia [104–106], squamous cell esophageal cancer [107], as well as cancers of the lung [8], pancreas [4], and prostate [5].

With regard to the stronger relation of red and processed meat to rectal cancer than to colon cancer, there is variation in several characteristics along the large intestine; for example, the average crypt length [108], apoptotic index [109], and propensity to form $O^6$-methylguanine adducts[110] (pro-carcinogenic and a marker of NOC exposure) is greater toward the rectum than in the proximal colon. Furthermore, there is variation throughout the colorectum in bacterial enzymes [111], in the fermentation of short chain fatty acids [112], in the expression of metabolic enzymes [113], and in the concentration of fecal matter, in which potential carcinogens are concentrated toward the rectum.

Despite abundant biologic pathways linking meat intake to carcinogenesis at numerous anatomic sites, this is the first comprehensive and prospective analysis of meat intake in relation to a full range of malignancies. A particular strength of this study includes the large size of the cohort, which enabled us to investigate low-incidence cancers that have not previously been prospectively explored. Our findings are strictly generalizable to US whites over 50 y old, but may readily extend to other populations, because it is unlikely that the mechanisms relating meat to carcinogenesis differ quantitatively between our study population and those to whom our results do not strictly apply. An additional strength was that our study encompassed a wide range of reported meat intake, providing adequate statistical power to detect associations. Furthermore, recall bias and reverse causation were minimized by the assessment of diet prior to cancer diagnoses.

Potential limitations of this study include some degree of measurement error associated with the assessment of dietary and lifestyle variables. The FFQ used in this study was compared with two 24-h recall diaries in a subgroup of individuals from this cohort. The energy-adjusted correlation coefficients for protein and saturated fat, the two most relevant macronutrients for meat, were 0.43 and 0.50 for men and women, respectively, for protein, and 0.76 and 0.69 for men and women, respectively, for saturated fat [114]. These correlations compared very favorably to other commonly used FFQs that have correlations ranging from 0.29 to 0.61 in men and from 0.16 to 0.67 in women for protein intake and from 0.64 to 0.76 in men and from 0.59 to 0.76 in women for saturated fat intake [114]. Furthermore, the correlations for red meat assessed from the FFQ compared with two 24-h recall dairies were 0.62 for men and 0.70 for

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women [12]. Although some measurement error remains, the error associated with FFQs tends to result in attenuated risks [115], and we attempted to minimize this error by energy adjustment of the models [116]. With regard to nondietary covariates, reviews and meta-analyses have concluded that self-reported smoking behavior is accurate in most studies as assessed by plasma cotinine levels [117], and the correlations for physical activity assessment in questionnaires similar to that used in our study produce reasonable correlations [118]. Furthermore, self-reported height and weight is a reliable method of estimating BMI.

Some of the observed associations between meat intake and cancer risk in our study may be explained by exposure to HCAs and PAHs from meats cooked well-done by high-temperature cooking techniques; however, we lacked data on detailed cooking preferences from baseline. In addition, because we analyzed cancer incidence at multiple sites, some of our findings may have occurred by chance.

In conclusion, a diet high in red or processed meat was associated with an elevated risk of both colorectal and lung cancer; in addition, red meat was associated with an elevated risk of esophageal and liver cancer. A decrease in the consumption of red and processed meat could reduce the incidence of cancer at multiple sites.

## Supporting Information

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**Alternative Language Abstract S1.** **German Translation of Abstract by M. F. Leitzmann**
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(21 KB DOC)

**Text S1.** **Meat and Cancer STROBE Statement for Study**
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## Author Contributions

AJC had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have given full approval to the final manuscript. AJC, MFL, MHG, AS, and RS were involved in the study design, analysis, and interpretation of the data. AJC, MFL, MHG, ARH, AS, and RS were all involved in the critical revision of the manuscript.

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510 1_ | ‡**9** 1‡**a** MEDLINE‡**b** v1n1, Oct. 2004-
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# Attachment 53c

# Medicine MeSH Descriptor Data 2022

Details | Qualifiers | MeSH Tree Structures | Concepts

| | |
|---|---|
| **MeSH Heading** | Medicine |
| **Tree Number(s)** | H02.403 |
| **Unique ID** | D008511 |
| **RDF Unique Identifier** | http://id.nlm.nih.gov/mesh/D008511 |
| **Annotation** | medicine only as a field, profession or discipline: differentiate from DELIVERY OF HEALTH CARE where the patient is emphasized; very general; it is divided broadly into experimental medicine ( = BIOMEDICAL RESEARCH) & CLINICAL MEDICINE, a specialty devoted to the diagnosis & management of human patients; / legislation & jurisprudence = LEGISLATION, MEDICAL or JURISPRUDENCE or FORENSIC MEDICINE; LEGAL MEDICINE see FORENSIC MEDICINE is also available |
| **Scope Note** | The art and science of studying, performing research on, preventing, diagnosing, and treating disease, as well as the maintenance of health. |
| **Entry Term(s)** | Insurance Medicine<br>Medical Specialities<br>Medical Specialties<br>Medical Specialty<br>Specialities, Medical<br>Specialties, Medical<br>Specialty, Medical |
| **See Also** | Economics, Medical<br>Education, Medical<br>History of Medicine<br>Insurance, Health<br>Legislation, Medical |
| **Public MeSH Note** | 1963; for SPECIALTIES, MEDICAL see SPECIALTIES, MEDICAL 1968-2009 |
| **History Note** | 1963 |
| **Entry Combination** | economics:Economics, Medical<br>education:Education, Medical<br>ethics:Ethics, Medical |

history:History of Medicine
legislation & jurisprudence:Legislation, Medical

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| **Date Established** | 1963/01/01 |
| **Date of Entry** | 1999/01/01 |
| **Revision Date** | 2021/07/06 |

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**550** __ |**a** Biosecurity
**550** __ |**a** Health literacy
**550** __ |**a** Medicine, Preventive
**550** __ |**a** National health services
**550** __ |**a** Sanitation

**670** __ |**a** CDC Foundation web site, viewed March 14, 2019 |**b** (What is public health? Public health is the science of protecting and improving the health of people and their communities. This work is achieved by promoting healthy lifestyles, researching disease and injury prevention, and detecting, preventing and responding to infectious diseases)

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245 00 Encyclopedia of analytical science.
250 Third edition / $b editor in chief, Paul J. Worsfold, Alan Townshend, Colin F. Poole, Manuel Miró.
264 1 Amsterdam : $b Elsevier, $c 2019.
300 1 online resource (10 volumes)
336 text $b txt $2 rdacontent
337 computer $b c $2 rdamedia
338 online resource $b cr $2 rdacarrier
588 0 Print version record.
520 The third edition of the Encyclopedia of Analytical Science is a definitive collection of articles covering the latest technologies in application areas such as medicine, environmental science, food science and geology. Meticulously organized, clearly written and fully interdisciplinary, the Encyclopedia of Analytical Science provides foundational knowledge across the scope of modern analytical chemistry, linking fundamental topics with the latest methodologies. Articles will cover three broad areas: analytical techniques (e.g., mass spectrometry, liquid chromatography, atomic spectrometry); areas of application (e.g., forensic, environmental and clinical); and analytes (e.g., arsenic, nucleic acids and polycyclic aromatic hydrocarbons), providing a one-stop resource for analytical scientists.--"Provided by publisher's website'.
650 0 Analytical chemistry $v Encyclopedias.
650 6 Chimie analytique $0 (CaQQLa)201-0008034 $v Encyclopédies. $0 (CaQQLa)201-0377762
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700 1 Worsfold, Paul, $e editor.
700 1 Townshend, A. $q (Alan), $d 1939- $e editor.

700 1  Poole, C. F., $e editor.
700 1  Miró, Manuel, $e editor.
776 08 $i Print version: $t Encyclopedia of analytical science. $b Third edition. $d Amsterdam : Elsevier, 2019 $z 9780081019832 $w (OCoLC)1085145007
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856 40 $3 VLeBooks $u
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# Attachment 55a

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# Attachment 55b

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



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*URL:* https://catalog.loc.gov/

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# Attachment 55c

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



**LC control no.:** sh 85019527
**LCCN Permalink:** https://lccn.loc.gov/sh85019527
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**906** __ |**t** 8741 |**u** fk07 |**v** 0
**953** __ |**a** xx00 |**b** fj25

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*URL:* http://authorities.loc.gov/
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# Attachment 55d

**OCLC** 1753562 **No holdings in XXX - 319 other holdings**

Continuing Resources

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246 1 $i Beginning in 1995, an additional annual vol. of six bimonthly numbers is issued, with title: $a International journal of cancer. $p Predictive oncology
246 1 $i Beginning in 2000, a second additional annual vol. of six bimonthly numbers is issued, with title: $a International journal of cancer. $p Radiation oncology investigations
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362 0 v. 1- Jan. 1966-
510 2 Chemical abstracts $x 0009-2258
515 Vol. numbering of additional annual vols. follows after that of main title each year, e.g., for 2000, v. 85-88 = International journal of cancer; v. 89 = International journal of cancer. Predictive oncology; v. 90 = International journal of cancer. Radiation oncology investigations.
546 English and French.
550 Publication of the International Union Against Cancer, <1999-
588 Latest issue consulted: Vol. 116, no. 6 (10 Oct. 2005).
650 0 Cancer $v Periodicals.
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856 4 $u http://www.interscience.wiley.com/jpages/0020-7136/ $z This former electronic address redirects to current address when searched on March 24, 2015.

