The Importance of Toxicological Testing for Safety of Dietary Supplement Ingredients

Testimony to the NIH Office of Dietary Supplements Methods and Reference Materials Program Stakeholders Meeting

by

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SUMMARY

An overall strategy for research and development for dietary supplement ingredients should include toxicological testing for safety of the supplement or its ingredients. A common public misconception is that substances are safe if they are natural, whereas they are likely to be hazardous if they are synthetically produced. We present evidence against this misconception. The idea that "natural is safe" may account in part for public concern about synthetic pesticide residues in the diet vs. public interest in and consumption of medicinal herbs. Dietary supplements, such as medicinal herbs, receive little regulatory scrutiny or limits compared to synthetic chemicals such as pesticide residues or pharmaceuticals, even though every chemical is toxic at some dose. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, dietary supplements may be sold without approval by FDA, and there are no standards for specific toxicological testing; this contrasts sharply with drugs, for which evidence of efficacy and safety must be presented to FDA prior to sale. We indicate in this statement that: (1) Gaining a broad perspective about the vast number of chemicals to which humans are exposed is important when setting research and regulatory priorities, and should include comparisons between ordinary exposure levels and the toxic dose level of a given chemical. (2) At usual human exposure levels, possible carcinogenic hazards from some naturally occurring dietary chemicals rank high compared to many other exposures. and (3) Like pharmaceuticals, dietary supplements (which have not been tested for carcinogenicity) rank high in possible toxic hazard. For dietary supplements, the recommended doses on product labels are high when compared to the toxic dose in rodents (LD_{50}), in contrast to highly regulated exposures such as food additives or pesticide residues in the diet. (4) Little quantitative toxicological data is available on herbal supplements to assess their potential health risks, despite the high doses recommended, the frequency with which herbals are taken chronically, and the fact that consumers are self-medicating with these products. In order to protect consumers from potentially harmful, long-term effects of dietary supplements, we suggest a defined battery of toxicological testing be required for evaluation of safety. (This testimony does not discuss micronutrients, which are also defined as dietary supplements.) (5) Regulatory scrutiny is also recommended because of the wide variety of toxic reactions that have been reported for dietary supplements, the lack of information on possible drug interactions, and the evidence that products are unstandardized, have been adulterated, and can contain pharmaceuticals or high levels of heavy metals.

I. Carcinogenicity of Natural vs. Synthetic Chemicals

The fact that a chemical is natural does not make it safe. Current cancer regulatory policy is based on the idea that rodent carcinogens are potential human carcinogens; however, the chemicals tested for carcinogenicity in rodents have been primarily synthetic. The enormous background of human exposures to natural chemicals, including medicinal herbs, has not been a focus of testing. Toxicological examination of synthetic chemicals, without similar examination of chemicals that occur naturally, has resulted in an imbalance in both data and perception about possible cancer hazards. The public tends to view chemicals as being only synthetic, and to think of synthetic chemicals as toxic; however, every natural chemical is also toxic at some dose. The regulatory process does not take into account that natural chemicals make up the vast bulk of chemicals to which humans are exposed, and that the toxicology of synthetic and natural toxins is not fundamentally different. Medicinal herbs and dietary supplements, which are naturally occurring substances, have not been a focus of carcinogenicity testing despite the fact that they are

often taken daily for long periods of time, and that the recommended doses are higher relative to toxicity than most other exposures (except pharmaceuticals and workplace exposures).

1) The vast proportion of chemicals to which humans are exposed, occur naturally. We estimate that the daily average U.S. exposure to burnt material in the diet is 2000 mg. The exposure to natural pesticides (the chemicals that plants produce to defend themselves) is 1500 mg; in comparison, the total daily exposure to all synthetic pesticide residues combined is 0.09 mg; thus, 99.99% of the pesticides humans ingest are natural (*1*). Despite this enormously greater exposure to natural chemicals, among the chemicals tested for carcinogenicity in rats and mice, 76% (450/590) are synthetic (i.e. do not occur naturally) (*2*).
2) Since the toxicology of natural and synthetic chemicals is similar (see 3 below), one expects and finds, a similar positivity-rate for carcinogenicity among synthetic and natural chemicals (Table 1). The positivity rate is about 50% for several subsets of our database of animals cancer tests. Since humans are exposed to so many more natural than synthetic chemicals (by weight and by number), humans are probably living in a sea of naturally-occurring rodent carcinogens as defined by high dose rodent tests. We have shown that even though only a tiny proportion of natural pesticides in plant foods have been tested, the 37 that are rodent carcinogens among the 71 tested, occur in more than 50 common plant foods. It is probable that almost every fruit and vegetable in the supermarket contains natural pesticides that are rodent carcinogens. (Table 2).
3) One argument that has been raised about the possibly greater safety of natural chemicals is that because they are part of human evolutionary history, whereas synthetic chemicals are recent, the mechanisms that have evolved in animals to cope with the toxicity of natural chemicals will protect against the natural but not the synthetic chemicals. This assumption is flawed for several reasons (*1, 3*), which suggest that possible toxic hazards will be similar for natural or synthetic chemicals. Thus, just because a substance occurs naturally, that does not indicate that it will be safe:

    (a) Humans have many natural defenses that buffer against normal exposures to toxins (*3*) and these are usually general, rather than tailored for each specific chemical. Thus they work against both natural and synthetic chemicals. Examples of general defenses include the continuous shedding of cells exposed to toxins — the surface layers of the mouth, esophagus, stomach, intestine, colon, skin and lungs are discarded every few days; DNA repair enzymes, which repair DNA that was damaged from many different sources; and detoxification enzymes of the liver and other organs which generally target classes of chemicals rather than individual chemicals. That human defenses are usually general, rather than specific for each chemical, makes good evolutionary sense. The reason that predators of plants evolved general defenses is presumably to be prepared to counter a diverse and ever-changing array of plant toxins in an evolving world; if a herbivore had defenses against only a set of specific toxins, it would be at a great disadvantage in obtaining new food when favored foods became scarce or evolved new chemical defenses.

Table 1. Proportion of chemicals evaluated as carcinogenic,[a] for several datasets in the Carcinogenic Potency Database

Chemicals tested in both rats and mice	350/590 (59%)
Naturally-occurring chemicals	79/139 (57%)
Synthetic chemicals	271/451 (60%)
Chemicals tested in rats and/or mice	
Natural pesticides	37/71 (52%)
Mold toxins	14/23 (61%)
Chemicals in roasted coffee	21/30 (70%)

[a]A chemical is classified as positive if the author of at least one published experiment evaluated results as evidence that the compound is carcinogenic.

(b) Various natural toxins, which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates (*3, 4*). Mold toxins, such as aflatoxin, have been shown to cause cancer in rodents and other species including humans. Many of the common elements are carcinogenic to humans at high doses, e.g., salts of cadmium, beryllium, nickel, chromium and arsenic, despite their presence throughout evolution. Furthermore, epidemiological studies from various parts of the world show that certain natural chemicals in the diet can be carcinogenic to humans; for example, the chewing of betel nut with tobacco has been correlated with oral cancer and the mold toxin, aflatoxin, is carcinogenic to humans and many other species. Among the agents identified as human carcinogens by the International Agency for Research in Cancer (IARC) 61% (31/51) occur naturally: 15 are natural chemicals, 11 are mixtures of natural chemicals, and 5 are infectious agents (*5, 6*).

