Review

Diet and toxicity of chemicals

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Introduction

Diet composition and intake influence toxicity and carcinogenicity of chemicals in laboratory animals.[1-4] Interactions between diet and toxins range from nonspecific effects, for example, effects due to an influence of the toxin on dietary intake, to highly specific metabolic or molecular interactions. Many nonspecific and some specific interactions have been elucidated in studies of dietary effects on drug disposition and activity; they include dietary influences on drug absorption, metabolism, and excretion and, conversely, alterations by drugs of intake, absorption, and utilization of nutrients.[5] Specific metabolic interactions of diet and chemicals include changes in the processing of chemicals through the microsomal oxygenase pathways that activate or inactivate chemicals and their metabolites (Phase I metabolism), the glutathione (GSH) conjugation pathways in which GSH reacts with chemicals at electrophilic sites, and the glucuronide or sulfate conjugation pathways that produce more highly soluble excretory products (Phase II metabolism). There are many dietary effects on detoxification, oxygenation, and conjugation of chemicals,[6] and knowledge of the substrate requirements and competing metabolic pathways indicates many other potential sites for interaction.[7,8]

There is an extensive literature on nutritional and dietary effects on chemical carcinogenesis and on the stages of carcinogenesis at which the effects occur.[1-4,9-10] Alterations of carcinogen metabolism and DNA alkylation and adduction are a major mechanism by which diet alters chemical carcinogenesis at initiation. In this review, interactions that occur in the chemical initiation of carcinogenesis or on the effects of chemical promoters are discussed, since they arise, at least in part, from dietary interactions with chemical metabolism and disposition and with cell components that may be relevant to chemical toxicity in general.

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In a 1982 review Wise[11] discussed general effects of diet upon the results of toxicological bioassays and other investigations in laboratory animals. He discussed the general effects of dietary deficiencies on appetite and, therefore, on intake of the test substance if it is present in the diet; deficiencies particularly likely to reduce feed intake are those of zinc and amino acids. The amount of dietary fiber may influence absorption of test compounds and alter intestinal bacteria and their metabolism of test compounds. Phytate can bind and reduce absorption of metals; calcium (Ca) can bind and reduce absorption of lead (Pb). There have been many reviews and discussions of general dietary effects on toxicity and carcinogenicity of chemicals and recommendations made of diets appropriate for use in bioassays.[12-15]

This review focuses on selected recent publications reporting metabolic and toxicological interactions of diet, nutrition, and chemical toxicity, including carcinogenicity, that indicate potential for direct therapeutic or chemopreventive measures.

Natural product versus purified diets

Differences in chemical toxicity and carcinogenicity in laboratory animals fed natural diets, that is, diets that may also be termed cereal-based or chow® type diets, or fed diets composed of purified ingredients, that is, diets in which the components are refined to a greater or lesser extent from whole food sources or, rarely, are chemically pure, have been recognized for some time and attributed to many causes. The possible causes include the presence of inducers of Phase I and Phase II enzymes, antioxidants, and protease inhibitors and differences in fiber content in the two types of diet. Hepatic and intestinal microsomal enzyme activity and cytochromes P450 are generally higher in laboratory rodents fed natural-product diets than in rodents fed purified diets; the enzymes can be induced by vegetables or vegetable extracts in animals fed purified diets.[16] However, extrapolation of data on enzyme induction in vivo to effects of tissue extracts on in vitro bacterial mutagenesis by, or DNA-binding of, chemicals is not entirely predictable or consistent, and the results may not correlate with dietary effects on tumorigenesis by the same chemical.[16-18]

Examples of differences in chemical carcinogenesis between rats fed natural-product or purified diets include greater tumor induction in the liver by N-2 fluorenylacetamide (AAF),[19] greater induction of potentially preneoplastic, enzyme-altered foci (EAF) in the liver by N-nitrosodiethylamine (DEN) and phenobarbital (Phb),[20] and greater tumor induction in the liver and in the pancreas by L-azaserine,[21] all in rats fed a purified diet compared to rats fed a natural-product diet.

The qualitative and quantitative associations of hepatic and renal "I-compounds" (DNA adduct-like compounds of unknown origin and identity that accumulate with age) with diet type may be useful in investigations of the diet-induced differences in effects of chemicals. The compounds are increased in liver and kidney in rats fed natural-product diets compared to rats fed the purified AIN-76A diet. Levels of the "I-compounds" are inversely related to exposure to chemical carcinogens and to risk for spontaneous tumors in laboratory animals.[22,23]

Toxins that are more potent in animals fed purified diets than in animals fed natural-ingredient diets include Pb and theobromine (TBR). In rats given Pb acetate (1 mg Pb per ml of drinking water for 5 weeks), toxicity and blood and tissue content of Pb were significantly increased in rats fed a purified diet compared to rats fed a natural-product diet. Rats fed the natural-product diet had increased urinary excretion of delta-aminolevulinic acid, a marker for Pb toxicity, but no clinical or hematogical evidence of Pb toxicity, while rats fed the purified diet had reduced weight gain and anemia. The purified diet was adequate in minerals, although marginal in copper; the natural-product diet contained levels of minerals two to five times the recommended amounts. The investigators found no amelioration of Pb toxicity if they fed rats the purified diet supplemented with individual minerals, including copper, of if they adjusted the content of fat, carbohydrate, or fiber to match the natural-ingredient diet. They concluded that total mineral content, rather than content of individual minerals, might be responsible for the difference in Pb toxicity in rats fed the two diets.[24]

Rats fed TBR, the major xanthine alkaloid in cocoa powder and chocolate and a metabolite of caffeine, manifested greater testicular toxicity and reduction of body weight gain if they were fed a purified diet than if they were fed a natural-ingredient diet; thymic toxicity of TBR was not affected by diet. Rats fed the purified diet had significantly greater blood levels of TBR and excretion of unchanged TBR and lower excretion of metabolites of TBR than rats fed the natural-ingredient diet; the investigators attributed the greater toxicity of TBR in rats fed the purified diet to their lower metabolism and clearance of the alkaloid.[25]

There are interesting, complex, and unresolved interactions between diet and the effects of certain chemicals that promote urinary bladder cancer in rats; the interactions appear to be related to differences between natural-product and purified diets but go beyond these distinctions. The chemicals studied most extensively are sodium salts of saccharin or l-ascorbate, which promote tumors initiated by one of several different carcinogens. The following mechanisms of the promoting action have been postulated: alteration of bladder epithelial cell membrane potential, intra- or extracellular or urine pH or sodium or other ion concentration, rate of cell proliferation, and urine volume.[26,27] The strength of the promoting effect of both sodium saccharin and sodium L-ascorbate is influenced by the type of natural-product diet fed, although the test diets are nutritionally complete, and differences in nutrient content appear minor.[27,28] In a comparison of natural-product and purified diets, Garland et al.[26] reported differences in stimulation by sodium saccharin of bladder epithelial hyperplasia in rats fed two different natural-product diets and no stimulation in rats fed the purified AIN-76A diet. Again, although the diets differed in many components, all three appeared nutritionally complete. Subsequently the same group reported that sodium saccharin promoted bladder tumors in rats fed the natural-product diet that supported the greatest hyperproliferation of the epithelium but not when the rats were fed the AIN-76A diet. They postulated that the lower urinary pH in rats fed the purified diet blocked the promoting effect of sodium saccharin;[29] in a second large study, the same group reported that differences in urinary pH and sodium also appeared to explain the differences between natural-product diets in supporting promotion.[28]

In the studies cited, the composition of the natural-ingredient and purified diets varied from one study to another. The results do not permit evaluation of the contribution of particular diet components to the different effects of the two general types of diet.

Ethanol

Acute or chronic exposure to ethanol can influence the effects of many classes of chemicals; examples are given in *Table 1*. Laboratory animal models for studies of ethanol effects are complex, and there is significant disagreement about their proper design.[30,31] Nonspecific alterations in feed and, in some cases, water intake can be a major problem in defining specific toxicity and dietary and nutritional effects of ethanol.[32,33] Recently studies have used the AIN-76A diet modified into a liquid form and containing 20–35% of calories as ethanol.[32-35] The liquid AIN-76A diet without alcohol supports normal growth in rats and mice; animals fed alcohol in the AIN-76A or other diets may have reduced weight gain and may become dehydrated if they do not have access to drinking water at all times.[32] Manifestations of ethanol toxicity are highly dependent upon diet composition and may be due in part to different dietary intake and growth, factors requiring pair-fed controls.[31,34,36] Ethanol may be given by gavage in single or multiple doses or may be given in the diet or drinking water before or simultaneously with toxin exposure. Gavage regimens tend to reduce hepatic glutathione (GSH) stores, increase hepatic tri-

Table 1 Effects of chemicals in male rats fed natural-ingredient diets and given ethanol by gavage

Rats		Ethanol regimen[a]	Effect of ethanol	Reference
Strain	Weight (g)			
Wistar	110–200	4 g/kg × 4, 21–48	Increased hepatotoxicity of aflatoxin B_1, hepatic aniline hydroxlase, paranitroanisole demethylase, lysosomal enzyme activity, lipid peroxidation, and intracellular CA^{2+}; decreased cytochrome B5, epoxide hydrolase activity, glutathione; no effect on NADPH-cytochrome c reductase, glutathione-S-transferase, cytochrome P450	Toskulkao et al., 1985, 1988, 1990[39-41]
		4 g/kg × 1, 0	No effect	Toskulkao et al., 1985 1988, 1990[39-41]
Sprague-Dawley	250–75	7 g/kg × 1, 24	Decreased toxicity of Cd, Cd concentrations in hepatocyte organelles; increased metallothionein concentration, sequestration of Cd in hepatocyte cytosol, total Cd in liver	Kershaw et al., 1990[42]
		5.56 g/kg/d × 30	Increased tissue Cd, reduced tissue Zn	Sharma et al., 1991[43]

[a] Given by gastric gavage; dose × no. of administrations, hours prior to administration of test chemical. Calorie control for ethanol not indicated.

glycerides and marker microsomal oxidases, and reduce epoxide hydrolase, whereas dietary exposure produces fatty liver of varying severity but less or no biochemical evidence of toxicity.

