GENERAL REMARKS

This fifty-sixth volume of *IARC Monographs* comprises a series of individual monographs on some naturally occurring substances, including two food items (salted fish and pickled vegetables), two naturally occurring plant substances (caffeic acid and *d*-limonene), some substances that occur in cooked meat and fish (IQ, MeIQ, MeIQx and PhIP) and some mycotoxins (aflatoxins, *Fusarium* toxins and ochratoxin A). IQ (IARC, 1986a), MeIQ (IARC, 1986b), MeIQx (IARC, 1986c), aflatoxins (IARC, 1972, 1976, 1987), T-2 toxin (T_2-trichothecene) (IARC, 1983a), zearalenone (IARC, 1983b) and ochratoxin A (IARC, 1983c) have been the subjects of previous IARC monographs. New data on carcinogenicity and other relevant aspects of these agents are summarized and evaluated in the present monographs.

Prior to the meeting of the Working Group, draft monographs were prepared on sesamol (a minor component of sesame oil), black pepper and piperine, chilli and capsaicin, estragole, and opium pyrolysis products. Because limited data and time were available to the present Working Group, these agents will be evaluated by future groups considering other spices and certain drugs of abuse.

In the monograph on salted fish, the Working Group attempted to separate the effects of Chinese-style salted fish, prepared in a manner which involves putrefaction, from those of salted fish in which putrefaction is either absent or minimal. This separation was facilitated by the fact that Chinese-style salted fish is generally consumed only by populations in southern China or by southern Chinese populations living in other areas.

Many of the substances implicated in the mutagenicity of pickled vegetables, such as the hydroxy flavones quercetin (IARC, 1983d) and kaempferol (IARC, 1983e), are present in vegetables that have not been pickled. Studies that included comparisons of pickled and unpickled vegetables would therefore be critical to a proper evaluation of pickled vegetables; such studies have not been done. As the traditional methods of preparing these foods vary from one region to another, epidemiological studies are difficult to carry out.

No epidemiological study was available for evaluation by the Working Group on caffeic acid or *d*-limonene (to which human exposures in fruit, vegetables and beverages are at levels of milligrams per day); however, caffeic acid was considered by a previous Working Group as a constituent of coffee (IARC, 1991). The present Working Group decided not to evaluate the large number of studies on consumption of citrus fruits and fruit juices (which contain *d*-limonene), although they noted that reviews by other groups have suggested that citrus fruits are protective against gastric and other cancers (US National Research Council, 1982, 1989).

Cooked muscle meats appear to be a major source of bacterial mutagenic activity and heterocyclic amines in the human diet. Known heterocyclic amines, and particularly MeIQx, are responsible for about 85% of the bacterial mutagenic activity in cooked beef; PhIP and

MeIQx constitute the majority of heterocyclic amines in cooked meats in general. Cooking method, temperature and time are determinants of bacterial mutagenic activity; frying and barbecueing at high temperatures and for long times produce the greatest activity. The relationship between heterocyclic amine formation and cooking conditions is less clear and requires further study.

The Working Group considered a number of mycotoxins. The presence of one mycotoxin in food and feed should automatically alert investigators for co-contamination by others: Numerous reports are available of multiple contaminations because (i) a single fungus can produce several mycotoxins and (ii) food or feed can be contaminated by several mycotoxin-producing fungi simultaneously. Finally, some mycotoxins have additive or synergistic effects.

Much human exposure to aflatoxins occurs in populations in which there is a high prevalence of hepatitis B virus infection. Hepatitis viruses are not evaluated in this volume of monographs but will be discussed by another IARC working group.

The mycotoxins considered in this volume are presented in the order of the three groups of *Fusarium* species involved, that is, *Fusarium graminearum*, *F. culmorum* and *F. crookwellense* (which produce zearalenone, deoxynivalenol, nivalenol and fusarenone X); *F. moniliforme* (which produces fumonisins B_1 and B_2 and fusarin C); and *F. sporotrichioides* (which produces T-2 toxin). The trichothecenes (deoxynivalenol, nivalenol, T-2 toxin and fusarenone X) are thus covered in relation to their sources.

The most widely distributed toxigenic species is *F. graminearum*, which causes disease in wheat and maize all over the world, except in dryland wheat and subtropical maize production. This fungus produces deoxynivalenol, zearalenone and nivalenol, depending on the strain. The closely related species, *F. culmorum* and *F. crookwellense*, produce the same toxins and occur in cooler and slightly warmer areas, respectively. Another important toxigenic *Fusarium* species is *F. moniliforme* and related species, such as *F. proliferatum*; these are ubiquitous in maize kernels wherever the plant is grown. *F. sporotrichioides*, which produces T-2 toxin, occurs rarely in wheat and maize.

Two naturally occurring compounds, ochratoxin A and d-limonene, the carcinogenicity of which is considered in this volume, have been linked with chronic nephropathies; however, the diseases differ in many respects. Ochratoxin A is the major cause of a chronic nephropathy in pigs; the renal lesions include degeneration of the proximal tubules, interstitial fibrosis and hyalinization of the glomeruli. This pathological picture is strikingly similar to that of human Balkan endemic nephropathy, which has been closely correlated with a high incidence of urinary tract tumours. A basically different chronic nephropathy has been observed in male but not in female rats after administration of d-limonene. In this case, a characteristic accumulation of hyaline droplets containing both $\alpha_{2\mu}$-globulin and *d*-limonene has been observed in the proximal tubules. In addition, cellular necrosis and increased cell proliferation have been found in this segment of the renal tubular system.

In the monographs in the present volume, the circumstances of human exposure were often derived from different studies from those in which effects were measured. Evaluation of the effects of *Fusarium* toxins in humans, for example, can be attempted only on the basis of data on the contamination of foods. In order to delineate specifically the effects on

humans of many of the substances considered, future studies should incorporate relevant biomarkers of exposure, mechanism or early effect. Such techniques are available.

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