Environmental Pollution, Pesticides, and the Prevention of Cancer: Misconceptions[1]

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ABSTRACT **The major causes of cancer are: *1*) smoking, which accounts for about a third of U.S. cancer and 90% of lung cancer; *2*) dietary imbalances: lack of sufficient amounts of dietary fruits and vegetables. The quarter of the population eating the fewest fruits and vegetables has double the cancer rate for most types of cancer than the quarter eating the most; *3*) chronic infections, mostly in developing countries; and *4*) hormonal factors, influenced primarily by lifestyle. There is no cancer epidemic except for cancer of the lung due to smoking. Cancer mortality rates have declined by 16% since 1950 (excluding lung cancer). Regulatory policy that focuses on traces of synthetic chemicals is based on misconceptions about animal cancer tests. Recent research indicates that rodent carcinogens are not rare. Half of all chemicals tested in standard high-dose animal cancer tests, whether occurring naturally or produced synthetically, are "carcinogens"; there are high-dose effects in rodent cancer tests that are not relevant to low-dose human exposures and which contribute to the high proportion of chemicals that test positive. The focus of regulatory policy is on synthetic chemicals, although 99.9% of the chemicals humans ingest are natural. More than 1000 chemicals have been described in coffee: 28 have been tested and 19 are rodent carcinogens. Plants in the human diet contain thousands of natural "pesticides" produced by plants to protect themselves from insects and other predators: 63 have been tested and 35 are rodent carcinogens.**

There is no convincing evidence that synthetic chemical pollutants are important as a cause of human cancer. Regulations targeted to eliminate minuscule levels of synthetic chemicals are enormously expensive: the Environmental Protection Agency has estimated that environmental regulations cost society $140 billion/year. Others have estimated that the median toxic control program costs 146 times more per hypothetical life-year saved than the median medical intervention. Attempting to reduce tiny hypothetical risks has other costs as well: if reducing synthetic pesticides makes fruits and vegetables more expensive, thereby decreasing consumption, then the cancer rate will increase, especially for the poor. The prevention of cancer will come from knowledge obtained from biomedical research, education of the public, and lifestyle changes made by individuals. A reexamination of priorities in cancer prevention, both public and private, seems called for.—Ames, B. N., Gold, L. S. Environmental pollution, pesticides, and the prevention of cancer: misconceptions. *FASEB J.* 11, 1041–1052 (1997)

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VARIOUS MISCONCEPTIONS ABOUT THE RELATIONSHIP between environmental pollution and human dis-

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ease, particularly cancer, drive regulatory policy. We highlight nine such misconceptions and briefly present scientific evidence that undermines each.

MISCONCEPTION #1: CANCER RATES ARE SOARING

Overall cancer death rates in the U.S. (excluding lung cancer due to smoking) have declined 16% since 1950 (1). The types of cancer deaths that have decreased since 1950 are primarily stomach, cervical, uterine, and colorectal. Those that have increased are primarily lung cancer (90% is due to smoking, as are 35% of all cancer deaths in the U.S.), melanoma (probably due to sunburns), and non-Hodgkin's lymphoma. If lung cancer is included, mortality rates have increased over time, but recently have declined in men due to decreased smoking (1). The rise in incidence rates in older age groups for some cancers (e.g., prostate) can be explained by known factors such as improved screening. "The reason for not focusing on the reported incidence of cancer is that the scope and precision of diagnostic information, practices in screening and early detection, and criteria for reporting cancer have changed so much over time that trends in incidence are not reliable" (2; see also refs 3, 4). Life expectancy has continued to rise since 1950.

