Rodent Carcinogens: Setting Priorities

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The human diet contains an enormous background of natural chemicals, such as plant pesticides and the products of cooking, that have not been a focus of carcinogenicity testing. A broadened perspective that includes these natural chemicals is necessary. A comparison of possible hazards for 80 daily exposures to rodent carcinogens from a variety of sources is presented, using an index (HERP) that relates human exposure to carcinogenic potency in rodents. A similar ordering would be expected with the use of standard risk assessment methodology for the same human exposure values. Results indicate that, when viewed against the large background of naturally occurring carcinogens in typical portions of common foods, the residues of synthetic pesticides or environmental pollutants rank low. A similar result is obtained in a separate comparison of 32 average daily exposures to natural pesticides and synthetic pesticide residues in the diet. Although the findings do not indicate that these natural dietary carcinogens are important in human cancer, they cast doubt on the relative importance for human cancer of low-dose exposures to synthetic chemicals.

The basis of current regulatory policy is the idea that rodent carcinogens are potential human carcinogens; however, the chemicals tested for carcinogenicity in rodents have been primarily synthetic (*1*, *2*). The enormous background of human exposures to natural chemicals has not been systematically examined. The regulatory process does not take into account that (i) natural chemicals make up the vast bulk of chemicals humans are exposed to; (ii) the toxicology of synthetic and natural toxins is not fundamentally different; (iii) about half of the natural chemicals tested chronically in rats and mice are carcinogens; (iv) testing for carcinogenicity at near-toxic doses in rodents does not provide enough information to predict the excess number of human cancers that might occur at low-dose exposures; and (v) testing at the maximum tolerated dose (MTD) frequently can cause chronic cell killing and consequent cell replacement (a risk factor for cancer that can be limited to high doses), and that ignoring this greatly exaggerates risks.

Ranking Possible Carcinogenic Hazards

We have emphasized that it is important to set priorities by gaining some perspective about the vast number of chemicals to which humans are exposed. One reasonable strategy for gaining a broadened perspective is to use a simple index to compare and rank possible carcinogenic hazards from a wide variety of chemical exposures at concentrations that humans typically receive and then to focus on those that rank highest (*3*, *4*). Ranking is a critical first step that can help to set priorities when selecting chemicals for chronic bioassay or mechanistic studies, for epidemiological research, and for regulatory policy. 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 the same methodology indicates numerous common human exposures with much greater possible hazards. The basis of our previous evaluation of possible hazards from known rodent carcinogens (*3*) was the HERP index (human exposure/rodent potency). In this article we address the relative ranking by HERP of many common human exposures to rodent carcinogens that either occur naturally in food or are present in food as residues of synthetic pesticides. We use HERP, which is an index of possible hazard rather than a direct estimate of risk, because bioassay results do not provide sufficient information to estimate human risk at low dose. In general, one would expect a similar rank order of "risk estimates" with the use of current regulatory risk assessment methodology for the same exposures because linear extrapolation from the TD_{50} (our measure of carcinogenic potency, defined below) generally leads to low-dose slope estimates similar to those determined on the basis of the linearized multistage model (*5*).

Selection of Chemicals to Be Ranked

Toxicological examination of synthetic chemicals, without similar examination of chemicals that occur naturally, has resulted in an imbalance in both the data on and the perception of chemical carcinogens. Three points that we have discussed (*1*, *3*, *6*) indicate that comparisons should be made with natural as well as synthetic chemicals.

1) The vast proportion of chemicals that humans are exposed to occur naturally. Nevertheless, the public tends to view chemicals as only synthetic and to think of synthetic chemicals as toxic despite the fact that every natural chemical is also toxic at some dose. The daily average exposure of Americans to burnt material in the diet is ~2000 mg, and exposure to natural pesticides (the chemicals that plants produce to defend themselves) is ~1500 mg (*1*). In comparison, the total daily exposure to all synthetic pesticide residues combined is ~0.09 mg (*7*). Thus, we estimate that 99.99% of the pesticides humans ingest are natural (*1*). Despite this enormously greater exposure to natural chemicals, 79% (378 out of 479) of the chemicals tested for carcinogenicity in both rats and mice are synthetic (that is, do not occur naturally) (*2*).

