WG 4 – Toxicology & Metabolism

2004 Acrylamide in Food Workshop

Chicago, IL

Progress in Understanding the Toxicology & Metabolism of AA

- Metabolic fate in rodents and humans
- Kinetics in rodents, progress in humans
- AA- and GA-Hb adducts as markers of exposure
- GA→DNA adducts (little evidence of AA-DNA adducts), germ cell mutagenicity, micronuclei
- Rat PBPK model published
- Progress on neurotox mechanisms
- Chronic rodent studies getting underway

Topical Areas

- Topic 1: Metabolism, kinetics, adducts
- Topic 2: Repro/developmental, germ cell effects, genotoxicity
- Topic 3: Carcinogenicity (incl. cancer epidemiology)
- Topic 4: Neurotoxicity

Metabolism, kinetics, adducts

Priority Research Needs

- Define critical events and dose metrics related to the mode(s) of action at relevant doses for the key toxicities of AA and GA
  - Qualitative schemes for MoA(s)
  - Dose metrics for target tissue exposure
  - Dose metrics for specific toxic effects

Metabolism, kinetics, adducts

Priority Research Needs

- Develop robust PBPK model(s) for rat, mouse, human
- Determine kinetics in humans
  - Extend across developmental stages and to potentially susceptible subpopulations, as needed.
- Relative bioavailability (e.g., food vs. drinking water [underway at NCTR])

Metabolism, kinetics, adducts

Other Research Needs

- Molecular and kinetic characterization of binding to sulfhydryls in target and non-target sites (e.g., rate constants of binding to critical targets vs. glutathione)
- Develop BBDR models to advance the qualitative understanding of the MoA to a quantitative simulation

Repro/developmental, germ cell effects, genotoxicity

Priority Research Needs

- Investigate formation of adducts of DNA and significant nuclear proteins (protamine, chromosomal motor proteins) at critical target sites such as somatic cells, sites of tumor formation, male germ cells

Repro/developmental, germ cell effects, genotoxicity

Priority Research Needs

- Develop dose response data for germ cell toxicity that addresses dose levels from AA in food (PAINT/DAPI & AMS?)
- Evaluate sperm chromosomal abnormalities (morphology and quality) in highly exposed human populations, if available

Repro/developmental, germ cell effects, genotoxicity

Other Research Needs

- Use of specifically genetically modified mouse strains (Big Blue, tk +/-) to assess mode of genotoxic damage in vivo
  - Big Blue done, tk +/- in progress [NCTR]
- Dominant lethal study in CYP2E1 knockout mice to assess role of glycidamide in germ cell toxicity [NIEHS]
  - Adduct levels in germ cells would be useful.

Repro/developmental, germ cell effects, genotoxicity

Other Research Needs

- Developmental tox in a non-rodent species (rabbit) including toxicokinetics
- Evaluate variation of human Hb adduct levels (or other marker of exposure/effect) with SCE, micronuclei, or other markers of chromosomal effects (HEATOX will correlate Hb adducts, micronuclei from food exposures)

Carcinogenicity

Priority Research Needs

- Evaluate carcinogenicity including perinatal exposure
  - Transplacental arm of neonatal mouse assay (being considered at NCTR)
  - Transplacental/neonatal group in 2-yr bioassay?
- Assess genotoxic and endocrine mediated mechanisms [some studies at NCTR]
  - Mech of thyroid tumor induction [NCTR, SNF]
  - Other mechanisms may be studied separately

Carcinogenicity

Other Research Needs

- Evaluate role of GA using CYP2E1 knockout mouse (DNA, Hb adducts) [NIEHS]
- Path Working Group to review combined tumor slides from 2 existing rat studies
- Epidemiology in non-occupationally exposed populations – assess feasibility of using existing available cohorts

Neurotoxicity

Priority Research Needs

- Evaluate mechanism of action in conjunction with dose, duration, and effect-levels and onset of neurotoxicity
  - Reversibility
  - Target site (nerve terminal, axon, other)
  - Protein adduct (formation/clearance kinetics)
  - CYP2E1 studies

Neurotoxicity

Priority Research Needs

- Improve weight-of-evidence regarding neurodevelopmental effects at doses relevant to food intake; establish NOAEL
  - Neurobehavioral/cognitive [studies planned at NCTR]
  - Mechanistic (cell adhesion, glial interaction, neurite outgrowth)
  - Consider reversibility

Neurotoxicity

Other Research Needs

- Include neurotoxicity evaluations in long-term bioassay [studies planned at NCTR]
- Evaluate existing surveillance studies (e.g. medical monitoring data) in occupational cohorts for additional data on exposure levels that do and do not cause neurotoxicity.

Neurotoxicity

Other Research Needs

- In animal models or prospective epidemiological analyses, assess potential additive effects to other pre-existing neurological disease such as multiple sclerosis, Parkinson's, and amyotrophic lateral sclerosis.

Some Major Issues

- Modes of action and dose metrics
- PBPK model
- Perinatal exposures/effects
- Dose-response for germ cell toxicity

THANKS FROM WG 4!