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Dietary pesticides (99.99% all natural)*

(carcinogens/mutagens/clastogens/coffee)

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ABSTRACT **The toxicological significance of exposures to synthetic chemicals is examined in the context of exposures to naturally occurring chemicals. We calculate that 99.99% (by weight) of the pesticides in the American diet are chemicals that plants produce to defend themselves. Only 52 natural pesticides have been tested in high-dose animal cancer tests, and about half (27) are rodent carcinogens; these 27 are shown to be present in many common foods. We conclude that natural and synthetic chemicals are equally likely to be positive in animal cancer tests. We also conclude that at the low doses of most human exposures the comparative hazards of synthetic pesticide residues are insignificant.**

Toxicological examination of synthetic chemicals such as pesticides and industrial pollutants, without similar examination of the chemicals in the natural world to use for comparison, has generated an imbalance in both data and perception about potential hazards to humans (1–6). In this and two accompanying papers (7, 8), we try to redress this imbalance and discuss in detail one major group of natural chemicals in our diet—nature's pesticides.

About half of all chemicals (whether natural or synthetic) tested chronically in animal cancer tests at the maximum tolerated dose (MTD) are carcinogens (7, 9–14).¶ The MTD of the test chemical is a near-toxic dose that can cause chronic mitogenesis, often as a result of cell killing (7). We have argued that mitogenesis increases mutagenesis, and therefore that a high percentage of all chemicals might be expected to be carcinogenic when tested chronically at the MTD (7). A high proportion of both natural and synthetic test chemicals are positive for carcinogenicity. Natural chemicals constitute the vast bulk of chemicals in the human diet and therefore should be used as a reference for evaluating possible carcinogenic hazards from synthetic chemicals. In recent years, we have compared the possible hazards of various rodent carcinogens, using the human exposure/rodent potency (HERP) ratio (1, 6). It should be emphasized that as the understanding of carcinogenesis mechanisms improves, these comparisons can be refined but they cannot provide a direct estimate of human hazard. This paper does not extend the HERP comparisons (1) because our purpose is different and space does not allow a proper analysis.

Nature's Pesticides: Mutagenicity and Carcinogenicity

> Plants are not just food for animals. . . . The world is not green. It is colored lectin, tannin, cyanide, caffeine, aflatoxin, and canavanine [Janzen (16)].

Dietary Pesticides Are 99.99% All Natural. Nature's pesticides are one important subset of natural chemicals. Plants produce toxins to protect themselves against fungi, insects, and animal predators (5, 16–23). Tens of thousands of these natural pesticides have been discovered, and every species of plant analyzed contains its own set of perhaps a few dozen toxins. When plants are stressed or damaged, such as during a pest attack, they may greatly increase their natural pesticide levels, occasionally to levels that can be acutely toxic to humans. We estimate that Americans eat about 1.5 g of natural pesticides per person per day, which is about 10,000 times more than they eat of synthetic pesticide residues (see below). As referenced in this paper (see refs. 16–21 and legends to Tables 1 and 2), there is a very large literature on natural toxins in plants and their role in plant defenses. The human intake of these toxins varies markedly with diet and would be higher in vegetarians. Our estimate of 1.5 g of natural pesticides per person per day is based on the content of toxins in the major plant foods (e.g., 13 g of roasted coffee per person per day contains about 765 mg of chlorogenic acid, neochlorogenic acid, caffeic acid, and caffeine; see refs. 22 and 23 and Table 2). Phenolics from other plants are estimated to contribute another several hundred milligrams of toxins. Flavonoids and glucosinolates account for several hundred milligrams; potato and tomato toxins may contribute another hundred, and saponins from legumes another hundred. Grains such as white flour and white rice contribute very little, but whole wheat, brown rice, and corn (maize) may contribute several hundred milligrams more. The percentage of a plant's weight that is toxin varies, but a few percent of dry weight is a reasonable estimate: e.g., 1.5% of alfalfa sprouts is canavanine and 4% of coffee beans is phenolics. However, the percentage in some plant cultivars is lower (e.g., potatoes and tomatoes).