2) It has often been wrongly assumed that humans have evolved defenses against the natural chemicals in our diet but not against the synthetic chemicals (*6*). However, defenses that animals have evolved are mostly general rather than specific for particular chemicals; moreover, defenses are generally inducible and therefore protect well from low doses of both synthetic and natural chemicals (*6*).

3) Because the toxicology of natural and synthetic chemicals is similar, one expects (and finds) a similar positivity rate for carcinogenicity among synthetic and natural chemicals (*1*, *2*, *6*, *8*, *9*). The positivity rate among chemicals tested in rats and mice is ~50% (*1*, *2*, *9*). Therefore, because humans are exposed to so many more natural than synthetic chemicals (by weight and by number), humans are exposed to an enormous background of rodent carcinogens, as defined by high-dose tests on rodents. We have shown that even though only a tiny proportion of natural pesticides in plant foods have been tested, the 29 that are rodent carcinogens among the 57 tested, occur in more than 50 common plant foods (*1*). It is probable that almost every fruit and vegetable in the supermarket contains natural pesticides that are rodent carcinogens.

We have argued that the high positivity rate in rodent studies is due to an increase in cell division produced by high doses rather than simply to selection of suspicious chemical structures (*8*, *10*). Most chemicals were selected for testing because of their use as industrial compounds, pesticides, drugs, or food additives [historically, there has

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Table 1. Carcinogenicity status of natural chemicals in roasted coffee.

Positive	Acetaldehyde, Benzaldehyde, Benzene, Benzofuran, Benzo(*a*)pyrene, Caffeic Acid, Catechol, 1,2,5,6-Dibenzanthracene, Ethanol, Ethylbenzene, Formaldehyde, Furan, Furfural, Hydrogen Peroxide, Hydroquinone, Limonene, MeIQ, Styrene, Toluene
Not positive	Acrolein, Biphenyl, Eugenol, Nicotinic Acid, Phenol, Piperidine [Uncertain: Caffeine (*43*)]
Yet to test	~ 1000 chemicals

been inadequate knowledge to allow prediction of carcinogenicity (*9*)].

Coffee is one example of the background of natural chemicals to which humans are chronically exposed (Table 1). A cup of coffee contains more than 1000 chemicals (*11, 12*). Only 26 were tested for carcinogenicity, and 19 of these were positive in at least one test, totaling at least 10 mg of rodent carcinogens per cup. The average coffee consumption of Americans is about three cups per day (*13*). Rodent carcinogens in coffee include the plant pesticides caffeic acid [present at 1800 parts per million (ppm)] (*11*) and catechol (100 ppm) (*14*). Two other plant pesticides, chlorogenic acid and neochlorogenic acid (present at 21,600 ppm and 11,600 ppm, respectively) (*11*), are metabolized to caffeic acid and catechol; however, these have not been tested for carcinogenicity. Chlorogenic acid and caffeic acid are mutagenic and clastogenic (*15*), and caffeic acid is carcinogenic in both rats and mice (*16*). For *d*-limonene, results from rodents may not be relevant to humans: carcinogenicity in the only target organ, the male rat kidney, is associated with a urinary protein that humans do not excrete (*17*). Some other rodent carcinogens in roasted coffee are products of cooking {for example, furfural, benzo(*a*)pyrene, and MeIQ [2-amino-3,4-dimethylimidazo(4,5-f)quinoline]}.

Ranking Natural and Synthetic Chemicals

In 1987 we compared possible hazards from several different exposures to rodent carcinogens by the HERP index (*3*). HERP indicates the percentage of the rodent potency (TD_{50}, in milligrams per kilogram per day) received by a human during a given lifetime exposure (milligrams per kilogram per day). TD_{50} is the daily lifetime dose rate estimated to halve the proportion of tumor-free animals by the end of a standard lifetime (*18*). Values of TD_{50} in our carcinogenic potency database (CPDB) span a 10-millionfold range.