# Attachment 56a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



MINI-REVIEW | Published: August 1997

# Production of D-ribose by fermentation

P. De Wulf & E. J. Vandamme

*Applied Microbiology and Biotechnology* **48**, 141–148 (1997) | Cite this article

**437** Accesses | **36** Citations | **9** Altmetric | Metrics

## Abstract

The production of D-ribose by fermentation has received much attention lately, possibly because of the use of this pentose to synthesize antiviral and anticancer drugs. This review briefly outlines the methods that have been used to synthesize D-ribose since it was identified in yeast RNA, and focuses in particular on the latest developments in D-ribose fermentation, which have led to D-ribose yields that exceed 90 g/l. Furthermore, the various transketolase-deficient D-ribose-producing mutants that are used, and the biochemical and genetic rationales applied to select them or to enhance their D-ribose productivities, are dealt with. Attention is also drawn to the unusual pleiotropic characteristics of the mutant strains, as well as to the industrial and academic applications of D-ribose.

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Motif Exhibit 1011, Page 959 of 1241

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## Author information

### Authors and Affiliations

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P. De Wulf

**Laboratory of Industrial Microbiology and Biocatalysis, Department of Biochemical and Microbial Technology, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure links 653, B-9000 Gent, Belgium Fax: ++ 32 9 264 62 31 Tel: ++ 32 9 264 60 27 e-mail: Erick.Vandamme@rug.ac.be, , , , , , BE**

E. J. Vandamme

## Additional information

Received: 29 January 1997 / Received revision: 13 March 1997 / Accepted: 15 March 1997

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## About this article

### Cite this article

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

Wulf, P., Vandamme, E. Production of D-ribose by fermentation. *Appl Microbiol Biotechnol* **48**, 141–148 (1997). https://doi.org/10.1007/s002530051029

Download citation

Issue Date
August 1997

DOI
https://doi.org/10.1007/s002530051029

Keywords
**Fermentation** **Mutant Strain** **Anticancer Drug** **Pentose** **Late Development**

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# Attachment 56b

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515    ##$aSome issues combined.
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# Attachment 56c

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510 0_ | ‡**9** 1‡**a** PubMed‡**b** v49n4, Apr. 1998-
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530 __ | ‡**a** Also issued online.
583 __ | ‡**3** Vol. 32, no. 3 (DEC 1989)‡**c** 19900108‡**f** Notice published‡**l** Printed on acid-free paper‡**x** Further review is required to determine exactly when acid-free paper was first used for this title
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650 _2 | ‡**a** Microbiology
655 _2 | ‡**a** Periodical
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911 __ | ‡**a** Electronic and print, print canceled 2017
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# Structured Fluids as Microreactors for Flavor Formation by the Maillard Reaction

S. Vauthey, Ch. Milo, Ph. Frossard, N. Garti, M. E. Leser, and H. J. Watzke

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Thermal reactions of cysteine/furfural and cysteine/ribose mixtures were studied in model systems to gain more insight into the influence of structured fluids such as $L_2$ microemulsions and cubic phases on the generation of aroma compounds. Formation of 2-furfurylthiol from cysteine/furfural was particularly efficient in $L_2$ microemulsions and cubic phases compared to aqueous systems. The reaction led to the formation of two new sulfur compounds, which were identified as 2-(2-furyl)thiazolidine and, tentatively, *N*-(2-mercaptovinyl)-2-(2-furyl)thiazolidine. Similarly, generation of 2-furfurylthiol and 2-methyl-3-furanthiol from cysteine/ribose mixtures was strongly enhanced in structured fluids. The cubic phase was shown to be even more efficient in flavor generation than the $L_2$ microemulsion. It was denoted “cubic catalyst” or “cubic selective microreactor”. The obtained results are interpreted in terms of a surface and curvature control of the reactions defined by the structural properties of the formed surfactant associates.

Keywords: Microemulsion; cubic phase; structured fluids; Maillard reaction; formation of thiols; flavor precursors; 2-furfurylthiol

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588        $aLatest issue consulted: Volume 69, issue 43 (November 3, 2021), (ACS Publications,
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321 Monthly, $b 1955-1959
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510 2 Chemical abstracts $x 0009-2258
525 Some issues <1978-Jan. 1995 accompanied by supplementary material on microfiche; Feb. 1995-<Feb. 1998, by supporting information on microfiche; current (1995- ) supporting information also available online.
530 Also issued on microfiche, microfilm, and online.
550 Volumes for 1953-<54 published by the American Chemical Society; <Jan./Feb. 1976- by the Books and Journals Division, American Chemical Society.
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650 0 Plants $x Nutrition $v Periodicals.
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650 2 Food-Processing Industry. $0 (DNLM)D005525
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856 41 $u http://pubs.acs.org/journals/jafcau/index.html

# Attachment 58a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

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# Myoglobin Chemistry and Meat Color

**Annual Review of Food Science and Technology**
Vol. 4:79-99 (Volume publication date February 2013)
First published online as a Review in Advance on November 26, 2012
https://doi.org/10.1146/annurev-food-030212-182623

**Surendranath P. Suman[1,*] and Poulson Joseph[2]**

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[2]Department of Food Science, Nutrition and Health Promotion, Mississippi State University, Mississippi State, Mississippi 39762; email: poulsonjoseph@gmail.com

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## Sections

ABSTRACT
KEYWORDS
INTRODUCTION
CHEMISTRY OF MEAT PIGMENTS
FACTORS INFLUENCING MEAT COLOR
MYOGLOBIN PRIMARY STRUCTURE AND COLOR STABILITY
INTERACTIONS BETWEEN MYOGLOBIN AND BIOMOLECULES
COLOR DEFECTS IN FRESH MEATS
COLOR DEFECTS IN COOKED MEATS
STRATEGIES TO IMPROVE FRESH MEAT COLOR
STRATEGIES TO IMPROVE COOKED MEAT COLOR
CONCLUSIONS

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

DISCLOSURE STATEMENT

## Abstract

Consumers rely heavily on fresh meat color as an indicator of wholesomeness at the point of sale, whereas cooked color is exploited as an indicator of doneness at the point of consumption. Deviations from the bright cherry-red color of fresh meat lead to product rejection and revenue loss. Myoglobin is the sarcoplasmic heme protein primarily responsible for the meat color, and the chemistry of myoglobin is species specific. The mechanistic interactions between myoglobin and multiple extrinsic and intrinsic factors govern the color of raw as well as cooked meats. The objective of this review is to provide an overview of the current research in meat color and how the findings are applied in the meat industry. Characterizing the fundamental basis of myoglobin's interactions with biomolecules in postmortem skeletal muscles is necessary to interpret the chemistry of meat color phenomena and to engineer innovative processing strategies to minimize meat discoloration–induced revenue loss to the agricultural economy.

## Keywords

heme protein, oxidation, pigment, cooked color, color defects

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Sulaiman K. Matarneh, Saulo L. Silva, and David E. Gerrard
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Gregory T. Sigurdson, Peipei Tang, and M. Mónica Giusti
Annual Review of Food Science and Technology

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

**New Developments on the Role of Intramuscular Connective Tissue in Meat Toughness**
Peter P. Purslow
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Simon M. Loveday
Annual Review of Food Science and Technology

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# Attachment 59a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

Advertisement

Journal of Food Science / Volume 53, Issue 2 / p. 658-658

# Identification of 2-Methyl-3-Furanthiol in the Steam Distillate from Canned Tuna Fish

D.ONALD A. WITHYCOMBE, C.YNTHIA J. MUSSINAN

First published: March 1988
https://doi.org/10.1111/j.1365-2621.1988.tb07781.x
Citations: 34

About

## ABSTRACT

The volatile components of canned tuna fish were isolated by steam distillation followed by solvent extraction. Analysis of the extract using a sulfur-specific detector and coupled gas chromatography -mass spectrometry permitted the identification of 2-methyl-3-furanthiol, a compound with an intense beef extract aroma. Mass spectral data are presented.

Citing Literature

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Case No. IPR2023-00206
U.S. Patent No. 9,943,096

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530    ##$aAlso issued online.
510    2#$aChemical abstracts $x0009-2258
500    ##$aTitle from cover.
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# Quantification of 2-Methyl-3-furanthiol, 2-Furfurylthiol, 3-Mercapto-2-pentanone, and 2-Mercapto-3-pentanone in Heated Meat

Roland Kerscher and Werner Grosch

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# Abstract

A stable isotope dilution assay was developed for quantification of the potent odorants 2-methyl-3-furanthiol (MFT), 2-furfurylthiol (FFT), 2-mercapto-3-pentanone (2M3P), and 3-mercapto-2-pentanone (3M2P) in heated meat. The volatiles of meat were extracted with dichloromethane, which was spiked with definite amounts of stable isotopomers of MFT, FFT, and 3M2P. The analytes and their labeled standards were enriched by reaction with *p*-hydroxymercuribenzoic acid, and after liberation, the thiols were assayed by dynamic headspace gas chromatography in combination with mass spectrometry. The following amounts (micrograms per kilogram) were found in meat samples boiled for 45 min: (beef) MFT, 7−28, FFT, 13−42, 3M2P, 55−73, 2M3P, 20−44; (pork) MFT, 6−9, FFT, 8−10, 3M2P, 66−117, 2M3P, 11−14; (lamb) MFT, 5−11, FFT, 9−14, 3M2P, 30, 2M3P, 10. Chicken contained per kilogram 4.5 μg of MFT, 2.4 μg of FFT, 100 μg of 3M2P, and 13 μg of 2M3P after a boiling period of 60 min.


