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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 → 55 (usually chosen as the quantifier), 72 → 54, 72 → 44, 72 → 27, and for the internal standard ($^{13}C_3$-acrylamide), 75 → 58 as quantifier and 75 → 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 ($\mu g\ kg^{-1}$ 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

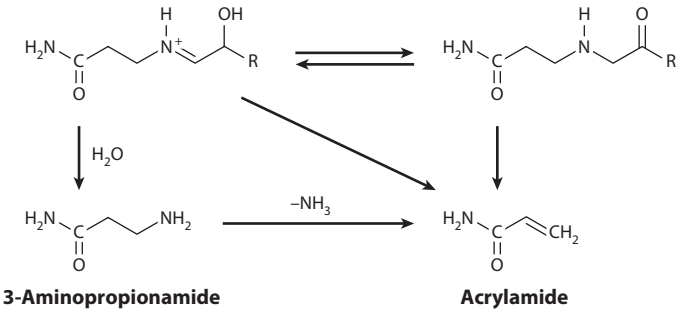

Figure 1

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

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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.

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

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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).

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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.

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