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Coffee, Tea, Mate, Methylxanthines and Methylglyoxal

Summary of Data Reported and Evaluation

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COFFEE
(Group 2B)

For definition of Groups, see Preamble Evaluation.

VOL.: 51 (1991) (p. 41)

5. Summary of Data Reported and Evaluation

5.1 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.

5.2 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.

5.3 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.

5.4 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*.

5.5 Evaluation

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

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

For definition of the italicized terms, see Preamble Evaluation.

N.B. - 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.

N.B. - M.J. Arnaud dissociated himself from the overall evaluation.

Synonyms

- Instant coffee
- Decaffeinated coffee
- Green coffee
- Medium-roasted coffee

Last updated: 17 November 1997

TEA
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 51 (1991 (p. 207)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Tea is an aqueous infusion prepared from the dried leaves of *Camellia sinensis*, which has been consumed since ancient times in Asia and since the late seventeenth century in most other parts of the world. Tea is the most widely consumed beverage in the world. About 80% of world production of tea is in Asian countries. Depending on manufacturing techniques, teas can be divided into two main types: black tea, which has undergone an enzymic oxidation called 'fermentation' during processing, and green tea, which has not. Black tea represents about 80% of world production.

Annual tea consumption varies from country to country, ranging from a high level of about 3 kg *per caput* to negligible values in many countries. World consumption is approximately 0.5 kg *per caput*. Green tea is the primary form consumed in China, Japan and some Middle Eastern countries. Instant tea and decaffeinated tea consumption is small, but the latter is becoming more significant in the USA.

Over 400 volatile compounds comprising many structural categories have been identified in black teas and over 200 in green teas; these contribute to the flavour and aroma of the beverage. In addition to the expected components of leaf matter (e.g., flavonols, flavanols and phenolic acids), other nonvolatile components are present; bisflavanols, theaflavins and thearubigins are found in black tea. Average caffeine levels in both black and green teas are 3-4% on a dry weight basis, resulting in about 30-50 mg caffeine per cup. Some black and green teas have traditionally been flavoured with natural agents such as oil of bergamot and jasmine flowers.

5.2 Experimental carcinogenicity data

Tea was tested for carcinogenicity in one study in rats by repeated subcutaneous injection of a total aqueous extract of tea leaves. A nonsignificant increase in the incidence of local tumours was observed.

In a number of studies, various known carcinogens were administered by different routes either simultaneously or sequentially with tea or its constituents by various routes. In one study in mice, skin application of black tea infusion containing 1% tannin after a single application of benzo[*a*]pyrene did not affect the incidence of skin tumours.

Administration of polyphenolic extracts of green tea in combination with known carcinogens resulted in decreased incidences of skin tumours in mice treated with benzo[*a*]pyrene diol epoxide, 3-methylcholanthrene or 7,12-dimethylbenz[*a*]anthracene and of duodenal tumours in mice treated with *N*-ethyl-*N*'-nitro-*N*-nitrosoguanidine, within a limited period of observation.

5.3 Human carcinogenicity data

Correlation studies on cancer risk associated with tea consumption have provided inconsistent reports of increased risks for cancers of the breast, intestine, larynx, lung and colon. Ecological studies of villages in the Caspian littoral have shown a broad correspondence between the occurrence of oesophageal cancer and tea consumption. An additional report found a relationship with the temperature at which the tea was drunk. A geographical study showed that in areas of Japan with high reported consumption of tea-gruel there were

higher mortality rates from oesophageal cancer.

(*a*) *Bladder and urinary tract cancer*

In two cohort studies in which bladder cancer risk was examined, no association was reported.

The overall evidence from 12 case-control studies indicates no consistent association between measures of tea consumption and risk for bladder cancer. Although the data are limited, a similar pattern of trend was apparent for transitional-cell cancers of the renal pelvis and ureter.

One cohort study found a positive dose-response relationship for cancer of the kidney, but there was inadequate adjustment for confounding. Case-control studies on adenocarcinoma of the kidney are scarce and do not provide evidence of an association with tea drinking.

(b) Pancreatic cancer

The effect of tea consumption was examined in four cohort studies: three reported no association, and one documented a small protective effect.

Six case-control studies were designed to evaluate the relationship between tea consumption and pancreatic cancer: one showed a positive association.

(c) Breast cancer

None of five studies in which results on tea consumption were presented showed an association with breast cancer.

(d) Ovarian cancer

In two case-control studies, there was no association between tea consumption and ovarian cancer.