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Abbreviation: MTD, maximum tolerated dose.

*This is paper no. 2 of a series. Paper no. 1 is ref. 7.

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¶References to, and analyses of, individual cancer tests are in the Carcinogenic Potency Database papers (10–13). Our analyses are based on this database, which reports only results of chronic, long-term bioassays that are adequate to detect a carcinogenic effect or lack of effect and to estimate potency. More than 4000 experiments met the inclusion criteria of the database, but thousands of others did not: e.g., tests that lack a control group, that are too short or include too few animals to detect an effect, that use routes of administration not likely to result in whole body exposure (like skin painting or subcutaneous administration), cocarcinogenesis studies, and bioassays of particulate or fibrous matters.

One-third of the chemicals in the database have been tested by the National Cancer Institute/National Toxicology Program, using standard protocols with tests in two species at the MTD (15). About half of the chemicals in the database, however, have been tested in only one species. Positivity rates and prediction between species have been analyzed (9).

We classify the results of an experiment as either positive or negative on the basis of the authors' opinion in the published paper and classify a chemical as positive if it has been evaluated as positive by the author of at least one experiment. We use the author's opinion to determine positivity because it often takes into account more information than statistical significance alone, such as historical control rates for particular sites, survival and latency, and/or dose response. Generally, this designation by author's opinion corresponds well with the results of statistical reanalyses of the significance of the dose–response effect (9).

Table 1. Forty-nine natural pesticides and metabolites found in cabbage

Glucosinolates:	2-propenyl glucosinolate (sinigrin),* 3-methylthiopropyl glucosinolate, 3-methylsulfinylpropyl glucosinolate, 3-butenyl glucosinolate, 2-hydroxy-3-butenyl glucosinolate, 4-methylthiobutyl glucosinolate, 4-methylsulfinylbutyl glucosinolate, 4-methylsulfonylbutyl glucosinolate, benzyl glucosinolate, 2-phenylethyl glucosinolate, propyl glucosinolate, butyl glucosinolate
Indole glucosinolates and related indoles:	3-indolylmethyl glucosinolate (glucobrassicin), 1-methoxy-3-indolylmethyl glucosinolate (neoglucobrassicin), indole-3-carbinol,* indole-3-acetonitrile, bis(3-indolyl)methane
Isothiocyanates and goitrin:	allyl isothiocyanate,* 3-methylthiopropyl isothiocyanate, 3-methylsulfinylpropyl isothiocyanate, 3-butenyl isothiocyanate, 5-vinyloxazolidine-2-thione (goitrin), 4-methylthiobutyl isothiocyanate, 4-methylsulfinylbutyl isothiocyanate, 4-methylsulfonylbutyl isothiocyanate, 4-pentenyl isothiocyanate, benzyl isothiocyanate, phenylethyl isothiocyanate
Cyanides:	1-cyano-2,3-epithiopropane, 1-cyano-3,4-epithiobutane, 1-cyano-3,4-epithiopentane, *threo*-1-cyano-2-hydroxy-3,4-epithiobutane, *erythro*-1-cyano-2-hydroxy-3,4-epithiobutane, 2-phenylpropionitrile, allyl cyanide,* 1-cyano-2-hydroxy-3-butene, 1-cyano-3-methylsulfinylpropane, 1-cyano-4-methylsulfinylbutane
Terpenes:	menthol, neomenthol, isomenthol, carvone*
Phenols:	2-methoxyphenol, 3-caffoylquinic acid (chlorogenic acid),* 4-caffoylquinic acid,* 5-caffoylquinic acid (neochlorogenic acid),* 4-(*p*-coumaroyl)quinic acid, 5-(*p*-coumaroyl)quinic acid, 5-feruloylquinic acid