In this paper we compare HERP indices for every rodent carcinogen in the CPDB (*19*) that occurs naturally in the diet or that is a synthetic pesticide currently in use for which reliable data are available on concentrations in food (*20, 21*). We double the number of HERP indices used in our previous paper (*3*), which discussed in detail several categories of exposure. Here we concentrate on natural chemicals in the diet and on synthetic pesticide residues, which have been added to the HERP ranking.

The 80 typical daily exposures in Table 2 are ordered by possible carcinogenic hazard (HERP). Results are reported for 49 exposures to natural chemicals in the diet, 15 synthetic pesticide residues, and 16 other exposures (including drugs, workplace air, indoor air in homes, food additives, and water pollutants). Two convenient reference points are the HERP of 0.001% for the average U.S. exposure to chloroform (a by-product of water chlorination) in a liter of tap water, and the upper-bound risk estimate used by regulatory agencies of one in a million (using the potency value Q_1^* derived from the linearized multistage model), which converts to a HERP of 0.00003% for rats and 0.00001% for mice. The median HERP for Table 2 is 0.003%.

Natural pesticides. Natural pesticides produced by plants to defend themselves against fungi, insects, and other predators are an important subset of natural chemicals in the diet. Although ~10,000 natural pesticides occur in the human diet, only 57 have been adequately tested in carcinogenesis bioassays. Thus, natural pesticides are markedly underrepresented in our analysis compared to synthetic pesticide residues because few natural chemicals have been tested for carcinogenicity. For each plant food listed, there are about 50 additional untested natural pesticides. In Table 2, many natural pesticide rodent carcinogens in common foods rank above the median, ranging up to a HERP of 0.3%. These include caffeic acid (lettuce, apple, pear, coffee, plum, celery, carrot, potato), estragole (basil), allyl isothiocyanate (mustard), *d*-limonene (mango, orange juice, black pepper), 8-methoxypsoralen (parsnip), safrole (in spices), and symphytine (comfrey herb tea). Caffeic acid is more widespread in plant species than are other natural pesticides.

Synthetic pesticides. Synthetic pesticides currently in use that are rodent carcinogens and that have been found by the Food and Drug Administration (FDA) as residues in food are all included in Table 2; exposures are reported for the most recent estimates. For pesticides no longer in use [ethylene dibromide (EDB), dichlorodiphenyldichloroethylene (DDE)-dichlorodiphenyltrichloroethane (DDT), and unsymmetrical dimethylhydrazine (UDMH) from Alar], exposures in Table 2 are before discontinuance. All synthetic pesticides are below the median and most are at or near the bottom of the ranking. Because uses for some current synthetic pesticides have been restricted by the Environmental Protection Agency (EPA), we investigated whether the low HERP values may be due to reduced usage. This is not the case, because HERPs for the past 10 years of FDA exposure data (*7, 20, 22*) change only marginally and are still at the bottom of the ranking.

Because the exposures in Table 2 for natural pesticides are for typical portions, whereas those for synthetic pesticides are for average daily intake, we examined whether the relative rankings of these two groups of chemicals would be changed if average consumption of each plant food was the basis for the HERP values of natural pesticides (Table 3) (*23*). Generally, the average daily intake is within a factor of 5 of the typical portions reported in Table 2, except for some less common foods (for example, mango and parsnip). Table 3 reports all exposures to natural pesticides and synthetic pesticides from Table 2 for which average consumption data are available. Strikingly, all HERP values that rank in the top third of Table 3 are for natural pesticides, even though few natural pesticides have been tested.