MISCONCEPTION #2: ENVIRONMENTAL SYNTHETIC CHEMICALS ARE AN IMPORTANT CAUSE OF HUMAN CANCER

Neither epidemiology nor toxicology support the idea that synthetic industrial chemicals are important as a cause of human cancer (4–6). Epidemiological studies have identified the factors likely to have a major effect on lowering cancer rates: reduction of smoking, improving diet (e.g., increased consumption of fruits and vegetables), hormonal factors, and control of infections (6). Although some epidemiological studies find an association between cancer and low levels of industrial pollutants, the associations are usually weak, the results are usually conflicting, and the studies do not correct for potentially large confounding factors such as diet. Moreover, exposures to synthetic pollutants are tiny and rarely seem toxicologically plausible as a causal factor, particularly when compared to the background of natural chemicals that are rodent carcinogens (5). Even assuming that worst-case risk estimates for synthetic pollutants are true risks, the proportion of cancer that the Environmental Protection Agency (EPA)[5] could prevent by regulation would be tiny (7). Occupational exposure to some carcinogens causes cancer, though exactly how much has been a controversial issue: a few percent seems a reasonable estimate (6), much of this from asbestos in smokers. Exposure to substances in the workplace can be much higher than the exposure to chemicals in food, air, and water. Past occupational exposures have sometimes been high, and therefore comparatively little quantitative extrapolation may be required from high-dose rodent tests to high-dose occupational exposures in order to assess risk. Since occupational cancer is concentrated among small groups with high levels of exposure, there is an opportunity to control or eliminate risks once they are identified; however, current permissible levels of exposure in the workplace are sometimes close to the carcinogenic dose in rodents (8).

Cancer is due, in part, to normal aging and increases exponentially with age in both rodents and humans (9). To the extent that the major external risk factors for cancer are diminished, cancer will occur at later ages and the proportion of cancer caused by normal metabolic processes will increase. Aging and its degenerative diseases appear to be due in good part to oxidative damage to DNA and other macromolecules (9). By-products of normal metabolism—superoxide, hydrogen peroxide, and hydroxyl radical—are the same oxidative mutagens produced by radiation. Mitochondria from old animals leak oxidants (10): old rats have about 66,000 oxidative DNA lesions per cell (11). DNA is oxidized in normal metabolism because antioxidant defenses, though numerous, are not perfect. Antioxidant defenses against oxidative damage include vitamins C and E and perhaps carotenoids (12), most of which come from dietary fruits and vegetables.

Smoking contributes to about 35% of cancer, about one-quarter of heart disease, and about 400,000 premature deaths per year in the U.S. (6, 13). Tobacco is a known cause of cancer of the lung, bladder, mouth, pharynx, pancreas, stomach, larynx, esophagus, and possibly colon. Tobacco causes even

and implications for cancer prevention, interspecies extrapolation, and regulatory policy. The Carcinogenic Potency Database, published as a CRC handbook, analyzes the results of 5000 chronic, long-term cancer tests on 1300 chemicals. Dr. Gold has served on the Panel of Expert Reviewers for the National Toxicology Program, on Boards of the Harvard Center for Risk Analysis and the Annapolis Center, and was a member of the Harvard Risk Management Group. Lois@potency.Berkeley.edu (510)486-7080.

[5] Abbreviations: EPA, Environmental Protection Agency; NTP, National Toxicology Program; NCI, National Cancer Institute, NAS, National Academy of Sciences; NRC, National Research Council; MTD, maximum tolerated dose; VSD, virtually safe dose; HERP, human exposure/rodent potency; ppb, parts per billion.

more deaths by diseases other than cancer. Smoke contains a wide variety of mutagens and rodent carcinogens. Smoking is also a severe oxidative stress and causes inflammation in the lung. The oxidants in cigarette smoke—mainly nitrogen oxides—deplete the body's antioxidants. Thus, smokers must ingest two to three times more vitamin C than nonsmokers to achieve the same level in the blood, but they rarely do. An inadequate concentration of vitamin C in plasma is more common among the poor and smokers. Men with inadequate diets or who smoke may damage both their somatic DNA and the DNA of their sperm. When the level of dietary vitamin C is insufficient to keep seminal fluid vitamin C at an adequate level, the oxidative lesions in sperm DNA are increased 250% (14–16). Male smokers have more oxidative lesions in sperm DNA (16) and more chromosomal abnormalities in sperm (17) than do nonsmokers. It is plausible, therefore, that fathers who smoke may increase the risk of birth defects and childhood cancer in their offspring (14, 15, 18). A new epidemiological study suggests that the rate of childhood cancers is increased in the offspring of male smokers: acute lymphocytic leukemia, lymphoma, and brain tumors are increased three to four times (19).

