Chemical food contaminants in the initiation of cancer

BY ANTHONY R. TRICKER AND ROLF PREUSSMANN
Institute of Toxicology and Chemotherapy, German Cancer Research Center, Im Neuenheimer Feld 280, D–6900 Heidelberg, Federal Republic of Germany

It is generally accepted that cancer incidences in various organs show strong geographical variations. Studies on immigrants show that different cancer incidences in various global regions are heavily dependent on the life-style and that the human diet is considered to be an important cause of human cancer (Wynder & Gori, 1977; Doll & Peto, 1981). According to our opinion, there are four major groups of carcinogenic, initiating compounds which may occur as contaminants in the human diet:
(1) polycyclic aromatic hydrocarbons (PAH) which result from the incomplete combustion of fossil fuels,
(2) mycotoxins formed as metabolic products of mould-contaminated foods,
(3) heterocyclic amines (protein pyrolysis products) formed by Maillard-type reactions during high-temperature preparation of protein-rich foods,
(4) N-nitroso compounds which are formed by the interaction of amines and nitrosating agents such as nitrite or nitrous oxides (NO_x).
To this list, several naturally occurring carcinogenic compounds (estragol, cycasin, safrole), food additives (saccharin, antioxidants such as butylated hydroxyanisole (BHA)), transition and heavy metals (arsenic, chromium, nickel, mercury) and several synthetic compounds such as dioxines and polychlorinated biphenyls (PCB) have to be included as potential human carcinogens occurring in the human diet. The following paper presents a brief overview of the occurrence of the major classes of carcinogenic food contaminants in the human diet. Whenever possible, the current situation concerning the contamination of foods in the UK is reviewed.

PAH

Contamination of foods by PAH results primarily from atmospheric deposition onto edible plants, by air and also from smoke-drying of foodstuffs (including tea), direct drying of cereals, smoking and grilling of foodstuffs (bacon, cheese, fish etc.) and by marine pollution of shellfish (Obana *et al.*1981). Early studies on the PAH contamination of foodstuffs have tended to concentrate on samples from heavily polluted environments. Dietary surveys (Santodonato *et al.* 1981) incorporating a large number of samples collected from polluted environments provide in our opinion biased (overestimated) evaluations of the human exposure to PAH.

The dietary exposure to PAH in the UK has been estimated by Dennis *et al.* (1983) based on a total diet survey of total diet samples collected in five geographically diverse areas of the UK. The major dietary sources of PAH are summarized in Table 1. The major contributors of PAH in the UK diet are oils–fats and cereals. Although the highest individual PAH levels appear in oils–fats, their contribution to the total diet is relatively small (5%). PAH levels in cereal and plant-based foodstuffs show considerable variation, in general the PAH levels are higher in crops grown in heavily industrialized areas

Table 1. *Major sources of polycyclic aromatic hydrocarbons (PAH) in the UK diet**

PAH	Exposure (μg/d)	Major dietary source: range μg/kg (% contribution)			
		Cereals (16)	Oils–fats (5)	Vegetables (20)	Fruits–sugars (12)
Fluoranthene	0·99	0·93–2·89 (32)	0·37–2·41 (14)	0·11–2·90 (19)	0·37–1·67 (16)
Pyrene	1·09	1·42–3·44 (39)	0·45–4·04 (20)	ND–2·27 (16)	0·34–1·22 (13)
Benz[a]anthracene	0·22	0·18–0·92 (38)	0·08–2·05 (34)	0·01–0·31 (12)	0·04–0·17 (9)
Chrysene	0·50	ND–2·30 (36)	ND–4·18 (19)	ND–1·65 (29)	ND–1·29 (8)
Benzo[e]pyrene	0·17	0·17–0·29 (31)	ND–3·20 (53)	ND–0·40 (9)	ND–0·08 (3)
Benzo[b]fluoranthene	0·18	0·12–0·48 (30)	0·11–2·28 (42)	0·02–0·56 (15)	0·04–0·10 (6)
Benzo[k]fluoranthene	0·06	0·03–0·18 (29)	0·04–0·81 (41)	0·004–0·24 (19)	0·01–0·03 (5)
Benzo[a]pyrene	0·25	0·12–0·79 (30)	0·19–3·74 (50)	0·02–0·17 (8)	0·03–0·10 (5)
Benzo[*g,h,i*]*perylene*	0·21	0·17–0·46 (30)	0·21–2·50 (48)	0·03–0·18 (9)	0·03–0·08 (5)
Dibenz[a,h]anthracene	0·03	0·04–0·14 (56)	ND–0·23 (20)	ND–0·03 (10)	ND–0·03 (8)
Total exposure	3·70				

