Acrylamide Scientific Issues: An Update

James R. Coughlin, Ph.D.

Coughlin & Associates

Laguna Niguel, California

jrcoughlin@cox.net

www.jrcoughlin-associates.com

Yum! Brands Presentation for CIC Meeting

October 17, 2003

Sacramento, CA

Presentation Topics

- Scope of the issue
- "The role or importance of the chemical matrix in which acrylamide is formed"
  - Complex chemical formation mechanisms
  - Beneficial effects of the Maillard Browning Reaction
- Some important toxicological considerations
- Recent dietary epidemiology studies
- Additional studies are needed to determine whether acrylamide in food poses a real risk to human health

[My Sept. 26 written submission and copies of references were contained in the CD-ROM that I supplied]

Swedish Discovery of Acrylamide in Foods

Tareke et al., *J. Agric. Food Chem.* 50: 4998-5006 (2002)

- Published in August 2002, following April 2002 press conference
- Acrylamide in foodstuffs was measured by two methods:
  - GC-MS detection [LD of 5 µg/kg] of brominated derivative
  - LC-MS-MS detection of underivatized acrylamide [LD of 10 µg/kg]
- Temperature/time dependence of acrylamide formation was shown:
  - Higher levels in carbohydrate-rich foods [150 - 4,000 µg/kg]
  - Moderate levels in protein-rich foods [5 - 50 µg/kg]
  - Acrylamide not detected in unheated control or boiled foods
  - Higher surface area foods had higher levels

Percent of Nutrients Contributed by Acrylamide-Containing Foods

- 38% of calories
- 33% of carbohydrates
- 36% of fiber
- 28% of fat
- 20% of calcium
- 47% of iron
- 25-35% of other nutrients
- 15% of vitamin A
- 34% of vitamin E
- 22-44% of vitamin B, vitamin C and folic acid

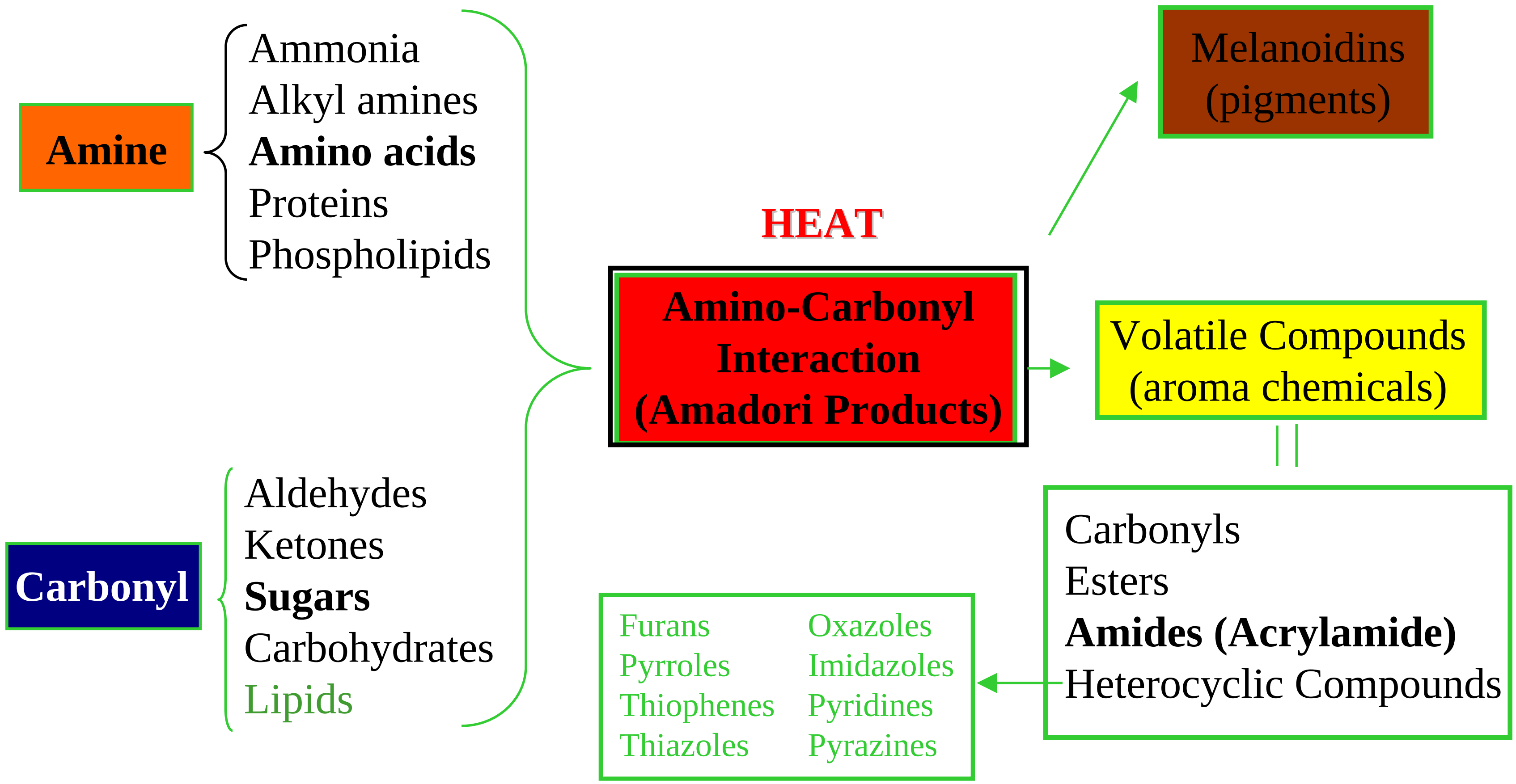
Source: Industry presentation to FDA's Food Advisory Committee, Feb. 24, 2003

