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ACRYLAMIDE IN FOOD

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INTRODUCTION

In April 2002, researchers at the Swedish National Food Administration and Stockholm University, using a new analytical procedure, announced they had discovered the presence of acrylamide in foods prepared by heating (frying, baking) at temperatures above 120°C (Swedish 2002; Tareke et al. 2002). Identification of acrylamide in these foods, which include french fries, potato chips (crisps), cookies (biscuits) and crackers, crispbreads, breakfast cereals, corn chips (crisps), and soft breads, had not been reported previously and the discovery prompted numerous verification studies in other European countries and in North America.

Acrylamide is a toxic, cancer-causing industrial chemical used primarily in the preparation of polyacrylamide (polymerized acrylamide), which is used principally in water and wastewater treatment and in pulp and paper processing. Most previous toxicological data on acrylamide were gathered from high-dose animal studies or from human exposure in the workplace. Before the Swedish study, no data were available on the effects of acrylamide at the low concentrations observed in food (i.e., in the microgram (µg)/kilogram (kg) [parts per billion (ppb)] range).

So acrylamide is not new, but its presence in food is newly discovered. Increased concern about the effect of acrylamide on human health prompted the United Nations' Food and Agricultural Organization (FAO) and the World Health Organization (WHO) to convene an Expert Consultation on "Health Implications of Acrylamide in Food" in June 2002 (UNFAO/WHO 2002). Numerous gaps in knowledge concerning the formation, occurrence, dietary exposure, and potential for adverse health risks of acrylamide were identified, and the resulting recommendations called for additional research on these topics. One of the foremost needs was to determine the range of affected food types and the extent to which acrylamide was formed, especially in non-Western diets. There seemed to be no urgent reason to promulgate new dietary guidance because, among other considerations, acrylamide is not new to the human food supply and the anticipated amount of human consumption is well below the amounts required to induce toxic effects in animal models.

Research efforts since April 2002 reflect an unprecedented extent of cooperation among scientists worldwide. Numerous international meetings have been held. Euro-

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pean food industries have shared research results widely through the Confédération des Industries Agro-Alimentaires de l'UE (CIAA). In the United States, release of research by the foods industry has been constrained, probably because of Proposition 65 in the state of California (California 1986), which allows the state to declare that a chemical is known to cause cancer or reproductive toxicity. When a chemical is so listed, as acrylamide was in 1990, a warning label is required or the manufacturer may be subject to civil penalties. The minimum level triggering a warning label (No Significant Risk Level [NSRL]) was set at 0.2 μg acrylamide/person/day. A recent proposal from the state of California would raise this level to 1.0 μg acrylamide/person/day for most foods and would establish an Alternative NSRL of 200 ppb acrylamide in breads and breakfast cereals (California 2005). Because no analogous regulation currently exists in Europe, it is not surprising that information on acrylamide in food is shared more freely in Europe than in the United States.

The call for reliable scientific information on this subject continues to increase significantly, especially after a preliminary risk assessment by the Joint Expert Committee on Food Additives (JECFA) in 2005, which proposed to reevaluate acrylamide as the results from new studies become available (JECFA 2005). The JECFA also recommended that appropriate efforts to reduce acrylamide concentration in foods continue, and that national authorities should continue to provide general advice on healthy eating (JECFA 2005). Currently there is no single method that works universally for reducing the amount of acrylamide in foods; the reduction must be addressed on a case-by-case basis for each food.

These considerations led the Council for Agricultural Science and Technology (CAST) to produce this Issue Paper. Specific topics addressed herein include acrylamide formation and detection, methods of mitigation and reduction, dietary exposure, toxicology and epidemiology, and the elements of accurate, effective risk communication.

Acrylamide Content in Foods

Acrylamide is found in many common food products; in total, these foods represent approximately 40% of calorie intake (Petersen 2003; Tareke et al. 2002). Acrylamide is present mostly in plant-based foods, in particular potato and wheat products that are cooked at high temperatures. Exposure assessments have identified those foods that contribute most significantly to intake. In general, fried potato products and breakfast cereals are the most significant sources of dietary acrylamide in the U.S. diet, but bread and coffee also are important sources (Table 1). For infants and children, cookies (biscuits) may be a significant source of acrylamide.

Not surprisingly, the top acrylamide sources vary somewhat by country, depending on local food choices

Table 1. Top 20 foods for acrylamide intake by consumption in the United States (USFDA-CFSAN 2004)

Food	Mean Acrylamide Intake (μg/kg-body weight [bw]/day)
French fries (fried)	0.058
French fries (oven baked)	0.051
Breakfast cereal	0.043
Potato chips	0.041
Cookies	0.036
Brewed coffee	0.029
Toast	0.023
Pies and cakes	0.020
Soft bread	0.019
Chile con carne	0.015
Corn snacks	0.011
Crackers	0.011
Pizza	0.007
Pretzels	0.007
Popcorn	0.007
Canned black olives	0.005
Peanut butter	0.004
Bagels	0.004
Soup mix	0.003
Breaded chicken	0.003

(Dybing et al. 2004). Food items with relatively low acrylamide concentration, consumed in great quantities—such as bread—may be important sources of acrylamide exposure because exposure considers both acrylamide concentration and food consumption. Several studies also have made the important point that the food groups contributing most to exposure are different for the low-percentile, average, and high-percentile consumer (Matthys et al. 2005).

Cooking temperature is directly related to acrylamide concentration. In general, the higher the cooking temperature, the higher the concentration of acrylamide. For example, bread crust, which reaches higher temperatures than the soft part of bread called the crumb, has more acrylamide than the crumb. In some products such as roasted coffee, however, prolonged heating or heating at very high temperatures can decrease acrylamide. No acrylamide has been reported in uncooked foods.

Acrylamide in Foods Cooked at Home

A significant source of dietary acrylamide is foods cooked and prepared at home, by catering services, or served in restaurants. For example, when bread (white or brown) is toasted, the acrylamide content increases by nearly tenfold depending on the toasting time and temperature (Ahn et al. 2002). Approximately 50% of acrylamide intake may be from such sources, but quantitative data are scarce (Dybing et al. 2005; Stadler and Scholz 2004).

Food Databases

The U.S. Food and Drug Administration (FDA) and European food authorities have established publicly avail-

able online databases for acrylamide concentration in foods (see USFDA–CFSAN 2006 for web link). In Europe, there also is a monitoring database that was set up between the European Union (EU) Joint Research Centre and the WHO (see EU/WHO 2006 for web link). Data listed on both the FDA and European sites indicate that potato products and ground coffee are among the foods that produce the greatest exposure to acrylamide (Stadler and Scholz 2004). Other comparisons are difficult to make because of the different food categories used, but in general, the overall median concentrations of acrylamide in similar categories are lower in the FDA database.