Ethanol induces a specific cytochrome P450 (IIE1) as well as other enzymes that affect metabolism of other alcohols, carbon tetrachloride, therapeutic drugs, drugs of abuse, aflatoxin B_1 (AFB_1), nitrosamines, and other carcinogens.[37] Selective induction of specific P450 isozymes may increase or decrease toxicity of test compounds. Trichlorethylene hepatotoxicity is increased by prior exposure to ethanol in the diet.[38] Increased toxicity of AFB_1 was reported in rats pretreated with ethanol gavage, presumably because the balance of AFB_1 metabolism had been altered in the direction of increasing the level of toxic metabolite(s) in the liver and because hepatic GSH was reduced.[39-41] Conversely, by increasing hepatic metallothionein (MT) concentration, ethanol reduced lethality and hepatotoxicity of cadmium (Cd) in rats. Rats were given a single large dose of ethanol, 7 mg/kg, by gavage and, 24 hours later, given a lethal or sublethal but toxic dose of Cd intravenously. Ethanol pretreatment reduced Cd-induced mortality from 100% to 17% and, in rats given the lower dose, markedly reduced enzyme markers for hepatocyte damage. Biliary excretion of Cd was reduced by ethanol while hepatic MT concentration increased 11-fold, and hepatic Cd concentration increased by 33%, virtually all of it bound to MT.[42] In another study, ethanol, given by gavage in a bolus of 5.56 g/kg/d for 30 days, increased hepatic and intestinal Cd in rats fed a complete, natural-product diet and tap water, but given no other source of Cd, as well as in rats given a daily intragastric dose of Cd of 10 mg/kg. No evidence of Cd toxicity was reported. Ethanol also decreased tissue zinc (Zn) content, an effect that may account for the shifts in Cd absorption and tissue deposition since the two metals are antagonistic.[43] Ethanol may have acted also by increasing tissue MT concentration and Cd binding.[42]

A recent study of interest in the area of interactions of diet and ethanol toxicity is the report that embryotoxicity of ethanol gavage (2.5 g/kg twice on gestation day 11) in rats was significantly increased by concomitant folate deficiency induced by dietary depletion and succinylsulfathiazole. Maternal ethanol toxicity, manifested by reduced weight gain, also was increased by the deficiency; folate-sufficient maternal rats showed no evidence of ethanol toxicity.[44]

Nutritional and dietary problems can interfere with assessment of toxicity of behavior-altering drugs such as delta-9-tetrahydrocannabinol (THC) and may magnify effects found in studies of embryotoxicity or teratogenicity of the test substance.[45] Ethanol, cocaine, THC, and other compounds can influence maternal behavior in ways, other than by altering dietary intake, that may be deleterious to the offspring but are not related directly to ethanol toxicity. In such cases, offspring may be fostered on surrogate dams. Studies of effects of drug combinations have been reported. Ethanol, fed for 6 days in a liquid AIN-76A diet to supply 25% of calories, significantly increased hepatotoxicity of a single dose of cocaine in both male and female mice. The control male mice pair-fed to the ethanol-fed mice showed markedly reduced toxicity of cocaine compared to control mice fed ad libitum, but no effect of reduced diet intake was reported in pair-fed females. Cytochrome P450 was induced by ethanol; pair-feeding had no effect in males but increased P450 somewhat in females. There was, therefore, not a clear correlation of cocaine toxicity with effects of ethanol or diet intake on the hepatic monooxygenase system that activates cocaine to toxic metabolite(s).

Pair-feeding and chronic ethanol exposure reduced hepatic GSH content by 23–64%, but the results again did not clearly correlate with cocaine toxicity.[35] Potentiation of toxicity of cocaine by ethanol was reported also in vitro in human hepatocytes exposed to both drugs in concentrations consistent with human exposures. The toxicity was manifested as depression of GSH concentration and abnormalities of urea and glycogen synthesis.[46]

Antioxidants

Many diet-induced alterations of chemical toxicity are postulated to be mediated by oxidant-antioxidant effects. GSH is a major intracellular protectant against many toxic chemicals and drugs. Cell content of GSH and of enzymes governing its redox state are highly responsive to nutrients, particularly riboflavin and Se, though the significance of dietary deficiency-induced reduction in the enzymes or in GSH concentrations is not clear.[8] Depletion of GSH, by prior or excessive exposure to compounds that form GSH conjugates either directly or via glutathione-S-transferases (GST) or to oxidative and other free radical stresses that require GSH peroxidase activity (GSH-PX), render cells susceptible to toxicity of chemicals detoxified by GSH.[47,48]

GSTs are induced by AFB_1 in hepatocytes, and GSH concentrations are decreased by AFB_1 exposure in hepatocytes in vitro. There is extensive evidence that AFB_1 toxicity and carcinogenicity in rodents are inversely related to both GST activity in hepatocytes and to sulfhydryl detoxification pathways.[49] The mechanism of protection against AFB_1 toxicity by agents such as butylated hydroxytoluene (BHT) that are nonspecific enzyme inducers may involve the balance of the many enzymes induced and the affinities of the GSTs for AFB_1 metabolites that produce cellular or gene toxicity. However, in vitro there is not a good correlation between cellular GSH content and AFB_1 toxicity to hepatocytes.[50]

Among thiol antioxidant chemoprotective compounds naturally present in foods are the dithiolthiones in cruciferous vegetables. The most extensively studied dithiolthione, oltipraz, is a synthetic dithiolthione antischistosomal drug. It reduced toxicity of AFB_1 and formation of hepatic AFB_1-DNA adducts, EAF and benign and malignant hepatocellular tumors in rats given a carcinogenic AFB_1 regimen; it induced GSTs, other Phase II enzymes, and cytochrome P450-associated monoxygenases.[49,51,52] The unsubstituted parent dithiolthione also markedly reduced in vivo formation of hepatocyte AFB_1-DNA adducts.[49]

Dietary Se is of interest because of its participation in and induction of the activity of glutathione peroxidases (GSH-Px) and its interactions in chemical toxicity and carcinogenicity.[53,54] Dietary Se deficiency in pregnant CD-1 mice, which reduced both Se-dependent and Se-independent peroxidases, increased the teratogenicity of phenytoin as evaluated by the incidence of cleft palate.[55] Toxicity of 1,2-dimethylhydrazine (DMH) is increased in Se-deficient rats;[56] there is a protective effect of Se on colon carcinogenesis by DMH, although the timing of the effect varies between experiments. The role of oxidative mechanisms is not clear.[57,58] Pence reported a positive correlation between colonic GSH-PX activity and dietary Se and a depression of colonic GSH and superoxide dismutase (SOD) by DMH. The changes demonstrated would be expected to decrease antioxidant activity in the colon of Se-deficient, DMH-treated rats, but no increase in peroxide was demonstrable in the colon of the rats.[54]

Selenium has somewhat variable effects on hepatic toxicity and carcinogenicity of AFB_1 and on induction of EAF by AFB_1. Both deficient (0.05 ppm) and excessive (5 ppm) Se intakes in drinking water increased AFB_1 toxicity and carcinogenicity in rats.[59] The lowest toxicity and carcinogenicity of AFB_1 were found in rats given 1 or 2 ppm Se, levels considerably higher than the nutritional requirement, 0.1 ppm. In contrast, excessive intake (5 ppm) has been reported to suppress the tumor-initiating activity of AFB_1 if rats were given phenobarbital as a promoter; deficiency had no effect on tumorigenesis in the same model.[60] Se-deficient rats, with significantly depressed hepatic but not esophageal mucosal GSH-Px, manifested the same response as Se-supplemented controls to the esophageal carcinogen, methylbenzylnitrosamine (MBN). Rats fed hypersupplemented diet (4 ppm) had increased esophageal but not hepatic GSH-Px, and, again, no consistent difference from controls in esophageal tumors.[61] A similar dietary Se content (4 ppm) reduced gastric carcinogenesis by the direct-acting carcinogen, N-methyl-N-nitro-N-nitrosoguanidine (MNNG).[62]

Selenium deficiency can increase, and Se supplementation can reverse to some extent, the enhancement of chemical carcinogenesis in the mammary gland of rats fed a high corn oil diet, an effect exerted primarily after initiation. However, in rats fed diets high in fat content composed of a mixture of food fats rather than only corn oil, Se has not consistently influenced tumorigenesis.[63-65] There is evidence that antiperoxidative activity may not be the mechanism by which Se acts.[63-65] Se reduces 7,12-dimethylbenzanthracene (DMBA) adduction to mammary gland DNA, and it may, therefore, have an independent role at initiation.[66] Since Se deficiency reduces, and Se supplementation above the requirement enhances, generation and activity of cytotoxic lymphocytes,[67] immunological mechanisms also are possible.

Nutrients, particularly anti- or pro-oxidants, can have direct chemical interactions with toxins. Ascorbic acid is a prime example with its ability to reduce toxic hexavalent chromium (Cr) to much less toxic trivalent chromium salts, discussed below.[68] Ascorbic acid also can reduce endogenous nitrosation of amines with reduction in tumorigenesis by and toxicity of the nitrosamine produced.[69,70]

Cancer chemotherapeutic agents

Dietary and nutritional influences on toxicity of cancer chemotherapeutic agents are of particular interest in considerations of interactions of diet and chemical

Table 2 Diet and toxicity of cancer chemotherapeutic agents in rats

Diet component	Strain	Sex	Age or weight	Tumor transplant	Drug	Effect of diet component	Reference
Riboflavin	Sprague-Dawley	M	10 wks	No	Doxorubicin	Deficiency reduced drug-induced aldosterone secretion	Pinto et al., 1990[78]
Riboflavin	Holtzman	M	9–15 wks	No	Doxorubicin	Drug-reduced ocular lens GSH in deficient rats only	Dutta et al., 1990[79]
Protein	WAG/Rij	F	150–160 g	R1Rhabdo-myosarcoma	Methotrexate	Severe deficiency delayed MTX excretion, increased marrow and gut toxicity	Dunki-Jacobs et al., 1989[72]
Protein	L/W	F	146–203 g	AC33 mammary tumor	5-Fluorouracil	Severe deficiency increased drug-induced diarrhea, leukocytopenia	Torosian et al., 1990[73]
Methyl	Sprague-Dawley	M	4 wks	No	Procarbazine	Marginal deficiency increased drug-induced disturbance of hepatic choline metabolism	Rogers et al., 1990[75]

toxicity (*Table 2*). The patients being treated are often malnourished or at risk for malnutrition because of their disease and its treatment. Many of the drugs are toxic to rapidly proliferating normal cells, bone marrow and gut epithelium, among others; some have specific target organ toxicity, including the heart, kidney, and nervous system; several are carcinogenic in laboratory animals; and a few have been identified as human carcinogens. The treatment regimens often induce anorexia, nausea, and vomiting. Therefore, provision of adequate nutrition and, if indicated, of dietary intake designed to block toxicity and carcinogenicity of the agents without interfering with their therapeutic efficacy is important. There are data on nutritional interactions with a few agents, but much more information is needed.

Severe protein deficiency in rats significantly increased toxicity of the chemotherapeutic antimetabolites, methotrexate (MTX)[71,72] and 5-fluorouracil (5-FU).[73] A single dose of MTX was cleared less rapidly from the blood of protein-deficient rats than from control rats; gut and bone marrow toxicity of the drug was considerably greater and more prolonged in the deficient rats.[72] Marrow and gut toxicity of 5-FU also was greater in protein-deficient than in normal rats.[73] Because MTX itself induces methyl deficiency,[74] its use in combination with potentially carcinogenic therapeutic agents is of some concern, and dietary or other provision of methyl may be important (see below).[75,76]

Toxicity of the cancer chemotherapeutic agent doxorubicin is manifested in functional and morphologic abnormalities of the heart, gastrointestinal tract, liver, and kidney. Doxorubicin and other anthracycline drugs complex with flavin coenzymes, competing with them for protein binding sites and inhibiting formation of flavin adenine dinucleotide from riboflavin in skeletal and cardiac muscle.[77] In a series of studies of interactions of doxorubicin and riboflavin in rats, it has been shown that doxorubicin increases serum aldosterone and that dietary riboflavin deficiency inhibits that rise. The mechanism by which the inhibition occurs is unknown.[78] In addition, riboflavin deficiency in rats depletes the ocular lens of GSH by about 26% and reduces the activity in the lens of glutathione reductase, the enzyme that regenerates GSH. Doxorubicin, alone, reduces lens GSH to 52% of normal in riboflavin-deficient rats but does not alter the reductase.[79] The functional significance of these interactions of drug and riboflavin is not clear.