Three synthetic pesticides, captan, chlorothalonil, and folpet, were evaluated by the National Research Council (NRC) as a relatively high risk to humans (*21*), and exposure data were also reported by the FDA in the total diet study. The extremely low HERP values for these exposures (chlorothalonil = 0.0000001%, folpet = 0.000000008%, captan = 0.000000006%) contrast with the high risk estimates of the NRC (which differ by a factor of 99,000 for chlorothalonil, 46,000 for folpet, and 116,000 for captan) because the exposure estimates used by the NRC (that is, the EPA theoretical maximum residue contribution) are hypothetical maximum exposure estimates, whereas the FDA monitors the actual food supply to estimate dietary intakes of pesticides. Hence, the use of hypothetical maxima results in much higher risk estimates than the use of measured residues.

Cooking and preparation of food. Chemicals that are rodent carcinogens can also be produced by cooking and the preparation of food. The HERP values in Table 2 for alcohol in wine (4.7%) and beer (2.8%) rank high. Urethane (ethyl carbamate), a fermentation product, is a rodent carcinogen and is present in both alcoholic beverages (HERP, sake = 0.003%) and bread (HERP, two slices whole wheat toast = 0.00003%). Furfural,

a chemical formed naturally when sugars are heated, is a widespread constituent of food flavor (*12*); it is found in coffee (HERP, 1 cup = 0.005%) and white bread (HERP, 2 slices = 0.002%). The average U.S. exposure to furfural in food is 2.7 mg per day (*13*). A variety of mutagenic and carcinogenic heterocyclic amines are formed during cooking; the highest HERP value is 0.0005% (for 85 g of cooked beef) (*24*). Nitrosamines formed from nitrite or nitrogen oxides (NO_x) and amines in food can give moderate HERP values (for example, bacon = 0.006%).

Occupational and pharmaceutical exposures. Most of the single chemical agents or industrial processes evaluated as human carcinogens have been identified by high-dose exposures in the workplace (*25*). The HERP values for occupational exposure to EDB and formaldehyde are at or near the top of the ranking (140% and 4.0%, respectively). For EDB, the permissible exposure limit (PEL) of the U.S. Occupational Safety and Health Administration (OSHA) is still above the TD_{50} in rodents (*4*); in contrast, the EPA banned the agricultural use of EDB, the main fumigant in the United States, because of the residue levels found in grain (HERP = 0.0004%). For occupational exposures with high HERP values, little quantitative extrapolation is required from the high (MTD) doses used in rodent bioassays to worker exposures.

Some pharmaceuticals are also clustered near the top of the ranking; however, because most are used for only short periods,

Table 2. Ranking possible carcinogenic hazards from natural (in bold) and synthetic chemicals. Daily human exposure: Reasonable daily intakes are used to facilitate comparisons; references are reported in (*44*). The calculations assume a daily dose for a lifetime, where drugs are normally taken for only a short period, we have bracketed the human exposure/rodent potency index (HERP). Possible hazard: The human dose of rodent carcinogen is divided by 70 kg to give a milligrams per kilogram of human exposure, and this dose is given as the percentage of the TD_{50} in the rodent (milligrams per kilogram) to calculate the 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 (*2*). Average TD_{50} values, reported in (*44*), have been calculated separately for rats and mice, and the more sensitive species is used for calculating possible hazard.

