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Ultra-processed foods and adverse health effects: many mechanistic hypotheses - including glycation - but what is the scientific evidence?

Maastricht, 17/09/2024

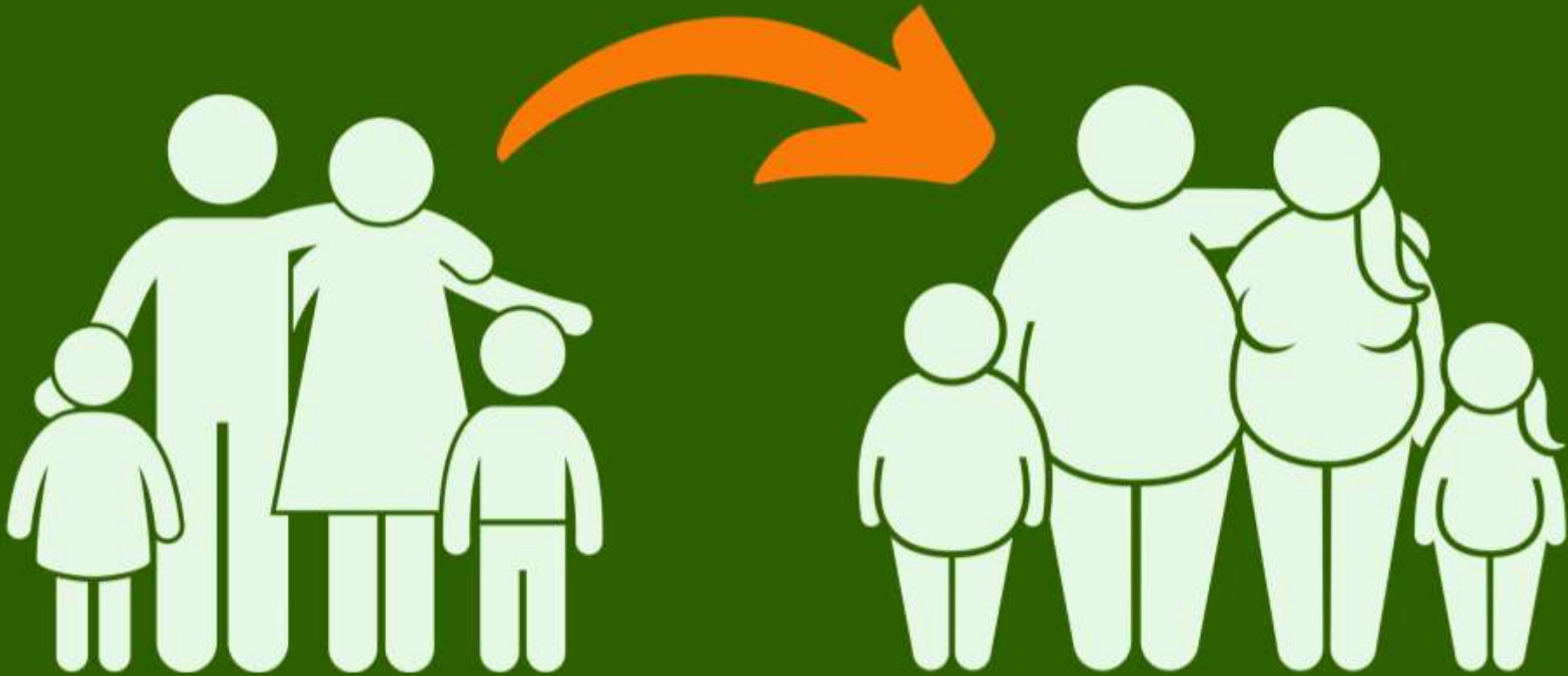
Frédéric J TESSIER

Professor, Analytical Chemistry, Nutrition, Maillard reaction & glycation

INSERM U1167, School of medicine, Lille University, France







For more than four decades a **nutritional transition** has been observed across the world, indicating the evolution of eating habits from ancestral diets to less balanced ones, richer in calories.



This trend shows **evidence** of a link to the rise in obesity, and of metabolic diseases.