Protein

In addition to the affect of protein deficiency on MTX and 5FU toxicity, effects on carcinogenicity of chemicals are known (*Table 3*). In an extreme case, short-term feeding of a diet consisting only of carbohydrate reduced hepatic metabolism of N-nitrosodimethylamine (DMN), its hepatotoxicity, and alkylation of hepatic DNA; alkylation of renal cortical tubule cell DNA was increased because of the large amount of unmetabolized DMN reaching the kidney; renal metabolism was less severely affected by the diet. The long-term result of these alterations was a decrease in hepatic tumors and an increase in renal tumors.[80-83] The carbohydrate diet had no effect on DNA alkylation by the direct-acting carcinogen, N-nitrosomethylurea (MNU), which does not require metabolic activation.[83]

In studies of less extreme protein deprivation, similar protection of the liver against carcinogenesis has been described. Hamsters fed an 8% casein, otherwise nutritionally complete, diet that reduces hepatic cytochrome P450 and given another nitrosamine, N-nitroso (2-hydroxypropyl) (2-oxopropyl)amine (HPOP), had reduced DNA alkylation, increased glucuronidation of HPOP, and, ultimately, a reduced incidence of hepatic and pancreatic tumors.[84] In rats fed marginal protein diets (8–12%) casein), AFB_1 was less toxic and probably less carcinogenic than in rats fed adequate to high (20–30%) casein, as judged by body weight, serum content of liver enzymes, and occurrence or histology of putative preneoplastic lesions in the liver.[85,86]

The metabolism of DMBA to DNA-adducting metabolites and mammary gland carcinogenesis by DMBA have been studied in relation to dietary protein content. Mammary cells isolated from rats fed 7.5% protein metabolized DMBA less rapidly and produced

Table 3 Dietary or nutritional effects on carcinogen metabolism and DNA adduction in vivo

Diet or diet components[a]	Carcinogen[a]	Species	Strain	Sex	Age or weight	Effect of diet	Reference
CHO only vs complete diet	DMN	Rat	Porton-Wistar or Sprague-Dawley	M	140–180 g	Decreased blood clearance, hepatic but not renal metabolism of DMN; decreased	Swann and McLean, 1971[80]
CHO only vs complete diet	DMN	Rat	Wistar	M	4 wks	Reduced alkylation of hepatocyte DNA; increased alkylation of DNA in renal cortical tubules and mesenchyme	Fan et al., 1989[83]
	NMU	Rat	Wistar	M	10–11 wks	None	
Protein (7.5% vs 15%)	DMBA	Rat	Sprague-Dawley	F	160–185 g	Decreased DMBA metabolism and DNA adduction by mammary gland cells in vitro; increased DNA adduction by hepatocytes in vitro with no significant effect on metabolism	Singletary and Milner, 1987a, 1987b[87,88]
Casein (8% vs 20%)	HPOP	Hamster	Syrian	M	85–90 g	Reduced hepatic cytochrome P450, DNA alkylation	Kokkinakis and Scarpelli, 1989[84]
Zn deficient vs Zn sufficient[b]	MBN	Rat	Sprague-Dawley	M	7 wks	Increased 06- and N7-methylguanine in esophageal DNA, 1–24 hrs	Barch and Fox, 1987[92]
Se (2 vs 0.1 ppm)	DMBA	Rat	Sprague-Dawley	F	55 d	Decreased DMBA-DNA adducts after 2–4 wks, but not after 1 week, of feeding	Ejadi et al., 1989[66]

[a] Abbreviations: AFB_1, aflatoxin B_1; AHH, arylhydrocarbon hydroxylase; CHO, carbohydrate; DMBA, 7,12-dimethylbenz(a)anthracene; DMN, N-nitrosodimethylamine; GST, glutathione-S-transferase; HPOP, N-nitroso (2-hydroxypropyl) (2-oxopropyl)amine; I3C, Indole-3-carbinol; MBN, N-nitrosomethylbenzylamine; NMU, N-nitrosomethylurea.
[b] Controls pair-fed to deficient rats.

lower amounts of DNA adducts than cells from rats fed 15% protein.[87] However, when hepatocytes were tested, using exogenous rather than endogenous DNA to measure adducts, cells from rats fed 7.5% protein produced larger amounts of DNA adducts than cells from rats fed 15% protein; the rates of DMBA metabolism in deficient and control hepatocytes were not different, so presumably there was less inactivation of active metabolites by the hepatocytes of deficient rats.[88] Since a single dose of DMBA is carcinogenic for the mammary gland but not for the liver, extrapolation of the in vitro results to DMBA carcinogenesis is not clear. There are conflicting data on the effects of dietary protein on DMBA carcinogenicity with no clear consensus.[87,88] The variability between experiments may be due, at least in part, to variations in the balance between hepatic and mammary gland metabolism of DMBA, with different amounts of active or inactive metabolites formed at the two tissue sites.

Minerals

Nutrient and non-nutrient metals can be toxic and have well-documented interactions in gastrointestinal absorption, distribution, tissue deposition, and excretion. An antagonistic Zn-Cd interaction can be demonstrated at high or deficient dietary intakes of Zn. Cd toxicity is thought to be due, at least partially, to interference by Cd in Zn-enzyme mediated metabolism. Cd toxicity can be blocked by excess dietary or other supply of Zn, as can Cd tumorigenicity in the testis and at the site of injection. Marginal dietary Zn deficiency increases Cd nephrotoxicity and tumorigenicity in rats. The mechanism of action of Zn deficiency may be reduction of MT, which is normally induced by Zn, permitting tissue accumulation of Cd without sequestration by binding to MT.[89]

Zn-Copper (Cu) interactions have led to the therapeutic use of Zn in Wilson's disease, a disease of abnormal metabolism and resultant toxicity of Cu. Zn reduces absorption of Cu from the gut, induces intestinal epithelial cell MT, and reduces the rate of Cu accumulation in tissues and hepatic toxicity of Cu, as measured by serum enzymes.[90] In rats a subcutaneous Zn depot also induced high MT levels in liver and small intestine and protected against hepatic accumulation and toxicity of a high Cu diet (750 μg Cu/g). Administration of Zn after Cu loading restored rats to normal growth rate and reduced hepatic toxicity of Cu without reducing total liver Cu. The extent of Cu binding to MT in liver was greatly increased while binding to other proteins was greatly decreased, a shift that was thought to account for the reduced hepatic toxicity.[90]

Zinc deficiency increases the methylation of esophageal DNA by methylbenzylnitrosamine (MBN), an esophageal carcinogen that is more effective in Zn-de-

ficient than in normal rats.[91,92] The increased methylation may be due to increased esophageal mucosal activation of MBN;[92] to increased cell division in the target epithelium;[91] or both. Zn deficiency reduces hepatic activity of a major enzyme for DNA repair, adenine dinucleotide phosphoryltransferase (ADPRT), an effect that may account for some of the effects of Zn deficiency on carcinogenesis;[93] however, Barch and Fox[92] found no evidence of a reduced rate of adduct removal in deficient rats. Other work has shown that hypersupplementation with molybdenum reduces MBN esophageal carcinogenesis in rats;[94] the mechanism is unknown.

There are interesting prospective epidemiological data associating increased body iron stores with increased risk for cancer, particularly colon cancer in men over 50 years of age; the results were corrected for smoking and indicated no association with reported dietary intake of iron or with hemoglobin and hematocrit.[95-98] Results from another prospective study gave weak support to an inverse relationship between body iron stores and lung cancer risk but not risk of other cancers in women. In contrast to the result in men, anemia and high total iron-binding capacity were associated with a significantly reduced risk of developing lung cancer.[99] Postulated mechanisms include the pro-oxidant effect of iron contributing to cell damage and tumor promotion, and a nutritional effect of iron on growth of tumor cells. However, the evidence for an effect is weak and requires confirmation in more focused studies.[100]

In the MNU-induced rat model for breast cancer, high dietary iron intake (1200 ppm in diet) was associated with greater final tumor incidence than either adequate (120 ppm) or low (2 ppm) intake. The increased tumor incidence did not appear until relatively late in the experiment.[101] DMH colon carcinogenesis was somewhat, although not significantly, increased in rats fed a diet high in iron (580 ppm) compared to rats fed an adequate amount (35 ppm). Acute toxicity of DMH was not affected by the high dietary iron.[98] In mice fed a much greater concentration of iron (3.5% iron fumarate in a natural-product diet) during a 10-week exposure to DMH and then fed a control diet, colon tumor number was increased significantly compared to mice fed the diet without iron.[102] Again, the effects are relatively weak; the organs affected are not major storage sites for iron, although iron does accumulate in them.

Calcium salts reduce absorption of Pb salts from the gut and reduce tissue Pb accumulation in rats. However, feeding Ca acetate at 0.3% or more in the diet of rats fed also 1% Pb acetate resulted in increased, rather than decreased, toxicity of the Pb, as judged by reduced weight gain and increased renal tumorigenesis. Paradoxically, renal lead content was reduced by the Ca feeding.[103]

Hexavalent chromium salts (Cr^6) are toxic and carcinogenic in humans and laboratory animals; trivalent chromium (Cr^3) is much less toxic and is not known to be carcinogenic. Cr^6 is reduced to Cr^3 in tissues by the action of GSH and other reducing pathways. Asorbic acid can protect against Cr^6 toxicity, presumably by reductive activity. Compared to control pigs, guinea pigs fed an ascorbic acid deficient diet and given a lower daily maintenance dose of ascorbate (0.5 mg) had severely reduced tissue ascorbate (7–12% of control). They showed significantly increased bone marrow chromosome aberrations in response to a single injection of Cr^6. Less severely deficient pigs given Cr^6 in drinking water had increased micronuclei in polychromatophilic erythrocytes, another indicator of genetic toxicity, compared to controls who showed no effect of Cr^6 exposure. Tissue vitamin C levels in the deficient pigs were 30–50% of control.[68]

Non-nutrient components of diet

There are many examples of non-nutrient food components that influence toxicity and carcinogenicity of chemicals in laboratory animals (*Table 4*) and, presumably, in humans, since mixed vegetable extracts and other diet components alter xenobiotic metabolism and conjugation in humans[104] as they do in laboratory rodents.[2,16] The chemopreventive activity of non-nutrient components may be responsible for some of the observed differences in chemical toxicity in animals fed purified versus natural-product diets.