Analytical Methods to Quantify Acrylamide Concentrations

Since the announcement of acrylamide in foods in April 2002, a high priority has been to develop reliable analytical methods to quantify low concentrations of acrylamide in cooked foods. Methods and sample preparation techniques to determine acrylamide in foodstuffs have been reviewed (Castle and Eriksson 2005; Wenzl, De La Calle, and Anklam 2003). To date, more than 20 methods applicable to a wide range of different foods have been published in peer-reviewed journals or made available through other sources, such as websites. The procedures vary with regard to sample extraction, clean-up procedures, and separation techniques.

The majority of analytical approaches focus on separation by liquid chromatography (LC) or gas-chromatography (GC), and determination by mass spectrometry (MS), in most instances using stable isotope-labeled acrylamide as an internal standard (Wenzl, De La Calle, and Anklam 2003). Because acrylamide is a small (molecular weight [MW] = 71 grams [g]/mol), highly water-soluble molecule, high-performance liquid chromatography-based techniques are attractive. But acrylamide has no significant spectral absorption above 220 nanometers and exhibits poor retention on conventional reversed-phase columns. Therefore, coupling the separation step to a universal detector such as a mass spectrometer provides a more reliable means of quantifying acrylamide. Most laboratories that have established LC-MS techniques prefer tandem mass spectrometers (MS/MS), because these have better sensitivity and more reliable confirmation of the *analyte*[1]. The final choice of the detector will depend on the complexity of the food matrix, sample clean-up steps, and the desired limits of detection and quantification.

In general, GC-MS methods used to determine acrylamide are more time consuming than the LC-MS method. The most common approach is to derivatize the molecule before analysis—for example, by addition of bromine to the carbon-carbon double bond—which increases its volatility and makes the analyte more amenable to GC. This step, leading to 2,3-dibromopropionamide, also provides cleaner extracts and less interference in the MS chromatogram because of the higher molecular mass of brominated acrylamide. Accordingly, GC-MS methods generally are less sensitive than LC-MS or LC-MS/MS techniques. Some laboratories performing GC-MS, however, omit the derivatization step and directly analyze the native compound. In this instance, additional care must be taken to avoid artifact formation (e.g., in the injector of the gas chromatograph), and, depending on the food matrix, a more thorough sample clean-up procedure may be necessary (Wenzl, De La Calle, and Anklam 2003).

In the past 2 years, several interlaboratory comparisons at the national, European, and international levels have been conducted on a wide range of food matrices: for example, crispbread, butter cookies, bread crumbs, and coffee. Consequently, the data accumulated since 2004 can be considered reliable.

Further needs with regard to the analytical science are being addressed by the European Commission (EC) Joint Research Centre, Institute for Reference Materials and Measurements task force on acrylamide. This group has identified the need for using fully validated reference methods (GC and LC-MS/MS) and, in conjunction with the German Institute for Materials Research and Testing, currently is preparing toasted bread and crispbread as certified reference materials.

Currently, no alternative or rapid methods (i.e., simple, cheap) are available to determine acrylamide at low concentrations in foods. Such tools would enable "at-line QC" (quality control), particularly for those foods in which color does not represent an appropriate endpoint of acrylamide formation.

Formation of Acrylamide

Importance of Asparagine and the Maillard Reaction

Mottram, Wedzicha, and Dodson (2002) and Stadler and colleagues (2002) were the first to report that acrylamide is the result of a thermal *Maillard pathway*. Specifically, the formation of acrylamide results from reactions between *asparagine* (a hydrophilic amino acid) and *reducing sugars* (glucose and fructose). Evidence that the carbon backbone and amide nitrogen of acrylamide originate from asparagine was provided by the use of stable isotope-labeled asparagine (Stadler et al. 2002; Zyzak et al. 2003). The Maillard pathway leading from asparagine to acrylamide is complex and may involve very different intermediates. Mottram, Wedzicha, and Dodson (2002) proposed that "Strecker degradation" is involved. Yaylayan,

[1]Italicized terms are defined in the Glossary.

Wnorowski, and Perez Locas (2003) and Zyzak and colleagues (2003) provided evidence for an alternative route involving the early decarboxylation of the asparagine *N*-glycoside.

Alternative Mechanisms of Acrylamide Formation

Model studies have shown that acrylamide can be formed by several indirect routes. For example, both *acrolein* and its oxidized product *acrylic acid* may react with ammonia to produce acrylamide (Becalski et al. 2003; Lingnert et al. 2002). In model experiments, reacting equal moles of glucose with *aspartic acid* at temperatures >120°C led to a yield of acrylic acid comparable to that of acrylamide from an analogous reaction with asparagine plus glucose, indicating a common route to vinyl compounds from the corresponding free amino acids and sugars (Stadler et al. 2003).

In certain conditions, acrolein together with asparagine may lead to the formation of acrylamide (Yasuhara et al. 2003). In this instance, acrolein rather than reducing sugars provides the carbonyl group for the Maillard reaction. Additionally, aspartic acid also can be converted to acrylic acid without the involvement of sugars or a carbonyl source following a concerted *decarboxylation/deamination pathway* (Yaylayan and Stadler 2005).

Preliminary studies have shown that other amino acids such as L-alanine and L-arginine also are capable of releasing acrylic acid at temperatures above 180°C, with yields within the same order of magnitude as aspartic acid. Carnosine in meat products can generate β-alanine through hydrolysis to form acrylic acid and eventually acrylamide or its derivatives (Yaylayan and Stadler 2005; Yaylayan et al. 2004). Yaylayan and colleagues (2004) found that creatine, a component of meat, may form N-methylacrylamide in cooked meat, but the importance of this formation is not known. Only low concentrations of acrylamide have been reported for cooked meat products.

Another route to the formation of acrylamide, which may occur in potatoes, is through the enzymatic decarboxylation of asparagine to produce 3-aminopropionamide (Granvogl et al. 2004). Cooking potatoes converts 3-aminopropionamide to acrylamide by a deamination reaction. The yields of this reaction are excellent (~ 60 mol%), but only traces (low mg/kg) of the precursor 3-aminopropionamide actually have been detected in potatoes, limiting the pathway's importance when compared with the final yields of the thermal Maillard pathway (Granvogl et al. 2004).

