Comment Submissions - Proposed Adoption of Exposures to Listed Chemicals in Coffee Posing No Significant Risk

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Consultants in Food/Nutritional/Chemical Toxicology & Safety
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August 30, 2018

Monet Vela
Office of Environmental Health Hazard Assessment ("OEHHA")
P. O. Box 4010
Sacramento, California 95812-4010

SUBJECT: Proposed Adoption of New Section Under Article 7 No Significant Risk Levels Section 25704 Exposures to Listed Chemicals in Coffee Posing No Significant Risk

Dear Ms. Vela:

These comments are submitted on my personal behalf as a food toxicologist who has not only been deeply involved with Proposition 65 since the law first passed, but also as a food industry scientist and independent consultant who has dedicated almost four decades of effort to understanding coffee and health science, including coffee and cancer. My brief bio is attached as Appendix A. I began my study of heat-induced carcinogens in foods with my Ph.D. and post-doctoral research at the University of California, Davis in the mid-1970's focused on chemicals formed during the Maillard Browning Reaction (MBR). The MBR's most visible global product is coffee, the subject of your June 15, 2018 notice and proposed regulation.

In 1981 I joined General Foods Corporation headquarters, where I first started working on coffee/health issues, and I continue to date with my scientific and regulatory involvement with coffee/health. In the interim, as you know, acrylamide was discovered (in April 2002) to occur in a broad array of heated foods and beverages, and acrylamide has since remained a very large issue under Proposition 65 in prominent legal/regulatory proceedings over French fries, potato chips, cereals and coffee. In the interests of transparency, I have been involved in extensive independent consulting activities on acrylamide for various clients across the globe since 2002, including food companies, food trade associations and their law firms on both Proposition 65 and non-Proposition 65 challenges. For your information, I have included in Appendix B a scientific literature review on acrylamide that I co-published with colleagues in 2012 (Lineback et al., 2012).

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With regard to the subject proposed adoption of a No Significant Risk Level (NSRL) for exposures to listed chemicals in coffee posing no significant risk, I am very gratified to be able to support your proposal wholeheartedly without any reservations. In fact, I would like to highlight here three statements taken from your June 15, 2018 Press Release that accompanied the proposed regulation and which provide my personal "conceptual framework" for fully supporting the scientific validity of these statements:

> "The proposed regulation states that drinking coffee does not pose a significant cancer risk, despite the presence of chemicals created during the roasting and brewing process that are listed under Proposition 65 as known carcinogens."
>
> "The proposed regulation is based on extensive scientific evidence that drinking coffee has not been shown to increase the risk of cancer and may reduce the risk of some types of cancer."
>
> "Coffee is a complex mixture of numerous chemicals that includes both known carcinogens – such as acrylamide, formed during the roasting of coffee beans and brewing coffee – and chemicals that protect against cancer, including antioxidants."

The "conceptual framework" I would like to add to your statements above is that of the "Coffee-Cancer Paradox"©, a concept I coined many years ago to describe and summarize these facts about coffee's relationship to human cancer. I have addressed this concept in numerous international conferences as noted here:

- My first public use of this framework or concept occurred during my oral presentation at an American Chemical Society three-day symposium on *"The Chemistry and Toxicology of Acrylamide"* held in Boston in August 2007 (the symposium agenda is attached as Appendix C and my PowerPoint presentation entitled "Risk-Benefit Assessment of Foods Containing Heat-induced Carcinogens" is attached as Appendix D).

- Then I gave two invited Keynote Presentations on this topic at successive conferences of the Association for Science and Information on Coffee (ASIC): (1) in October 2010 at the 23rd ASIC Conference in Bali, Indonesia (my PowerPoint is attached as Appendix E), and (2) in November 2012 at the 24th ASIC Conference in San Jose, Costa Rica (my manuscript in the ASIC Proceedings was published jointly with Dr. Astrid Nehlig and is attached as Appendix F; Dr. Nehlig is the current ASIC President).

- More recently I again addressed this topic at the Second International Congress on Cocoa, Coffee and Tea (CoCoTea) in Naples, Italy in October 2013 (attached as Appendix G is my invited presentation entitled "Heat-processed Carcinogens: What Can We Learn from the Coffee-Cancer Paradox"©).

- I have also addressed the "Coffee-Cancer Paradox"© in more recent national and international venues, and as time has progressed, the evidence from additional epidemiologic studies of populations across the globe has continued to expand and strengthen, that in spite of the trace presence of numerous animal carcinogens in roasted/brewed coffee, coffee drinking not only does <u>not</u> increase human cancer risk but actually <u>reduces</u> the risk in numerous organs.

The most succinct summary I can provide from my decades of study on coffee and caner and other health endpoints is captured in the following statements about the "Coffee-Cancer Paradox"©:

- Global health and regulatory authorities, including the International Agency for Research on Cancer, now agree that coffee drinking is NOT causing any increased risk of human cancer.
- In fact, human studies show significant risk reductions for numerous cancers in spite of the presence of trace levels of many animal carcinogens in roasted coffee.
- How can this be?
    - Naturally occurring antioxidants in coffee (the chlorogenic acids)
    - Heat-formed antioxidants (the brown melanoidin polymers in coffee that make up coffee's color)
    - Chemicals in coffee that have been shown to induce detoxification enzymes such as glutathione-S-transferase.
- The Paradox is the result of doing a "Benefit-Risk" evaluation using the "Holistic Approach," i.e., examining the health effects of the overall beverage, not just individual trace-level contaminants produced during coffee roasting.
- So, we are left with this Paradox: Coffee contains trace levels of many animal carcinogens, including acrylamide, but coffee drinking actually reduces some tumor risks without raising others.

As you can see from the three statements I highlighted above from your Press Release (and more fully developed in your *Initial Statement of Reasons* and your proposed regulation), the "conceptual framework" described in my "Coffee-Cancer Paradox"© fully captures and describes the facts and scientific basis underpinning your proposed regulation on coffee. As your staff reviews the public comments on this proposed regulation, I would be happy to provide any additional information to support your successful finalization of this important public health decision.

Sincerely,

James R. Coughlin, Ph.D. CFS

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Lineback DR, Coughlin JR, and Stadler RH. 2012. "Acrylamide in foods: A review of the science and future considerations." Annu. Rev. Food Sci. Technol. 3:15-35. [Appendix B]

Coughlin JR. 2013. "Heat-processed carcinogens: What can we learn from the Coffee - Cancer Paradox"© *Second International Congress on Cocoa, Coffee and Tea (CoCoTea),* Naples, Italy, October. [Appendix G]

APPENDIX A

JAMES R. COUGHLIN, Ph.D. CFS

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Academic Background:

- B.S. in Chemistry, Siena College, Loudonville, New York.
- M.S. in Food Science and Technology, University of California, Davis.
- Ph.D. in Agricultural and Environmental Chemistry, University of California, Davis.
- Postdoctoral Trainee in Environmental Toxicology, University of California, Davis.

Industrial/Professional Experience:

Dr. Coughlin has 40 years of experience in food/nutrition science and regulatory affairs; food, chemical and environmental toxicology and safety; chemical risk assessment; diet and cancer evaluations, especially on coffee and meats; benefit-risk evaluation of foods and food ingredients; GRAS food additive safety evaluations; safety and benefits of functional foods; California Proposition 65; health effects of caffeine, dietary nitrite/nitrate, Maillard carcinogens such as acrylamide and furan; safety of imported food ingredients and biotechnology-derived foods; food and environmental chemical analyses; naturally occurring food toxicants; antioxidants in foods and supplements; and scientific risk communication. He provides strategic scientific, toxicologic, nutritional, communications and regulatory counsel to many food, functional food, dietary supplement, chemical and consumer products companies and their trade associations, law firms and public relations firms.

- Before undertaking his current role as an independent consultant in 1991, Dr. Coughlin spent two years at Armour Foods on meat safety and then ten years at General Foods Corp. and Kraft General Foods Inc. managing external toxicology, safety and regulatory affairs, including several years as Director of International Scientific Relations. Health and regulatory issues surrounding coffee/caffeine, nitrite/processed meats, food additives and contaminants, pesticide residues and environmental toxicants in drinking water and beverages were among his areas of expertise.

- In the early 1990's, he served as President of the Association for Science and Information on Coffee (ASIC), the Paris-based scientific society dedicated to improving worldwide research on coffee growing, processing, biotechnology, quality, health and safety. He is a frequently invited speaker at ASIC's international conferences and has been serving for over a decade as a Member of the ASIC Board and Scientific Committee.

- He has been deeply involved in the assessment and management of California Proposition 65 requirements since the law's passage in 1986. He served for many years on the Editorial Advisory Board of *Prop 65 News* and the *Prop. 65 Clearinghouse* Advisory Board. Acrylamide and other heat-induced carcinogens in foods, as well as toxic metals like lead and arsenic, have been among his key issues under Prop 65.

- He is a Professional Member, Fellow and Certified Food Scientist of the Institute of Food Technologists (IFT), has been elected three times as Chair of the Toxicology & Safety Evaluation Division and helped to establish the International Division. He served for six years on the IFT Expert Panel assisting FDA in assessing food bioterrorism defense, recently served on two IFT Expert Panels assisting FDA with FSMA implementation and continues his long service as IFT's Codex Alimentarius Commission Subject Expert on food contaminants. He has been serving as an IFT Food Science Communicator and is a frequent symposium organizer and invited speaker.

- Dr. Coughlin served as Vice President of the International Society for Trace Element Research in Humans (ISTERH) and organized numerous ISTERH symposia. He guided a decade-long scientific research program trying to establish the human essentiality of boron as a nutrient and has also developed extensive expertise on the risk assessment of essential trace elements as well as toxic trace elements (lead, cadmium, mercury, arsenic).

Honors and Awards:

2013	Certified Food Scientist (CFS), Institute of Food Technologists.
2009	Elected Fellow, Institute of Food Technologists.
2003	U.S. FDA/CFSAN Director's Special Citation, IFT Bioterrorism Threat Assessment Group.
2000	American Meat Institute, Industry Advancement Award for Sodium Nitrite Safety Defense.
1991	Medal of Honor, Association for Science and Information on Coffee.

APPENDIX B

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Acrylamide in Foods: A Review of the Science and Future Considerations

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Abstract

Acrylamide occurs in foods commonly consumed in diets worldwide. It is formed from the reaction of reducing sugars (e.g., glucose or fructose) with the amino acid asparagine via the Maillard reaction, which occurs during heat processing of foods, primarily those derived from plant origin, such as potato and cereal products, above 120°C (248°F). The majority of epidemiological studies concerning potential relationships between acrylamide consumption and different types of cancer have indicated no increased risk, except with a few types that warrant further study. Efforts to reduce the formation of acrylamide in food products have resulted in some successes, but there is no common approach that works for all foods. Reduction in some foods is probably not possible. The results from a major toxicological study (aqueous intake of acrylamide by rats and mice) are in the process of being released. The status of current knowledge in these areas is reviewed.

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INTRODUCTION

The occurrence of acrylamide in foods was first reported by scientists from the Swedish National Food Authority and the University of Stockholm in April 2002 (Tareke et al. 2002). The researchers, initially investigating exposure of tunnel workers after accidental spillage of grouting agent, were seeking an explanation for why individuals not previously exposed to acrylamide (controls) had measurable levels of acrylamide-hemoglobin adduct in their blood. This led to the discovery that acrylamide was readily formed when potatoes (carbohydrate rich) were heated at temperatures above 120°C (248°F) (Törnqvist 2005). When foods obtained from stores in Stockholm were analyzed, acrylamide was found in many carbohydrate-rich food products. Acrylamide contents were much lower in meat (protein-rich) products.

Acrylamide is an industrial chemical produced in large quantities. Its primary use is in the production of polyacrylamide. It also finds use in grouting agents, i.e., as a concrete binder. Polyacrylamide also is used as a flocculant in water treatment, as a conditioner in soil treatment, in the manufacture of paper, in ore processing, and in gel electrophoresis (scientific research).

The chemical and toxicological properties of acrylamide have been the subject of numerous studies. Using high-dose animal studies, primarily rodents, it has been found to be a carcinogen and genotoxin. It is a neurotoxin in humans, primarily peripheral neuropathy. Primarily on the basis of the animal studies, the International Agency for Research on Cancer (IARC) has classified acrylamide as Group 2A—"probably carcinogenic to humans" (IARC 1994).

The Swedish report was rapidly verified in several countries and attracted worldwide attention and concern because of potential adverse human health effects. As a result, the United Nations' Food and Agricultural Organization (FAO) and World Health Organization (WHO) rapidly convened an Expert Consultation on "Health Implications of Acrylamide in Food" in June 2002. Numerous gaps in knowledge were identified and recommendations included the need for additional research in the areas where knowledge gaps existed (FAO/WHO 2002). This led to an unprecedented extensive worldwide collaborative effort that today continues.

It was not anticipated that these efforts would take so long. However, the lack of toxicological data pertaining to human exposure to the low amounts of acrylamide present in most food products has contributed to much of the delay. This review concentrates on major advances in our knowledge of this important issue and future considerations of importance.

ANALYSIS IN FOODS

With the widespread industrial use of acrylamide, methods were developed for its analysis prior to it being reported in foods. However, these were not sufficiently sensitive for determination of the relatively small amounts [$\mu g\ kg^{-1}$ and parts per billion (ppb)] found in foods. Since the beginning of the acrylamide in food issue in 2002, a plethora of different analytical methods have been published, and several review articles on the subject emphasize that the most commonly applied techniques are gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–mass spectrometry (LC-MS) with use of an isotope-labeled internal standard (Wenzl et al. 2003, Castle & Eriksson 2005, Castle 2006). In fact, both methods have been validated through interlaboratory studies and been found to give comparable results (Castle & Eriksson 2005, Owen et al. 2005, Klaffke et al. 2005).

LC-MS methods are considered simpler and less time consuming, but the main drawbacks are potential matrix interferences and ion suppression, particularly for foods such as cocoa and coffee (Delatour et al. 2004, Andrzejewski et al. 2004). Therefore, emphasis is usually placed on the extraction and clean-up stages of the method that provide adequately clean sample extracts,

particularly important when single quadrupole MS instruments are employed. For LC-MS based methods, different solid phase extraction (SPE) cartridges have been applied as an effective clean-up step to eliminate interfering compounds, the effort required being dependent on the sensitivity of the equipment. Apolar (C8 or C18), strong anion exchanger (SAX) or strong cation exchanger (SCX) cartridges can be used alone or consecutively coupled (Riediker & Stadler 2003, Roach et al. 2003, Andrzejewski et al. 2004). Acrylamide in aqueous solution is only partially retained on apolar phases or on mixed apolar-polar phases, and both require optimization of the clean-up and solvent elution steps. The use of mix-mode cartridges combining the aforementioned characteristics may be the most effective approach in terms of providing a clean extract, e.g., isolute multimode or oasis multimode (Rosen & Hellenas 2002, Senyuva & Gökmen 2006). For the analysis of acrylamide in coffee, the use of SPE columns such as isolute multimode and isolute ENV+® have been reported and the method evaluated in a collaborative interlaboratory trial (Wenzl et al. 2009).

The majority of the proposed LC-MS methods make use of a triple quadrupole instrument (MS/MS), and most methods describe electrospray ionization (ESI), although a few have reported good experience with atmospheric pressure chemical ionization (APCI), e.g., for coffee and cocoa (Aguas et al. 2006), potato- and cereal-based products (Senyuva & Gökmen 2006), and for more general matrices (Senyuva & Gökmen 2005). The advantage of APCI over ESI is that it is considered as less prone to ion suppression. In MS/MS detection, the use of multiple reaction monitoring significantly enhances the selectivity of the method. Typical transitions are *m/z*: $72 \rightarrow 55$ (usually chosen as the quantifier), $72 \rightarrow 54$, $72 \rightarrow 44$, $72 \rightarrow 27$, and for the internal standard ($^{13}C_3$-acrylamide), $75 \rightarrow 58$ as quantifier and $75 \rightarrow 30$ as qualifier.

Because of the low volatility and polarity of acrylamide, most GC-MS methods are based on a derivatization by bromination, i.e., addition of bromine to the olefine moiety (Tareke et al. 2002, Pittet et al. 2004, Ahn et al. 2002). Bromination of the aqueous extract is usually done in a bromine-water solution with HBr and KBr, or the safer being a $KBr + KBrO_3$ mixture (Zhang et al. 2006). After derivatization, the excess bromine is neutralized by addition of a sodium thiosulfate solution, and the apolar derivative is extracted by liquid-liquid extraction into an organic solvent, e.g., ethylacetate. This organic extract may be subjected to further clean-up steps, for example, over a Florisil column that removes a significant part of coextractives (Pittet et al. 2004) or diatomaceous earth (Jezussek & Schieberle 2003).

However, the final derivative, 2,3-dibromopropionamide is rather unstable and may decompose in the GC injector to 2-bromopropenamide. The addition of triethylamine affords 2-bromopropenamide, which then represents the target analyte. The GC columns most commonly employed for the analysis of the bromo-derivative are mid-polar to polar columns, e.g., DB-17 and ZB-Wax, respectively (Ahn et al. 2002, Pittet et al. 2004).

This ensures a better volatility of acrylamide, concomitantly leading to higher molecular weight and hence more selective ions. The derivative can be analyzed in the positive chemical ionization (+CI) mode with methane (Rothweiler et al. 2004) or with ammonia as reaction gases, or in negative CI (Robarge et al. 2011). The use of +CI significantly increases the selectivity as less fragmentation takes place compared to electron impact (EI).

Direct analysis of acrylamide by GC-MS in the EI mode without derivatization may be problematic. A further issue is the risk of generating acrylamide in situ in the heated GC injector, particularly if acrylamide precursors are present in the final extract. This may be avoided by selecting the appropriate extraction solvent that does not coextract potential precursors, e.g., 1-propanol (Biedermann et al. 2002, Dunovska et al. 2006).

The use of high-resolution MS has also been reported but cannot be considered a routine tool in analytical testing operations (Dunovska et al. 2006).

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Non-MS based methods such as liquid chromatography with an untraviolet detector have found some application with potato products and instant noodles (Paleogolos & Kontominas 2005) in which sensitivity initially was not an issue because of higher contents of acrylamide in potato products. However, over the past years, acrylamide concentrations have steadily decreased, causing questions about the suitability of UV-based methods. There has been considerable interest in developing a rapid, sensitive, and accurate method for determining acrylamide in food products. However, very little success has been reported so far.

OCCURRENCE IN FOODS

Acrylamide is not present in native (raw) ingredients, such as raw potatoes. It is formed during heat processing (heat preparation) of carbohydrate-rich foods at elevated temperatures, normally considered as 120°C (248°F) or above, such as encountered during frying, broiling, baking, roasting, grilling, and toasting (Tareke et al. 2002). Food products derived from plant ingredients, such as potatoes and cereals, tend to contain the highest amounts of acrylamide. This is primarily due to the natural presence of the reactants (glucose/fructose and asparagine) involved in the formation of acrylamide. Meat products contain little or no acrylamide because of the lack of these necessary reactants.

Dietary exposure is a function of the acrylamide content of the food products and the amounts consumed. Thus, even though a food product is low in acrylamide content, it can still be a major contributor to dietary acrylamide exposure when consumed frequently or in large amounts, e.g., coffee. Sources of acrylamide in the diet include foods/food products produced in homes, in restaurants, commercially, and by catering services.

Acrylamide occurs in a wide variety of food products that are commonly consumed daily in diets worldwide. Exposure from dietary acrylamide is not limited to consumption of one or a few particular foods/food products; it is an overall food problem. In the United States, it has been estimated that foods containing acrylamide contribute 38% of daily calories, 36% of fiber, 33% of carbohydrates, and greater than 25% for a number of micronutrients (Petersen & Tran 2005).

Examples of several foods and food groups with their acrylamide contents (μg kg^{-1} and ppb) are shown in **Table 1**. These are illustrative of values from various reports and are adapted from Mills et al. (2009) and Petersen & Tran (2005).

A problem of concern that has been encountered and has complicated the reporting of acrylamide contents in foods/food products is the variation in values determined within a category or product (such as potato chips). These variations occur between different production runs from the same manufacturer, within the same batches, between different manufacturers, between different varieties and/or producers, and between the same product containing ingredients from different crop years. This variability also complicates determination of dietary exposure to acrylamide, an important factor in further consideration of potential adverse human health effects and in risk assessments.