Green tea extracts reduced AFB_1-induced bone marrow chromosome aberrations in rats. Both the whole extract and its tannin components were effective if given 24 hours but not 2 hours before AFB_1 administration. In contrast, other components—caffeine and ellagic acid—were most effective if given 2 hours before AFB_1.[105] Green coffee beans and, to a lesser extent, roasted coffee products contain compounds, such as kahweol and cafestol palmitate, that induce glutathione-S-transferase (GST) activity and inhibit polycyclic aromatic hydrocarbon (PAH) carcinogenesis in rat mammary gland and hamster cheek pouch. Since the beans and caffeine also reduce weight gain, the reduction in carcinogenesis in the models may be a result not only of changes in carcinogen metabolism but also of reduced weight gain.[106-8]

Ellagic acid, a coumarin-related lactone present in fruits, nuts, and vegetables, as well as in green tea, reduces hepatic carcinogenesis by AAF[109] and binds to carcinogenic metabolites of PAH, thereby reducing DNA adduction and skin, mammary gland, and forestomach carcinogenesis by PAH's in rodents.[10] Ellagic acid is active in the skin tumor models, whether given by topical application or in the diet, and in PAH-induced lung tumorigenesis, whether given in diet or intraperitoneally (ip), although ip injection is more effective.[109] Ellagic acid reduces also esophageal carcinogenesis by MBN,[110] activation of MBN and methyl-DNA adduct formation in esophageal explants[111] and reduces AFB_1 microbial mutagenicity and DNA adduction in tracheobronchial explants.[112]

When fed in the diet, ellagic acid induces hepatic and esophageal cytochromes P450, hepatic arylhydrocarbon hydroxylase (AHH), and esophageal, but not

Table 4 Effects of non-nutrient components on nuclear, genetic, or chromosomal in vivo assays of toxicity of chemicals

Diet component	Species	Strain	Sex	Age or weight	Chemical	Effect of diet component	References
Indole-3-carbinol	Mouse	ICR Swiss	M	30 g	B(a)P DMN	Reduced B(a)P, DMN binding to hepatic DNA, protein	Shertzer 1983, 1984[117,118]
Diallyl sulfide	Rat	F-344	M	120–150 g	DMH	Reduced DNA adducts and prevented necrosis in liver	Hayes et al., 1987[135]
Diallyl sulfide	Rat	Sprague-Dawley	M	100–125 g	MBN	Reduced esophageal nuclear aberrations; reduced MBN metabolism by hepatic microsomes but had no effect on esophageal metabolism	Wargovich et al., 1988[130]
Ellagic acid	Rat	Sprague-Dawley	M	7 wks	MBN	Reduced esophageal but not hepatic MBN metabolism; reduced 06 but not N7 methylation of guanine in esophageal DNA	Barch and Fox, 1988, 1989[114,115]
Green tea extract,[a] tannins,[a] caffeine,[b] ellagic acid[c]	Rat	Wistar	M	4–5 wks	AFB_1	Reduced bone marrow chromosome aberrations	Ito et al., 1989[105]

[a] 24 hrs before AFB_1; not effective if given 2 hrs before or after AFB_1.
[b] 24 or 2 hrs before AFB_1.
[c] 2 hrs before AFB_1; not effective if given 24 hrs before AFB_1.

hepatic, MBN metabolism in vivo and in vitro.[113-115] It reduced formation of 0^6 methylguanine but not other DNA adducts of MBN in the esophagus in vivo, but in vitro formation of DNA adducts by MBN was not altered by prior in vivo exposure to ellagic acid. Prior exposure of the DNA to ellagic acid reduced alkylation by MBN; binding of ellagic acid to DNA appeared to block, selectively, methylation of guanine at 0^6.[114] Therefore, ellagic acid appears to act in the esophagus both by reducing activation of MBN and by blocking specific DNA sites of adduction. Ellagic acid fed in the diet at the anticarcinogenic dose of 4g/kg is not toxic to rats.[110]

The indole glucosinolates are a class of compounds in plants that yield biologically active components that are of interest because of their metabolic and anticarcinogenic effects.[116] The major dietary vegetable sources of the indole glucosinolates are cabbage, Brussels sprouts, broccoli, turnips, and cauliflower. The active metabolites, of which indole-3-carbinol (I3C) is the most extensively studied, induce activity of xenobiotic metabolizing enzymes in intestine and liver in mice and rats and prevent carcinogen adduction to DNA.[117,118] In higher doses they induce Phase II enzymes, GST, and epoxide hydratase. They can reduce carcinogenesis in the lung, gastrointestinal tract, and mammary gland by PAH and in the liver by AFB_1, although in some cases feeding I3C or the whole vegetables has increased chemical carcinogenesis in rats[119,120] and trout.[121,122] The pure compound, I3C, has been studied extensively in AFB_1-exposed trout and, more recently, in rats. When fed to trout before and during AFB_1 exposure, it reduces hepatocarcinogenesis in a dose-responsive manner that correlates with reduction of AFB_1-DNA binding.[123] However, I3C promotes hepatic tumor development in trout when they are fed beginning immediately, or as late as 12 weeks, after AFB_1. The effective doses are similar to the doses that block carcinogenesis at initiation. The results with whole vegetables or I3C raise interesting questions about the probable balancing of promoting and anti-promoting or anti-initiating agents in vegetables and other plant products.[121,122]

Formulation of diets containing large amounts of freeze-dried or otherwise processed vegetables requires significant attention to nutrient content and balance because of the bulk, fiber, and nutrient content of the vegetables. Birt et al.[120] reported enhanced nitrosamine carcinogenesis in pancreas and gallbladder in hamsters fed approximately 10% freeze-fried cabbage, compared to hamsters fed a control diet composed of the same components except cabbage and adjusted carefully for nutrient and calorie content. They monitored the animals closely and detected no evidence of nutritional abnormality that might account for the increase in tumors in cabbage-fed animals. In a similar experiment in mice, they found that cabbage feeding increased skin tumorigenesis by DMBA.

Glucarate, an anticarcinogenic component of fruits that is converted to D-glucaro-1,4-lactone in the stomach, inhibits B-glucuronidase in rat mammary gland, colon, and in small intestine, as well as in other tissues, and inhibits carcinogenesis by several different chemicals in rats and mice. It may inhibit carcinogenesis by preventing hydrolysis of glucuronides of carcinogens and their metabolites, thereby preventing enterohepatic recirculation or local activity of active compounds or, as demonstrated in the mammary gland, by inhibiting DNA synthesis.[124-27] Rat tumor models in which calcium glucarate inhibits tumorigenesis include DMBA-induced mammary tumors[124] and azoxymethane-induced colon tumors.[125] The amounts

of glucarate fed give no evidence of toxicity, and the compound has inhibiting activity at both initiation and promotion of tumors by carcinogenic chemicals.

Garlic extracts have significant effects on the toxicities of DMH, carbon tetrachloride, and DMN and also on the carcinogenicity of several chemicals in rodents. The extracts and pure chemicals isolated from them reduce markedly esophageal carcinogenesis by MBN, colonic carcinogenesis by DMH and related compounds, and lung and forestomach tumor induction by benzo(a)pyrene.[128-32] The reduction of carcinogenicity appears to be the result of inhibition or inactivation of monoxygenase and cytochromes P450 that activate the carcinogens in the liver and target organs and the induction of other monooxygenases, cytochromes P450 and GSTs.[129,130,133] In addition to its influence on xenobiotic metabolism, the major component of garlic studied, diallylsulfide (DAS), appears to influence DNA repair mechanisms.[130,134] In all cases, garlic extracts and the individual components tested exert their effects when given before but not when given after exposure to chemical carcinogens. DAS protected liver against DMH-induced toxicity much more effectively than it protected against DMH-induced DNA adducts or abnormal foci, a possible indication that different metabolites are responsible for toxicity than for carcinogenesis, at least in the liver.[135] There are in vitro data suggesting that DAS and other garlic components may be protective against AFB_1, but anticarcinogenic activity has not been reported.[136]

The effects in the skin tumor models are interesting, although somewhat tangential to a consideration of dietary effects. Application of garlic oil to the skin of Sencar mice, 30 minutes prior to application of DMBA, significantly reduced tumor induction; in contrast to the effects of ingested extracts, cutaneous application was effective also after carcinogen exposure. Application of garlic extract to the cheek pouches of hamsters for 3 weeks, followed after 11 weeks by DMBA applications, reduced tumorigenesis.[137] Several mechanisms of action of topical application have been proposed and include, in addition to alteration of carcinogen metabolism, inhibition of cell division, antitoxidant activity, and inhibition of lipoxygenase and cyclooxygenase.[138]

Methyl group donor deficiency

Dietary deficiency of methyl group donors, primarily methionine, choline, folate, and vitamin B12, often designated as lipotrope deficiency or methyl deficiency, has marked effects on chemical toxicity and carcinogenicity.[76,139,140] In early studies on chemical toxicity, it was shown that methyl deficiency reduces the hepatotoxicity in rats of a single dose of AFB_1 while increasing the toxicity, as well as the carcinogenicity, of multiple small doses. The deficiency reduces also the hepatotoxicity of the pyrrolizidine alkaloids, lasiocarpine and monocrotaline.[141,142] There was evidence that reduced metabolism of AFB_1 and the two alkaloids was responsible for the decreased acute toxicity in methyl-deficient rats, but the mechanism of the increased toxicity and carcinogenicity of multiple doses of AFB_1 and of many other hepatocarcinogenic chemicals is not known. There is a large body of literature on methyl nutriture and toxicity and carcinogenicity of chemicals.[76] It has been found that the deficiency alone is hepatocarcinogenic, perhaps by inducing hypomethylation of DNA and altering expression of oncogenes and other genes[143,144] as well as by inducing hyperproliferation of hepatocytes and many other biochemical and metabolic changes.[76]

There have been studies of antitoxic and antitumor effects of injected S-adenosylmethionine (Adomet), which may or may not act by similar mechanisms. Parenteral Adomet reduces the acute toxicity of ethanol, carbon tetrachloride, acetaminophen, and other chemicals.[145-47] It gives some protection against the mycotoxin, anguidine, or diacetoxyscirpenol, which is toxic to the gut, hematopoietic tissues, and the cardiovascular system.[148] The mechanisms of action of Adomet in these experiments are unknown, and their relevance to methyl nutrition is not clear.

There is evidence of methyl donor deficiency during exposure to repeated doses of chemical carcinogens.[76,139,140] A new type of interaction was found recently in experiments examining the role of methyl deficiency in procarbazine (PCZ) carcinogenesis in rats. Procarbazine is a cancer chemotherapeutic agent used in treatment of Hodgkin's disease and other tumors. In rats made methyl deficient by diet or by repeated injections of MTX, PCZ was a more effective mammary gland carcinogen than in control rats. Surprisingly, PCZ treatment caused markedly elevated hepatic choline and phosphocholine.[75] This result contrasts with effects of certain other carcinogens or toxins that reduce Adomet or alter the balance of folate compounds in the liver.[74,76,139,140] The deficient diet or chronic exposure to MTX alone reduced hepatic choline and phosphocholine as well as other choline metabolites and Adomet.[74] PCZ presumably interferes with choline utilization, an effect that may contribute to its carcinogenesis.

