Nominations: Three separate nominations of selected HCAs:

1) **PhIP** (2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine),
2) **MeIQ** (2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline), and
3) **MeIQx** (2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline).

Review committee: NTP Executive Committee Working Group for the Report on Carcinogens - **RG2**

Review Date: 10/02/02

Application of criteria

Exposure

PhIP, MeIQ, and MeIQx are heterocyclic amines (HCAs) that are formed by condensation of creatinine with amino acids during the cooking of meat. Formation is a function of cooking method and is related to temperature and duration. Human exposure to HCAs range from <1 to 17 ng/kg bw/day.

PhIP, the most abundant HCA detected in foods, has been detected in meats (beef, pork, chicken and fish) commonly consumed in the United States. PhIP occurs at the highest concentrations in grilled chicken and at very low concentrations in grilled pork. Mean intake values of PhIP (ng/day) ranged from 285.5 to 457 in three large cohort studies from the United States (two Nurse's Health Studies and the Health Professionals Follow-up Study).

In studies where MeIQ is reported, it is found at much lower levels in food than MeIQx and PhIP and was not evaluated in the cohort studies from the United States. The highest concentrations apparently occur in cooked fish.

MeIQx has been detected in meats (beef, pork, chicken and fish) commonly consumed in the United States. Highest levels appear to be in well-done grilled chicken and beef (hamburger or steak). Intake values of MeIQx (ng/day) ranged from 33 to 36 in three large cohort studies from the United States (two Nurse's Health Studies and the Health Professionals Follow-up Study)

The RG2 felt that there was sufficient evidence for human exposure for all three of the nominated chemicals.

- **Carcinogenicity**
-

Animal Data:

PhIP. The RG2 felt there was sufficient evidence of carcinogenicity for PhIP in experimental animals. Oral administration of PhIP induced tumors in multiple species and at multiple tissue sites by a relevant route of exposure. In mice, PhIP induced lymphoma in both sexes and tumors of the small intestine in males. In rats, PhIP induced tumors of the colon, prostate, small intestine and lymphoma in males and tumors of the mammary gland in females.

MeIQ. The RG2 felt there was sufficient evidence of carcinogenicity for MeIQ in experimental animals. Oral administration of MeIQ induced tumors in multiple species and at multiple tissue sites

by a relevant route of exposure. In mice, MeIQ induced forestomach tumors in both sexes and tumors of the cecum, colon and liver in females. In rats, MeIQ induced tumors of the colon, oral cavity and Zymbal gland in both sexes, mammary gland tumors in females and skin tumors in males.

MeIQx. The RG2 felt there was sufficient evidence of carcinogenicity for MeIQx in experimental animals. Oral administration of MeIQx induced tumors in multiple species and at multiple tissue sites by a relevant route of exposure. In mice MeIQx, induced liver tumors in both sexes, lung tumors in females and lymphoma and leukemia in males. In rats, MeIQx induced tumors of the liver and Zymbal gland in both sexes, and skin tumors in males and clitoral gland tumors in females.

Human Data:
The RG2 felt that it was difficult to draw any conclusions from the human epidemiology studies on the carcinogenicity of PhIP, MeIQ, or MeIQx in humans. The human epidemiology studies were inconsistent in their findings and were potentially influenced by other carcinogenic substances found in cooked meats, such as PAHs. Moreover, the committee felt exposure assessment of PhIP, MeIQ, and MeIQx is difficult using current methodology of food frequency questionnaires, color photographs of cooked food and databases containing HCAs amounts in cooked food. Recalling dietary exposure is also a problem in these studies.

Other Scientific Concerns

Genotoxicity and Other Relevant Data:
There is sufficient evidence of genotoxicity and mutagenicity for PhIP, MeIQ and MeIQx. Each chemical is rapidly absorbed and distributed in both humans and experimental animals. They are activated by the P450 enzymes and form DNA adducts.

Recommendation

Motion:
Recommend that PhIP, MeIQ, and MeIQx be listed in the RoC as separate compounds and that each compound be listed in the RoC as *reasonably anticipated to be a human carcinogen* based on sufficient evidence in animals that indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in multiple species of experimental animals with supporting evidence of genotoxicity.

Vote on the motion: 8 yes votes to 0 no votes