Shortly after the announcement of the occurrence of acrylamide in foods, the necessity for monitoring and collecting data on the occurrence and extent of acrylamide in foods was recognized. This led to the establishment of acrylamide monitoring databases, particularly in Europe and the United States (Lineback et al. 2005). Large databases are maintained by the U.S. Food and Drug Administration (FDA), with analytical data for the period 2002–2006 (FDA 2006), and the European Commission (EC 2006). The European Food Safety Authority (EFSA) has had member states monitor the acrylamide contents of foods for a three-year period (2007–2009) and report the results on an annual basis; this has been extended for another three years through 2012 (EFSA 2011). This was done to determine whether mitigation efforts were having an effect on reducing

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Table 1 Summary of reported amounts of acrylamide in different products and product groups. Adapted from Mills et al. (2009) and Petersen & Tran (2005)

Product/product group	Acrylamide range ($\mu g\ kg^{-1}$)
Potatoes (raw)	<10–<50
Potato chips/crisps	117–4,215
French fries/chips	59–5,200
Bakery products and biscuits	18–3,324
Breads	<10–3,200
Bread (toast)	25–1,430
Breakfast cereals	<10–1,649
Other fruit and vegetable products	<10–70
Chocolate products	<2–826
Roasted coffee	45–935
Coffee substitute	80–5,399
Coffee extract/powder	87–1,188
Meats	<10–116
Dairy products	<10–100
Baby food and infant formula	<10–130

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the acrylamide content in a number of foods. An additional benefit is a better determination of the acrylamide content of foods for use in determining dietary exposure, particularly for use in risk assessments.

MECHANISM OF FORMATION

The main pathway leading to acrylamide in foods is the Maillard reaction (Stadler et al. 2002, Mottram et al. 2002, Zyzak et al. 2003). Stable isotope-labeled experiments have shown that the backbone of the acrylamide molecule originates from the amino acid asparagine (Stadler et al. 2002, Zyzak et al. 2003). Asparagine alone could in principle afford acrylamide by direct decarboxylation and deamination, but the reaction is inefficient with extremely low yields (Granvogl & Schieberle 2006). However, asparagine in the presence of reducing sugars (hydroxycarbonyl moiety) or reactive dicarbonyls furnishes acrylamide in the range of up to 1 mol% in model systems (Stadler et al. 2004).

Several research groups have investigated the mechanisms underlying the formation of acrylamide in foods, leading to a number of possible pathways and intermediates. Stadler and coworkers (2004) published a comprehensive study that investigates the intermediates procured in reactions of asparagine with either dicarbonyls or reducing sugars, employing smaller sugar fragments to determine relative yields. A salient intermediate in the reaction pathway proposed already in 2003 is 3-aminopropionamide (3-APA) (Zyzak et al. 2003), detected in several foods, such as potatoes (Granvogl et al. 2004), cocoa, and cereal products (Granvogl & Schieberle 2007), at concentrations comparable or slightly higher than acrylamide. Deamination of 3-APA provides a very good yield of acrylamide of up to 60 mol%, depending on the reaction conditions (Granvogl et al. 2004).

A closer look at the mechanistic details en route to acrylamide shows that the nature of the carbonyl reactants to a large degree determines the chemical intermediates and efficacy of the reaction. The first step in the sequence is the condensation of asparagine with a reactive carbonyl (reducing sugar or carbonyl originating from the Maillard reaction) and dehydration to

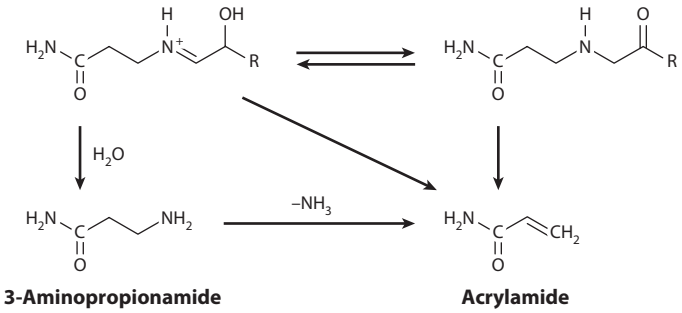

Figure 1

Salient precursors in the pathway leading to acrylamide (adapted from Stadler et al. 2004 and Perez-Locas & Yaylayan 2008).

the Schiff base. Decarboxylation through a 5-oxazolidinone intermediate, identified in models by Fourier transform infrared (FTIR) (Perez-Locas & Yaylayan 2008), yields the stable azomethine ylides. The neutral amine (decarboxylated Amadori compound) is formed by proton transfer, and subsequent beta elimination affords acrylamide (**Figure 1**) (Stadler et al. 2004). However, a hydroxyl function in the beta position to the nitrogen atom favors rearrangement to the Amadori intermediate and thus decomposition under thermal conditions by Hofmann-type elimination to generate acrylamide directly. Alternately, a carbonyl group in the beta position to the nitrogen in asparagine-dicarbonyl conjugates would not lead to the Amadori compound, but rather a keto-imine that upon hydrolysis releases 3-APA, typical of a Strecker-type reaction. Granvogl & Schieberle (2006) proposed an alternative pathway to 3-APA in the reaction sequence of asparagine with reducing sugars (e.g., glucose) that encompasses oxidation of the glycosylamine to an oxo-imine. 3-APA can then be formed after subsequent decarboxylation, keto-enol tautomerization, and hydrolysis, equating in total to a five-step reaction sequence from the Schiff base, and that can be considered of marginal importance versus direct C-N cleavage. Perez-Locas & Yaylayan (2008) demonstrated a more effective release of acrylamide from the glycosylamine when the latter is converted to an imminium ion (i.e., the ring-opened form), that favors Hofmann elimination. In fact, the glycosylamine was >25-fold and fourfold more efficient in generating acrylamide than 3-APA in wet and dry model systems, respectively.

The evidence of the studies published to date corroborate the importance of 3-APA more in reactions involving dicarbonyls driven by a Strecker-type degradation (Granvogl & Schieberle 2006). A food matrix that is subjected to thermal conditions can be considered a rich source of carbonyl reactants, and hence the pathways may proceed through several intermediates.

Several nonasparagine routes leading to acrylamide have been published over the past years. Acrylic acid is structurally a good candidate and can react with ammonia—released during thermal degradation of amino acids and proteins—to generate acrylamide (Yaylayan & Stadler 2005). The formation of acrylic acid could be via (*a*) the Maillard reaction, analogous to acrylamide but starting from aspartic acid (Stadler et al. 2003), or (*b*) acrolein, a well-known lipid degradation product. Acrolein could also react with asparagine, essentially providing a carbonyl moiety for the Maillard reaction (Yasuhara et al. 2003). Specific amino acid sequences identified in wheat gluten may also release acrylamide under certain pyrolytic conditions, albeit at relatively low yield versus the asparagine pathway (Claus et al. 2006). However, these nonasparagine pathways can be considered as of marginal importance because studies in potato- and cereal-based foods have demonstrated the importance of asparagine by effectively reducing acrylamide through the use of the substrate-selective enzyme asparaginase.

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MITIGATION/REDUCTION STRATEGIES

Significant efforts at a global scale have been undertaken to devise strategies that reduce acrylamide in the main foods of concern, encompassing potato products, cereal-based products (biscuits and bakery wares, breakfast cereals, bread, and crisp bread), and coffee. Over the past five to six years, the experiences of the food industry and scientists working on acrylamide mitigation in the pertinent product categories have been collated in a guidance document termed the Food Drink Europe [FDE, formerly termed the CIAA (Confederaton of the European Food and Drink Industries)], Toolbox (FDE 2011). Many of the approaches defined in the FDE Toolbox have recently been summarized in a Codex, *Code of Practice for the Reduction of Acrylamide in Foods* document (Codex 2009). The Codex paper covers the important food groups, and analogous to the FDE Toolbox, addresses the main avenues of mitigation at the different stages of manufacture, i.e., raw material, ingredient (recipe), and food processing (heating). This section summarizes the main reduction measures identified in these two key documents for potato and cereal-based products.

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Potato-Based Products

Potato products represent a very diverse category, including finished and semifinished products intended to be baked, roasted, or fried. Potato crisps and french fries encompass a major part of the potato-product basket, and in the case of the latter acrylamide is formed during final preparation. Sugar control in the tuber and final fry and bake temperature in the finished products are today considered the most effective mitigation measures to achieve an acrylamide reduction in potato products. In the case of sugar control, guidance for producers encompasses (*a*) selection of potato variety, (*b*) adherence to agronomy best practice, (*c*) paying attention to the maturity of tubers at harvest, (*d*) selection of lots based on sugars or color assessment, (*e*) controlled storage conditions for tubers from farm to factory (>6°C), and (*f*) reconditioning the potatoes when appropriate. However, environmental factors, such as climatic conditions, growing location, and fertilization regimes, are not to be neglected, as these may have an impact on the sugar concentration of the tubers (Haase 2006). In potato tubers, asparagine is the dominant free amino acid, contributing 33% to 59% of the total free amino acid pool. Tubers are high in asparagine concentration when exposed to high soil nitrogen, but the increase is positively correlated to all amino acids and not selectively asparagine (Lea et al. 2007). Other plant nutrients, such as potassium, may also play a role in asparagine storage (Gerendas et al. 2004), and these effects warrant further study to assess the degree of potential benefits (if any) in the final products.

Potato processing is executed in multiple steps. A well-established procedure in the french fries industry is blanching (Hendriksen et al. 2009). This step removes surface reactants, such as sugars, contributing to a reduction of acrylamide in the final product. Both the blanching water composition (amount of solutes) and temperature of the blanching water can impact the effectiveness of this measure (Mestdagh et al. 2008). Pyrophosphate is usually added to the blanching water to prevent discoloration, and as a secondary effect it lowers the pH (FDE 2011) (**Table 2**), thereby inhibiting Maillard-driven reactions.

Research, conducted mainly in potato model systems, provides additional leads at the processing stage to reduce acrylamide by employment of ingredients, such as citric acid salts, ascorbic acid, calcium salts, lactic and acetic acids, and antioxidants (Mestdagh et al. 2007). These can be added to the potato matrix in a number of ways, e.g., by direct addition to a dry mix or dough, or via a dipping bath or spraying solution. Citric acid can be effective in some potato dough products at an industrial scale but may have a negative impact on the organoleptic properties of the final product (**Table 2**). Reductions of acrylamide above 60% in both french fries and potato chips are

Table 2 Selected strategies to reduce acrylamide in potato- and cereal-based products[a]

Parameter	Key finding/description	Comments (Source)
Fabricated potato products (dough based)		
Recipe stage		
Calcium salts	Used in the dough (<0.3%)	Can be effective, variable reductions depending on the product (FDE 2011)
Citric or ascorbic acid	Leads to reductions but dependent on the product	Can lead to quality issues (FDE 2011)
Partial replacement of potato by other ingredients	Dilution approach to add ingredients that are lower in key reactants (e.g., rice, maize)	Impact on quality/organoleptic properties of the products (FDE 2011)
Asparaginase	Can work but depends on recipe and contact time (process dependent)	Care must be taken to avoid off flavors due to byproducts of the reaction (FDE 2011)
French fries		
Agtron color test: incoming potatoes	Agtron color evaluation as a predictor of acrylamide formation in raw material	(Medeiros Vinci et al. 2011, FDE 2011)
Blanching	Removes reactants at the surface and thereby controls reducing sugars. Pyrophosphate added to blanching water (parfried process) to prevent discoloration. As a secondary effect, it lowers the pH	Current practice in the industry (FDE 2011)
Surface area/volume ratio (SVR)	Cutting thicker strips	Reduces the SVR and hence lowers acrylamide formation (FDE 2011, Haase 2006)
Color after cook	Color is a good indicator of acrylamide in the final product. Appropriate cooking instructions are key (cook to golden yellow color) Cook at a maximum of 175°C for the prescribed time. Reduce cooking time when cooking small amounts	(FDE 2011)

[a]Includes main findings of recent research work (at lab or pilot scale).

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claimed by one supplier of sodium citrate, albeit with a slight acidic taste profile of some finished products (Citroma 2009).

Any acid treatment reduces the pH of the food matrix and thereby the formation of Maillard-driven compounds. Low and coworkers (2006) added binary mixes of glycine plus citric acid, the former leading to a higher total volatile yield by promoting the formation of certain allylpyrazines. The addition of glycine therefore partly compensated for the effect of citric acid. A further acrylamide mitigation measure frequently reported in the literature for potato products is the addition of antioxidants, such as bamboo leaf extracts (Zhang et al. 2007). The mechanism(s) governing the effect of antioxidants in reducing acrylamide is not fully clear, and research indicates that polyphenols may interact with active aldehydes (Totlani & Peterson 2006) or scavenge free-radical sugar fragments that are intermediates in the pathway to acrylamide (Hedegaard et al. 2008). However, most of these studies are based on bench-scale work and have not been thoroughly evaluated in a factory setting. Scaling up in some cases shows that results cannot be reproduced or the measure simply lacks application because of organoleptic deviations in the final products.

A promising route described relatively recently is the use of the enzyme asparaginase, which converts the precursor asparagine to aspartic acid and ammonia, albeit with some reactivity towards glutamine (Pedreschi et al. 2008, 2011). Commercial enzymes, mainly from the companies Novozymes and DSM became available around 2008, and most applications focused on potato

products and cereal-based foods. The enzyme is widely applied in many different foods as judged by the entries in the FDE Toolbox and communication on mitigation tools by the different food sectors (FDE 2011).

Pedreschi and coworkers (2011) have performed lab-scale studies on the effect of blanching of potato slices and asparaginase treatment on acrylamide formation, claiming up to 90% reduction when combining the two treatments. Blanching makes the tissues more permeable and consequently the enzyme is more accessible to the substrate. Hendriksen et al. (2009) have made similar observations. Blanching of potato pieces and subsequent treatment with asparaginase reduced acrylamide concentrations in french fries and potato chips by up to 60%. However, blanching is not a common practice in the potato chip industry, as it has a major negative impact on quality (texture and flavor) as well as the nutritional properties of the fried product (oil content and vitamin C) (Foot et al. 2007). Moreover, any studies conducted at laboratory scale without appropriate quality testing must be interpreted with caution. Results must be confirmed by production at factory scale and delivering a final product of comparable quality and shelf-life stability (Medeiros Vinci et al. 2011).

Trials on the application of asparaginase in chilled french fries have shown some promise (Medeiros Vinci et al. 2011). In this study, longer enzyme-substrate contact times resulted in a major reduction of asparagine in the enzyme-treated fries after four days of cold storage. As expected, acrylamide contents in these fries were significantly reduced by approximately 90% with no effects on the sensorial properties of the product upon final frying. However, introduction of this measure implies major line modification to ensure better temperature control (Medeiros Vinci et al. 2011).

An alternative to removing asparagine in potatoes is the consumption of reducing sugars, e.g., through fermentation. Lactic acid bacteria metabolize simple sugars rapidly, producing lactic acid, which lowers pH and reduces the Maillard reaction. This method has been applied to french fries prior to the prefrying step, with a reduction of up to 90%. However, to the knowledge of the authors, this has not yet been applied in commercial products, possibly because of the impact on quality/sensorial properties of the finished products (Blom et al. 2009).

Future opportunities include breeding of new varieties with lower reducing sugar content and/or less cold sweetening effect, i.e., sugar mobilization at low temperatures.

Cereals and Bakery Products

Several reviews have been published that summarize the main mitigation measures for cereals and bakery products (Stadler 2006, Konings et al. 2007, Claus et al. 2008, Sadd et al. 2008). In the past three to four years, some of the previously identified tools tested mainly at the laboratory or pilot scale have been successfully implemented at factory level, and these are briefly described in this section.

Asparagine, rather than reducing sugars, is the main determinant of acrylamide formation in products made from cereal grains, and its concentration in grains varies widely. Ranges of asparagine in wheat are typically from 69–443 mg kg^{-1}, with slightly higher amounts reported in rye (319–791 mg kg^{-1}) (Konings et al. 2007). Studies in model systems and different cereal products/bakery wares have shown that the amount of asparagine in the grains or dough is directly correlated to the amount of acrylamide in the final products (FDE 2011). Acrylamide formation is, however, not determined by the amount of sugars in wheat-based products (FDE 2011). Therefore, controlling or specifying asparagine in the grains may be a viable option to reduce acrylamide in the cereal category but is today not feasible because of the large varietal variability (both within and between varieties), significant impact of growing conditions, and environmental factors.

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Therefore, agronomic measures to mitigate acrylamide are limited, and so far only adequate sulfur fertilization for wheat and rye can be recommended to avoid surplus asparagine storage (Muttucumaru et al. 2006, FDE 2011).

The majority of the tools proposed to reduce acrylamide in this diverse category are focused on the processing stage, i.e., recipes/ingredients and thermal input. Common to many products is careful setting of oven-baking profiles, adapting the final moisture and color optimization (Konings et al. 2007, CAOBISCO 2008). In the case of recipes, significant reductions could be achieved in products, such as gingerbread, by replacing the chemical raising agent ammonium bicarbonate with the corresponding sodium salt (CAOBISCO 2008). Ammonium contributes to the breakdown of sugars, leading to the formation of reactive intermediates that enhance acrylamide formation via the Maillard pathway (Amrein et al. 2006). The replacement of fructose, which may furnish more reactive intermediates than other sugars, has also been proposed for biscuit/gingerbread products. A CAOBISCO survey on the use and efficacy of mitigation tools conducted in 2010 shows that sugar modification can achieve a reduction of 25% to 50% on average across all categories (CAOBISCO 2010). Addition of asparaginase affords even higher reductions in acrylamide, typically 50% to 90% have been reported by manufacturers across a few categories but mainly in semisweet biscuits and cereal dough–based snacks. Implementation of asparaginase in gingerbread allows for the reintroduction of ammonium salts and thereby has little to no impact on the sensorial and quality properties of the products. Asparaginase does not work well in all cases, as its efficacy is dependent on water content, dosage of the enzyme, contact time, and temperature. In whole-grain products, its application has had limited success so far because of limited accessibility of the enzyme to the substrate, i.e., difficulty of permeation into the cereal grain.

Fermentation is a further tool stipulated in the FDE Toolbox and warrants mention in the cereal category. Products made from fermented dough are in most cases characterized by lower amounts of acrylamide versus similar nonfermented products. Yeast rapidly assimilates asparagine and sugars, and by lowering the reactants in the dough less acrylamide is formed, as in the case of fermented crisp bread. Yeast fermentation of wheat bread gave >80% reduction in acrylamide but only 17% in sourdough-fermented rye bread (Granby et al. 2008), apparently because of the fact that sourdough reduces asparagine to a lesser extent than yeast fermentation, and rye flour typically has higher amounts of asparagine than wheat flour. Trials with cracker dough revealed an approximately threefold reduction of asparagine concentration after 100 minutes (Sadd et al. 2008). Applying longer yeast fermentation times or doubling the amount of low gassing yeast may afford a reduction in acrylamide, and studies on each of the measures have been performed on cracker doughs, certain biscuit doughs, and bread doughs (FDE 2011, Konings et al. 2007, Sadd et al. 2008).

Other minor ingredients, such as calcium, glycine, antioxidants (rosemary extract, tea polyphenols), phytic acid, and organic acids, have been tested either at laboratory, pilot, or factory scale (Sadd et al. 2008, Konings et al. 2007, Capuano et al. 2009). Calcium fortification of bread reduces acrylamide by approximately 30% and is a required practice in the United Kingdom. As most of the acrylamide is formed in the crust, the addition of calcium to the tin releasing agent that allows easier removal of the bread loaf is an effective measure (FDE 2011). Several reports on the use of glycine in different models and products have been published, e.g., in flat breads (Brathen et al. 2005), breakfast cereals (Konings et al. 2007), gingerbread, and short sweet biscuits (FDE 2011). Based on available reports, none of these applications have so far been applied at industrial scale, as relatively high amounts are added to the dough (e.g., 80–400 mmol kg^{-1}), and thereby have an unacceptable impact on the sensorial and quality aspects of the products (Konings et al. 2007).

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Several of the tools identified above may impact product quality. Hence, manufacturers must individually assess whether any sensorial deviations are acceptable to their products, as the final choice is made by the consumer. Moreover, any measures identified to work in an industrial line should not violate health targets, e.g., by increasing sodium or reducing the portion of whole grain in the products (FDE 2011).

HEALTH RISKS

Acrylamide's most pertinent health issue related to its widespread occurrence in foods is its potential to cause cancer in humans (JECFA 2011). It is classified by the IARC as "probably carcinogenic to humans (Group 2A)" (IARC 1994), by the U.S. National Toxicology Program's (NTP) *Report on Carcinogens* as "reasonably anticipated to be a human carcinogen" (NTP 2011a), and by the U.S. Environmental Protection Agency (EPA) as "likely to be carcinogenic to humans" (EPA 2011a), with each classification based on "sufficient evidence of carcinogenicity" from studies in experimental animals. Acrylamide is also well known to be a central nervous system (CNS) toxicant at high doses, although this toxic endpoint is thought not to occur in humans from dietary exposure (JECFA 2011). There are several recent detailed reviews on the health effects of acrylamide in humans and animals, including its carcinogenic effects (EPA 2011b, Hogervorst et al. 2010, JECFA 2011, Mucci & Adami 2009, Pelucchi et al. 2011, Shipp et al. 2006). Several key aspects of acrylamide's health risk issues are summarized below.

