

October 30, 2002

Dockets Management Branch (HFA-305),
Food and Drug Administration
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

**RE: Docket No. 02N-0393 Acrylamide in the Food Supply
67 Fed. Reg. 57827 (September 12, 2002)**

The Center for Food and Nutrition Policy (CFNP, or the "center") of Virginia Tech—Alexandria is an independent, non-profit research and education organization that is dedicated to advancing rational, science-based food and nutrition policy. It is recognized as a Center of Excellence on such matters by the Food and Agriculture Organization of the United Nations (FAO). The center uniquely operates like an independent "think-tank," while maintaining its academic affiliation with a major land-grant university. The research, education, outreach, and communications activities of the faculty are conducted in a relevant, time-sensitive manner that helps inform the public policy process on food and nutrition policy issues.

Encompassed in the center's activities on food and nutrition policy are its interests in regulatory issues involving risk analysis including risk assessment, management, and communication. As such, the Center respectfully submits the following comments in response to the Food and Drug Administration's (FDA) request for comment on acrylamide in the food supply, docket no. 02N-0393 as published in the Federal Register.¹

Overview of the Comments

The Center recognizes the critical importance of FDA's role in protecting the public health and commends the agency's aggressive action plan to address the issues of acrylamide in the food supply. The sudden "discovery" of acrylamide in foods raised many important public health questions. Yet finding potential carcinogens in foods is not unique to acrylamide. The comments contained herein will:

02N-0393

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¹ Federal Register, Notices: *Assessing Acrylamide in the U.S. Food Supply*, September 12, 2002 (Volume 67, Number 177), Pages 57827-57828.

1. Summarize the Ceres[®] Roundtable *Acrylamide: Lessons Learned, Plans Ahead* convened by the Center for Food and Nutrition Policy on September 9, 2002;
2. Recommend implementation of a comprehensive risk analysis that more fully addresses risk management and risk communication.

Ceres[®] Roundtable Focuses on Acrylamide

The center is active in the international scientific response to the discovery of acrylamide in commonly consumed foods. In addition to convening a Ceres[®] Roundtable on the topic, faculty from the center have also made presentations on its risk assessment at the Joint Institute for Food Safety and Applied Nutrition (JIFSAN)—Center for Food Safety and Applied Nutrition (CFSAN) seminar series; participated in the Acrylamide in Food workshop hosted by the National Center for Food Safety and Technology (NCFST) and JIFSAN in Chicago, IL; and provided verbal comments at the FDA public meeting on September 30, 2002.

On September 9, 2002, CFNP hosted a Ceres Roundtable entitled *Acrylamide: Lessons Learned, Plans Ahead*. The roundtable addressed several key questions. First, Dr. Steve Tannenbaum from Massachusetts Institute of Technology addressed the questions: Why now? Why did it take so long to “discover” this substance in our foods? Second, what we know and what *should* we know about the toxicology of acrylamide was addressed by Dr. Ian Munro from CANTOX. Third, Dr. Richard Forshee from the Center for Food and Nutrition Policy presented his preliminary risk assessment study on how much acrylamide consumers are exposed to from food. Fourth, Dr. Rick Canady from FDA discussed the agency’s experience with acrylamide. And finally, Dr. Sanford Miller from CFNP and former director of the Center for Food Safety and Applied Nutrition, FDA, offered some insights from past experiences, such as nitrosamines found in some alcoholic beverages.

Acrylamide Forms Naturally during Food Cooking and Processing. Naturally-occurring carcinogens and other environmental toxicants, like mycotoxins, are present in our foods without a doubt. Acrylamide, however, is not known to occur naturally in the environment, and it is not unique with regard to the formation of potential carcinogens during the cooking process.

Cooking foods to enhance flavor and provide protection from foodborne pathogens can lead to formation of acrylamide. Indeed, this is not the first time that science has discovered a potential carcinogen that is formed during the cooking or processing of a food. In his presentation at the Ceres[®] Roundtable, Professor Steven Tannenbaum of the Massachusetts Institute of Technology identified several carcinogens that arise naturally in the environment or as a result of processing or cooking foods—polycyclic aromatic hydrocarbons, heterocyclic amines, mycotoxins, nitrosamines, urethane, chloropropanols, and acrylamide. He also noted that individuals are exposed to acrylamide through sources other than food. For example, smokers have nearly four

times more internal exposure to acrylamide than non-smokers, as measured by hemoglobin adduct formation.