(c) Humans have not had time to evolve a "toxic harmony" with all of their dietary plants. The human diet has changed markedly in the last few thousand years. Indeed, very few of the plants that humans eat today, e.g., coffee, cocoa, tea, potatoes, tomatoes, corn, avocados, mangoes, olives and kiwi fruit, would have been present in a hunter-gatherer's diet. Natural selection works far too slowly for humans to have evolved specific resistance to the food toxins in these newly introduced plants.

(d) Since no plot of land is immune to attack by insects, plants need chemical defenses — either natural or synthetic — to survive pest attack. One consequence of disproportionate concern about synthetic pesticide residues is that some plant breeders develop plants to be more insect-resistant by making them higher in natural toxins. A recent case illustrates the potential hazards of this approach to pest control: When a major grower introduced a new variety of highly insect-resistant celery into commerce, people who handled the celery developed rashes when they were subsequently exposed to sunlight. Some detective work found that the pest-resistant celery contained 6,200 parts per billion (ppb) of carcinogenic (and mutagenic) psoralens instead of the 800 ppb present in common celery (*3*).

Table 2. Carcinogenicity status of natural pesticides tested in rodents [a]

Carcinogens:[b] N=37	acetaldehyde methylformylhydrazone, allyl isothiocyanate, arecoline.HCl, benzaldehyde, benzyl acetate, caffeic acid, capsaicin, catechol, clivorine, coumarin, crotonaldehyde, 3,4-dihydrocoumarin, estragole, ethyl acrylate, *N*2-γ-glutamyl-*p*-hydrazinobenzoic acid, hexanal methylformylhydrazine, *p*-hydrazinobenzoic acid.HCl, hydroquinone, 1-hydroxyanthraquinone, lasiocarpine, *d*-limonene, 3-methoxycatechol, 8-methoxypsoralen, *N*-methyl-*N*-formylhydrazine, α-methylbenzyl alcohol, 3-methylbutanal methylformylhydrazone, 4-methylcatechol, methylhydrazine, monocrotaline, pentanal methylformylhydrazone, petasitenine, quercetin, reserpine, safrole, senkirkine, sesamol, symphytine
Noncarcinogens: N=34	atropine, benzyl alcohol, benzyl isothiocyanate, benzyl thiocyanate, biphenyl, *d*-carvone, codeine, deserpidine, disodium glycyrrhizinate, ephedrine sulphate, epigallocatechin eucalyptol, eugenol, gallic acid, geranyl acetate, β-*N*-[γ-*l*(+)-glutamyl]-4-hydroxymethylphenylhydrazine, glycyrrhetinic acid, *p*-hydrazinobenzoic acid, isosafrole, kaempferol, *dl*-menthol, nicotine, norharman, phenethyl isothiocyanate, pilocarpine, piperidine, protocatechuic acid, rotenone, rutin sulfate, sodium benzoate, tannic acid, 1-trans-δ^9-tetrahydrocannabinol, turmeric oleoresin, vinblastine

[a]Fungal toxins are not included.

[b]These rodent carcinogens occur in: absinthe, allspice, anise, apple, apricot, banana, basil, beet, broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, cardamom, carrot, cauliflower, celery, cherries, chili pepper, chocolate, cinnamon, cloves, coffee, collard greens, comfrey herb tea, corn, coriander, currants, dill, eggplant, endive, fennel, garlic, grapefruit, grapes, guava, honey, honeydew melon, horseradish, kale, lemon, lentils, lettuce, licorice, lime, mace, mango, marjoram, mint, mushrooms, mustard, nutmeg, onion, orange, paprika, parsley, parsnip, peach, pear, peas, black pepper, pineapple, plum, potato, radish, raspberries, rhubarb, rosemary, rutabaga, sage, savory, sesame seeds, soybean, star anise, tarragon, tea, thyme, tomato, turmeric, and turnip.

II. **Ranking Possible Cancer Hazards to Known Rodent Carcinogens**.

It is important to set priorities among possible cancer hazards by gaining perspective about the vast number of chemicals to which humans are exposed. One reasonable strategy is to use a rough index to compare and rank possible carcinogenic hazards from a wide variety of chemical exposures at levels that humans typically receive, and then to focus on those that rank highest. If naturally occurring chemicals rank high in possible hazard compared to synthetic pollutants or food additives, then this is further evidence that chemicals are not safe just because they are natural. Although one cannot say whether the ranked chemical exposures are likely to be of major or minor importance in human cancer, it is not prudent to focus attention on the possible hazards at the bottom of a ranking if, using the same methodology, there are numerous common human exposures with much greater possible hazards.

Our analyses are based on the HERP index (Human Exposure/Rodent Potency), which indicates what percentage of the rodent carcinogenic potency (TD_{50} in mg/kg/day) a human receives from a given daily lifetime exposure (mg/kg/day). TD_{50} values in our CPDB span a 10 million-fold range across chemicals in our Carcinogenic Potency Database which analyzes re-

sults of 5500 animal cancer tests on 1400 chemicals (*2, 7*). In general, the ranking by the simple HERP index will be similar to a ranking of regulatory "risk estimates" such as those of the U.S. Environmental Protection Agency (EPA) that use a linearized multistage model to estimate risk.

Table 3 is a ranking by HERP of all rodent carcinogens in our Carcinogenic Potency Database for which average exposure information was available in the published literature. Overall, our analyses in Table 3 show that possible carcinogenic hazards (HERP values) for some historically high exposures in the workplace and some pharmaceuticals rank high, and that there is an enormous background of naturally occurring rodent carcinogens in typical portions of common foods that cast doubt on the relative importance of low-dose exposures to synthetic chemicals such as pesticide residues or synthetic food additives (*8, 9*).

The HERP ranking presented in Table 3 includes 82 average or recommended exposures to rodent carcinogens: 46 natural chemicals (including 5 dietary supplements) and 36 synthetic chemicals (including 6 pharmaceuticals and 5 workplace exposures). Few dietary supplements have been tested for carcinogenicity; those that are rodent carcinogens (Table 3) tend to rank high in HERP, like some pharmaceutical drugs, because of the high dose relative to the rodent carcinogenic dose (in Table 3, the dietary supplements are reported in italics). The possible hazard for herbal remedies may be even relatively greater because some of the pharmaceuticals are not used chronically (noted in brackets in Table 3), whereas the herbal remedies that are rodent carcinogens are recommended for chronic use.

Comfrey is a medicinal herb that is carcinogenic in rats. Formerly, it was recommended for well-being, but currently the PDR for Herbal Medicines (*10*) indicates: "One should entirely forgo internal administration of the drug [comfrey], due to the presence, however small, of pyrrolizidine alkaloids which have hepatotoxic and carcinogenic effects. It has been determined that traces of the alkaloids present a danger."

Comfrey is a medicinal herb whose roots and leaves have been shown to be carcinogenic in rats. The formerly recommended dose of 9 daily comfrey-pepsin tablets has a HERP value of 6.2%. Symphytine, a pyrrolizidine alkaloid (PA) plant pesticide that is present in comfrey-pepsin tablets and comfrey tea, is a rodent carcinogen; the HERP value for symphytine is 1.3% in the pills and 0.03% in comfrey herb tea. Comfrey also contains the PA lasiocarpine, which induces tumors at many sites in rats(*7*). Comfrey pills are no longer widely sold, but are available on the World Wide Web. Comfrey roots and leaves can be bought at health food stores and on the Web and can thus be used for tea, although comfrey is recommended for topical use only in the *PDR for Herbal Medicines* (*10*). Poisoning epidemics by pyrrolizidine alkaloids have occurred in the developing world. In the U.S. poisonings, including deaths, have been associated with use of herbal teas containing comfrey (*11*). Recently the FDA issued a warning about comfrey and asked manufacturers to withdraw their comfrey products after several people became ill from taking comfrey as a supplement or as tea.