Absorption, Distribution, Metabolism, Excretion, Bioavailability, and Biomarkers

The absorption, distribution, metabolism, and excretion of acrylamide in experimental animals and humans have been well studied and reviewed (Doerge et al. 2005a,b, 2007; Shipp et al. 2006). Distribution studies of acrylamide have demonstrated that it is distributed rapidly to all tissues with no evidence for any accumulation, and it can also be found in the fetuses of pregnant animals and in breast milk (JECFA 2011). Acrylamide is metabolized primarily through the action of cytochrome P450 2E1 to a reactive epoxide metabolite, glycidamide, thought to be responsible for its genotoxic effects. Acrylamide also undergoes a detoxification reaction in rats, mice, and humans by direct conjugation with glutathione via enzymatic action of glutathione-*S*-transferase, and it is detected in the urine as cysteine metabolites; glycidamide can also be enzymatically conjugated with glutathione, yielding cysteine metabolites as urinary metabolites (Doerge et al. 2007, Doroshyenko et al. 2009, Kopp & Dekant 2009). Glycidamide also undergoes hydrolysis to give the nontoxic 2,3-dihydroxypropanamide (glyceramide) and subsequently, 2,3dihydroxypropionic acid (Sumner et al. 2003). The metabolic conversion of acrylamide to glycidamide occurs to a lesser extent in humans as compared with rodents at low exposure doses (Walker et al. 2007, Young et al. 2007, Sweeney et al. 2010).

Acrylamide and glycidamide also react with cysteine residues in blood hemoglobin (Hb) and other proteins, with the N-terminal valine of Hb, and with proteins and peptides, such as amino and sulfhydryl groups (Friedman 2003, Kopp & Dekant 2009, Shipp et al. 2006, Zamora et al. 2010). Acrylamide and glycidamide adducts at the N-terminal valine residue of Hb are not toxic but have been demonstrated to be useful biomarkers of occupational, smoking, and dietary exposure to acrylamide (JECFA 2011). However, the high reactivity of acrylamide toward nucleophilic food components, such as sulfhydryl, amino, and hydroxyl groups of peptides, proteins, and melanoidins in acrylamide-containing foods, might be responsible for such an apparently reduced bioavailability (Baum et al. 2008, Hoenicke & Gatermann 2005).

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Genetic, Reproductive, and Nervous System Toxicity

The genetic toxicity of acrylamide and glycidamide has been thoroughly reviewed in recent publications, demonstrating positive effects in bacterial cells and clastogenic and mutagenic effects in mammalian cells. In contrast, however, acrylamide without metabolic activation has not been found to be mutagenic or genotoxic at biologically relevant concentrations (Besaratinia & Pfeifer 2007, NTP 2011b, Shipp et al. 2006). Acrylamide reacts slowly with DNA via the Michael addition reaction, but glycidamide is considerably more reactive than acrylamide with DNA, to give a number of DNA adducts in vitro and in vivo (Doerge et al. 2005c, Gamboa da Costa et al. 2003), whereas the formation of DNA adducts from acrylamide in humans has not been reported.

The reproductive and developmental effects of acrylamide in animals and humans have recently been reviewed (NTP 2005, Shipp et al. 2006). There is no evidence for adverse reproductive or developmental effects from exposure to acrylamide in the general population. Although occupational exposure to acrylamide can be associated with neurotoxicity, it is currently not known if reproductive and/or developmental toxicity also occurs.

Evidence in humans suggests that acrylamide acts principally on the nervous system (LoPachin 2004). Occupational exposure to acrylamide has not been linked to overall cancer mortality. However, studies that have investigated this link are limited in size, and potential cofounders, such as tobacco smoking and dietary intake of acrylamide, were not considered (Shipp et al. 2006).

Carcinogenicity in Rats and Mice

Acrylamide's carcinogenicity has been tested in mice and rats by various routes of exposure, but the two most pertinent chronic oral lifetime studies were conducted only in rats. Male and female Fischer 344 (F344) rats were given one of four doses of acrylamide in the drinking water for two years (Johnson et al. 1986). Male rats receiving the highest dose had a significant increase in thyroid gland adenoma and mesothelioma of the tunica vaginalis of the testes, and an increase in testicular tumors also occurred at the second highest dose. Female rats receiving the highest dose had significant increases in mammary gland fibroma or fibroadenoma, CNS tumors, and thyroid gland adenoma or adenocarcinoma. Then in a subsequent study, male F344 rats were administered one of three doses of acrylamide in the drinking water for two years, and female F344 rats were similarly given one of two doses (Friedman et al. 1995). In male rats treated with the highest dose, there was a significant increase in thyroid gland adenoma and mesothelioma of the tunica vaginalis of the testes, and in female rats given both doses, there was an increase in benign mammary gland fibroadenoma, combined mammary gland fibroadenoma or adenoma, and combined thyroid gland follicular cell adenoma or carcinoma. In contrast to the Johnson et al. (1986) study that demonstrated an increased incidence of CNS tumors in females, there was not a significant increase in CNS tumors in either sex in this study.

The potential risks of dietary acrylamide exposure to humans were difficult to estimate from these two earlier rat studies. Consequently in 2002, after acrylamide's discovery in foods, the FDA nominated acrylamide and glycidamide for evaluation by the NTP in order to provide meaningful data for a more complete risk assessment. The results of the acrylamide bioassay in rats and mice were reported in *NTP Draft Technical Report No. 575* (NTP 2011b), and this report was peer-reviewed by the NTP Peer Review Panel at a public meeting in April 2011. Groups of male and female F344/N Nctr rats were given acrylamide in drinking water ad libitum for two years with four dose concentrations, resulting in an average daily consumption of approximately 0.33 to 2.71 mg acrylamide/kg of body weight (bw) in male rats and 0.44 to 4.02 mg acrylamide/kg bw in female rats. In parallel, groups of male and female B6C3F1 mice were also administered

acrylamide in the drinking water, with resulting average daily consumptions of 1.04 to 8.93 mg acrylamide/kg bw in male mice and 1.10 to 9.96 mg acrylamide/kg bw in female mice. Numerous benign and malignant tumors were observed in several organs of both rats and mice, generally in agreement with the types of tumors seen in the earlier rat studies (Friedman et al. 1995, Johnson et al. 1986). In sum, there was clear evidence of carcinogenic activity of acrylamide in male and female rats and mice, although significantly decreased animal survival at the top two doses may be an indication that the maximum tolerated dose of acrylamide might have been exceeded.

Carcinogenicity in Humans

The carcinogenicity of acrylamide in humans after occupational or dietary exposure has been thoroughly reviewed (Hogervorst et al. 2010, IARC 1994, Mucci & Adami 2009, Pelucchi et al. 2011, Shipp et al. 2006). In individuals exposed occupationally to acrylamide, there has been no consistent dose-related increase in cancer incidence at any organ site, with the possible exception of the pancreas. To date, a large number of epidemiology studies have investigated possible associations between dietary intake of acrylamide-containing foods and the incidence of several types of cancer in humans. The majority of these studies have failed to show an association with acrylamide-containing foods.

The most recent comprehensive review and meta-analysis of dietary acrylamide's role in human cancer was published by a team of European researchers (Pelucchi et al. 2011). The meta-analysis studied 25 relevant studies chosen from a much larger database. Relative risks were calculated for an increase of 10 $\mu g\ day^{-1}$ of acrylamide intake and were close to 1.0 for all the cancers considered None of the associations was statistically significantly increased. The authors concluded that the available studies consistently suggested a lack of an increased risk of most types of cancer from exposure to acrylamide.

Exposure and Risk Assessment

JECFA has twice assessed acrylamide dietary exposure and the risk of human cancer from the consumption of acrylamide-contaminated foods (JECFA 2006, 2011). The most recent analysis of human food consumption and an acrylamide dietary exposure assessment for eight countries were evaluated at a JECFA meeting held in early 2010 (JECFA 2011). The major foods contributing to the total mean dietary exposures for most countries were fried potatoes (in the United States, french fries) (10%–60%), potato crisps (in the United States, potato chips) (10%–22%), bread and rolls/toast (13%–34%), and pastry and sweet biscuits (in the United States, cookies) (10%–15%). Generally, other food items contributed less than 10% to the total dietary exposures. Based on national and regional estimates, a dietary exposure to acrylamide of 1 μg/kg of bw/day was taken to represent the mean for the general population (including children), and a dietary exposure of 4 μg/kg of bw/day was taken to represent consumers with a high dietary exposure.

A margin of exposure (MOE) approach was employed by JECFA (2011) to try to determine the potential human risk of exposure to acrylamide at the levels noted above. Such MOE estimates are based on the difference between the dose causing a low but defined incidence of cancer (usually in animal bioassays) and estimated human exposure. For contaminants like acrylamide and glycidamide that are both genotoxic and carcinogenic, this approach provides advice to inform risk managers of how close human exposures are to those anticipated to produce a measurable effect in laboratory animals or humans. Subsequently, the level of regulatory or nonregulatory interventions that might be considered take account of the size of the MOE.

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It has been recognized that more biological mechanism-based research is needed to better assess and understand dose-response cancer effects in the low dose range corresponding to the human dietary acrylamide intakes recently estimated by JECFA and other health bodies. Tardiff et al. (2010) used a physiologically-based toxicokinetic model (PBTK or PBPK) for internal acrylamide dosimetry (developed by Sweeney et al. 2010) to interpret results from chronic rodent carcinogenicity studies as being primarily consistent with hormonal dysregulation in the carcinogenic mechanism of acrylamide and/or glycidamide. These researchers calculated cancer risk values for either acrylamide or glycidamide and used these values in MOE comparisons with human internal exposures predicted from daily exposure to 1 μg acrylamide/kg of bw/day (mean consumption) or 4 μg acrylamide/kg of bw/day (high consumption). Using the risk values for male and female F344 rat tumors in the literature described above, MOEs were calculated to be 200 (for mean human consumption) or 50 (for high consumption), assuming that acrylamide is the toxic species, and 1,200 or 300, respectively, assuming glycidamide to be the toxic species. In general, these predicted MOEs for acrylamide were similar to those previously reported by JECFA (2006).

Subsequently, in JECFA's more recent evaluation (JECFA 2011), MOEs were again calculated based on the tumor findings in the preliminary rat and mouse data provided by the NTP bioassay described previously. When average and high dietary acrylamide exposures were compared with the risk values for the induction of female mammary benign tumors in rats, the MOE values were calculated to be 310 and 78, respectively. When average and high dietary acrylamide exposures were compared with the risk values for the induction of Harderian gland tumors in male mice, the MOE values were 180 and 45, respectively. JECFA considered that for a compound that is both genotoxic and carcinogenic, these MOEs indicated a human health concern. The Committee recognized that these MOE values were similar to those it determined at their earlier meeting (JECFA 2006). The Committee also concluded that the extensive new data from the NTP cancer bioassays in rats and mice, PBPK modeling of internal dosimetry, a large number of recent epidemiological studies, and updated dietary exposure assessments supported their previous evaluation.

RISK MANAGEMENT

Risk management of acrylamide in foods issues has been on a voluntary collaborative basis involving national regulatory agencies and companies producing foods containing acrylamide. No country has used regulatory action yet to set limits on the acrylamide content in foods or in the diet.

Germany developed and adopted (2002) an acrylamide minimization concept (Kliemant & Göbel 2007) to encourage minimization, to the extent possible, of the acrylamide content in foods, i.e., an ALARA (as low as reasonably achievable) approach. Food products were classified into defined commodity groups. A signal value was established for each of these as the lowest acrylamide level in the top 10% of foods within that group. The signal value, once set, could not be raised and could not be set greater than 1,000 μg kg^{-1}. Results are evaluated annually and the signal value lowered if the reduction in acrylamide was such that a new signal value was lower than the current one. When products were observed with acrylamide contents above the signal value, the producer was contacted and discussions held on minimization. The system has met with success for some products, with others actually increasing in acrylamide content.

The European Commission (EC) requested member states to monitor, for a three-year (2007–2009) period, acrylamide contents in foods containing higher amounts of acrylamide and/or contributing significantly to dietary intake. During that time, only 3 of 22 groups had a trend to lower contents of acrylamide; six groups showed no change and two increased (EFSA 2011).

Using monitoring data (2007–2008), the EC has developed indicative values for acrylamide contents in 10 food categories as shown in **Table 3** (EC 2011). These values are not safety

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Table 3 Indicative values for acrylamide contents in 10 food categories[a]

Food category	Indicative Value ($\mu g\ kg^{-1}$)
French fries, ready-to-eat	600
Potato crisps	1,000
Soft bread	150
Breakfast cereals (excluding muesli and porridge)	400
Biscuits, crackers, wafers, crisp bread, and similar, excluding ginger bread	500
Roast coffee	450
Instant (soluble) coffee	900
Baby foods, other than processed biscuits and rusks	80
Biscuits and rusks for infants and young children	250
Processed cereal-based foods for infants and young children, excluding biscuits and rusks	100

[a]From EC (2011).

thresholds, but are intended to indicate the need for investigating the reasons acrylamide contents in foods in the particular category exceed the indicative value. Together with continued monitoring in 2011 and 2012, reports from these investigations will be reviewed by December 31, 2012 as the basis for a decision whether there is a need for other appropriate measures.

Most of the major countries of the world have advised consumers to follow the dietary recommendations for a balanced diet issued by their food regulatory agency. The data available to date have been insufficient to warrant any recommendation for a significant change in the dietary recommendations.

CONCLUDING COMMENTS

Since the discovery of acrylamide in foods, numerous investigations into the issues arising from this unexpected finding have been initiated and accomplished internationally and are still in progress. The occurrence, analysis, amounts in food, mechanisms of formation, and exposure in different countries and age groups now are well understood. Numerous investigations into methods for reduction of acrylamide in food products have been shared, with successful application occurring in some foods. Current epidemiological and toxicological evidence are insufficient to indicate that the amounts of acrylamide consumed in the normal diet are likely to result in adverse human health effects, particularly cancer.

SUMMARY POINTS

1. The occurrence of acrylamide in foods is not limited to a few specific foods or food products but involves a wide variety of foods common to daily diets worldwide.
2. Available epidemiological studies consistently suggest the lack of an increased risk of most types of cancer from exposure to acrylamide from food.
3. No one approach or single method for mitigation/reduction of acrylamide in foods is applicable to all foods.
4. Substantial reduction of the acrylamide content of many foods is unlikely without affecting the quality and acceptance of the food or developing additional food safety issues.

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FUTURE ISSUES

1. Research and development assessing the potential of alternative or new technologies is important to successfully mitigate/reduce acrylamide content of foods on a commercial scale.
2. Epidemiological studies are needed using a sufficiently large subject base to obtain the discriminatory power required to detect the small increase in cancer risks that may occur.
3. Additional mechanism-based research is needed to better assess and understand dose-response health effects in the low dose range, corresponding to dietary intake, to achieve science-based risk assessment. Special consideration must be given with respect to kinetics of activating and detoxifying biotransformations and their impact on biological outcome at low dosage. Inclusion of advanced physiologically based toxicokinetic modeling, together with the best-available methodology, is necessary in order to approach, as closely as possible, human intake levels.
4. Quantitative methods must be developed to conduct risk-risk and risk-benefit assessments considering different toxic effects and the nutritional aspects of foods.

DISCLOSURE STATEMENT

James R. Coughlin has consulted on acrylamide for several food companies and food trade associations since 2002.

LITERATURE CITED

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APPENDIX C

AMERICAN CHEMICAL SOCIETY
AGRICULTURAL AND FOOD CHEMISTRY DIVISION
Symposium on Chemistry and Toxicology of Acrylamide
Boston, MA 19 – 23 August 2007

Tuesday 21 August

James E. Klaunig	Indiana University School of Medicine, USA	Review of the mutagenicity and carcinogenicity of acrylamide
Matthias Baum	University of Kaiserslautern, Germany	Genotoxicity of glycidamide in comparison to N-nitroso compounds and interactions of acrylamide with food matrix components
Richard M. LoPachin	Albert Einstein College of Medicine, USA	Molecular mechanisms of neurotoxicity: Acrylamide targets thiolate sulfhydryls of catalytic triads
Terrence Gavin	Iona College, USA	Neurotoxic mechanism of acrylamide: Correlation of Type-2 alkene-thiol reactivity with parameters derived from quantum mechanical calculations
Margareta Törnqvist	Stockholm University, Sweden	Dietary acrylamide and cancer risk estimation on the basis of toxicological data
Lorelei A. Mucci	Harvard University School of Public Health, USA	Acrylamide intake through diet and human cancer risk

Marvin A. Friedman	University of Louisville School of Medicine, USA	Inhibition of krp proteins and not DNA adducts drive acrylamide risk assessment
Timothy R Fennell	RTI International, USA	Acrylamide metabolism, elimination kinetics and hemoglobin adducts
Daniel R. Doerge	NCTR, USA	PBPK/PD Modeling of acrylamide: Integration of kinetic and biomarker data for use in risk assessment
Hubert W. Vesper	CDC, USA	Cross-sectional study on acrylamide exposure, using hemoglobin adducts as biomarkers: results from the EPIC study
Hongfang Sun	Peking University, China	Acrylamide adduction with biomacromolecules at environmental dose levels and its inhibition studied by accelerator mass spectrometry
Juergen Angerer	University Erlangen-Nuremberg, Germany	Acrylamide - human metabolism and exposure

Wednesday 22 August

Donald. S. Mottram	University of Reading, United Kingdom	The Maillard reaction and its role in the formation of acrylamide in foods
Varoujan A. Yaylayan	McGill University, Canada	Heat and pH induced generation of acrylamide from N-(1-deoxy-D-fructos-1-yl)-3'-aminopropionamide
Bronislaw Wedzicha	University of Leeds, England	Modelling the kinetics of the formation and fate of acrylamide in food
Michael Granvogl	Technical University of Munich, Germany	Interactions of acrylamide with other food constituents
Thomas M. Amrein	Swiss Federal Institute of Technology (ETH), Switzerland	Acrylamide formation under mild conditions: The promoting effect of ammonium bicarbonate and detection of acrylamide in dried fruit
Michael Murkovic	University of Technology, Graz, Austria	Formation of acrylamide during roasting of coffee
Francisco J. Hidalgo	Instituto de la Grasa, CSIC, Spain	Contribution of oxidized lipids to the formation of acrylamide in thermally processed foods

Dennis E. Marroni	SNF S.A.S, France	Human exposure to acrylamide: a brief history
Erik V. Petersson	Uppsala University, Sweden	Extraction of acrylamide from foods
L Sune Eriksson	Lantmännen Analycen AB, Sweden	Analysis of evaporated acrylamide from food products and biological materials
Takayuki Shibamoto	University of California, Davis, USA	Acrylamide analysis in a complex matrix
Kerstin I. Skog	Lund University, Sweden	Heat derived toxicants in food – some findings of a collaborative European research project
Guy A Channell	University of Nottingham, United Kingdom	Rapid screening of acrylamide formation in a model matrix reactor under different compositional and processing conditions

Thursday 23 August

James R. Coughlin	Coughlin & Associates, USA	Risk-benefit assessment of foods containing heat-induced carcinogens
Craig Mills	Food Standards Agency, United Kingdom	Dietary exposure estimates for acrylamide intake
Mendel Friedman	Western Regional Research Center, ARS, USDA, USA	Overview of possible approaches to reducing the acrylamide content of the diet
Wendy Matthews	Food Standards Agency, United Kingdom	European regulatory perspective on the acrylamide issue
Richard H. Stadler	Nestlé Product Technology Centre, Orbe, Switzerland, Switzerland	The acrylamide “Toolbox” approach of the European Food & Drink Federation (CIAA)
Nigel G. Halford	Rothamsted Research, United Kingdom	Agronomic and genetic approaches to reducing acrylamide precursors in wheat and potato

Thursday 23 August

J. Stephen Elmore	University of Reading, United Kingdom	The effects of sulfur nutrition on acrylamide and aroma compounds in cooked wheat and potato
Colin G Hamlet	RHM Technology, United Kingdom	Raw material variability: a tool to minimise acrylamide formation in baked cereal products?
Peter A. Sadd	RHM Technology, United Kingdom	Effectiveness of methods for reducing acrylamide in bakery products
Vural Gökmen	Hacettepe University, Turkey	Simulation of acrylamide formation in French fries and potential strategies for mitigation
Frédéric Mestdagh	Ghent University, Belgium	Chemical pre-treatments of potato products: mechanisms of acrylamide mitigation and effects on the sensorial quality
Polly Boon	RIKILT - Institute of Food Safety, Netherlands	Mitigation and resulting reductions in the dietary exposure to acrylamide

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APPENDIX D

Risk-Benefit Assessment of Foods Containing Heat-induced Carcinogens

James R. Coughlin, Ph.D.