* Original data from Dennis *et al.* (1983).
ND, Not detected.

or close to major roads due to atmospheric deposition. In a review on PAH contamination of German foods, Fritz & Soos (1981) showed that vegetables and other plant-based foods were the major dietary source of PAH.

PAH represent the most important class of carcinogens present in smoked–grilled foods or foods exposed to drying gases or atmospheric deposition, aromatic ring systems of three or more rings being more potent carcinogens than smaller ring systems.

MYCOTOXINS

Mycotoxins are an important class of over 400 naturally occurring toxic compounds produced by fungi (moulds), of which only a small minority have been shown to be toxic to mammals. Mycotoxin contamination of foodstuffs is a major problem in most tropical and subtropical countries where fungal growth is favoured by bad agricultural practice, high humidity and bad storage conditions.

Aflatoxins, a group of furanocourmarin fungal metabolites produced by *Aspergillus flavus*, *A. parasiticus* and *Penicillium puberulum* remains the most serious world-wide mycotoxin problem. In experimental animals, aflatoxins are potent hepatic carcinogens in rats, weak carcinogens in monkeys and inactive in mice. Aflatoxin B_1 (AFB_1) is the most potent hepatocarcinogen known producing a 100% incidence of liver tumours in rats at a total dose of 95 μg/kg (Wogan & Newberne, 1967), indicating that levels of 10 μg/kg (10 ppb) in foods for human consumption may pose a considerable health risk. Aflatoxins AFB_1, AFB_2, AFG_1 and AFG_2 are natural contaminants of several foods including peanuts, various tree nuts, rice, cereal grains, cassava, soya beans, peas and sorghum seed. Aflatoxins AFM_1 and AFM_2 (hydroxylated metabolites of AFB_1 and AFB_2) have been found in liver, milk, blood and kidneys of animals given aflatoxin-contaminated feeds. The world-wide occurrence of mycotoxins in foods and animal feeds has recently been reviewed (Jelinek *et al.* 1989). Despite regulatory levels for aflatoxins in foods (total aflatoxins 5–20 μg/kg AFB_1, AFB_2, AFG_1 and AFG_2 in most countries; 10 μg/kg in the UK) and animal feeds (20–50 μg/kg), comparatively few developing countries have managed to control the contamination to acceptable levels in susceptible commodities.

The *Penicillium* mycotoxin ochratoxin A (also produced by *Aspergillus*) is a common contaminant of cereals and other plant products at levels exceeding 1000 μg/kg. The occurrence of ochratoxin A has been reviewed by Krogh (1980) who reported a mean level of 1035 μg/kg in cereals and meat products. Ochratoxin A is a fairly potent carcinogen in mice inducing hepatic and renal adenomas, concomitant AFB_1 exposure synergistically enhances ochratoxin A hepatocarcinogenesis (Kanisawa & Suzuki, 1978). Patulin (produced by several species of *Penicillium* and *Aspergillus*, and by *Byssochlamys nivea*) is still a major mycotoxin problem in some vegetables, fruits and fruit products, in particular apple juice; however, there is some doubt about the carcinogenic potential of this compound (International Agency for Research on Cancer, 1986).

Citrinin (produced by *P. citrinin* and *P. vividicatum*) is a common contaminant of cereal grains and grain products, it often occurs as a co-contaminant in grains containing ochratoxin A. It exhibits strong nephrotoxicity, as does ochratoxin A, and induces renal tumours in rats (Arai & Hibino, 1983). However, insufficient information is available to evaluate the human exposure to this compound.

