4. Summary of Data Reported and Evaluation

4.1 Exposure data

Coffee is a beverage that has been consumed in many parts of the world for centuries. The two main types of cultivated coffee are arabica and robusta. Green coffee is one of the major commodities of world trade and is exported mainly from tropical countries. Ground roasted coffee is brewed in many different ways, including decoction/boiling, infusion, filtration and percolation. Instant (soluble) coffee and decaffeinated coffee are more recent developments. Instant coffee is the dried pure water extract of ground roasted coffee and is used directly to prepare the beverage. Caffeine, the major pharmacologically active purine present in coffee, can be effectively and selectively removed from green coffee beans to give, ultimately, decaffeinated coffee.

Worldwide consumption of roasted coffee was estimated to be 4.3 million tonnes per year in 1983-87. Per-caput consumption in Nordic countries is two or three times higher than that in Canada, the USA and other countries of Europe. These regions have higher consumption levels than in the rest of the world.

Over 700 volatile compounds in many structural categories have been identified in roasted coffee, as well as numerous nonvolatile components (e.g., polysaccharides, melanoidins, protein-like products, chlorogenic acids). Arabica and robusta green coffees contain average caffeine levels of 1.2% and 2.2%, respectively, on a dry weight basis. Depending on the brewing method and species of coffee used, caffeine levels in the beverage are generally in the range of 70-150 mg per cup. Many volatile aldehydes and ketones have been characterized in coffee, including glyoxal and methylglyoxal. Occasional contamination of green coffees with mycotoxins has been reported.

4.2 Experimental carcinogenicity data

Coffee was tested for carcinogenicity in one study in mice and in two studies in rats by oral administration. The mice received instant coffee in the diet for their lifetime, including the gestation period; no increase in tumour incidence was reported. Rats were given brewed coffee as the drinking fluid in one study; a slight increase in the number of tumour-bearing animals was seen only among males in the lowest dose group. In another study, rats were given different samples of instant coffee, decaffeinated coffee or decaffeinated coffee supplemented with caffeine; no increase in tumour incidence was observed.

These three studies are suggestive of an absence of relationship between coffee and cancer in experimental animals, but the incomplete reporting of the study in mice precludes a definitive evaluation at present.

In a number of studies, various known carcinogens were administered by different routes either simultaneously or sequentially with coffee in water as the drinking fluid or in the diet. Several of these studies, however, suffered from various limitations and were not considered for the evaluation.

In one of the adequate studies, coffee reduced the number of pancreatic tumours per animal in azaserine-treated rats maintained on a high-fat diet; the result may have been due in part to impaired growth. No significant effect of coffee was found on the number of pancreatic tumours per animal induced in hamsters by *N*-nitrosobis(2-oxypropyl)amine. In separate experiments, rats on two different diets were treated intravenously or orally with a single dose of 7,12-dimethylbenz[*a*]anthracene in combination with coffee. No difference in the number of rats with mammary tumours was found as compared to animals receiving 7,12-dimethylbenz[*a*]anthracene only; a significant decrease in the number of

mammary tumours per animal was observed after administration of coffee only in rats treated intravenously and not in those treated orally with 7,12-dimethylbenz[*a*]anthracene.

4.3 Human carcinogenicity data

(*a*) *Descriptive studies*

The risk for cancer associated with coffee consumption has been investigated in several descriptive geographical and temporal studies. There was no consistent association between coffee intake, usually estimated indirectly from trade data, and cancer risk, although significant results were occasionally reported in a number of studies. Pancreatic cancer was correlated with coffee consumption in all of the studies in which the relationship was examined. None of the ecological studies showed an association with risk for bladder cancer.

(*b*) *Analytical studies*

(i) *All sites*

A cohort study in which a case-control analysis was used showed a nonsignificant reduction in risk for mortality from cancer at all sites with increased coffee consumption. A second cohort study with longer follow-up reported a nonsignificant increase in mortality after adjustment for age, smoking and other confounders.

(ii) *Bladder and urinary tract cancer*

Two cohort studies reported findings on bladder cancer incidence. In one, there was a nonsignificant increase in risk; the second showed neither an increase nor a decrease.

Of the 26 case-control studies considered that provided information on the possible relationship between coffee drinking and the occurrence of urinary tract cancers, predominantly of the bladder, in very different populations, 22 were used to make the evaluation. In 16 studies, a weak positive association was seen with consumption of coffee as compared to nonconsumption; in seven of these the association was significant, with a dose-response relationship in three. No association was seen in the six remaining studies. The association persisted, but was less clear, when reported nonsmokers were considered in seven of the 16 studies, suggesting that confounding by tobacco smoking is unlikely to be the sole explanation for this finding. The association was also found in men and women separately, suggesting that occupational factors could not fully explain the finding.