(e) Cancer of the large bowel

One cohort study found a strong positive dose-response relationship for cancer of the rectum, but another indicated no relationship with rectal cancer and a nonsignificant 'protective' effect for colon cancer.

The association between tea consumption and cancer of the colon and rectum was investigated in four case-control studies. Two showed no association. One study found a decreased risk for cancer of the rectum but not for cancer of the colon among drinkers of black tea relative to nondrinkers; another found an increased risk in the high consumption group. Taken together, these studies do not suggest the existence of an association.

(f) Gastric cancer

One cohort study found an increased risk for gastric cancer, which remained after inadequate adjustment for social class.

The role of tea drinking as a risk factor for cancer of the stomach was considered in five case-control studies. Four of these found no association. A negative association was observed in one study, but no dose-response relationship was seen.

(g) Cancer of the oesophagus

Five case-control studies were carried out, in Iran, the USSR, Brazil and Singapore, to investigate the effect of tea drinking on the frequency of cancer of the oesophagus. One study in Brazil did not show an association between tea drinking and oesophageal cancer, but the subjects were not asked about the temperature at which they drank tea. The other four studies, three of which were conducted in the Caspian area, stressed the role of the temperature of tea. All four studies showed that ingestion of very hot tea was associated with a two- to three-fold increase in the risk for oesophageal cancer. Only one of these studies investigated the effect of frequency of tea ingestion irrespective of temperature; no association was found. Taken together, these studies suggest that the temperature may be more important than the composition of the beverage, but the results are not conclusive.

One case-control study on oral cancer and one on cancer of the extrahepatic bile ducts reported no clear association with tea drinking.

(h) Nasopharyngeal cancer

Three case-control studies showed no evidence of an association between tea drinking and nasopharyngeal cancer.

(i) Cancers at other sites

One cohort study found no association with liver cancer. Another showed a significant positive dose-response relationship for lung cancer after adjusting for age and smoking; these findings could, however, be attributed to residual confounding by smoking.

One case-control study showed no association between tea drinking and cancer of the vulva. Another indicated a possible effect of maternal tea drinking during pregnancy on the frequency of Wilms' tumour in the offspring.

5.4 Other relevant data

The few informative studies concerning the effect of tea consumption during pregnancy on the frequency of adverse reproductive effects did not show an association.

In a number of studies, no association was seen between consumption of tea and the frequency of coronary heart disease.

Black tea, green tea and several unspecified teas were mutagenic to bacteria. Teas were found to reduce the activity of known mutagens both *in vivo* and *in vitro*.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity in humans of tea drinking.

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

For definition of the italicized terms, see Preamble Evaluation.

Overall evaluation

Tea is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Synonyms

- Black tea
- Decaffeinated tea
- Green tea
- Instant tea
- Oolong tea

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MATE
Mate (Group 3)
Hot mate (Group 2A)

For definition of Groups, see Preamble Evaluation.

VOL.: 51 (1991) (p. 273)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Mate, an aqueous infusion prepared from dried leaves of *Ilex paraguariensis*, is consumed mainly in Argentina, Bolivia, Brazil, Chile, Ecuador, Paraguay and Uruguay. It is usually drunk very hot following repeated addition of almost boiling water to the infusion. In Paraguay and southwestern Brazil, however, it is also drunk cold. Among numerous constituents, caffeine, theobromine and a number of chlorogenic acids have been identified in mate.

5.2 Experimental carcinogenicity data

No data were available to the Working Group.

5.3 Human carcinogenicity data

Three case-control studies in South America have investigated the association between mate drinking and oesophageal cancer. Two studies from Uruguay reported an increased risk among drinkers and dose-response relationships, even after adjustment for confounding variables, including alcohol consumption and smoking. Heavy drinkers of mate were approximately ten times more likely to develop cancer than people who did not drink mate. Another study in southern Brazil showed a nonsignificant increase in risk for oesophageal cancer among daily drinkers of mate after adjustment for confounding variables; however, intake levels were lower than in the previous studies, and no attempt was made to assess a possible dose-response relationship.

The role of mate in oral cancer was the subject of another case-control investigation in Brazil. The crude analysis showed a dose-response effect with the frequency of mate drinking, but this effect was no longer present after adjustment for smoking and alcohol consumption. After such adjustment, mate drinkers were 1.6 times more likely to have oral cancer than nondrinkers of mate - a nonsignificant difference. A case-control study from Uruguay reported a dose-response association between mate drinking and oropharyngeal cancer, which remained after adjustment for age, alcohol and smoking.

One study from Uruguay reported a three-fold increased risk for laryngeal cancer among mate drinkers, with a significant dose-response relationship after adjustment for age, tobacco and alcohol.