Hepatic toxicity of chemicals can be studied in vitro in short-term hepatocyte cultures from rats pretreated in vivo with dietary alterations or drugs or toxins.[149] Methyl deficiency had a detectable but not significant effect in the system, decreasing susceptibility of hepatocytes to toxicity of MTX. Ethanol feeding decreased hepatocyte susceptibility to toxicity of doxorubicin, MTX, cycloheximide, and AFB_1. Pretreatment with AFB_1, other hepatocarcinogens, or doxorubicin decreased susceptibility to toxicity of numerous chemicals while pretreatment with MTX reduced susceptibility only to its own toxicity. This model, which is particularly useful for study of mechanisms of multiple drug resistance in tumor cells, may be useful also for studies of diet-induced changes in chemical responses of hepatocytes. Multiple drug resistance is a characteristic of hepatocytes in EAF and of hepatocellular carcinoma; one demonstrated mechanism for the change is a marked increase in capacity for drug or

chemical excretion through induction of a plasma membrane-bound enzyme. Another mechanism of chemical resistance in preneoplastic hepatocytes is the loss of lipoprotein receptors that bind chylomicron remnants and of asialoglycoprotein receptors. Ethionine, a hepatocarcinogen and an antimetabolite of methionine that may act by mechanisms similar to methyl deficiency, as well as AAF and AFB_1 all reduce both receptors early in the carcinogenic process. The receptors are specific for hepatocytes.[150]

Fatty acids

Pharmacological and dietary modifiers of synthesis and activity of eicosanoids have wide-ranging effects on chemical toxicity and carcinogenesis. The biologically active eicosanoids induce or influence many aspects of tissue responses to injury.[151,152] Dietary modulation of eicosanoid synthesis is accomplished by changes in fat composition, since n-3 polyunsaturated fatty acids, such as are found in fish and some plant oils, generate a different group of eicosanoids than n-6 polyunsaturated fatty acids present in the more commonly used plant oils. The fatty acids are also incorporated into phospholipids of cell membranes and may influence chemical toxicity by altering the properties of the membranes and, therefore, of enzyme receptors and other factors that interact with or depend upon membrane structure.[153-58]

Cyclosporine, an immunosuppressive drug widely used in organ transplant patients, is nephrotoxic. The mechanism is thought to be related to altered eicosanoid synthesis and balance. Studies in rats showed that fish oil supplements reduced cyclosporine nephrotoxicity.[159] Supplementation of patients on long-term cyclosporine therapy with fish oil for 3 months gave evidence of reversal of renal damage, compared to results in patients given corn oil supplements.[160]

There is a recent report that acetaminophen toxicity is reduced in mice fed a 20% fish oil diet compared to mice fed a 20% olive oil diet.[158] The mechanism of the reduction was thought to be an alteration of drug metabolism, although questions of eicosanoid influences and cell membrane changes were raised. However, there was a significant difference in weight gain between the two groups of mice, and diet composition was not given, so the specificity of the findings is not clear.

There are numerous reports of reduced growth and metastasis of tumors, particularly of mammary gland and colon, in laboratory animals fed diets with increased ratios of n-3 to n-6 fatty acids; in most cases the effect was found during tumor promotion and progression.[156,161-63] These effects are, therefore, not evidence of a direct effect of fish oils upon chemical toxicity.

Obesity

Obesity, or the dietary patterns associated with it, can alter drug toxicity. There are clinical reports of increased toxicity of aminoglycoside antibiotics and of halogenated anesthetic gases in obese patients and reports that aminoglycoside toxicity is increased in obese patients even if blood levels are kept within the accepted range.[164] In an overfed, obese rat model, renal toxicity of furosemide and gentamycin was increased when doses were adjusted to produce blood levels of the drug comparable to levels in controls. If the adjustment was not made, and doses were given on the basis of body weight, toxicity was more markedly increased. The composition of the diets fed to obsese rats differed from the control diet, a factor that may have contributed to the apparent effect of obesity, but obese rats were fed the control diet for 1–2 weeks before drug exposure, a period sufficient to normalize urine pH and probably to normalize gentamycin excretion.[164] In studies of hepatic and renal toxicity of acetaminophen, in which lean and obese rats were fed the same diet but consumed different amounts of it, the metabolism and clearance of acetaminophen were similar in obese and nonobese rats, but toxicity was greater in obese rats.[164,165] Corcoran and Salazar[164] postulated that the kidney and the liver of obese rats may be more susceptible to injury than tissues of controls by unknown mechanisms not related to drug metabolism or excretion. The subject is interesting and clinically relevant and requires further investigation.

Summary

Nutrient and non-nutrient diet components influence the biological activity of many chemicals in different ways and by different mechanisms. The most intensive investigation has focused on interactions between diet and chemical carcinogenicity, and some general metabolic interactions have been elucidated that are applicable to groups of chemicals or diet components. Similar interactions are known for noncarcinogenic chemicals and for drugs. In most cases, however, present knowledge consists of observed phenomena without mechanisms or explanations. These cases present opportunities for research that will permit greater understanding and generalization of results.

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References

1 Rogers, A.E., and Longnecker, M.P. (1988). Dietary and nutritional influences on cancer: a review of epidemiologic and experimental data. *Lab. Invest.* **59**, 729–759

2 Wattenberg, L.W. (1990). Inhibition of carcinogenesis by naturally occurring and synthetic compounds. *In: Antimutagenesis Mechanisms II* (Y. Kuroda et al., eds), pp. 155–166, Plenum Publishing Corporation, NY

3 Poirier, L.A., Newberne, P.M., and Pariza, M.W. (eds) (1986). *Essential Nutrients in Carcinogenesis*, Plenum Press, NY

4 Jacobs, M. (ed) (1991). *Vitamins and Minerals in the Preven-*

tion and Treatment of Cancer. CRC Press, Boca Raton, FL
5 Roe, D.A. (1984). Nutrient and drug interactions. *Nutr. Rev.* **42,** 141–154
6 Meydani, M. (1987). Dietary effects on detoxification processes. *In: Nutritional Toxicology* (J.N. Hathcock, ed.), pp. 1–39, Academic Press, Inc., Orlando, FL
7 Belinsky, S.A., Kaufmann, F.C., and Thurman, R.G. (1987). Effect of nutrition on monooxygenation and conjugation in the liver. *In: Nutritional Toxicology* (J.N. Hathcock, ed.), pp. 41–61, Academic Press, Inc., Orlando, FL
8 Beutler, E. (1989). Nutritional and metabolic aspects of glutathione. *Annu. Rev. Nutr.* **9,** 287–302
9 Committee on Diet, Nutrition, and Cancer. (1982). *Diet, Nutrition, and Cancer*. National Academy Press, Washington, DC
10 Boone, C.W., Kelloff, G.J., and Malone, W.E. (1990). Identification of candidate cancer chemopreventive agents and their evaluation in animal models and human clinical trials: a review. *Cancer Res.* **50,** 2–9
11 Wise, A. (1982). Interaction of diet and toxicity. The future role of purified diet in toxicological research. *Arch. Toxicol.* **50,** 287–299
12 Knapka, J.J., Smith, K.P., and Judge, F.J. (1974). Effects of open and closed formula rations on the performance of three strains of laboratory mice. *Lab. Animal Sci.* **24,** 480–487
13 Bieri, J.G. (1980). Second report of the ad hoc committee on standards for nutritional studies. *J. Nutr.* **110,** 1726
14 Hamm, T.E., Jr. (1985). Design of a long-term animal bioassay for carcinogenicity. *In: Handbook of Carcinogen Testing*, (Milman, H.A. and Weisburger, E.K., ed), pp. 252–267, Noyes Publications, Park Ridge, NJ
15 Haseman, J.K., Huff, J.E., Rao, G.N., and Eustis, S.L. (1989). Sources of variability in rodent carcinogenicity studies. *Fundam. Appl. Toxicol.* **12,** 793–804
16 Hendrich, S. and Bjeldanes, L.F. (1986). Effects of dietary schizandra chinesis, Brussels sprouts and illicium verum extracts on carcinogen metabolism systems in mouse liver. *Food Chem. Toxicol.* **24,** 903–912
17 Suit, J.L., Rogers, A.E., Jetten, M.E.R., and Luria, S.E. (1977). Effects of diet on conversion of Aflatoxin B_1 to bacterial mutagen(s) by rats in vivo and by rat hepatic microsomes in vitro. *Mutation Res.* **46,** 313–323
18 Suit, J.L., Miranda-da Cruz, B.B., Sito, L., and Rogers, A.E. (1984). Enhancing activity of rat tissue extracts for induction of lambda prophage by l-azaserine. *Environ. Mutagenesis* **6,** 559–572
19 Engel, R.W. and Copeland, D.H. (1951). Protective action of stock diets against the cancer-inducing action of 2-acetylaminofluorine in rats. *Cancer Res.* **11,** 211–215
20 Russell, J.J., Staffeldt, E.F., Wright, B.J., Prapuolenis, A., Carnes, B.A., and Peraino, C. (1987). Effects of rat strain, diet composition, and phenobarbital on hepatic gamma-glutamyl transpeptidase histochemistry and on the induction of altered hepatocyte foci and hepatic tumors by diethylnitrosamine. *Cancer Res.* **47,** 1130–1134
21 Longnecker, D.S., Kuhlmann, E.T., Roebuck, B.D., and Curphey, T.J. (1987). Pancreatic carcinogenesis in azaserine-treated rats: inhibition by a solvent mixture in the diet. *Food Chem. Toxicol.* **25,** 823–828
22 Li, D. and Randerath, K. (1990). Association between diet and age-related DNA modifications (I-compounds) in rat liver and kidney. *Cancer Res.* **50,** 3991–3996
23 Randerath, K., Li, D., and Randerath, E. (1990). Age-related DNA modifications (I-compounds): modulation by physiological and pathological processes. *Mutation Res.* **238,** 245–253
24 Mylroie, A.A., Moore, L., Olyai, B., and Anderson, M. (1978). Increased susceptibility to lead toxicity in rats fed semipurified diets. *Environ. Res.* **15,** 57–64
25 Shively, C.A., White, D.M., and Tarka, Jr., S.M. (1986). Diet-induced alterations in theobromine disposition and toxicity in the rat. *Toxicol. Appl. Pharmacol.* **84,** 593–598
26 Garland, E.M., Sakata, T., Fisher, M.J., Masui, T., and Cohen, S.M. (1989). Influences of diet and strain on the proliferative effect on the rat urinary bladder induced by sodium saccharin. *Cancer Res.* **49,** 3789–3794
27 Fukushima S. (1991). Modification of tumor development in the urinary bladder. Modification of tumor development in rodents. *In: Progress in Experimental Tumor Research* (Ito, N., Sugano, H. eds.), 33:154–174, Karger, NY
28 Cohen, S.M., Ellewin, L.B., Okamura, T., Masui, T., Johansson, S.L., Smith, R.A., Wehner, J.M., Khachab, M., Chappel, C.I., Schoenig, G.P., Emerson, J.L., and Garland, E.M. (1991). Comparative bladder tumor promoting activity of sodium saccharin, sodium ascorbate, related acids, and calcium salts in rats. *Cancer Res.* **51,** 1766–1777
29 Okamura T., Garland, E.M., Masui, T., Sakata, T., St. John, M., and Cohen, S.M. (1991). Lack of bladder tumor promoting activity in rats fed sodium saccharin in AIN-76A diet. *Cancer Res.* **51,** 1778–1782
30 Vavrousek-Jakuba, E.M., Baker, R.A., and Shoemaker, W.J. (1991). Effect of ethanol on maternal and offspring characteristics: comparison of three liquid diet formulations fed during gestation. *Alcoholism* **15,** 129–135
31 Sankaran, H., Baba, G.C., Deveney, C.W., and Rao, G.A. (1991). Enteral macronutrients abolish high blood alcohol levels in chronic alcoholic rats. *Nutr. Res.* **11,** 217–222
32 Misslbeck, N.G., Campbell, T.C., and Roe, D.A. (1984). Effect of ethanol consumed in combination with high or low fat diets on the postinitiation phase of hepatocarcinogenesis in the rat. *J. Nutr.* **114,** 2311–2323
33 Rogers, A.E. and Conner, M.W. (1986). Alcohol and cancer. *In: Essential Nutrients in Carcinogenesis* (Poirier, L., Newberne, P.M., and Pariza, M.W., eds.), pp. 473–496, Plenum Press, NY
34 Rogers, A.E. and Conner, B.H. (1990). Dimethylbenzanthracene-induced mammary tumorigenesis in ethanol-fed rats. *Nutr. Res.* **10,** 915–928
35 Boyer, C.S and Petersen, D.R. (1990). Potentiation of cocaine-mediated hepatotoxicity by acute and chronic ethanol. *Alcoholism* **14,** 28–31
36 Guthrie, G.D., Myers, K.J., Gesser, E.J., White, G.W., and Koehl, J.R. (1990). Alcohol as a nutrient: interactions between ethanol and carbohydrate. *Alcoholism* **14,** 17–22
37 Lieber, C.S. (1988). Biochemical and molecular basis of alcohol-induced injury to liver and other tissues. *New Engl. J. Med.* **319,** 1639–1650
38 Okino, T., Nakajima, T., and Nakano, M. (1991). Morphological and biochemical analyses of trichloroethylene hepatotoxicity: differences in ethanol- and phenobarbital-pretreated rats. *Toxicol. Appl. Pharmacol.* **108,** 379–389
39 Toskulkao, C., Yoshida, T., Glinsukon, T., and Kuroiwa, Y. (1986). Potentiation of aflatoxin B_1 induced hepatotoxicity in male Wistar rats with ethanol pretreatment. *J. Toxicol. Sciences* **11,** 41–51
40 Toskulkao, C. and Glinsukon, T. (1988). Hepatic lipid peroxidation and intracellular calcium accumulation in ethanol potentiated aflatoxin B_1 toxicity. *J. Pharmacobio-Dyn.* **11,** 191–197
41 Toskulkao, C. and Glinsukon, T. (1990). Hepatic mitochondrial function and lysosomal enzyme activity in ethanol-potentiated aflatoxin B_1 hepatotoxicity. *Toxicol. Lett.* **52,** 179–190
42 Kershaw, W.C., Iga, T., and Klaassen, C. (1990). Ethanol decreased cadmium hepatotoxicity in rats: possible role of hepatic metallothionein induction. *Toxicol. Appl. Pharmacol.* **106,** 448–455
43 Sharma, G., Sandhir, R., Nath, R., and Gill, K. (1991). Effect of ethanol on cadmium uptake and metabolism of zinc and copper in rats exposed to cadmium. *J. Nutr.* **121,** 87–91
44 Lin, G.W.-J. (1991). Effect of dietary folic acid levels and gestational ethanol consumption on tissue folate contents and rat fetal development. *Nutr. Res.* **11,** 223–230.
45 Hutchings, D.E., Brake, S., Morgan, B., Lasalle, E., and Shi, T.H. (1987). Developmental toxicity of prenatal delta-9-tetrahydrocannabinol: Effects of maternal nutrition, offspring growth, and behavior. *NIDA Research Monograph* **76,** 363–369
46 Jover, R., Ponsoda, X., Jose Gomez-Lechon, M., Herrero, C., Del Pino, J., and Castell, J.V. (1991). Potentiation of