Of the four available case-control studies, three indicated a slightly increased risk for transitional-cell cancers of the renal pelvis and ureter, but none of the

results was significant. Six case–control studies and one cohort study do not provide evidence of a consistent association between adenocarcinoma of the kidney and coffee drinking.

Although drinking of decaffeinated coffee was addressed in six case–control studies, it was not possible to distinguish the effects from those of coffee containing caffeine.

Taken as a whole, these data are consistent with a weak positive relationship between coffee consumption and the occurrence of bladder cancer, but the possibility that this is due to bias or confounding cannot be excluded.

(iii) *Breast cancer*

None of the seven case–control studies has suggested the existence of an association between breast cancer risk and the consumption of coffee. All of the studies gave relative risk estimates that were near unity. One study presented results on instant coffee separately and also found no association; three studies showed no association with decaffeinated coffee consumption. Confounding due to recognized risk factors for breast cancer was controlled in most studies. There is no reason to believe that measurement error or confounding was responsible for the finding.

(iv) *Cancer of the large bowel*

Cohort studies that addressed the issue of coffee drinking and risk for cancer of the colon or rectum were not particularly informative but have generally been interpreted as showing no association.

Of the 12 informative case–control studies, 11 indicated inverse ('protective') associations between coffee consumption and risk for colorectal cancer, which reached significance in five. A significant dose–response relationship was seen in one study. At present, it is not possible to exclude bias and confounding as the source of the apparent inverse association, but the collective evidence is also compatible with a 'protective' effect.

(v) *Pancreatic cancer*

Six cohort studies provide data on the relationship between coffee consumption and pancreatic cancer. None reported a significant association with increased consumption; any nonsignificant increase was reduced following adjustment for smoking.

Twenty–one case–control studies have reported on the relationship between coffee consumption and pancreatic cancer. An early report showed a positive relationship, with a significant dose–response, in women but not in men, which persisted after removing those controls with digestive disorders. Another study

reported a significant relationship with decaffeinated coffee but not with consumption of all kinds of coffee. Nineteen subsequent reports have been less positive overall. In ten of these studies, a positive association was seen; in three of these, the findings were significant, with a dose–response relationship in two studies. No association was seen in seven studies, and a weakly negative association was found in another. A nonsignificant increase in risk for the highest exposure group has been a more consistent finding, but this has generally become weaker after adjustment for smoking and may be the result of residual confounding. Potential biases associated with the comparability of case and control groups also complicate interpretation, and methodological problems were noted in some studies.

Taken as a whole, the data are suggestive of a weak relationship between high levels of coffee consumption and the occurrence of pancreatic cancer, but the possibility that this is due to bias or confounding is tenable.

The results with regard to decaffeinated coffee are less comprehensive but have generally been negative.

(vi) *Ovarian cancer*

In two case–control studies of coffee drinking and risk for ovarian cancer, a significant increase in risk was found, whereas in five others small, nonsignificant increases were noted. An overall analysis of the data indicates a marginal, significant increase in relative risk, but bias from unidentified sources or even chance cannot be ruled out.

The few available studies do not suggest that drinking decaffeinated coffee increases the risk for ovarian cancer.

(vii) *Gastric cancer*

The relationship between coffee drinking and gastric cancer was studied in five case–control investigations, none of which showed an association.

(viii) *Cancers of the upper digestive tract*

Six case–control studies assessed the association between coffee drinking and cancers of the oesophagus, mouth and pharynx. After adjustment for confounding variables, the frequency of coffee drinking was not associated with risk for cancer in any of these studies. Overall, no association was found between coffee drinking and cancers of the upper digestive tract, except when populations who drink coffee at very high temperatures were studied.

(ix) *Cancers at other sites*

In one case–control study, no association with the occurrence of liver cancer was found among coffee drinkers after adjustment for smoking and alcohol consumption.

Two cohort studies and one case–control study showed no association with lung cancer.

A cohort study reported associations between coffee drinking and Hodgkin's disease and lymphatic and myeloid leukaemia; no association was reported with the occurrence of non–Hodgkin's lymphoma, malignant melanoma, or other and unspecified leukaemias. One case–control study showed an increased incidence of carcinoma of the vulva among coffee drinkers. A single cohort study showed an association with cervical cancer.

4.4 Other relevant data

(*a*) *Toxic effects*

The available evidence cannot be used to establish a significant, independent relationship between coffee consumption and morbidity or mortality from coronary heart disease. The question remains open, however, especially in view of the finding that some methods of coffee preparation are associated with an elevation in plasma levels of cholesterol and low–density lipoproteins.