Dietary Exposure Assessments in Europe and the U.S.

- Recent mean intake estimates are considerably lower than the original FAO/WHO high-end estimate of 56 µg/day

- Five studies [IARC/EPIC (Germany), Sweden, Netherlands, Norway and U.S.] show mean intake estimates of 8.4 – 38 µg/day

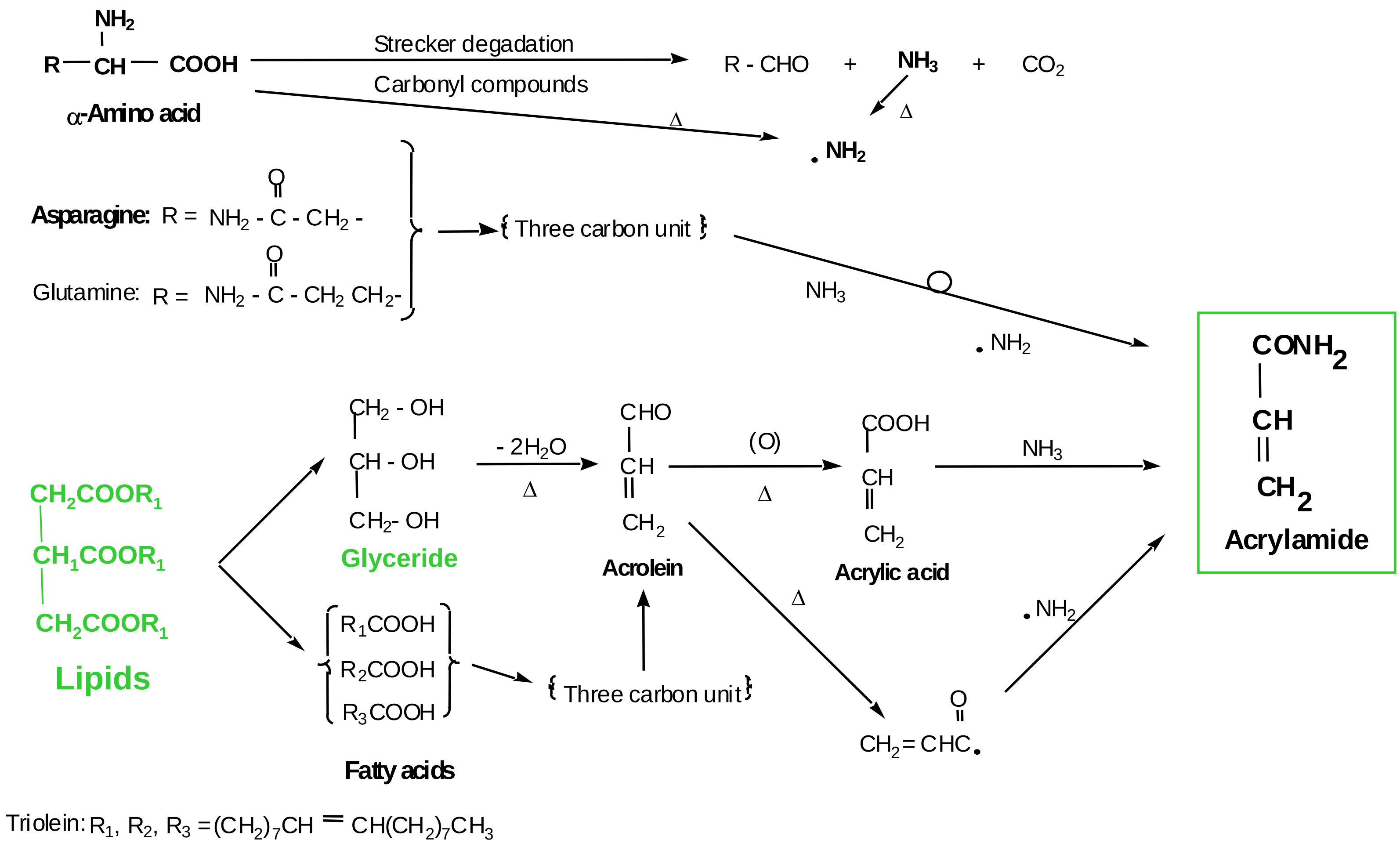
General Scheme of Maillard Browning Reaction