Factors Affecting Acrylamide Formation

Factors that affect the rate of acrylamide formation include reactant concentration and reactant ratio as well as temperature, pH, and water content. Because there are multiple factors and because foods are so different from one another, it is extremely unlikely that a universal method could be developed that would decrease acrylamide in all foods. The presence and concentration of reactants affect formation, but the presence of inhibitors or substances that compete with reducing sugars and/or amino acids in the Maillard reaction also are important. Potato samples with the highest reducing sugar content had the highest acrylamide concentrations (Amrein et al. 2003; Haase, Matthaus, and Vosmann 2003). Glucose, glyoxal, 2-deoxyglucose, or glycerol react with asparagine to form acrylamide (Stadler et al. 2002) as do octanal and 2-octanone. D-glucose, 2-deoxyglucose, ribose, glyceraldehydes, and especially glyoxal also produce acrylamide on reaction with asparagine (Zyzak et al. 2003).

Glucose and fructose are the major reducing sugars in plant foods, including potatoes, and therefore have the largest influence on acrylamide formation. A study of 74 samples of potatoes from 17 different cultivars demonstrated that acrylamide content correlated most closely with fructose (Amrein et al. 2003). But in potatoes the glucose content typically is twice that of fructose, so overall, glucose and fructose seem to influence the formation of acrylamide similarly.

Potato tubers stored at 2°C exhibited higher concentrations of glucose and fructose than tubers stored at 20°C. When such low-temperature-stored potatoes were fried into chips, the resulting product was darker and had higher acrylamide concentrations than chips from potato tubers stored at 20°C (Noti et al. 2003). Amino acid and asparagine content were unaffected by storage temperature (Chuda et al. 2003). Concentration of reducing sugars decreases when potatoes are tempered at higher temperatures but not to the same concentration as before storage (Grob et al. 2003). Greenish potatoes (evidence of sunlight damage) have much higher amounts of reducing sugar, and acrylamide concentrations were 3–8 times higher when these potatoes were fried (Biedermann et al. 2003).

No acrylamide was formed when a glucose-asparagine model solution was heated for 10–15 minutes (min) at temperatures below 140°C (Becalski et al. 2003) or at 120°C for 20 min (Mottram, Wedzicha, and Dodson 2002) or in boiled or raw foods, indicating that the formation of acrylamide is subject to both temperature and time. Because acrylamide forms at temperatures that also drive the Maillard reaction, simply lowering the cooking temperature to decrease acrylamide production also would necessitate increasing the processing time to obtain acceptable color, flavor, and texture. For many products, lowering the cooking temperature will not work, because producing a food with acceptable sensory qualities while avoiding acrylamide formation would be difficult.

In general, acrylamide formation increases with increasing temperature from 120°C to 170°C (Stadler et al. 2002; Tareke et al. 2002). When potato slices were deep-fried, acrylamide formation increased with increasing temperature up to 185°C (Gertz and Klostermann 2002). At higher temperatures, more acrylamide formed when potatoes were fried for the same length of time (Grob et al. 2003; Haase, Matthaus, and Vosmann 2003).

There is disagreement about what happens to acrylamide above 190°C; in some studies, the acrylamide content was lower when the temperature was above 190°C, suggesting either that acrylamide reacts further or that an alternative reaction mechanism occurs that bypasses acrylamide (Amrein et al. 2003; Biedermann and Grob 2003; Claeys, De Vleeschouwer, and Hendrix 2005).

The extent of browning also increases with processing temperature and time, but the extent of browning does not necessarily indicate the amount of acrylamide present in a food (Taubert et al. 2004). For example, Surdyk and colleagues (2004) found that adding fructose or asparagine to bread dough increased the concentration of acrylamide without affecting the dry crust color.

Both pH and water content are important factors in the Maillard reaction. The effect of pH was investigated indirectly by considering the effect of adding citric acid. Jung, Choi, and Ju (2003) found that increasing the citric acid content of fried and baked corn chips and incorporating citric acid in a prewash before frying for french fries decreased the acrylamide concentration. The practical application of this finding, however, is not clear.

Methods of Mitigation and Reduction

Disrupt the Reactions Leading to Acrylamide Formation

Several different approaches have been suggested and assessed to inhibit the formation of acrylamide during the Maillard reaction. Among these approaches are reducing the pH or adding chemicals thought to inhibit the reactions leading to acrylamide formation. Examples of added chemicals include flavonoid spice mixes (Fernandez, Kurppa, and Hyvonen 2003), natural antioxidants such as rosemary (Becalski et al. 2003), or amino acids to compete with aspargine for reaction with reducing sugar (Rydberg et al. 2003). The practical significance of these approaches, however, is unclear.

Remove the Reactants

Because the formation of acrylamide is a second-order reaction requiring the presence of asparagine and reducing sugars, removal of either or both of these substrates is a potential strategy for reducing acrylamide in foods. The basic approaches include processing to remove reactants or selection of raw materials low in asparagine and/or reducing sugar.

Soaking potato slices to lower reducing sugar and asparagine can lower resultant acrylamide formed during cooking (CIAA 2004; Jung, Choi, and Ju 2003; Kita et al. 2004). In general, the amount of substrate removed increases with the temperature of the blanch solution and with time. It also seems possible to enzymatically degrade reactants (asparagine, reducing sugar) in instances where the reactants are accessible (for example, in flour). But it is far more challenging to devise methods for effectively disrupting the reaction(s) leading to acrylamide formation when the reactants are located in the cytoplasm of intact cells and therefore protected by intact cell membranes. This circumstance occurs with a potato slice in which only the cells located at the cut surface may be damaged sufficiently to remove the reactants by blanching or enzymatically. It is difficult even to imagine penetrating the membrane before heat processing to reduce reactants (reducing sugar, asparagine) without also adversely affecting the quality of the final product.

Process the Food

Acrylamide is not a stable molecule, and its net formation in any food will be a balance of the rates of formation and elimination by chemical or physical means. Coffee illustrates this point well: most acrylamide is formed in the early stages of the roasting process, reaching > 7 mg/kg and then declining steeply toward the end of the roasting cycle because of higher rates of elimination. In fact, roughly 95% of the acrylamide formed is degraded during roasting, and darker roasted coffee beans have been shown to have lower concentrations of acrylamide than lighter roasted coffees (Taeymans et al. 2004). In coffee, acrylamide is not stable in the packed finished product, and concentrations have been shown to decrease with storage time, with losses of up to 60% throughout several months recorded for ground coffees stored at room temperature (Andrzejewski et al. 2004).