cocaine hepatotoxicity by ethanol in human hepatocytes. *Toxicol. App. Pharmacol.* **107,** 526–534
47 Farber, J.L. and Gerson, R.J. (1984). Mechanisms of cell injury with hepatotoxic chemicals. *Pharmacol. Rev.* **36,** 71A–74S
48 Reed, D.J. and Fariss, M.W. (1984). Glutathione depletion and susceptibility. *Pharmacol. Rev.* **36,** 25S–33S
49 Kensler, T.W., Egner, P.A., Dolan, P.M., Groopman, J.D., and Roebuck, B.D. (1987). Mechanism of protection against aflatoxin tumorigenicity in rats fed oltipraz and related 1,2-dithiol-3-thiones and1,2-dithiol-3-ones. *Cancer Res.* **47,** 4271–4277
50 Hayes, M.A., Murray, C.A., and Rushmore, T.H. (1986). Influences of glutathione status on different cytocidal responses and monolayer rat hepatocytes exposed to Aflatoxin B_1 or acetaminophen. *Toxicol. Appl. Pharmacol.* **85,** 1–10
51 Roebuck, B.D., Liu, Y.-L., Rogers, A.E., Groopman, J.D., and Kensler, T.W. (1991). Inhibition of Aflatoxin-induced liver cancer in the rat by oltipraz, 5-(2-pyrazinyl)-4-methyl-1, 2-dithiole-3-thione. *Cancer Res.*, in press.
52 Liu, Y.-L., Roebuck, B.D., Yager, J.D., Groopman, J.D., and Kensler, T.W. (1988). Protection by 5-(2-pyrazinyl)-4-methyl-1,2-dithiol-3-thione (Oltipraz) against the hepatotoxicity of Aflatoxin B_1 in the rat. *Toxicol. Appl. Pharmacol.* **93,** 442–451
53 Diplock, A.T. (1987). Metabolic defenses against oxygen and xenobiotic toxicity: biochemical interrelationships. *In: Selenium in Biology and Medicine* (Combs, G.F., Spallholz, J.E., Levander, O.A., and Oldfield, J.E., eds), Part A, pp. 90–103, AVI, Westport, CT
54 Pence, B.C. (1991). Dietary selenium and antitoxidant status: toxic effects of 1,2-dimethylhydrazine in rats. *J. Nutr.* **121,** 138–144
55 Siksay, D.L.A., Ozolins, T.R.S., and Wells, P.G. (1991). Modulation of murine phenytoin teratogenicity by dietary deprivation of selenium. *FASEB J.* A1570
56 Pence, B.C. and Buddingh, F. (1985). Effects of dietary selenium deficiency on incidence and size of 1,2-dimethylhydrazine-induced colon tumors in rats. *J. Nutr.* **115,** 1196–1202
57 Jacobs, M.M. (1983). Selenium inhibition of 1,2-dimethylhydrazine induced colon carcinogenesis, *Cancer Res.* **43,** 1646
58 Reddy, B.S., Sugie, S., Maruyama, H., and Marra, P. (1988). Effect of dietary excess of inorganic selenium during initiation and postinitiation phases of colon carcinogenesis in F344 rats. *Cancer Res.* **48,** 1777–1780
59 Newberne, P.M., Punyarit, P., de Camargo, J., and Suphakarn, V. (1987). The role of necrosis in hepatocellular proliferation and liver tumors. *Arch. Toxicol. Suppl.* **10,** 54–67
60 Milks, M.M., Wilt, S.R., Ali, I.I., and Couri, D. (1985). The effects of selenium on the emergence of Aflatoxin B_1-induced enzyme-altered foci in rat liver. *Fundamen. Appl. Toxicol.* **5,** 320–326
61 Nauss, K.M., Bueche, D., Soule, N., Fu, P., Yew, K., and Newberne, P.M. (1986). Effect of dietary selenium levels on methylbenzylnitrosamine-induced esophageal cancer in rats. *Cancer Lett.* **33,** 107–116
62 Kobayashi, M., Kogata, M., Yamamura, M., Takada, H., Hioki, K., and Yamamoto, M. (1986). Inhibitory effect of dietary selenium on carcinogenesis in rat glandular stomach induced by N-methyl-N-nitro-N-nitrosoguanidine. *Cancer Res.* **46,** 2266–2270
63 Ip, C. and Sinha, D.K. (1981). Enhancement of mammary tumorigenesis by dietary selenium deficiency in rats with a high polyunsaturated fat intake. *Cancer Res.* **41,** 31–34
64 Ip, C. (1985). Selenium inhibition of chemical carcinogenesis. *Fed. Proc.* **44,** 2573–2578
65 L'Abbe, M.R., Fischer, P.W.F., Campbell, J.S., and Chavez, E.R. (1989). Effects of dietary selenium on DMBA-induced carcinogenesis in rats fed a diet high in mixed fats. *J. Nutr.* **119,** 757–765
66 Ejadi, S., Bhattacharya, I.D., Voss, K., Singletary, K., and Milner, J.A. (1989). In vitro and in vivo effects of sodium selenite on 7,12-dimethylbenz[a]anthracene-DNA adduct formation in isolated rat mammary epithelial cells. *Carcinogenesis* **10,** 823–826
67 Roy, M., Kiremidjian-Schumacher, L., Wishe, H.I., Cohen, M.W., and Stotzk, G. (1990). Selenium and immune cell functions. II. Effect on lymphocyte-mediated cytotoxicity. *P.S.E.B.M.* **193,** 143–148
68 Ginter, E., Chorvatovicova, D., and Kosinova, A. (1989). Vitamin C lowers mutagenic and toxic effects of hexavalent chromium in guinea pigs. *Internat. J. Vit. Nutr. Res.* **59,** 161–166
69 Mirvish, S.S., Wallcave, L., Eagen, M., and Shubik, P. (1972). Ascorbate-nitrate reaction. Possible means of blocking the formation of carcinogenic N-nitroso compounds. *Science* **177,** 65–68
70 Helser, M.A., Hotchkiss, J.H., and Roe, D.A. (1991). Temporal influence of ascorbic acid dose on the endogenous formation of N-nitrosoproline and N-nitrosothiazolidine-4-carboxylic acid in humans. *J. Nutr. Biochem.* **2,** 268–273
71 Torosian, M.H., Buzby, G.P., Presti, M.E., Stein, T.P., Zinnser, K., and Mullen, J.L. (1982). Reduction of methotrexate toxicity with improved nutritional status. *Surg. Forum* **33,** 109
72 Dunki-Jacobs, P.B., Ruevekamp, M., Varossiau, F.J., Hart, G.A.M., and De Graaf, P.W. (1989). Alterations in serum levels, anti-tumor activity and toxicity of methotrexate in rats after a short period of nutritional depletion. *Eur. J. Cancer Clin. Oncol.* **25,** 415–22
73 Torosian, M.H., Jalali, S., and Nguyen, H.Q. (1990). Protein intake and 5-fluorouracil toxicity in tumor-bearing animals. *J. Surg. Res.* **49,** 298–301
74 Pomfret, E.A., da-Costa, K.A., and Zeisel, S.H. (1990). Effects of choline deficiency and methotrexate treatment upon rat liver. *J. Nutr. Biochem.* **1,** 533–541
75 Rogers, A.E., Akhtar, R., and Zeisel, S.H. (1990). Procarbazine carcinogenicity in methotrexate-treated or lipotrope-deficient male rats. *Carcinogenesis* **11,** 1491–1495
76 Rogers, A.E., Zeizel, S.H., and Akhtar, R. (1991). Choline, methionine, folate and carcinogenesis. *In: Vitamins and Minerals in the Prevention and Treatment of Cancer* (Jacobs, M., ed.), CRC Press, Boca Raton, FL
77 Pinto, J., Raiczyk, G.B., Huang, Y.P., and Rivlin, R.S. (1986). New approaches to the possible prevention of side effects of chemotherapy by nutrition. *Cancer* **58,** 1911–1914
78 Pinto, J.T., Delman, B.N., Dutta, P., and Nisselbaum, J. (1990). Adriamycin-induced increase in serum aldosterone levels: Effects in riboflavin-sufficient and riboflavin-deficient rats. *Endocrinology* **127,** 1495–1501
79 Dutta, P., Rivlin, R.S., and Pinto, J. (1990). Enhanced depletion of lens reduced glutathione by Adriamycin in riboflavin-deficient rats. *Biochem. Pharmacol.* **40,** 1111–1115
80 Swann, P.F. and McLean, A.E.M. (1971). Cellular injury and carcinogenesis: the effect of a protein-free high-carbohydrate diet on the metabolism of dimethylnitrosamine in the rat. *Biochem. J.* **124,** 283–288
81 Parkin, H.B.W.R. and Stoddart, D.J. (1977). The effect of a protein-free diet, a sugar diet and of carbon tetrachloride administration on the toxicity and rate of metabolism of dimethylnitrosamine in different rat stains. *Br. J. Exp. Path.* **58,** 225–229
82 Swann, P.F., Kauffman, D.G., Magee, P.N., and Mace, R. (1980). Induction of kidney tumours by a single dose of dimethylnitrosamine: dose-response and influence of diet and benzo(a)pyrene treatment. *Br. J. Cancer* **41,** 285–294
83 Fan, G.Y., Butler, W.H., and O'Connor, P.J. (1989). Cell and tissue specific localization of O^6-methylguanine in the DNA of rats given N-nitrosodimethylamine: effects of protein deficient and normal diets. *Carcinogenesis* **10,** 1967–1970
84 Kokkinakis, D.M. and Scarpelli, D.G. (1989). Carcinogenicity of N-nitroso (2-hydroxypropyl)(2-oxopropyl)amine, N-nitrosobis (2-hydroxypropyl)amine and *cis*-N-nitroso-2,6-dimethylmorpholine administered continuously in the Syrian hamster, and the effect of dietary protein on N-nitroso(2-