The results of a case-control study of bladder cancer in Argentina showed no evidence of trend in risk with increasing consumption of mate.

Overall, the case-control studies on mate drinking and cancer of the upper gastrointestinal tract suggest a strong association, whereas no such association was seen in one study of bladder cancer. These findings would be compatible with an effect of mate drinking due either to the composition of the beverage or to the temperature at which it is consumed or both, since all of these studies were conducted in populations that consume hot mate. No data were available on populations that drink cold mate. Some issues must be resolved before a conclusive result is obtained: (i) Awareness of the possibility that mate drinking may increase the risk of cancer of the upper gastrointestinal tract may have led to increased reporting of mate drinking for cancer

cases as compared to controls. (ii) The results require confirmation by other groups of investigators. (iii) The possibility of residual confounding by alcohol drinking and tobacco smoking cannot be excluded entirely, although this was adjusted for in all of the studies.

5.4 Other relevant data

An endoscopic survey from southern Brazil showed that daily drinkers of hot mate had a prevalence of histologically confirmed oesophagitis which was three times higher than that of nondrinkers of mate.

5.5 Evaluation

There is *limited evidence* for the carcinogenicity of hot mate drinking in humans. No data were available on the drinking of cold mate.

There are no data on the carcinogenicity of mate in experimental animals.

Overall evaluation

Mate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Hot mate drinking is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

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CAFFEINE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 51 (1991) (p. 291)

CAS No.: 58-08-2
Chem. Abstr. Name: 3,7-Dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Caffeine is a methylxanthine, which occurs naturally in more than 60 plant species throughout the world. It is prepared on an industrial scale by methylation of theobromine.

Global per-caput consumption of caffeine from all sources was estimated to be 70 mg per day in 1981-82.

Caffeine is consumed in beverages such as coffee, tea and mate and in soft drinks to which caffeine is added. Coffee is the main source of dietary caffeine consumption. The caffeine content of beverages varies widely. Caffeine is also used in numerous prescription and non-prescription pharmaceutical preparations.

5.2 Experimental carcinogenicity data

Caffeine was tested for carcinogenicity in five studies in rats by oral administration. In two of these studies, no significant difference in the incidence of tumours at any site was found. The other three studies were found to be inadequate for evaluation.

Studies on oral and intraperitoneal administration of caffeine to mice were found to be inadequate for evaluation.

In one study, decaffeinated coffee to which caffeine was added was tested by oral administration to rats; overall, no increase in tumours at any site was observed as compared to appropriate controls.

Administration of caffeine in combination with known carcinogens resulted in decreased incidences of lung tumours in mice treated with urethane, of mammary tumours in rats treated with diethylstilboestrol and of skin tumours in mice treated with either ultra-violet light or cigarette-smoke condensate. Caffeine did not influence the incidence of bladder tumours induced in rats by *N*-nitroso-*N*-butyl(4-hydroxybutyl)amine in three experiments or of pancreatic tumours induced in rats by 4-hydroxyaminoquinoline-1-oxide in another study.

5.3 Human carcinogenicity data

A cohort study with a short follow-up period showed no association between caffeine consumption and mortality from cancers at all sites, although there were few deaths on which to base an analysis.

Three case-control studies of breast cancer in which an attempt was made to measure methylxanthine intake showed no association. A slight increase in risk was seen in premenopausal women in one study, but in general the relative risks were below unity.

One case-control study of bladder cancer showed a weak association with caffeine consumption.

Caffeine and coffee consumption are highly correlated in most of the populations studied; thus, it is very difficult to separate the two exposures in epidemiological studies. It was therefore not possible to evaluate adequately the effect of caffeine *per se*.

5.4 Other relevant data

Caffeine intake from pharmaceutical sources has not been related to teratogenic effects in humans. High levels of either coffee or caffeine consumption were related to an increased frequency of low birthweight.

Quantitative and qualitative differences in the metabolism of caffeine are seen between humans and experimental animals.

On the basis of the available evidence, caffeine consumed in moderate amounts does not cause any persistent increase in blood pressure in normotensive subjects. Whether caffeine consumed in amounts present in coffee or tea causes cardiac arrhythmias in healthy subjects or in patients with heart disease remains an open question.