Use Selected Agronomic Methods

Selective breeding of crops, whether through transgenic manipulation or traditional breeding approaches, is another potential method for reducing acrylamide formation by decreasing the amounts of the reactants. This approach has been used for years to decrease undesirable traits in plants, for example, glycoalkaloids in potatoes or cucurbidicin in cucumbers. Recent surveys of the variability in various plants of free asparagine, and to some extent of reducing sugar, suggest that selective breeding could result in low-asparagine varieties. Doyle (2002) surveyed the published literature and found up to a 20-fold variation in

reported free asparagine content in a variety of crops (Table 2).

Amrein and colleagues (2003, 2004b) found about a 2-fold variation in free asparagine in the cultivars of potatoes they studied, but nearly a 50-fold variation in total reducing sugar in those same varieties. The authors concluded that reducing sugar content was a key determinant for the formation of acrylamide in cooked potatoes. Williams (2005) reached the same conclusion.

Improper storage and even rough handling of potatoes are known to increase reducing sugar; the effect of those same conditions on asparagine is unknown, although Amrein and colleagues (2004b) report an increase in free asparagine under conditions that cause a decrease in reducing sugar. Similar genetic variability in free asparagine has been found in wheat flour (CIAA 2004). In contrast to the findings in potato, Amrein and colleagues (2004a) found that free asparagine content was a key determinant of acrylamide formation in gingerbread.

It might be reasonable to conclude from all available data that for crops relatively high in reducing sugar, the generally far greater variation in this parameter offers more degrees of freedom for genetic and/or agronomic intervention. On the other hand, for crops or crop varieties that already are relatively low in reducing sugar, variation in amounts of free asparagine might be exploited to provide further reduction in acrylamide formation.

Table 2. Asparagine content of various food crops[a] (adapted from Doyle 2002)

Crop	Asparagine Content (mg/g)
Potato	0.5–10.0
Corn	0.6–1.0
Wheat	0.02–2.0
Rye	0.2–2.8
Asparagus	5.4–108
Cocoa (raw)	30.9
Roasted at 125°C	14.5
Roasted at 135°C	9.4
Cheese	20–300

[a]Also in peanuts, soybeans, onions, coffee, tomatoes, fruit, and other foods.

Exposure Overview

Acrylamide exposure, before its discovery in foods, was known to occur through drinking water, cigarette smoke, occupational or environmental conditions, and through exposure to trace amounts of acrylamide in a number of consumer products, including cosmetics and packaging materials. A review of acrylamide toxicity by an expert panel from the National Toxicity Program–Center for the Evaluation of Risks to Human Reproduction (NTP–CERHR 2004) identified occupational exposure, smoking, and foods as the most significant potential sources of acrylamide exposure. Although exposure through smoking and the workplace can be higher than food exposures—evidence suggests that smokers are exposed to an internal dose of acrylamide three to four times higher than in nonsmokers—exposure to foods is obviously a concern for the entire population.

Assessing Exposure to Acrylamide in Foods

Typically, dietary intake or exposure assessments estimate the intake of a particular compound by combining data from measurements of that compound in various foods with data on dietary patterns in a particular country or region. For example, the FDA generated acrylamide intake estimates for U.S. consumers (DiNovi and Howard 2004) by combining data from the FDA acrylamide testing program (USFDA 2004a, b) with data from the U.S. Department of Agriculture's "Continuing Survey of Food Intake by Individuals."

Using limited data, an FAO/WHO Expert Consultation estimated daily acrylamide intake at 0.3–0.8 μg/kg-body weight (bw)/day (UNFAO/WHO 2002). Table 3 highlights exposure assessments that were published since the WHO consultation and that incorporate new data on acrylamide concentrations in foods. The mean daily intake values reported in the table fall in or near the range initially identified by the WHO consultation (Dybing et al. 2004). Daily intake values for the average consumer (including adults and children) range from 0.2 to 1.4 μg/kg-bw/day. For consumers at the 90–97.5 percentile of consumption, the daily intake values range from 0.6 to 4 μg/kg-bw/day. Children and/or adolescents typically have higher dietary acrylamide intakes than adults on a bw basis, both because of the higher consumption of certain acrylamide-containing foods (such as potato chips and french fries) and because children have a lower mean bw than adults (Dybing et al. 2004; FAO/WHO 2002).

As mentioned previously in the section on "Acrylamide Content in Food," exposure assessments have identified foods that contribute most significantly to acrylamide intake. In addition to assessing dietary intake, researchers also have used exposure assessments to model the effects of mitigation strategies, but the gains from these mitigation studies are not as large as might be hoped. For example, the FDA exposure assessment found that removing *all* acrylamide from french fries, snack foods, or breakfast cereals would lower the acrylamide intake for the mean U.S. consumer by only 12–14% each (DiNovi and Howard 2004). Because only limited reductions in acrylamide may be possible for many foods, the actual reduction in acrylamide exposure would be lower. Boon and colleagues (2005) modeled more realistic acrylamide reductions of 35% in french fries and 60% in gingerbread and found reductions in total acrylamide exposure for Dutch

Table 3. Acrylamide exposures estimated in selected exposure assessments (adapted from Dybing et al. 2004)

	Daily Acrylamide Intake (μg/kg-bw/day) for Mean or Higher Percentile Consumers		
Source of Exposure Assessment	Mean Consumer[a]	Upper Percentile Consumer	Reference
Australia	0.4–0.5 (≥ 2 years) 1.0–1.3 (2–6 years)	1.4–1.5 (95th) 3.2–3.5 (95th)	Croft et al. 2004
Belgium	0.51 (13–18 years)	1.09 (95th)	Matthys et al. 2005
EC	0.2–0.4		EC 2002
FAO/WHO	0.3–0.8		UNFAO/WHO 2002
France	0.5 (> 15 years) 1.4 (2–14 years)	1.1 (95th) 2.9 (95th)	AFSSA 2003
Germany	1.1 (15–18 years)	3.4 (95th)	BfR 2003
JECFA	1	4	JECFA 2005
Netherlands	0.48 (1–97 years) 1.04 (1–6 years) 0.71 (7–18 years)	0.60 (95th) 1.1 (95th) 0.9 (95th)	Konings et al. 2003
Norway	0.49 (males) 0.46 (females)	1.01 (90th) 0.86 (90th)	Dybing and Sanner 2003
Sweden	0.45 (18–74 years)	1.03 (95th)	Svensson et al. 2003
Switzerland	0.28 (16–57 years)		SFOPH 2002
United Kingdom	0.3 (19–64 years) 1.0 (1.5–4.5 years)	0.6 (97.5th) 1.8 (97.5th)	UK FSA 2005
United States	0.43 (> 2 years) 1.06 (2–5 years)	0.92 (90th) 2.31 (90th)	DiNovi and Howard 2004

[a]Age range specified, if available.

consumers of 13% and 4%, respectively.