In most developing countries, human exposure to mycotoxins still presents a serious

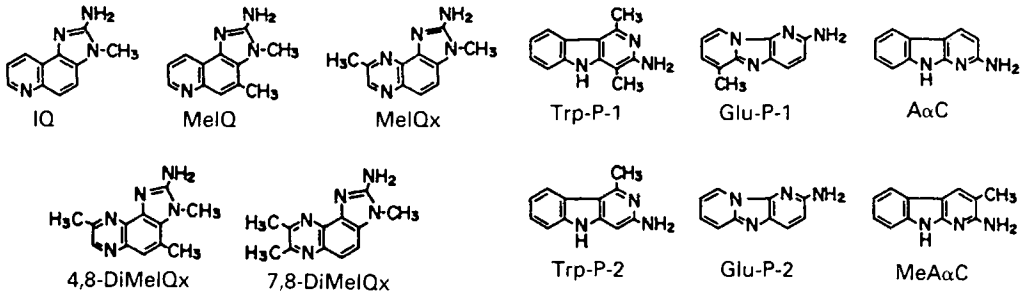

Fig. 1. Structures of some heterocyclic amines (protein pyrolysis products).

health problem as demonstrated by recent episodes of ergot alkaloid poisoning by *Claviceps purpurea* in Ethiopia (Demeke *et al.* 1979) and India (Krishnamachari & Bhat, 1977). A positive association between AFB_1 ingestion and incidence of primary hepatocellular cancer has been reported in several countries including China, Kenya, Mozambique, Swaziland and Thailand. However, this association may be confounded by the presence of hepatitis B infection (Lutwick, 1979). Acute toxic effects due to aflatoxin exposure (estimated to be 1–6 mg/d for several weeks) has been reported in Gujurat and Rajasthan in northwestern India (Van Rensburg, 1977) and possible ochratoxin exposure in cases of Reye's syndrome (endemic Balkan nephropathy) in Czechoslovakia (Dvorackova *et al.* 1977). There are circumstantial, but unconfirmed, reports that the occurrence of toxigenic strains of *Fusarium* and trichothecenes in maize (250–4000 μg 4-deoxynivalenol/kg and 1500–10 000 μg zearalenone/kg) may be aetiological risk factors for oesophageal cancer in the Transkei (Marasas *et al.* 1979). *Fusarium* production of T-2 toxin which induces cardiovascular lesions and various types of tumours in the digestive tract and brain of rats (Schoental, 1979) has been speculated as a causal agent for oesophageal cancer in China and South Africa (Stoloff, 1982).

Recent dietary surveys show that the dietary levels of ochratoxin A, 4-deoxynivalenol, sterimatocysin and patulin in the UK are currently negligible, while aflatoxin levels in most susceptible products (with the exception of some peanut products) are generally within the regulatory limits, AFM_1 levels in milk and dairy products are $<0{\cdot}1$ μg/kg (Ministry of Agriculture, Fisheries and Food, 1987).

HETEROCYCLIC AMINES (PROTEIN PYROLYSIS PRODUCTS)

Heterocyclic amines (Fig. 1) constitute an important class of mutagenic and carcinogenic compounds (Table 2) found in cooked and charred foods. The total daily per capita consumption has been estimated to be as high as 100 μg (Sugimura, 1985). The specific mutagenic activities of some heterocyclic amine mutagens formed by Maillard-type reactions during high temperature food preparation (in excess of 300°) are considerably higher than those for other carcinogenic food contaminants such as PAH, mycotoxins and N-nitroso compounds when tested under the same conditions using TA98 in the Ames *Salmonella* test.

Under normal cooking conditions, the development of an increased mutagenic

Table 2. *Heterocyclic amines isolated from cooked foods: mutagenicity and carcinogenicity*