*Discussed below; all others untested. *Clastogenicity*. Chlorogenic acid (25) and allyl isothiocyanate are positive (26). Chlorogenic acid and its metabolite caffeic acid are also mutagens (27–29), as is allyl isothiocyanate (30). *Carcinogenicity*. Allyl isothiocyanate induced papillomas of the bladder in male rats (a neoplasm that is unusually rare in control rats) and was classified by the National Toxicology Program as carcinogenic. There was no evidence of carcinogenicity in mice; however, it was stated "the mice probably did not receive the MTD" (31, 32). Sinigrin (allyl glucosinolate, i.e., thioglycoside of allyl isothiocyanate) is cocarcinogenic for the rat pancreas (33). Carvone is negative in mice (34). Indole-3-acetonitrile has been shown to form a carcinogen, nitroso indole acetonitrile, in the presence of nitrite (35). Caffeic acid is a carcinogen (36, 37) and clastogen (25) and is a metabolite of its esters 3-, 4-, and 5-caffoylquinic acid (chlorogenic and neochlorogenic acid). *Metabolites*. Sinigrin gives rise to allyl isothiocyanate when raw cabbage (e.g., coleslaw) is eaten; in cooked cabbage it also is metabolized to allyl cyanide, which is untested. Indole-3-carbinol forms dimers and trimers on ingestion, which mimic dioxin (8). *Occurrence*. See refs. 18, 21, and 38–40. *Toxicology*. The mitogenic effects of goitrin (which is goitrogenic) and various organic cyanides from cabbage suggest that they may be potential carcinogens (41, 42). Aromatic cyanides related to those from cabbage have been shown to be mutagens and are metabolized to hydrogen cyanide and potentially mutagenic aldehydes (43).

Concentrations of natural pesticides in plants are usually measured in parts per thousand or million (16–23) rather than parts per billion, the usual concentration of synthetic pesticide residues or of water pollutants (1, 24). We estimate that humans ingest roughly 5000 to 10,000 different natural pesticides and their breakdown products (16–23). For example, Table 1 shows 49 natural pesticides (and metabolites) that are ingested when cabbage is eaten, and indicates how few have been tested for carcinogenicity or clastogenicity. Lima beans contain a completely different array of 23 natural toxins that, in stressed plants, range in concentration from 0.2 to 33 parts per thousand fresh weight; none appears to have been tested yet for carcinogenicity or teratogenicity (19). Many Leguminosae contain canavanine, a toxin arginine analog that, after being eaten by animals, is incorporated into protein in place of arginine. Feeding alfalfa sprouts (1.5% canavanine dry weight) or canavanine to monkeys causes a lupus erythematosus-like syndrome (44). Lupus in humans is characterized by a defect in the immune system that is associated with autoimmunity, anti-nuclear antibodies, chromosome breaks, and various types of pathology. The toxicity of nonfood plants is well known: plants are among the most commonly ingested poisonous substances for children under 5 years.

Surprisingly few plant toxins have been tested for carcinogenicity (10–13, 45). Among 1052 chemicals tested in at least one species in chronic cancer tests, only 52 are naturally occurring plant pesticides (10–13). Among these, about half (27/52) are carcinogenic.‖ Even though only a tiny proportion of the plant toxins in our diet have been tested so far, the 27 natural pesticides that are rodent carcinogens are present in the following foods: anise, apple, apricot, banana, basil, broccoli, brussels sprouts, cabbage, cantaloupe, caraway, carrot, cauliflower, celery, cherries, cinnamon, cloves, cocoa, coffee, collard greens, comfrey herb tea, currants, dill, eggplant, endive, fennel, grapefruit juice, grapes, guava, honey, honeydew melon, horseradish, kale, lentils, lettuce, mango, mushrooms, mustard, nutmeg, orange juice, parsley, parsnip, peach, pear, peas, black pepper, pineapple, plum, potato, radish, raspberries, rosemary, sesame seeds, tarragon, tea, tomato, and turnip. Thus, it is probable that almost every fruit and vegetable in the supermarket contains natural plant pesticides that are rodent carcinogens. The levels of these 27 rodent carcinogens in the above plants are commonly thousands of times higher than the levels of synthetic pesticides. Table 2 shows a variety of natural pesticides that are rodent carcinogens occurring in the parts-per-million range in plant foods.