**The recent introduction of a new food classification, NOVA*,
is reopening the debate
on the impact of our changing diet on health.**

NOVA Food classification

Unprocessed or minimally processed foods	Processed culinary ingredients	Processed foods	Ultra-processed foods
<p>Foods which did not undergo processing or underwent minimal processing technics, such as fractioning, grinding, pasteurization and others.</p> 	<p>These are obtained from minimally processed foods and used to season, cook and create culinary dishes.</p> 	<p>These are unprocessed or minimally processed foods or culinary dishes which have been added processed culinary ingredients. They are necessarily industrialized.</p> 	<p>These are food products derived from foods or parts of foods, being added cosmetic food additives not used in culinary.</p> 
<p>Legumes, vegetables, fruits, starchy roots and tubers, grains, nuts, beef, eggs, chicken, milk</p>	<p>Salt, sugar, vegetable oils, butter and other fats.</p>	<p>Bottled vegetables or meat in salt solution, fruits in syrup or candied, bread, cheeses, purees or pastes.</p>	<p>Breast milk substitutes, infant formulas, cookies, ice cream, shakes, ready-to-eat meals, soft drinks and other sugary drinks, hamburgers, nuggets.</p>

A food classification system developed by Carlos Monteiro et al. at the University of Sao Paulo, Brazil (Monteiro et al., 2010).

Could ultra-processed foods be harmful for us?

 Twenty years ago, no-one had heard of the term ultra-processed foods but about half the things we now eat in the UK are made that way.



Cheap
Attractive
Convenient



The long read

Eat me!

It's cheap, attractive and convenient, and we eat it every day - it's difficult not to. But is 'ultra-processed' food making us ill? By **Bee Wilson**

Nearly three decades ago, when I was an overweight teenager, I sometimes ate six pieces of sliced white toast in a row, each one slathered in butter or jam. I remember the spongy texture of the bread as I took it from its plastic bag. No matter how much of this supermarket toast I ate, I hardly felt satiated. It was like eating without really eating. Other days, I would buy a box of Crunchy Nut Cornflakes or a tube of Pimpeps: sour onion and onion flavour stackable snack chips, which were an exciting novelty at the time, having only arrived in the UK in 1995. Although the carton was big enough to feed a crowd, I could demolish most of it by myself in a sitting. Each chip, with its salty and powdery sour cream coating, sent me back for another one. I loved the way the chips curved like roof tiles - would dissolve slightly on my tongue.

After one of these binges - because that is what they were - I would speak to myself with self-loathing. "What is wrong with you?" I would say to the *me* - stained face in the mirror. I blamed myself for my lack of self-control. But now I feel I was asking myself the wrong question. It shouldn't have been "What is wrong with you?" but "What is wrong with this food?"

Back in the 90s, there was no word to cover all the items I used to binge on. Some - crisps or chocolate or fast-food burgers - could be classified as junk food, but others, such as bread and cereal, were more like household

By singling out “ultra-processed” foods, NOVA, in my opinion, is just repeating what has been scientifically observed for decades.

Ultra-processed foods

These are food products derived from foods or parts of foods, being added cosmetic food additives not used in culinary.



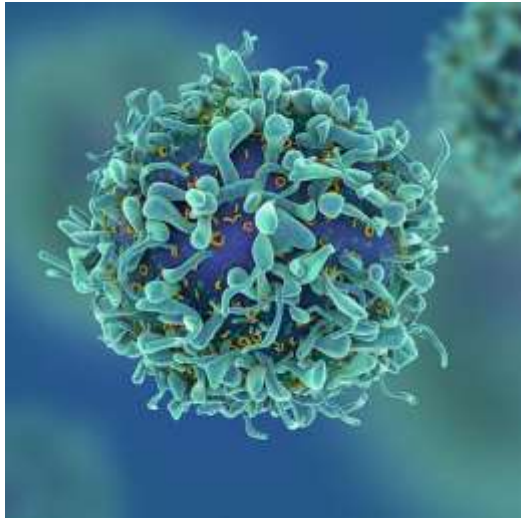
Breast milk substitutes, infant formulas, cookies, ice cream, shakes, ready-to-eat meals, soft drinks and other sugary drinks, hamburgers, nuggets.

Junk food
Empty calories
Energy dense food
“Bad” nutrition profile
Low fiber foods
High glycemic index
Obesogenic foods

**Well known
determinants
of chronic
disease risk**



Other scientists consider the **low nutritional value** of these foods is **not the only reason** for the health issues but rather, that “elements” arising from the industrial transformation of the food are the cause.



Increased risk of **cancer**, in particular, is attributed to the consumption of UPFs in some studies

Cohort Study

risk factor

disease



Ultra-processed food consumption, cancer risk and cancer mortality: a large-scale prospective analysis within the UK Biobank

Kiara Chang,^{a,*} Marc J. Gunter,^b Fernanda Rauber,^{c,d} Renata B. Levy,^{c,d} Inge Huybrechts,^b Nathalie Kliemann,^b Christopher Millett,^{a,e} and Eszter P. Vamos^a

This UK-based cohort study recruited participants (40–69 years) who completed 24-h dietary recalls between 2009 and 2012 (n = **197 426**, 55% women) and were followed up until Jan 31, 2021

Our findings show that higher consumption of ultra-processed foods is associated with a greater risk of overall cancer and specifically **ovarian** and **brain cancer**, ...