(*b*) *Effects on reproduction and prenatal toxicity*

The teratogenic potential of coffee and caffeine–containing beverages was investigated in two cohort and four case–control studies. Two studies (one cohort and one case–control) found significant positive associations between the consumption of caffeine–containing drinks and the risk for malformations. The remaining four studies (one cohort and three case–control), which included the three most informative reports, failed to find an association. Taken together, these studies do not provide evidence of a teratogenic effect of coffee intake.

Eight studies, from Costa Rica, the Federal Republic of Germany, the UK and the USA, reported an association between decreased birth weight and intake of coffee and caffeine–containing beverages, which was statistically significant in the crude analyses. After correction for confounding variables, including smoking, four of the studies reported positive associations which were significant. Of two other studies, one reported an increased risk among heavy consumers which, however, was not significant, and the other reported a positive association of only borderline significance. The two remaining studies did not show an association after adjustment for confounding. Reporting of coffee consumption was usually most complete for the first and second trimesters, while the greatest impact on birth

weight may be from consumption during the last trimester. Overall, the data provide an indication that maternal coffee drinking reduces the birth weight of offspring.

Of the three studies with adequate design and interpretation, only one showed a clear dose–response relationship.

Information concerning prematurity was insufficient for conclusions to be drawn about an effect of coffee consumption. One study provided evidence of a relationship between late spontaneous abortions and moderate to heavy coffee consumption.

No effect on reproduction was observed in rats given percolated or drip (filtered) coffee as the drinking fluid. Developmental delays were observed in the offspring of coffee-treated rats, including decreased fetal and neonatal body weights and delayed ossification. No teratogenic effect was observed.

No teratogenic effect or effect on reproduction was observed in rats given instant coffee as the drinking fluid or as crystals in the diet. In the offspring of treated rats, delayed development was observed, including decreased fetal and neonatal body weight and delayed ossification shortly before birth.

No teratogenic effect or effect on reproduction was observed in rats given decaffeinated coffee (either brewed or instant) as the drinking fluid, although a decrease in body weight of offspring was observed.

The reproductive effects seen in these studies occurred only at levels of coffee much higher than those to which humans are exposed.

(*c*) *Genetic and related effects*

Otherwise healthy splenectomized coffee drinkers, some of whom occasionally drank tea, had an increased frequency of micronuclei in both reticulocytes and mature erythrocytes.

The urine of coffee drinkers was not mutagenic to bacteria but induced chromosomal aberrations in cultured mammalian cells.

Brewed coffee induced chromosomal aberrations and sister chromatid exchange in cultured human lymphocytes. Sister chromatid exchange was also induced in cultured mammalian cells. In insects, negative results were obtained for aneuploidy, chromosomal aberrations, dominant lethal effects and sex-linked recessive lethal mutation; brewed coffee gave weakly positive results in assays for somatic cell mutation and mitotic recombination. In bacteria, it was mutagenic, particularly to strains with enhanced sensitivity to oxidative mutagens, and induced DNA damage.

Instant coffee did not induce sister chromatid exchange or micronuclei in the bone-marrow cells of rodents treated *in vivo*. It induced chromosomal aberrations in cultured human lymphocytes and induced mutations and sister chromatid

exchange in cultured mammalian cells. In insects, negative results were obtained for aneuploidy, chromosomal aberrations, dominant lethal effects and sex-linked recessive lethal mutations; instant coffee gave weakly positive results in assays for somatic cell mutation and mitotic recombination. In bacteria, instant coffee was mutagenic, particularly to strains sensitive to oxidative mutagens, and induced DNA damage; it was not mutagenic in host-mediated bacterial mutagenicity assays.

Decaffeinated coffee induced chromosomal aberrations in cultured human lymphocytes and sister chromatid exchange in cultured mammalian cells. It gave negative results in assays for somatic cell mutation and mitotic recombination assays in insects. In bacteria, decaffeinated coffee was mutagenic, particularly in strains with enhanced sensitivity to oxidative mutagens, and induced DNA damage.

Coffee reduced the genotoxic activity of several model mutagens both *in vivo* and *in vitro*.

4.5 Evaluation[1]

There is *limited evidence* in humans that coffee drinking is carcinogenic in the urinary bladder.

There is *evidence suggesting lack of carcinogenicity* of coffee drinking in the human female breast and in the large bowel.

There is *inadequate evidence* in humans that coffee drinking is carcinogenic in the pancreas, ovary and other body sites.

There is *inadequate evidence* in experimental animals for the carcinogenicity of coffee.

Overall evaluation[2,3]

Coffee is *possibly carcinogenic to the human urinary bladder (Group 2B)*.

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[1]For description of the italicized terms, see Preamble, pp. 27–31.

[2]There is some evidence of an inverse relationship between coffee drinking and cancer of the large bowel; coffee drinking could not be classified as to its carcinogenicity to other organs.

[3]M.J. Arnaud dissociated himself from the overall evaluation.