Many relevant questions remain about the formation of acrylamide during food cooking and processing. A few of these questions are:

- What is the strength of the relationship between formation of acrylamide and cooking temperatures?
- Is this relationship non-linear such that slight reductions in maximum temperatures could lead to large reductions in acrylamide without affecting the safety or quality of the food?
- Would changes in cooking processes have unintended negative consequences, such as increasing the fat content of the product or increasing risk of illness from foodborne pathogens?
- What effect does the composition of the raw food materials have on acrylamide formation in the cooked product?
- What other components are related to acrylamide concentration?
- Can acrylamide concentration be significantly reduced by altering the composition of foods being prepared?

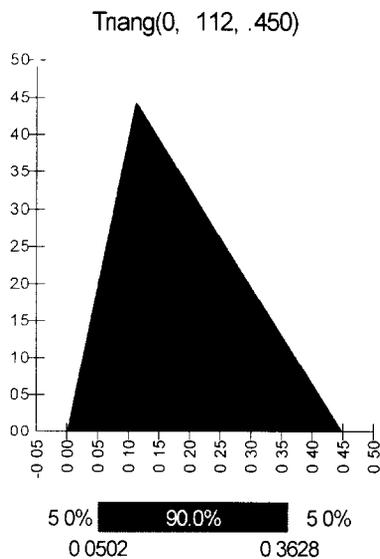
The Center's Preliminary Risk Assessment. In its action plan, FDA recognizes the need for more information on the concentration of acrylamide in foods. In the FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) report, the data on acrylamide consisted of only 248 samples of foods. Most of the food categories had fewer than 10 samples and many had only one or two samples. To compound the problem, many of the samples had acrylamide concentrations that were below the limits of detection and quantification. In bakery products, for example, there were 19 samples and the median value was reported as less than the limit of detection and quantification. Beer provides the most extreme example of these problems—one sample was tested and acrylamide concentration was found to be less than the limit of detection and quantification.

Another difficulty with the current data is that the results for most food categories are highly skewed—a few samples have very high concentrations of acrylamide compared to the rest of the samples. This has important implications for risk assessment and, potentially, for risk management. The samples with high concentrations have a major impact on the mean and shape of the probability distribution of acrylamide concentration. Typically, when a probability distribution is highly skewed, the most probable values are clustered near the central tendency (the mean or median) and a long tail with low probability extends out to the extreme values. Our exposure assessments for acrylamide from food will vary significantly depending on the amount of skew and the shape of the probability distributions for acrylamide concentrations.

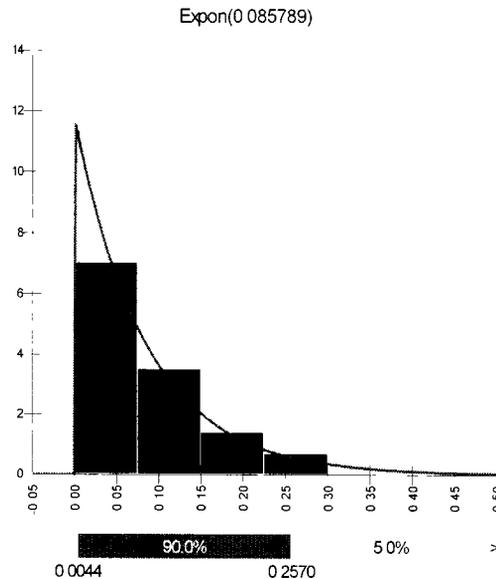
Two plausible, alternative probability distributions for acrylamide concentration in bakery products are shown in Figure 1. Both are consistent with the mean, minimum, and maximum values reported in the FAO/WHO Annex 3, but the distributions have

Figure 1.
Alternative Probability Distributions for Acrylamide Concentration in Bakery Products

“Triangle” Distribution
 (Min. 0, Mean 0.112, Max. 0.450)



Exponential Distribution
 (Min. 0, Mean 0.112, Max. 0.450)



dramatically different shapes and would lead to very different conclusions about the levels of exposure to acrylamide from foods. For example, in the triangle distribution 90 percent of the values lie between 0.05 and 0.36 $\mu\text{g/g}$ of food; in the exponential distribution, 90 percent of the values lie between 0.004 and 0.257 $\mu\text{g/g}$ of food. The current data on acrylamide concentration in foods are not strong enough to make an informed choice about which of these is the more accurate distribution.