These associations persisted after adjustment for a range of socio-demographic, smoking status, physical activity, and **key dietary factors**.

Food processing and cancer risk in Europe: results from the prospective EPIC cohort study

Nathalie Kliemann, Fernanda Rauber, Renata Bertazzi Levy, Vivian Viallon, Eszter P Vamos, Reynalda Cordova, Heinz Freisling, Corinne Casagrande, Genevieve Nicolas, Dagfinn Aune, Konstantinos K Tsilidis, Alicia Heath, Matthias B Schulze, Franziska Jannasch, Bernard Srour, Rudolf Kaaks, Miguel Rodriguez-Barranco, Giovanna Tagliabue, Antonio Agudo, Salvatore Panico, Eva Ardanaz, María-Dolores Chirlaque, Paolo Vineis, Rosario Tumino, Aurora Perez-Cornago, Julie Louise Munk Andersen, Anne Tjønneland, Guri Skeie, Elisabete Weiderpass, Carlos Augusto Monteiro, Marc J Gunter, Christopher Millett, Inge Huybrechts

EPIC cohort study recruited participants between 1991 and 2001, from 23 centres in ten European countries. **450 111** were included in this analysis (71% participants were female individuals)

This study suggests that the **replacement** of processed and ultra-processed foods and drinks **with an equal amount of minimally processed foods** might reduce the risk of various cancer types.

Most of the associations (UPFs-Cancer) remained significant when models were additionally adjusted for BMI....**dietary intake**, and quality.

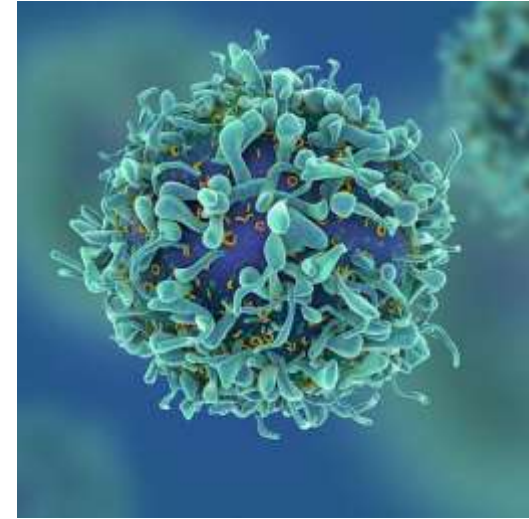


**Positive association
Correlation**



**Increase risk
of cancer**

Causal relationship?



**NO scientific evidence,
NO mechanistic explanation,
JUST some hypothesis**

What are the hypothesis?



UK biobank study

Besides their poorer nutritional composition, UPFs may additionally increase cancer risk through neo-formed contaminants during industrial processing, use of some controversial food additives, and certain materials of packaging implicated in exhibiting carcinogenic and/or endocrine disrupting properties.



EPIC cohort study

Intake of ultra-processed foods might increase cancer risk through obesogenic properties and reduced nutritional value, as well as through exposure to food additives and neoformed processing contaminants (heterocyclic amines, polycyclic aromatic hydrocarbons, acrylamide)

**The presence of
neoformed contaminants (NFCs)
in Ultra-processed foods
is often suggested as a potential cause.**

What is a neo-formed compound (NFC) ?

Neo-formed compounds (NFCs) are commonly found in all kinds of foods due to the complex reaction between components **during processing**.

Acrylamide, benzo(a)pyrene and **heterocyclic amines** are the main types of NFCs in foods enriched with **carbohydrate, fats** and **proteins**, respectively.



They have exhibited **diverse toxicity**, such as neurotoxicity, genotoxicity, potentially carcinogenic and reproductive toxicity.

1912

Reaction studied, a little over a hundred years ago, by **Louis Camille Maillard**. Action des acides aminés sur les sucres: formation des mélanoidines par voie méthodique. 1912, C.R. Academy Sciences 154, 66–68.