We (6) estimate that unbalanced diets account for about one-third of cancer risk, in agreement with an earlier estimate by Doll and Peto (3). Low intake of fruits and vegetables is a major risk factor for cancer (See Misconception #3). There has been considerable interest in calories (and dietary fat) as a risk factor for cancer, in part because caloric restriction markedly lowers the cancer rate and increases life span in rodents (6, 20, 21).

Chronic inflammation from chronic infection results in the release of oxidative mutagens from phagocytic cells and is a major contributor to cancer (6, 22). White cells and other phagocytic cells of the immune system combat bacteria, parasites, and virus-infected cells by destroying them with potent, mutagenic oxidizing agents. These oxidants protect humans from immediate death from infection, but they also cause oxidative damage to DNA, chronic cell killing with compensatory cell division, and mutation (23, 24); thus, they contribute to the carcinogenic process. Antioxidants appear to inhibit some of the pathology of chronic inflammation. Chronic infections cause about 21% of new cancer cases in developing countries and 9% in developed countries (25).

Endogenous reproductive hormones play a large role in cancer, including that of the breast, prostate, ovary, and endometrium (26, 27), contributing to as much as 20% of all cancer. Many lifestyle factors such as reproductive history, lack of exercise, obesity, and alcohol influence hormone levels and therefore affect risk (6, 26–28).

Other causal factors in human cancer are excessive alcohol consumption, excessive sun exposure, and viruses. Genetic factors also play a significant role and interact with lifestyle and other risk factors. Biomedical research is uncovering important genetic variation in humans.

MISCONCEPTION #3: REDUCING PESTICIDE RESIDUES IS AN EFFECTIVE WAY TO PREVENT DIET-RELATED CANCER

Reductions in synthetic pesticide use will not effectively prevent diet-related cancer. Fruits and vegetables are of major importance in reducing cancer; if they become more expensive due to a reduced use of synthetic pesticides, cancer is likely to increase. People with low incomes eat fewer fruits and vegetables and spend a higher percentage of their income on food.

Dietary fruits and vegetables in cancer prevention

High consumption of fruits and vegetables is associated with a lowered risk of degenerative diseases including cancer, cardiovascular disease, cataracts, and brain dysfunction (6, 9). More than 200 studies in the epidemiological literature have been reviewed that show, with great consistency, an association between low consumption of fruits and vegetables and cancer incidence (29–31) (**Table 1**). The quarter of the population with the lowest dietary intake of fruits and vegetables vs. the quarter with the highest intake has roughly twice the cancer rate for most types of cancer (lung, larynx, oral cavity, esophagus, stomach, colorectal, bladder, pancreas, cervix, and ovary). Eighty percent of American children and adolescents, and 68% of adults (32, 33) did not meet the intake recommended by the National Cancer Institute (NCI) and the National Research Council (NRC): five servings of fruits and vegetables per day. Publicity about hundreds of minor hypothetical risks can cause loss of perspective on what is important: half the U.S. population does not know that fruit and vegetable consumption is a major protection against cancer (34).

Some micronutrients in fruits and vegetables are anticarcinogens

Antioxidants in fruits and vegetables may account for some of their beneficial effect, as discussed in Misconception #2. However, it is difficult to disentangle by epidemiological studies the effects of dietary antioxidants from effects of other important vitamins and ingredients present in fruits and vegetables (30, 31, 35).