Coltsfoot, which is a liver carcinogen in rats, has a HERP value for a cup of herbal tea of 0.9%. Both the flowers and the leaves of coltsfoot can be purchased on the Internet. The PDR for Herbal Medicines (*10*) cautions that the PAs in flowers are possibly hepatotoxic and carcinogenic.

Several other plants that have medicinal uses have been shown to be carcinogenic in rodents, including *Farfugium japonicum*, *Petasites japonicus*, *Senecio longilobus*, and *S. nemorensis*. Both *F. japonicum* and P. japonicus contain senkirkine and petasitenine, which are PAs that induce tumors in rats (*7*).

Botanical products containing aristolochic acid have been found to induce urinary tract cancer in humans (*12*). The FDA has issued warnings about dietary supplements and traditional medicines that contain aristolochic acid (*13*); http://www.cfsan.fda.gov/%20~dms/ds-bot.html. *Aristolochia* is listed in the Chinese pharmacopoeia (*14*).

Table 3. Ranking Possible Carcinogenic Hazards from Average U.S. Exposures. *Daily human exposure*: Reasonable daily intakes are used to facilitate comparisons. Calculations assume a daily dose for a lifetime. For dietary supplements on the HERP index, the recommended dose is used. *Possible hazard:* The human dose of rodent carcinogen is divided by 70 kg to give a mg/kg/day of human exposure, and this dose is given as the percentage of the TD_{50} in the rodent (mg/kg/day) to calculate the *H*uman *E*xposure/*R*odent *P*otency index (HERP). TD_{50} values used in the HERP calculation are averages calculated by taking the harmonic mean of the TD_{50}s of the positive tests in that species from the Carcinogenic Potency Database. Average TD_{50} values, have been calculated separately for rats and mice, and the more potent value is used for calculating possible hazard. Substances in *italics* are dietary supplements. Exposures to synthetic chemicals are reported in **bold**. Drugs in brackets "[ ]" are not used chronically.

Possible hazard: HERP (%)	Average daily US exposure	Human dose of rodent carcinogen	Potency TD_{50} (mg/kg/day) [a]		Exposure references
			Rats	Mice	
140	**EDB: workers (high exposure) (before 1977)**	**Ethylene dibromide, 150 mg**	1.52	(7.45)	(*15, 16*)
17	**Clofibrate**	**Clofibrate, 2 g**	169	.	(*17*)
14	**Phenobarbital, 1 sleeping pill**	**Phenobarbital, 60 mg**	(+)	6.09	(*18*)
[14]	**Isoniazid**	**Isoniazid, 300 mg**	(150)	30	(*19*)
6.8	**1,3-Butadiene: rubber workers (1978-86)**	**1,3-Butadiene, 66.0 mg**	(261)	13.9	(*20*)
6.2	*Comfrey-pepsin tablets, 9 daily*	*Comfrey root, 2.7 g*	626	.	(*21, 22*)
6.1	**Tetrachloroethylene: dry cleaners with dry-to-dry units (1980-90)**	Tetrachloroethylene, 433 mg	101	(126)	(*23*)
[5.6]	**Metronidazole**	**Metronidazole, 2 g**	(542)	506	(*19*)
4.0	**Formaldehyde: workers**	**Formaldehyde, 6.1 mg**	2.19	(43.9)	(*24*)
2.1	Beer, 257 ml	Ethyl alcohol, 13.1 ml	9110	(–)	(*25*)
1.4	**Mobile home air (14 hours/day)**	**Formaldehyde, 2.2 mg**	2.19	(43.9)	(*26*)
1.3	*Comfrey-pepsin tablets, 9 daily*	*Symphytine, 1.8 mg*	1.91	.	(*21, 22*)
0.9	**Methylene chloride: workers (1940s-80s)**	**Methylene chloride, 471 mg**	724	(918)	(*27*)
0.9	*Coltsfoot tea, 1 cup (1.5 g flower)*	*Coltsfoot*	2520	.	(*28*)
0.5	Wine, 28.0 ml	Ethyl alcohol, 3.36 ml	9110	(–)	(*25*)
0.5	*Dehydroepiandrosterone (DHEA)*	*DHEA supplement, 25 mg*	68.1	.	
0.4	**Conventional home air (14 hours/day)**	**Formaldehyde, 598 μg**	2.19	(43.9)	(*29*)
[0.3]	**Phenacetin (formerly used in analgesics)**	**Phenacetin, 300 mg**	1250	(2140)	(*30*)
0.2	**Fluvastatin**	**Fluvastatin, 20 mg**	125	.	(*31*)
0.1	Coffee, 500 ml (13.3 g beans)	Caffeic acid, 23.9 mg	297	(4900)	(*25, 32*)
0.04	Lettuce, 14.9 g	Caffeic acid, 7.90 mg	297	(4900)	(*33, 34*)
0.03	Safrole in spices	Safrole, 1.2 mg	(441)	51.3	(*35*)