Amino acids

+

Simple
carbohydrates

=



**The Maillard reaction
(glycation)**

Acrylamide

Furane

dAGEs

**Heterocyclic Amines
(HCAs)**



**Benzo-a-pyrene
(other PAHs)**

Health effect (risk) of dietary acrylamide

International Agency for Research on Cancer



World Health
Organization

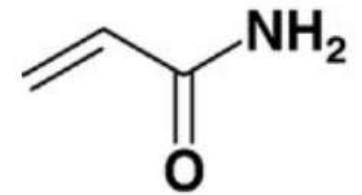
Acrylamide is Classified “**2A**”
Probably carcinogen to
humans (1994)

A multi-organ carcinogen (rodents) :
tumors in lungs, uterus, skin, brain...



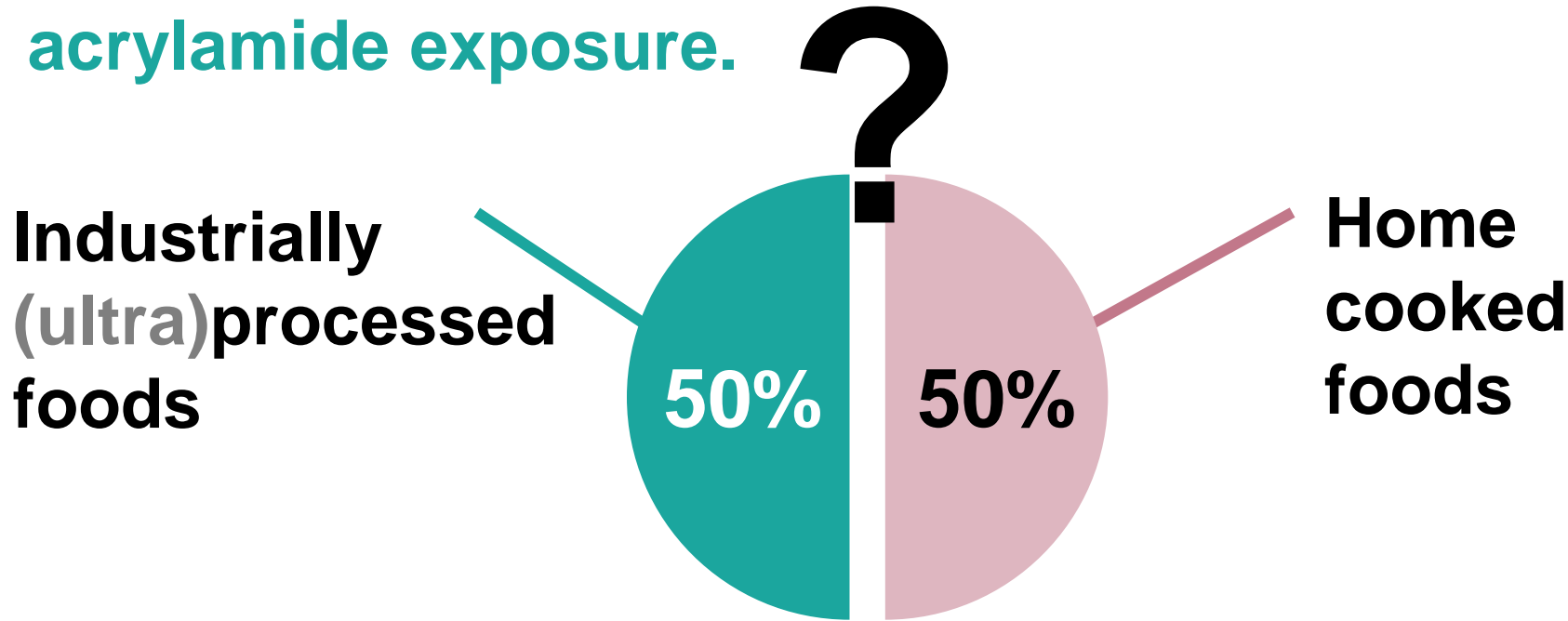
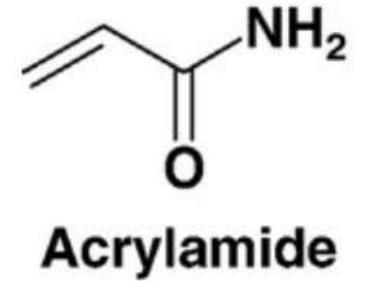
Currently, studies on **human subjects** have provided **limited and inconsistent evidence of increased risk of developing cancer.**

However, studies on **laboratory animals** have shown that exposure to acrylamide through the diet increased the likelihood of developing gene mutations and tumours in various organs.



Acrylamide

Very little information is available on acrylamide concentrations in home-cooked foods and on the overall contribution of home-cooked foods to acrylamide exposure.