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AGFD Symposium on *"Chemistry and Toxicology of Acrylamide"*

ACS 234th National Meeting
Boston, MA
August 23, 2007

Abstract: The assessment of the human health risk of food contaminants has historically been conducted without considering the potential health benefits of the whole food. When a heated-food contaminant such as acrylamide is found in a food, there is a need to determine the safe consumption range of the contaminant as well as the overall risks and benefits of the whole food. While the Maillard Browning Reaction is well known to produce numerous animal carcinogens, the dietary cancer risk of a heated foodstuff (such as coffee) cannot properly be assessed by examining just the concentrations and potencies of the individual animal carcinogens contained in the product. Instead, browned foods should be evaluated using an approach that takes into account the nutrient content of the food as well as the presence of other health-protective compounds, including naturally occurring polyphenolic antioxidants, compounds that can induce detoxification enzymes and various Maillard-produced compounds (antioxidants such as the melanoidins and some heterocyclic compounds).

Outline

- Foods & food chemicals - Safety framework
- Maillard Browning Reaction - Positive health effects
- Coffee, coffee constituents and cancer
- Some other acrylamide considerations:
  - Chemical reactions in vivo
  - Bioavailability
  - Nutritional content of foods
  - Mitigation concerns
- Is it time to consider risk-benefit assessment?

Foods & Food Chemicals - Safety Framework

- Usually test individual food chemicals, not whole foods (except with epidemiology)
- For whole foods, we must identify bioactive component(s)
- Determine appropriate mechanisms/modes of action of specific chemicals (carcinogens, repro- and neuro-toxicants, etc.)
- Critical importance of dose-response relationships
- Interactions with diet/nutrients, environment, drugs
- Explore sensitive populations (young, old, pregnant, immune)
- Risk/Benefit Assessment is crucial to Risk Management:
  - For additives, do benefits exceed the risks?
  - For contaminants, is any risk acceptable? Factor in benefits?
  - Are regulations necessary? Or just increased knowledge/choice?

➔ Overall Goal: NO “significant or unreasonable” risk!!

Some Key Controversies in Risk Evaluation of Foods and Food Chemicals

- ✓ Interpretation of rodent cancer bioassays of extreme chemical doses
- ✓ Assessing individual food chemicals (especially carcinogens) vs. the safety of whole foods
- ✓ Failure to give any weight to NEGATIVE epidemiology studies
- ✓ Failure to consider the POSITIVE health benefits of foods (especially heated foods!)

Carcinogenicity of Individual Food Chemicals

"Carcinogens and Anticarcinogens in the Human Diet." NAS/NRC, 1996.

- "The great majority of individual naturally occurring and synthetic chemicals in the diet appears to be present at levels below which any significant adverse biologic effect is likely, and so low that they are unlikely to pose an appreciable cancer risk."

- "The varied and balanced diet needed for good nutrition also provides significant protection from natural toxicants."

- "Current evidence suggests that the contribution of excess macronutrients and excess calories to cancer causation in the United States outweighs that of individual food microchemicals, both natural and synthetic."

Carcinogens in Heated Foods

- Ongoing worldwide effort to determine the intake and toxicities of these chemicals and possible mitigation strategies is certainly to be commended, as are the unprecedented global cooperation and collaborations brought by acrylamide

- Overarching goal is to understand their true risk to humans (acrylamide, furan, HEATOX efforts, etc.)

- My current beliefs:
  - Cancer warnings on heated foods are not currently justified
  - Any warnings should be deferred pending the evaluation of ongoing research efforts.

Q. Is there anything wrong with this focus on individual animal carcinogens in heated foods?

A. Regulatory and health authorities are not considering the POSITIVE health benefits of heated foodstuffs that contain these carcinogens!

“One by One” vs. “Holistic” Approach

- Foods can contain huge numbers of chemical components that can have strongly divergent and even directly opposite health effects (e.g., in the same food we have both pro-oxidants and anti-oxidants, mutagens and anti-mutagens).
- Assessing these chemical components “one by one” is highly likely to be misleading and overly conservative.
- However, if we are to consider risks and benefits, how do we compare/weight them overall?
- I believe that the health assessment of foods, especially complex heated foods, requires a **HOLISTIC** approach, as opposed to the current “one by one” chemical risk assessments.

General Scheme of Maillard Browning Reaction

Amine

- Ammonia
- Alkyl amines
- **Amino acids**
- Proteins
- Phospholipids

Carbonyl

- Aldehydes
- Ketones
- **Sugars**
- Carbohydrates
- Lipids

HEAT

Amino-Carbonyl Interaction (Amadori Products)

Melanoidins (pigments)

Volatile Compounds (aroma chemicals)

Carbonyls
Esters
Amides (Acrylamide)
Heterocyclic Compounds

Furans	Oxazoles
Pyrroles	Imidazoles
Thiophenes	Pyridines
Thiazoles	Pyrazines

Benefits of “Maillard Browning Reaction”

- Flavors, aromas, colors and texture of browned foods
- Antioxidants produced by heat may protect against diseases linked to oxidative damage (cancer, diabetes, atherosclerosis, arthritis, inflammation, etc.)
- Specific Maillard Reaction Products (MRPs), including melanoidin polymers and heterocyclic compounds, are known to have antioxidant, anti-carcinogenic and anti-mutagenic effects; and some can also induce protective detoxification enzymes.

Two Important Reviews

"Toxicology and antioxidant activities of non-enzymatic browning reaction products: Review."
Lee K-G and Shibamoto T, *Food Rev. Intl.* 18:151-175 (2002)

"Review: Five years of research on health risks and benefits of Maillard reaction products: An update."
V. Somoza, *Mol. Nutr. Food Res*. 49: 663-672 (2005)

MRPs Aid Detoxification by Enhancing Expression of Glutathione-S-transferase (GST) Enzymes

Faist et al., *Intl. Congress Ser*. 1245: 313-320 (2002)

- Well-known MRP, N^{ϵ}–carboxymethyllysine (CML), a 2-carbon protein adduct, enhanced GST expression in rats and in cultured human Caco-2 intestinal cells:
  - Rats fed casein-linked CML and bread crust-linked CML showed the inductive effect of CML on GST activity in the kidneys
  - The Caco-2 studies also confirmed these inductive effects

- Significance: while the Maillard Reaction does create carcinogens, it also creates this protective chemical adduct – CML – possibly resulting in increased detoxification of some carcinogens found in the same browned foods

- Numerous studies are continuing on other MRPs for their ability to induce protective Phase II enzymes; this may have a significant impact on reducing the human risk from trace levels of carcinogens in foods.

Identification of a Chemopreventive Compound in Coffee Beverage Using *in Vitro* and *in Vivo* Techniques.

Somoza et al., *J. Agric. Food Chem.* 51: 6861-6869 (2003)

- Chemo-preventive effects on GST activity were found for the N-methylpyridinium ion; structure was elucidated by LC-MS and NMR, and confirmed by synthesis
- Coffee beverage and N-methylpyridinium ions tested in a 15-day feeding experiment in rats:
  - In the liver, feeding of 4.5% coffee beverage resulted in increases of GST and UDP-GT activities by 24 and 40%, respectively, compared to controls
  - Plasma total AOX capacity and plasma tocopherol were elevated in animals fed the coffee beverage and the N-methylpyridinium-containing diet
- Results showing a strong *in vitro* antioxidant activity for coffee were confirmed by the rat feeding study.

Antioxidant Activities of Volatile Heterocyclic Compounds

Fuster et al. (2000); Yanagimoto et al. (2002, 2004)

- AOX activity (hexanal to hexanoic acid) measured in aq. solutions containing 100 - 500 µg/mL of each compound:
  - Furans (most abundant): unsubst'd furan was most active of 5 furans, with 500 µg/mL = 94% inhibition, similar to inhibition by 50 µg/mL BHT
  - Pyrroles: 78 - 98% inhibition
  - Thiophenes: 2-Methyl- gave 100% inhibition at highest conc.
  - All combined in coffee might be comparable to activities of known AOX

- Water-insoluble DCM extracts of brewed coffee (5-100 µg/mL) also showed up to 100% inhibition of aldehyde oxidation
  - Earlier fractions from silica gel chrom of DCM extracts gave 100% inhibition (many heterocyclic volatiles were identified)
  - Residual aq. fractions contained potent AOX activity, probably due to the large number of polyphenols.

J. Agric. Food Chem. (2006) 54:853

Investigation of the Correlation of the Acrylamide Content and the Antioxidant Activity of Model Cookies

CARMELINA SUMMA, THOMAS WENZL, MARCEL BROHEE, BEATRIZ DE LA CALLE, AND ELKE ANKLAM*

European Commission, Directorate General Joint Research Centre, Institute for Reference Materials and Measurements, Retieseweg 111, 2440 Geel, Belgium

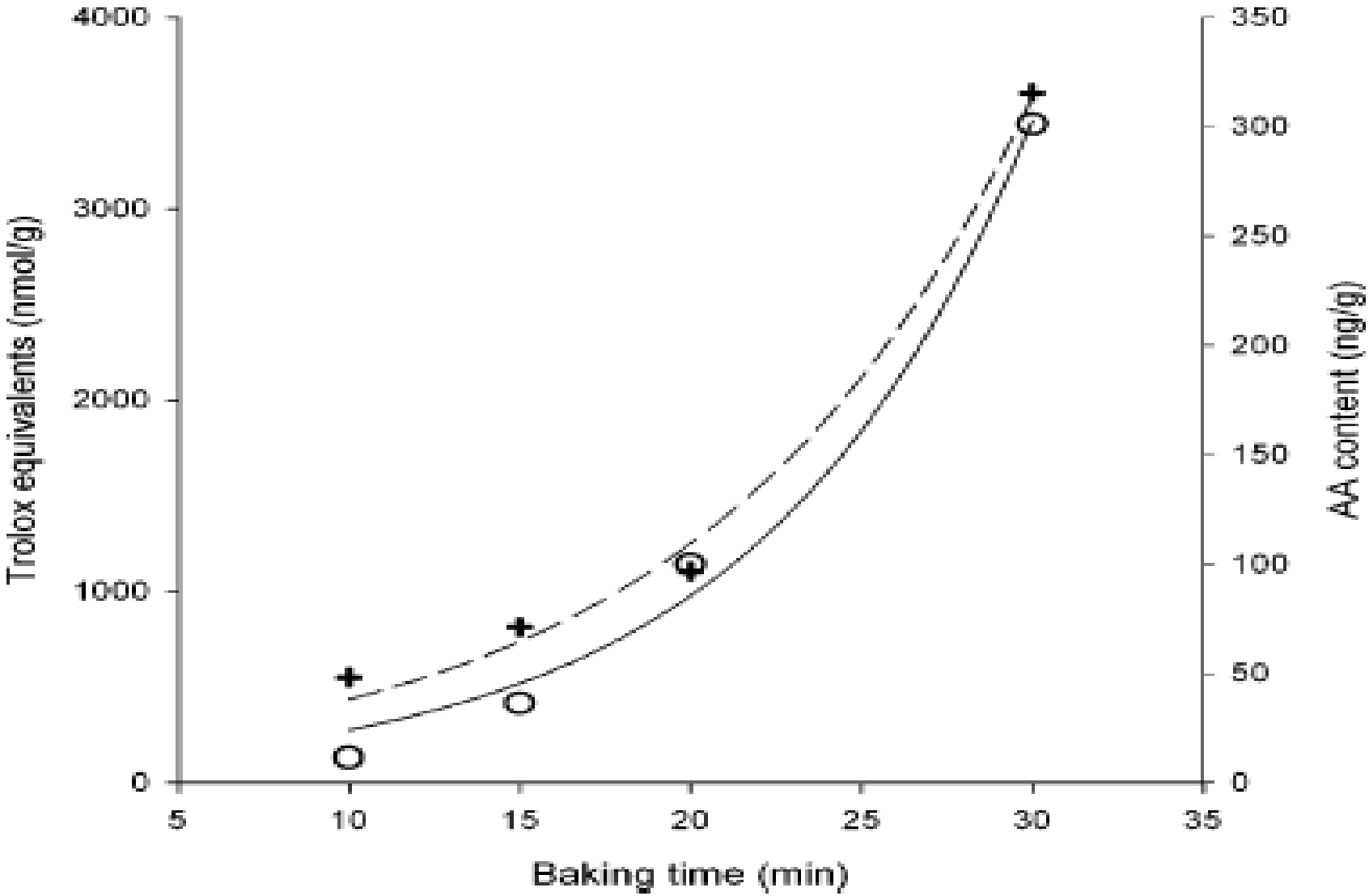


Figure 1. Influence of the baking time on the concentration of AA and on the AOA in recipe 2 cookies containing 37% (w/w) sucrose: (○) AA values; (+) AOA values; solid line, regression curve for AOA; broken line, regression curve for AA content.

COFFEE

"Coffee and Cancer Paradox"©

- Coffee contains almost 2,000 identified compounds, including trace levels of up to 50 animal carcinogens: acrylamide, furan, caffeic acid, various aldehydes, PAHs, ochratoxin A, etc.

- While the earlier literature linked coffee with various forms of human cancer (e.g., pancreatic cancer), health authorities now agree that coffee drinking is **NOT** a cancer risk

- In fact, epidemiologic studies now show significant risk reductions for colorectal, liver, renal and breast cancers; similar relationships also seen with type 2 diabetes, Parkinson's disease, liver cirrhosis

- Coffee's naturally-occurring and heat-formed antioxidants are thought to be key protective compounds, as well as other not yet determined components.

Coffee and Colorectal Cancer

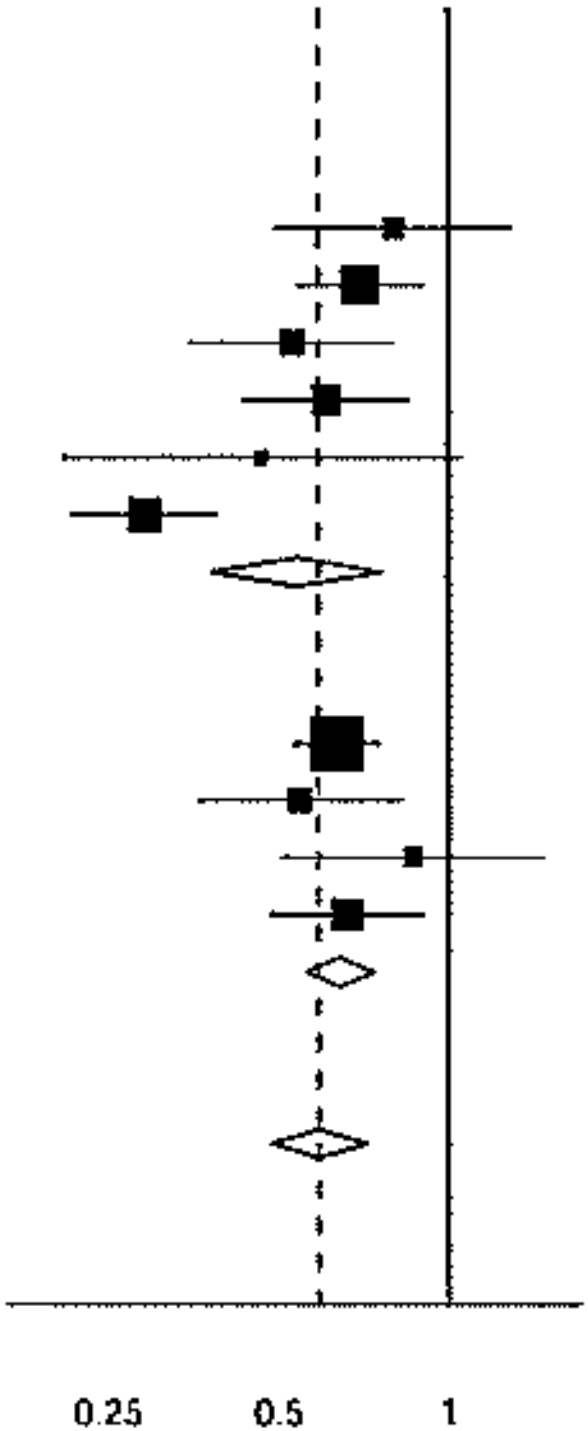
Lee et al., *Int. J. Cancer* 121: 1312-1318 (2007).

- Prospective cohort study, Japan, M&F, 96,000 subjects:
  - RR = 0.44 (0.19 - 1.04) for invasive colon cancer in women; no association in men; no association with rectal cancer

- Meta-analyses:
  - 12 case-control studies, high vs. low, RR = 0.72 (0.61 - 0.84)
  - 5 prospective studies, no apparent association

- Hypotheses:
  - Reduced levels of bile acids and neutral sterols in the bowel
  - Increased colonic motility due to coffee consumption
  - Antioxidant compounds (caffeic acid, chlorogenic acids, melanoidins)
  - Anti-mutagenic properties (like kahweol and cafestol)
  - Melanoidins bind carcinogens in the gut.

Study	Cases drinker/non-drinker	RR	95% CI
Case-control studies			
Kuper et al., 2000	297/36	0.80	0.50–1.29
Gallus et al., 2002	408/93	0.70	0.54–0.90
Gelatti et al., 2005	206/44	0.53	0.35–0.80
Montella et al., 2007	158/27	0.61	0.43–0.85
Ohfuji et al., 2006	48/25	0.47	0.21–1.05
Tanaka et al., 2007	82/127	0.29	0.22–0.39
Pooled estimate	1,199/352	0.54	0.38–0.76
Cohort studies			
Inoue et al., 2005	173/161	0.64	0.53–0.76
Shimazu et al., 2005, cohort 1	41/29	0.55	0.36–0.83
Shimazu et al., 2005, cohort 2	35/12	0.87	0.51–1.47
Kurozawa et al., 2005	155/103	0.66	0.48–0.91
Pooled estimate	404/305	0.64	0.56–0.74
Pooled estimate of all studies	1,603/657	0.59	0.49–0.72



Chemical Reactions of Acrylamide and Glycidamide.

Mendel Friedman, *J. Agric. Food Chem.* 51: 4504-4526 (2003)

- ACRYLAMIDE
  - Undergoes classic Michael-type, nucleophilic additions
  - Very reactive with –SH groups, less so with amino groups
  - Thus very reactive with proteins (Hb) and amino acids (cysteine, GSH); reacts slowly with DNA

- GLYCIDAMIDE
  - Reactive epoxide, especially with heating foods
  - Formed by biochemical epoxidation of acrylamide
  - Reacts with proteins (Hb); reacts with DNA

- But what about reaction with dietary proteins and amino acids in the GI tract?

J. Agric. Food Chem. (2004) 52:4021

Reduction of Acrylamide Uptake by Dietary Proteins in a Caco-2 Gut Model

JENS SCHABACKER,[§] THOMAS SCHWEND,[§] AND MICHAEL WINK*

Institut für Pharmazie und Molekulare Biotechnologie, Universität Heidelberg, Im Neuenheimer Feld 364, 69120 Heidelberg, Germany

The report of elevated acrylamide levels in some foods raised an international health alarm, because acrylamide probably has carcinogenic, neurotoxic, and genotoxic properties. However, data on the bioavailability of acrylamide from food matrices in humans are limited. In particular, only little is known about the interactions of acrylamide with food ingredients. Using a human intestine model (Caco-2 cells), this study shows that acrylamide monomers are highly bioavailable and pass the cell monolayer via passive diffusion. Furthermore, acrylamide binds to dietary proteins such as chicken egg albumin under intestinal and cooking conditions. This binding reduces the concentration of acrylamide monomers and leads to a reduced uptake by Caco-2 cells. Hence, it is concluded that a protein-rich diet may reduce acrylamide uptake.