Keywords: Isotope dilution assay; 2-methyl-3-furanthiol; 2-furfurylthiol; 3-mercapto-2-pentanone; 2-mercapto-3-pentanone; beef; chicken; pork; lamb; flavor

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# Attachment 61a

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# Studies on the Formation and Stability of the Roast-Flavor Compound 2-Acetyl-2-thiazoline

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2-(1-Hydroxyethyl)-4,5-dihydrothiazole (HDT) was identified by $^{1}H$- and $^{13}C$-NMR measurements as the main volatile product formed by storage of an aqueous solution of cysteamine and methylglyoxal at low temperatures (6 °C). The structure of HDT was confirmed by synthesis. Systematic studies on the thermal stability of the HDT under different conditions either in aqueous solution or during high-resolution gas chromatography revealed that HDT is an important intermediate in the formation of the intensely roasty smelling food flavor compound 2-acetyl-2-thiazoline (AT). Model studies showed that more than 10% of the precursor HDT was converted into AT simply by heating for 10 min in water. The activation energy of this reaction was 57.4 kJ/mol. Experiments on the thermal stability of AT itself revealed that heating in aqueous solution also led to a degradation of AT, whereas heating in an oil significantly stabilized the flavor compound.

**Keywords:** *2-(1-Hydroxyethyl)-4,5-dihydrothiazole; 2-acetyl-2-thiazoline; flavor precursor; stable isotope dilution analysis*

## INTRODUCTION

2-Acetyl-2-thiazoline (AT) has been reported for the first time among food flavors as a volatile constituent of beef broth (Tonsbeek et al., 1971). The compound was later identified in roast beef (Hartmann et al., 1983) and, also, overpasteurized beer (Tressl et al., 1983).

Using aroma extract dilution analysis (AEDA), the flavor compound, eliciting an attractive roasty, popcorn-like odor, has recently been established as a key contributor to several processed meat products, such as chicken broth (Gasser and Grosch, 1990), roast beef (Cerny and Grosch, 1993), stewed beef (Guth and Grosch, 1993), boiled trouts (Milo and Grosch, 1993), and roasted white sesame seeds (Schieberle, 1993). Furthermore, AT was detected among the odor-active volatiles of stewed beef juice (Guth and Grosch, 1994).

Volatile fractions generated by reacting cysteine with carbohydrates exhibit flavors resembling processed beef meat. Investigations on the chemical composition of such fractions have led to the identification of AT among the numerous volatiles generated from such precursor mixtures (Sakaguchi and Shibamoto, 1978; Silwar, 1992). Recent studies applying AEDA on the volatiles formed by the reaction of ribose/cysteine (Hofmann and Schieberle, 1995) have revealed that AT in fact contributes significantly to the roasty odors, and it was concluded that AT is a key odorant of such Maillard-type reaction flavors containing cysteine.

Hayashi and Shibamoto (1985) have reported that AT is formed in relatively high yields by reacting 1-mercapto-2-aminoethane (cysteamine) with 2-oxopropanal (methylglyoxal). This result suggested both compounds are important intermediates in AT formation from cysteine and carbohydrates. On the basis of the fact that at lower temperatures the 2-acetylthiazolidine was predominantly formed, it has been assumed (Hayashi and Shibamoto, 1985) that the flavor compound may be formed by oxidation of this intermediate.

Precursors generating meat-like odorants upon heating are of special interest since they would offer the possibility to enhance the desired flavor *in situ* during cooking.

The following investigation was undertaken to gain a more detailed insight into the intermediates and reaction mechanisms governing the formation of AT from cysteine and carbohydrates and, furthermore, to study the thermal stability of AT.

## MATERIALS AND METHODS

**Chemicals.** 1-Mercapto-2-aminoethane hydrochloride (cysteamine hydrochloride), 2-oxopropanal (methylglyoxal; 40% in water), hydroxypropanoic acid nitrile, and lithium aluminum hydride were obtained commercially (Aldrich, Steinheim, Germany).

**Synthesis.** *2-(1-Hydroxyethyl)-4,5-dihydrothiazole (HDT).* A mixture of cysteamine hydrochloride (12 mmol), 2-hydroxypropanoic acid nitrile (4 mmol), and ammonium acetate (1 g) in methanol (4 mL) was stirred for 32 h at room temperature. After the addition of water (10 mL), the HDT formed was extracted with diethyl ether (total volume 50 mL), and an aliquot was purified by flash chromatography as detailed in the following: The stationary phase (Bakerbond Diol; 40 μm) was filled 15 cm high into a glass column (35.9 × 1.9 cm; J. T. Baker No. 7022-01) which was equipped with a reservoir (250 mL) and a pressure regulator. The material was then equilibrated by flushing with *n*-pentane/diethyl ether (100 mL, 8 + 2 by vol) under a slight pressure of nitrogen. After application of the concentrated reaction mixture (10 mL) onto the column, elution (6 mL/min) was performed using the following *n*-pentane/diethyl ether mixtures: 180 mL/8 + 2 by vol (fraction A), 180 mL/7 + 3 by vol (fraction B), 150 mL/6 + 4 by vol (fraction C1), 30 mL/6 + 4 by vol (fraction C2), 30 mL/1 + 1 by vol (fraction D1) and another 150 mL/1 + 1 by vol (fraction D2). The 2-(1-hydroxyethyl)-4,5-dihydrothiazole, eluting in fractions C2–D2 (overall yield 61%) was characterized by $^{1}H$-NMR (cf. Tables 1 and 2) and mass spectral measurements.

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650 6 Aliments $x Analyse $v Périodiques.
650 6 Plantes $x Nutrition $v Périodiques.
650 7 58.34 food technology. $0 (NL-LeOCL)07760671X $2 bcl
650 7 Agricultural chemistry. $2 fast $0 (OCoLC)fst00800560
650 7 Food $x Analysis. $2 fast $0 (OCoLC)fst00930460
650 7 Plants $x Nutrition. $2 fast $0 (OCoLC)fst01066060
655 2 Periodical. $0 (DNLM)D020492
655 7 Periodicals. $2 fast $0 (OCoLC)fst01411641
655 7 Periodicals. $2 lcgft
710 2 American Chemical Society. $b Books and Journals Division.
776 08 $i Online version: $t Journal of agricultural and food chemistry (Online) $x 1520-5118 $w (DLC)sn 98004593 $w (OCoLC)39281168
850 CPT $a DLC $a DNAL $a DNGA $a ICRL $a InU $a NN $a NRU $a NcRS $a OrU-S
856 41 $u http://pubs.acs.org/journals/jafcau/index.html

# Attachment 62a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

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# Flavours and fragrances : chemistry, bioprocessing and sustainability



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| 005 | | 20120525094211.0 |
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| 082 | 00 | \|**a** 664/.07 \|**2** 22 |
| 245 | 00 | \|**a** Flavours and fragrances : \|**b** chemistry, bioprocessing and sustainability / \|**c** R.G. Berger (ed.). |
| 260 | __ | \|**a** Berlin ; \|**a** New York : \|**b** Springer, \|**c** c2007. |

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|---|---|---|
| 300 | __ | \|**a** xvi, 648 p. : \|**b** ill. (some col.) ; \|**c** 24 cm. |
| 504 | __ | \|**a** Includes bibliographical references and index. |
| 650 | _0 | \|**a** Flavoring essences. |
| 650 | _0 | \|**a** Food \|**x** Odor. |
| 650 | _0 | \|**a** Perfumes, Synthetic. |
| 650 | _0 | \|**a** Industrial microbiology. |
| 700 | 1_ | \|**a** Berger, Ralf G., \|**d** 1953- |
| 856 | 42 | \|**3** Publisher description \|**u** http://www.loc.gov/catdir/enhancements/fy0824/2006939012-d.html |
| 856 | 41 | \|**3** Table of contents only \|**u** http://www.loc.gov/catdir/enhancements/fy0824/2006939012-t.html |
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# Attachment 62b

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



**LC control no.:** sh 85050205
**LCCN Permalink:** https://lccn.loc.gov/sh85050205
**HEADING:** Food Odor

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**001** 4701871
**005** 20120323073951.0
**008** 860211i| anannbabn |a ana
**010** __ |**a** sh 85050205
**035** __ |**a** (DLC)sh 85050205
**035** __ |**a** (DLC)48556
**040** __ |**a** DLC |**c** DLC |**d** DLC
**150** __ |**a** Food |**x** Odor
**450** __ |**a** Aroma of food
**450** __ |**a** Food odor
**450** __ |**a** Food odors
**550** __ |**w** g |**a** Odors
**906** __ |**t** 9740 |**u** te03 |**v** 0
**953** __ |**a** xx00 |**b** jc02

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Washington, DC 20540

# Attachment 62c

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



**LC control no.:** sh 85099841
**LCCN Permalink:** https://lccn.loc.gov/sh85099841
**HEADING:** Perfumes, Synthetic

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**001** 4749646
**005** 20120327100107.0
**008** 860211i| anannbabn |b ana
**010** __ |**a** sh 85099841
**035** __ |**a** (DLC)sh 85099841
**035** __ |**a** (DLC)96331
**040** __ |**a** DLC |**c** DLC |**d** DLC
**053** _0 |**a** TP983
**150** __ |**a** Perfumes, Synthetic
**450** __ |**a** Synthetic perfumes
**550** __ |**w** g |**a** Synthetic products
**906** __ |**t** 9499 |**u** ---- |**v** 0
**953** __ |**a** xx00

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# Attachment 63a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



Published: March 2000

# Investigation of the boiled potato flavor by human sensory and instrumental methods

D. Ulrich, E. Hoberg, W. Neugebauer, H. Tiemann & U. Darsow

*American Journal of Potato Research* **77**, 111–117 (2000) | Cite this article

**383** Accesses | **37** Citations | Metrics

## Abstract

The flavor of boiled potatoes was investigated using sensory and instrumental methods to get basic information concerning sensory features and aroma compounds for use in breeding research and quality control. The sensory odor profiles of three genotypes were found to differ especially in negative sensations like “burnt”, “fodder” and “musty”. The aroma volatiles were isolated by a modified simultaneous steam distillation and extraction method. Nineteen character impact compounds of boiled potato aroma were pointed out by gas chromatography with nitrogen specific detection, gas chromatography —mass spectrometry and gas chromatography —olfactometry. The comparison of the quantified odor impressions in three genotypes by chromatography —olfactometry revealed the substances responsible for the typical boiled potato odorants and off-flavor notes.