0.03	Orange juice, 138 g	*d*-Limonene, 4.28 mg	204	(–)	(*33, 36*)
0.03	Pepper, black, 446 mg	*d*-Limonene, 3.57 mg	204	(–)	(*25, 37*)
0.03	*Comfrey herb tea, 1 cup (1.5 g root)*	*Symphytine, 38 μg*	1.91	.	(*22*)
0.02	Mushroom (*Agaricus bisporus* 2.55 g)	Mixture of hydrazines, etc. (whole mushroom)	–	20,300	(*25, 38, 39*)
0.02	Apple, 32.0 g	Caffeic acid, 3.40 mg	297	(4900)	(*40, 41*)
0.02	Coffee, 500 ml (13.3 g beans)	Catechol, 1.33 mg	118	(244)	(*25, 42, 43*)
0.02	Coffee, 500 ml (13.3 g beans)	Furfural, 2.09 mg	(683)	197	(*25*)
0.009	**BHA: daily US avg (1975)**	**BHA, 4.6 mg**	745	(5530)	(*44*)
0.008	Beer (before 1979), 257 ml	Dimethylnitrosamine, 726 ng	0.124	(0.189)	(*25, 45, 46*)
0.008	Aflatoxin: daily US avg (1984-89)	Aflatoxin, 18 ng	0.0032	(+)	(*47*)
0.007	Cinnamon, 21.9 mg	Coumarin, 65.0 μg	13.9	(103)	(*48*)
0.006	Coffee, 500 ml (13.3 g beans)	Hydroquinone, 333 μg	82.8	(225)	(*25, 42, 49*)
0.005	**Saccharin: daily US avg (1977)**	**Saccharin, 7 mg**	2140	(–)	(*50*)
0.005	Carrot, 12.1 g	Aniline, 624 μg	194[b]	(–)	(*33, 51*)
0.004	Potato, 54.9 g	Caffeic acid, 867 μg	297	(4900)	(*33, 52*)
0.004	Celery, 7.95 g	Caffeic acid, 858 μg	297	(4900)	(*53, 54*)
0.004	White bread, 67.6 g	Furfural, 500 μg	(683)	197	(*25*)
0.003	Nutmeg, 27.4 mg	*d*-Limonene, 466 μg	204	(–)	(*25, 55*)
0.003	**Conventional home air (14 hour/day)**	**Benzene, 155 μg**	(169)	77.5	(*29*)
0.002	Carrot, 12.1 g	Caffeic acid, 374 μg	297	(4900)	(*33, 54*)
0.002	**Ethylene thiourea: daily US avg (1990)**	**Ethylene thiourea, 9.51 μg**	7.9	(23.5)	(*56*)
0.002	**DDT: daily US avg (before 1972 ban)**	**DDT, 13.8 μg**	(84.7)	12.3	(*57*)
0.001	Plum, 2.00 g	Caffeic acid, 276 μg	297	(4900)	(*41, 58*)
0.001	**BHA: daily US avg (1987)**	**BHA, 700 μg**	745	(5530)	(*44*)
0.001	Pear, 3.29 g	Caffeic acid, 240 μg	297	(4900)	(*25, 41*)
0.001	**UDMH: daily US avg (1988)**	**UDMH, 2.82 μg (from Alar)**	(–)	3.96	(*40*)
0.0009	Brown mustard, 68.4 mg	Allyl isothiocyanate, 62.9 μg	96	(–)	(*25, 59*)
0.0008	**DDE: daily US avg (before 1972 ban)**	**DDE, 6.91 μg**	(–)	12.5	(*57*)
0.0007	**TCDD: daily US avg (1994)**	**TCDD, 12.0 pg**	0.0000235	(0.000156)	(*60*)
0.0007	Bacon, 11.5 g	Diethylnitrosamine, 11.5 ng	0.0237	(+)	(*25, 61*)
0.0006	Mushroom (*Agaricus bisporus* 2.55 g)	Glutamyl-*p*-hydrazino-benzoate, 107 μg	.	277	(*25, 62*)
0.0004	Bacon, 11.5 g	*N*-Nitrosopyrrolidine, 196 ng	(0.799)	0.679	(*25, 61*)
0.0004	Bacon, 11.5 g	Dimethylnitrosamine, 34.5 ng	0.124	(0.189)	(*25, 63*)
0.0004	**EDB: Daily US avg (before 1984 ban)**	**EDB, 420 ng**	1.52	(7.45)	(*64*)
0.0004	**Tap water, 1 liter (1987-92)**	**Bromodichloromethane, 13 μg**	(72.5)	47.7	(*65*)
0.0003	Mango, 1.22 g	*d*-Limonene, 48.8 μg	204	(–)	(*58, 66*)
0.0003	Beer, 257 ml	Furfural, 39.9 μg	(683)	197	(*25*)
0.0003	**Tap water, 1 liter (1987-92)**	**Chloroform, 17 μg**	(262)	90.3	(*65*)
0.0003	**Carbaryl: daily US avg (1990)**	**Carbaryl, 2.6 μg**	14.1	(–)	(*67*)
0.0002	Celery, 7.95 g	8-Methoxypsoralen, 4.86 μg	32.4	(–)	(*53, 68*)
0.0002	**Toxaphene: daily US avg (1990)**	**Toxaphene, 595 ng**	(–)	5.57	(*67*)

0.00009	Mushroom (*Agaricus bisporus*, 2.55 g)	*p*-Hydrazinobenzoate, 28 μg	.	454[b]	(*25, 62*)
0.00008	**PCBs: daily US avg (1984-86)**	**PCBs, 98 ng**	1.74	(9.58)	(*69*)
0.00008	**DDE/DDT: daily US avg (1990)**	**DDE, 659 ng**	(–)	12.5	(*67*)
0.00007	Parsnip, 54.0 mg	8-Methoxypsoralen, 1.57 μg	32.4	(–)	(*70, 71*)
0.00007	Toast, 67.6 g	Urethane, 811 ng	(41.3)	16.9	(*25, 72*)
0.00006	Hamburger, pan fried, 85 g	PhIP, 176 ng	4.29[b]	(28.6[b])	(*33, 73*)
0.00005	Estragole in spices	Estragole, 1.99 μg	.	51.8	(*25*)
0.00005	Parsley, fresh, 324 mg	8-Methoxypsoralen, 1.17 μg	32.4	(–)	(*70, 74*)
0.00003	Hamburger, pan fried, 85 g	MeIQx, 38.1 ng	1.99	(24.3)	(*33, 73*)
0.00002	**Dicofol: daily US avg (1990)**	**Dicofol, 544 ng**	(–)	32.9	(*67*)
0.00001	Beer, 257 ml	Urethane, 115 ng	(41.3)	16.9	(*25, 72*)
0.000005	Hamburger, pan fried, 85 g	IQ, 6.38 ng	1.89[b]	(19.6)	(*33, 73*)
0.000001	**Lindane: daily US avg (1990)**	**Lindane, 32 ng**	(–)	30.7	(*67*)
0.0000004	**PCNB: daily US avg (1990)**	**PCNB (Quintozene), 19.2 ng**	(–)	71.1	(*67*)
0.0000001	**Chlorobenzilate: daily US avg (1989)**	**Chlorobenzilate, 6.4 ng**	(–)	93.9	(*67*)
0.00000008	**Captan: daily US avg (1990)**	**Captan, 115 ng**	2080	(2110)	(*67*)
0.00000001	**Folpet: daily US avg (1990)**	**Folpet, 12.8 ng**	(-)	1550	(*67*)
<0.00000001	**Chlorothalonil: daily US avg (1990)**	**Chlorothalonil, <6.4 ng**	828 [c]	(-)	(*67, 75*)

[a] "." = no data in CPDB; (–) = negative in cancer test; (+) = positive cancer test(s) not suitable for calculating a TD_{50}.

[b] TD_{50} harmonic mean was estimated for the base chemical from the hydrochloride salt.

[c] Additional data from the EPA that is not in the CPDB were used to calculate these TD_{50} harmonic means.

In a diet clinic in Belgium, among female patients given aristolochic acid, 105 developed Chinese-herb nephropathy, 39 had surgery for end-stage renal disease, and of these 18 developed urothelial tract carcinoma (*12*). The period of dosing patients in the diet clinic averaged 13.3 months. The mutagenic and carcinogenic effects of aristolochic acid in rodent bioassays were demonstrated two decades ago (*76-78*). The dose levels of *Aristolochia* that produced cancer in humans were even lower than the doses given to rats (Table 4). The results of experiments on aristolochic acid in rats were unusual for bioassays because malignant tumors were induced rapidly in the forestomach, kidney and bladder within 6 months. No HERP has been calculated because the short exposure and experiment lengths do not meet the inclusion rules of the CPDB.

Dehydroepiandrosterone (DHEA), a hormonal dietary supplement, has a HERP value of 0.5 for the recommended dose of 1 capsule containing 25 mg DHEA. It "was reportedly the fastest-selling product in health food stores" in 1997 (*79*). We note that the mechanism of liver carcinogenesis in rats is peroxisome proliferation (like clofibrate), which makes it unlikely to pose a significant liver cancer risk to humans. It has been hypothesized that DHEA supplementation might be a risk factor for prostate cancer because it increases insulin-like growth factor-I (IGF-I) levels and bioavailability in the blood (*79*).