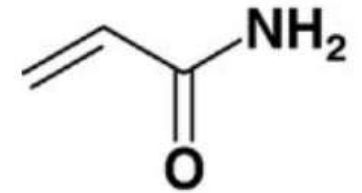


Acrylamide mainly formed in :
Roasted,
Fried,
Baked foods

And not typically found in :
Microwaved,
Steamed,
Boiled foods

Dietary intake of acrylamide and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

M. Obón-Santacana¹, N. Slimani², L. Lujan-Barroso¹, N. Travier¹, G. Hallmans³, H. Freisling², P. Ferrari⁴, M. C. Boutron-Ruault^{5,6,7}, A. Racine^{5,6,7}, F. Clavel^{5,6,7}, C. Saieva⁸, V. Pala⁹, R. Tumino¹⁰, A. Mattiello¹¹, P. Vineis^{12,13}, M. Argüelles¹⁴, E. Ardanaz^{15,16}, P. Amiano^{16,17}, C. Navarro^{16,18,19}, M. J. Sánchez^{16,20}, E. Molina Montes^{16,20}, T. Key²¹, K.-T. Khaw²², N. Wareham²³, P. H. Peeters^{24,25}, A. Trichopoulou^{26,27}, C. Bamia²⁶, D. Trichopoulos^{27,28,29}, H. Boeing³⁰, R. Kaaks³¹, V. Katzke³¹, W. Ye^{32,33}, M. Sund³⁴, U. Ericson³⁵, E. Wirfält³⁶, K. Overvad³⁷, A. Tjønneland³⁸, A. Olsen³⁸, G. Skeie³⁹, L. A. Åslí³⁹, E. Weiderpass^{39,40,41}, E. Riboli²⁵, H. B. Bueno-de-Mesquita^{42,43,†} & E. J. Duell^{1,†*}

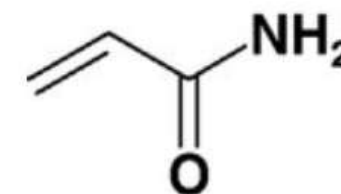


Acrylamide

Dietary intake of AA was not associated with an increased risk of **pancreatic cancer** in the EPIC cohort.

Dietary intake of acrylamide and esophageal cancer risk in the European Prospective Investigation into Cancer and Nutrition cohort

Leila Lujan-Barroso ¹, Carlos Alberto González, Nadia Slimani, Mireia Obón-Santacana, Pietro Ferrari, Heinz Freisling, Kim Overvad, Françoise Clavel-Chapelon, Marie-Christine Boutron-Ruault, Antoine Racine, Verena Katzke, Tilman Kühn, Anne Tjønneland, Anja Olsen, J Ramón Quirós,



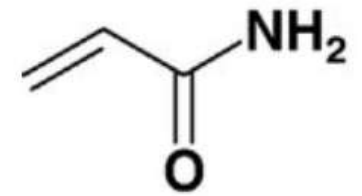
Acrylamide

In the EPIC cohort, an association between estimated **dietary acrylamide intake** and an increased risk of developing EC was observed in the middle quartiles **but not in the highest quartile**;

however, results from other larger cohorts or consortia, and results from biomarker studies, might add to the evidence provided by this analysis, **suggesting that acrylamide is not an important risk factor for Esophageal Cancer.**

Dietary intake of acrylamide and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition cohort

M Obón-Santacana¹, R Kaaks², N Slimani³, L Lujan-Barroso¹, H Freisling³, P Ferrari⁴, L Dossus^{5,6,7}, N Chabbert-Buffet^{5,6,7,8}, L Baglietto^{9,10}, R T Fortner², H Boeing¹¹, A Tjønneland¹², A Olsen¹², K Overvad¹³, V Menéndez¹⁴, E Molina-Montes¹⁵, N Larrañaga^{15,16}, M-D Chirlaque^{15,17}, E Ardanaz^{15,18}, K-T Khaw¹⁹, N Wareham²⁰, R C Travis²¹, Y Lu²², M A Merritt²², A Trichopoulou^{23,24}, V Benetou²⁵, D Trichopoulos^{23,24,26}, C Saieva²⁷, S Sieri²⁸, R Tumino²⁹, C Sacerdote^{30,31}, R Galasso³², H B Bueno-de-Mesquita^{33,34,35}, E Wirfält³⁶, U Ericson³⁷, A Idahl^{38,39}, N Ohlson⁴⁰, G Skeie⁴¹, I T Gram⁴¹, E Weiderpass^{41,42,43,44}, N C Onland-Moret⁴⁵, E Riboli²² and E J Duell^{*,1}