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U.S. Patent No. 9,943,096

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H. Tiemann & U. Darsow

**Dragoco, Gerberding & Co. AG, Holzminden, Germany**
W. Neugebauer

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

Corresponding author

Correspondence to D. Ulrich.

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## About this article

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https://doi.org/10.1007/BF02853738

Download citation

Accepted
07 September 1999

Issue Date
March 2000

DOI
https://doi.org/10.1007/BF02853738

Additional Key Words

**Cooked potato** **potato flavor** **potato aroma** **human sensory** **quantitative descriptive analysis** **gas chromatography** **gas chromatography olfactometry** **character impact compounds**

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# Attachment 63b

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260    ##$aOrono, Me. : $bPotato Association of America
260    3#$3<2008>- $aNew York : $bSpringer
310    ##$aBimonthly
336    ##$atext $btxt $2rdacontent
337    ##$acomputer $bc $2rdamedia
338    ##$aonline resource $bcr $2rdacarrier
362    1#$aBegan with v. 75, no. 1 (Jan. 1998).
500    ##$aRefereed/Peer-reviewed
550    ##$a"An official publication of the Potato Association of
America."
588    ##$aDescription based on: Vol. 75, no. 1 (Jan. 1998); title
from pdf image of article (SpringerLink, viewed Nov. 14, 2011).
588    ##$aLatest issue consulted: Vol. 92, no. 5 (Oct. 2015)
(viewed Nov. 10, 2015).
650    #0$aPotatoes $vPeriodicals.
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653    ##$aPlant Sciences
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655    #0$aElectronic journals.
776    ##$x1099-209X
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$w(DLC)sn91016058 $x2381-7828
710    2#$aPotato Association of America.
906    ##$aJOURNAL
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# Attachment 63c

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



**LC control no.:** sh 85105652
**LCCN Permalink:** https://lccn.loc.gov/sh85105652
**HEADING:** Potatoes

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**001** 4755306
**005** 20120327100916.0
**008** 860211i| anannbabn |a ana
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**035** __ |**a** (DLC)sh 85105652
**035** __ |**a** (DLC)101991
**040** __ |**a** DLC |**c** DLC |**d** DLC
**053** _0 |**a** QK495.S7 |**c** Botany
**053** _0 |**a** SB211.P8 |**c** Culture
**053** _0 |**a** TP444.P6 |**c** Food processing
**150** __ |**a** Potatoes
**450** __ |**a** Irish potatoes
**450** __ |**a** Solanum tuberosum
**450** __ |**a** White potatoes
**550** __ |**w** g |**a** Solanum
**906** __ |**t** 9107 |**u** fk05 |**v** 1
**953** __ |**a** xx00 |**b** td04
**985** __ |**e** GAP

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# Attachment 64a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096
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# BLAST Basic Local Alignment Search Tool

BLAST finds regions of similarity between biological sequences. more...

The Basic Local Alignment Search Tool (BLAST) finds regions of local similarity between sequences. The program compares nucleotide or protein sequences to sequence databases and calculates the statistical significance of matches. BLAST can be used to infer functional and evolutionary relationships between sequences as well as help identify members of gene families.
Learn more about how to use the new BLAST design

## BLAST Assembled Genomes

Choose a species genome to search, or list all genomic BLAST databases.

- Human
- Mouse
- Rat
- *Arabidopsis thaliana*

- *Oryza sativa*
- *Bos taurus*
- *Danio rerio*
- *Drosophila melanogaster*

- *Gallus gallus*
- *Pan troglodytes*
- *Microbes*
- *Apis mellifera*

## Basic BLAST

Choose a BLAST program to run.

| | |
|---|---|
| nucleotide blast | Search a **nucleotide** database using a **nucleotide** query<br>*Algorithms:* blastn, megablast, discontiguous megablast |
| protein blast | Search **protein** database using a **protein** query<br>*Algorithms:* blastp, psi-blast, phi-blast |
| blastx | Search **protein** database using a **translated nucleotide** query |
| tblastn | Search **translated nucleotide** database using a **protein** query |
| tblastx | Search **translated nucleotide** database using a **translated nucleotide** query |

## Specialized BLAST

Choose a type of specialized search (or database name in parentheses.)

- Make specific primers with Primer-BLAST
- Search trace archives
- Find conserved domains in your sequence (cds)
- Find sequences with similar conserved domain architecture (cdart)

- Search sequences that have gene expression profiles (GEO)
- Search immunoglobulins (IgBLAST)
- Search for SNPs (snp)
- Screen sequence for vector contamination (vecscreen)
- Align two sequences using BLAST (bl2seq)
- Search protein or nucleotide targets in PubChem BioAssay

## Your Recent Results New!

All Recent results...

## News

**Find specific primers with Primer-BLAST!**

Primer-BLAST combines primer design (using Primer3) and a specificity check with BLAST.
2008-07-22 09:26:51

More BLAST news...

## Tip of the Day

**Using Tree View to Examine Relationships Between Sequences.**

The new Tree View option on the NCBI Web BLAST service presents a dendrogram or tree display that clusters sequences according to their distances from the query sequence. This display is helpful for recognizing the presence of aberrant or unusual sequences or potentially natural groupings of related sequences such as members of a gene families or homologs from other species in the BLAST output.

More tips...

# Attachment 65a

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U.S. Patent No. 9,943,096
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# Codes Used in Sequence Description

## Nucleotide

### Nucleotide Base Codes

The nucleotide base codes that are used with the International Nucleotide Sequence Database is as follows.

Sequence data is expressed with small letters only. Capital letter will be automatically converted to small letter.

| Symbol | Meaning | Explanation |
|---|---|---|
| a | a | adenine |
| c | c | cytosine |
| g | g | guanine |
| t | t | thymine in DNA; uracil in RNA |
| m | a or c | amino |
| r | a or g | purine |
| w | a or t | |
| s | c or g | |
| y | c or t | pyrimidine |
| k | g or t | keto |
| v | a or c or g | not t |
| h | a or c or t | not g |
| d | a or g or t | not c |
| b | c or g or t | not a |
| n | a or c or g or t | any |

[References]

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

- Cornish-Bowden, A. Nucl Acid Res 13, 3021-3030 (1985)
- Feature Table Definition: 7.4.1 Nucleotide base codes (IUPAC)

## Modified Base Abbreviations

An example for description of the modified base in FEATURES line.

Example

```
     FEATURES             Location/Qualifiers
          modified_base   15
                          /mod_base="m2g"
```

| Abbreviation | Modified base description |
|---|---|
| ac4c | 4-acetylcytidine |
| chm5u | 5-(carboxyhydroxylmethyl)uridine |
| cm | 2'-O-methylcytidine |
| cmnm5s2u | 5-carboxymethylaminomethyl-2-thiouridine |
| cmnm5u | 5-carboxymethylaminomethyluridine |
| dhu | dihydrouridine |
| fm | 2'-O-methylpseudouridine |
| gal q | beta,D-galactosylqueuosine |
| gm | 2'-O-methylguanosine |
| i | inosine |
| i6a | N6-isopentenyladenosine |
| m1a | 1-methyladenosine |
| m1f | 1-methylpseudouridine |
| m1g | 1-methylguanosine |
| m1i | 1-methylinosine |
| m22g | 2,2-dimethylguanosine |
| m2a | 2-methyladenosine |
| m2g | 2-methylguanosine |

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

| Abbreviation | Modified base description |
|---|---|
| m3c | 3-methylcytidine |
| m4c | N4-methylcytosine |
| m5c | 5-methylcytidine |
| m6a | N6-methyladenosine |
| m7g | 7-methylguanosine |
| mam5u | 5-methylaminomethyluridine |
| mam5s2u | 5-methoxyaminomethyl-2-thiouridine |
| man q | beta,D-mannosylqueuosine |
| mcm5s2u | 5-methoxycarbonylmethyl-2-thiouridine |
| mcm5u | 5-methoxycarbonylmethyluridine |
| mo5u | 5-methoxyuridine |
| ms2i6a | 2-methylthio-N6-isopentenyladenosine |
| ms2t6a | N-((9-beta-D-ribofuranosyl-2-methyltiopurin-6-yl)carbamoyl)threonine |
| mt6a | N-((9-beta-D-ribofuranosylpurine-6-yl)N-methyl-carbamoyl)threonine |
| mv | uridine-5-oxyacetic acid methylester |
| o5u | uridine-5-oxyacetic acid (v) |
| osyw | wybutoxosine |
| p | pseudouridine |
| q | queuosine |
| s2c | 2-thiocytidine |
| s2t | 5-methyl-2-thiouridine |
| s2u | 2-thiouridine |
| s4u | 4-thiouridine |
| m5u | 5-methyluridine |
| t6a | N-((9-beta-D-ribofuranosylpurine-6-yl)carbamoyl)threonine |
| tm | 2'-O-methyl-5-methyluridine |
| um | 2'-O-methyluridine |

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

| Abbreviation | Modified base description |
|---|---|
| yw | wybutosine |
| x | 3-(3-amino-3-carboxypropyl)uridine, (acp3)u |
| OTHER | Other (/note qualifier に修飾塩基を記載します) |

[References]

- Sprinzl, M. and Gauss, D.H. Nucl Acid Res 10, r1 (1982).(note that in Cornish_Bowden, A. Nucl Acid Res 13, 3021-3030 (1985)the IUPAC-IUB declined to recommend a set of abbreviations for modified nucleotides)
- Feature Table Definition: 7.4.2 Modified base abbreviations

# Amino Acid

## Amino Acid Codes

The amino acid code that is used with the International Nucleotide Sequence Database is as follows.

These amino acids are described with one letter abbreviation in /translation qualifier of CDS feature.

The listed amino acid abbreviations are legal values for qualifiers /transl_except and /anticodon.