Table 4. Aristolochic Acid (AA) Carcinogenicity in Rats and Humans

Species	Target site	Administered Dose (mg/kg/day)	Time to disease	Incidence
Rats (1982)	Forestomach tumors	0.075-0.5	13-52 weeks	9/11
	Kidney tumors	5.0	26 weeks	13/18
	Urinary bladder tumors	5.0	26 weeks	6/18
Humans (1990-99)	End-stage renal failure among AA patients with nephropathy,	0.015	2 to 9 years	43/105
	Urothelial carcinoma among AA kidney transplant patients,	0.015	4 to 9 years	18/39

References: (*12, 76*)

The HERP ranking makes exposure assessment critical at the outset because it compares average exposures, or for drugs and supplements, it compares recommended doses for each rodent carcinogen to the carcinogenic dose in rodents. The HERP ranking in Table 3 indicates that just because a chemical is natural does not mean that it is safer at usual exposure levels than a synthetic chemical. Table 3 also indicates that commercial dietary supplements rank high in possible carcinogenic hazard compared to other exposures; the HERP values for dietary supplements that are rodent carcinogens are much higher than HERP values for synthetic chemicals in the diet which receive detailed regulatory attention. These results argue for greater regulatory scrutiny of dietary supplements on the grounds that they may be carcinogens in rodents and that if they are carcinogens, they are likely to rank high in possible carcinogenic hazard because, like pharmaceuticals, they are often used chronically at doses close to the carcinogenic dose.

III. Ranking Possible Toxic Hazards to Dietary Supplements and Other Dietary Chemicals that Have Not Been Tested for Carcinogenicity

An additional analysis presented in Table 5 ranks possible toxic hazards to dietary supplements and compares these to possible hazards from high-concentration chemical exposures to naturally-occurring food constituents in commonly consumed foods.

Our initial interest in food constituents that occur naturally was to identify chemicals that might reasonably be tested for carcinogenicity because they are consumed in high amounts in the U.S. diet compared to their toxic doses but that have not been tested because the focus of cancer testing has been synthetic chemicals. In Table 5 we have added common, commercial dietary supplements to this ranking; our purpose is to describe how high the possible toxic hazards of supplements are relative to food constituents in commonly consumed foods. The common supplements for which we were able to obtain LD_{50} values and which are in Table 5 are ginger, ginkgo, ginseng, garlic, and valerian.

We use an index, HERT, which is analogous to HERP: the ratio of Human Exposure/Rodent Toxicity. HERT uses readily available LD_{50} values rather than the TD_{50} values from animal cancer tests that are used in HERP. This approach to prioritizing chemicals makes as-

sessment of human exposure levels critical at the outset. (See Appendix for details of methodology.) We have thus calculated HERT values using LD_{50} values as a measure of toxicity in combination with available data on (a) recommended doses of dietary supplements and (b) concentrations of natural dietary chemicals that have not been tested for carcinogenicity in rodents, and data on average consumption of those foods in the U.S. diet. For dietary supplements the LD_{50} values are for the extracts that correspond to the recommended doses, and the dose used in HERT is the highest value in the recommended range. For food constituents we considered any chemical with available data on rodent LD_{50}, that had a published concentration ≥ 10 ppm in a common food, and for which estimates of average U.S. consumption of that food were available. Among the set of 127 HERT values we were able to calculate, the HERT ranged 4 million fold.

The ranking in Table 5 indicates that dietary supplements rank high in possible toxic hazards when compared to food constituents that occur in high concentrations in common foods. Since supplements are often used chronically for long periods of time, by itself this result indicates the importance for safety of a defined battery of toxicological testing. The LD_{50} values for the extracts of supplements are weak; however, the recommended doses are high. The HERT values for ginger, ginkgo, ginseng, and garlic extracts range from 0.1 to 0.8; i.e. the recommended dose for humans (mg/kg/day) is from 0.1 to 0.8 percent of the lethal dose (mg/kg/day) in rodents. The HERT for valerian extract is 0.01.

Some natural chemicals in foods also rank high in HERT, suggesting the importance of testing for carcinogenicity since HERT and HERP are highly correlated (see Appendix). We have nominated these chemicals for carcinogenicity testing to the National Toxicology Program (NTP). Most of the high ranking chemicals in foods are natural pesticides and many have pharmacological effects, e.g. caffeine (a stimulant in coffee, tea, cola), trigonelline (in coffee), α-chaconine (a neurotoxin in potato), theobromine (in chocolate) and piperine (in black pepper). Natural pesticides are indicated in Table 5 by an asterisk next to the chemical name.

The high HERT values for dietary supplements make them similar to pharmaceutical drugs, for which HERP values are high and for which our calculated (not shown) HERT values are also high. For the 4 drugs in the HERP table that are rodent carcinogens, we calculated HERT using LD_{50} values instead of the TD_{50} values used in HERP. The HERT values ranged from 3.2 for isoniazid (which is not indicated for chronic, long-term use) to 0.5 for phenacetin (also not long-term administration). Thus, dietary supplements are similar to pharmaceuticals in terms of ranking high in possible toxic hazard. This is expected since the pharmacologically active dose for both pharmaceuticals and herbal supplements is high relative to toxicity. Because the recommended dose is close to the toxic dose, and because about half of natural chemicals are rodent carcinogens in standard animal cancer tests, it is likely that many dietary supplements from plants will be rodent carcinogens that would rank high in possible carcinogenic hazard (HERP) if they were tested for carcinogenicity. If the active chemical in the plant were identified and tested, it would likely have a high HERP value if it turned out to be a rodent carcinogen. We note that the HERT values for the synthetic chemicals in the diet in Table 3 (HERP) would all rank below the HERT values for the dietary supplements.

Whereas pharmaceuticals are federally regulated for purity, identification, and manufacturing procedures and additionally require evidence of efficacy, dietary supplements do not; however, possible toxic hazards are similar when measured by the percentage of the toxic dose that is recommended. Toxicological testing requirements for dietary supplements would help to identify possible hazards and safe dose levels, which is desirable for consumer protection.

IV. Reported Adverse Effects of Dietary Supplements

There is no mandatory reporting of adverse effects of dietary supplements by the manufacturer or distributor; therefore, adverse effects are probably underreported. A recent review summarizes and references many papers that document case reports and monitoring studies indicating for herbal remedies many toxic reactions, allergic reactions, drug interactions, adverse effects from the desired pharmacologic effect of the supplement, contamination, and misidentification of the product or plant (*80*). Severe reactions have been reported to herbal products, including hepatitis, liver failure, anaphylactic shock, and death.

Some examples of contamination of botanical supplements follow. Several reports indicate contamination, e.g. with *Digitalis lanata*, which cause serious illness including heart block (*81*). A recent study of traditional Chinese patent medicines sold in California retail stores found that 32% of the products contained heavy metals (e.g. arsenic, mercury, lead) or pharmaceuticals (e.g. ephedrine, phenacetin, methyltestosterone) that were not indicated on the product (*82*). The median level of arsenic (180 ppm) and mercury (329 ppm) in the contaminated products, far exceeded the usual limit for metals in pharmaceuticals in the U.S. Pharmacopeia (*83*). Arsenic and mercury are added to such Chinese products for medicinal purposes. Some products contained as much as 114,000 ppm arsenic and 5,070 ppm mercury. Contamination with lead had a median level of 30 ppm and a highest level of 319 ppm, exceeding allowable intakes from other environmental exposures. An analysis of Chinese herbal skin creams recommended for eczema found that most contained the steroid dexamethasone; the concentration of dexamethasone was 5 times higher in creams prescribed for children than adults. Patients were not aware of the ingredients (*84*).

