Acrylamide in Foods: Toxicology, Epidemiology and Research Initiatives

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Hemoglobin Adducts in Humans

- Workers with neurotoxic symptoms
  - Chinese and Korean workers, polyacrylamide manufacture
  - Swedish workers, tunnel construction
  - > 500 to 18,000 picomoles/g globin
- Controls with no occupational exposure
  - Smoking 116 picomoles/g globin
  - Non-smoking 31 picomoles/g globin
- Laboratory workers
  - Polyacrylamide gels 54 picomoles/g globin
# Average Acrylamide per Serving*

<table>
<thead>
<tr>
<th>Food</th>
<th>Acrylamide, PPB or ug per kg food</th>
<th>Approximate Serving Size**</th>
<th>Acrylamide, ug per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast Cereal</td>
<td>133</td>
<td>2 ounces</td>
<td>7.3</td>
</tr>
<tr>
<td>Brewed Coffee</td>
<td>8</td>
<td>1 cup</td>
<td>2.0</td>
</tr>
<tr>
<td>Cookies</td>
<td>222</td>
<td>1 ounce</td>
<td>6.6</td>
</tr>
<tr>
<td>French Fries, (RF)</td>
<td>322</td>
<td>2 ½ ounces</td>
<td>22.5</td>
</tr>
<tr>
<td>French Fries, (OB)</td>
<td>698</td>
<td>2 ½ ounces</td>
<td>48.8</td>
</tr>
<tr>
<td>Potato Chips</td>
<td>548</td>
<td>1 ounce</td>
<td>16.4</td>
</tr>
<tr>
<td>Soft Bread</td>
<td>44</td>
<td>1 slice</td>
<td>2.2</td>
</tr>
<tr>
<td>Toast</td>
<td>213</td>
<td>1 slice</td>
<td>9.8</td>
</tr>
</tbody>
</table>

*FDA exploratory data on acrylamide in foods through Feb 2003

**Nutrition Label Serving Sizes (21 CFR 101.12, Table 2)
Formation of Acrylamide in Food

- Side reaction of browning reactions in food
- Non-enzymatic browning
  - Maillard reaction
  - Reducing sugar (glucose, fructose) + amino acids
- Acrylamide formation
  - Reducing sugar + asparagine
  - Temperature > 100 deg C
  - Low moisture
June 2002
Confirmed presence of acrylamide in foods
Estimated average intake, 0.3 to 0.8 ug/kg bw/d
No neurotoxic effects expected at these levels
Carcinogenic potency of acrylamide in animals
  Similar to other carcinogens in human diet
  Likely overall human intake is higher
  No evidence on carcinogenesis in humans
  Major concern based on induction of cancer and heritable mutations in animals
FAO/WHO Recommendations on Acrylamide in Food

• **Interim advice**
  • Food should not be cooked excessively
    ◦ But must be cooked thoroughly to destroy pathogens
  • Eat a balanced and varied diet
    ◦ Plenty of fruits and vegetables
    ◦ Moderate consumption of fried and fatty foods
  • Investigate possibilities for reducing acrylamide in foods
  • Establish an international network to share data and ongoing work
## FDA Estimate of Mean Acrylamide Intake
**CFSII 1994-96, 1998; Ages 2 and Older**

<table>
<thead>
<tr>
<th>Food</th>
<th>Mean acrylamide intake (ug/kg bw/d)</th>
<th>Percent of total intake</th>
<th>Cumulative percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>French Fries (RF)</td>
<td>0.056</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>French Fries (OB)</td>
<td>0.049</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Breakfast Cereal</td>
<td>0.044</td>
<td>11</td>
<td>54</td>
</tr>
<tr>
<td>Potato Chips</td>
<td>0.041</td>
<td>10</td>
<td>52</td>
</tr>
<tr>
<td>Cookies</td>
<td>0.040</td>
<td>10</td>
<td>62</td>
</tr>
<tr>
<td>Brewed Coffee</td>
<td>0.027</td>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td>Toast</td>
<td>0.023</td>
<td>6</td>
<td>77</td>
</tr>
<tr>
<td>Soft Bread</td>
<td>0.020</td>
<td>5</td>
<td>82</td>
</tr>
<tr>
<td>Other Foods Tested</td>
<td>0.070</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0.37</strong></td>
<td><strong>100</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
### Other Tested Foods Contributing to FDA’s Estimate of Acrylamide Intake