Those that are not included in "Amino acid codes", please refer to Modified and unusual Amino Acids.

| Abbreviation | 1 letter abbreviation | Amino acid name |
|---|---|---|
| Ala | A | Alanine |
| Arg | R | Arginine |
| Asn | N | Asparagine |
| Asp | D | Aspartic acid |
| Cys | C | Cysteine |
| Gln | Q | Glutamine |
| Glu | E | Glutamic acid |
| Gly | G | Glycine |
| His | H | Histidine |
| Ile | I | Isoleucine |
| Leu | L | Leucine |

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| Abbreviation | 1 letter abbreviation | Amino acid name |
|---|---|---|
| Lys | K | Lysine |
| Met | M | Methionine |
| Phe | F | Phenylalanine |
| Pro | P | Proline |
| Pyl | O | Pyrrolysine |
| Ser | S | Serine |
| Sec | U | Selenocysteine |
| Thr | T | Threonine |
| Trp | W | Tryptophan |
| Tyr | Y | Tyrosine |
| Val | V | Valine |
| Asx | B | Aspartic acid or Asparagine |
| Glx | Z | Glutamic acid or Glutamine |
| Xaa | X | Any amino acid |
| Xle | J | Leucine or Isoleucine |
| TERM | | termination codon |

[References]


- IUPAC-IUB Joint Commission on Biochemical Nomenclature.Nomenclature and Symbolism for Amino Acids and Peptides. Eur. J. Biochem. 138: 9-37 (1984).
- Feature Table Definition: 7.4.3 Amino acid abbreviations


## Modified and Unusual Amino Acids

For other amino acids, those that are not included in Amino Acid Codes, abbreviation listed below is used. All of these amino acids are described with one letter abbreviation "X" in /translation qualifier of CDS feature.

| Abbreviation | Amino acid name |
|---|---|
| Aad | 2-Aminoadipic acid |
| bAad | 3-Aminoadipic acid |

| Abbreviation | Amino acid name |
|---|---|
| bAla | beta-Alanine, beta-Aminoproprionic acid |
| Abu | 2-Aminobutyric acid |
| 4Abu | 4-Aminobutyric acid, piperidinic acid |
| Acp | 6-Aminocaproic acid |
| Ahe | 2-Aminoheptanoic acid |
| Aib | 2-Aminoisobutyric acid |
| bAib | 3-Aminoisobutyric acid |
| Apm | 2-Aminopimelic acid |
| Dbu | 2,4-Diaminobutyric acid |
| Des | Desmosine |
| Dpm | 2,2'-Diaminopimelic acid |
| Dpr | 2,3-Diaminoproprionic acid |
| EtGly | N-Ethylglycine |
| EtAsn | N-Ethylasparagine |
| Hyl | Hydroxylysine |
| aHyl | allo-Hydroxylysine |
| 3Hyp | 3-Hydroxyproline |
| 4Hyp | 4-Hydroxyproline |
| Ide | Isodesmosine |
| aIle | allo-Isoleucine |
| MeGly | N-Methylglycine, sarcosine |
| MeIle | N-Methylisoleucine |
| MeLys | 6-N-Methyllysine |
| MeVal | N-Methylvaline |
| Nva | Norvaline |
| Nle | Norleucine |
| Orn | Ornithine |

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| Abbreviation | Amino acid name |
|---|---|
| OTHER | Other ( (Amino acid not found in this list should be described in /note qualifier) |

[References]

- Feature Table Definition: 7.4.4 Modified and unusual Amino Acids

Last modified: 2018-02-09

# Attachment 66a

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U.S. Patent No. 9,943,096
The Wayback Machine - https://web.archive.org/web/20151126093040/http://www.hmicronpowder.com:80/products/product/mikro-pulverizer-ham...



# MIKRO PULVERIZER® HAMMER & SCREEN MILL



Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

The Mikro Pulverizer® Hammer & Screen Mill is a high speed mechanical impact mill designed for continuous size reduction of a wide range of materials down to D90 < 45 μm. This device has evolved into the preeminent industrial mill with thousands of worldwide installations.

**Design & Options:**

- Laboratory (1 HP) to production (200 HP) available
- Process 250 gram batches up to 15 tons/hour
- Economical milling to D90 < 45 μm
- Easy to operate and maintain
- Available in mild steel, stainless steel and with wear protection
- Pressure shock resistant (PSR) models available
- Various configurations available to produce a wide range of products and results
- Very durable & reliable designs for years of production
- Compact and easy to clean design
- Suitable for Chemical, Pharmaceutical, Food, Mineral and Cosmetic applications
- Cryogenic grinding possible

VIDEO CONTACT US

Description **Materials** **Resources**

**The Mikro Pulverizer®** consists of a high speed rotor assembly fitted with hammers. The grinding chamber is fitted with a cover containing a multiple deflector liner and a retaining screen at the point of mill discharge.

A screw mechanism is often used to introduce feed material into the grinding chamber. The grinding process is affected by three basic variables: the type of hammers, the rotor speed, and the size and shape of the screen opening.

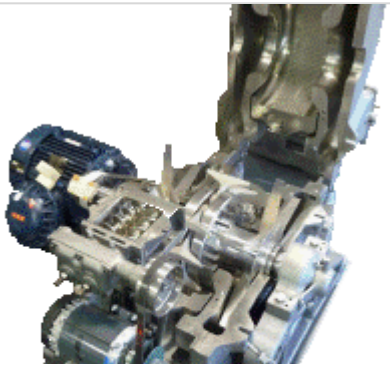
There are two types of hammers: the “stirrup,” recommended where a fine particle size is desired; and the “bar,” which generates a coarser grind with a minimum of fines. Both types are tipped at the wearing edge with various abrasion resistant alloys. Rotor speed affects the fineness of the grind as follows: low speeds result in a coarse grind and high speeds produce a fine grind. Size and shape of the retaining screen openings also affect the product. In general, a finer screen opening will result in a finer grind. The retaining screen does not function as a sifting screen, except in coarse granulations.

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**Controlled Particle Size**
Optimum particle size reduction can greatly affect chemical reaction speeds, solubility, weight, color, volume, appearance and strength of ground products. Mikro-Pulverizers® provide accuracy in particle size control because the grinding action is entirely mechanical. Once a mill is set to deliver a certain product, it will continue to produce exactly the same result without adjustment.

**Grind, Blend and Disperse**
Mikro Pulverizers® grind, blend and disperse in a single operation. Intensive action thoroughly mixes dissimilar ingredients into a finished product. Heat sensitive materials are handled by adjustment of mill speed, hammers, screen and discharge air relief, as well as with pneumatic conveying. Conditioned air may be bled into a grinding chamber, or the feed may be pre-conditioned or chilled. The MikroPulverizers® comes in many model sizes from small pilot scale to massive production models.

## Related Products


Mikro Atomizer® Air Classifying Mill


Mikro Bantam® Hammer & Screen Mill

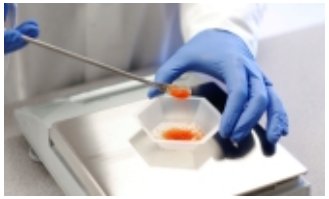

Mikro® UMP Universal Milling System

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U.S. Patent No. 9,943,096



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U.S. Patent No. 9,943,096
The Wayback Machine - https://web.archive.org/web/20021005023146/http://www.exploratorium.edu:80/cooking/meat/INT-what-meat-color.html



# What Gives Meat Its Color?



Beef



Pork



Fish

There are basically two types of meat: dark and white.

**Red, or dark meat** is made up of muscles with fibers that are called *slow-twitch.* These muscles are used for extended periods of activity, such as standing or walking, and need a consistent energy source. The protein *myoglobin* stores oxygen in muscle cells, which use oxygen to extract the energy needed for constant activity. Myoglobin is a richly pigmented protein. The more myoglobin there is in the cells, the redder, or darker, the meat.

When dark meat is cooked, myoglobin's color changes depending on what the meat's interior temperature is. Rare beef is cooked to 140° F, and myoglobin's red color remains unchanged. Above 140° F, myoglobin loses its ability to bind oxygen, and the iron atom at the center of its molecular structure loses an electron. This process forms a tan-colored compound called *hemichrome,* which gives medium-done meat its color. When the interior of the meat reaches 170° F, hemichrome levels rise, and the myoglobin becomes *metmyoglobin,* which gives well-done meat its brown-gray shade.

**White meat** is made up of muscles with fibers that are called *fast-twitch.* Fast-twitch muscles are used for quick bursts of activity, such as fleeing from danger. These muscles get energy from glycogen, which is also stored in the muscles.

White meat has a translucent "glassy" quality when it is raw. When it's cooked, the proteins denature and recombine, or *coagulate,* and the meat becomes opaque and whitish.

Cows and pigs are both sources of dark meat, though pig is often called "the other white meat." Pigs' muscles do contain myoglobin, but the concentration is not as heavy as it is in beef. Chickens have a mixture of both dark and white meat, and fish is mainly white meat.

Different types of meat require different cooking times. The best way to determine if meat is done is to use a meat thermometer to check the internal temperature. Beef can be cooked to a variety of temperatures: rare (140° F), medium (160° F), and well-done (170° F). Pork, chicken, and fish

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have less leeway. It's recommended that pork be cooked to 170° F, chicken to 180° F, and fish to 165° F.

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# Attachment 68a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

ScienceDirect

Food Chemistry
Volume 345, 30 May 2021, 128761

# Reinvestigation of 2-acetylthiazole formation pathways in the Maillard reaction

Xiao-Yuan Wang [a], Yun-Jiao Ma [a], Yu Guo [a], Xiao-Lin Luo [a], Ming Du [a], Liang Dong [a], Pei Yu [b] ✉, Xian-Bing Xu [a] ✉

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Received 17 August 2020, Revised 15 October 2020, Accepted 27 November 2020, Available online 2 December 2020, Version of Record 10 December 2020.