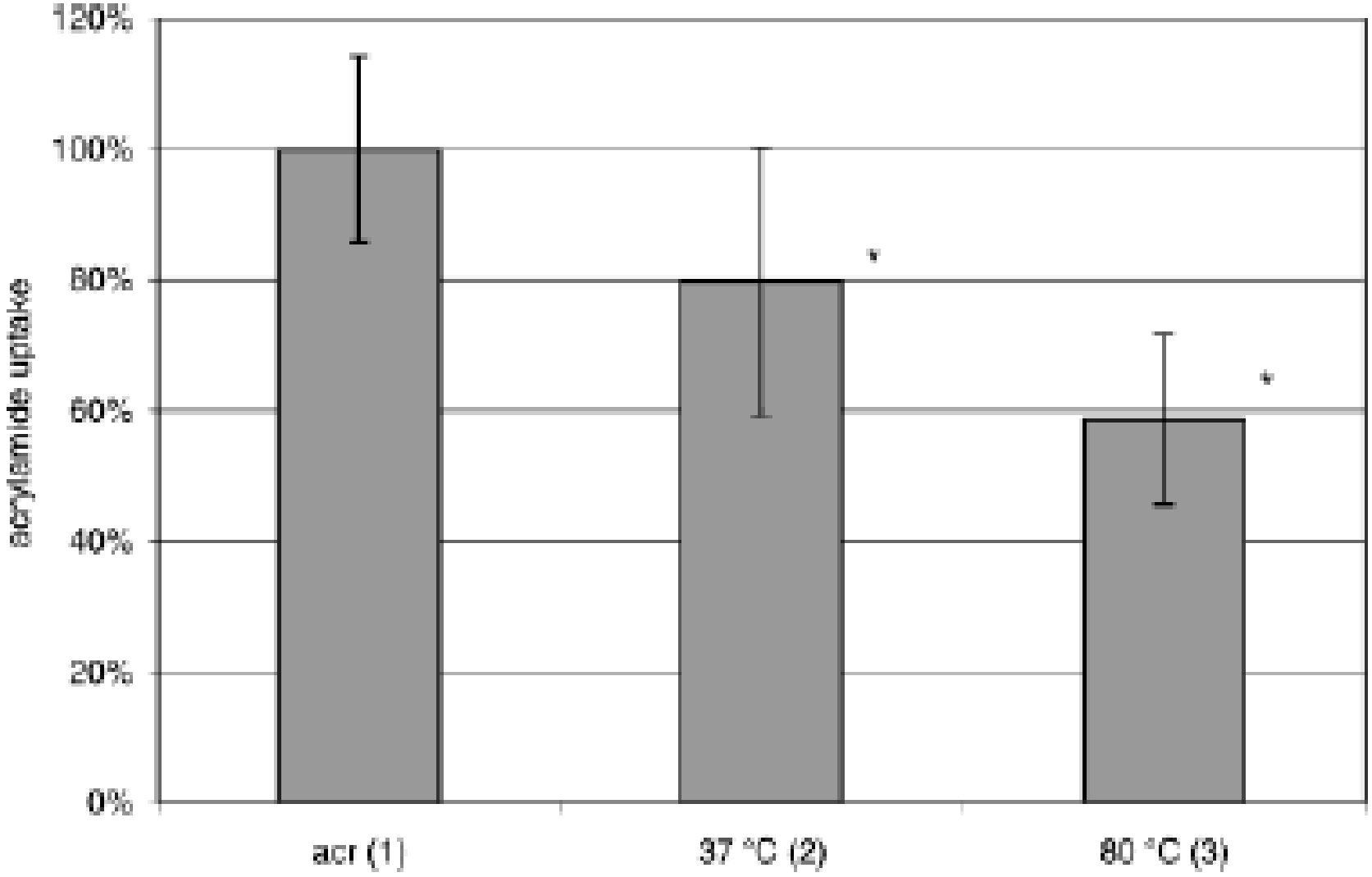


Figure 4. Reduced uptake of acrylamide by Caco-2 cells in the presence of dietary proteins. Preincubation of 1 mM acrylamide in a 5% dietary protein solution for 45 min at 37 °C (pH 7.4) leads to a reduced uptake of acrylamide by Caco-2 cells (2) compared to an untreated acrylamide

Percent of Caloric Energy and Nutrients Contributed by Acrylamide-Containing Foods in U.S. Diet

- 38% of total calories
- Macronutrients:
  - 33% of carbs, 36% of fiber, 28% of fat
- Micronutrients:
  - 20% of calcium
  - 47% of iron
  - 15% of vitamin A
  - 34% of vitamin E
  - 22 - 44% of vitamin B, vitamin C and folic acid

Source: FDA Food Advisory Committee, Feb. 24, 2003

Cautions about Mitigation Techniques

Changing cooking/processing methods to reduce just acrylamide (or other heated food carcinogens) may have unintended adverse consequences on:

- ✓ nutritional choices of otherwise healthy foods
- ✓ if lower temps for frying, more fat absorbed
- ✓ microbial food safety may be compromised
- ✓ production of health-protective chemicals

European Food Safety Authority (EFSA) "Risk-Benefit Analysis" Colloquium (July 2006)

- Open debate on scientific approaches/methods available and tools and data needed for conducting a risk-benefit analysis of foods and food components
- Explored opportunities and limitations for defining whether qualitative, semi-quantitative or fully quantitative assessments were possible
- Participants agreed that the "state-of-the-art" of risk-benefit assessment had advanced beyond the brainstorming stage; now time to advance to "learning by doing"
- Too premature to develop a prescriptive framework for risk-benefit assessment, but attendees suggested that a guidance document be developed by EFSA with respect to methodology, approaches, tools and potential pitfalls in the risk-benefit assessment.

Conclusions on Heated Foods

- "Carcinogens" produce tumor increases in high-dose rodent bioassays, but are these results relevant to human cancer risk estimation? I believe we need some "new and expanded thinking" on this question.

- Epidemiology studies may support the lack of cancer risk and even an overall cancer-protective effect of that food (e.g., coffee)

- The beneficial health effects of a whole food may outweigh the health effects of trace levels of animal carcinogens in that food

➔ We must press health and regulatory authorities globally to:

- *Use improved risk assessment methodologies*
- *Assess whole foods, not just individual food chemicals 1 X 1*
- *Consider the health benefits of heated foods*
- *Keep appropriate focus on nutritional and microbial risks as well.*

APPENDIX E

Coffee and Health - Facts and Myths: The Need for the Risk-Benefit Holistic Approach

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23rd ASIC International Conference on Coffee Science
Bali, Indonesia
October 4, 2010

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A 30-Year Coffee/Health Perspective

…on Rats, Mice and Humans

…on “Good” and “Bad” Science

…on “Good” and “Bad” Media Coverage

…on Coffee’s Beneficial Health Effects

…on “Holistic” Risk-Benefit Evaluation

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Conclusions: 1980 - 2010

… First 15 Years:

Mostly **Bad News!** Coffee and Caffeine were linked to almost **every** known animal and human disease!

… Mid-1990's to Today, a **Big Turn Around:**

The **"Good News"** is that almost all of the Bad News was **WRONG!**

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Why Did the Bad Myths Happen and Why Do Some Still Persist?

… Acute vs. Chronic effects:

- ✓ **Partial / full tolerance to caffeine develops in humans consistently consuming caffeine and coffee**

… Most of the Myths and Fears are based on:

- ✓ **Acute effects testing of naive subjects**
- ✓ **Massive doses of individual chemicals fed to animals for a lifetime.**

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Why have Coffee/Caffeine been so maligned?

- **Dramatically increased interest in health and nutrition; much consumer worry about enjoying too much of a good thing!**

- **What we eat…or don't eat…is always being linked to disease, and there is much Consumer Anxiety from dietary headlines**

- **AVOID or REDUCE: salt, fat (fries and chips), meat, carbohydrates, coffee and caffeine!!**

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Much Confusion over Coffee and Caffeine

"Perhaps no substance has been the subject of more conflicting media and scientific reports in recent years than caffeine. So, is a cup of coffee bad for you or not?"

Los Angeles Times, September 11-13, 1994 risk series

- No one was even asking back then -

"So, is a cup of coffee <u>good</u> for you or not?"

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The “Maligning” Started in the Late 1970’s and Ballooned in the 1980’s and Early 1990’s

- Coffee and heart attacks
- Coffee and bladder & pancreatic cancer
- Caffeine and birth defects in rats (U.S. FDA)
- Caffeine and osteoporosis
- Caffeine “Addiction”

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ON SECOND THOUGHT... MAKE MINE HOT CHOCOLATE.
COFFEE
UNITED FEATURE SYN — ©1986 DAYTON DAILY NEWS JOURNAL HERALD

Coffee and Pancreatic Cancer - My Personal "Baptism by Fire"!

- **Brian MacMahon (Harvard) study – *New Engl J Med,* 1981**
- **Intense media coverage and months of lost coffee sales**
- **His methodology and results were severely criticized by university and industry scientists**
- **MacMahon eventually retracted his conclusions almost completely in 1986, but only in a brief letter in the *NEJM***
- **This study's limitations have become famous teaching points in dietary epidemiology coursework.**

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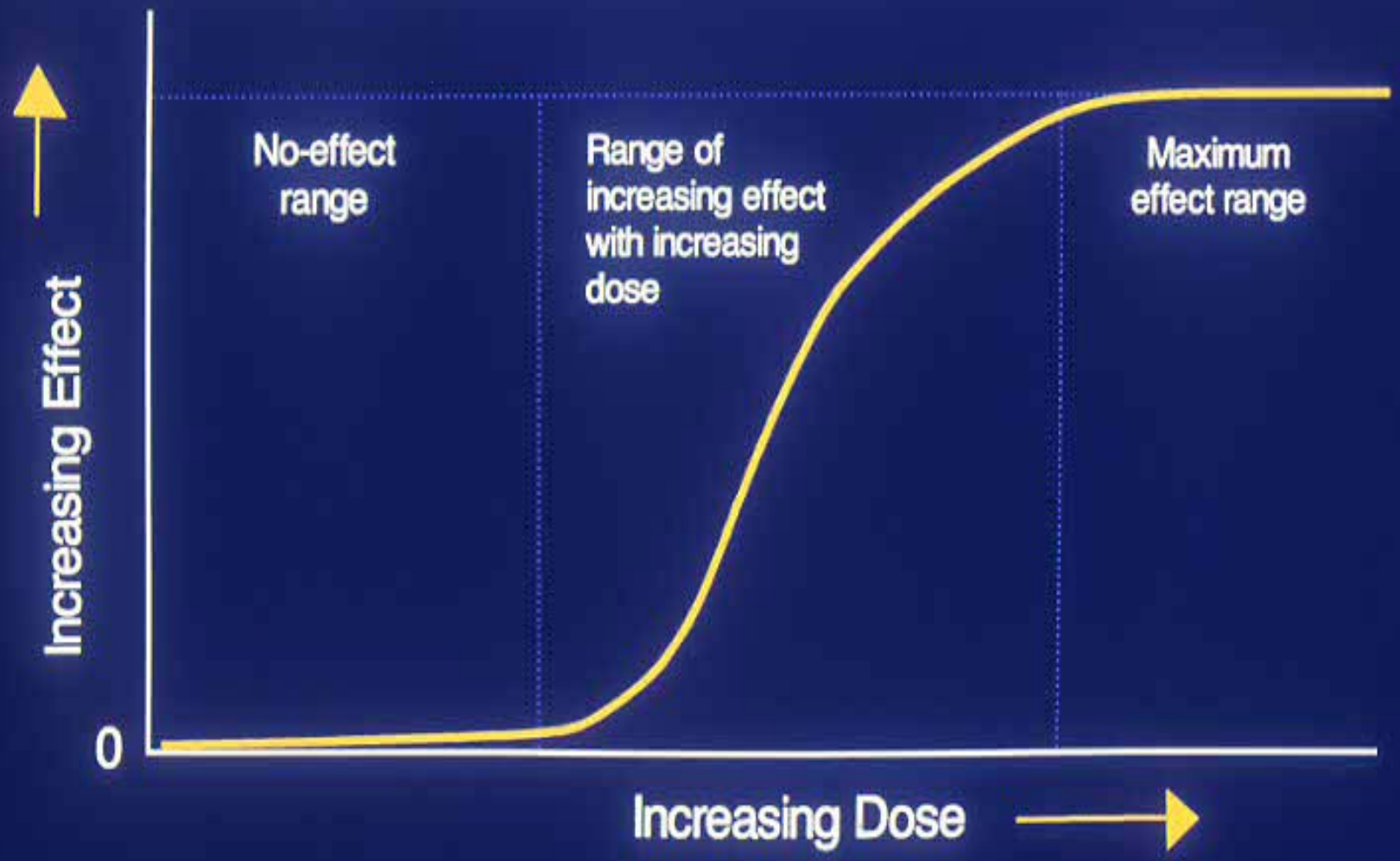
COFFEE

DOSE-RESPONSE CURVE



As we entered the 21st Century…

The preponderance of medical and scientific evidence clearly supported the conclusion that moderate coffee consumption (3 - 4 cups per day), as part of a varied, balanced diet, was safe and was not associated with any adverse human health consequences.

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But since 2000 or so…

- **The evidence has been building strongly that coffee may actually be GOOD for us!!!**
- **Let's briefly examine the evidence…**

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Caffeine's Physiological Effects

- **Mild central nervous system (CNS) stimulant**
- **Improves cognitive performance and mental processing; increases wakefulness; improves work performance and enhances mood**
- **Increases capacity for physical work / exercise; improves muscular performance and endurance sports**
- **Relaxes smooth muscle, especially bronchial (opens airways), and increases blood flow in heart and kidneys**
- **Produces a slightly higher metabolic rate (some evidence of an ergogenic "fat burning" effect).**

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Cardiovascular Disease

- **Endpoints:** heart attack, hypertension (with stress), ↑ blood cholesterol (2 constituents in boiled coffee), arrhythmias

- Andersen et al., 2006 (*Am J Clin Nutr* 83:1039-46) – Iowa Women's Health Study, decreased risk of death

- Lopez-Garcia et al., 2006 (*Circulation* 113:2045-53) – Harvard cohort study in men and women, no increased risk

- Lopez-Garcia et al. , 2008 (*Ann Intern Med 148: 904-914)* – Harvard cohort study, no increased mortality and possible modest benefit on all-cause and CVD mortality

- Dr. Chen will take us more deeply into these effects.

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Caffeine and Reproductive Effects

- **Began with birth defects in rats from very high-dose testing**
- **Humans: delayed conception; premature birth; low birth weight babies; fetal death; spontaneous abortion (miscarriage), congenital malformations.**
- **Now more than 25 Published Reviews:**
  - **Peck, Leviton, Cowan (*Food & Chemical Toxicology*, October 2010):**

    "The weight of evidence does not support a positive relationship between caffeine consumption and adverse reproductive or perinatal outcomes."

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Caffeine and Osteoporosis

- **Calcium excretion & bone loss in post-menopausal women causes millions of bone (hip) fractures**

- **Acute, 24-hour human studies on caffeine-naive subjects were originally misinterpreted**

- **Many longer-term human clinical studies have shown little excess calcium excretion or bone loss and no increased osteoporosis risk.**

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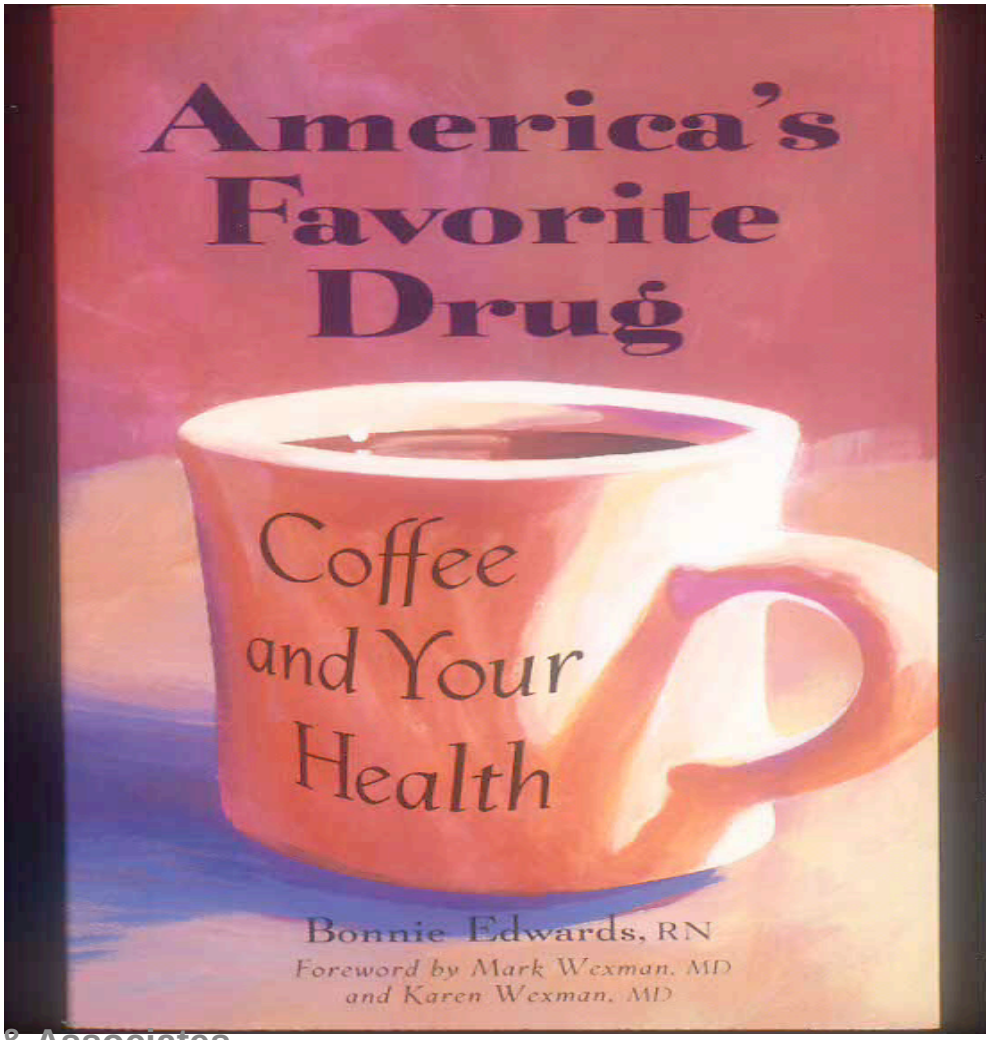
Caffeine and “Addiction”



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Caffeine and “Addiction”

- **Dependence, tolerance and withdrawal headache cited in many published studies (mostly among psychiatric patients)**

- **Headlines since the late 1980’s:**
  - **“Caffeine Addiction More Than Just Java Jive -- Caffeine Junkies”**
  - **“Study Finds Caffeine Has Qualities of Addictive Drug”**

- **Current View:**
  - **Caffeine is not classified as an addictive drug**
  - **Addiction over-warnings trivialize dangers of real drugs of abuse.**

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Coffee and Cancer Risk

- **Coffee contains dozens of <u>animal</u> carcinogens, many produced by the "Maillard Browning Reaction" in the presence of heat -**
  - **acrylamide, furan, caffeic acid, various aldehydes and other lipid oxidation products, PAHs, ochratoxin A**

- **Hundreds of human epidemiology studies have been published since the 1970's on many organs**

- **But, after 3 decades of epidemiologic research, <u>most</u> health authorities across the globe now agree that coffee drinking is <u>NOT</u> a cancer risk!**

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"Epidemiologic Evidence on Coffee and Cancer." Lenore Arab (U. of California, Los Angeles). *Nutrition and Cancer* 62: 271–283 (2010).