Based on the ranking results in Tables 3 and 4, adverse effects are not surprising; the recommended doses for herbal remedies are close to the toxic doses (mg/kg/day) in rodents. In this respect the herbal dietary supplements resemble pharmaceutical drugs, and are in contrast to some highly regulated exposures to synthetic chemicals such as water pollutants, pesticide residues, or food additives. Herbal products may have many beneficial effects, but their safety requires greater toxicological testing, including carcinogenicity testing. There is an absence of quantitative toxicological data on these products in the available published literature.

Consideration might be given to some of the following: Especially because consumers are medicating themselves and because of the increasing popularity of dietary supplements, tracking and surveillance of adverse effects should be increased and the reporting process should be well-publicized and documented. For products known to have had toxic effects, consideration could be given to limiting distribution to adults (e.g. *ma huang*), or restricting access so that a product can only be dispensed by a licensed practitioner. Given the popularity of herbal supplements, the possibility of drug interactions, and the fact that consumers medicate themselves, it would be beneficial for physicians and medical students to receive training about herbal supplements from knowledgeable, licensed individuals. As more data and testing are developed for these products, this will be of increasing importance.

Our results provide evidence in support of greater regulatory scrutiny of dietary supplements for safety purposes.

Table 5. Ranking Possible Toxic Hazards on the HERT index (Human Exposure/Rodent Toxicity as LD_{50}) for naturally occurring dietary chemicals and dietary supplements that have not been tested for carcinogenicity

Daily human exposure: The average amount of the food consumed daily per person in the U.S.; when a chemical is listed rather than a food item, the value is the per person average in the total diet. For dietary supplements, the usual or therapeutic dose. Calculations assume a daily dose for a lifetime. *Possible hazard:* The amount of chemical reported under "Human dose of chemical" is divided by 70 kg to give a mg/kg of human exposure. The HERT is this human dose (mg/kg/day) as a percentage of the rodent LD_{50} (mg/kg). LD_{50}: Values are from the Registry of Toxic Effects of Chemical Substances (RTECS). Parentheses indicate the species with the higher (weaker) LD_{50}, which is not used in the HERT calculation. A "*" preceding a chemical name indicates that the chemical is a natural pesticide. Synthetic chemicals are in bold. Dietary supplements are in *italics*. Abbreviations for LD_{50} values: P = intraperitoneal, V = intravenous.

Possible hazard: HERT (%)	Average consumption or recommended dose	Average human consumption of chemical	LD_{50} (mg/kg) Rats	Mice	Exposure References
4.3	Coffee, 500 ml (13.3 g beans)	*Caffeine, 381 mg	(192)	127	(*25, 85, 86*)
0.8	*Ginger*	*Ginger extract, 2000 mg*	3500LD_{30}	.	
0.7	*Ginkgo*	*Ginkgo leaf extract, 760 mg*	1500P	.	
0.7	*Ginseng*	*Ginseng methyl alcohol extract, 300 mg*	629V	.	
0.3	Tea, 60.2 ml (903 mg leaf)	*Caffeine, 29.4 mg	(192)	127	(*25, 86-92*)
0.3	Potato, 54.9 g	*α-Chaconine, 4.10 mg	(84P)	19P	(*33, 93, 94*)
0.3	*Ginseng*	*Ginseng water extract, 300 mg*	1400	.	
0.2	Cola, 174 ml	*Caffeine, 20.8 mg	(192)	127	(*91, 92, 95*)
0.1	*Garlic*	*Garlic extract, 2400 mg*	(>30,000)	30,000P	
0.1	Coffee, 500 ml (13.3 g beans)	*Chlorogenic acid, 274 mg	4000P	.	(*25, 86, 96*)
0.09	Black pepper, 446 mg	*Piperine, 21.0 mg	(514)	330	(*25*)
0.08	Chocolate, 3.34 g	*Theobromine, 48.8 mg	(1265)	837	(*25, 86*)
0.05	Coffee, 500 ml (13.3 g beans)	*Trigonelline, 176 mg	5000	.	(*25, 86, 97*)
0.05	Lemon juice, 1.33 ml	*Geranial, 19.2 mg	500	.	(*95, 98*)
0.03	Chocolate, 3.34 g	*Caffeine, 2.30 mg	(192)	127	(*25, 99*)
0.02	Isoamyl alcohol: US avg (mostly beer, alcoholic beverages)	Isoamyl alcohol, 18.4 mg	1300	.	(*25*)
0.02	*Garlic*	*Garlic extract, 2400 mg*	.	173,800	
0.01	Potato chips, 5.2 g	*α-Chaconine, 136 μg	(84P)	19P	(*25, 100*)
0.01	Beer, 257 ml	Isoamyl alcohol, 13.6 mg	1300	.	(*25, 101*)
0.01	*Valerian*	*Valerian ethyl alcohol extract, 200 mg*	24,000	.	
0.01	Coffee, 500 ml (13.3 g beans)	2-Furancarboxylic acid, 821 μg	.	100P	(*25, 42, 86, 102*)
0.01	Lima beans, 559 mg	Hydrogen cyanide, 28.5 μg	.	3.7	(*95, 103, 104*)
0.01	Sweet potato, 7.67 g	*Ipomeamarone, 336 μg	.	50	(*25, 105*)
0.009	Potato, 54.9 g	*α-Solanine, 3.68 mg	590	.	(*33, 93, 94*)
0.008	Hexanoic acid: US avg (beer, grapes, wine)	Hexanoic acid, 15.8 mg	3000	(5000)	(*25*)
0.008	Isobutyl alcohol: US avg	Isobutyl alcohol, 14.1 mg	2460	.	(*25*)
0.007	Phenethyl alcohol: US avg	Phenethyl alcohol, 8.28 mg	1790	.	(*25*)