The catechol-type phenolics, such as tannins, and caffeic acid and its esters (chlorogenic and neochlorogenic acids), are more widespread in plant species than other natural pesticides (e.g., Tables 1 and 2). It may be that these phenolics have an antimicrobial role analogous to the respiratory burst of oxygen radicals from mammalian phagocytic

‖The list of 52 natural plant pesticides includes 7 toxins from edible mushrooms because mushrooms are commonly considered a plant food. Fungal toxins are not included but are given below.

Plant pesticides. Carcinogens: acetaldehyde methylformylhydrazone, allyl isothiocyanate, arecoline hydrochloride, benzaldehyde, benzyl acetate, caffeic acid, catechol, clivorine, cycasin/methylazoxymethanol acetate mixture, estragole, ethyl acrylate, glutamyl *p*-hydrazinobenzoic acid, *p*-hydrazinobenzoic acid, lasiocarpine, *N*-methyl-*N*-formylhydrazine, D-limonene, α-methylbenzyl alcohol, methylhydrazine, 8-methoxypsoralen, monocrotaline, pentanal methylformalhydrazone, petasitenine, reserpine, safrole, senkirkine, sesamol, and symphytine. [Cycasin as well as its metabolite methylazoxymethanol are positive in numerous tests (45) that do not meet the inclusion criteria of the database.] 5- and 8-Methoxypsoralen and psoralen are light-activated mutagens (17, 45, 46). 8-Methoxypsoralen is positive in a National Toxicology Program gavage study (without light) and is in the database (47). 5-Methoxypsoralen and psoralen have only been tested in a skin painting study (with light) and are positive (46); they are not in our database, because the route of administration would not result in whole body exposure. Noncarcinogens: atropine, benzyl alcohol, biphenyl, caffeine, carvone, deserpidine, disodium glycyrrhizinate, emetine dihydrochloride, ephedrine sulfate, eucalyptol, eugenol, β-*N*-[γ-L(+)-glutamyl]-4-hydroxymethylphenylhydrazine, isosafrole, kaempferol, DL-menthol, nicotine, norharman, pilocarpine, piperidine, rotenone, rutin sulfate, sodium benzoate, and vinblastine. Uncertain: *trans*-anethole and quercetin.

Fungal toxins. Among 16 fungal toxins tested for carcinogenicity, 11 were positive. Carcinogens: aflatoxin, 5-azacytidine, azaserine, citrinin, griseofulvin, luteoskyrin, mitomycin C, ochratoxin A, sterigmatocystin, streptozotocin, and zearalenone. Noncarcinogens: erythromycin stearate, fusarenon X, oxytetracycline hydrochloride, patulin, and penicillin VK.

Table 2. Some natural pesticide carcinogens in food

Rodent carcinogen	Conc., ppm	Plant food
5-/8-Methoxypsoralen	14	Parsley
	32	Parsnip, cooked
	0.8	Celery
	6.2	Celery, new cultivar
	25	Celery, stressed
p-Hydrazinobenzoate	11	Mushrooms
Glutamyl *p*-hydrazinobenzoate	42	Mushrooms
Sinigrin* (allyl isothiocyanate)	35–590	Cabbage
	250–788	Collard greens
	12–66	Cauliflower
	110–1,560	Brussels sprouts
	16,000–72,000	Mustard (brown)
	4,500	Horseradish
D-Limonene	31	Orange juice
	40	Mango
	8,000	Pepper, black
Estragole	3,800	Basil
	3,000	Fennel
Safrole	3,000	Nutmeg
	10,000	Mace
	100	Pepper, black
Ethyl acrylate	0.07	Pineapple
Sesamol	75	Sesame seeds (heated oil)
α-Methylbenzyl alcohol	1.3	Cocoa
Benzyl acetate	82	Basil
	230	Jasmine tea
	15	Honey
Catechol	100	Coffee (roasted beans)
Caffeic acid	50–200	Apple, carrot, celery, cherry, eggplant, endive, grapes, lettuce, pear, plum, potato
	>1,000	Absinthe, anise, basil, caraway, dill, marjoram, rosemary, sage, savory, tarragon, thyme
	1,800	Coffee (roasted beans)
Chlorogenic acid† (caffeic acid)	50–500	Apricot, cherry, peach, plum
	21,600	Coffee (roasted beans)
Neochlorogenic acid† (caffeic acid)	50–500	Apple, apricot, broccoli, brussels sprouts, cabbage, cherry, kale, peach, pear, plum
	11,600	Coffee (roasted beans)