"For most cancer sites, there is a significant amount of evidence showing no detrimental effect of consumption of up to 6 cups of coffee/day in relation to cancer occurrence. In fact, some of the evidence…suggests that coffee might prevent some cancers." [based on over 500 publications]

- **Hepatocellular (liver) and endometrial - a strong and consistent protective association**
- **Colorectal - the association is borderline protective**
- **Breast, pancreatic, kidney, ovarian, prostate, gastric - no increased risk**

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Conclusions on the “Bad” Health Effects

- **Long established history of safe global use**
- **More animal, clinical and epidemiologic studies and continued media attention are sure to come**
- **More recent studies and re-examinations of older disease issues have been quite reassuring**
- **Consumers can be assured that their health will not be adversely affected by the enjoyment of coffee and caffeine as currently consumed.**

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“Risk Reductions” with Coffee Consumption

- Some cancers (already reviewed)
- Type 2 diabetes
- Chronic liver disease
- Parkinson’s Disease
- Alzheimer’s Disease

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Coffee and Type 2 Diabetes

- **Diabetes "epidemic" in Western societies with links to obesity and premature death**
- **Epidemiological studies have all shown a substantial reduction in risk with coffee consumption (Dose/Response)**
- **Mechanistic studies of promising coffee constituents are underway, and longer term human trials are needed**
- **Identification of coffee constituents with beneficial effects on glucose metabolism may lead to the selection of coffees with more positive health effects.**

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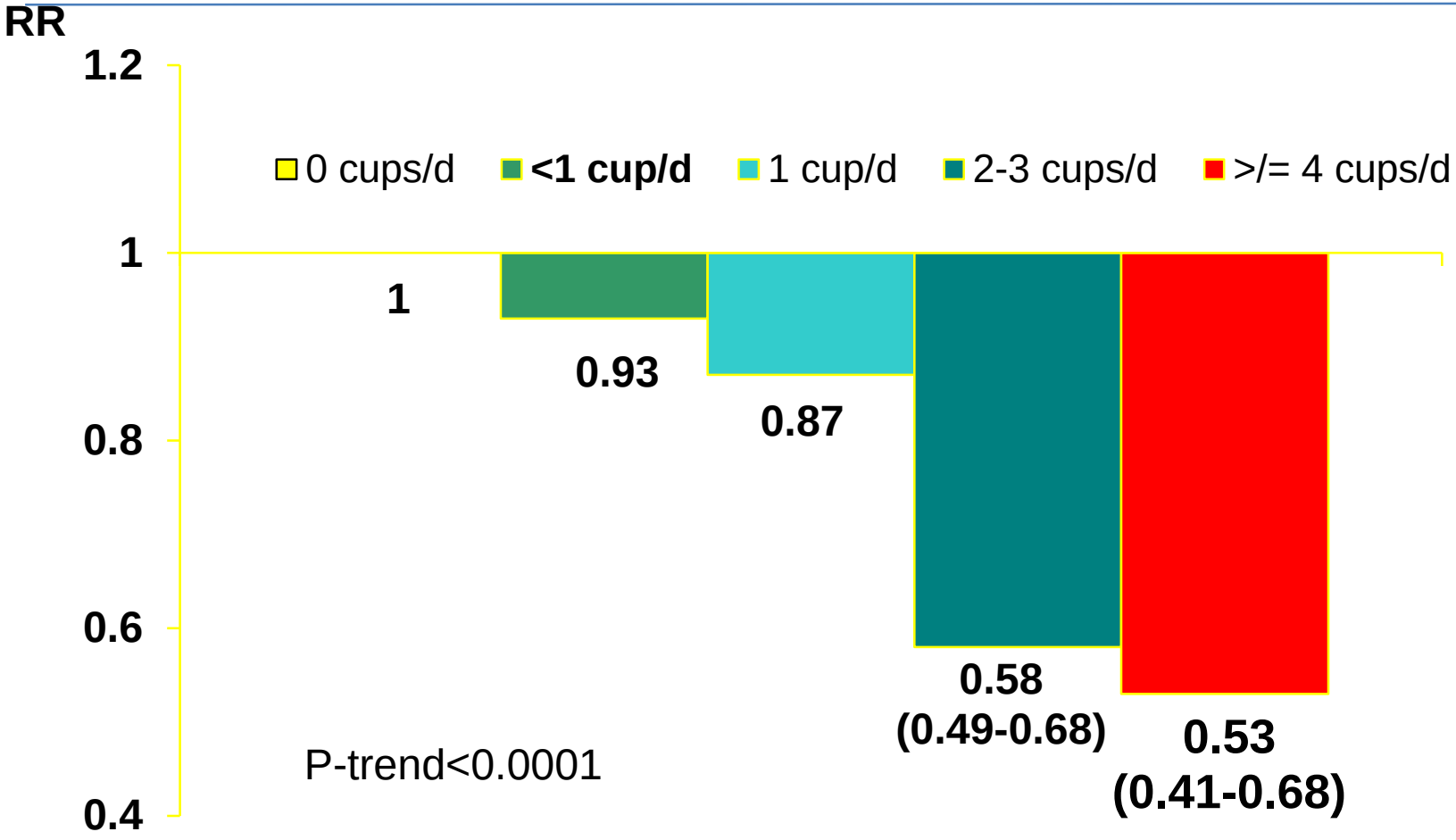
Coffee consumption and risk of type 2 diabetes in U.S. women



van Dam RM, et al. *Diabetes Care,* 2006

Liver Cancer and Liver Cirrhosis

- **Liver cancer is 5th most common cancer in the world, and liver cirrhosis is a major risk factor for it**
- **Coffee inhibits liver enzymes and produces a liver-protective effect that seems to reduce the risk of both cirrhosis and liver cancer by as much as 45%, based on published meta-analyses**
- **This is coffee's strongest cancer-protective effect**
- **Mechanistic studies are also providing strong biological support.**

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Coffee Consumption and Reduced Risk of Parkinson's Disease (PD)

- **9 retrospective and prospective studies found regular coffee consumers were 50-80% less likely to develop PD (Dose/Response)**

- **In 2007, two large cohort studies also showed a dose-response decrease in risk**

- **Although a causal relation due to caffeine's neuroprotective effects has been suggested, further studies are required for a definitive conclusion.**

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Coffee and Reduced Risk of Alzheimer's Disease (AD)

- **Both case-control and prospective cohort studies have shown that coffee consumption is associated with a reduced risk of AD**

- **Caffeine has shown neuroprotective effects after chronic administration in experimental animal models, possibly via modulation of neurotransmitter and receptor systems**

- **We'll hear much more about this from Dr. De Mendonca and Dr. Arendash.**

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Key Questions about Coffee's Antioxidants

- **Fundamental question: What do antioxidants (AOX) really do for human health?**
- **What kinds and amounts of AOX occur in coffee?**
- **Are coffee's AOX absorbed by the body and are they "bioavailable" in the body?**
- **Are coffee's AOX actually protecting us from disease?**
- **We'll hear much more on this from Dr. Croft.**

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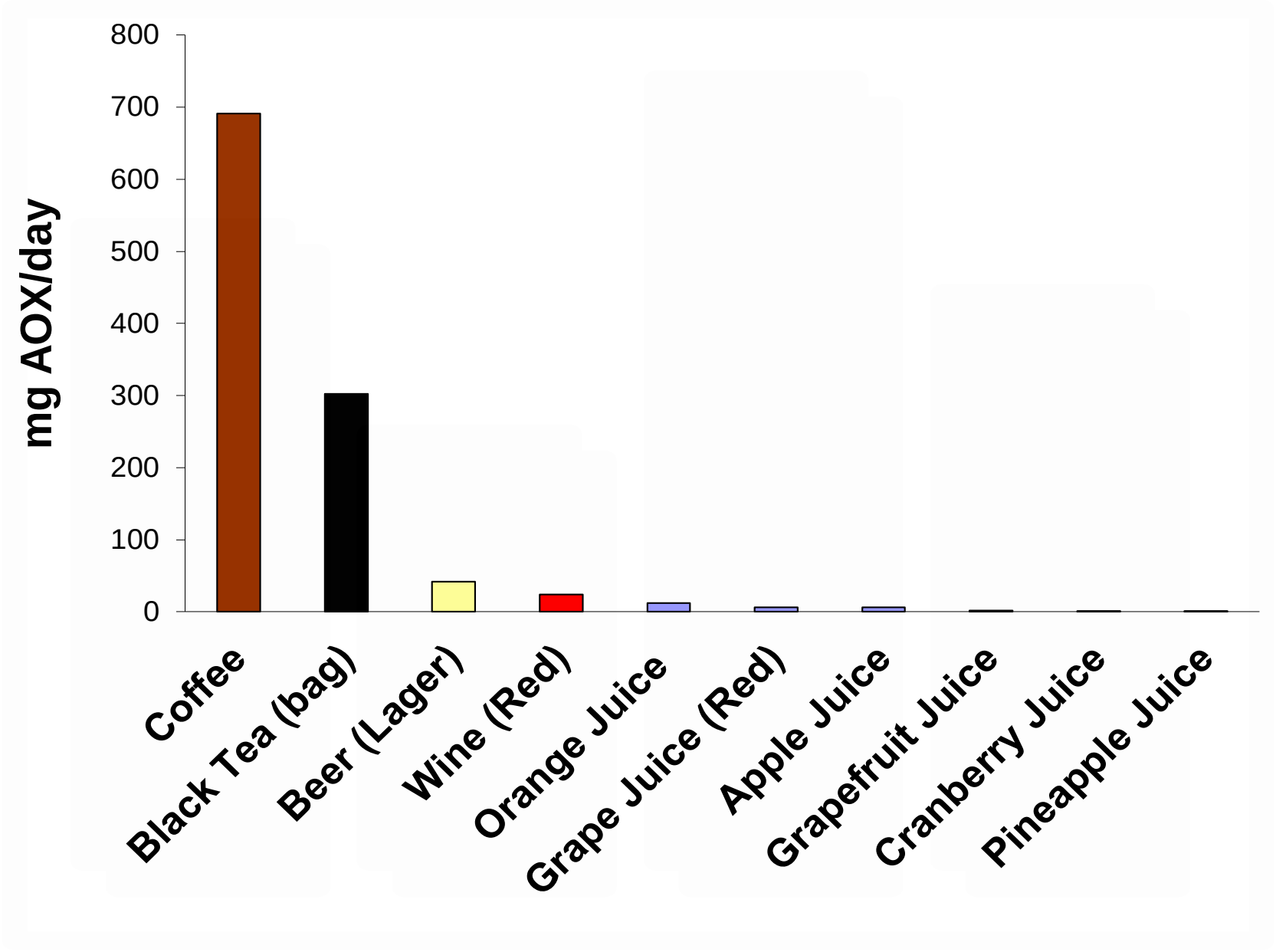
mg AOX/day
800
700
600
500
400
300
200
100
0
Coffee
Black Tea (bag)
Beer (Lager)
Wine (Red)
Orange Juice
Grape Juice (Red)
Apple Juice
Grapefruit Juice
Cranberry Juice
Pineapple Juice

Risk-Benefit Evaluation

and

The *"Holistic"* Approach

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“One by One” vs. the “Holistic” Approach

- **Foods and beverages contain huge numbers of different chemical components that can have directly opposite health effects**

- **Assessing these chemicals “one by one” is highly likely to be misleading and overly conservative, especially for carcinogens produced in complex heated foods**

- **I believe the correct way forward for complex heated foods requires the “Holistic” Risk-Benefit approach, as opposed to the current “one by one” chemical assessments.**

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BRAFO

This Specific Support Action project is carried out with the financial support of the European Commission, DG Research under the Sixth Framework Programme (FP6), Priority 5, Food Quality and Safety, Contract Number: FOOD-CT-2007-031731

Risk Benefit Analysis of Foods

As the burden of health costs within society increases due to a longer lifespan, overall balanced nutrition can play an important role in disease prevention. There is considerable disparity in the way benefits and risks are compared for compounds found in food, relying almost always on subjective judgement. This prevents adequate comparison of alternatives and renders resource prioritisation difficult. In addition, it is extremely difficult to provide comprehensible advice to consumers. It is therefore vital that an effective strategy be developed to enable a holistic analysis of the net health impact of chemicals in food to be assessed and quantified, in a manner analogous to the current assessment of risk.

ILSI

EU's "BRAFO" Project

www.brafo.org

- European Commission financial support; ILSI Europe coordination role; many institutes & universities; September 2007 – December 2010

- Impact of heat processing on foods (acrylamide, benzo(a)pyrene, furan, heat treatment of milk)

- Among the Key Questions:
  - What risks and benefits should be considered?
  - How do we handle different / sensitive population groups?
  - Where does risk-benefit assessment end and risk management by governments and health authorities begin?

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European Food Safety Authority

Committed to ensuring that Europe's food is safe

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Home > Scientific Documents > Guidance on human health risk-benefit asse...

- Definitions of EFSA scientific outputs
- Printed science publications
- Requests and mandates

Guidance on human health risk-benefit assessment of foods

Question number: EFSA-Q-2007-0043

Adopted: 29 June 2010

Summary (0.1 Mb)

Opinion (0.4 Mb)

Summary

The European Food Safety Authority (EFSA) asked its Scientific Committee to prepare a guidance document for performing risk-benefit assessments of food related to human health risks and human health benefits.

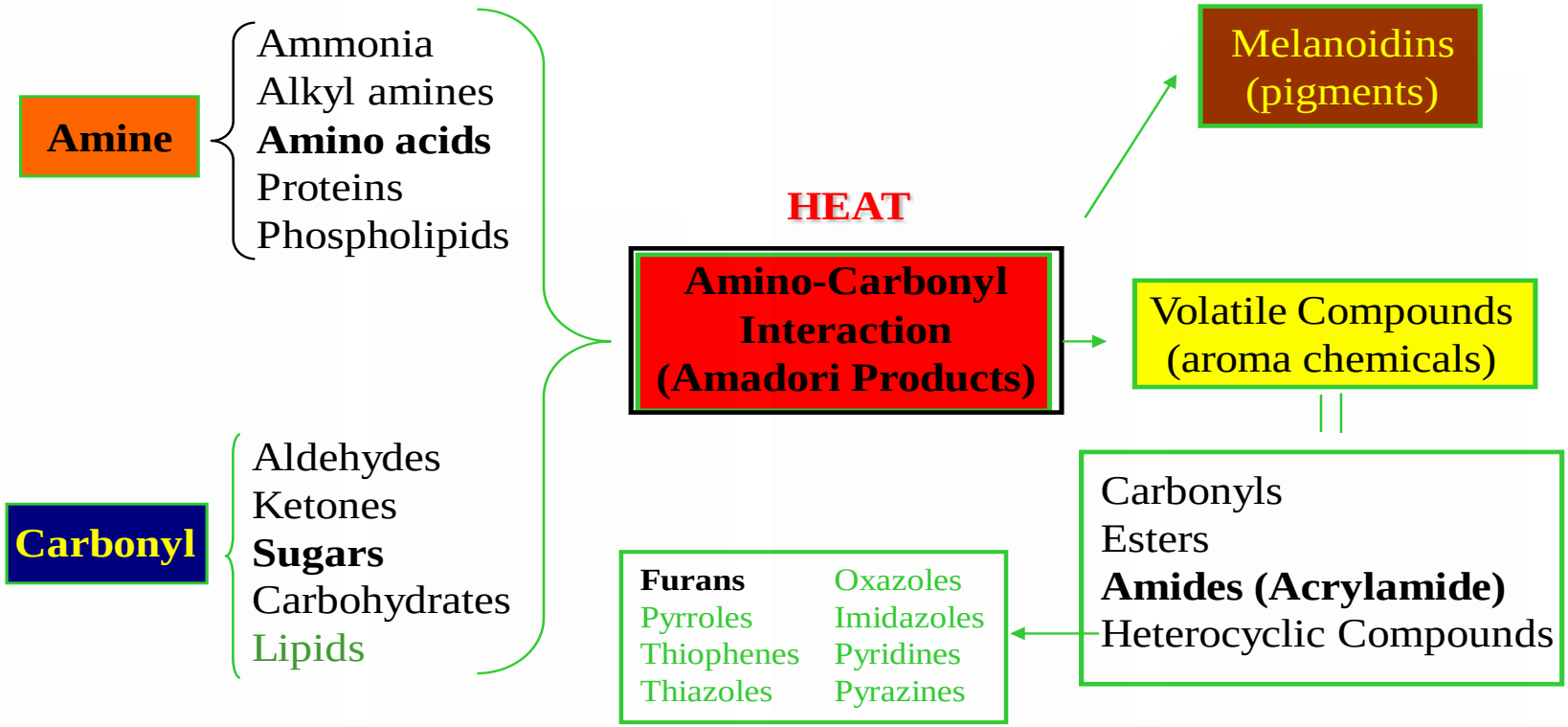
Risk-benefit assessments are performed in different disciplines, under various perspectives and use a wide range of quantitative or semi-quantitative tools. In this opinion, guidance for performing risk-benefit

COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Making Decisions about the Risks of Chemicals in Foods with Limited Scientific Information

An IFT Expert Report Funded by the IFT Foundation

General Scheme of Maillard Browning Reaction



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European Commission

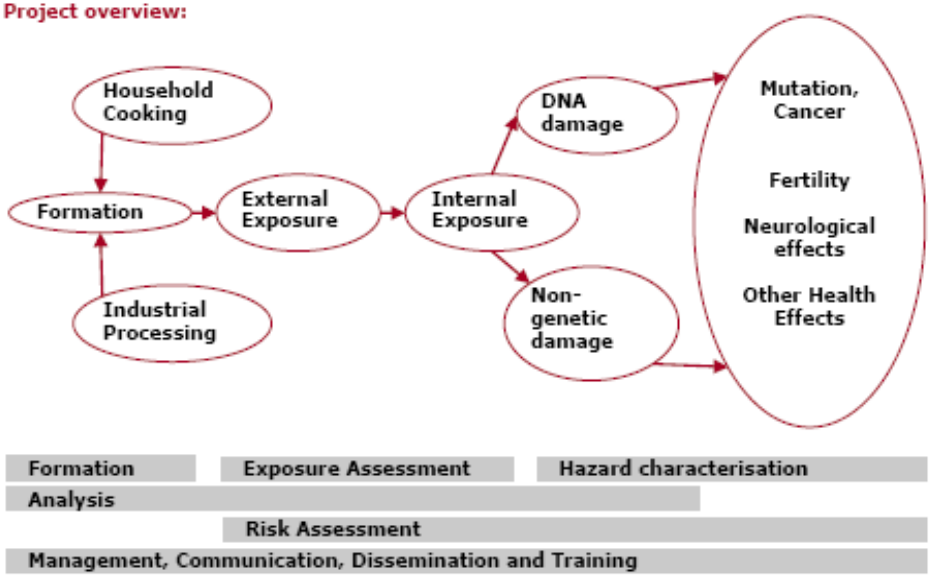
Food Quality and Safety

Project no. 506820 HEATOX

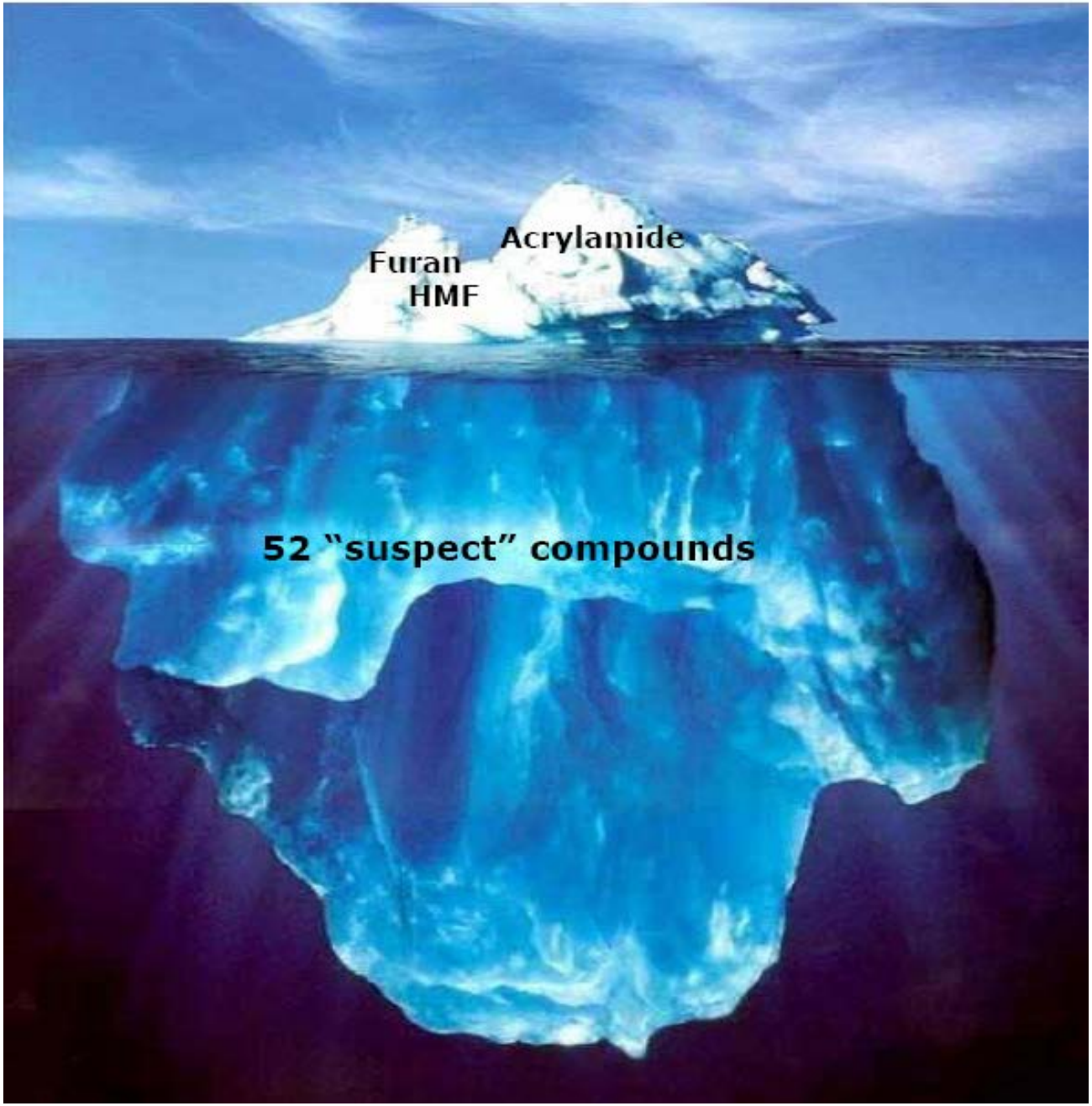
Heat-Generated Food Toxicants; Identification, Characterisation and Risk Minimisation

Co-ordinator: Kerstin Skog, Lund University
Scientific officer: Jürgen Lucas, European Commission

Project overview:



theheatoxproject


Acrylamide
Furan
HMF
52 "suspect" compounds

Acrylamide in Coffee

- Animal carcinogen found by Sweden in 2002 to be in hundreds of foods and beverages; French fries and potato crisps the highest
- Massive worldwide research effort by industry, academia and government; human epidemiology studies have found only a small relationship with ovarian and endometrial cancers
- Brewed coffee contains about 10 ppb, but is among the top 5 - 10 food contributors; however, coffee consumption reduces the risk of some cancers, including endometrial cancer
- Significant pressure on coffee because it is proving difficult to reduce the levels in roasted coffee.

