

Heterocyclic Amines: Dietary Carcinogens with Estrogenic Activity Are Consumed at High Levels by African American, Asian and Caucasian Adolescents. Kris Kulp, Brian Bennion, Monique Cosman, Mark Knize, Jennifer Montgomery, Garrett Keating, Ken Bogen, Felice Lightstone and Jim Felton, Energy and Environment and Chemistry, Materials and Life Sciences Directorates, Lawrence Livermore National Laboratory

Heterocyclic amines (HCAs) are potent mutagens formed at elevated levels in well-done cooked meats. HCAs induce cancer at multiple sites in animal bioassays and appear to elevate colon, prostate and breast cancer risk in humans. Although HCAs are known to cause DNA damage, these compounds have also been shown to have estrogenic effects in cellular assays, implying a possible role in tumor promotion as well as initiation. We are investigating the effects of the mutagenic HCAs, PhIP, MeIQx, and IFP, on estrogen receptor activation and cell proliferation in breast cancer cell lines. In human MCF-7 breast cancer cells, PhIP increases estrogenic activity up to 1.8- fold compared to untreated cells and increases cell number 20-30% greater than control. PhIP binding to the estradiol-binding domain of the estrogen receptor was shown with computational analyses and confirmed with NMR competition experiments against estradiol. In contrast, MeIQx and IFP, which are closely related structurally to PhIP, are not able to activate the estrogen receptor and stimulate cell growth. In fact, in estradiol competition assays, these compounds demonstrate potent anti-estrogenic activity. Our results suggest that the ultimate biological consequence of exposure to over-cooked meat may depend upon not only the amount of the compounds ingested but also the ratio of the heterocyclic amines formed in the meat.

We are also conducting HCA exposure assessments that indicate that African Americans ingest 2 - 3 times more HCAs than other ethnic groups and that HCA intake per body weight is greatest during childhood (0 - 15 years). Greater HCA intake among African Americans is attributed to greater preference for well-done meats and greater consumption of grilled and fried chicken, cooked meats with especially high HCA concentrations. Given the carcinogenic and estrogenic properties of HCAs, we suggest that HCA intake be evaluated as a risk factor in studies of the environmental causes of breast cancer.

(This work was performed under the auspices of the U. S. D.O.E. by LLNL under Contract No. W-7405-Eng-48. Supported by CBCRP 7WB-003, NCI CA55861 and LLNL LDRD 02-FS-006)

--