In addition to affecting the exposure model to acrylamide in foods, the shape of the distribution may affect how risk management is addressed. If most food samples have acrylamide concentrations that are near or below the limits of detection and quantification and only a few have very high concentrations, the most appropriate strategy may be to focus on reducing the concentrations in those few foods that have high concentrations of acrylamide.

Finally, the currently available data on acrylamide concentrations are “samples of convenience” based on informed hunches about which foods might contain acrylamide. There has not yet been any systematic sampling of food groups or foods within the groups. This is not surprising since the discovery of acrylamide in foods was recent and unexpected, but it is a problem that FDA appears to be addressing in its action plan.

It is important to note that while the data issues just discussed present problems for exposure and risk assessment, they also represent an important research opportunity.

Discovering why there is great variability in the concentration of acrylamide may provide clues about how to reduce or limit exposure, if indeed it is necessary and feasible.

Research Questions

The Center is conducting an exposure assessment of acrylamide from foods. The goal of this project is to determine more precise estimates of acrylamide exposure from food intake in the U.S. by relevant age/gender groups. The exposure assessment addresses three key questions:

- What is the average exposure to acrylamide?
- What is the high range or upper limit of exposure to acrylamide?
- Do certain subpopulations receive higher exposures than others?

Methods

Our analysis focuses on the foods identified in the FAO/WHO Summary Report, Annex 3 as containing acrylamide. These are: potato chips, French fries, bakery products, crackers, breakfast cereals, corn chips, bread, batter/breaded chicken, beef, pork, game, organs, fish (combined), coffee powder, and beer. Using the food codes and individual food records from the Continuing Survey of Food Intake by Individuals 1994-96, 1998 (CSFII), we identified all foods in the categories listed in the FAO/WHO Annex 3.

To calculate point estimates (means and 95th percentiles for each age/gender group) and probability distributions of food intake, these food categories were aggregated up to the individual level and a 2-day average was calculated. Whenever possible, the pre-existing CSFII categories were used.

The data from the FAO/WHO Annex 3 were used to calculate probability distributions of acrylamide concentration in each identified food group. Conservative assumptions were made to calculate the probability distributions of acrylamide concentration. Typically, a triangle distribution was used to determine the probability distribution for acrylamide concentration in a food category.

A triangle distribution is defined by only three parameters: the minimum, the maximum, and the most likely value. The “peak” (the outcome with the highest probability of occurrence) of a triangle distribution is the most likely value. From that point, the probability of each concentration value of acrylamide falls in two straight lines to the minimum value and the maximum value (see Figure 1). Our use of the triangle distribution was conservative in several ways. Since the acrylamide concentrations were typically positively skewed, the mean was usually equal to or larger than the median. Also, in a triangle distribution, the probability of high concentration falls at a slow, linear rate. By contrast, in most skewed distributions, the probability of high values falls rapidly and becomes a long, skinny “tail” in the distribution (see Figure 1). By choosing the triangle distribution, it is unlikely that we have underestimated the probability of high concentration values. More than likely, we have overestimated the probability of high concentration value, perhaps by a large amount.

