

Chapter 6

Carcinogenic effects

Human studies

Chapter 4 reviewed epidemiological studies of cancer, in a few of which the reported relative risks for high versus low consumption of either fruit or vegetables were significantly greater than 1.0 (for example, some studies of cancer of the colorectum, breast and prostate). In general, these were extreme examples of estimates that overall tended to centre close to the null. None of these results were evaluated by the Working Group as evidence of carcinogenicity in humans.

For some specific food constituents, such as β -carotene (IARC, 1998) and some vegetables (e.g., bracken fern; IARC, 1986), there is some evidence of carcinogenicity to humans, but this does not affect the evaluations of the overall cancer preventive activity of total fruit or total vegetables.

Fruit and vegetables have sometimes been regarded as a possible vehicle for carcinogens, either intrinsic to the plant itself or as external contaminants (e.g., pesticides and herbicides) (Ames *et al.*, 1990).

Pickled vegetables, as prepared traditionally in parts of China, Japan and Korea by fermentation of local vegetables, have been found to be associated with cancers of the stomach, oesophagus and nasopharynx (IARC, 1993). High levels of aflatoxin contamination have been found in groundnuts and maize in regions of

Africa, south-east Asia and southern China, where these foods are dietary staples (IARC, 2002). Lower levels have been observed in other grains, cereal products and nuts. Exposures in other countries arise as a result of importing foods from areas where aflatoxin contamination is high, but at lower levels than in the hot humid areas where aflatoxin-producing *Aspergillus* species are present. Exposure to aflatoxin B₁ is consistently associated with hepatocellular carcinoma.

Animal studies

A few studies in experimental animals have found increased tumour yields after administration of fruit and vegetables in the diet.

Only one study was conducted on spontaneous tumours. Groups of 50 male and 50 female Wistar rats were fed one of the following diets: a semi-purified animal diet (A, control); diet A in which fruit and vegetables replaced macro- and micronutrients (B); an uncooked human diet (meat, bread and eggs) supplemented with semi-purified micronutrients (C); diet C with fried or baked products (D); or a complete human diet consisting of cooked products, fruit and vegetables (E). Diets B, C, D and E were prepared according to mean dietary composition figures for the Netherlands. The animal diets contained 21.6% energy fat and the human diets contained 40.6%

energy fat. Rats were fed *ad libitum* for 142 weeks. Male but not female rats fed the human diets (C, D or E) had a significantly higher incidence of epithelial tumours than those fed the animal diet, mainly accounted for by tumours of the pituitary and thyroid glands. Compared to the uncooked human diet, addition of fruit and vegetables (diet E) induced minor non-significant differences in tumour incidence (Alink *et al.*, 1989).

Out of a total of 30 experiments that examined the effects of high quantities of 13 different individual fruit or vegetables on chemically induced carcinogenesis, none reported adverse tumorigenic effects. Six experiments evaluated the effects of low amounts of a mixture of fruits and vegetables on colon cancer. Four of these showed preventive effects (Rijnkels *et al.*, 1997a,b,c; Rijnkels & Alink, 1998; see Chapter 4) and two showed evidence of an adverse effect, as detailed below.

The effect of addition of fruit and vegetables to a simulated human diet or a rodent diet on 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis was evaluated by Alink *et al.* (1993). Groups of four-week-old male Wistar rats (36–43 rats/group) were fed a rodent diet or a European human diet (21.6 and 40.6% fat energy, respectively) with or without 19.5% fruit and vegetables replacing potato starch. After four weeks, all rats were given subcutaneous injections of 50 mg/kg bw DMH once per week for 10 weeks. The experiment was

terminated 28 weeks after the first DMH dose. The multiplicity of colon adenocarcinomas was significantly higher ($p < 0.05$) in animals fed the human diet containing fruit and vegetables than in those fed the control human diet.

Another study evaluated the effects of dietary fat and a fruit-vegetable mixture on intestinal tumorigenesis in *APC^{Min}* mice (van Kranen *et al.*, 1998).

Female and male *APC^{Min}* mice were fed during the mating period a low-fat (20% fat energy) or high-fat (40% fat energy) diet with or without 19.5% fruit-vegetable mixture substituting for total carbohydrates. Both male and female mice born to these mice were weaned to their respective low- and high-fat diets with or without the fruit-vegetable mixture and were continued on these diets until 90 days of

age. The fruit-vegetable mixture added to the high-fat diet significantly increased the multiplicity of small intestinal tumours in male mice (27.7 versus 17.1 tumours per tumour-bearing mouse) and in female mice (25.8 versus 16.0 tumours per tumour-bearing mouse) compared with those fed the high-fat control diet.