Exposure Research Needs

Exposure assessments are a critical component in determining what risk acrylamide in foods poses to consumers. Research areas where more information is needed include incorporating data on home-cooked foods into exposure assessments and obtaining intake data from countries outside Europe and North America (Dybing et al. 2004; JECFA 2005).

Toxicology Overview

Acrylamide has been studied extensively for four decades, resulting in a broad base of scientific knowledge covering various toxicological endpoints, metabolism, kinetics, mode of action, and human health effects. To date, the only known human health effect is neurotoxicity as a result of relatively high doses occurring through occupational exposures. Acrylamide toxicity stems from its ability to chemically modify proteins through *nucleophilic reaction* with the SH groups of cysteine, homocysteine, glutathione, the α-NH_2 of free amino acids and N-terminal residues, the ϵ-NH_2 of lysine, and the ring NH of histidine (Friedman 2003). In addition, glycidamide, an *epoxide* that is readily biotransformed from acrylamide, is a highly reactive compound that can promptly *alkylate* protein and DNA through *nucleophilic attack*. Significant progress has been made in the last few years in understanding the metabolism of acrylamide and glycidamide through various routes of administration and dosing regimens, particularly in humans. This information has been especially useful in modeling the kinetics of acrylamide exposure, thus allowing for better human health risk assessment for dietary acrylamide.

Metabolism and Kinetics

The absorption of acrylamide in humans is understood poorly, but some data available through reports of poisoning or accidental occupational exposure show that acrylamide is absorbed readily through oral, dermal, and inhalation routes (IARC 1994; Sumner et al. 2003). Studies in rats, pigs, dogs, rabbits, and rodents indicate that acrylamide is distributed rapidly through the body independent of the route of administration (Miller, Carter, and Sipes 1982). The major metabolic pathways for acrylamide seem to be qualitatively similar in humans and experimental animals; however, quantitative differences between species and

by dose are significant and can have profound effects for any human health risk assessment (Sumner et al. 1997).

One major pathway for acrylamide biotransformation is via *glutathione conjugation* catalyzed by the hepatic enzyme glutathione-S-transferase (GST). A second major pathway is oxidation catalyzed by the saturable hepatic enzyme cytochrome P450, leading to the formation of glycidamide, which in turn can be metabolized through conjugation with GST or metabolized further by epoxide hydrolase.

Data on acrylamide elimination are sparse, especially in humans, but it is known that excretion of the parent compound is low and metabolite excretion occurs predominately in the urine (Fennell et al. 2005; Kirman et al. 2003; Sumner et al. 1997, 2003). Pharmaco- and toxicokinetic models (Calleman 1996; Doerge et al. 2004) offer an opportunity to gain insights into the mode of action by which acrylamide exerts its toxic effects.

DNA/Protein Adducts and Bioavailability

Studies of acrylamide metabolism and disposition in rats and mice using several routes of administration show that acrylamide is highly bioavailable from aqueous *gavage* and from acrylamide-fortified foods. In both species, oral routes of administration attenuate acrylamide bioavailability somewhat; however, an accompanying increase in the internal exposure to glycidamide is observed for oral routes. Acrylamide and glycidamide are widely distributed to tissues. Deoxyribonucleic acid (DNA) *adduct formation* has been observed in all organs examined, including those sites for tumor formation previously observed in rodent carcinogenicity bioassays, and repeat dosing with acrylamide leads to DNA adduct accumulation (Doerge et al. 2005a,b; Twaddle et al. 2004). Both acrylamide and glycidamide form adducts with proteins, as well as with DNA, and the binding of glycidamide to hemoglobin serves as a biomarker of exposure that is especially useful for human dosimetry determination. In this regard, consumption of acrylamide in foods is reflected in the internal dose level of hemoglobin adducts (Bergmark 1997; Hagmar et al. 2005).

Studies of acrylamide and glycidamide adduct formation across species, routes of administration, and doses indicate that glycidamide-DNA adducts are found in a variety of tissues (Fennell et al. 2003; Sumner et al. 2003). By comparison, acrylamide-DNA adduct yields and rates of formation are relatively low and are poorly characterized with respect to *genotoxicity* (Segerback et al. 1995). Because of the measurement of DNA adducts in different tissues, glycidamide seems to be evenly distributed in the body. Segerback and colleagues (2003) conclude that "this supports the notion that organ-specificity in acrylamide carcinogenesis can not be explained by a selective accumulation of DNA-reactive metabolite in target organs." The most recent studies of DNA adducts derived from the administration of acrylamide and glycidamide to rats and mice found that glycidamide typically produced higher levels of DNA adducts than observed with acrylamide, and this finding provided strong support for a genotoxic mechanism of acrylamide carcinogenicity in rodents (Doerge et al. 2005a; Maniere et al. 2005).

Genetic and Germ Cell Toxicity

The genetic toxicity of acrylamide has been studied in a number of in vitro and in vivo assays with the following results: (1) negative or at best weakly positive in bacterial and mammalian mutagenicity; (2) positive for chromosomal aberrations, micronuclei, *sister chromatid exchange*, *polyploidy*, *aneuploidy*, and other mitotic disturbances; (3) negative for unscheduled DNA synthesis; and (4) positive for mammalian cell transformations. The weight of the available evidence indicates that acrylamide is not a direct-acting mutagen, but data are convincing that it acts as a *clastogen* and binds to nuclear proteins (Dearfield et al. 1995).

Paulsson and colleagues (2003) demonstrated that, after treatment with acrylamide and glyidamide, glycidamide is the predominant genotoxic factor in acrylamide exposure. Using the sensitive flow cytometer-based mouse micronucleus assay, chromosomal breaks (clastogenicity) were shown to result from treatment with acrylamide (Abramsson Zetterbeg 2003). There was no indication of an *aneugenic effect* (i.e., binding to nuclear proteins). In contrast, glycidamide is clearly mutagenic and is much more reactive in its binding to DNA, having been shown to bind to the N-7 site of guanine as well as other specific loci (Gamboa da Costa et al. 2003; Segerback et al. 1995). Unscheduled DNA synthesis, micronuclei, and other types of chromosomal damage also have been attributed to glycidamide (Dearfield et al. 1995; Paulsson, Grawe, and Törnqvist 2002).

