6. Carcinogenicity

6.1 Human studies

The most direct test of carcinogenicity in human populations has been provided by trials of dietary supplementation with vitamin A that are described in detail in Section 4.1.2.

The Beta-Carotene and Retinol Efficacy Trial (CARET; see Section 4.1.2.1(*b*)) included 18 314 American adults, aged 45–74 years, at relatively high risk of lung cancer because of tobacco use or occupational exposure to asbestos. The trial was randomized, double-blinded and placebo-controlled, and the active treatment comprised a combination of 30 mg of β-carotene and 25 000 IU of retinol, taken once a day in a single tablet. The study was halted early, after an average of four years of follow-up, due to an increased occurrence of lung cancer in the active treatment group (RR, 1.3; 95% CI, 1.0–1.6) (Omenn *et al.*, 1996a). The only other cancer that showed increased incidence in the treatment group was leukaemia (26 cases observed; RR, 2.2; 95% CI, 1.0–5.0).

It is not clear how these results should be explained. The randomization process produced study groups that were well matched for the known major risk factors. Compliance with the trial regime was high, as measured both by capsule consumption and by serum vitamin levels (compared with the placebo group, β-carotene levels were more than 10 times higher and retinol levels were raised by about 10% in the active treatment group). The excess lung cancer risk was observed among both asbestos-exposed workers and smokers (although there was a statistically non-significant decrease of 20% among treated former smokers), and applied to all histological types of tumour (with the exception of small cell carcinomas) (Omenn *et al.*, 1996b). If there was indeed an adverse effect of the treatment, it is not possible to distinguish the influences of β-carotene and retinol. However, similar results have been reported from the Finnish ATBC study of chemoprevention among heavy smokers, in which the active treatment included β-carotene (and/or α-tocopherol), without a retinol component. This study included 29 133 males who were current smokers and were followed for a median period of 6.1 years. There was an increase of 16% in the incidence of lung cancer in the group receiving β-carotene (no effect was observed with vitamin E) (ATBC Cancer Prevention Study Group, 1994).

The Working Group was not aware of any other epidemiological study that reported data on vitamin A and incidence of leukaemia.

No intervention study including vitamin A supplementation other than the CARET study has reported an increase in cancer rates. In a study in Linxian County, China (see Section 4.1.2.1(*a*)), 29 584 adults aged 40–69 years were randomly allocated to one of eight study groups to test the effects of four different combinations of vitamins and minerals (Blot *et al.*, 1993). One of these combinations included retinol (5000 IU per day) and zinc (22.5 mg zinc oxide per day). At the end of the study, plasma retinol levels were higher in subjects who received this treatment (mean 54.0 μg/dL compared with 43.0 μg/dL in controls). After five years of follow-up, there was no observed effect on cancer mortality of supplementation with retinol and zinc (RR, 1.0, 95% CI 0.9–1.1). Due to small numbers, lung cancers were not reported separately.

A separate trial in Linxian compared the effects on cancer incidence and mortality of supplementation with a combination of vitamins and minerals (including vitamin A) in 3318 subjects with oesophageal dysplasia (Li, 1993). After six years of follow-up, total cancer mortality was 4% lower in the intervention group (RR, 1.0; 95% CI, 0.7–1.3).

An intervention study with former asbestos workers in Western Australia included two randomly assigned treatment groups (and no placebo) (de Klerk *et al.*, 1998; Musk *et al.*, 1998). 512 participants received β-carotene (30 mg/day) and an equal number received retinol (25 000 IU/day as retinyl palmitate). Median follow-up time was 232 weeks. 54 participants who developed side-effects or abnormal liver function tests suggestive of toxicity

were transferred from the retinol group to β-carotene. There were fewer cases of mesothelioma in the retinol-treated group (RR, 0.24; 95% CI, 0.07–0.86), and also fewer lung cancers (RR, 0.7, 95% CI 0.2–2.3). Deaths from other cancers were evenly spread between the treatment groups (RR, 1.0, 95% CI 0.2–3.9).

In a study in the United States, 525 adults with a history of multiple basal cell or squamous cell carcinoma of the skin were randomly assigned to receive oral retinol (25 000 IU/day) or placebo or isotretinoin for three years. New skin cancers occurred more commonly in the retinol-treated group than among those receiving placebo, but the difference was not statistically significant (Levine *et al.*, 1997).