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Furan in Brewed Coffee

- **Rat and mouse liver carcinogen; "possibly carcinogenic to humans" (IARC, 1995)**
- **"Margin of Exposure" calculations = 750 - 4,300 lower than the lowest risk level (Carthew et al., 2010)**
- **Brewed coffee reported up to 199 ppb (by far the highest dietary contributor of all foods and beverages); but coffee PROTECTS against human liver cancer!**
- **Guenther et al. (2010): furan is reduced significantly during roasting, grinding, storage, brewing and drinking; levels are closer to 10 - 35 ppb.**

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“Maillard Reaction Products” (MRPs) - Possible Beneficial Health Effects

- While flavors, aromas, colors and textures of browned foods depend on the MBR, animal carcinogens are also formed
- But Antioxidants are also produced by the MBR, and they may protect against diseases linked to oxidative damage (cancer, diabetes, atherosclerosis, arthritis, inflammation, etc.)
- The brown melanoidin polymers and some heterocyclic compounds (furan) have been shown to have antioxidant properties
- Some MRPs can also induce protective detoxification enzymes, including ones that detoxify the carcinogen acrylamide.

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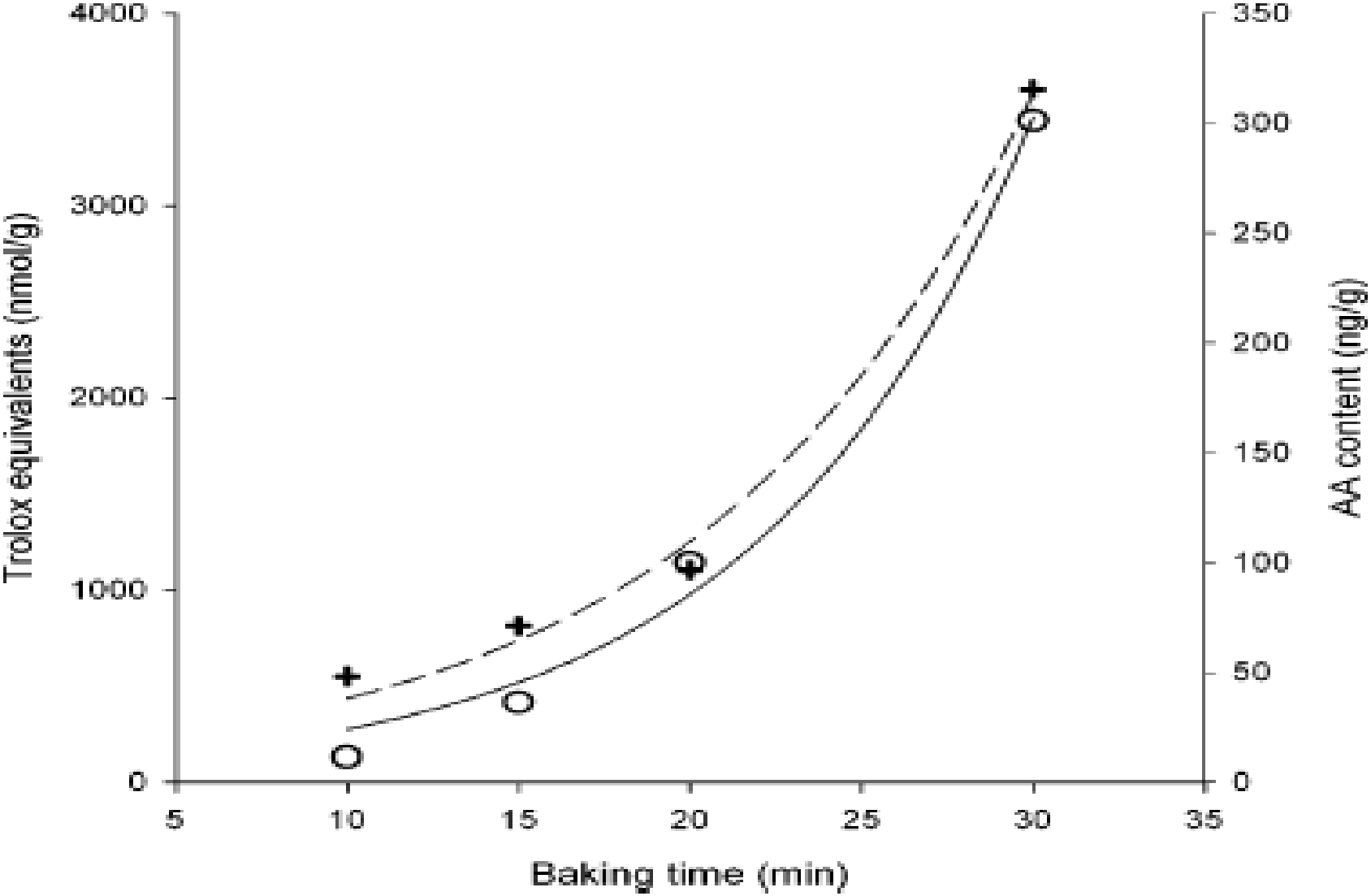

Figure 1. Influence of the baking time on the concentration of AA and on the AOA in recipe 2 cookies containing 37% (w/w) sucrose: (○) AA values; (+) AOA values; solid line, regression curve for AOA; broken line, regression curve for AA content.

“Coffee - Cancer Paradox”©

- Coffee contains nearly 2,000 compounds (many are flavors), including trace levels of dozens of animal carcinogens
- But global health authorities now agree that coffee drinking is NOT causing any significant increase in risk of cancer in any organ
- In fact, epidemiologic studies show significant reductions for liver, colorectal and endometrial cancer risks
- How can this be?
- Coffee’s naturally occurring antioxidants (chlorogenic acids) and heat-formed antioxidants (the brown melanoidin polymers), as well as other known and undetermined components, may be the keys to these cancer reductions.

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Use the Holistic Risk-Benefit Approach

- **The beneficial health effects of certain whole foods may outweigh the effects of trace levels of animal carcinogens and other toxicants – COFFEE is one of these foods!**

- **We must press global health and regulatory authorities to:**
  - ***Use improved toxicology and risk assessment methods on individual chemicals tested at high doses***
  - ***Do more research / evaluation on qualitative and quantitative assessment of the benefits of whole foods***
  - ***Consider the health benefits of protective compounds naturally occurring and produced by heating***
  - ***Assess the safety and benefits of the whole food, not just individual food carcinogens / toxicants one by one.***

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Hi-Ho, Hi-Ho, it's off to work we go.

THE *Health Beverage!*

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APPENDIX F

Reference: Proceeding of the 24th International Conference of the Association for Science and Information on Coffee (ASIC), San Jose, Costa Rica, November 12.

Coffee and Cancer: A Benefit-Risk Evaluation of the Experimental and Epidemiological Evidence

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SUMMARY

Animal carcinogens found in heated foods and beverages have been a significant health concern since the 1970's, when trace levels of these compounds were discovered in many foods. Many of these compounds have been studied in the U.S. National Toxicology Program's (NTP) carcinogen bioassays in rats and mice as well as in the European Union's HEATOX Project, including acrylamide, furan and 4-methylimidazole (4-MEI), all of which have been found in roasted coffee as a result of the Maillard Browning Reaction (MBR). Perhaps the most prominent animal carcinogen in coffee is acrylamide, but there is now extensive epidemiologic evidence indicating that it is not a human dietary carcinogen. Furan, a rodent liver carcinogen, is also well-known constituent in coffee, and coffee is known to be the primary dietary source of furan. But paradoxically, coffee consumption actually reduces the risk of human liver cancer, the target organ for furan. And 4-MEI has been shown to induce only mouse lung tumors in chronic testing, while in the same NTP bioassay it reduced the incidence of tumors in several organs of the rat.

Currently there is little human epidemiologic evidence linking these trace level animal carcinogens in coffee with the risk of human disease, including cancer. The health benefits of a food such as coffee, including the effects of many health-protective, naturally occurring compounds (e.g., chlorogenic acids) and those produced by heat in the MBR (e.g., melanoidins), are often neglected by public health and regulatory authorities when assessing the overall safety of a food. In fact, coffee consumption has actually been shown to reduce the risk of several human cancers while not increasing cancer risk in other organs systems, in spite of the fact that coffee contains trace levels of many animal carcinogens. While it is obviously important to evaluate the toxicological risks of individual heat-induced carcinogens in foods including coffee, it is equally important to fully evaluate the safety of whole foods containing these carcinogens using a combination of modern clinical, toxicological, nutritional and

epidemiological techniques using a benefit-risk evaluation of the whole food. Such an evaluation gives us the new concept of the "Coffee-Cancer Paradox."©

INTRODUCTION

The assessment of risk to human health of foods, food ingredients/contaminants and nutrients has historically been conducted independently of possible health benefits. In addition, different scientific approaches have been used to estimate health risks and benefits of foods and their constituents. When a food or food constituent is associated with both potential health risks and benefits, and when the health effects appear to be dependent on the level of intake, there is a need to determine a safe consumption range with an acceptable balance of risks and benefits.

The extensive database on the health effects of global coffee consumption developed over the past 30 years provides an excellent opportunity to investigate this balance between risks and benefits. While the health risks of coffee and its key ingredients, particularly caffeine, have been the focus of thousands of published scientific/medical studies addressing almost all known animal toxicity endpoints and human disease outcomes, more recent research attention has been focused on investigating the possible health benefits of coffee consumption. As evidenced by the conclusions of many recent expert reviews, a growing literature appears to be concluding that moderate coffee consumption may be associated with reduced risk of type 2 diabetes, coronary heart disease, Alzheimer's disease, Parkinson's disease and even some cancers, in addition to the well-established database on the benefits of human coffee and caffeine consumption in improving both physical and mental performance (Higdon and Frei, 2006).

In concert with this "good news" about coffee consumption are extensive investigations underway in many laboratories throughout the world to determine the biochemical mechanisms by which these beneficial health effects may be operating. One of the most exciting areas of mechanistic research is the possible cancer-protective role of coffee's naturally occurring polyphenolic antioxidants (the chlorogenic acid derivatives) (Hoelzl et al., 2010) and heat-produced antioxidants (various Maillard Reaction Products, including volatile heterocyclic compounds and brown melanoidin polymers) (Moreira et al., 2012; Somoza, 2005). Studies in many countries have shown that coffee is actually the major individual source of dietary antioxidant potential, and laboratory studies have shown that some coffee constituents can induce the formation of carcinogen-detoxifying enzymes such as glutathione-S-transferase, which has been shown to detoxify acrylamide in the human body. Therefore, while trace parts-per-billion levels of many animal carcinogens can be found in brewed coffee, there are also many compounds now identified in coffee that may reduce the risk of cancer.

What we do or don't eat or drink is oftentimes linked to an increased risk of human cancer, where we have witnessed the "carcinogen-of-the-month" syndrome. However, a great deal of this information has been preliminary in nature and based largely on extremely high-dose animal cancer studies and small epidemiologic studies. But once a larger body of studies has been accumulated, especially human studies as it has for

coffee over the past decade, the absence of any real human cancer concern over coffee has been demonstrated, and there is now strong evidence that coffee consumption is reducing the risk of several forms of human cancer. This paper will address key animal and human studies on coffee and its components and the need to take a "Holistic Approach" [a "risk vs. benefit" approach] in determining the health effects of coffee in today's diet, especially in relation to the possible protective effect of coffee in human cancer.

HUMAN EPIDEMIOLOGIC EVIDENCE

Coffee consumption is a major and frequent dietary exposure in diverse cultures around the globe, but its safety related to human cancer causation has been questioned and studied for decades. A substantial body of epidemiologic evidence (over 500 studies) relating coffee consumption to cancer of various organ sites has been accumulated to date. Numerous, organ-specific studies using meta-analysis, as well as comprehensive reviews, have been undertaken more recently, and have concluded that there is not only no increased cancer risk for numerous organs but also a reduced risk for several other forms of cancer.

With the emergence of many more studies over the past decade, Arab (2010) comprehensively reviewed and summarized the findings of meta-analyses and of more than 500 studies on site-specific human cancers among coffee consumers. This reviewer concluded that the evidence largely points to an overall lack of effect across all cancer sites (breast, pancreatic, kidney, ovarian, prostate, gastric cancer): "For most cancer sites, there is a significant amount of evidence showing no detrimental effect of consumption of up to 6 cups of coffee/day in relation to cancer occurrence. In fact, some of the evidence…suggests that coffee might prevent some cancers." Arab concluded that there is evidence of a strong and consistent preventive effect in hepatocellular and endometrial cancer and, possibly, breast cancer, and that the association between colorectal cancer appears to be borderline protective. She noted that the risk of bladder cancer appears to be very weak when associated with heavy coffee consumption in some study populations, but that this effect may be an indication of confounding by smoking.

In a review of methylxanthines and health, Beaudoin and Graham (2011) concluded that the research did not find a strong association between long-term coffee consumption and the risk of colorectal, breast, lung and bladder cancers. These reviewers found that the strongest beneficial association between coffee and cancer is for liver cancer and that this protective, dose-dependent association is evident even in low consumers (one cup of coffee daily). In another recent major review and meta-analysis of 59 epidemiological studies evaluating the risk of cancer associated with one cup/day increments of coffee consumption, the authors found that an increase in consumption of one cup of coffee per day was associated with a 3% reduced risk of cancers (Yu, et al., 2011). In subgroup analyses, the authors also noted that coffee drinking is associated with reduced risk of bladder, breast, buccal and pharyngeal, colorectal, endometrial, esophageal, hepatocellular, leukemic, pancreatic and prostate cancers. Findings from this meta-analysis suggest that coffee consumption may reduce total cancer incidence and it also has an inverse association with some types of cancers.

Another large-scale cohort study in Japan that followed 97,753 Japanese men and women aged 40-79 for 16 years found no association between coffee consumption and total cancer mortality among men, whereas a weak inverse association was found among women (Tamakoshi et al., 2011). And the European Investigation into Cancer and Nutrition (EPIC) prospective cohort study that investigated the association between coffee consumption and the risk of chronic diseases (including cancer) in the 42,659 participants that were followed over the 8.9 year period found no association between caffeinated or decaffeinated coffee consumption and total cancer risk (Floegel et al., 2012).

As noted above, there has been some concern that coffee consumption may be associated with a weak increase in risk of bladder cancer in some earlier studies. Zhou et al. (2012), however, recently evaluated 23 case-control studies with 7,690 cases and 13,507 controls, as well as 5 cohort studies with 700 cases and 229,099 participants. They concluded that although data from case-control studies suggested that coffee was a risk factor for bladder cancer, there was no conclusive evidence on this association because of inconsistencies between case-control and cohort studies.

ANIMAL CARCINOGENS IN COFFEE

Coffee contains trace levels of over two dozen identified animal carcinogens, including acrylamide, furan, caffeic acid, various aldehydes, polycyclic aromatic hydrocarbons, ochratoxin A and others. While a few of these chemicals are naturally occurring in green coffee beans, many of the others are chemicals formed at trace levels during the roasting of coffee by means of the Maillard Browning Reaction (MBR) (Somoza, 2005). Carcinogens from heated foods, produced by the MBR between carbohydrates and amino acids and proteins, have been a health concern since the 1970s. Following acrylamide's discovery in foods, the European Commission undertook a 40-month project to research and evaluate many heat-generated food toxicants and issued a very comprehensive report on this effort (HEATOX Project, 2007). But an important toxicological consideration that has received little attention to date is that many MBR products are beneficial to health because many demonstrate anti-oxidative, anti-mutagenic and anti-carcinogenic properties, and some MBR products even induce the formation of carcinogen-detoxifying enzymes such as glutathione-S-transferase.

For roasted coffee overall, however, the International Agency for Research on Cancer (IARC, 1991) concluded that animal studies of long-term coffee consumption (brewed and dried instant coffee powder) have demonstrated no increased risk of cancer. But it is important here to discuss two animal carcinogens in coffee, acrylamide and furan, each of which has gained widespread attention and concern over the past decade.

Acrylamide.

Acrylamide was discovered in a wide array of carbohydrate-rich Maillard browned foods by Swedish researchers and was first reported in 2002 (see Lineback et al., 2012 for a comprehensive review). Coffee was one of many browned products shown to contain acrylamide (typical levels in brewed coffee are 8-13 parts per billion). As

noted in Figure 1, much has been learned about acrylamide's toxicology and carcinogenicity, including the recent reporting of the NTP two-year chronic carcinogenicity bioassay of acrylamide in rats and mice (Beland et al., 2013). The updated NTP animal tumor results should now lead the FAO/WHO Joint Expert Committee on Food Additives (JECFA) to reevaluate the human risk of acrylamide. JECFA should consider dismissing consideration of the NTP's benign tumors in the rat mammary gland and mouse Harderian gland as not biologically relevant to human risk assessment.

Figure 1. Acrylamide Snapshot: Chemistry and Toxicology

- Human occupational neurotoxin, genotoxic / mutagenic in cell cultures
- Known rat carcinogen, classified as a "probable human carcinogen"
- Metabolized to glycidamide (an epoxide), an animal carcinogen
- Acrylamide & glycidamide can bind to DNA/amino acids/proteins
    - DNA adducts → carcinogenic potential
    - Blood hemoglobin adducts → biomarker of exposure
    - Dietary proteins may reduce acrylamide uptake in humans
    - Protective enzymes can detoxify acrylamide and glycidamide
- NTP Acrylamide Bioassay (July 2012 Report) –

  "Clear Evidence of Carcinogenicity" for male and female rats and mice

---

While these were the most sensitive tumor endpoints, they are not malignant tumors and are not tumor types relevant to human risk. Therefore, JECFA and others (FDA, European Union, Health Canada) should reevaluate acrylamide's potential for human risk based on the lower incidences of more relevant NTP malignant rat and mouse tumor endpoints, since acrylamide is too important and too widespread a contaminant in the human diet to have its risk determined by biologically irrelevant rodent tumor endpoints and with no consideration of acrylamide's lack of increased risk in humans.

There are two recent comprehensive reviews of dietary acrylamide's human cancer epidemiology. The first concluded that "Available studies consistently suggest a lack of an increased risk of most types of cancer from exposure to acrylamide" (Pelucchi et al., 2011). And more recently Lipworth et al. (2012) concluded that "…epidemiologic studies of dietary acrylamide intake have failed to demonstrate an increased risk of cancer." The authors further concluded that "…continued epidemiologic investigation of acrylamide and cancer risk appears to be a misguided research priority."

Most of the major countries of the world have advised consumers to follow the dietary recommendations for a balanced diet issued by their food regulatory and public health agencies. The data available to date have been insufficient to warrant any

recommendation for a significant change in dietary recommendations because of acrylamide's occurrence in foods. Current epidemiologic and toxicologic evidence are insufficient to indicate that the amounts of acrylamide consumed in the normal diet are likely to result in adverse human health effects, particularly cancer.

So, does acrylamide in foods, including coffee, pose a real risk to human health? We conclude that, in spite of acrylamide's known animal carcinogenicity, the human cancer epidemiology database is reassuring and supports the conclusion that there is little if any increased cancer risk in humans. Furthermore, acrylamide's potential dietary risk should be assessed in light of the known health-protective, beneficial components of many acrylamide-containing foods.

Furan.

Furan is a simple heterocyclic flavor compound produced by heating many foods and beverages, and it has been known for decades to occur at trace ppb levels in many heat-processed foods (e.g., coffee and other browned foods). Its formation, exposure, toxicity, carcinogenicity and aspects of its risk assessment have recently been reviewed (Moro et al., 2012). Furan is a known rat and mouse liver carcinogen and has been classified by IARC as "possibly carcinogenic to humans." Brewed coffee has been found to be responsible for about 70% of total furan exposure in the human diet. It has been reported at levels up to about 200 ppb in some roasted, but Guenther et al. (2010) demonstrated that furan is reduced significantly during roasting, grinding, storage, brewing and drinking, and that actual levels in roasted coffees are probably closer to 10-35 ppb.

Furan, however, is certainly the best example of the "Coffee-Cancer Paradox"© (discussed below). While furan has been shown to produce only liver tumors in rats and mice, and although coffee is the top dietary contributor to furan intake, the human cancer epidemiology described above shows that coffee consumption actually protects against human liver cancer in spite of the presence of this animal liver carcinogen.

BENEFIT-RISK EVALUATION – THE "HOLISTIC APPROACH"

Considerations of comparing health risks and benefits are critical in determining whether the consumption of a particular food or beverage should be considered safe. Consequently, benefit-risk evaluation is absolutely essential to assess the safety of foods containing heat-produced carcinogens. Regulators and public health authorities have been much too focused in the past decades on simply evaluating the risk of individual chemicals in a food or beverage one by one. Thus, we believe that the correct approach going forward is to evaluate the safety of the whole food by comparing its risks vs. benefits using the "Holistic Approach."