Figure 2a.
Point Estimates of Exposure to Acrylamide from Foods

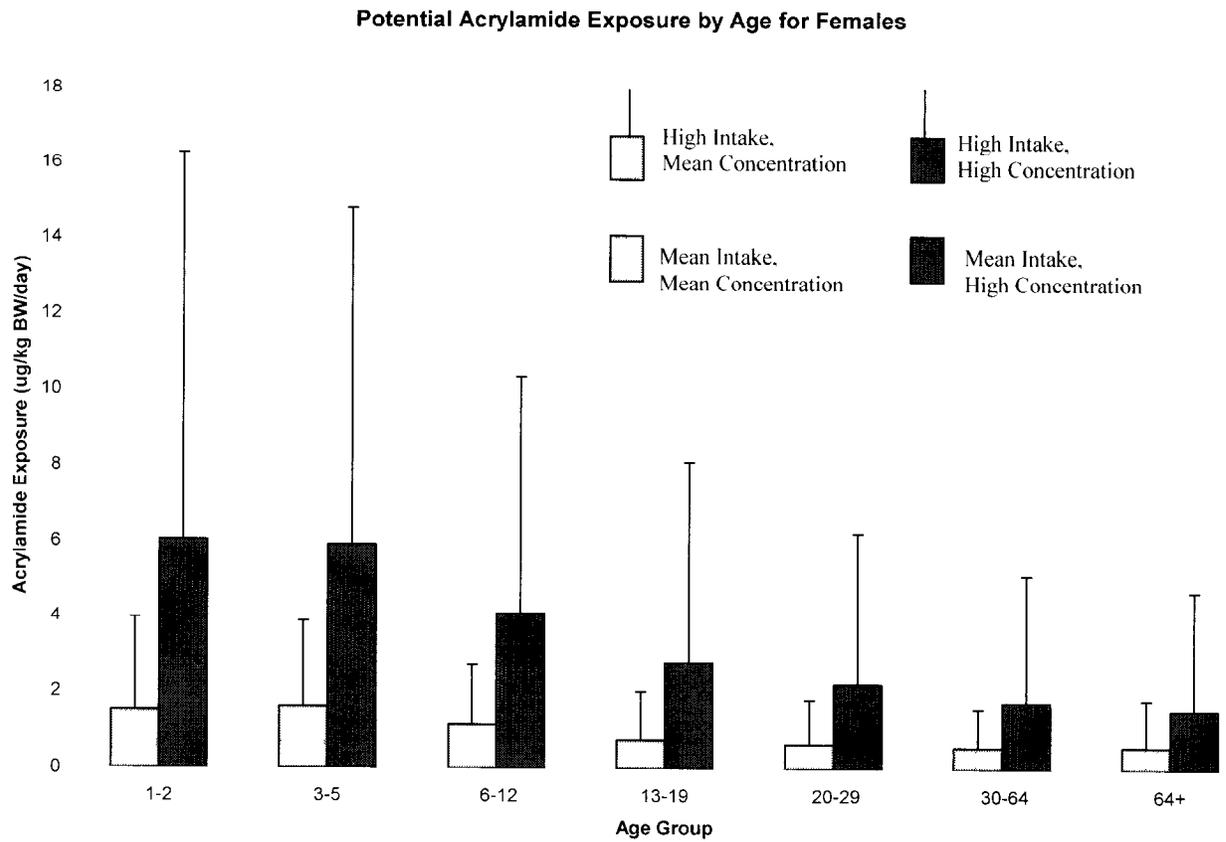


Figure 2b.
