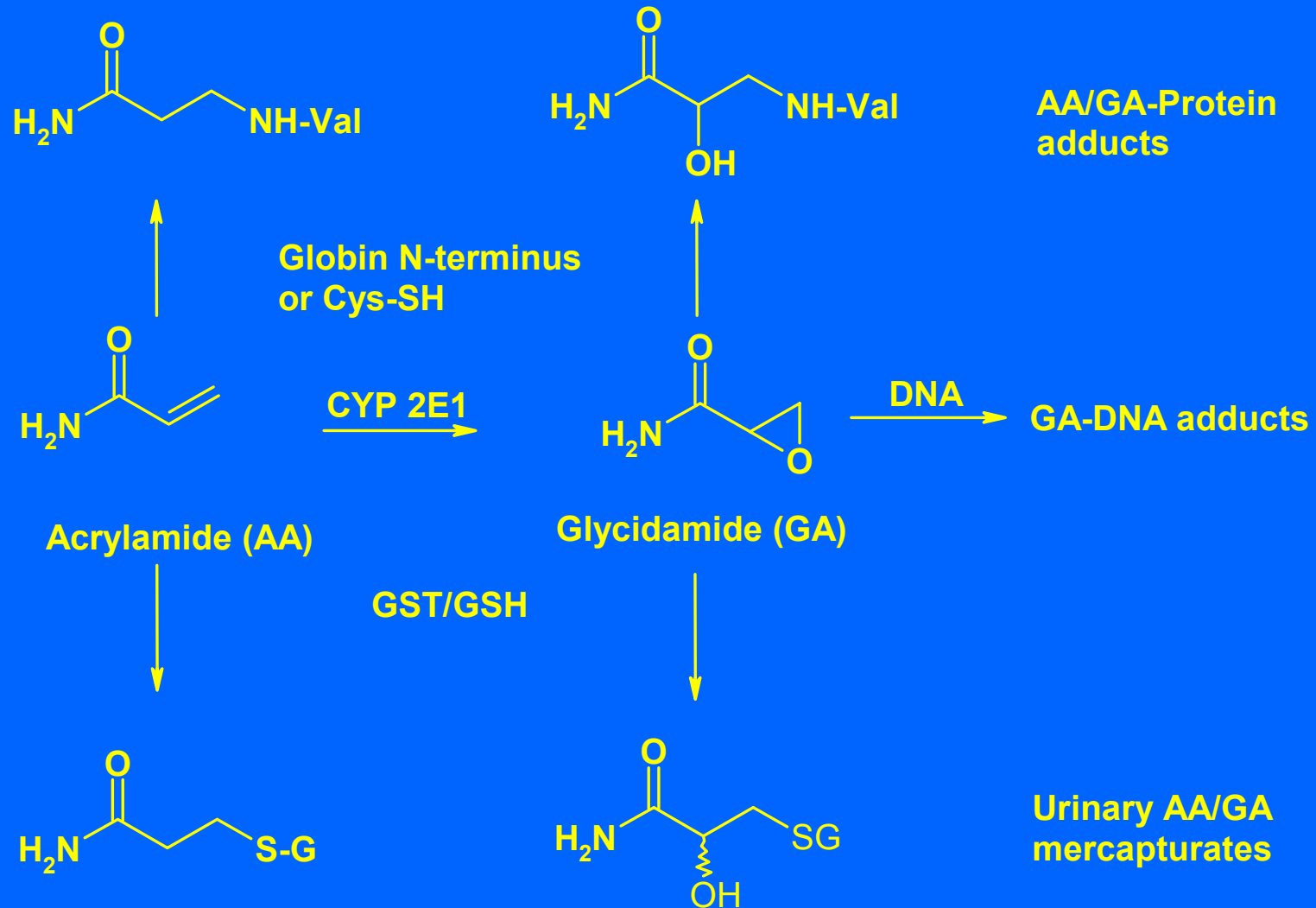


# Metabolism of Acrylamide and Potential Biomarkers



# Comparative Hemoglobin Adduct Formation-Rodents

|             | <u>RAT</u> | <u>MOUSE</u> |
|-------------|------------|--------------|
| Hb-AA       | 26.2*      | 20.0*        |
| Hb-GA       | 6.8*       | 24.5*        |
| Hb-GA/Hb-AA | 0.26       | 1.2          |

\* nmol/g globin per mmol ip/kg body

# Comparative Hemoglobin Adduct Formation-Humans

|             | <u>HUMAN</u>   |
|-------------|--|
| Hb-AA       | 0.03 nmol/g (controls)<br>0.05 nmol/g (PAGE workers)<br>0.1 nmol/g (smokers)<br>0.3-34 nmol/g (occupational) |
| Hb-GA       | 1.6-32 nmol/g (occupational)   |
| Hb-GA/Hb-AA | 0.7;0.1  |

# 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 *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 ( $\leq 1$  mg/kg)
- Determine liver/leukocyte DNA adduct dose-response (1-1000  $\mu\text{g}/\text{kg}$  AA for 30 days)