<table>
<thead>
<tr>
<th>Tested Foods Providing the Remaining 18% of Estimated Mean Acrylamide Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn snacks, Crackers, Pretzels, Popcorn, Baked beans, Breaded chicken, Peanut butter, Soup mix</td>
</tr>
</tbody>
</table>
FDA Preliminary Exposure Assessment Implications

- Estimated average US exposure
  - Similar to international estimates
  - 1000 x below animal neurotoxic or carcinogen levels
- Exposure of small children
  - 2-3 times greater per kg body weight
  - Expected based on body size and food intake
Workers Exposed to AA in Three U.S. & One Dutch Chemical Plants

- Cohort of 8508 workers potentially exposed to AA at 3 U.S. chemical plants & one plant in Netherlands 1925-89 (Collins et al, 1989)
- Data on cohort updated covering 11 yrs. (Marsh et al., 1999)
- “Most definitive study of the human carcinogenic potential of exposure to AA conducted to date.”
• Authors of study found increased SMRs of rectal, esophageal, pancreatic & kidney cancers for some categories of exposure to AA, but little evidence of exposure-response relations
• 2.26-fold risk (95% CI 1.03 – 4.29) found for pancreatic cancer among workers with cumulative exposure to AA >0.30 mg/m³ yrs, but no consistent exposure-response relation
Authors noted limitations of study to be a large proportion of short term workers, low AA exposure, incomplete smoking data

- Low statistical power to detect cancers of brain & CNS, thyroid gland, testis & other male genital organs
- Good statistical power to detect respiratory cancers
- Authors concluded little evidence for a causal relation between exposure to AA and mortality from any cancer site
Epidemiology Study on Dietary Acrylamide and Cancer Risk

- Case-control study, January, 2003
- Men and women in Stockholm, Sweden
- Aged 51 to 77
- Found no positive association between dietary acrylamide and incidence of cancer of large bowel, bladder, kidney
Evaluations of Workers Studies

• In addition to evaluations by original authors, this chemical plant study has been evaluated by Sobel et al (1986), Hogan & Scott (1990) with reply by Collins et al. (1990). Also Granath et al. (2001) with reply by Marsh et al. (2001)

• Various authors disagree on conclusions, statistical power and limitations of original study
Epidemiology Study on Dietary Acrylamide and Cancer Risk

• Dietary acrylamide
  • Food frequency questionnaire
  • Swedish acrylamide food data
  • Various fried and baked potatoes, crisp breads, soft breads, breakfast cereals, biscuits
  • Did not include coffee or toasting of soft breads

• Subjects
  • 538 controls
  • 591 large bowel cancer
  • 263 bladder cancer
  • 133 kidney cancer

• Source: Mucci et al., 2003
Study Evaluation

• Authors concluded that
  “Acrylamide intake through dietary sources may thus be effectively detoxified within the range of human exposure.”

• Strengths
  This was a well-conducted study with strengths that reduced the possibility of selection bias and recall bias, and adjusted for major confounding variables.

• Limitations
  The limitations of the study could explain the observed lack of association, even if a true association exists
Limitations of Study

• May prevent detection of an association if there is a true association
  • Limited statistical power to detect a small risk if one exists
  • Possible uniformity of acrylamide intake
  • Omission of some food sources of acrylamide
  • Did not adjust for possible residual confounding by additional nutrients, food components
  • Did not study possible excess risk of acrylamide intake at other cancer sites
Authors’ Recommendations

- Determine cooking methods that avoid acrylamide formation during food preparation
- Validation of food questionnaires for acrylamide intake should be a high priority
- Additional epidemiological evidence is needed
  - Other cancer sites
  - Neurological and other disorders
Epidemiology Study on Fried/Baked Potatoes and Cancer Risk

- Pelucchi et al., Int. J. Cancer, May, 2003
- A group of coordinated case-control studies
- Men and women in Switzerland and Italy
- Aged up to 79 years
- Hospital-based control groups
- Found no positive association between
  - Intake of fried/baked potatoes
  - Incidence of cancer of oral cavity, throat, larynx, large bowel, breast, ovary
Implications of Current Knowledge of Acrylamide in Food