Chemical name	Abbreviation	Mutagenicity		Carcinogenicity in rodents	
		TA98	TA100	Mouse	Rat
2-Amino-3-methylimidaz[4,5-f]quinoline	IQ	443 000	7000	Liver, forestomach, lung	Liver, intestine, Zymbal gland, clitoral gland, skin
2-Amino-3,4-dimethylimidaz[4,5-f]quinoline	MeIQ	661 000	30 000	Liver, forestomach	Zymbal gland, oral cavity, large intestine, skin, mammary gland
2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline	MeIQx	145 000	14 000	Liver, lung, lymphoma	Liver, Zymbal gland, skin, clitoral gland
2-Amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline	4,8-diMeIQx	183 000	8000	Not tested	Not tested
2-Amino-3,7,8-trimethylimidazo[4,5-f]quinoxaline	7,8-diMeIQx	163 000	9900	Not tested	Not tested
3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole	Trp-P-1	39 000	1700	Liver	Liver
3-Amino-1-methyl-5H-pyrido[4,3-b]indole	Trp-P-2	104 200	1800	Liver	Liver
2-Amino-6-methyldipyrido[1,2-a:3′,2′-d]imidazole	Glu-P-1	49 000	3200	Liver, blood vessel	Liver, intestine, Zymbal gland, clitoral gland
2-Aminodipyrido[1,2-a:3′,2′-d]imidazole	Glu-P-2	1900	1200	Liver, blood vessel	Liver, intestine, Zymbal gland, clitoral gland
2-Amino-9H-pyrido[2,3-b]indole	AαC	300	20	Liver, blood vessel	Not tested
2-Amino-3-methyl-9H-pyrido[2,3-b]indole	MeAαC	200	120	Liver, blood vessel	Not tested

* Data obtained from various sources.

Table 3. *Occurrence of heterocyclic amines* in foods (μg/kg)†*

Foodstuff	AαC	MeAαC	Glu-P-1	Glu-P-2	IQ	MeIQ	MeIQx	Trp-P-1	Trp-P-2
Broiled or fried beef§	651	63·5	—	—	<20·1	1–2·4	1·5	53‡	1·6
Hamburger	—	—	—	—	0·02	<1·0	—	—	—
Beef extract‖	—	—	—	—	<0·2	<0·2	<69	—	3·2
Worcestershire sauce	—	—	0·1	0·3	—	—	—	—	—
Grilled–broiled chicken	180	15·1	—	—	—	—	2·1	—	—
Broiled sun-dried sardine¶	—	—	—	—	158	72	—	13·3	13·1
Smoked, dried bonito (fish)	—	—	—	—	—	—	2–3	—	—
Smoked, dried mackerel	—	—	—	—	—	—	0·8	—	—
Fried Walleye pollack (fish)**	—	—	—	—	0·16	0·03	6·4	—	—
Broiled salmon	—	—	—	—	<0·4	<0·9	—	—	—
Broiled sun-dried cuttlefish	—	—	—	280	—	—	—	—	—
Grilled Chinese mushrooms	47·2	5·4	—	—	—	—	—	—	—
Grilled onion	1·5	—	—	—	—	—	—	—	—

* See Table 2 for full chemical names.
† Data obtained from several sources.
‡ Expressed on dry weight basis.
§ Also contains 0·5 μg/kg DiMeIQx and 15 μg/kg PhIP.
‖ Also contains <0·3 μg/kg 4,8- and 7,8-DiMeIQx.
¶ Also contains up to 9 μg/kg Phe-P-1.
** Also contains 0·1 μg/kg 4,8-DiMeIQx and 69·2 μg/kg PhIP.

response indicating the formation of mutagens on cooking is largely restricted to protein-rich foods with low carbohydrate and lipid content (Hargraves & Pariza, 1984). Examples of such foods include baked meat loaf, fried beef, pork and fish, broiled extracts of pork and beef, and broiled fish. Subsequent investigations have shown that these foods are the major dietary sources of heterocyclic amines as summarized in Table 3.

Several carcinogenic heterocyclic amines including Trp-P-1 and Trp-P-2 (Manabe *et al.* 1987), MeIQx (Yanagisawa *et al.* 1986) and IQ-type amines have been detected in dialysis fluids, and the accumulation of Glu-P-1 and Glu-P-2 in plasma of patients with uraemia (Manabe *et al.* 1987) has been reported. The biological monitoring of Trp-P-1 and Trp-P-2 in human plasma (Manabe & Wada, 1988), and MeIQx in human urine (Murray *et al.* 1989) show that humans are widely exposed to measurable quantities of these compounds. The fact that microsomal fractions of human liver can convert both MeIQx (Murray *et al.* 1988) and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) (McManus *et al.* 1989) to potent mutagens in the Ames *Salmonella* test, and the fact that N-acetylated metabolic products of Glu-P-1 and Glu-P-2 have been found in human urine, bile, liver and kidney (Kanai *et al.* 1988) indicate that these compounds may be suspect human carcinogens. However, until more information is obtained about the carcinogenicity of these compounds in dose–response studies, including low exposures, and in animal species other than rats and mice, in which their potency is only