On the basis of a small number of observational studies, there is no evidence that vitamin A in the diet leads to an increase in the overall incidence of cancer, although increased risks have been reported for some sites. For example, several case–control investigations observed higher levels of vitamin A intake among participants with prostate cancer than controls (Kolonel *et al.*, 1987; Graham *et al.*, 1983; Heshmat *et al.*, 1985). However, the retinol and carotenoid components were not always distinguished, the pattern of effect by age varied between these studies, and the findings in one study may have been largely influenced by differential consumption of a single carotenoid-rich food item (papaya) (Le Marchand *et al.*, 1991). Other case–control studies have reported no increase in risk (for example, West *et al.*, 1991), even among men in the sub-category with highest consumption (Rohan *et al.*, 1995). Two cohort studies, both in the United States, have reported on the relationship between vitamin A intake and occurrence of prostate cancer. One found that high intake levels were associated with increased risk among men aged under 75 years, but were protective for older men (Hsing *et al.*, 1990a). The second study found an association between retinol intake from food sources (but not supplements) and prostate cancer, but this applied only to men over the age of 70 years—no association was observed between any measure of vitamin A intake and cancer among younger men (Giovannucci *et al.*, 1995). The CARET study, it should be noted, reported similar incidence of prostate cancer in the active-treatment and placebo groups (RR, 1.0; 95% CI, 0.8–1.3) (Omenn *et al.*, 1996b).

Liver, dairy products and meat are by far the chief sources of retinol. Direct associations between these food groups have been reported with cancer at several sites (e.g., oral cavity, pharynx, oesophagus, colon, rectum, prostate, etc.). However, it should not be assumed that retinol is necessarily responsible for the cancer-enhancing effects of dairy products and meat, since these are also important sources of saturated fat and caloric excess in western populations and it is difficult to control fully for these variables in epidemiological analyses. For example, the observational epidemiological studies of dietary preformed vitamin A suggest that there may be an increased risk of cancers of the upper aerodigestive tract (see Section 4.1.1). This pattern appears to be particularly pronounced in populations with high intake of alcohol (McLaughlin *et al.*, 1988; Gridley *et al.*, 1990). Several observational studies have reported on the effect of supplements: there was a tendency to find a protective effect of vitamin A which, however, in the largest study (Gridley *et al.*, 1992), appeared to be accounted for by vitamin E supplementation (see Section 4.1.1). It is not possible to discount totally the possibility that preformed vitamin A in food sources may increase rates of head and neck cancers, especially in the presence of a carcinogen, but residual confounding by saturated fat or other dietary factors, tobacco or alcohol almost certainly applies in these studies.

Ecological studies shed little light on the carcinogenic potential of vitamin A. There are some populations which may have been exposed, historically, to high levels of vitamin A in the diet (for example, native Alaskans and the Indians and Inuit of northern Canada). However, there are no reliable historical cancer data available, and comparisons based on present cancer rates are likely to be confounded by many other dietary and social factors (Bell *et al.*, 1997); furthermore, historical patterns are not a reliable guide to modern dietary practices (Godel *et al.*, 1996).

In summary, there is not convincing evidence that retinol is carcinogenic.

6.2 Experimental models

Three groups of 50 male and 50 female F344/DuCrj rats were given drinking water containing retinyl acetate in the form of gelatinized beadlets suspended in distilled water at doses of 0.25 or 0.125%. The control group was given 0.25% of placebo beadlets. All surviving animals were killed at 108 weeks. Body weight gain was significantly lower in females of the high-dose group. Malignant phaeochromocytomas developed in 3 (6.1%), 4 (8.0%) and 11 (22.9%) of the male control, low-dose and high-dose groups, respectively. The incidence in the high-dose group was significantly higher ($p < 0.05$) than in controls. One female rat of the low-dose group developed a malignant phaeochromocytoma. Benign phaeochromocytomas developed in 15 (30.6%), 23 (46.0%) and 28 (58.3%) males and in 3 (6.0%), 10 (20.4%) and 20 (41.7%) females of the control, low-dose and high-dose groups, respectively. The incidence in the high-dose groups was significantly different from controls ($p < 0.001$ and $p < 0.01$ for males and females, respectively). No significant difference in tumour incidence in other organs and tissues was observed (Kurokawa *et al.*, 1985).

Four groups of 200 female Sprague-Dawley rats, six weeks of age, were administered vitamin A (retinyl acetate/palmitate 50 : 50) at dose levels of (1) 3.9, (2) 16.9, (3) 75 and (4) 150 IU/g of diet for life (168 weeks). At death, all animals were necropsied and major organs and tissues examined histopathologically. A higher incidence of mammary adenocarcinomas was observed: (1) 11/200 (5.5%); (2) 27/200 (13.5%); (3) 26/200 (13.0%) and (4) 30/200 (15.0%). The numbers of mammary adenocarcinomas per 100 animals were as follows: (1) 7.5, (2) 16.0, (3) 16.0 and (4) 18.5. There was no dose–response relationship in the three supplemented groups. [The Working Group noted that the incidence of tumours in other tissues and organs was not reported] (Soffritti *et al.*, 1996).

Certain retinoic acid metabolites that have been approved as drugs, e.g., Accutane®, are known to cause haemangiosarcoma in mice (see *Physicians' Desk Reference*, 1997). No published reports of studies using retinol were identified.