0.006	Ethyl acetate: US avg (mostly alcoholic beverages)	Ethyl acetate, 16.5 mg	(5620)	4100	(*25*)
0.005	Coffee, 500 ml (13.3 g beans)	*3-Methylcatechol, 203 μg	.	56V	(*25, 49, 86*)
0.005	Coffee, 500 ml (13.3 g beans)	*Oxalic acid, 25.2 mg	7500	.	(*25, 86, 106*)
0.004	Beer, 257 ml	Phenethyl alcohol, 5.46 mg	1790	.	(*25, 101*)
0.004	Corn, 33.8 g	Methylamine, 906 μg	.	317	(*25, 51*)
0.004	Peppermint oil, 5.48 mg	*Menthone, 1.33 mg	500	.	(*25*)
0.004	White bread, 67.6 g	Propionaldehyde, 2.09 mg	(1410)	800	(*25, 107*)
0.004	Beer, 257 ml	Isobutyl alcohol, 6.40 mg	2460	.	(*25, 101*)
0.004	Carrot, boiled, 12.1 g	*Oxalic acid, 22.7 mg	7500	.	(*33, 108*)
0.003	Tomato, 88.7 g	Methyl alcohol, 13.4 mg	5628	(7300)	(*33, 109, 110*)
0.003	Coffee, 500 ml (13.3 g beans)	Pyrogallol, 555 μg	.	300	(*25, 42, 86*)
0.003	Lettuce, 14.9 g	Methylamine, 567 μg	.	317	(*33, 51*)
0.003	Beer, 257 ml	Propyl alcohol, 3.29 mg	1870	(6800)	(*25, 101*)
0.003	Butyl alcohol: US avg (mostly apple, beer)	Butyl alcohol, 1.45 mg	790	.	(*25*)
0.003	Wine, 28.0 ml	Isoamyl alcohol, 3.00 mg	1300	.	(*25, 111*)
0.002	Banana, 15.7 g	trans-2-Hexenal, 1.19 mg	(780)	685	(*33, 112*)
0.002	Tomato, 88.7 g	**p*-Coumaric acid, 1.02 mg	.	657P	(*33, 113*)
0.002	Apple, 32.0 g	*Epicatechin, 1.28 mg	.	1000P	(*40, 114*)
0.002	Beer, 257 ml	Ethyl acetate, 4.42 mg	(5620)	4100	(*25, 115*)
0.002	Tomato, 88.7 g	*Tomatine, 621 μg	.	500	(*33, 116*)
0.002	White bread, 67.6 g	Butanal, 3.44 mg	2490	.	(*25, 107, 117*)
0.002	Wine, 28.0 ml	Ethyl lactate, 4.16 mg	(>5000)	2500	(*25, 111, 118*)
0.002	Tea, 60.2 ml (903 mg leaf)	*Theobromine, 1.11 mg	(1265)	837	(*25, 86, 119, 120*)
0.001	Apple, 32.0 g	**p*-Coumaric acid, 573 μg	.	657P	(*40, 41*)
0.001	Apple, 32.0 g	*Chlorogenic acid, 3.39 mg	4000P	.	(*40, 121, 122*)
0.001	Tea, 60.2 ml (903 mg leaf)	*Oxalic acid, 6.67 mg	7500	.	(*25, 86, 106, 108*)
0.001	5-Methylfurfural: US avg (mostly coffee)	5-Methylfurfural, 1.71 mg	2200	.	(*25*)
0.001	β-Pinene: US avg (mostly pepper, lemon oil, nutmeg)	*β-Pinene, 3.28 mg	4700	.	(*25*)
0.001	Coffee, 500 ml (13.3 g beans)	Maltol, 462 μg	(1410)	550	(*25, 42, 86*)
0.001	Coffee, 500 ml (13.3 g beans)	Nonanoic acid, 188 μg	.	224V	(*25, 86, 123*)
0.0009	Orange juice, 138 ml	Methyl alcohol, 3.48 mg	5628	(7300)	(*33, 124-126*)
0.0009	α-Pinene: US avg (mostly pepper, nutmeg, lemon oil)	*α-Pinene, 2.25 mg	3700	.	(*25*)
0.0009	White bread, 67.6 g	2-Butanone, 1.65 mg	2737	(4050)	(*25, 107*)
0.0008	Acetone: US avg (mostly tomato, bread, beer)	Acetone, 1.74 mg	(5800)	3000	(*25*)
0.0008	Cucumber, pickled, 11.8 g	Dimethylamine, 182 μg	(698)	316	(*25, 51*)
0.0008	Cabbage, raw, 12.9 g	Methylamine, 169 μg	.	317	(*25, 51*)
0.0008	Coffee, 500 ml (13.3 g beans)	Pyridine, 519 μg	891	(1500)	(*25, 86, 127*)
0.0007	Chocolate, 3.34 g	*Oxalic acid, 3.91 mg	7500	.	(*25, 106*)
0.0007	Cabbage, raw, green, 12.9 g	**p*-Coumaric acid, 303 μg	.	657P	(*25, 128*)

0.0007	Tomato, 88.7 g	*Chlorogenic acid, 2.06 mg	4000P	.	(*33, 129*)
0.0007	Coffee, 500 ml (13.3 g beans)	2-Methylpyrazine, 894 μg	1800	.	(*25, 86, 127*)
0.0007	Coffee, 500 ml (13.3 g beans)	2,6-Dimethylpyrazine, 432 μg	880	.	(*25, 86, 127*)
0.0007	Wine, 28.0 ml	Methyl alcohol, 2.84 ml	5628	(7300)	(*25, 111*)
0.0006	Peach, 9.58 g	*Chlorogenic acid, 1.78 mg	4000P	.	(*25, 122, 130, 131*)
0.0006	Tomato, 88.7 g	*Oxalic acid, 3.24 mg	7500	.	(*33, 106, 108*)
0.0006	Black pepper, 446 mg	*3-Carene, 2.00 mg	4800	.	(*25, 132*)
0.0006	Coffee, 500 ml (13.3 g beans)	Butyric acid, 785 μg	2000	.	(*25, 86, 123*)
0.0006	Coffee, 500 ml (13.3 g beans)	2,5-Dimethylpyrazine, 399 μg	1020	.	(*25, 86, 127*)
0.0005	Coffee, 500 ml (13.3 g beans)	5-Methylfurfural, 798 μg	2200	.	(*25, 86, 127*)
0.0005	Grapes, 11 g	*Chlorogenic acid, 1.38 mg	4000P	.	(*25, 122*)
0.0005	Black pepper, 446 mg	*β-Pinene, 1.50 mg	4700	.	(*25, 132*)
0.0004	Potato chips, 5.2 g	*α-Solanine, 179 μg	590	.	(*25, 133*)
0.0004	Lettuce, 14.9 g	Benzylamine, 172 μg	.	600P	(*33, 51*)
0.0004	Banana, 15.7 g	2-Pentanone, 424 μg	1600	1600	(*33, 112*)
0.0004	Lemon juice, 1.33 ml	Octanal, 1.60 mg	5630	.	(*95, 98*)
0.0004	Coffee, 500 ml (13.3 g beans)	Propanoic acid, 785 μg	2600	.	(*25, 86, 123*)
0.0004	Black pepper, 446 mg	*α-Pinene, 1.02 mg	3700	.	(*25, 132*)
0.0004	α-Phellandrene: US avg (mostly pepper)	*α-Phellandrene, 1.59 mg	5700	.	(*25*)
0.0003	Pear, 3.29 g	*Chlorogenic acid, 823 μg	4000P	.	(*25, 122*)
0.0003	Grapes, 11 g	*Epicatechin, 243 μg	.	1000P	(*25, 122, 134*)
0.0003	Carrot, 12.1 g	*Chlorogenic acid, 780 μg	4000P	.	(*33, 135*)
0.0003	Celery, 7.95 g	*Oxalic acid, 1.39 mg	7500	.	(*53, 108*)
0.0003	Lemon oil, 8 mg	*γ-Terpinene, 681 μg	3650	.	(*25, 136-138*)
0.0003	Lemon oil, 8 mg	*Geranial, 90.4 μg	500	.	(*25, 136, 138, 139*)
0.0003	Onion, raw, 14.2 g	Dipropyl trisulfide, 189 μg	.	800	(*25*)
0.0003	Coffee, 500 ml (13.3 g beans)	2-Ethyl-3-methylpyrazine, 186 μg	880	.	(*25, 86*)
0.0003	Lemon oil, 8 mg	*β-Pinene, 832 μg	4700	.	(*25, 136-138*)
0.0002	Broccoli (raw), 6.71 g	**p*-Coumaric acid, 90.6 μg	.	657P	(*53, 128*)
0.0002	Potato, 54.9 g	*Oxalic acid, 1.26 mg	7500	.	(*33, 108*)
0.0002	Corn, 33.8 g	*Oxalic acid, 1.12 mg	7500	.	(*25, 140*)
0.0002	White bread, 67.6 g	Hexanal, 1.35 mg	4890	(8292)	(*25, 107*)
0.0002	Lemon oil, 8 mg	*Citral, 600 μg	4960	(6000)	(*25, 141*)
0.0001	Pear, 3.29 g	*Epicatechin, 80.9 μg	.	1000P	(*25, 41, 114*)
0.0001	Orange, 10.5 g	*Oxalic acid, 651 μg	7500	.	(*33, 108*)
0.0001	Apple, 32.0 g	*Oxalic acid, 704 μg	7500	.	(*40, 108*)
0.0001	Corn, canned, 33.8 g	Dimethyl sulfide, 324 μg	3300	(3700)	(*25, 142, 143*)
0.0001	Isoamyl acetate: US avg (mostly beer, banana)	Isoamyl acetate, 1.70 mg	16600	.	(*25*)
0.0001	Coffee, 500 ml (13.3 g beans)	Hexanoic acid, 245 μg	3000	(5000)	(*25, 86, 123*)
0.00009	Lettuce, 14.9 g	*Oxalic acid, 447 μg	7500	.	(*33, 106*)
0.00007	Nutmeg, 27.4 mg	*Myristicin, 207 μg	4260	.	(*144*)
0.00006	Banana, 15.7 g	Methyl alcohol, 236 μg	5628	(7300)	(*33, 112*)
0.00005	Strawberry, 4.38 g	*Oxalic acid, 261 μg	7500	.	(*25, 106, 108*)