hydroxypropyl)(2-oxopropyl)amine carcinogenesis. *Carcinogenesis* **10,** 699–704

85 Mirmomeni, M.H., Suzangar, M., Wise, A., Messripour, M., and Emami, H. (1979). Biochemical studies during Aflatoxin B_1-induced liver damage in rats fed different levels of dietary protein. *Int. J. Cancer* **24,** 471–476

86 Dunaif, G.E. and Campbell, T.C. (1987). Dietary protein level and aflatoxin B_1-induced preneoplastic hepatic lesions in the rat. *J. Nutr.* **117,** 1298–1302

87 Singletary, K.W. and Milner, J.A. (1987). Influence of prior dietary protein intake on metabolism, DNA binding and adduct formation of 7,12-dimethylbenz[a]anthracene in isolated rat mammary epithelial cells. *J. Nutr.* **117,** 587–592

88 Singletary, K.W. and Milner, J.A. (1987). Prior dietary protein intake and DNA-binding 7,12-dimethylbenz[a]anthracene metabolites formed by isolated rat hepatocytes. *J. Natl. Cancer Inst.* **78,** 727–733

89 Waalkes, M.P., Kovatch, R., and Rehm, S. (1991). Effect of chronic dietary zinc deficiency on cadmium toxicity and carcinogenesis in the male Wistar [Hsd:(WI)BR]rat. *Toxicol. Appl. Pharmacol.* **108,** 448–456

90 Lee, D.Y., Brewer, G.J., and Wang, Y. (1989). Treatment of Wilson's disease with zinc. VII. Protection of the liver from copper toxicity by zinc-induced metallothionein in a rat model. *J. Lab. Clin. Med.* **114,** 639–46

91 Schrager, T.F., Busby, Jr., W.F., Goldman, M.E., and Newberne, P.M. (1986). Enhancement of methylbenzylnitrosamine-induced esophageal carcinogenesis in zinc-deficient rats: effects on incorporation of [^{3}H]thymidine into DNA of esophageal epithelium and liver. *Carcinogenesis* **7,** 1121–1126

92 Barch, D.H. and Fox, C.C. (1987). Dietary zinc deficiency increases the methylbenzylnitrosamine-induced formation of O^6-methylguanine in the esophageal DNA of the rat. *Carcinogenesis* **8,** 1461–1464

93 Seres, D.S., Bunk, M.J., Osborne, M.P., Rivlin, R.S., and Tiwari, R.K. (1991). Effects of marginal dietary zinc deficiency and vitamin E supplementation on hepatic adenine dinucleotide phosphoribosyl transferase activity in female Sprague-Dawley rats. *Nutr. Res.* **11,** 337–345

94 Komada, H., Kise, Y., Nakagawa, M., Yamamura, M., Hioki, K., and Yamamoto, M. (1990). Effect of dietary molybdenum on esophageal carcinogenesis in rats induced by N-methyl-N-benzylnitrosamine. *Cancer Res.* **50,** 2418–2422

95 Graf, E. and Eaton, J.W. (1985). Dietary suppression of colonic cancer: fiber or phytate? *Cancer* **56,** 717–718

96 Stevens, R.G., Beasley, R.P., and Blumberg, B.S. (1986). Iron-binding proteins and risk of cancer in Taiwan. *J. Natl. Cancer Inst.* **76,** 605–610

97 Stevens, R.G., Jones, D.Y., Micozzi, M.S., and Taylor, P.R. (1988). Body iron stores and the risk of cancer. *N. Engl. J. Med.* **319,** 1047–1052

98 Nelson, R.L., Yoo, S.J., Tanure, J.C., Andrianopoulos, G., and Misumi, A. (1989). The effect of iron on experimental colorectal carcinogenesis. *Anticancer Res.* **9,** 1477–1482

99 Selby, J.V. and Friedman, G.D. (1988). Epidemiologic evidence of an association between body iron stores and risk of cancer. *Int. J. Cancer* **41,** 677–682

100 Anonymous (1989). Iron nutriture and risk of cancer. *Nutr. Rev.* **47,** 176–178

101 Thompson, H.J., Kennedy, K., Witt, M., and Juzefyk, J. (1990). Effect of dietary iron deficiency or excess on the induction of mammary carcinogenesis by 1-methyl-1-nitrosourea. *Carcinogenesis* **12,** 26–29

102 Siegers, C.P., Bumann, D., Baretton, G., and Younes, M. (1988). Dietary iron enhances the tumor rate in dimethylhydrazine-induced colon carcinogenesis in mice. *Cancer Lett.* **41,** 251–256

103 Kasprzak, K.S., Hoover, K.L., and Poirier, L.A. (1985). Effects of dietary calcium acetate on lead subacetate carcinogenicity in kidneys of male Sprague-Dawley rats. *Carcinogenesis* **6,** 279–282

104 Anderson, K.E., Pantuck, E.J., Cooney, A.H., and Kappas, A. (1985). Nutrient regulation of chemical metabolism in humans. *Fed. Proc.* **44,** 130–133

105 Ito, Y., Ohnishi, S., and Fujie, K. (1989). Chromosome aberrations induced by aflatoxin B_1 in rat bone marrow cells in vivo and their suppression by green tea. *Mutation Res.* **222,** 253–261

106 Lam, L.K.T., Sparnins, V.L., and Wattenberg, L.W. (1982). Isolation and identification of kahweol palmitate and cafestol palmitate as active constituents in green coffee beans that enhance glutathione S-transferase activity in the mouse. *Cancer Res.* **42,** 1193–1198

107 Wattenberg, L.W. (1983). Inhibition of neoplasia by minor dietary consitiuents. *Cancer Res.* **43,** 2448s–53s

108 Miller, E.G., Formby, W.A., Rivera-Hidalgo, F., and Wright, J.M. (1988). Inhibition of hamster buccal pouch carcinogenesis by green coffee beans. *Oral Surg., Med., Pathol.* **65,** 745–749

109 Tanaka T., Iwata, H., Niwa, K., Mori, Y., and Mori, H. (1988). Inhibitory effect of ellagic acid on N-2-fluorenylacetamide-induced liver carcinogenesis in male ACI/N rats. *Jpn. J. Cancer Res. (Gann)* **79,** 1297–1303

110 Mandal, S. and Stoner, G.D. (1990). Inhibition of N-nitrosobenzylmethylamine-induced esophageal tumorigenesis in rats by ellagic acid. *Carcinogenesis* **11,** 55–61

111 Mandal, S., Shivapurkar, N.M., Galati, A.J., and Stoner, G.D. (1988). Inhibition of N-nitrosobenzylmethylamine metabolism and DNA binding in cultured rat esophagus by ellagic acid. *Carcinogenesis* **9,** 1313–1316

112 Mandal, S., Ahuja, A., Shivapurkar, N.M., Cheng, S.J., Groopman, J.D., and Stoner, G.D. (1987). Inhibition of aflatoxin B_1 mutagenesis in *Salmonella typhimurium* and DNA damage in cultured rat and human tracheobronchial tissues by ellagic acid. *Carcinogenesis* **8,** 1651–1656

113 Conney, A.H. (1982). Induction of microsomal enzymes by foreign chemical and carcinogenesis by polycyclic aromatic hydrocarbons: GHA Clowes memorial lecture. *Cancer Res.* **42,** 4875–4917

114 Barch, D.H. and Fox, C.C. (1988). Selective inhibition of methylbenzylnitrosamine-induced formation of esophageal O^6-methylguanine by dietary ellagic acid in rats. *Cancer Res.* **48,** 7088–7092

115 Barch, D.H. and Fox, C.C. (1989). Dietary ellagic acid reduces the esophageal microsomal metabolism of methylbenzylnitrosamine. *Cancer Lett.* **44,** 39–44

116 McDanell, R., McLean, A.E.M., Hanley, A.B., Heaney, R.K., and Fenwich, G.R. (1988). Chemical and biological properties of indole glucosinolates (glucobrassicins): a review. *Food Chem. Toxicol.* **26,** 59–70

117 Shertzer, H.G. (1983). Protection by indole-3-carbinol against covalent binding of benzo[a]pyrene metabolites to mouse DNA and protein. *Food Chem. Toxicol.* **21,** 31–35

118 Shertzer, H.G. (1984). Indole-3-carbinol protects against covalent binding of benzo[a]pyrene and N-nitrosodimethylamine metabolites to mouse liver macromolecules. *Chemico-Biol. Interactions* **48,** 81–90

119 Pence, B.C. Buddingh, F., and Yang, S.P. (1986). Multiple dietary factors in the enhancement of dimethylhydrazine carcinogenesis: main effect of indole-3-carbinol. *J. Natl. Cancer Inst.* **77,** 269–276

120 Birt, D.F., Pelling, J.C., Pour, P.M., Tibbels, M.G., Schweickert, L., and Bresnick, E. (1987). Enhanced pancreatic and skin tumorigenesis in cabbage-fed hamsters and mice. *Carcinogenesis* **8,** 913–917

121 Bailey, G.S., Hendricks, J.D., Shelton, D.W., Nixon, J.E., and Pawlowski, N.E. (1987). Enhancement of carcinogenesis by the natural anticarcinogen indole-3-carbinol. *J. Natl. Cancer Inst.* **78,** 931–934

122 Dashwood, R.H., Fong, A.T., Williams, D.E., Hendricks, J.D., and Bailey, G.S. (1991). Promotion of Aflatoxin B_1 carcinogenesis by the natural tumor modulator indole-3-carbinol: influence of dose, duration, and intermittent exposure on indole 3-carbinol promotional potency. *Cancer Res.* **51,** 2362–2365