Possible hazard: HERP (%)	Daily human exposure	Human dose of rodent carcinogen
140	EDB: workers' daily intake (high exposure)	EDB, 150 mg (before 1977)
17	Clofibrate (avg daily dose)	Clofibrate, 2 g
16	Phenobarbital, 1 sleeping pill	Phenobarbital, 60 mg
[14]	Isoniazid pill (prophylactic dose)	Isoniazid, 300 mg
6.2	Comfrey-pepsin tablets, 9 daily	Comfrey root, 2.7 g
[5.6]	Metronidazole (therapeutic dose)	Metronidazole, 2 g
4.7	Wine (250 ml)	Ethyl alcohol, 30 ml
4.0[a]	Formaldehyde: workers' avg daily intake	Formaldehyde, 6.1 mg
2.8	Beer (12 oz; 354 ml)	Ethyl alcohol, 18 ml
1.4[a]	Mobile home air (14 hour/day)	Formaldehyde, 2.2 mg
1.3	Comfrey-pepsin tablets, 9 daily	Symphytine, 1.8 mg
0.4[a]	Conventional home air (14 hr/day)	Formaldehyde, 598 μg
[0.3]	Phenacetin pill (avg dose)	Phenacetin, 300 mg
0.3	Lettuce, 1/8 head (125 g)	Caffeic acid, 66.3 mg
0.2	Natural root beer (12 oz; 354 ml)	Safrole, 6.6 mg (banned)
0.1	Apple, 1 whole (230 g)	Caffeic acid, 24.4 mg
0.1	1 Mushroom (15 g)	Mix of hydrazines, etc.
0.1	Basil (1 g of dried leaf)	Estragole, 3.8 mg
0.07	Mango, 1 whole (245 g; pitted)	d-Limonene, 9.8 mg
0.07	Pear, 1 whole (200 g)	Caffeic acid, 14.6 mg
0.07	Brown mustard (5 g)	Allyl isothiocyanate, 4.6 mg
0.06	Diet cola (12 oz; 354 ml)	Saccharin, 95 mg
0.06	Parsnip, ¼ (40 g)	8-Methoxypsoralen, 1.28 mg
0.04	Orange juice (6 oz; 177 ml)	d-Limonene, 5.49 mg
0.04	Coffee, 1 cup (from 4 g)	Caffeic acid, 7.2 mg
0.03	Plum, 1 whole (50 g)	Caffeic acid, 6.9 mg
0.03	Safrole: US avg from spices	Safrole, 1.2 mg
0.03	Peanut butter (32 g; 1 sandwich)	Aflatoxin, 64 ng
0.03	Comfrey herb tea (1.5 g)	Symphytine, 38 μg
0.03	Celery, 1 stalk (50 g)	Caffeic acid, 5.4 mg
0.03	Carrot, 1 whole (100 g)	Caffeic acid, 5.16 mg
0.03	Pepper, black: US avg (446 mg)	d-Limonene, 3.57 mg
0.02	Potato, 1 (225 g; peeled)	Caffeic acid, 3.56 mg
0.008	Swimming pool, 1 hour (for child)	Chloroform, 250 μg
0.008	Beer, before 1979 (12 oz; 354 ml)	Dimethylnitrosamine, 1 μg
0.006	Bacon, cooked (100 g)	Diethylnitrosamine, 0.1 μg
0.006[a]	Well water, 1 liter contaminated (worst in Silicon Valley, CA)	Trichloroethylene, 2.8 mg
0.005	Coffee, 1 cup (from 4 g)	Furfural, 630 μg
0.004	Bacon, pan fried (100 g)	N-nitrosopyrrolidine, 1.7 μg
0.003	Nutmeg: US avg (27.4 mg)	d-Limonene, 466 μg
0.003	1 Mushroom (15 g)	Glutamyl p-hydrazinobenzoate, 630 μg
0.003[a]	Conventional home air (14 hr/day)	Benzene, 155 μg
0.003	Sake (250 ml)	Urethane, 43 μg
0.003	Bacon, cooked (100 g)	Dimethylnitrosamine, 300 ng
0.002	White bread, 2 slices (45 g)	Furfural, 333 μg
0.002	Apple juice (6 oz; 177 ml)	UDMH, 5.89 μg (from Alar, 1988)
0.002	Coffee, 1 cup (from 4 g)	Hydroquinone, 100 μg
0.002	Coffee, 1 cup (from 4 g)	Catechol, 400 μg
0.002	DDT: daily dietary avg	DDT, 13.8 μg (before 1972 ban)
0.001	Celery, 1 stalk (50 g)	8-Methoxypsoralen, 30.5 μg
0.001	Tap water, 1 liter	Chloroform, 83 μg (US avg)
0.001	Heated sesame oil (15 g)	Sesamol, 1.13 mg
0.0008	DDE: daily dietary avg	DDE, 6.91 μg (before 1972 ban)
0.0006[a]	Well water, 1 liter contaminated (Woburn, MA)	Trichloroethylene, 267 μg
0.0005	1 Mushroom (15 g)	p-Hydrazinobenzoate, 165 μg
0.0005	Hamburger, pan fried (3 oz; 85 g)	PhIP, 1.28 μg
0.0005	Jasmine tea, 1 cup (2 g)	Benzyl acetate, 460 μg
0.0005	Salmon, pan fried (3 oz; 85 g)	PhIP, 1.18 μg
0.0004	EDB: Daily dietary avg	EDB, 420 ng (from grain; before 1984 ban)
0.0004	Beer (12 oz; 354 ml)	Furfural, 54.9 μg
0.0003	Well water, 1 liter contaminated (Woburn, MA)	Tetrachloroethylene, 21 μg
0.0003	Carbaryl: daily dietary avg	Carbaryl, 2.6 μg (1990)[b]
0.0002	Apple, 1 whole (230 g)	UDMH, 598 ng (from Alar, 1988)
0.0002	Parsley, fresh (1 g)	8-Methoxypsoralen, 3.6 μg
0.0002	Toxaphene: daily dietary avg	Toxaphene, 595 ng (1990)[b]
0.00008	Hamburger, pan fried (3 oz; 85 g)	MeIQx, 111 ng
0.00008	DDE/DDT: daily dietary avg[f]	DDE, 659 ng (1990)[b]
0.00003	Whole wheat toast, 2 slices (45 g)	Urethane, 540 ng
0.00002	Dicofol: daily dietary avg	Dicofol, 544 ng (1990)[b]
0.00002	Cocoa (4 g)	α-Methylbenzyl alcohol, 5.2 μg
0.00001	Lager beer (12 oz; 354 ml)	Urethane, 159 ng
0.000008	Hamburger, pan fried (3 oz; 85 g)	IQ, 23.4 ng
0.000001	Lindane: daily dietary avg	Lindane, 32 ng (1990)[b]
0.0000004	PCNB: daily dietary avg	PCNB (Quintozene), 19.2 ng (1990)[b]
0.0000001	Hamburger, pan fried (3 oz; 85 g)	MeIQ, 1.28 ng
0.0000001	Chlorobenzilate: daily dietary avg	Chlorobenzilate, 6.4 ng (1989)[b]
<0.00000001	Chlorothalonil: daily dietary avg	Chlorothalonil, <6.4 ng (1990)[b]
0.000000008	Folpet: daily dietary avg	Folpet, 12.8 ng (1990)[b]
0.000000007	Coffee, 1 cup (from 4 g)	MeIQ, 0.064 ng
0.000000006	Captan: daily dietary avg	Captan, 11.5 ng (1990)[b]