TABLE 1. *Review of epidemiological studies of cancer showing protection by consumption of fruits and vegetables*[a]

Cancer site	Fraction of studies showing significant cancer protection	Relative risk (median) low vs. high quartile of consumption
Epithelial		
Lung	24/25	2.2
Oral	9/9	2.0
Larynx	4/4	2.3
Esophagus	15/16	2.0
Stomach	17/19	2.5
Pancreas	9/11	2.8
Cervix	7/8	2.0
Bladder	3/5	2.1
Colorectal	20/35	1.9
Miscellaneous	6/8	—
Hormone dependent		
Breast	8/14	1.3
Ovary/endometrium	3/4	1.8
Prostate	4/14	1.3
Total	129/172	

[a] From ref 29.

Folate deficiency, one of the most common vitamin deficiencies, causes extensive chromosome breaks in human genes (36). Approximately 10% of the U.S. population (37) has a blood folate level lower than that at which chromosome breaks can occur (36). In two small studies of low-income (mainly African-American) elderly persons (38) and adolescents (39), nearly half had folate levels that were that low. The mechanism of damage is deficient methylation of uracil to thymine and the subsequent incorporation of uracil into human DNA (4 million/cell) (36). During repair of uracil in DNA, transient nicks are formed; two opposing nicks cause a chromosome break. High DNA uracil levels and chromosome breaks in humans are both reversed by folate administration (36). Chromosome breaks could contribute to the increased risk of cancer and cognitive defects associated with folate deficiency in humans (36). Folate deficiency also damages human sperm (40), causes neural tube defects in the fetus, and is responsible for about 10% of the risk for heart disease in the U.S. (41).

Micronutrients whose main dietary sources are other than fruits and vegetables are also likely to play a significant role in the prevention and repair of DNA damage, and thus are important to the maintenance of long-term health. Deficiency of vitamin B_{12} causes a functional folate deficiency, accumulation of homocysteine (a risk factor for heart disease) (42), and misincorporation of uracil into DNA (43). Strict vegetarians are at increased risk for developing vitamin B_{12} deficiency (42). Niacin contributes to the repair of DNA strand breaks by maintaining nicotinamide adenine dinucleotide levels for the poly ADP-ribose protective response to DNA damage (44). As a result, dietary insufficiencies of niacin (15% of some populations are deficient) (45), folate, and antioxidants may interact synergistically to adversely affect DNA synthesis and repair. Diets deficient in fruits and vegetables are commonly low in folate, antioxidants (e.g., vitamin C), and many other micronutrients, and result in DNA damage and higher cancer rates (6, 29, 46).

Optimizing micronutrient intake can have a major effect on health at a low cost. More research in this area as well as efforts to increase micronutrient intake and to improve diets should be high priorities for public policy.

MISCONCEPTION #4: HUMAN EXPOSURES TO CARCINOGENS AND OTHER POTENTIAL HAZARDS ARE PRIMARY TO SYNTHETIC CHEMICALS

Contrary to common perception, 99.9% of the chemicals humans ingest are natural. The amounts of synthetic pesticide residues in plant foods, for example, are insignificant compared to the amount of natural "pesticides" produced by the plants themselves (47–49). Of all dietary pesticides that humans eat, 99.99% are natural: these are chemicals produced by plants to defend themselves against fungi, insects, and other animal predators (47, 48). Each plant produces a different array of such chemicals. On average, Americans ingest roughly 5,000 to 10,000 different natural pesticides and their breakdown products. Americans eat about 1,500 mg of natural pesticides per person per

TABLE 2. *Carcinogenicity of natural plant pesticides tested in rodents (49)*[a]