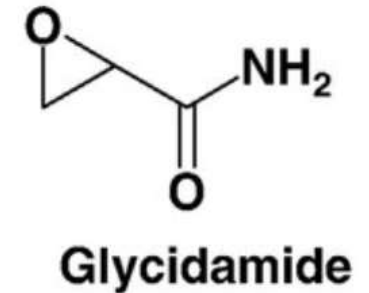
Acrylamide

Dietary intake of acrylamide was not associated with overall or type-I endometrial cancer risk;

however, positive associations with type I were observed in women who were both non-users of OCs and never smokers

Acrylamide and glycidamide hemoglobin adduct levels and endometrial cancer risk: A nested case-control study in nonsmoking postmenopausal women from the EPIC cohort

Mireia Obón-Santacana¹, Heinz Freisling², Petra H. Peeters^{3,4}, Leila Lujan-Barroso¹, Pietro Ferrari², Marie-Christine Boutron-Ruault^{5,6,7}, Sylvie Mesrine^{5,6,7}, Laura Baglietto^{8,9}, Renee Turzanski-Fortner¹⁰, Verena A. Katzke¹⁰, Heiner Boeing¹¹, J. Ramón Quirós¹², Elena Molina-Portillo^{13,14}, Nerea Larrañaga^{14,15}, María-Dolores Chirlaque^{14,16,17}, Aurelio Barricarte^{14,18,19}, Kay-Tee Khaw²⁰, Nick Wareham²¹, Ruth C. Travis²¹, Melissa A. Merritt⁴, Marc J. Gunter⁴, Antonia Trichopoulou²², Pagona Lagiou^{22,23}, Androniki Naska^{22,23}, Domenico Palli²⁴, Sabina Sieri²⁵, Rosario Tumino²⁶, Valentina Fiano²⁷, Rocco Galassom²⁸, H. B(as) Bueno-de-Mesquita^{4,29,30,31}, N. Charlotte Onland-Moret³², Annika Idahl^{33,34}, Eva Lundin³⁵, Elisabete Weiderpass^{36,37,38,39}, Hubert Vesper⁴⁰, Elio Riboli⁴ and Eric J. Duell¹



Hemoglobin **adducts** of acrylamide or glycidamide **were not associated with endometrial cancer** or type-I EC risk in 768 nonsmoking postmenopausal women from the EPIC cohort.

Dietary Advanced Glycation End-Products and Colorectal Cancer Risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study

Elom K. Aglago¹, Ana-Lucia Mayén¹, Viktoria Knaze², Heinz Freisling¹, Veronika Fedirko³, David J. Hughes⁴, Li Jiao⁵, Anne Kirstine Eriksen⁶, Anne Tjønneland⁶, Marie-Christine Boutron-Ruault^{7,8}, Joseph A. Rothwell^{7,8}, Gianluca Severi^{7,8,9}, Rudolf Kaaks¹⁰, Verena Katzke¹⁰, Matthias B. Schulze^{11,12}, Anna Birukov¹¹, Domenico Palli¹³, Sabina Sieri¹⁴, Maria Santucci de Magistris¹⁵, Rosario Tumino¹⁶, Fulvio Ricceri^{17,18}, Bas Bueno-de-Mesquita¹⁹, Jeroen W. G. Derksen²⁰, Guri Skeie²¹, Inger Torhild Gram²¹, Torkjel Sandanger²¹, J. Ramón Quirós²², Leila Luján-Barroso²³, Maria-Jose Sánchez^{24,25,26,27}, Pilar Amiano^{24,28}, María-Dolores Chirlaque^{24,29}, Aurelio Barricarte Gurrea^{24,30,31}, Ingegerd Johansson³², Jonas Manjer^{33,34}, Aurora Perez-Cornago³⁵, Elisabete Weiderpass³⁶, Marc J. Gunter¹, Alicia K. Heath³⁷, Casper G. Schalkwijk^{38,†} and Mazda Jenab^{1,*,†}

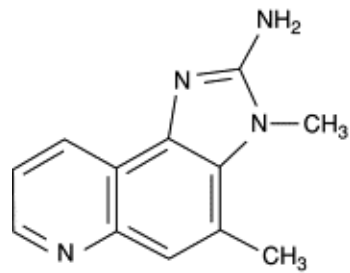
Contrary to the initial hypothesis, our findings suggest an inverse association between **dAGEs** and **colorectal cancer** risk.