Table 4. *Dietary surveys and daily N-nitrosodimethylamine (NDMA) intake*

Country	NDMA intake (μg/d)	Major NDMA source	Reference
UK	0·53*	Cured meats (81%)	Gough *et al.* (1978)
Holland	0·38	Beer (71%)	Stephany & Schuller (1980)
W. Germany (1979–80)	1·02 (men) 0·57 (women)	Beer (65%) Cured meats (10%)	Spiegelhalder *et al.* (1980)
W. Germany (1981)	0·53 (men) 0·35 (women)	Beer (40%) Cured meats (18%)	Spiegelhalder (1983)
Japan	1·8	Dried fish (91%)	Maki *et al.* (1980)
Japan	0·5	Fish products (88%)	Yamamoto *et al.* (1984)
Sweden	0·29	Meat products (61%) Beer (30%)	Österdahl (1988)
China	No values	Marine foods	Song & Hu (1988)
Italy	No values	Cured meats	Gavinelli *et al.* (1988)

* Beer not included in the survey.

moderate, and more comprehensive information on their occurrence in foods is available, the potential human cancer risk presented by these compounds will be hard to evaluate.

N-NITROSAMINES

The occurrence of N-nitroso compounds in foodstuffs probably represents the most comprehensively researched exposure situation for any class of genotoxic carcinogenic compounds in the human diet, and has been a subject of recent reviews (Forman, 1987; Tricker & Preussmann, 1988). The carcinogenic effects of these compounds in experimental animals (Preussmann & Stewart, 1984) and their relevance to human cancer (Bartsch & Montesano, 1984) have also been extensively reviewed.

The dietary exposure to N-nitrosodimethylamine (NDMA) and other volatile N-nitrosamines has been calculated in a number of food surveys (Table 4). The major food items most frequently found to contain N-nitroso compounds are cured meats (especially bacon after frying), beer and salt-dried-smoked fish. In cured meats and beer, reductions in the use of nitrates used during curing and modification of malting techniques have resulted in significant reductions in the levels of N-nitroso compounds over the last 5 years. In West Germany, the daily NDMA exposure from beer of 0·74 μg/d in 1979–80 (Spiegelhalder *et al.* 1980) has been reduced to 0·1 μg/day in 1987 (Frommberger, 1989). Thus, the current NDMA exposure levels are probably lower than the values quoted in Table 4.

Volatile N-nitroso compounds represent only a small proportion of the total N-nitroso compound burden. In cured bacon, volatile and non-volatile N-nitroso compounds (Tricker *et al.* 1984) constitute about 0·45% (0·06–1·08%) and 2·74% (0–6·86%) of the total N-nitroso compounds present respectively (Massey *et al.* 1988). At least 80% of the N-nitroso compounds found in cured meats are protein-bound (Tricker *et al.* 1985), the majority of which appear to be in the form of N-nitrosoproline (Sen *et al.* 1987). Due to the lack of suitable analytical methods, the exposure to the majority of non-volatile N-nitroso compounds cannot currently be evaluated. However, most non-volatile

Table 5. *Environmental levels and exposure to carcinogenic metals in the UK**

Metal	Environmental level			Adult exposure (μg/d)†	
	Air (ng/m³)	Water (μg/l)	Total diet (μg/kg)	Inhalation	Total ingestion diet + water
Arsenic‡	20·0	1·2	110·0	0·04	130·0
Chromium‡	7·0	0·2	50·0	0·14	60·0
Nickel‡	20·0	8·0	130·0	0·4	170·0
Cadmium	30·0	—	25·0	0·6	30·0
Lead	2000·0	10·0	90·0	40·0	180·0§
Mercury	7·0	—	4·0	0·14	15·0
Selenium	3·0	0·2	60·0	0·06	70·0
Tin	30·0	0·04	200·0	0·6	200·0
Zinc	300·0	40·0	10 000·0	6·0	10 000·0

* Modified data from Bennett (1986).

† Based on consumption of 1200 g food/d and 1·2 l water/d.

‡ Metals for which sufficient evidence is available to show that either the metal or some of its compounds are carcinogenic to man (Sunderman, 1986).

§ Includes 60 μg/d from surface contamination of food.