Point Estimates of Exposure to Acrylamide from Foods

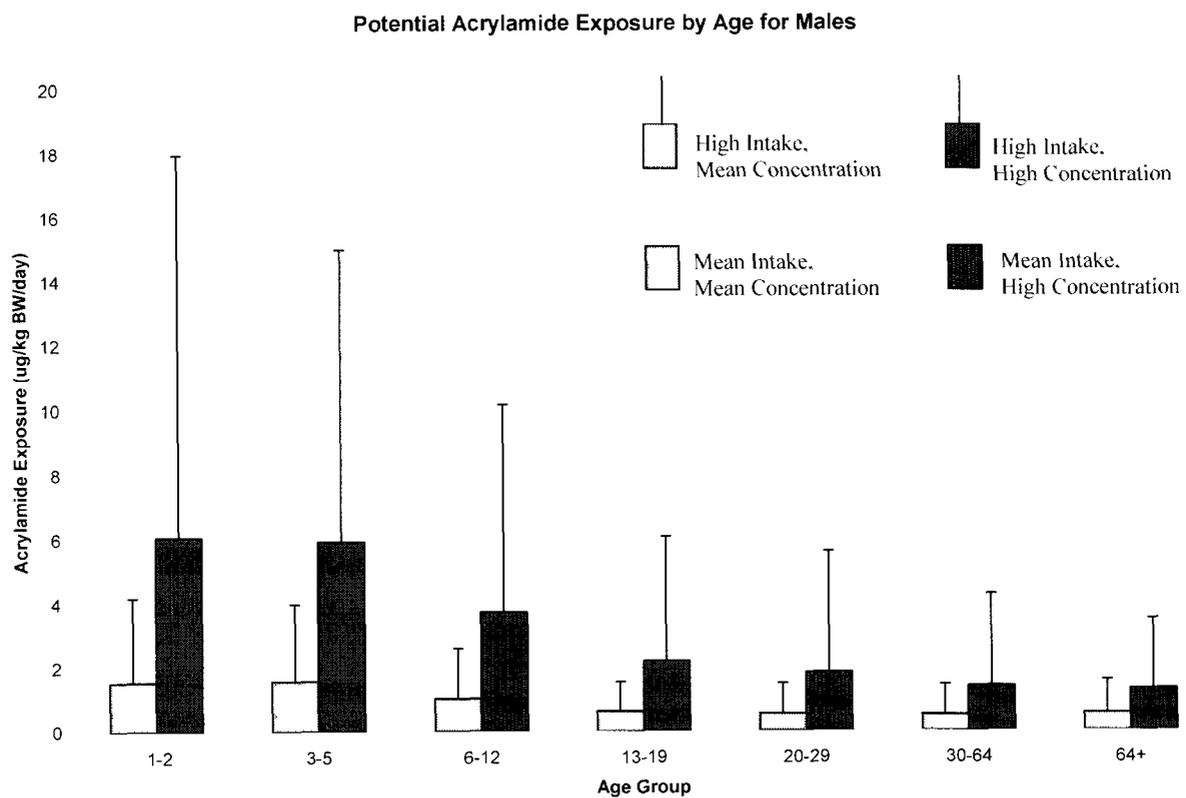
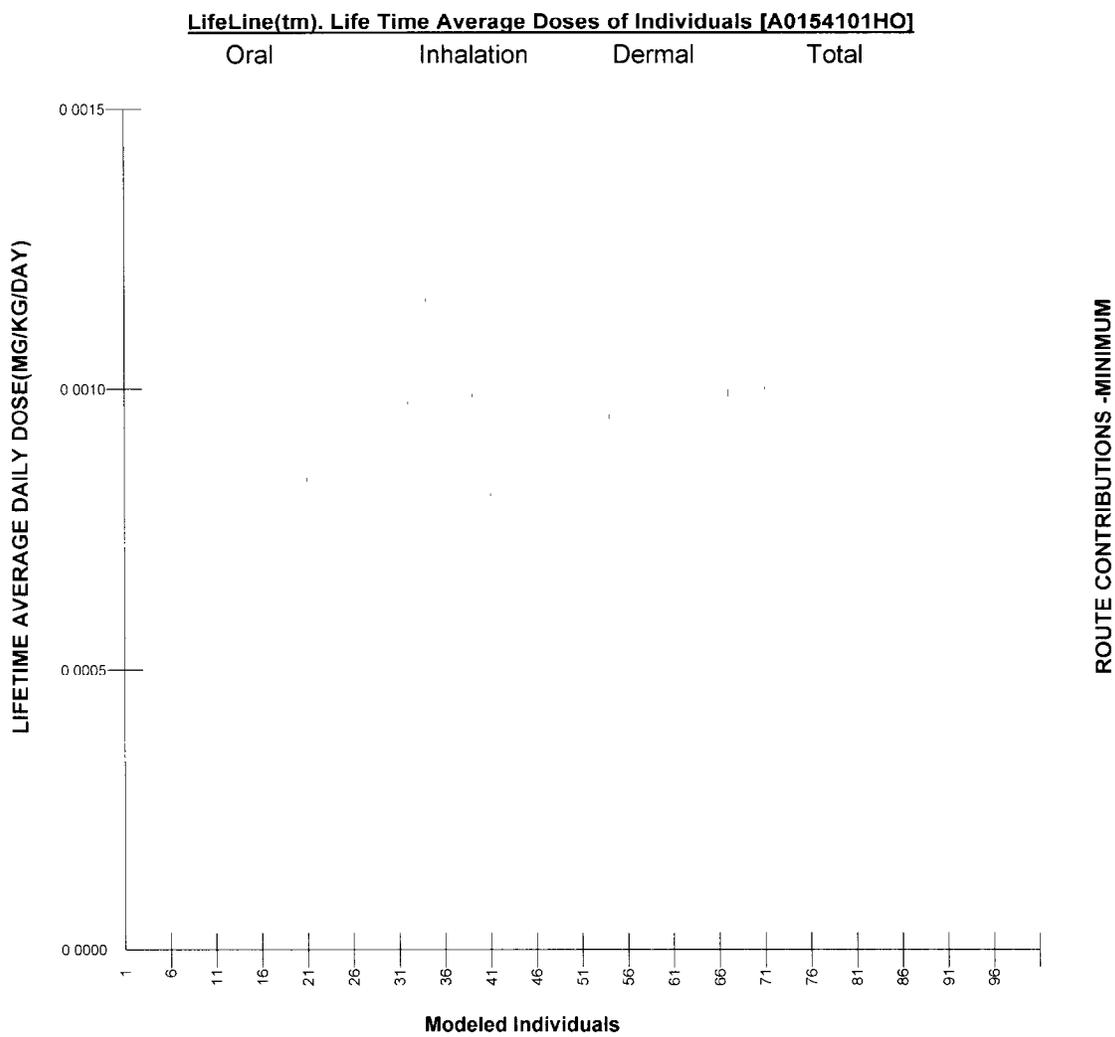