Carcinogens:[b] N = 35	Acetaldehyde methylformylhydrazone, allyl isothiocyanate, arecoline·HCl, benzaldehyde, benzyl acetate, caffeic acid, catechol, clivorine, coumarin, crotonaldehyde, cycasin and methylazoxymethanol acetate, 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, 8-methoxypsoralen, *N*-methyl-*N*-formylhydrazine, α-methylbenzyl alcohol, 3-methylbutanal methylformylhydrazone, methylhydrazine, monocrotaline, pentanal methylformylhydrazone, petasitenine, quercetin, reserpine, safrole, senkirkine, sesamol, symphytine
Noncarcinogens: N = 28	Atropine, benzyl alcohol, biphenyl, *d*-carvone, deserpidine, disodium glycyrrhizinate, emetine·2HCl, ephedrine sulphate, eucalyptol, eugenol, gallic acid, geranyl acetate, β-*N*-[γ-*l*(+)-glutamyl]-4-hydroxymethylphenylhydrazine, glycyrrhetinic acid, *p*-hydrazinobenzoic acid, isosafrole, kaempferol, *d*-menthol, nicotine, norharman, pilocarpine, piperidine, protocatechuic acid, rotenone, rutin sulfate, sodium benzoate, 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 milk, cinnamon, cloves, cocoa, 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.

day, which is about 10,000 times more than they consume of synthetic pesticide residues.

Even though only a small proportion of natural pesticides has been tested for carcinogenicity, half of those tested (35/63) are rodent carcinogens; naturally occurring pesticides that are rodent carcinogens are ubiquitous in fruits, vegetables, herbs, and spices (49) (**Table 2**).

Cooking of foods produces burnt material (about 2000 mg per person per day) that contains many rodent carcinogens. In contrast, the residues of 200 synthetic chemicals measured by the Federal Drug Administration, including the synthetic pesticides thought to be of greatest importance, average only about 0.09 mg per person per day (47, 49). In a single cup of coffee, the natural chemicals that are rodent carcinogens are about equal in weight to an entire year's worth of synthetic pesticide residues that are rodent carcinogens, even though only 3% of the natural chemicals in roasted coffee have been adequately tested for carcinogenicity (5) (**Table 3**). This does not mean that coffee or natural pesticides are dangerous, but rather that assumptions about high-dose animal cancer tests for assessing human risk at low doses need reexamination. No diet can be free of natural chemicals that are rodent carcinogens (49).

MISCONCEPTION #5: CANCER RISKS TO HUMANS CAN BE ASSESSED BY STANDARD HIGH-DOSE ANIMAL CANCER TESTS

Approximately half of all the chemicals that have been tested in standard animal cancer tests, whether natural or synthetic, are rodent carcinogens (5, 50) (**Table 4**). Why such a high positivity rate? In standard cancer tests, rodents are given chronic, near-toxic doses, the maximum tolerated dose (MTD). Evidence is accumulating that cell division caused by the high dose itself, rather than the chemical per se, is increasing the positivity rate. High doses can cause chronic wounding of tissues, cell death, and consequent chronic cell division of neighboring cells, which is a risk factor for cancer (51). Each time a cell divides the probability increases that a mutation will occur, thereby increasing the risk for cancer. At the low levels to which humans are usually exposed, such increased cell division does not occur. In addition, tissues injured by high doses of chemicals (e.g., phenobarbital, carbon tetrachloride, tetradecanoylphorbol acetate) have an inflammatory immune response involving activation of recruited and resident macrophages in response to necrosis (52–58). Activated macrophages release mutagenic oxidants (including peroxynitrite, hypochlorite, and H_2O_2). Therefore,

TABLE 3. *Carcinogenicity in rodents of natural chemicals in roasted coffee*[a]

Positive: N = 19	Acetaldehyde, benzaldehyde, benzene, benzofuran, benzo(a)pyrene, caffeic acid, catechol, 1,2,5,6-dibenzanthracene, ethanol, ethylbenzene, formaldehyde, furan, furfural, hydrogen peroxide, hydroquinone, limonene, styrene, toluene, xylene
Not positive: N = 8	Acrolein, biphenyl, choline, eugenol, nicotinamide, nicotinic acid, phenol, piperidine
Uncertain:	Caffeine
Yet to test:	~1000 chemicals

[a] From ref 50.