Plasma concentrations of advanced glycation end-products and colorectal cancer risk in the EPIC study

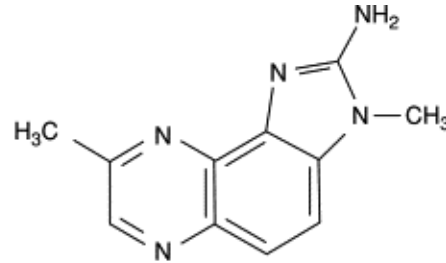
Elom K.Aglago^{1,*}, Casper G.Schalkwijk², Heinz Freisling^{1,*}, Veronika Fedirko^{3,*}, David J.Hughes⁴, Li Jiao⁵, Christina C.Dahm⁶, Anja Olsen^{6,7,*}, Anne Tjønneland^{7,8,*}, Verena Katzke^{9,*}, Theron Johnson^{9,*}, Matthias B.Schulze^{10,11}, Krasimira Aleksandrova^{11,12}, Giovanna Masala^{13,*}, Sabina Sieri^{14,*}, Vittorio Simeon¹⁵, Rosario Tumino¹⁶, Alessandra Macciotta¹⁷, Bas Bueno-de-Mesquita¹⁸, Guri Skeie¹⁹, Inger Torhild Gram^{19,*}, Torkjel Sandanger¹⁹, Paula Jakszyn^{20,21}, Maria-Jose Sánchez^{22,23,24,25}, Pilar Amiano^{25,26}, Sandra M.Colorado-Yohar^{25,27,28}, Aurelio Barricarte Gurrea^{25,29,30}, Aurora Perez-Cornago^{31,*}, Ana-Lucia Mayén¹, Elisabete Weiderpass^{32,*}, Marc J.Gunter¹, Alicia K.Heath³³ and Mazda Jenab^{1,*}

Although **individual plasma AGEs concentrations appear to be inversely associated with colorectal cancer risk**, a higher ratio of methylglyoxal-derived AGEs versus those derived from glyoxal (calculated by [CEL+MG-H1: CML] ratio) showed a strong positive risk association.

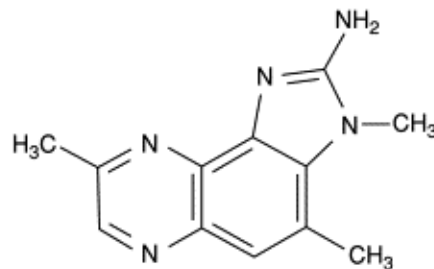
Heterocyclic amines (HCAs) are the carcinogenic and mutagenic chemicals formed from cooking muscle meats such as beef, pork, fowl, and fish. HCAs form when **amino acids & creatine** react at high cooking temperatures and are formed in greater quantities when meats are overcooked or blackened. Seventeen different HCAs resulting from the cooking of muscle meats have been identified, which **may pose human cancer risk**. (1)



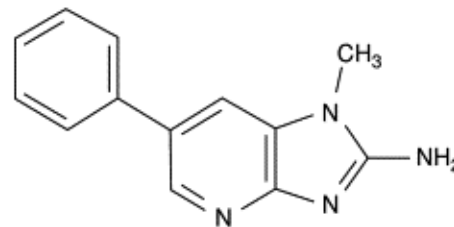
MeIQ



MeIQx



DiMeIQx



PhIP

**Stomach,
Colorectal,
Pancreatic,
Breast
cancers**

Structures of selected heterocyclic amines. MeIQ, 2-amino-3,4-dimethylimidazo[4,5-f]-quinoline; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine.

The role of heterocyclic aromatic amines in colorectal cancer: the evidence from epidemiologic studies

Loïc Le Marchand

Since Dr. Sugimura's discovery of heterocyclic aromatic amines (HAA) in broiled fish, many epidemiological studies have been conducted to investigate their **role in human cancers**, often focusing on **colorectal cancer**. The difficulty in measuring HAA exposure from meat and fish intake in these studies has resulted in inconsistent findings.

Dietary heterocyclic aromatic amine intake and cancer risk: epidemiological evidence from Japanese studies

Motoki Iwasaki^{1*}  and Shoichiro Tsugane²

We also found that the **limited and inconsistent findings among epidemiological studies are due to the difficulty in assessing exposure levels of HAAs**. In addition to further evidence from prospective cohort studies in Japanese based on dietary HAA intake estimated by FFQs, studies using other methods to assess HAA exposure, such as biomarkers, are highly anticipated.