- Average human exposure through food
  - About 1000 times lower per kg body weight than
    - Animal neurotoxicity
    - Animal genotoxicity and carcinogenesis
  - Lack of data on human health risk at this exposure level
  - Partial data on acrylamide levels in food
    - Types of foods
    - Processing, preparation methods
- Advice for consumers should not create one problem by solving another
Current FDA Advice to Consumers about Acrylamide

- Until more is known, FDA recommends that consumers
  - Eat a balanced diet
  - Choose a variety of foods
    - Low in trans fat and saturated fat
    - Rich in high-fiber grains, fruits, vegetables
Acrylamide Web Page Links

- FDA CFSAN Acrylamide web page
  http://www.cfsan.fda.gov/~lrd/pestadd.html#acrylamide

- JIFSAN Acrylamide INFONET
  http://www.acrylamide-food.org/

- FAO/WHO Acrylamide web page
  http://www.who.int/fsf/Acrylamide/Acrylamide_index.htm
NIOSH Acrylamide Workers Study

• Evaluate workers’ exposure to AA & congeners using ambient area & personal & dermal sampling, reported exp. Data & exp. Biomarkers (urinary metab., Hb adduct levels)
• Assess male reproductive health (semen quality, sperm DNA integrity, hormone levels, PSA levels & reported reproductive health history)
NIOSH Study (cont’d)

• Assess neurobehavioral parameters (sensation-tactile, postural stability, grooved pegboard, simple reaction time tests)
• Assess relative sensitivities of reproductive & neurological effects.
• Project Officer: William Moorman. Investigators: S. Reutman, S. Schrader, T. Turner, L. Mickelson, E. Hitchcock, J. Kesner

• Study has undergone peer review and HSRB. Final approval in process.
Studies at Center for Disease Control & Prevention

• Objectives:
  • Obtain population-based data on AA exposure using NHANES population
  • Ensure comparability of epidemiological and toxicological data
  • Develop and apply appropriate biomonitoring methods to measure AA exposure
  • Establish a working group on technical issues of AA exposure
Status of CDC Studies

- Method development is ongoing. Hb adducts of AA and GC to be quantitated by HPLC tandem mass spectrometry using newly developed stable isotope labeled peptides
- Methodology is based on established methods used for analyzing glycated HbA1c in diabetes
- NHANES sample collection/storage began in Jan. 03
- First interagency meeting on methodology held in Jan. ‘03
Acrylamide levels in food

- FDA – testing of U.S. of supply, JIFSAN contract for private lab testing, Total Diet Study planned (several hundred samples)
- Environmental World watch, Inc. – California foods
- Measurements in foods from other countries: Sweden, UK, Germany, Canada, Norway, Swit., Japan, Jordan, Korea, Italy, Belgium, Netherlands, France et al.
- Extensive worldwide effort to develop and standardize methods of analysis
- Source: T. A. McDOnald, OEHHA, CA EPA
Food stock, food storage & modulation of AA through cooking practices

- FDA-NCFST – AA formation, including home cooking.
- JIFSAN-consortium sponsored academic research
- Private industry
  - Proctor & Gamble (mechanisms of formation)
  - Frito Lay (reaction variables in food prep.)
  - Nestle Research Ctr. (Maillard reaction)

Source: T.A. McDonald, OEHAA, CA

EPA
AA Formation and Reduction (cont’d)

• Academic research
  • Univ. of WI-Madison (compilation of studies regarding asparagine levels in var. food stocks & changes in asparagine levels from storage, irradiation & other process variables)
  • Univ. WI-Madison (mechanisms of formation, food engineering)
  • Univ. Reading, UK (Maillard reaction/AA formation)
  • Stockholm Univ. (AA formation, reaction variables)
  • McGill Univ. (asparagine conversion to AA)
  • Source: T.A. McDonald, OEHHA, CA EPA
• Academic Research
  • Univ. Arkansas  (effect of frying on food quality & safety)
  • Instituto del Frio (reduce AA in coking & processing)
  • Ongoing research at other governmental organizations
    < Health Canada, Finland, German, Norway (several groups,), Sweden, UK (several projects)