There is sufficient evidence on *germ cell toxicity* from studies with laboratory animals to conclude that acrylamide administration causes heritable genetic damage. Results from studies of spermatogonia aberrations, dominant lethal mutations, and other experiments indicate that acrylamide treatment produces mammalian germ cell toxicity by both mutagenic and clastogenic action (NTP-CERHR 2004). Studies with CYP2E1 knockout mice (animals lacking the P450 enzyme necessary to metabolize acrylamide to glycidamide) provide clear evidence that the dominant lethal effects seen in male germ cells are at least partly because of glycidamide (Adler et al. 2000; Ghanayem et al. 2005), although further research is needed to elucidate more clearly the mechanism of action responsible for germ cell toxicity. The significance of these findings to human health from chronic dietary exposure at lower levels (from 10^4-10^6 times lower) is uncertain, although some investigators

have begun to explore this area of genetic risk assessment (Allen et al. 2005; Dearfield et al. 1995).

Carcinogenicity

The evidence for acrylamide to act as a carcinogen principally rests with two chronic bioassays involving rats administered the test agent through drinking water (Friedman, Dulak, and Stedham 1995; Johnson et al. 1986). Based on these data and other supportive evidence of carcinogenicity (Bull, Robinson, and Stober 1984; Bull et al. 1984), including the aforementioned evidence of genotoxicity and clastogenicity, the International Agency for Research on Cancer (IARC) classified acrylamide as "probably carcinogenic for humans (Group 2A)" (IARC 1994). Both rat bioassays produced increased incidences of benign and/or malignant tumors of the mammary gland, thyroid, and testis, whereas tumors of the uterus, clitoral gland, pituitary, adrenal, and oral cavity were found in only one of the two studies. Both bioassays showed tumors of the spinal cord and brain, but the data were not dose-responsive or statistically significant. Because glycidamide readily alkylates DNA, it, in fact, may be the proximate genotoxic carcinogen (Rice 2005).

Reproductive and Developmental Toxicity

Multigeneration reproductive and crossover breeding toxicology studies in mice and rats with acrylamide administered by gavage or via drinking water have demonstrated adverse effects on implantation and pup survival (Chapin et al. 1995; Tyl et al. 2000a, b; Wise et al. 1995). As mentioned previously, numerous short- and long-term studies resulted in dominant lethality and adverse effects on sperm cells. Thus, it has been demonstrated conclusively that acrylamide is a male reproductive toxicant (when administered at high doses), although evidence to date seems to indicate that acrylamide is not a female reproductive toxicant at doses that are 10,000-fold greater than human exposure (NTP-CERHR 2004). Because evidence from dominant lethal studies has indicated that male germ cell genotoxicity seems to be the most sensitive reproductive endpoint of acrylamide, dose-response data at amounts relevant to human dietary exposure are needed to better understand any potential human health implications.

Acrylamide is not *teratogenic* in mice or rats after oral treatment of dams at levels up to the toxic level; however, minor developmental effects have been demonstrated at doses associated with maternal toxicity that are likely secondary to toxicity to the dam (Tyl and Friedman 2003; Tyl et al. 2000a, b). Because some of these adverse developmental effects were neurological (e.g., grip strength), and given that the only known human effect of acrylamide is neurotoxicity, further studies with improved sensitivity for neurodevelopmental endpoints are needed to strengthen the confidence in establishing a developmental toxicity No-Observed-Adverse-Effect-Level (NOAEL).

Neurotoxicity

The neurotoxicity of acrylamide has been studied extensively in mice, rats, cats, dogs, monkeys, and humans (Friedman 2003). Using a variety of routes of administration and dosing regimens, these studies have demonstrated consistently the gross, morphological, and/or biochemical signs of neuropathology. Whereas a study by Spencer and Schaumburg (1978) has long been considered a classic example of acrylamide-induced peripheral-distal *axonopathy*, recent research has revealed data to support two distinct mechanisms of neurotoxic action. Work by Sickles and colleagues (Sickles, Stone, and Friedman 2002; Sickles et al. 1996) indicates that inhibition of kinesin (a neuronal transport protein) and the subsequent decrease of *antegrade axonal transport* are the critical elements of acrylamide neurotoxicity. Research by LoPachin and colleagues (LoPachin 2002; LoPachin, Ross, and Lehning 2002; LoPachin et al. 2002) has shown a strong dose-rate influence on acrylamide neurotoxicity expression as well as nerve terminal degeneration and axonal degeneration in the central and peripheral nervous system (brain and spinal cord) as the primary sites of action. The neurotoxic consequences of long-term consumption of low dietary amounts of acrylamide and the potential to promote or exacerbate neurodegenerative diseases that might develop late in life remain unclear.

EPIDEMIOLOGY

Six epidemiologic studies to date have explored whether exposure to acrylamide through diet could increase the risk of human cancer, and one of these studies was a large prospective cohort study (Mucci, Adami, and Wolk 2006; Mucci et al. 2003, 2004, 2005; Pelucchi et al. 2003, 2005). The evidence from these studies has been converging, indicating that intake of dietary acrylamide is not associated with an increased risk of any of the several types of cancers studied. Organs that have been assessed for cancer in these studies are the oral cavity, pharynx/larynx, esophagus, large bowel (colon), breast, ovary, prostate, bladder, and kidney. Indeed, in a few of the studies there was a suggestion of a lower risk of colorectal cancer among those with the highest intake of acrylamide. In addition, the data in the case-control studies also have demonstrated uniformly a lack of association between specific acrylamide-containing foods—including fried potato products—and the risk of cancer. As mentioned, the first prospective study of acrylamide in foods has been completed recently, an examination of the risk of colon and rectal cancers in a large cohort of Swedish women (Mucci, Adami, and Wolk 2006). There was no association reported between estimated acrylamide intake and colorectal cancer. Furthermore, intake of specific food items with elevated

acrylamide (e.g., coffee, crispbread, or fried potato products) was not associated with cancer risk. Whereas the epidemiological studies to date have not found any correlation to high acrylamide intake and increased cancer risk, the possibility of disclosing such a low cancer risk in human studies as that which acrylamide constitutes is very difficult. The number of subjects simply may not be sufficient to generate the discrimination needed to determine such a low cancer risk. At the JECFA risk assessment meeting in February 2005, the available epidemiological studies were considered "not suitable for use in risk assessment of acrylamide." The Mucci, Adami, and Wolk (2006) study has sufficient statistical power to detect a meaningful excess risk of colorectal cancer only associated with dietary intake of acrylamide.

