Metabolism of Acrylamide and Potential Biomarkers

- **Acrylamide (AA)**
  - CYP 2E1
  - GST/GSH
  - Urinary AA/GA mercapturates
  - AA/GA-Protein adducts

- **Glycidamide (GA)**
  - DNA
  - GA-DNA adducts
  - Globin N-terminus or Cys-SH

Chemical structures and pathways are shown with arrows indicating the metabolic processes.
# Comparative Hemoglobin Adduct Formation - Rodents

<table>
<thead>
<tr>
<th></th>
<th>RAT</th>
<th>MOUSE</th>
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<tbody>
<tr>
<td>Hb-AA</td>
<td>26.2*</td>
<td>20.0*</td>
</tr>
<tr>
<td>Hb-GA</td>
<td>6.8*</td>
<td>24.5*</td>
</tr>
<tr>
<td>Hb-GA/Hb-AA</td>
<td>0.26</td>
<td>1.2</td>
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</tbody>
</table>

*nmol/g globin per mmol ip/kg body
Comparative Hemoglobin Adduct Formation-Humans

<table>
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<tr>
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<th>HUMAN</th>
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<tbody>
<tr>
<td>Hb-AA</td>
<td>0.03 nmol/g (controls)</td>
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<tr>
<td></td>
<td>0.05 nmol/g (PAGE workers)</td>
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<tr>
<td></td>
<td>0.1 nmol/g (smokers)</td>
</tr>
<tr>
<td></td>
<td>0.3-34 nmol/g (occupational)</td>
</tr>
<tr>
<td>Hb-GA</td>
<td>1.6-32 nmol/g (occupational)</td>
</tr>
<tr>
<td>Hb-GA/Hb-AA</td>
<td>0.7;0.1</td>
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</table>
Evidence for AA Mutagenicity and Carcinogenicity

• Struc. similar to other alkylating carcinogens
• AA (-), GA (+) in *Salmonella* mutagenicity tests
• AA clastogenic/mutagenic *in vivo*
• AA = male germ cell mutagen
• AA active in initiation/promotion assay of skin carcinogenicity in mice (topical/oral)
• AA carcinogenic in rats from two 2-yr drinking water exposure studies (testes, mammary gland, thyroid, CNS)
• IARC 1995: “probably carcinogenic to humans”
Metabolism & Disposition of AA in Rodents

- AA rapidly absorbed, eliminated ($t_{1/2}$ 1.5hr); wide tissue distribution; urinary excretion
- GA formed by CYP 2E1; mouse $>$ rat (2x); saturable formation \textit{in vivo} and % conversion to GA incr. as low [AA] decr.
- GA elimination kinetics similar to AA
- No data from dietary administration
Proposed Mechanistic Studies: E2146 GA-DNA Adducts

- Synthesize/characterize GA-DNA adducts
- Synthesize stable labeled analogs
- Develop/validate LC-ES/MS/MS quantitative method for major DNA adducts
- Determine DNA adduct accumulation and repair from rodent exposures to AA (0-75 days) in leukocytes and liver (≤ 1 mg/kg)
- Determine liver/leukocyte DNA adduct dose-response (1-1000 µg/kg AA for 30 days)