Caffeine has been shown to cause adverse reproductive and developmental effects in mice, rats, rabbits and monkeys. Testicular atrophy was observed at high dose levels in rats. Reproductive studies in mice showed no effect on pregnancy but there was a decrease in litter size at birth. Teratogenic effects were usually associated with high, single, daily doses that were also associated with other signs of maternal toxicity. High daily levels given as divided doses were less toxic to the conceptus that when given as a single dose. Reduced fetal body weight was observed in rats. A reversible delay in ossification of the sternum was observed in rats at a relative low dose given by gavage. With administration in drinking-water, similar effects were seen, but at higher doses.

One epidemiological study revealed no effect of caffeine (in coffee-drinking subjects) on the sex ratio of their children. In lymphocytes of normal, caffeine-exposed people, chromosomal aberrations were not observed. An increased frequency of micronucleated blood cells was observed in otherwise healthy splenectomized people exposed to caffeine. Urine of caffeine-exposed persons was not mutagenic to *Salmonella typhimurium*.

Although it has been suggested that caffeine may induce gene mutations in mammals and man, direct evidence *in vivo* is limited and the indirect evidence is largely based on extrapolation from results in lower organisms, in which there is no doubt about the mutagenic action of caffeine, and from cultured mammalian cells, in which caffeine is clastogenic at high concentrations.

Overall, caffeine affects photoreactivation, excision repair and postreplication repair. The antagonistic effect of caffeine on mutations has induced by ultra-violet radiation has been explained on the basis of inhibition of an error-prone, postreplicative, recombination repair process. Caffeine can modulate the effects of xenobiotics by acting on (i) cytochrome P450, (ii) cAMP metabolism, (iii) DNA metabolism, chromatin structure and function and (iv) nucleotide pools.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity in humans of caffeine.

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

Overall evaluation

Caffeine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- Anhydrous caffeine
- Caffeedrine
- Coffeine
- Coffeinum
- Dexitac
- Guaranine
- Methyltheobromine
- Methyltheophylline
- No Doz [Nodoz]
- Quick Pep
- Thein
- Theine
- Tirend
- 1,3,7-Trimethyl-2,6-dioxopurine
- 1,3,7-Trimethylxanthine
- Vivarin

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THEOPHYLLINE
(Group 3)

For definition of Groups, see Preamble Evaluation.

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CAS No.: 58-55-9
Chem. Abstr. Name: 3,7-Dihydro-1,3-dimethyl-1*H*-purine-2,6-dione

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Theophylline is found in black tea and to a lesser extent in green coffee, cocoa cotyledon and dried mate. Theophylline is synthesized on an industrial scale and is used principally in pharmaceutical preparations.

Per-caput daily intake of theophylline from black tea in the USA has been estimated to be 0.14 mg.

5.2 Experimental carcinogenicity data

No data on the carcinogenicity of theophylline were available.

In the one adequate study, theophylline applied to the skin of female mice induced a significantly smaller number of ultraviolet light-induced tumours than in controls.

5.3 Human carcinogenicity data

No data were available to the Working Group to evaluate the carcinogenicity of theophylline *per se*.

For descriptions of studies on methylxanthines, see the monograph on caffeine.

5.4 Other relevant data

Limited data on mothers taking theophylline during pregnancy showed no excess in the frequency of malformations in their offspring.

Theophylline given by gavage at high doses decreased testicular weight in rats and mice, but there was no change in semen characteristics. Administration of theophylline in the diet at dose levels that were mildly toxic to adults caused decreased numbers of litters per breeding pair, decreased live litter size, an increased number of resorptions and decreased neonatal weight. Abnormal sperm were observed in rats but not in mice at high dose levels.

Theophylline induced sister chromatid exchange in Chinese hamsters *in vivo* but did not induce dominant lethal mutations in mice or chromosomal aberrations in the bone marrow of rats. Theophylline gave negative results in a host-mediated assay with *Salmonella typhimurium* in mice. In cultured human cells, theophylline induced sister chromatid exchange and chromosomal breaks but not micronuclei or chromosomal aberrations. It induced sister chromatid exchange and chromosomal aberrations but not micronuclei or gene mutation in animal cells *in vitro*. Results on the induction of chromosomal aberrations in plants are equivocal. In lower eukaryotes, it induced gene mutations. Theophylline gave negative results in the *Salmonella*/mammalian microsome assay but induced mutation in other bacteria.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity in humans of theophylline.