In addition, the epidemiologic evidence for the carcinogenicity of acrylamide among exposed workers fails to reveal any increase in total occupational cancer incidence (reviewed by Erdreich and Friedman 2004). A possible increase in pancreatic cancer incidence was mentioned in one occupational study.

The question remains: how to assess the contribution to overall cancer risk to humans who have differing genetic backgrounds and who consume varied diets containing a compound shown to be a genotoxic carcinogen in laboratory animal studies, widely distributed in foods at relatively high concentrations, and consumed in combination with other carcinogenic and anticarcinogenic naturally occurring or food-process-related compounds.

Toxicology and Epidemiology Research Needs

The specific functional proteins modified by acrylamide and/or glycidamide adducts leading to toxicity are not yet fully elucidated, although some progress has been made in identifying target proteins involved in acrylamide neurotoxicity. Human data on acrylamide and glycidamide DNA-adduct characterization and rate of formation also are lacking and are needed to understand better the toxicity and cancer risk posed by acrylamide. Additional research needs include (1) an increased understanding of the bioavailability from food; (2) an assessment of the metabolic rate constant differences across subpopulations and developmental stages, as well as between animals and humans; (3) and molecular kinetic characterization of acrylamide and glycidamide binding to target and nontarget sites (i.e., for determining biomarkers of effect). Improvements in biomarkers of exposure and effect and pharmaco- and toxicokinetic models should contribute to a better understanding of the human health risk.

Further research also is warranted to elucidate the genotoxic and/or nongenotoxic (e.g., endocrine-mediated) mechanisms responsible for the carcinogenic action of acrylamide in animals. Studies to evaluate carcinogenicity in perinatal exposure conditions and to evaluate the specific role of glycidamide would be valuable toward more fully understanding the risk implications for human health. Because the possible human carcinogenicity of dietary acrylamide seems to be the endpoint of most concern to risk assessors at this time, it will be critical to assess carefully the forthcoming results of the NTP chronic bioassay studies of acrylamide and glycidamide (administered in drinking water to rats and mice) to determine more accurately the modes of action and to predict better the potential risk to humans.

Epidemiological studies in general—especially those that are prospectively designed and include accurate exposure assessments through biomonitoring of hemoglobin adducts and/or urinary metabolites of acrylamide—are valuable in addressing the role of dietary acrylamide exposure and risk of human cancer. Although these studies can never exclude a small effect of acrylamide on cancer risk, a well-designed study can document an effect that would be meaningful with respect to predicting potential effects on public health. Certainly no single study can provide the final answer on the health effects of acrylamide in diet, but an accumulation of evidence through additional well-conducted studies will shed light on this important public health concern.

Risk Communication

Even though food risk management has improved globally, consumer expectations of food safety may not keep pace with reality. For a long time food was exempt from this kind of anxiety because people were more likely to worry about living next to nuclear power plants or being exposed to emissions from waste incinerators or coal power plants. But food scares in Europe, such as bovine spongiform encephalopathy and the dioxin crisis in Belgium in 1999, have led to a dramatic decrease in the general public's trust in the safety of foods, the quality of existing food safety assessment and management procedures, and the ability of public authorities to regulate and ensure the safety of the food supply.

In addition, the increasing complexity of food chain production systems—with changes in processing and distribution, increasing globalization of trade, the internal market in Europe, changes in the composition of foods, and shifts in eating habits and consumer sentiments—influences societal discussions on food safety and quality.

The Swedish finding of acrylamide in foods in 2002 was confirmed rapidly by several governments; subsequently, all available data on acrylamide were reviewed by international agencies including the WHO, the FAO, the European Commission's Scientific Committee on Food, and, in February 2005, by the JECFA. Before the Swedish study, food was not analyzed for acrylamide because its occurrence was not expected in foods. It also is necessary to keep in mind that, besides acrylamide, there are many

other chemicals in foods that have not yet been studied and that may be of equal concern.

Risk Communication and Acrylamide: A Case Study

The information available on acrylamide in foods in 2002 was not sufficient to draw firm conclusions about the cancer risk to humans. There is scant evidence that the consumption of foods containing acrylamide is harmful to humans. Therefore, significant questions remain regarding true risk and bioavailability of acrylamide in foods. The FDA, the WHO, the EU, and other bodies have stated that there is no indication at this time that consumers need to change their eating habits in response to the acrylamide findings, but instead they advise consumers to follow established dietary guidelines and eat a healthful, balanced diet consisting of a wide variety of foods. Nevertheless, the news headlines in the weeks after the announcement of the findings in Sweden were "Potato Chips Cause Cancer" (Tritscher 2003).

According to the European Consumers' Organisation (Bureau Européen des Unions de Consommateurs [BEUC] 2004), media coverage and direct consumer concerns varied widely throughout Europe. Whereas in Italy and Spain acrylamide was no issue at all and little reaction was observed in Switzerland, Belgium, and Austria, in the Nordic countries, Germany, Ireland, Great Britain, France, and the Netherlands substantial reaction by media, individual consumers, and consumer organizations was reported. Likewise, the responses of national governments in Europe varied widely (Freshfields Bruckhaus Deringer 2003). The federal and state authorities in Germany, for instance, introduced product-specific "signal values" for acrylamide in various foodstuffs as a means of monitoring and regulating acrylamide concentrations. In the United States, media coverage peaked just after the Swedish discovery with nearly 100 articles filed in daily newspapers but then declined to approximately 10 articles in early 2004, following a few spikes as the FDA released data on the acrylamide content of certain branded foods. Coverage of Proposition 65 in California has sparked a new round of articles on acrylamide.

Consumer research conducted for the International Food Information Council in April 2003 (IFIC 2003) found that most U.S. consumers were not concerned about acrylamide and would not change their eating behaviors as a result. The research concluded there were four major reasons for this lack of concern:

1. Most consumers have become highly skeptical of research studies in general, given past experience with contradictory studies;
2. Until a study passes the test of time by being confirmed by other studies, many consumers will not take note;
3. The sensationalism that surrounded some of the reports on acrylamide undermined their credibility; and
4. Many people already had changed their behavior or had been told they should decrease consumption of many foods containing acrylamide—such as fries, snacks, and chips—for other health reasons, so the latest warnings had little incremental impact.