Figure 3.
LifeLine™ Model of Lifetime Average Exposure to Acrylamide (g/kg/day)



Using these data, we calculated exposure to acrylamide using two methods. First, we calculated exposure based on point estimates of food intake and acrylamide concentration. Average exposure for various age/gender categories was based on average food intake and average acrylamide concentration in each category. An upper limit of exposure was based on the 95th percentile of food intake and the 90th percentile of acrylamide concentration. In the second method, we used the LifeLine™ model to calculate average lifetime exposure based on 100 simulated “lives.” For technical reasons, the LifeLine model did not include acrylamide concentration distributions for crumbed or battered meat products, coffee powders, or beer. The results of the two approaches were consistent with one another and with the exposure assessments reported in the FAO/WHO report.

Two Approaches Used to Assess Exposure to Acrylamide

Point Estimates Approach. The point estimate approach showed that average exposure to acrylamide from foods was between 0.66 µg/kg body weight (BW)/day and 0.49 µg/kg BW/day for adults in the various age/gender categories. For children and teens, average exposure was between 1.62 µg/kg BW/day for and 0.60 µg/kg BW/day. The upper limits of exposure were 6.23 µg/kg BW/day for adults (women 20-29) and 17.95 µg/kg BW/day for children (boys 1-2). The full results are shown in Figures 2a-b.

Simulated Lifetime Exposure Approach

The LifeLine™ model is presented in Figure 3. It shows that lifetime average exposure for the 100 simulated lives generally ranged between 0.5 µg/kg BW/day and 1.0 µg/kg BW/day. Only three of the simulated individuals had a lifetime average exposure greater than 1.0 µg/kg/day. The patterns of individual lifetime exposure were consistent with the results reported in the point estimate analysis. Specifically, children had higher exposures as measured in µg/kg BW/day units, which fell into the range of about 0.5-1.0 µg/kg BW/day as they reached adulthood.

All of these results, together with the FAO/WHO report, estimate exposure to acrylamide from food well below the No Observable Adverse Effect Limit (NOAEL) for neuropathy, which is 500 µg/kg BW/day. All of the estimates of average exposure to acrylamide from food are 25 to 100 times lower than the NOAEL for neuropathy. However, the estimates are greater than the reference dose of 0.2 µg/kg BW/day established by the U.S. Environmental Protection Agency (EPA) for acrylamide in drinking water. Significant research is required to improve these exposure assessments and the estimates of cancer risks from exposure to acrylamide in food. This is particularly important because the bioavailability of acrylamide from food may be significantly different than it is from water.

Toxicology and Cancer Risk of Acrylamide in Foods. During the Ceres Roundtable, Dr. Ian Munro summarized the brief literature on acrylamide and cancer risk. To date, animal studies show minimal cancer risk from acrylamide. In cancer studies using very high doses of acrylamide in drinking water, male rats receiving the highest dose of acrylamide had significantly more benign tumors of the thyroid and testes, but no more malignant tumors of the thyroid or central nervous system and spinal cord than control

rats. Female rats receiving the two highest doses of acrylamide in drinking water developed more benign tumors of the mammary gland and thyroid, but no greater incidence of malignant thyroid tumors than control female rats.

There is no epidemiological evidence that acrylamide is a human carcinogen. Cohort studies conducted in the 1980s showed no increase in cancer rates among industrial workers exposed to acrylamide through the skin and by inhalation. Once acrylamide enters the body we know the biochemical pathways that metabolize and excrete it. But with regard to exposure through foods, we do not know how much acrylamide is actually excreted without absorption by the gut.

Several international organizations classify acrylamide either as a carcinogen or a probable carcinogen, but much more research is needed in this area.

Lessons Learned from Nitrosamines. Issues such as the acrylamide situation occur regularly, so there are historical examples on which the FDA can draw. At the September 9th roundtable, Dr. Sanford Miller discussed the lessons that can be drawn from the FDA's experience with nitrosamines in malted beverages.