Various "benefit-risk" evaluations have recently been undertaken around the world. The U.S. FDA's 2009 "Draft Risk and Benefit Assessment of Fish" evaluated the risks of methyl mercury contamination vs. health-protective omega-3 fatty acids. The European Food Safety Authority has provided detailed guidance on human health risk-

benefit assessment of foods (EFSA, 2010). Some additional expert guidance was also provided by the *Risk-Benefit Analysis for Foods* (BRAFO) project, an effort funded by the European Commission and coordinated by the International Life Sciences Institute/Europe to develop a framework that allows a quantitative comparison of human health risks and benefits of foods and food compounds, using a common scale of measurement (Hoekstra et al., 2012). A very ambitious evaluation of acrylamide's benefit-risk considerations was contained in a comprehensive expert report that was commissioned by the International Life Sciences Institute/Europe, an effort by 12 collaborating institutes, universities and food companies (Seal et al., 2008). This study reported on risk-benefit considerations of mitigation measures on the acrylamide content of foods, including case studies on potatoes, cereals and coffee. Key issues addressed were the impact of pre-harvest, post-harvest and processing conditions on acrylamide formation, consideration of the nutritional value and beneficial health impact of consuming these commodities and the calculated impact of mitigation using probabilistic risk-benefit modeling to demonstrate the principle of this approach.

When both the benefits and risks of a heat-processed food are assessed, instead of just a single focus on one carcinogen in this food, the beneficial health effects of certain whole foods may be shown to outweigh the health effects of trace levels of animal carcinogens and other toxicants in these foods. We believe that coffee is one of the best examples of such a food, where the health benefits of its constituents do outweigh the risks. Coffee's benefit-risk evaluation, therefore, provides us with some key principles that should be taken into account when evaluating the safety of a whole food:

(1) we must press global health and regulatory authorities to use improved toxicology, epidemiology and risk assessment methods on individual carcinogens tested at very high doses in animals;
(2) we must undertake more research and evaluation on both the qualitative and quantitative assessment of the benefits of whole foods;
(3) we must consider the health benefits of protective compounds both naturally occurring and those produced by heating; and
(4) we must assess the safety and benefits of the whole food, not just individual food carcinogens and toxicants one by one.

THE "COFFEE-CANCER PARADOX"©

Coffee contains about 2,000 identified compounds (hundreds are flavors and aromas), including trace levels of many animal carcinogens noted above. But global health and regulatory authorities now agree that coffee consumption is not causing any increased risk of human cancer, and in fact, epidemiological studies show significant risk reductions for several forms of human cancer in spite of the trace level presence of numerous animal carcinogens. How can this paradox be explained? We believe that the presence of many health-protective compounds in roasted coffee may be responsible for the observed cancer risk reductions, including naturally occurring antioxidants (the chlorogenic acids), heat-formed antioxidants (the brown melanoidin polymers), inducers of detoxification enzymes such as glutathione-S-transferase and numerous as yet identified beneficial compounds. So herein lies the "Paradox" –

although coffee contains numerous animal carcinogens, the consumption of the whole food product most likely reduces human cancer risk. This conclusion can serve as the basis for using a similar "Holistic Approach" in conducting benefit-risk evaluations on a wider range of other heat-processed food products beyond coffee.

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APPENDIX G

Heat-Processed Carcinogens: What Can We Learn from the "Coffee-Cancer Paradox"©

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CoCoTea 2013

Second International Congress

Naples, Italy

October 9, 2013

Outline of “Concepts” Paper

- ✓ **My Historical Perspective on Coffee & Health**
- ✓ **Animal Carcinogens in Coffee**
- ✓ **Epidemiologic Evidence on Coffee and Cancer**
- ✓ **California Proposition 65 Battleground**
- ✓ **Benefit-Risk Evaluation -**
  - **– The “Holistic Approach”**
  - **– The “Coffee-Cancer Paradox”©**

A 32-Year Coffee/Caffeine Health Perspective

…on Rats, Mice & Humans

…on Almost Every Disease

…on "Good" & "Bad" Science and Policy

…on "Good" & "Bad" Media Coverage

…on Coffee/Caffeine's Beneficial Health Effects

…on "Holistic" Benefit-Risk Evaluation

Coffee & Caffeine Health Conclusions: 1981 - 2013

… **First 20 Years**:

Mostly Bad News! Coffee and Caffeine were linked to almost every known animal and human disease!

… **Last 15 or so years…Big Turn Around:**

The "Good News" is that almost all of the Bad News was WRONG…and coffee may actually be good for us!

[My collaborations with NCA/SAG, ASIC and ILSI Caffeine Committee since 1981; IFIC Caffeine Committee since 1987; PEC Committee & ISIC in Europe since late 1980's]

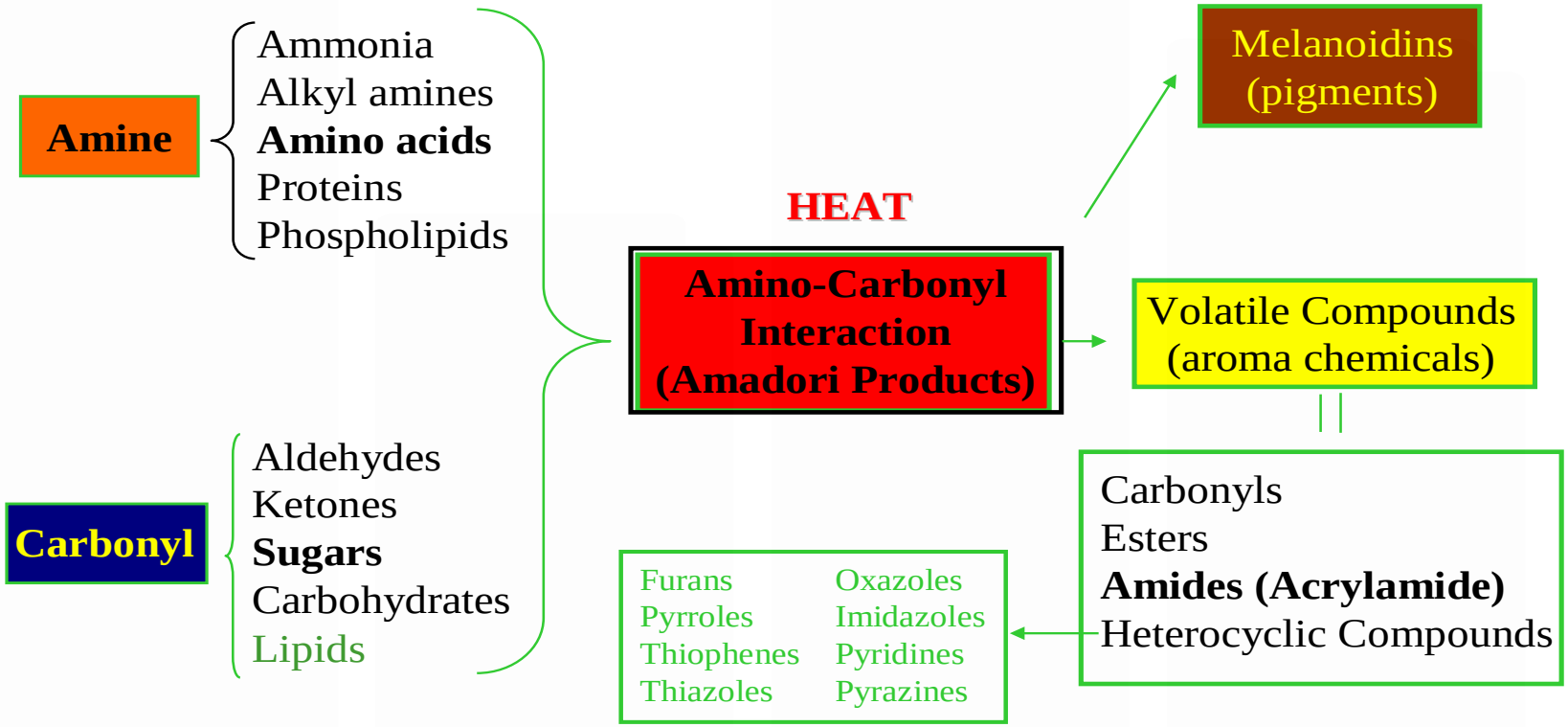
So with all this good news, why are we still concerned?

~

We Just Can't Escape the <u>Animal</u> Carcinogens in Coffee

Acrylamide is not the sole problem.

General Scheme of Maillard Browning Reaction



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DOI: 10.1080/01635580903407122

Epidemiologic Evidence on Coffee and Cancer

Lenore Arab
David Geffen School of Medicine, University of California at Los Angeles, USA

"FOR MOST CANCER SITES, THERE IS A SIGNIFICANT AMOUNT OF EVIDENCE SHOWING <u>NO DETRIMENTAL EFFECT</u> OF CONSUMPTION OF UP TO 6 CUPS OF COFFEE/DAY IN RELATION TO CANCER OCCURRENCE. IN FACT, SOME OF THE EVIDENCE…SUGGESTS THAT <u>COFFEE MIGHT PREVENT SOME CANCERS</u>."
[REVIEW BASED ON OVER 500 PUBLICATIONS]

Yu et al. BMC Cancer 2011, 11:96
http://www.biomedcentral.com/1471-2407/11/96

BMC Cancer

RESEARCH ARTICLE Open Access

Coffee consumption and risk of cancers: a meta-analysis of cohort studies

Xiaofeng Yu, Zhijun Bao, Jian Zou*, Jie Dong

Abstract

Background: Coffee consumption has been shown to be associated with cancer of various sites in epidemiological studies. However, there is no comprehensive overview of the substantial body of epidemiologic evidence.

Methods: We searched MEDLINE, EMBASE, Science Citation Index Expanded and bibliographies of retrieved articles. Prospective cohort studies were included if they reported relative risks (RRs) and corresponding 95% confidence intervals (CIs) of various cancers with respect to frequency of coffee intake. We did random-effects meta-analyses and meta-regressions of study-specific incremental estimates to determine the risk of cancer associated with 1 cup/day increment of coffee consumption.

Results: 59 studies, consisting of 40 independent cohorts, met the inclusion criteria. Compared with individuals who did not or seldom drink coffee per day, the pooled RR of cancer was 0.87 (95% CI, 0.82-0.92) for regular coffee drinkers, 0.89 (0.84-0.93) for low to moderate coffee drinkers, and 0.82 (0.74-0.89) for high drinkers. Overall, an increase in consumption of 1 cup of coffee per day was associated with a 3% reduced risk of cancers (RR, 0.97; 95% CI, 0.96-0.98). In subgroup analyses, we noted that, coffee drinking was associated with a reduced risk of bladder, breast, buccal and pharyngeal, colorectal, endometrial, esophageal, hepatocellular, leukemic, pancreatic, and prostate cancers.

Conclusions: Findings from this meta-analysis suggest that coffee consumption may reduce the total cancer incidence and it also has an inverse association with some type of cancers.

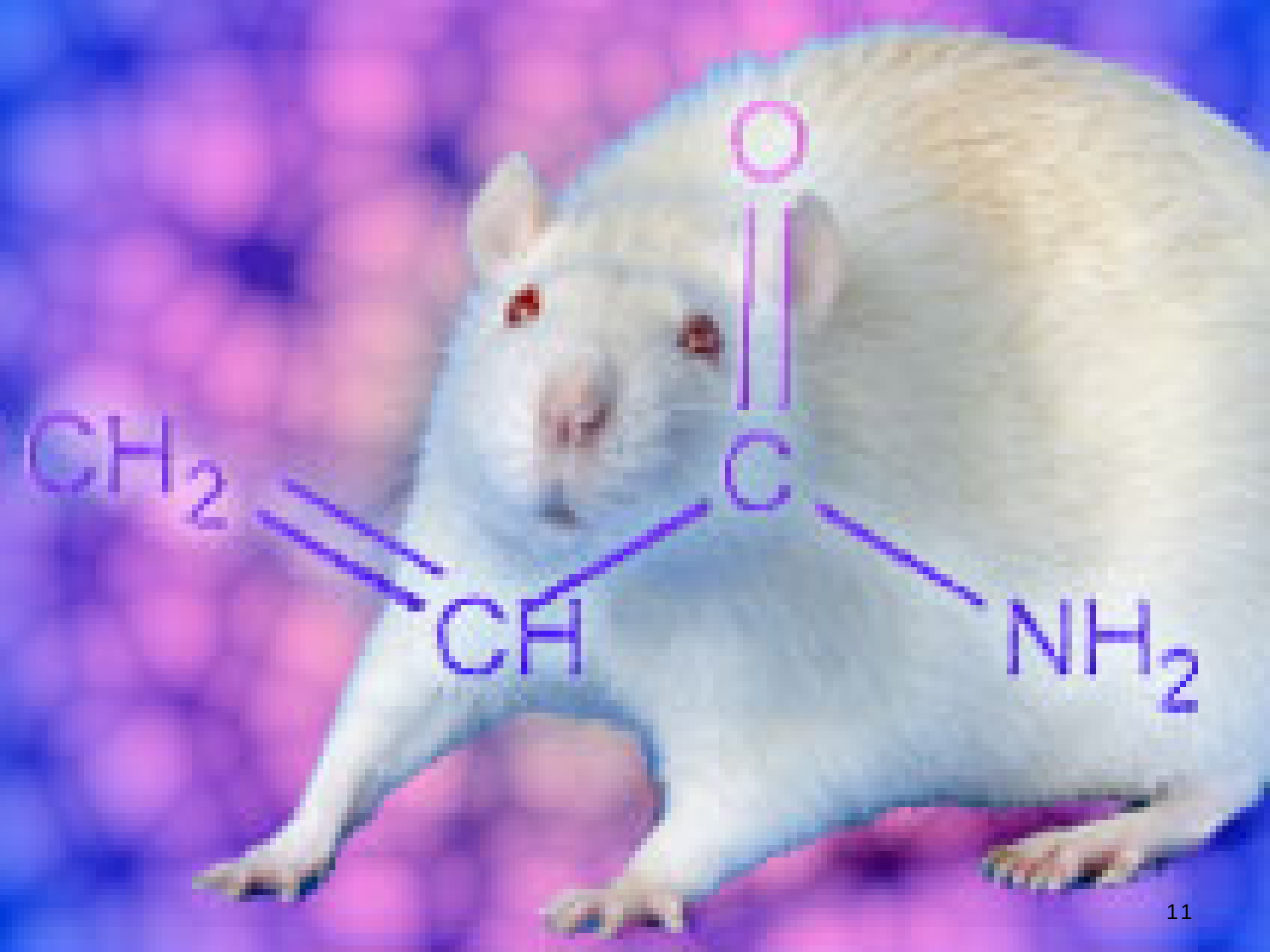
The “Coffee-Cancer Paradox”©

- ✓ **Coffee contains ~ 2,000 identified compounds (mostly flavors & aromas), including trace levels of dozens of animal carcinogens [acrylamide, furan, 4-MEI, caffeic acid, PAHs, aldehydes & dicarbonyls, OTA, metals, etc.]**

- ✓ **But human studies show significant risk reductions for numerous cancer sites, in spite of the presence of these animal carcinogens**

The Paradox then –

Coffee is loaded with animal carcinogens but most likely reduces human cancer risk!


CH2
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Review of epidemiologic studies of dietary acrylamide intake and the risk of cancer

Loren Lipworth[a,b], Jennifer S. Sonderman[a], Robert E. Tarone[a,b] and Joseph K. McLaughlin[a,b]

Conjectured associations between dietary acrylamide intake and cancer have been evaluated in more than 15 epidemiologic studies examining almost every major cancer site. We have critically reviewed the epidemiologic studies of estimated dietary acrylamide exposure and cancer. As substantially greater acrylamide exposure occurs through tobacco smoke than dietary exposure, we present the results separately for never smokers or adjusted statistically for smoking status, where possible. After an extensive examination of the published literature, we found no consistent or credible evidence that dietary acrylamide increases the risk of any type of cancer in humans, either overall or among nonsmokers. In particular, the collective evidence suggests that a high level of dietary acrylamide intake is not a risk factor for breast, endometrial, or ovarian cancers, which have generated particular interest because of a conjectured hormonal mechanism of acrylamide. Moreover, the absence of a positive association between smoking and ovarian and endometrial cancers suggests that any association of these cancers with the much lower, more sporadic dietary acrylamide intake is unlikely. In conclusion, epidemiologic studies of dietary acrylamide intake have failed to demonstrate an increased risk of cancer. In fact, the sporadically and slightly increased and decreased risk ratios reported in more than two dozen papers examined in this review strongly suggest the pattern one would expect to find for a true null association over the course of a series of trials. Therefore, continued epidemiologic investigation of acrylamide and cancer risk appears to be a misguided research priority. *European Journal of Cancer Prevention* 21:375–386 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: acrylamide, breast, cancer, diet, endometrial, epidemiology, ovarian, review

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Acrylamide in Foods: A Review of the Science and Future Considerations

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“Proposition 65”

California Law

“Safe Drinking Water and Toxic Enforcement Act of 1986”

- Right-to-Know Warnings

- Prohibition of Discharge

Welcome to
SUN! FUN!
CALIFORNIA
WARNING: THIS STATE CONTAINS CHEMICALS KNOWN TO THE STATE OF CALIFORNIA TO CAUSE CANCER, BIRTH DEFECTS, OR OTHER REPRODUCTIVE HARM.
2006
CENTER FOR CONSUMER FREEDOM

Acrylamide Battleground under Prop 65

- ✓ **Listed as carcinogen 1990; "Safe Harbor" level = 0.2 µg/day; but if it's just detectable, even a 1-ounce serving of any food exceeds this level**
- ✓ **French Fries & Potato Chips: Attorney General's cases settled in 2008; warnings up on fries, none on chips**
- ✓ **Cereals: 2009 "Bounty hunter" suit still pending**
- ✓ **"Brewed" Coffee suit: April 2010, ~ 10 ppb, cancer warning signs went up in coffee shops a year later**
- ✓ **"Roasted" Coffee suit: May 2011, a huge court battle is still ongoing.**

California Coffee Shops' Proposition 65 Warning

Human Relevance of Rodent Cancer Bioassays is Being Questioned

- Some eminent toxicologists have questioned the human relevance of tumors seen in lifetime rodent cancer bioassays
- They believe it's time to STOP doing chronic rodent bioassays at the "Maximum Tolerated Dose" (MTD)
- We toxicologists make two possibly flawed assumptions about chronic cancer bioassay results…
  - Dose Extrapolation – effects seen at high rodent doses will also occur at much lower human doses
  - Species Extrapolation – if cancer is seen in rodents, then cancer probably occurs in humans
- BUT…we need to better understand Mechanisms and Modes of Action for a chemical, before we can reliably use bioassay tumor results for regulatory or warning purposes.

Using a Benefit-Risk Approach for Coffee…

"Holistic Approach"

&

"Coffee - Cancer Paradox"©

Key “Risk-Benefit” Controversies

- ✓ **Interpretation of rodent cancer bioassays of extreme chemical doses has been shown to be overly conservative**
- ✓ **In the past, we have assessed individual food chemicals one by one, but we need to consider risks & benefits of whole foods using a “Holistic Approach”**
- ✓ **Failure to give proper weight to human epidemiology studies showing little or no increased risk of foods containing the chemical**
- ✓ **Failure to consider the POSITIVE health benefits of foods containing only trace levels of carcinogens & toxicants.**

Potential Mechanisms for the "Coffee-Cancer Paradox"©

- ✓ **Naturally occurring PP antioxidants (chlorogenic acids)**
- ✓ **Heat-formed PP compounds (the melanoidin polymers) – chemopreventive, antioxidant, antimicrobial, dietary fiber, metal chelation**
- ✓ **N-methylpyridinium ion induces detoxification enzymes like GST (e.g., for acrylamide detoxification)**
- ✓ **To determine coffee's overall cancer risk to humans, we must:**
  - ✓ **Continue to study the health effects of coffee's naturally occurring and heat-produced compounds, both "bad" and "good"**
  - ✓ **Recognize that some of these compounds may be health-protective and outweigh the effects of trace levels of carcinogens.**

What Can We Learn from the "Coffee-Cancer Paradox"©?

- ✓ **The beneficial health effects of certain whole foods may outweigh the effects of trace levels of animal carcinogens and other toxicants – COFFEE is one of these foods!**

- ✓ **The animal cancer bioassays of individual MTD-tested carcinogens (like acrylamide and furan) have probably been giving us false signals of risk**

- ✓ **We must press global health and regulatory authorities to:**
  - ✓ ***Use improved toxicology and risk assessment methods on individual chemicals tested at high animal doses***
  - ✓ ***Do more research & evaluation on qualitative and quantitative assessment of the benefits of whole foods***
  - ✓ ***Consider the health benefits of protective compounds both naturally occurring and produced by heating***
  - ✓ ***Assess the safety and benefits of the whole food, not just individual food carcinogens / toxicants one by one.***

ASIC COLOMBIA

Leveraging knowledge for coffee sustainability

SAVE THE DATE

The 25th International Conference on Coffee Science

September 8 - 14, 2014

Armenia, Colombia

DISCOVER HOW SCIENCE AND KNOWLEDGE CAN PAVE THE WAY FOR COFFEE SUSTAINABILITY

Contact Us : asic.2014@cafedecolombia.com

ASIC
Association for Science and Information on Coffee
Association pour la science et l'information sur le café

Café de Colombia

Hi-Ho, Hi-Ho, it's off to work we go.

Thank You!

Questions?