Chemical Formation Mechanisms of Acrylamide in Foods and Model Systems

- Several publications on formation mechanisms began appearing in September 2002
- Acrylamide was initially found in Maillard Browning Reaction model systems due to the reaction of <u>glucose</u> and <u>asparagine</u>, based on elegant labeling studies
- Professor Shibamoto was the first to show (earlier this year) additional complex mechanisms involving carbonyls (acrolein, acrylic acid) from heating ***lipids***, <u>without the involvement of carbohydrates at all</u>, and he showed the nitrogen source to be ***ammonia*** from the deamination of amino acids
- Nestle Research Center scientists in Switzerland (Stadler et al.) just demonstrated other reaction mechanisms <u>not</u> requiring asparagine

Proposed Formation Mechanisms of Acrylamide



Maillard Browning Reaction Issues Presented at the OEHHA Acrylamide Workshop (May 12, 2003)

- Benefits of the Maillard Browning Reaction (Coughlin and Shibamoto presentations):

  - Antioxidants produced during Maillard browning are known to be health protective for diseases linked to oxidative damage/stress (cancer, atherosclerosis, diabetes, inflammation, arthritis, immune deficiencies); many heterocyclic compounds have been shown to be antioxidants

  - Specific Maillard Reaction Products (MRPs) have anti-carcinogenic and anti-mutagenic effects, and they can also induce protective enzymes

  - While being one of the mechanisms for acrylamide formation, the Browning Reaction also plays a major role in determining the desirability and acceptability of food by consumers because of its impact on palatability

Important Toxicological Considerations

- Must study comparative metabolism and pharmacokinetics in rodents vs. humans to determine if acrylamide is metabolized differently by humans

- Humans have well-known acrylamide detoxifying enzymes that may protect them from low level exposures to carcinogens such as acrylamide:

  - Glutathione conjugation via glutathione transferase, then urinary excretion

  - DNA repair enzyme systems

Metabolic & Toxicokinetic Studies will Assist in Human Risk Assessment: Activation vs. Detoxification

- Metabolic activation:
  - Studies have shown that acrylamide is metabolized to glycidamide by the cytochrome P-450 2E1 oxidative enzyme pathway, the probable pathway for the carcinogenic effects of acrylamide
- Fortunately, major detoxification pathways also exist for acrylamide and glycidamide:
  - Glutathione pathway leads to enhanced excretion of acrylamide
  - Glycidamide is further metabolized by epoxide hydrolase to yield 2,3-dihydroxypropionamide
- **Key Point**: The balance of competing metabolic processes and their relative rates are important determinants of toxicity
  - These can differ between animals and humans and between high animal doses and drastically lower human intakes