In 2003, acrylamide disappeared entirely from the headline news in the United Kingdom, Ireland, Belgium, France, Italy, and Norway. But consumer organizations remained active in the field through the publication of product-testing results combined with advice on how best to avoid the unnecessary formation of acrylamide during household cooking.

The acrylamide "outrage" factor has not been as high as might have been expected. This outcome is probably because acrylamide seems to be a seminatural phenomenon: the chemical substances that cause the formation of acrylamide during processing are present in the raw material, and the formation of acrylamide is influenced by different types of food processing. People tend to accept naturally caused risks better than they accept man-made risks. Acrylamide seems to fall into a middle category: partly natural/partly man-made. Another aspect of the acrylamide risk is that acrylamide seems to be present in many staple foods and must have been there for some time. Although somewhat contradictory, this fact probably could help consumers manage the risk (Reksnes 2003). Avoiding acrylamide could lead to drastic dietary changes unacceptable to consumers.

The following assumptions, however, have been challenged in regard to acrylamide in foods:

- The public is a passive receiver of risk information. If only the public were willing to learn about risk issues, they would understand and accept risk information.
- Science alone can provide "objective" truths.
- Scientific and technical experts are the only possible sources of "correct" risk information (Scherer 1991).

Consumer organizations in Europe have asked for the improvement of risk communication, especially in relation to

- Giving advice to avoid the unnecessary intake of acrylamide;
- Updating consumers about the activities undertaken by scientists and risk managers, but also by industry; and
- Relating honestly to uncertainties or knowledge gaps.

Conclusions

This Issue Paper has reviewed acrylamide formation and detection, methods of mitigation and reduction, dietary exposure, toxicology and epidemiology, and the elements of accurate, effective risk communications. Acrylamide has been studied extensively for more than 40 years, resulting in a broad base of scientific knowledge covering various toxicological endpoints, metabolism, kinetics, mode of action, and human health effects. Recent research efforts have reflected an unprecedented extent of cooperation worldwide. But to date there is no single method for getting rid of acrylamide in foods; reduction must be done on a case-by-case basis.

Exposure assessments are a critical component in determining what risk acrylamide in foods poses to consumers and in communicating effectively the complexity of the message to be distributed to different audiences. Effective risk communication is an important tool to improve the process of risk analysis and to contribute to comprehensive risk management decisions. An equally intensive reconciliation of opinions is essential to understand the complex correlations. The awareness of acrylamide in foods could be used as an example to learn ways to improve risk communication to the general public. It is critical to use trusted sources of expertise to provide consumers with answers to their questions and refute inaccurate "scare stories" in an understandable language. It also is necessary to keep in mind that, besides acrylamide, there are many other chemicals in foods that have not yet been studied and that may be of equal concern.

Consumers in the United States and many parts of the world have responded rationally to information that governments and academic researchers have made available so far on acrylamide. Current estimates predict that definitive scientific findings will increase by 2007, so the nature of those findings will determine to what extent consumers are reassured or concerned. Risk communication principles must be used, regardless of the outcome, when explaining these conclusions to the public.

Glossary

Acrolein. A chemical compound (CH_2CHCHO) that can be formed from cooking oils when heated, such as during frying. Industrially, it is used in the manufacture of chemicals and pharmaceuticals.

Acrylic acid. A chemical compound (H_2C:CHCOOH) that can be formed from cooking oils when heated, such as during frying. Industrially, it is used in the manufacture of acrylate resins found in paint and varnishes.

Adduct formation. An adduct is a chemical compound that forms from the addition reaction of two or more substances. Acrylamide reacts with hemoglobin to form an acrylamide-hemoglobin adduct that can be used to measure exposure to acrylamide.

Alkylate. To introduce one or more alkyl groups into a compound.

Analyte. A substance or chemical constituent that is undergoing analysis.

Aneugenic effect. An absence of whole chromosomes.

Aneuploidy. An abnormal balance of chromosomes, i.e., having a chromosome number that is not a multiple of the haploid number for the species. (Compare with Polyploidy.)

Antegrade axonal transport. The movement of substances from the nerve cell along the axon toward the terminals.

Asparagine. An amino acid found in many proteins and present in large amounts in some plants, for example potatoes. Also, the beta-amide of aspartic acid.

Aspartic acid. A nonessential amino acid that occurs in proteins and is found in young sugar cane and sugar beet molasses.

Axonopathy. A disorder disrupting the normal functioning of the axons.

Clastogen. Any substance that causes chromosomal breaks.

Decarboxylation/deamination pathway. A reaction mechanism (pathway) involving removal of a carboxyl or an amine group from a chemical compound.

Epoxide. A cyclic ether with only three atoms (two carbon and one oxygen) in the ring.

Gavage. Introduction of nutritive material into the stomach by means of a tube.

Genotoxicity. The ability of a chemical or other agent to damage cellular DNA, resulting in mutations or cancer.

Germ cell toxicity. Toxicity to germ cells that are involved in the reproduction of organisms.

Glutathione conjugation. A detoxification reaction occurring in a wide range of living organisms, including humans, where glutathione (a peptide containing three amino acids) is covalently attached to a chemical toxicant via the enzyme glutathione-S-transferase, making the toxicant more water soluble and thus more easily excreted from the body.

Maillard pathway. A complex reaction, usually requiring heat, between reducing sugars, such as glucose and fructose, and amino acids; described by Louis-Camille Maillard in 1912. Like caramelization, it is a form of nonenzymatic browning. It is an important reaction pathway in the production of flavors and colors in heated foods.

Nucleophilic attack/Nucleophilic reaction. A nucleophile (or nucleophilic reagent) is a reagent that forms a bond to its reaction partner (the electrophile) by donating both bonding electrons. A "nucleophilic substitution reaction" is a heterolytic reaction in which the reagent supplying the entering group acts as a nucleophile.

Polyploidy. Having multiple times the haploid number of chromosomes in the cell nucleus. (Compare with Aneuploidy.)

Reducing sugars. A type of sugar (such as glucose and fructose) in which the aldehyde group in the terminal (C1) position acts as a mild reducing agent. Fructose, a keto-sugar, functions as a reducing sugar because it is in equilibrium in solution with the open-chain form.

Sister chromatid exchange. An exchange of homologous segments of genetic material between the sister chromatids of a chromosome.

Teratogenic. Causing nonheritable genetic mutations or malformations in the developing fetus.

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