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

Overall evaluation

Theophylline is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- Accurbron
- Aerolate
- Afonilum
- Aquaphyllin
- Armophylline
- Asthmophylline
- Bronchoretard
- Bronkodyl
- 1,3-Dimethylxanthine
- Duraphyl
- Elixicon
- Franol
- Franyl
- Labophylline
- Labid
- Lasma
- Nuelin
- Optiphyllin
- Oralphyllin
- Phyldrox
- Physpan
- Primatene
- Pro-vent
- Quibron
- Quibron-T
- Tancolin
- Taumasthman
- Tedral
- Thealtabl
- Theoliz
- Theobid
- Theocap
- Theocin
- Theoclear
- Theocontin
- Theocord
- Theodel
- Theodrine
- Theo-Dur
- Theofed
- Theofedral

- Theograd
- Theolair
- Theolate
- Theolixir
- Theoliz
- Theon-300
- Theophenyllin
- Theophyl
- Theophyl-SR
- Theoral
- Theosol
- Theospan
- Theostat
- Theovent
- Unicontin
- Uniphyllin

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THEOBROMINE
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 51 (1991) (p. 421)

CAS No.: 83-67-0
Chem. Abstr. Name: 3,7-Dihydro-3,7-dimethyl-1*H*-purine-2,6-dione

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Theobromine is the principal alkaloid of the cacao bean. It is extracted from the bean husks and used in the synthesis of caffeine. It has been used in various pharmaceutical products. Theobromine is consumed in cocoa and chocolate beverages and in arious forms of chocolate-based foods. Theobromine is also present in small amounts in green coffee beans, tea and mate.

Daily per-caput consumption of theobromine in the USA in 1980 from food and beverages was estimated to be 39 mg.

5.2 Experimental carcinogenicity data

No data on the carcinogenicity of theobromine were available.

5.3 Human carcinogenicity data

No data were available to the Working Group to evaluate the carcinogenicity of theobromine *per se*.

For descriptions of studies on methylxanthines, see the monograph on caffeine.

5.4 Other relevant data

Oral administration of high doses of theobromine to rats caused severe testicular atrophy, which was largely irreversible. Administration of lower levels for prolonged periods had no significant adverse effect on the testis. Mice, hamsters and dogs were less sensitive than rats or were resistant to the effect of theobromine in causing testicular changes. No adverse reproductive effect was observed in a three-generation study in rats given cocoa powder containing theobromine in their diet. Teratogenic effects were observed in rabbits after gavage but not after dietary administration of theobromine. The signs of developmental toxicity observed at the lowest dose level included decreased fetal body weight and increased skeletal variations in rabbits. No teratogenic effect was seen in rats.

In vivo, theobromine did not induce dominant lethal effects in mice or rats. It induced sister chromatid exchange and micronuclei but not chromosomal aberrations in the bone marrow of Chinese hamsters. In human cells *in vitro*, theobromine induced sister chromatid exchange and chromosomal breaks. In cultured mammalian cells, it induced gene mutations and sister chromatid exchange but not chromosomal aberrations or cell transformation. In plants, theobromine did not induce chromosomal aberrations. It induced gene mutations in lower eukaryotes and bacteria but gave negative results in the *Salmonella*/mammalian microsome assay.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity in humans of theobromine.

There are no data on the carcinogenicity of theobromine in experimental animals.

Overall evaluation

Theobromine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- 3,7-Dimethylxanthine
- Riddospas
- Riddovydrin
- Santheose
- Seominal
- Theobrominum
- Theoguardenal
- Theominal
- Théoxalvose

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METHYLGLYOXAL
(Group 3)

For definition of Groups, see Preamble Evaluation.

VOL.: 51 (1991) (p. 443)

CAS No.: 78-98-8
Chem. Abstr. Name: 2-Oxopropanal

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Methylglyoxal is present in many foods and drinks, including coffee, and is produced during glycolysis and sugar fermentation. It is produced by many strains of bacteria present in the intestinal tract. It is also present in tobacco smoke.

5.2 Experimental carcinogenicity data

No adequate study was available for the evaluation of methylglyoxal.

5.3 Human carcinogenicity data

No data were available to the Working Group.

5.4 Other relevant data

Methylglyoxal induced sister chromatid exchange, chromosomal aberrations and micronuclei in cultured human cells. It induced sister chromatid exchange and gene mutations in cultured mammalian cells. In yeast, it increased the frequencies of reverse mutations and of mitotic gene conversion. In prokaryotes, methylglyoxal was mutagenic in the absence of an exogenous metabolic system. Methylglyoxal forms adducts with guanine bases and nucleic acids.

5.5 Evaluation

There are no data on the carcinogenicity in humans of methylglyoxal.

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

Overall evaluation

Methylglyoxal is *not classifiable as to its carcinogencity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

Synonyms

- Acetylformaldehyde

- 2-Ketopropionaldehyde
- Pyruvaldehyde

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