123 Dashwood, R.H., Arbogast, D.N., Fong, A.T., Pereira, C.,

Hendricks, J.D., and Bailey, G.S. (1989). Quantitative interrelationships between Aflatoxin B_1 carcinogen dose, indole-3-carbinol anti-carcinogen dose, target organ DNA adduction and final tumor response. *Carcinogenesis* **10,** 175–181

124 Abou-Issa, H.M., Duruibe, V.A., Minton, J.P., Larroya, S., Dwivedi, C., and Webb, T.E. (1988). Putative metabolites derived from dietary combinations of calcium glucarate and N-(4-hydroxyphenyl) retinamide act synergistically to inhibit the induction of rat mammary tumors by 7,12-dimethylbenz[a]anthracene. *Proc. Natl. Acad. Sci.* (USA) **85,** 4181–4184

125 Dwivedi, C., Oredipe, O.A., Barth, R.F., Downie, A.A., and Webb, T.E. (1989). Effects of the experimental chemopreventative agent, glucarate, on intestinal carcinogenesis in rats. *Carcinogenesis* **10,** 1539–1541

126 Dwivedi, C., Heck, W.J., Downie, A.A., Larroya, S., and Webb, T.E. (1990). Effect of calcium glucarate on beta-glucuronidase activity and glucarate content of certain vegetables and fruits. *Biochem. Med. Metabol. Biol.* **43,** 83–92

127 Walaszek, Z., Hanausek, M., Sherman, U., and Adams, A.K. (1990). Antiproliferative effect of dietary glucarate on the Sprague-Dawley rat mammary gland. *Cancer Lett.* **49,** 51–57

128 Sparnins, V.L., Barany, G., and Wattenberg, L.W. (1988). Effects of organosulfur compounds from garlic and onions on benzo[a]pyrene-induced neoplasia and glutathione S-transferase activity in the mouse. *Carcinogenesis* **9,** 131–134

129 Wargovich, M.J. (1987). Diallyl sulfide, a flavor component of garlic (*Allium sativum*), inhibits dimethylhydrazine-induced colon cancer. *Carcinogenesis* **8,** 487–489

130 Wargovich, M.J., Woods, C., Eng, V.W.S., Stephens, C., and Gray, K. (1988). Chemoprevention of N-nitrosomethylbenzylamine-induced esophageal cancer in rats by the naturally occurring thioether, diallyl sulfide. *Cancer Res.* **48,** 6872–6875

131 Brady, J.F., Li, D., Ishizaki, H., and Yang, C.S. (1988). Effect of diallyl sulfide on rat liver microsomal nitrosamine metabolism and other monooxygenase activities. *Cancer Res.* **48,** 5937–5940

132 Brady, J.F., Wang, M.-H., Hong, J.-Y., Xiao, F., Li, Y., Yoo, J-S. H., Ning, S.M., Lee, M.-J., Fukuto, J.M., Gapac, J.M., and Yang, C.S. (1991). Modulation of rat hepatic microsomal monooxygenase enzymes and cytotoxicity by diallyl sulfide. *Toxicol. Appl. Pharmacol.* **108,** 342–354

133 Hong, J.Y., Smith, T., Lee, M.J., Li, W., Ma, B.L., Ning, S.M., Brady, J.F., Thomas, P.E., and Yang, C.S. (1991). Metabolism of carcinogenic nitrosamines by rat nasal mucosa and the effect of diallyl sulfide. *Cancer Res.* **51,** 1509–1514

134 Baer, A.R. and Wargovich, M.J. (1989). Role of ornithine decarboxylase in diallyl sulfide inhibition of colonic radiation injury in the mouse. *Cancer Res.* **49,** 5073–5076

135 Hayes, M.A., Rushmore, T.H., and Goldberg, M.T. (1987). Inhibition of hepatocarcinogenic responses to 1,2-dimethylhydrazine by diallyl sulfide, a component of garlic oil. *Carcinogenesis* **8,** 1155–1157

136 Tadi, P.P., Teel, R.W., and Lau, B.H.S. (1991). Organosulfur compounds of garlic modulate mutagenesis, metabolism, and DNA binding of aflatoxin B_1. *Nutr. Cancer* **15,** 87–95

137 Meng, C.L. and Shyu, K.W. (1990). Inhibition of experimental carcinogenesis by painting with garlic extract. *Nutr. Cancer* **14,** 207–217

138 Perchellet, J.P., Perchellet, E.M., and Belman, S. (1990). Inhibition of DMBA-induced mouse skin tumorigenesis by garlic oil and inhibition of two tumor-promotion stages by garlic and onion oil. *Nutr. Cancer* **14,** 183–193

139 Poirier, L. (1985). The role of methionine in carcinogenesis in vivo. *In: Essential Nutrients in Carcinogenesis* (Poirier, L., Newberne, P.M., and Pariza, M.W., eds), pp. 269–292, Plenum Press, NY

140 Newberne, P.M. and Rogers, A.E. (1990). Lipotropic factors and carcinogenesis. *In: Human Nutrition: Cancer and Nutrition* (Alfin-Slater, R., and Kritchevsky, D., eds.), pp. 159–185, Plenum Press, New York

141 Rogers, A.E. and Newberne, P.M. (1971). Lasiocarpine: factors influencing its toxicity and effects on liver cell division. *Toxicol. Appl. Pharmacol.* **18,** 356–366

142 Newberne, P.M., Wilson, R., and Rogers, A.E. (1971). Effects of a low-lipotrope diet on the response of young male rats to the pyrrolizidine alkaloid, monocrotaline. *Toxicol. Appl. Pharmacol.* **18,** 387–397

143 Wainfan, E., Dizik, M., Stender, M., and Christman, J.K. (1989). Rapid appearance of hypomethylated DNA in livers of rats fed cancer-promoting, methyl-deficient diets. *Cancer Res.* **49,** 4094–4097

144 Dizik, M., Christman, J.K., and Wainfan, E. (1991). Alterations in expression and methylation of specific genes in livers of rats fed a cancer promoting methyl-deficient diet. *Carcinogenesis* (in press)

145 Stramentinoli, G., Gualano, M., and Ideo, G. (1977). Protective role of S-adenosyl-L-methionine on liver injury induced by D-galactosamine in rats. *Biochem. Pharmacol.* **27,** 1431–1433

146 Stramentinoli, G., Pezzoli, C., and Galli-Kienle, M. (1979). Protective role of S-adenosyl-L-methionine against acetaminophen induced mortality and hepatotoxicity in mice. *Biochem. Pharmacol.* **28,** 3567–3571

147 Feo, F., Pascale, R., Garcea, L., Daino, L., Pirisi, S., Frassetto, M.E., Ruggiu, DiPadova, C., and Stramentinoli, G. (1986). Effect of the variations of S-adenosyl-L-methionine liver content on fat accumulation and ethanol metabolism in ethanol-intoxicated rats. *Toxicol. Appl. Pharmacol.* **83,** 331–341

148 Malarkey, D.E., Conner, B.H., Rogers, A.E., Conner, M.W., and Newberne, P.M. (1989). Reduction of anguidine toxicity in rats by atropine and methylatropine. *Toxicol. Appl. Pharmacol.* **97,** 512–524

149 Carr, B. (1987). Pleiotropic drug resistance in hepatocytes induced by carcinogens administered to rats. *Cancer Res.* **47,** 5577–5583

150 Barnard, F.G., Erickson, S.K., Nagata, Y., and Cooper, A.D. (1989). Reduced binding and removal of chylomicron remnants by ethionine-induced premalignant liver. *Hepatology* **9,** 731–739

151 Tiegs, G. and Wendel, A. (1988). Leukotriene-mediated liver injury. *Biochem. Pharmacol.* **37,** 2569–2573

152 Endres, S., Ghorbani, R., Kelley, V.E., Georgilis, K., Lonnemann, G., Van Der Meer, J.W.M., Cannon, J.G., Rogers, T.S., Klempner, M.S., Weber, P.C., Schaefer, E.J., Wolff, S.M., and Dinarello, C.A. (1989). The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N. Engl. J. Med.* **320,** 265–71

153 Nassar, B.A., Huang, Y.-S., and Horrobin, D.F. (1986). Response of tissue phospholipid fatty acid composition to dietary (n-6) and replacement with marine (n-3) and saturated fatty acids in the rat. *Nutr. Res.* **6,** 1397–1409

154 Abou El-Ela, S.H., Prasse, K.W., Carroll, R., and Bunce, O.R. (1987). Effects of dietary primrose oil on mammary tumorigenesis induced by 7,12-dimethylbenz(a)anthracene. *Lipids* **22,** 1041–1044

155 Zuniga, M.E., Lokesh, B.R., and Kinsella, J.E. (1989). Disparate effects of dietary fatty acids on activity of 5-nucleotidase of rat liver plasma membrane. *J. Nutr.* **119,** 152–160

156 Cameron, E., Bland, J., and Marcuson, R. (1989). Divergent effects of omega-6 and omega-3 fatty acids on mammary tumor development in C_3H/Heston mice treated with DMBA. *Nutr. Res.* **9,** 383–393

157 Fritsche, K.L. and Johnston, P.V. (1990). Effect of dietary alpha-linolenic acid on growth, metastasis, fatty acid profile and prostaglandin production of two murine mammary adenocarcinomas. *J. Nutr.* **120,** 1601–1609

158 Speck, R.F. and Lauterburg, B.H. (1991). Fish oil protects mice against acetaminophen hepatotoxicity in vivo. *Hepatology,* **13,** 557–561

159 Elzinga, L., Kelley, V.E., Houghton, D.C., and Bennett, W.M. (1987). Modification of experimental nephrotoxicity with fish oil as the vehicle of cyclosporine. *Transplantation* **43,** 27

160 Homan Van Der Heide, J.J., Bilo, H.J.G., Tegzess, A.M., and Donker, A.J.M. (1990). The effects of dietary supplementation with fish oil on renal function in cyclosporine-treated renal transplant recipients. *Transplantation* **49,** 523–527

161 Abou El-Ela, S.H., Prasse, K.W., Carroll, R., Wade, A.E., Dharwadkar, S., and Bruce, O.R. (1988). Eicosanoid synthesis in 7,12-dimethylbenz(a)anthracene-induced mammary carcinomas in Sprague-Dawley rats fed primrose oil, menhaden oil or corn oil diet. *Lipids* **23,** 948–954

162 Canizzo, F. and Broitman, S.A. (1989). Postpromotional effects of dietary marine or safflower oils on large bowel or pulmonary implants of CT-26 in Mice. *Cancer Res.* **49,** 4289–4294

163 Hirose, M., Masuda, A., Ito, N., Kamano, K., and Okuyama, H. (1990). Effects of dietary perilla oil, soybean oil and safflower oil on 7,12-dimethylbenz(a)anthracene (DMBA) and 1,2-dimethylhydrazine (DMH)-induced mammary gland and colon carcinogenesis in female SD rats. *Carcinogenesis* **11,** 731–735

164 Corcoran, G.B. and Salazar, D.E. (1989). Obesity as a risk factor in drug-induced organ injury. IV. Increased Gentamicin nephrotoxicity in the obese overfed rat. *J. Pharmacol Exp. Therapeutics* **248,** 17–22

165 Wong, B.K., Ernest, S.W., and Corcoran, G.B. (1986). An overfed rat model that reproduces acetaminophen disposition in obese humans. *Drug Metabol. Dispos.* **14,** 674–679