Carcinogen tests are referenced in refs. 10–13 and the following: 5-methoxypsoralen (light-activated) and 8-methoxypsoralen (46, 47) (psoralen, which is carcinogenic by skin painting, and many other mutagenic psoralen derivatives are also present in parsley and celery); *p*-hydrazinobenzoate and glutamyl *p*-hydrazinobenzoate (48, 49); allyl isothiocyanate (31, 32); D-limonene (50); estragole and safrole (45, 51); ethyl acrylate and benzyl acetate (52); α-methylbenzyl alcohol (53); caffeic acid (37); sesamol (37); catechol (37). Concentration references are as follows: 5- and 8-methoxypsoralen (17, 55–59); *p*-hydrazinobenzoates (in commercial mushrooms) (48, 49); sinigrin (38–40, 60); D-limonene (61–63); estragole and safrole (64–67); ethyl acrylate (68); benzyl acetate (69–71), α-methylbenzyl alcohol (23); caffeic acid, chlorogenic acid, and neochlorogenic acid (72–80) [in coffee (81)]; catechol (83, 84); sesamol (85). For mutagenicity and clastogenicity references, see text.

*Sinigrin is a cocarcinogen (33) and is metabolized to the rodent carcinogen allyl isothiocyanate, although no adequate test has been done on sinigrin itself. The proportion converted to allyl isothiocyanate or to allyl cyanide depends on food preparation (38–40).

†Chlorogenic and neochlorogenic acid are metabolized to the carcinogens caffeic acid and catechol (a metabolite of quinic acid) but have not been tested for carcinogenicity themselves. The clastogenicity and mutagenicity of these compounds are referenced in Table 1.

cells. The phenolics oxidize when a plant is wounded, yielding a burst of mutagenic oxygen radicals (e.g., the browning when an apple is cut).

Caution is necessary in interpreting the implications of the occurrence in the diet of natural pesticides that are rodent carcinogens. It is not argued here that these dietary exposures are necessarily of much relevance to human cancer. Indeed, a diet rich in fruit and vegetables is associated with lower cancer rates (86, 87). This may be because anticarcinogenic vitamins and antioxidants come from plants (86, 87). What is important in our analysis is that exposures to natural rodent carcinogens may cast doubt on the relevance of far lower levels of exposures to synthetic rodent carcinogens.

Residues of Synthetic Pesticides. A National Research Council report (88) has discussed the regulation of of synthetic pesticides that are rodent carcinogens, but ignored natural pesticides. The U.S. Food and Drug Administration (FDA) has assayed food for 200 chemicals including the synthetic pesticide residues thought to be of greatest importance and the residues of some industrial chemicals such as

polychlorinated biphenyls (PCBs) (24). The FDA found residues for 105 of these chemicals: the U.S. intake of the sum of these 105 chemicals averages about 0.09 mg per person per day, which we compare to 1.5 g of natural pesticides (i.e., 99.99% natural).** Other analyses of synthetic pesticide residues are similar (90). About half (0.04 mg) of this daily intake of synthetic pesticides is composed of four chemicals (24) that were not carcinogenic in rodent tests: ethylhexyl diphenyl phosphate, chlorpropham, malathion, and dicloran (10, 89). Thus, the intake of rodent carcinogens from synthetic residues is only about 0.05 mg a day (averaging about 0.06 ppm in plant food) even if one assumes that all the other residues are carcinogenic in rodents (which is unlikely).

