Nomination: Selected HCAs: PhIP, MeIQ, MeIQx
Review Committee: RG1
Review date: 8/6/02

Discussion

General/Introduction

The committee felt the background document on Selected Heterocyclic Amines (HCAs): PhIP, MeIQ, and MeIQ was generally well organized, thorough, and adequate for the purpose of reviewing the nomination of Selected HCAs for listing in the RoC. There was some discussion on whether Selected HCAs as a class/category or the individual compounds should be considered for listing and the background document was considered suitable to support either listing.

Human exposure

The committee concluded that the evidence of human exposure was adequate to support listing PhIP, MeIQ and MeIQx in the RoC. Such a conclusion is documented by the occurrence of HCAs in typical foods consumed by a substantial portion of the US population on a routine basis, published dietary intake estimations, and studies demonstrating presence of HCAs and their metabolites in human urine. Presence of HCAs in other non-dietary sources (e.g., cigarette smoke, cooking process aerosols) indicates the presence of additional exposure pathways for the general population and workers. Evidence for human exposure was somewhat weaker for MeIQ both in terms of available information and the extent of anticipated or measured exposure, but overall the committee concluded the available data indicate human exposure does occur.

Human cancer studies

There is evidence that consumption of meat, particularly red meat, is associated with colon and rectum cancer, and weaker evidence for associations with cancer of the breast, prostate, kidney, and pancreas. There is also evidence that cooking practices known to produce HCAs in meat are associated with cancer of the colon and lung, and weaker evidence for associations with cancer of the bladder and stomach. These exposures (i.e., meat and cooking practices) involve exposures in addition to HCAs, e.g. protein, fat, nitrosamines, PAHs, etc, that have also been associated with cancer, so the foregoing data are not specific for HCAs.

Evidence of an association of cancer with specific HCAs is inconsistent. The data come primarily from case-control studies using food-frequency questionnaires together with data describing HCAs in specific foods and preparation methods. Eleven studies of PhIP have been conducted: four (two of breast cancer and one each of colon and stomach cancer) found a statistically significant positive association, with evidence of dose-response. One study of bladder cancer found a weaker association. The other six studies (one each of colon, rectum, breast, prostate, lung, and kidney) found null or inverse associations. PhIP causes cancer at four sites in animals; of these, human studies found inconsistent results for breast and colon and null results for prostate; no studies have examined lymphoma.

Nine studies have considered the relationship of MeIQx to cancer. Three studies (one each of breast, lung, and colorectal adenoma) found a statistically significant positive association; the first two showed dose-response. One additional study of breast cancer found a nonsignificant positive association. The other five studies (one each of colon adenomas and rectum, breast, bladder and kidney) found null or inverse associations. MeIQx causes cancer at five sites in animals; of these there was concordance for lung (one study) and no data for lymphoma, leukemia, liver, or GI tract.

Only one study (of four cancer sites) considered MeIQ. Weak positive associations were found for colon and rectum; no relationship was observed for bladder and kidney.

These studies are limited primarily by the difficulties involved in retrospective assessment of diet. Recall bias could produce spurious associations. Conversely, measurement error could lead to nondifferential misclassification and make it more difficult to observe an association. Another important weakness is limited power, due both to small sample size and to low exposure levels in a number of the populations studied; again this would make it more difficult to observe an association. Studies conducted in populations with higher levels of meat consumption were in general more likely to observe associations of cancer with HCAs; this may explain some of the discrepancies among studies. Selection bias may exist in hospital-based studies. Data analysis also presents challenges. Most studies controlled for potential confounders. However, overcontrolling by including several highly correlated variables in one model, as was done in several studies, may make it difficult to observe an association.

In summary, the evidence for individual HCAs is inconsistent. Limitations of most studies may have produced false positive or false negative results. The committee concluded that, although consumption of meat and cooking practices appear to be associated with human cancer, the data available from epidemiologic studies are not adequate to evaluate the association of individual HCAs with human cancer.

Studies of cancer in experimental animals

For all three HCAs, the committee concluded there is strong evidence of carcinogenicity in experimental animals by the relevant route of exposure (oral). The evidence consists of positive findings in short-term cancer models evaluating preneoplastic lesions and tumors at specific sites, long-term dietary administration studies, and cancer modulation and tumor initiation-promotion studies. Tumors were observed at multiple sites in multiple species and in both sexes in these studies. Tumor sites (lymphoma, colon, mammary gland, liver, lung, prostate, small intestine, and others) were somewhat variable among studies and also among the different HCAs. Some of this variation resulted from studies that were designed to assess tumorigenic effects only at specific sites. Overall the available data provide sufficient evidence for carcinogenicity in animals.

Genotoxicity/Mechanistic concerns/Other relevant data

Genotoxicity for all three HCAs has been adequately demonstrated in a variety of test systems, including *in vivo* studies following oral exposure. Furthermore, the committee concluded from

studies demonstrating that toxicokinetics, metabolic pathways, and adduct formation are qualitatively similar in rodents and humans, that carcinogenic effects observed in animal models are relevant to humans. The committee noted the following points:

1) HCAs are genotoxic in human cells, inducing micronuclei, mutations, UDS, SCE, CA, and DNA strand breaks.
2) The metabolic pathway of N-hydroxylation followed by acetylation produces mutagenic DNA reactive intermediates.
3) Metabolites derived from the metabolic activation pathway have been measured in human urine.
4) The phase I (CYP1A2 mediated N-hydroxylation) and phase II (NAT1 and NAT2) enzymes have been documented in human breast, prostate, and colon tissue.
5) Humans have a higher capacity to activate HCAs compared to rodents. Rats metabolize much of the dose by ring hydroxylation. Therefore, humans may be more sensitive than rodents.
6) DNA adducts of HCAs have been identified in human tissue (colon, breast, rectum and kidney) following exposure to dietary relevant doses of PhIP or MeIQx. When expressed on a per unit dose basis, human colon tissue had significantly more HCA-DNA adducts than rat colon tissue.
7) Tumor suppressor gene mutations in rodent tumors (G to T transversions) are consistent with a role of HCA induced guanine adducts.

Recommendation

The majority of the committee felt that PhIP and MeIQx should each be listed individually as reasonably anticipated to be a human carcinogen (Vote: 5 yes; 1 no). The dissenting member considered the evidence sufficient to list PhIP and MeIQx each individually as known to be a human carcinogen based on (i) suggestive epidemiologic evidence; (ii) human exposure information; (iii) animal cancer data; and (iv) the seven mechanistic factors listed above. The committee voted unanimously (6/0) to list MeIQ as reasonably anticipated to be a human carcinogen.