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## Highlights

- The C-4 and C-5 of 2-acetylthiazole were also derived from the carbons of glucose.
- The potential of glyoxal in the formation of 2-acetylthiazole for the first time.
- The formation pathways of 2-acetylthiazole were elucidated.

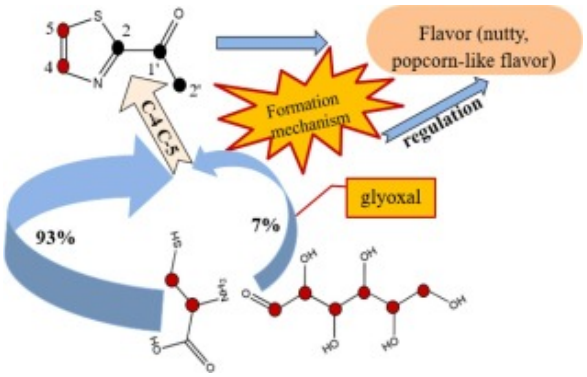
## Abstract

2-Acetylthiazole possesses a nutty, cereal-like and popcorn-like aroma and a low odor threshold, and this compound has been identified in some processed foods, while the formation pathway of 2-acetylthiazole has not been clearly elucidated. Here, a model reaction of D-glucose and L-cysteine was constructed to

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investigate the formation pathway of 2-acetylthiazole. L-Cysteine, D-glucose and the corresponding intermediates, namely, dicarbonyl compounds (DCs), were involved in the formation of 2-acetylthiazole and detected by high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS), high-performance ion chromatography (HPIC) and HPLC, respectively. The carbon module labeling (CAMOLA) technique revealed that the C-4 and C-5 of 2-acetylthiazole were derived from the carbons of glucose. The potential of glyoxal, which is degraded by glucose, to form 2-acetylthiazole was revealed for the first time. A novel route to form 2-acetylthiazole by the reaction of glyoxal and methylglyoxal produced by D-glucose with $H_2S$ and $NH_3$ produced by L-cysteine was proposed.

## Graphical abstract




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## Keywords

2-Acetylthiazole; L-cysteine; D-glucose; Glyoxal; Formation pathway

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Reduced asynchronism between regenerative cysteine and fragments of deoxyosones promoting formation of sulfur-containing compounds through extra-added xylose and elevated temperature during thermal processing of 2-threityl-thiazolidine-4-carboxylic acid

2023, Food Chemistry

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Investigation on key odorants in braised chicken thigh meat and their changes during storage

2022, Journal of Food Composition and Analysis

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Maillard reaction chemistry in formation of critical intermediates and flavour compounds and their antioxidant properties

2022, Food Chemistry

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Aroma compounds identified in cooked meat: A review

2022, Food Research International

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Development of meat flavors in peony seed-derived Maillard reaction products with the addition of chicken fat prepared under different conditions

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Degradation of 2-Threityl-Thiazolidine-4-Carboxylic Acid and Corresponding Browning Accelerated by Trapping Reaction between Extra-Added Xylose and Released Cysteine during Maillard Reaction

2021, Journal of Agricultural and Food Chemistry

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538    ##$aMode of access: World Wide Web.
588    ##$aDescription based on: Vol. 52, issue 1 (1995); title from
contents screen (ScienceDirect, viewed Oct. 13, 2003).
588    ##$aLatest issue consulted: Vol. 83, issue 4 (Dec. 2003),
viewed Oct. 13, 2003.
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655    #4$aElectronic journals.
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776    1#$x0308-8146
906    ##$aJOURNAL
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# Attachment 69a

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# Volatile Character-Impact Sulfur Compounds and their Sensory Properties

Apr 6th, 2016 | By Mans H. Boelens, Leo J. van Gemert

Volatile organic sulfur compounds are important constituents for the flavor of food, beverages and natural isolates. Character-impact sulfur compounds have been found in foods (bread, potato and prepared meat), beverages (beer and coffee), vegetables (aIlium species, truffle and radish), fruits (grapefruit, pineapple, grape, tomato, melon, passion fruit and black currant) and natural isolates like essential oils, absolutes and oleoresins (rose, hop, galbanum, absinth, cassia, patchouli, pepper, helichrysum and geranium). These character-impact sulfur compounds are, often in a certain low concentration, characteristic for the sensory properties of the material. Although these facts are generally accepted in the flavor and fragrance industry, still some questions can be put forward, namely:

l What are the identities of these compounds?

l What are their sensory properties? That is, what is their odor and flavor character and in which concentration can they be perceived?

In this article we will try to answer these questions as much as possible mainly based on a survey of the available literature.

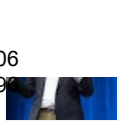
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**Customizing small flavor molecules by oligomeric glycosylation**

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## More in Ingredients

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SWEET APPLICATIONS

### Silky Smooth MicroCreamery Debuts All-Natural Sugar-Free Keto-friendly Sweetener Blend

The blend is said to be the world's only flavor-enhancing sweetener of its kind.

Nov 2nd, 2022

INGREDIENTS

### Organoleptic Characteristics of Flavor Materials

This month’s column features valeric acid, savory oil, orange terpenes and more.

Nov 1st, 2022

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MilliporeSigma

INGREDIENTS

## Flavor Bites: Ethyl 3-hydroxybutyrate

The ingredient applies mostly to fruit flavors and often forms a significant component of the perception of freshness.

Oct 31st, 2022

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### 3 Ways to Transform Citrus Critics into Connoisseurs

Citrus is one of the most prevalent flavors in the world, yet a large percentage of consumers remain unconvinced. Discover three strategies to help transform these citrus critics into connoisseurs.

Nov 2nd, 2022

NEWS

### See The Latest Buzzing Headlines in Flavor and Fragrance

See which companies made headlines this week in F&F.

Oct 21st, 2022

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VIDEO

### [video] Discover IFF NEO™ for Global Beverage Market Formulations

*P&F+* connects with IFF's RE-MASTER CITRUS™ innovation flavorist, Natalie Mordt-Sullivan, to discuss the usage and versatility of IFF NEO™.

Oct 20th, 2022

INGREDIENTS

### BioNootkatone, the Gold Standard for Natural Nootkatone

Woody, peely, and bursting with juicy nuance, BioNootkatone is an indispensable ingredient for natural citrus flavor creation. Developed through biotechnology, it is sustainable and independent of the citrus supply chain.

Oct 19th, 2022

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NEWS

### IFF Debuts Neo Citrus Portfolio

The IFF Neo collection of natural citrus flavors is developed for beverage applications, as well as in liquid and dry formulations.

Oct 17th, 2022

AUDIO

### [podcast] Two Sense: *Flavorcon* Speaker Cyndie Lipka Prepares to Take the Stage

Get a taste of Lipka's upcoming session with VCF Online and hear about what she's been up to lately!

Oct 17th, 2022

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FLAVOR

### *Perfumer & Flavoris+* October Issue Flavor Highlights

From industry insights to better-for-you treats, this month's issue features a variety of flavorful reads.

Oct 10th, 2022

FLAVORCON COVERAGE

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Find out what a selection of exhibitors plan on showcasing at the two-day event.

Oct 7th, 2022

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| 015 | __ | \|**a** 014143372 \|**2** dnb |
| 016 | 7_ | \|**a** 014143372 \|**2** DE-101 |
| 016 | 7_ | \|**a** 761059-2 \|**2** DE-600 |
| 016 | 7_ | \|**a** 9882897 \|**2** DNLM |
| 016 | 7_ | \|**a** SR0060110 \|**2** DNLM |
| 016 | 7_ | \|**a** 007522872 \|**2** Uk |
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| 035 | __ | \|**a** (OCoLC)ocm06751162 |
| 037 | __ | \|**b** Allured Publishing Corporation, 362 S. Schmale Rd., Carol Stream, IL 60188-2787 |
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| 082 | 0_ | \|**a** 668/.54/05 |
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| 222 | _0 | \|**a** Perfumer & flavorist |
| 245 | 00 | \|**a** Perfumer & flavorist. |
| 246 | 3_ | \|**a** Perfumer and flavorist |
| 246 | 13 | \|**a** P & F |
| 260 | __ | \|**a** Wheaton, IL : \|**b** Allured Pub. Corp., \|**c** ©1980- |
| 300 | __ | \|**a** volumes : \|**b** illustrations ; \|**c** 28 cm |
| 310 | __ | \|**a** Twelve times a year, \|**b** 2006- |
| 321 | __ | \|**a** Bimonthly, \|**b** 1980-2003 |
| 321 | __ | \|**a** Eight times a year, \|**b** 2004-2005 |
| 336 | __ | \|**a** text \|**b** txt \|**2** rdacontent |
| 337 | __ | \|**a** unmediated \|**b** n \|**2** rdamedia |
| 338 | __ | \|**a** volume \|**b** nc \|**2** rdacarrier |
| 362 | 0_ | \|**a** Vol. 5, no. 1 (Feb./Mar. 1980)- |
| 500 | __ | \|**a** Published: Carol Stream, IL, <1998-> |
| 588 | __ | \|**a** Latest issue consulted: Vol. 31, no. 4 (spring 2006). |
| 590 | __ | \|**a** SERBIB/SERLOC merged record |
| 650 | _0 | \|**a** Perfumes \|**v** Periodicals. |
| 650 | _0 | \|**a** Flavoring essences \|**v** Periodicals. |
| 650 | _0 | \|**a** Flavoring essences. |
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| 906 | __ | \|**a** 7 \|**b** cbc \|**c** serials \|**d** 2 \|**e** ncip \|**f** 19 \|**g** n-oclcserc |
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| 984 | __ | \|**a** srvf \|**d** 2001-08-30 |
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# Attachment 69c

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PRODUCT MARKETING (HTTPS://WEB.ARCHIVE.ORG/WEB/20220331013638/HTTPS://KLUE.COM/BLOG/CATEGORY/MARKETING)

# Beyond Meat vs. Impossible Foods: The very real battle between the biggest 'fake-meat' competitors



Adam McQueen

As is my usual routine, I watched an embarrassing amount of basketball over the weekend. You know the days where you sit for so long that all you have to show for your past eight hours of existence is a full body imprint on the couch.