0.00005	Strawberry, 4.38 g	*Chlorogenic acid, 136 μg	4000P	.	(*25, 122*)
0.00005	Broccoli, 6.71 g	*Oxalic acid, 268 μg	7500	.	(*53, 140*)
0.00005	Banana, 15.7 g	Isoamyl acetate, 584 μg	16600	.	(*33, 145*)
0.00005	Lemon oil, 8 mg	*α-Pinene, 139 μg	3700	.	(*25, 136-138*)
0.00004	Black pepper, 446 mg	*α-Phellandrene, 162 μg	5700	.	(*25, 132*)
0.00003	Cabbage, boiled, 12.9 g	*Oxalic acid, 155 μg	7500	.	(*25, 108*)
0.00003	Grapes, 11 g	*Oxalic acid, 138 μg	7500	.	(*25, 140*)
0.00002	Grapefruit juice, 3.29 ml	Methyl alcohol, 95.4 μg	5628	(7300)	(*25, 126, 146-148*)
0.00002	Peach, canned, 9.58 g	*Oxalic acid, 115 μg	7500	.	(*25, 108*)
0.00002	Cucumber (raw flesh), 11.8 g	*Oxalic acid, 118 μg	7500	.	(*106*)
0.00002	Lemon oil, 8 mg	*α-Terpinene, 23.2 μg	1680	.	(*25, 136, 138*)
0.00001	Garlic, blanched, 53.3 mg	Diallyl disulfide, 2.05 μg	260	.	(*95, 149*)
0.00001	Lemon oil, 8 mg	*Terpinolene, 29.6 μg	4390	.	(*25, 136, 138*)
0.00001	Lemon oil, 8 mg	*α-Terpineol, 29.6 μg	.	2830	(*25, 136, 138*)
0.00001	Black pepper, 446 mg	*α-Terpineol, 25.0 μg	.	2830	(*25, 132*)
0.000008	Garlic, blanched, 53.3 mg	Diallyl trisulfide, 592 ng	.	100	(*95, 149*)
0.000006	Onions, green, cooked, 137 mg	*Oxalic acid, 31.5 μg	7500	.	(*95, 140*)
0.000001	Garlic, blanched, 53.3 mg	Diallyl sulfide, 2.28 μg	2980	.	(*95, 149*)

Appendix of Methods for HERT Table (Table 5)

The top 10 foods consumed in the U.S. as reported by 3 sources were selected for analysis: Flavor and Extract Manufacturers' Association (*25*), Technical Assessment Systems (*33*), and the USDA (*70*). Combining the foods from these 3 sources yielded the following 22 foods: apple, banana, beer, bread, broccoli, cabbage, carrot, celery, corn, cucumber, grape, grapefruit, lettuce, melons, onion, orange, peach, pear, potato, strawberry, tomato and wine. We added coffee, tea, and cola as common beverages, and chocolate as a common dessert ingredient. We added a few high concentrations in spices which are consumed in small amounts, i.e., garlic, lemon, and black pepper. The only values reported in the HERT table are for chemicals for which the following were available in the published literature: an LD_{50} value, a concentration ≥10 ppm in one of the common foods listed above, and a US average consumption estimate of that food.

For each of these foods a search was conducted for published concentrations of chemicals excluding those already tested for carcinogenicity and analyzed in the CPDB (whether carcinogenic or not) (*7*). The rodent carcinogens are included in the HERP table. The search included the compendium by CIVO, *Volatile Compounds in Foods* (*150*), and the on-line (Dialog) versions of Food Science and Technology Abstracts (1969 to the present) and Chemical Abstracts (1967 to the present). For each chemical concentration in a given food, we report the mean of published concentrations across varieties of fruit or vegetable. We only report average concentrations in a given food that are ≥10 ppm; there are many chemicals with concentration <10 ppm for each food, and none of these have been included in the table.

All LD_{50} values are for rats or mice, and are taken from the on-line version of the Registry of Toxic Effects of Chemical Substances (RTECS) (*151*). An oral LD_{50} was selected whenever available. When the oral LD_{50} was not available we used LD_{50}s based on intravenous injection or intraperitoneal injection and noted the route in the table.

To calculate HERT, one needs an LD_{50} and an estimate of chemical consumption. Chemical consumption is obtained as follows:

Chemical intake (mg) = average US consumption of the food (kg)
× chemical concentration (ppm)

Since LD_{50} is reported in mg/kg, chemical intake (mg/day) is divided by human body weight (70 mg) to obtain intake in mg/kg/day.

HERT is expressed as the ratio of chemical exposure (mg/kg/day) to LD_{50} (mg/kg) and multiplied by 100 to convert it to percentage:

HERT is calculated using the following formula:

HERT = chemical consumption (mg/kg) / (LD_{50} (mg/kg) × 100)

For example, for caffeine in coffee:

HERT = (381 mg / 70 kg) / (127 mg/kg × 100 = 4.3)

The validity of the HERT approach is supported by 3 analyses: First, we have found that for the exposures to rodent carcinogens for which we have calculated HERP values (N=68), the ranking by HERP and HERT are highly correlated (Spearman rank order correlation = 0.89). Second, we have shown that without conducting a bioassay the regulatory VSD can be approximated by dividing the MTD by 740,000 (*152*). Since the MTD is not known for all chemicals, and MTD and LD_{50} are both measures of toxicity, acute toxicity (LD_{50}) can reasonably be used as a surrogate for chronic toxicity (MTD). Third, we and others (*153*) have found that LD_{50} and carcinogenic potency are correlated; therefore, HERT is a reasonable surrogate index for HERP since it simply replaces TD_{50} with LD_{50}.

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