N-nitrosamines found in foods such as N-nitrosoproline and other N-nitrosated amino acids are non-carcinogenic. N-nitrososarcosine is an exception which is an oesophageal carcinogen of moderate potency in rats.

METAL RESIDUES

Exposure to carcinogenic metals by chronic exposure of low-level metal contaminants, residues or additives in food and water is summarized in Table 5 (Bennett, 1986). Drinking water is usually a secondary source of metal exposure, except in areas where drinking water is collected from mineralized areas or is contaminated by industrial or mining effluent and agricultural residues. Lead contamination is elevated when Pb piping is used for soft water. Certain foodstuffs show elevated concentrations of particular metals such as mercury accumulation in fish and cadmium in offals and shell fish. Metal accumulation on dust and dirt by atmospheric deposition may provide an important exposure source for Pb, particularly for children eating uncleaned foodstuffs.

There is sufficient epidemiological evidence to show that inorganic and organic arsenic compounds, chromates and certain nickel compounds are carcinogenic to man, and that beryllium and certain organic and inorganic Pb compounds may be carcinogenic (Sunderman, 1986). The determination of total dietary metal exposure (Table 5) provides a rather misleading evaluation since the total metal content is determined regardless of the oxidation state (free metal, organic or inorganic compounds, or both). In most cases, metal compounds of known carcinogenic potential in animal experiments are not expected to be present in foods (i.e. Ni carbonyls and chromate salts).

FOOD ADDITIVES

The use of nitrates (and nitrites) as food additives during meat curing and cheese fermentation is often falsely claimed to represent a carcinogenic risk. Ingested nitrate

per se is not carcinogenic; however, it acts as a precursor to nitrite (via in vivo bacterial reduction) which reacts either directly or indirectly (again via bacteria) to produce genotoxic carcinogenic N-nitroso compounds. As a result, nitrate should be regarded as an 'indirect risk' factor and N-nitroso compounds as a 'direct risk' factor in human carcinogenesis (Preussmann & Tricker, 1988).

The previously reported carcinogenic potential of saccharin has also been subject to sufficient doubt that it has recently been re-released as an artificial sweetener in the United States.

SYNTHETIC CHEMICALS

Several synthetic chemicals of known carcinogenic potential occur in a limited range of foodstuffs. In the majority of cases, it is impossible to calculate human exposure and to generalize on susceptible food products. In the case of PCB, analytical studies confirm that most adults carry significant body burdens of PCB in their adipose tissues (0·1–1·0 mg/kg) indicating an earlier widespread environmental exposure to PCB. Current trends show that the contamination of foodstuffs with PCB is minimal, only fresh water fish from aquatic environments with high levels of PCB providing a significant human dietary source of PCB. In animal studies, PCB can act as carcinogens *per se* as well as modulators of carcinogenesis by PAH, aflatoxin B_1 and N-nitroso compounds. PCB are probably more likely to be promoters rather than genotoxic initiators of carcinogenesis. This is probably also the case for other polychlorinated industrial chemicals.

Agricultural chemical residues, in particular DDT and chlorinated pesticides, dieldrin, daminozide and several plant fungicides (captan and ethylene thiourea) are still causes for concern in several fruit and vegetable products.

The migration of plasticizers di-2-ethylhexylphthalate (DEHP) and di-2-ethyl-hexyladipate (DEHA) from food contact materials (PVC wrappings etc.) into food products results in an average daily exposure of about 1600 μg DEHA/d and 20 μg DEHP/d. As both these compounds only show (probably non-genotoxic) carcinogenicity at very high doses, the human risk from the levels found in foods appears negligible.

The light-dependent formation of ethylcarbamate (urethane) in some stone fruit brandies (<9000 μg/l) is still a cause for concern in a limited range of products. In other alcoholic beverages and fermented foods (bread, yoghurt and cheese), urethane concentrations are low to non-detectable (Dennis *et al.* 1989). Urethane is a proven carcinogen in several animal species (Schmähl *et al.* 1977).

CONCLUSIONS

The contamination of foods by both genotoxic and non-genotoxic carcinogens is a cause for concern, and further attempts to reduce human exposure are warranted. However, the concentrations of known *initiating* carcinogens in foods are usually low, to very low, and we, therefore, do not support the postulated theory that 30% of human cancers are caused by the low human exposure to these compounds in the diet.

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