TABLE 4. *Proportion of chemicals evaluated as carcinogenic*

Chemicals tested in both rats and mice[a]	330/559 (59%)
Naturally occurring chemicals	73/127 (57%)
Synthetic chemicals	257/432 (59%)
Chemicals tested in rats and/or mice[a]	
Chemicals in Carcinogenic Potency Database	668/1275 (52%)
Natural pesticides	35/63 (56%)
Mold toxins	14/23 (61%)
Chemicals in roasted coffee	19/28 (68%)
Innes negative chemicals retested[a,b]	16/34 (47%)
Physician's Desk Reference (PDR): drugs with reported cancer tests[c]	117/241 (49%)
FDA database of drug submissions[d]	125/282 (44%)

[a] From the Carcinogenic Potency Database (50). [b] The 1969 study by Innes et al. (84) is frequently cited as evidence that the proportion of carcinogens is low, as only 9% of 119 chemicals tested (primarily pesticides) were positive. However, these tests, which were performed only on mice with few animals per group, lacked the power of modern tests. Of the 34 Innes negative chemicals that have been retested using modern protocols, 16 were positive. [c] Davies and Monro (85). [d] Contrera et al. (86). 140 drugs are in both the FDA and PDR databases.

the very low levels of chemicals to which humans are exposed through water pollution or synthetic pesticide residues may pose no or only minimal cancer risks.

We have discussed (59) the argument that the high positivity rate is due to selecting more suspicious chemicals to test, which is a likely bias since cancer testing is both expensive and time-consuming, and it is prudent to test suspicious compounds. One argument against selection bias is the high positivity rate for drugs (Table 4), because drug development tends to select chemicals that are not mutagens or expected carcinogens. A second argument against selection bias is that knowledge to predict carcinogenicity in rodent tests is highly imperfect, even now, after decades of testing results have become available on which to base prediction. For example, a prospective prediction exercise was conducted by several experts in 1990 in advance of the 2-year National Toxicology Program (NTP) bioassays. There was wide disagreement among the experts as to which chemicals would be carcinogenic when tested; accuracy varied, thus indicating that predictive knowledge is highly uncertain (60). Moreover, if the main basis for selection were suspicion rather than human exposure, then one should select mutagens (79% are positive compared to 49% of nonmutagens), yet 55% of the chemicals tested are nonmutagens (59).

It seems likely that a high proportion of all chemicals, whether synthetic or natural, might be "carcinogens" if run through the standard rodent bioassay at the MTD: for nonmutagens, carcinogenicity would be due primarily to the effects of high doses; for mutagens, it would result from a synergistic effect between cell division at high doses and DNA damage (61–63). Without additional data on the mechanism of carcinogenesis for each chemical, the interpretation of a positive result in a rodent bioassay is highly uncertain. The carcinogenic effects may be limited to the high dose tested.

In regulatory policy, the "virtually safe dose" (VSD), which corresponds to a maximum hypothetical cancer risk of 1 in 1 million, is estimated from bioassay results by using a linear model. To the extent that carcinogenicity in rodent bioassays is due to the effects of high doses for nonmutagens and a synergistic effect of cell division at high doses with DNA damage for mutagens, then this model is inappropriate. Moreover, as currently calculated, the VSD can be known without ever conducting a bioassay: for 96% of the NCI/NTP rodent carcinogens, the VSD is within a factor of 10 of the ratio MTD/740,000 (64). This is about as precise as the estimate obtained from conducting near-replicate cancer tests of the same chemical (64).