I'd say I'm ashamed to admit this, but anyone who knows me won't be surprised at all.

More importantly, there are three big questions that have been bouncing around my brain following an ungodly amount of television consumption.

- How can anyone think playoff basketball isn't the best?
- What species is LeBron, because he's definitely not human?
- Does *every* single restaurant now boast a plant-based meat alternative?

Nearly every single food-related commercial I sat through advertised their newest plant-based alternative. Starbucks. Burger King. McDonald's.

You name it, and they're likely spending serious advertising money to showcase their newest plant-based recipes.

It got me thinking: how big has this market gotten, and who's cashing in?

As it turns out, there's some very *real* competition happening in the 'fake-meat' world.

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## Who sits atop the meatless food chain?

According to **Bloomberg, (https://web.archive.org/web/20220331013638/https://www.bloomberg.com/news/articles/2021-04-16/beyond-meat-bynd-impossible-foods-battle-over-future-of-fake-meat-industry)** the market for plant-based meat alternatives is expected to reach $450 billion by 2040. In the U.S. alone, plant-based meat sales **grew by 45%, (https://web.archive.org/web/20220331013638/https://www.fooddive.com/news/plant-based-food-worth-7b-in-2020-posting-27-growth/597865/)** for a total of $1.4 billion.

And leading the way for this plant-based revolution has been Beyond Meat. The company established themselves in 2009 and enjoyed a significant first mover advantage as the first to market with mainstream 'meatless meat' products.

Beyond's products are found in 42,000 U.S. restaurants, 80+ international markets, and account for 22% of the frozen/refrigerated retail meat alternatives. After going public in 2019, the company quickly blew up to **a $13 billion valuation.**

**(https://web.archive.org/web/20220331013638/https://www.forbes.com/sites/oliviergarret/2019/09/11/missed-out-on-beyond-meat-buy-these-2-ipos-this-week/?sh=5212d3a31b60)** They were considered disruptors in the market, trying to make a dent in the gargantuan (and seemingly unsustainable) meat industry.

Meat alternatives were nothing new. But Beyond's strategy was. Rather than confining themselves to the niche vegetarian audience, Beyond targeted the much larger market of meat-eaters.




Vox **wrote in a 2019 article, (https://web.archive.org/web/20220331013638/https://www.vox.com/2019/5/28/18626859/meatless-meat-explained-vegan-impossible-burger)** that Beyond's strategy was to "ensure that their product has the flavour, macronutrient balance, and cooking experience of meat."

If they could nail these key parts of their food and cater more towards meat-eaters, not only did it create a much larger total addressable market of consumers, but their product would already be differentiated within that market.

As it turned out, the feel-good ethical and health reasons for consuming meat alternatives actually helped their product stand out far better than having to compete against other vegetarian food options.

They even commissioned the **University of Michigan to research and compare the environmental impact of producing a Beyond Burger and a regular beef patty. (https://web.archive.org/web/20220331013638/http://css.umich.edu/publication/beyond-meats-beyond-burger-life-cycle-assessment-detailed-comparison-between-plant-based)** Talk about some data-backed marketing!



No alt text provided for this image

Beyond set out to lower the barrier to turn meat-eaters into consumers, and their distribution strategy followed suit. Their focus was to make plant-based alternatives mainstream.

“The promise there was, ‘we’re going to have plant-based protein’, we’re not going to sell it in the frozen veggie food aisle, we’re going to sell it in the meat aisle of the grocery store, we’re going to go to restaurants, we’re going to go to retail. We’ll expand our distribution and go overseas. There’s a constant flow of product innovation and a constant expansion of product distribution,” said Al Root, Sr. Writer at Barron’s on ‘**The Readback’ podcast. (https://web.archive.org/web/20220331013638/https://open.spotify.com/episode/3Z3LUxciFHyE5BH51kZiRz)**

Beyond’s partnership with dine-in restaurants was a strong brand play, and it also normalized their product to meat-eaters. While some consumers might be skeptical about cooking it themselves, there’s more comfort in trying it at a restaurant.

Although this strategy allowed Beyond to climb atop of the meatless food chain and make a dent in the larger meat industry, the early success of their approach has paved the way for serious competition to enter the fray.

## Impossible Foods are coming for the crown

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Just like my weekend viewing showcased the new generation of hoopers that are in line to take over the league from the elder statesmen, there are newer plant-based meat alternatives that are taking bites out of Beyond Meat's lead.

Their competitive advantage in terms of having a monopoly of power in the market has been dwindling, and Impossible Foods has emerged as their most serious competitor. There are two main reasons why Impossible has made inroads.

## The pandemic dip

Beyond's strategy to place their product within dine-in restaurants took a significant hit due to the pandemic.

Their revenue split from big restaurants to small operators **went from 30%-70% in 2019, to 42%-58% in mid 2020. (https://web.archive.org/web/20220331013638/https://www.bloomberg.com/news/articles/2021-04-16/beyond-meat-bynd-impossible-foods-battle-over-future-of-fake-meat-industry)** And this revenue change wasn't because of adding large chains, but due to the rapid decline in smaller businesses.

Meanwhile, the majority of Impossible Food's initial partnerships were with large chain restaurants that offered drive-thru and delivery options. These distributors were more resilient during the pandemic, allowing Impossible to scale quickly and reduce costs.

Beyond is now pivoting towards larger chain partnerships, most notably with McDonalds and Yum Brands!, but they're in the unfamiliar territory of playing catch-up.

## Pricing wars in the battle for market share

When a first mover like Beyond has a monopoly advantage, they can price its product without the competitive pressures from a rival.

It's a necessary evil for consumers **as the Rutgers Business Review explains (https://web.archive.org/web/20220331013638/https://rbr.business.rutgers.edu/article/sustaining-first-mover-advantage-fast-growing-meat-substitute-market)**:

"The first-mover spends a considerable amount of time and resources in creating and introducing its product in the market."

But, this high price point limits your consumer base. And while Beyond's strategic decision to compete against meat products has paid off, they were still a long way away from matching cheap meat prices.

Meanwhile, Impossible Food's rapid growth over the pandemic — hitting production records and achieving greater economies of scale — allowed them to drastically slash their prices by 20% in restaurants and grocery stores earlier this year in an attempt to better compete with meat. They made their product more buyable to the broader consumer base, and with an eye on taking advantage of Beyond's leader status.

"We were thinking about cost reductions and getting to the cost structure of commodity ground beef from the very beginning," said David Lee, chief financial officer of Impossible Foods, in **an interview with Vox. (https://web.archive.org/web/20220331013638/https://www.vox.com/future-perfect/2021/2/2/22260454/impossible-foods-burger-plant-based-meat)** "We knew that if we had the best product at the same cost, then consumers would vote with their stomachs."

## The more competition... the better?

While Impossible Foods has stolen market share from Beyond in the meat alternative space, ultimately the roadmap that Beyond has set out actually means that these competitors are working in lockstep.

Yes, they're competing against each other as the preeminent meat alternative, but both are angling to take market share from agricultural companies producing animal meats.

Considering that plant-based meats are only **an estimated 3% of packaged meat sales in the U.S., (https://web.archive.org/web/20220331013638/https://www.bloomberg.com/news/articles/2021-04-16/beyond-meat-bynd-impossible-foods-battle-over-future-of-fake-meat-industry)** the rise in meat alternative competition can lift all boats. Beyond's year-over-year sales growth continues to accelerate despite their market share shrinking.

And many other companies — even massive meat producers — are now **creating their own meatless product lines, (https://web.archive.org/web/20220331013638/https://www.forbes.com/sites/greatspeculations/2020/09/14/competition-will-eat-beyond-meat-alive/?sh=63fc73b02946)** allowing even more consumers to try plant-based options.

—

The lessons of Beyond’s approach are applicable across any business. They thought about their competitive set beyond just the narrow scope of the vegetarian meat market — they went after all meats. Being able to see the forest from the trees is how unicorn businesses are born.

And now Beyond has paved the way for competitors to flood the market, which isn’t bad for them either! As the established leader that still possesses the best brand awareness amongst customers, more products in the category will only help. As Crispin Read mentioned in his article, **‘Positioning Done Right’: (https://web.archive.org/web/20220331013638/https://www.productmarketinghive.com/positioning-done-right-are-you-marketing-your-competitor/)**

“A challenger in a competitive market is guilty until proven innocent. The leader is the obvious choice. If you fail to differentiate, buyers will assume that there is no difference, and buy from the leader.”

However, Beyond must continue innovating its product, distribution, and partnerships in order to hold off competitors like Impossible from taking not only a slice of the pie, but the whole damn thing.

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# Attachment 72a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



Original Article | Published: 06 November 2010

# Hydrocolloids as thickening and gelling agents in food: a critical review

Dipjyoti Saha & Suvendu Bhattacharya

*Journal of Food Science and Technology* **47**, 587–597 (2010)

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## Abstract

Hydrocolloids are widely used in many food formulations to improve quality attributes and shelf-life. The two main uses are as thickening and gelling agents. As thickening agents, they find uses in soups, gravies, salad dressings, sauces and toppings while as gelling agents, they are extensively used in products like jam, jelly, marmalade, restructured foods and low sugar/calorie gels. The role of specific hydrocolloids for thickening and for gel formation is reviewed pinpointing specific applications in food formulations and for product development.