[a]The value differs from that reported in our earlier HERP paper (*3*), owing to more recent experimental results in the CPDB. [b]Estimate is based on average dietary intake for 60- to 65-year-old females, the only adult group reported for 1990. Because of the agricultural usage of these chemicals and the prominence of fruits and vegetables in the diet of older Americans, the residues are generally slightly higher than for other adult age groups.

and because HERP is an index for a lifetime exposure, the possible carcinogenic hazards would usually be markedly lower than indicated in Table 2.

Discussion and Conclusions

Caution is necessary in drawing conclusions from the occurrence in the diet of natural chemicals that are rodent carcinogens. It is not argued here that these dietary exposures are necessarily of much relevance to human cancer. What is important in our analysis is that widespread exposures to naturally occurring rodent carcinogens may cast doubt on the relevance to human cancer of far lower exposures to synthetic rodent carcinogens. In view of the finding that a high percentage of all chemicals appear to be rodent carcinogens, these results call for a reevaluation of the utility of animal cancer tests done at the MTD for providing information that is useful in protecting humans against low doses of rodent carcinogens. To the extent that increases in tumor incidence in rodent studies are due to the secondary effects of inducing cell division by the MTD, any chemical is a likely carcinogen at the MTD, and carcinogenic effects at low doses are likely to be much lower than a linear model would predict (and may often be zero). With mutagens there is some theoretical justification for thinking that carcinogenic effects may occur at low doses even though no cell division is induced, although the complexities of inducible protection systems may produce a dose-response threshold or even protective effects at very low doses, such as with radiation (26).