The issue of nitrosamines in malted beverages came about because of a study conducted by the German Max Plank Institute for Food Toxicology that discovered nitrosamines in beer. German regulators informed FDA of this discovery, and the agency began a process to determine how much nitrosamines were present in U.S. malted beverages.

Before that process was completed, the Ontario Department of Public Health in Canada discovered that there were also nitrosamines in other malted distilled beverages, such as American bourbon. Canada immediately blocked the importation of American bourbon into Ontario. In response, the United States conducted an analysis of a number of distilled malted beverages including scotch. It was discovered that all whiskey, including Canadian whiskey, contained some amount of nitrosamines. The Canadian block of American bourbon quickly ended.

The end of the trade dispute, however, was not the end of the issue for the FDA. The agency was now faced with a problem. Nitrosamine was a known human carcinogen that was present in these distilled beverages. The issue attracted a great deal of media attention, and some groups advocated a ban on these beverages, especially since beer and other distilled beverages are not necessary for a healthy diet.

Obviously, the FDA did not ban all distilled beverages in response to this finding, but the agency decided it needed to take some kind of action. The FDA recognized that there was insufficient information to make an informed policy decision, so it developed an action plan in collaboration with the malt beverage industry.

By this time the beer brewers had discovered that the origin of the nitrosamines occurred during the drying of the malted hops. This kilning was mostly done by direct

drying, such as gas-heated forced air. The agency, together with the industries, agreed that the agency would not take any regulatory action, but they would monitor the research that was being done by the industry. This is an important point—the research was being done by the industry, and monitored by the agency. The end result was that a kilning process called indirect heating was developed, and the new indirect heating process solved the nitrosamine problem.

The important issue in the nitrosamine case was twofold. First, the FDA did not acquiesce to the pressures from Congress and others to take immediate action on malt beverages before it had developed the necessary science and evaluated alternative courses of action. Second, the FDA worked with the industry in supervising the research, making sure that standards were met and that the resources were being devoted to nitrosamine research.

Conclusions from the Roundtable—The Science on Acrylamide is Lacking. The science shows that acrylamide is a known neurotoxin and suggests that it may be a carcinogen. The discovery of acrylamide in commonly consumed foods raises many important public health questions. Unfortunately, the current science on acrylamide is not adequate to properly assess the risk it poses to human health or to formulate appropriate and effective regulatory policies. Critical areas for research include:

1. Understanding how acrylamide forms during food cooking and processing;
2. Analyzing the concentration of acrylamide in food products;
3. Validating the detection methodology among and within laboratories;
4. Funding research to understand the human health effects from exposure to acrylamide through foods; and,
5. Incorporating the results of these research programs into comprehensive risk assessment models to evaluate whether regulatory interventions are necessary and, if so, which policy options would most effectively protect public health.

Crafting Efficient and Appropriate Policies

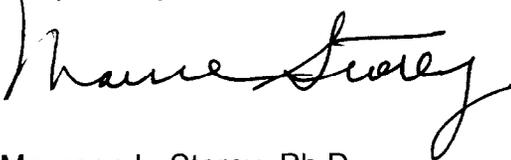
The Center applauds FDA's action to conduct research that will shed more light on a number of aspects related to acrylamide in the food supply. FDA should take this opportunity to develop a comprehensive plan that includes all elements of a risk analysis—risk assessment, risk management, and risk communication.

Future research will undoubtedly identify other compounds in foods that may or may not pose a health risk. It is therefore critical that the agency implement an action plan efficiently and effectively to protect the public health when the risk is great, as well as protect the public from scare tactics when there is little or no risk.

The Center urges FDA to:

1. Assess the risk to public health from foods containing acrylamide and use this assessment as a template for other substances that surely will be “discovered” in the future. This risk assessment should include: a) a thorough and critical re-examination of the literature on cancer risk and acrylamide and b) a critical evaluation of research gaps that need to be filled before a regulatory policy is put in place;
2. Manage the public health risk from acrylamide in foods if a hazard exists. The center suggests that FDA collaborate with scientists from industry and academia to eliminate or minimize the hazard if the risk assessment shows that there is a risk to be managed.
3. Develop a risk communication plan together with communications experts from the public relations and/or advertising industry, media, and consumer advocacy groups that accurately communicates the level of risk to public health from acrylamide in cooked foods and from foodborne illness from improperly cooked foods.

Respectfully Submitted,



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