A review and meta-analysis of prospective studies of red and processed meat, meat cooking methods, heme iron, heterocyclic amines and prostate cancer

Lauren C. Bylsma¹ and Dominik D. Alexander^{1,2*}

No significant summary relative risk estimates were observed for any of the meat cooking methods, HCA, or heme iron analyses

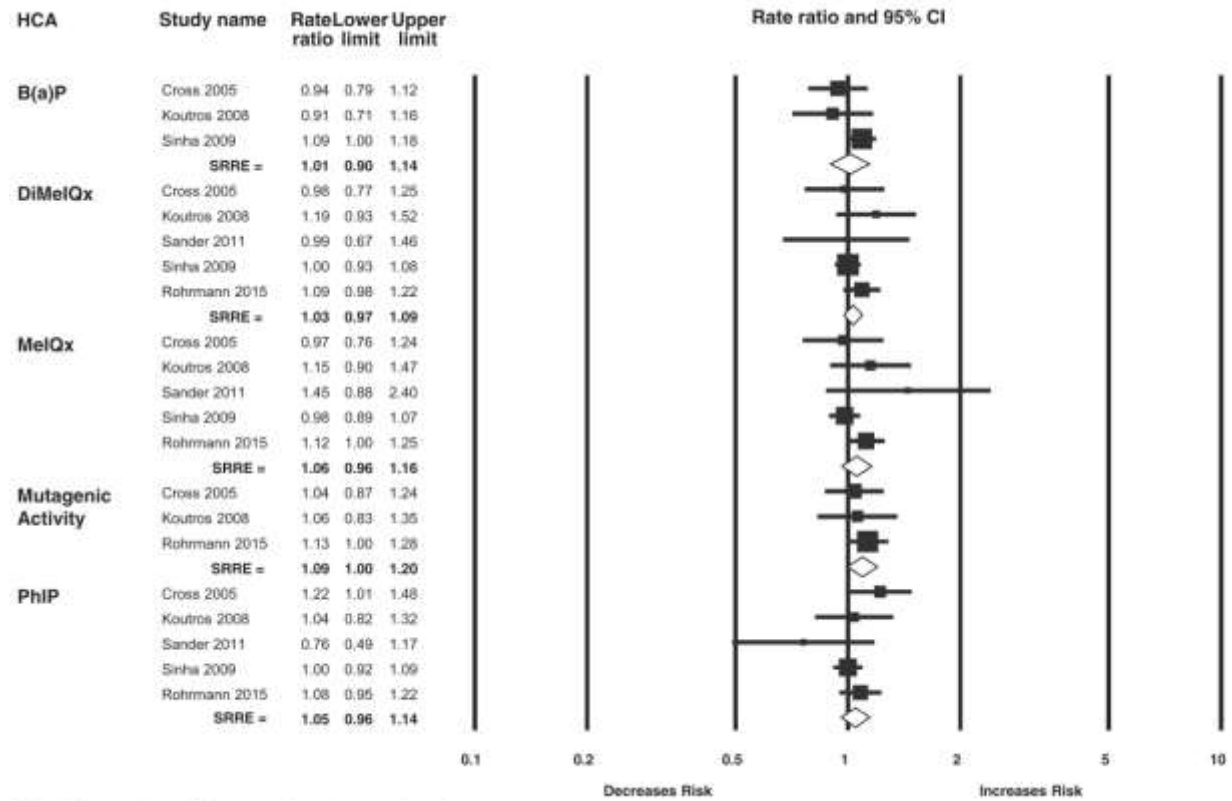


Fig. 4 Meta-analysis of heterocyclic amines and total prostate cancer

Actually, studies on digestion, and the biological effects of NFCs show a possible toxicity on cellular or animal models but there is still **no evidence in humans**. Further studies are needed to affirm the link with pathologies to NFCs.

*“The Nova classification ...rests on **poorly defined** food processes and the presence of food additives from a chemically heterogeneous group, easily leading to **misclassification**.”*

A Astrup & CA Monteiro, Am J Clin Nutr 2022;00:1–7.

Nova classification adds little to existing nutrient profiling systems

Maybe **Ultra-formulated** but Not Ultra-processed

Why we might never know the truth about ultra-processed foods

28 July 2024

Share <



Philippa Roxby
Health reporter



Philippa Roxby
Health reporter for the BBC, 28 July 2024

Workshop organized as a satellite event of the COST Action 927 Meeting
“Thermally Processed Foods: Possible Health Implications”

Mol. Nutr. Food Res. 2007, 51, 1069–1070

17 years ago

Editorial

M. Pischetsrieder



“Although (or because) excellent work on this topic has been published in the last couple of years, there is still a highly controversial debate on the health implications of dietary AGEs.”

Acknowledgement

Michael Howsam

Chantal Fradin

Matheus Thomaz Nogueira

Hieu Nguyen

Eric Boulanger

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The RID-AGE Unit from the Lille University