Our results indicate that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. However, these results do not necessarily indicate that coffee consumption, for example, is a significant risk factor for human cancer even though it is thousands of times the HERP equivalent to the one-in-a-million worst-case risk used by EPA. Epidemiological evidence may help to clarify this risk (27). Adequate risk assessment from animal cancer tests requires more information about many aspects of toxicology, such as effects on cell division, induction of defense and repair systems, and species differences (28).

With respect to natural pesticides in plant foods, strong epidemiological evidence indicates that low intake of fruits and vegetables doubles the risk of most types of cancer compared to high intake (29, 30). This can probably be attributed to the presence of anticarcinogenic antioxidants and vitamins in fruits and vegetables (30–32). However, only 9% of adult Americans (29) eat the recommended five servings of fruits and vegetables per day (30); we should be eating more of these foods, not less. Particular natural pesticides can be bred out of plants, and cooking methods can be modified, provided that further studies on mechanism or epidemiology indicate that it is important to do so.

The HERP rankings presented indicate that there is an enormous background of human exposure to rodent carcinogens in the diet and that perspective is clearly needed in setting priorities for regulatory policy and research. Although our ranking does not assess the risks to humans, it can be regarded as a way of setting priorities for concern. The number of people exposed is also relevant. By this index, synthetic pesticide residues and water pollution seem to be a minor concern for human cancer. A similar result is expected if the ranking were to use the usual EPA linearized risk assessment methodology for the same exposure values. This is because the upper-bound risk estimate is obtained by multiplying exposure by potency, and because potency estimates from rodent tests are restricted to a narrow range about the high dose tested (33). The usual "one-in-a-million risk" can be approximated merely by dividing the high dose in a positive experiment by 380,000 (34).

It is by no means clear that many significant risk factors for human cancer are single chemicals that will be discovered by screening assays (27). The major preventable risk factors for cancer identified thus far are tobacco (35), dietary imbalances (29–32), hormones (36), and chronic infections (36, 37). High-dose exposures, often to complex mixtures, in an occupational setting (4, 38) may also contribute to a few percent of human cancers (36, 37). High-dose animal cancer tests are clearly relevant for some occupational or medicinal exposures that can be at doses close to the MTD, as discussed. Epidemiological studies do not implicate low-dose exposures to synthetic pollutants or pesticide residues as important risk factors for human cancer (36, 37, 39). High caloric (or protein) intake may be the most striking rodent carcinogen because restriction markedly lowers cancer rates and increases longevity (40).

The arguments presented in this article thus undermine many assumptions of current regulatory policy and necessitate a rethinking of policy designed to reduce human cancer. Economic analyses indicate that, even if current risk assessment methodology is assumed to be correct, the enor-

Table 3. Comparison of average exposures to natural (in bold) and synthetic pesticides.