Cooking Food. The cooking of food is also a major dietary source of potential rodent carcinogens. Cooking produces about 2 g (per person per day) of mostly untested burnt material that contains many rodent carcinogens—e.g., polycyclic hydrocarbons (81, 91), heterocyclic amines (92, 93), furfural (22, 23), nitrosamines and nitroaromatics (1, 94)—as well as a plethora of mutagens (91–95). Thus, the number and amounts of carcinogenic (or total) synthetic pesticide residues appear to be minimal compared to the background of naturally occurring chemicals in the diet. Roasted coffee, for example, is known to contain 826 volatile chemicals (22); 21 have been tested chronically and 16 are rodent carcinogens (10–13); caffeic acid, a nonvolatile rodent carcinogen, is also present (Table 2). A typical cup of coffee contains at least 10 mg (40 ppm) of rodent carcinogens (mostly caffeic acid, catechol, furfural, hydroquinone and hydrogen peroxide) (Table 2). The evidence on coffee and human health has been recently reviewed, and the evidence to date is insufficient to show that coffee is a risk factor for cancer in humans (81, 86). The same caution about the implications for humans of rodent carcinogens in the diet that were discussed above for nature's pesticides apply to coffee and the products of cooked food.

Clastogenicity and Mutagenicity Studies. Results from *in vitro* studies also indicate that the natural world should not be ignored and that positive results are commonly observed in high-dose protocols. Ishidate *et al.* (26) reviewed experiments on the clastogenicity (ability to break chromosomes) of 951 chemicals in mammalian cell cultures. Of these 951 chemicals, we identified 72 as natural plant pesticides, and 35 (48%) were positive for clastogenicity in at least one test. This is similar to the results for the remaining chemicals, of which 467/879 (53%) were positive in at least one test.

Of particular interest are the levels at which some of the carcinogenic plant toxins in Table 2 were clastogenic (26). Allyl isothiocyanate was clastogenic at a concentration of 0.0005 ppm, which is about 200,000 times less than the concentration of sinigrin, its glucosinolate, in cabbage. Allyl isothiocyanate was among the most potent chemicals in the compendium (26) and is also effective at unusually low levels in transforming (96) and mutating (30) animal cells. (See also the discussion of cancer tests in Table 1.) Safrole was clastogenic at a concentration of about 100 ppm, which is 30 times less than the concentration in nutmeg and roughly equal to the concentration in black pepper. The rodent carcinogens safrole and estragole, and a number of other related dietary natural pesticides that have not been tested in animal cancer tests, have been shown to produce DNA adducts in mice (97). Caffeic acid was clastogenic at a concentration of 260 and 500 ppm, which is less than its concentration in roasted coffee beans and close to its concentration in apples, lettuce, endive, and potato skin. Chlorogenic acid, a precursor of caffeic acid, was clastogenic at a concentration of 150 ppm, which is 100 times less than its concentration in roasted coffee beans and similar to its concentration in apples, pears, plums, peaches, cherries, and apricots. Chlorogenic acid and caffeic acid are also mutagens (Table 1). Coffee is genotoxic to mammalian cells (98). Plant phenolics such as caffeic acid, chlorogenic acid, and tannins (esters of gallic acid) have been reviewed for their mutagenicity and antimutagenicity, clastogenicity, and carcinogenicity (99).

**Figures here are based on men aged 25–30 in 1982–1984. Cancer test results are in refs. 10–13. The negative test on 2-ethylhexyl diphenyl phosphate is in ref. 89. The latest FDA figures on actual exposures do not include every known synthetic pesticide, and diets vary. Nevertheless, 0.05 mg of possibly carcinogenic pesticide residues consumed in a day seems to be a reasonable rough estimate.

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