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

- Well-known Maillard reaction product, N^{ϵ}–carboxymethyllysine (CML), a 2-carbon adduct on protein, enhanced the expression of GST, the primary detoxification enzyme for acrylamide, in rats and in cultured human Caco-2 intestinal cells:
  - Rats fed casein-linked CML and bread crust-linked CML showed an inductive effect of CML on GST activity in the kidneys
  - Cell culture studies also confirmed these inductive effects
- Significance: while the browning reaction does create acrylamide, it also creates a protective chemical adduct – CML – resulting in increased detoxification of the acrylamide found in the same browned foods
- Studies are continuing on other MRPs for their ability to induce protective enzymes, which may have a significant impact on reducing the human risk from acrylamide, if any

Effects of dietary N^{ϵ}–carboxymethyllysine on expression of the biotransformation enzyme, glutathione-S-transferase, in the rat. Faist et al., Intl. Congress Ser. 1245:313-320 (2002)

First Cancer Epidemiology Study of Acrylamide in the Diet was Published

- Sweden's Karolinska Institute and Harvard School of Public Health; food frequency data and acrylamide levels; population-based case-control study of Swedish adults:
  - Large bowel cases (N = 591)
  - Bladder cases (N = 263)
  - Kidney cases (N = 133)
  - Healthy controls (N = 538)

- "We found consistently <u>a lack of an excess risk</u>, or any convincing trend, of cancer of the bowel, bladder, or kidney in high consumers of 14 different food items with a high (range 300-1200 µg kg^{-1}) or moderate (range 30-299 µg kg^{-1}) acrylamide content." (emphasis added)

- Found an <u>inverse</u> trend ($p = 0.01$) for large bowel cancer, with a 40% <u>reduced</u> risk in the highest compared to the lowest quartile

- "We found reassuring evidence that dietary exposure to acrylamide in amounts typically ingested by Swedish adults in certain foods <u>has no measurable impact</u> on risk of three major types of cancer." (emphasis added)

Ref. Mucci et al., Br. J. Cancer 88:84-89 (2003)

Second Cancer Epidemiology Study of Acrylamide in the Diet was Published

- Italy's Mario Negri Institute, IARC and Harvard School of Public Health; hospital-based case-control study in Italy and Switzerland between 1991-2000; food frequency questionnaire:
  - Large bowel cases (N = 1,953)
  - Breast cases (N = 2,569)
  - Ovary cases (N = 1,031)
  - Esophagus (395), oral cavity & pharynx (749), larynx (527)
  - Hospital controls for each cancer site

- "All the odds ratios (OR) for the highest vs. the lowest tertile of intake ranged between 0.8 - 1.1." (OR = 1.0 is defined as no association)

- <u>Inverse</u> trend ($p < 0.05$) found for large bowel and colon cancer overall

- "Thus, our data provide reassuring evidence for the <u>lack of an association</u> between moderate consumption of fried/baked potatoes and cancer risk at the investigated sites." (emphasis added)

Ref. Pelucchi et al., Int. J. Cancer 105:558-560 (2003)

Additional Studies Are Needed to Determine Whether Acrylamide in Food Poses a Real Risk to Human Health

- Does acrylamide in cooked food pose a real risk to humans?

  A reliable answer based on sound science demands a variety of complex studies to fill the <u>significant data gaps</u> in our current understanding of the risk, if any, posed to humans.

- A comprehensive risk assessment must include:
  - Rodent cancer bioassays with acrylamide in <u>feed</u>
  - <u>Bioavailability</u> in foods – acrylamide may be less bioavailable in some foods than in water
  - Biomarker and metabolic studies – to investigate exposures and toxic effects at potential target organs
  - Proper animal to human risk extrapolations
  - The existence and impact of detoxifying and protective enzymes that may <u>reduce</u> the impact of acrylamide on humans
  - Dietary epidemiology studies of large populations