HERP (%)	Average daily human exposure	Human dose of rodent carcinogen
0.1	**Coffee (from 13.3 g) [3 cups]**	**Caffeic acid, 23.9 mg**
0.04	**Lettuce (14.9 g) [1/67th head]**	**Caffeic acid, 7.90 mg**
0.03	**Safrole in spices**	**Safrole, 1.2 mg**
0.03	**Orange juice (138 ml) [4/5th glass]**	**d-Limonene, 4.28 mg**
0.03	**Pepper, black (446 mg)**	**d-Limonene, 3.57 mg**
0.02	**Mushroom (2.55 g) [1/6th]**	**Mix of hydrazines, etc**
0.02	**Apple (32.0 g) [1/7th]**	**Caffeic acid, 3.40 mg**
0.01	**Celery, (21.6 g) [2/5th stalk]**	**Caffeic acid, 2.33 mg**
0.006	**Coffee (13.3 g) [3 cups]**	**Catechol, 1.33 mg**
0.004	**Potato (54.9 g; peeled) [1/4th]**	**Caffeic acid, 867 μg**
0.003	**Nutmeg (27.4 mg)**	**d-Limonene, 466 μg**
0.003	**Carrot (12.1 g) [1/10th]**	**Caffeic acid, 624 μg**
0.002	**[DDT: daily dietary avg]**	**[DDT, 13.8 μg (before 1972 ban)]**
0.002	**[Apple juice (6 oz; 177 ml)]**	**[UDMH, 5.89 μg (from Alar, 1988)]**
0.001	**Plum (1.86 g) [1/25th]**	**Caffeic acid, 257 μg**
0.001	**Pear (3.29 g) [9/100th]**	**Caffeic acid, 240 μg**
0.0009	**Brown mustard (68.4 mg)**	**Allyl isothiocyanate, 62.9 μg**
0.0008	**[DDE: daily dietary avg]**	**[DDE, 6.91 μg (before 1972 ban)]**
0.0006	**Celery (21.6 g) [2/5th stalk]**	**8-Methoxypsoralen, 13.2 μg**
0.0006	**Mushroom (2.55 g) [1/6th]**	**Glutamyl-p-hydrazinobenzoate, 107 μg**
0.0004	**[EDB: Daily dietary avg]**	**[EDB, 420 ng (before 1984 ban)]**
0.0003	**Carbaryl: daily dietary avg**	**Carbaryl, 2.6 μg (1990)**
0.0002	**Toxaphene: daily dietary avg**	**Toxaphene, 595 ng (1990)**
0.0002	**[Apple, 1 whole (230 g)]**	**[UDMH, 598 ng (from Alar, 1988)]**
0.0001	**Mango (522 mg) [1/500th]**	**d-Limonene, 20.9 μg**
0.00009	**Mushroom (2.55 g) [1/6th]**	**p-Hydrazinobenzoate, 28 μg**
0.00008	**DDE/DDT: daily dietary avg**	**DDE, 659 ng (1990)**
0.00007	**Parsnip (54.0 mg) [1/3300th]**	**8-Methoxypsoralen, 1.57 μg**
0.00005	**Parsley, fresh (324 mg)**	**8-Methoxypsoralen, 1.17 μg**
0.00002	**Dicofol: daily dietary avg**	**Dicofol, 544 ng (1990)**
0.00001	**Cocoa (3.34 g) [4/5th serving]**	**α-Methylbenzyl alcohol, 4.3 μg**
0.000001	**Lindane: daily dietary avg**	**Lindane, 32 ng (1990)**
0.0000004	**PCNB: daily dietary avg**	**PCNB (Quintozene), 19.2 ng (1990)**
0.0000001	**Chlorobenzilate: daily dietary avg**	**Chlorobenzilate, 6.4 ng (1989)**
<0.00000001	**Chlorothalonil: daily dietary avg**	**Chlorothalonil, <6.4 ng (1990)**
0.000000008	**Folpet: daily dietary avg**	**Folpet, 12.8 ng (1990)**
0.000000006	**Captan: daily dietary avg**	**Captan, 11.5 ng (1990)**

mous amount of money spent trying to prevent "one-in-a-million risks" can be counterproductive and involve economic and health-related trade-offs (*41*). In the case of synthetic pesticides, the concern with minuscule residues makes fruits and vegetables more expensive and thus serves to decrease consumption of foods that help to prevent cancer (*29*). Risk assessment guidelines of the EPA state that risk estimates are an upper bound on risk and that the true risk at low dose may be zero (*42*). The public might be well served if each "risk assessment" for a particular chemical included such a cautionary explanation and compared the risk to similarly estimated risks for coffee, beer, and other natural dietary exposures. Regulatory agencies have an important educational role to play, and this would put hypothetical risks in perspective. Such agencies should at least establish a threshold of attention for hypothetical cancer risks that are low compared to the background risk; otherwise, resources may be diverted from important risks.

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