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525 $aSome issues accompanied by supplementary materials or supporting information.

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Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

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| 362 | 1_ | $aPrint began with vol. 1, no. 1 (Apr. 1953). |
| 500 | | $aRefereed/Peer-reviewed |
| 525 | | $aSome issues accompanied by supplementary materials or supporting information. |
| 588 | | $aDescription based on print version record, (ACS Publications, viewed Aug. 29, 2006); title from contents page. |

588 $aLatest issue consulted: Volume 69, issue 43 (November 3, 2021), (ACS Publications, viewed Nov. 9, 2021).

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# Attachment 74b

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510 2 Chemical abstracts $x 0009-2258
525 Some issues <1978-Jan. 1995 accompanied by supplementary material on microfiche; Feb. 1995-<Feb. 1998, by supporting information on microfiche; current (1995- ) supporting information also available online.
530 Also issued on microfiche, microfilm, and online.
550 Volumes for 1953-<54 published by the American Chemical Society; <Jan./Feb. 1976- by the Books and Journals Division, American Chemical Society.
650 0 Agricultural chemistry $v Periodicals.
650 0 Food $x Analysis $v Periodicals.
650 0 Plants $x Nutrition $v Periodicals.
650 2 Chemistry, Agricultural. $0 (DNLM)D002622
650 2 Food-Processing Industry. $0 (DNLM)D005525
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856 41 $u http://pubs.acs.org/journals/jafcau/index.html

# Attachment 75a

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

## MARC Bibliographic Record

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Case No.: IPR2023-00206
U.S. Patent No. 9,943,096

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650    _0    $aChemistry, Organic$vPeriodicals.
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# Attachment 75b

**OCLC** 5458841 **No holdings in XXX - 284 other holdings**

Continuing Resources

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650 0 Agricultural chemistry $v Periodicals.
650 0 Chemistry, Organic $v Periodicals.
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# Attachment 75c

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



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Washington, DC 20540

**Library of Congress Authorities**
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**Library of Congress Online Catalog**
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**Questions, comments, error reports:** Contact Us

# Attachment 76a

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# Attachment 76b

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



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# Attachment 76c

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



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**Library of Congress Authorities**
*URL:* http://authorities.loc.gov/
**Library of Congress Online Catalog**
*URL:* https://catalog.loc.gov/

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# Attachment 76d

**OCLC** 1782923 **No holdings in XXX - 780 other holdings**

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060 00 Film S02695
070 0 442.8 $b J8224
072 0 X300
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090 $b
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260 3 $3 <Feb. 2002-; $a Amsterdam $b Elsevier
300 volumes $b illustrations $c 26 cm
310 Twenty-four no. a year, $b 2013-
321 6 times a year, $b 1959-1960
321 12 numbers a year, $b 1961-
321 Three times a month, $b <Jan. 6, 1976-

321 2 times a month, $b <20 Jan. 1985-Dec. 1993
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336 text $b txt $2 rdacontent
337 unmediated $b n $2 rdamedia
338 volume $b nc $2 rdacarrier
362 0 Volume 1, number 1 (April 1959)-
510 2 Chemical abstracts $x 0009-2258
588 0 Volume 1, number 1 (April 1959); title from cover
588 Latest issue consulted: V. 425, issue 20 (Oct. 23, 2013).
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650 0 Biochemistry $v Periodicals.
650 0 Molecular biology $v Periodicals.
650 0 Bacteriology.
650 0 Biochemistry.
650 0 Biology.
650 12 Bacteriology $0 (DNLM)D001432
650 22 Biochemistry $0 (DNLM)D001671
650 22 Biology $0 (DNLM)D001695
650 6 Biologie $0 (CaQQLa)201-0000137 $v Périodiques. $0 (CaQQLa)201-0378307
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650 7 42.13 molecular biology. $0 (NL-LeOCL)077603028 $2 bcl
650 7 Bacteriology. $2 fast $0 (OCoLC)fst00825257
650 7 Biochemistry. $2 fast $0 (OCoLC)fst00831961
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776 08 $i Online version: $t Journal of molecular biology (Online) $x 1089-8638 $w (DLC)sn 96047032 $w (OCoLC)34479722
850 DLC $a DNAL $a InU $a NCH $a PU

# Attachment 76e

# LIBRARY OF CONGRESS AUTHORITIES



**LC control no.:** sh 85010864

**LCCN Permalink:** https://lccn.loc.gov/sh85010864

**HEADING:** Bacteriology

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**001** 4663783

**005** 20120321074140.0

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**035** __ |**a** (DLC)10468

**040** __ |**a** DLC |**c** DLC |**d** DLC

**053** _0 |**a** QR

**150** __ |**a** Bacteriology

**360** __ |**i** subdivision |**a** Microbiology |**i** under individual animals and groups of animals, individual plants and groups of plants, individual diseases and types of diseases, individual organs and regions of the body, and individual materials and types of materials, e.g. |**a** Fishes--Microbiology; Corn--Microbiology; Tuberculosis--Microbiology; Heart--Microbiology; Metals--Microbiology

**550** __ |**w** g |**a** Microbiology

**680** __ |**i** Here are entered works on the science of studying bacteria. Works on bacteria are entered under |**a** Bacteria.

**681** __ |**i** Note under |**a** Bacteria

**906** __ |**t** 9351 |**u** te05 |**v** 0

**953** __ |**a** xx00 |**b** td14

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*URL:* https://catalog.loc.gov/

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# Attachment 76f

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



**LC control no.:** sh 85014171

**LCCN Permalink:** https://lccn.loc.gov/sh85014171

**HEADING:** Biochemistry

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**001** 4666952

**005** 20201020060008.0

**008** 860211i| anannbabn |a ana

**010** __ |**a** sh 85014171

**035** __ |**a** (DLC)sh 85014171

**035** __ |**a** (DLC)13637

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**053** _0 |**a** QD415 |**b** QD436 |**c** Chemistry

**053** _0 |**a** QH345 |**c** Biology

**053** _0 |**a** QP501 |**b** QP801 |**c** Physiology

**150** __ |**a** Biochemistry

**360** __ |**i** subdivision |**a** Composition |**i** under individual animals and groups of animals, e.g. |**a** Fishes--Composition; Cattle--Composition

**450** __ |**w** nne |**a** Biological chemistry

**450** __ |**a** Chemical composition of organisms

**450** __ |**a** Organisms |**x** Composition

**450** __ |**w** nne |**a** Physiological chemistry

**550** __ |**w** g |**a** Biology

**550** __ |**w** g |**a** Chemistry

**550** __ |**w** g |**a** Medical sciences

**670** __ |**a** MeSH browser, July 29, 2020 |**b** (Biochemistry. SN The study of the composition, chemical structures, and chemical reactions of living things. In MeSH Tree Structures under Biological Science Disciplines and under Chemistry)

**670** __ |**a** Web. 3.

**670** __ |**a** Hennepin.

**670** __ |**a** McGraw-Hill dict. of sci. and tech. terms, c2003 |**b** (biochemistry [CHEM] The study of chemical substances occurring in living organisms and the reactions and methods for identifying these substances)

**670** __ |**a** Tröjbom, M. Chemistry data from surface ecosystems in Forsmark and Laxemar-Simpevarp, 2010: |**b** p. 3 ("chemical composition of the regolith and biota of the terrestrial, limnic, and marine ecosystems")

**670** __ |**a** Biology dictionary, via WWW, July 29, 2020 |**b** (Chemical Biology: a scientific discipline that combines chemistry and biology by using chemistry and chemical techniques to study biological systems. The main difference between chemical biology and biochemistry is that chemical biology involves adding novel chemical compounds to a biological system, while biochemistry is the study of chemical reactions that naturally happen inside organisms. Examples of chemical biology research include controlling cell division and other cell activities, using small molecules as targets for treatment, and manipulating stem cells. Differences between chemical biology and biochemistry: Chemical biology adds chemical compounds to biological systems in order to see what effect these chemicals have on cells and tissues. Chemical biologists often synthesize and add new compounds to cells. The goal of chemical biology research is to develop techniques that can eventually be applied to cells in a living organism, such as treatment options for cancer and other diseases. Biochemistry, on the other hand, is all about the chemical processes that already occur naturally in the cell. Instead of adding chemical compounds to cells to see the effects, biochemistry researchers study the chemical reactions that occur in organisms and the molecular makeup of these compounds. Biochemists also tend to study larger molecules like proteins and nucleic acids, while chemical biologists study smaller molecules) |**u** https://biologydictionary.net/chemical-biology/

**680** __ |**i** Here are entered works on the study of naturally occurring chemical reactions in organisms. Works on the use of chemistry and chemical techniques to study biological systems are entered under |**a** Chemical biology.

**681** __ |**i** Note under |**a** Chemical biology

**910** __ |**a** Proposal saved by tc03 on 07/31/2020 at 10:12:44

**952** __ |**a** Made for existing bibliographic records

**952** __ |**a** LC pattern: Biophysics

**906** __ |**t** 1125 |**v** 0

**906** __ |**t** 2009 |**v** 0

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# Attachment 76g

Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



**LC control no.:** sh 85014203
**LCCN Permalink:** https://lccn.loc.gov/sh85014203
**HEADING:** Biology

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**005** 20211124060011.0
**008** 860211i| anannbabn |b ana |
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**360** __ |**i** headings beginning with the word |**a** Biological
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**550** __ |**a** Life (Biology)
**550** __ |**a** Natural history
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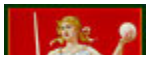
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Case No.: IPR2023-00206
U.S. Patent No. 9,943,096



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# Attachment 77a

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246    10    $aFood science and nutrition
246    14    $aCRC critical reviews in food science and nutrition
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338          $avolume$bnc$2rdacarrier
362    0_    $aVol. 12, issue 3 ([June] 1980)-
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# Attachment 77b