MISCONCEPTION #6: SYNTHETIC CHEMICALS POSE GREATER CARCINOGENIC HAZARDS THAN NATURAL CHEMICALS

Gaining a broad perspective about the vast number of chemicals to which humans are exposed can be helpful when setting research and regulatory priorities (5, 48, 49, 65). Rodent bioassays provide little information about the mechanisms of carcinogenesis and low-dose risk. The assumption that synthetic chemicals are hazardous has led to a bias in testing so that synthetic chemicals account for 77% (432/559) of the chemicals tested chronically in both rats and mice (Table 4). The natural world of chemicals has never been tested systematically.

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 focus on those that rank highest (5, 50). Ranking is a critical first step that can help set priorities when selecting chemicals for chronic bioassay or mechanistic studies, for epidemiological research, and for regulatory policy. Al-

though 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, by using the same methodology to identify hazard, there are numerous common human exposures with much greater possible hazards. Our analyses are based on the HERP (Human Exposure/Rodent Potency) index, which indicates what percentage of the rodent carcinogenic potency (TD_{50} in mg/kg/day) a person receives from a given daily dose for a lifetime of exposure (mg/kg/day) (66) (**Table 5**). A ranking based on standard regulatory risk assessment would be similar.

Overall, our analyses have shown that HERP values for some historically high exposures in the workplace and certain 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 residues of synthetic chemicals such as pesticides (5, 8, 50). A committee of the NRC/National Academy of Sciences (NAS) recently reached similar conclusions about natural vs. synthetic chemicals in the diet and called for further research on natural chemicals (67).

The possible carcinogenic hazards from synthetic pesticides (at average exposures) are minimal compared to the background of nature's pesticides, though neither may present a hazard at the low doses consumed (Table 5). Table 5 also indicates that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. For many natural chemicals, the HERP values are in the top half of the table, even though natural chemicals are markedly underrepresented because so few have been tested in rodent bioassays. 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. Our results call for a reevaluation of the utility of animal cancer tests for protecting the public against minor hypothetical risks.

MISCONCEPTION #7: THE TOXICOLOGY OF SYNTHETIC CHEMICALS IS DIFFERENT FROM THAT OF NATURAL CHEMICALS

It is often assumed that because natural chemicals 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 fail to protect against synthetic chemicals. This assumption is flawed for several reasons (48, 51).

Humans have many natural defenses that buffer against normal exposure to toxins (48); usually these are general rather than tailored to each specific chemical. Thus, the defenses work against both natural and synthetic chemicals. Examples of general defenses include the continuous shedding of cells exposed to toxins—surface layers of the mouth, esophagus, stomach, intestine, colon, skin, and lungs are discarded every few days; DNA repair enzymes, which repair DNA that has been damaged from many different sources; and detoxification enzymes of the liver and other organs, which generally target classes of toxins rather than individual toxins. That defenses are usually general, rather than specific for each chemical, makes good evolutionary sense. The reason that predators of plants evolved general defenses presumably was 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 toxins.

Various natural toxins that have been present throughout vertebrate evolutionary history nevertheless cause cancer in vertebrates (48, 50). Mold toxins, such as aflatoxin, have been shown to cause cancer in rodents and other species, including humans (Table 4). 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 food may be carcinogenic risks to humans; for example, the chewing of betel nuts with tobacco has been correlated with oral cancer.

Humans have not had time to evolve a "toxic harmony" with all of the plants in their diet. 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 (relatively) newly introduced plants.

DDT is often viewed as the prototypically dangerous synthetic pesticide because it concentrates in the tissues and persists for years, being slowly released into the bloodstream. DDT, the first synthetic pesticide, eradicated malaria from many parts of the world, including the U.S. It was effective against many vectors of disease such as mosquitoes, tsetse flies, lice, ticks, and fleas. DDT was also lethal to many crop pests, and significantly increased the supply and lowered the cost of food, making fresh, nutritious foods more accessible to poor people. It was also of low

TABLE 5. *Ranking possible carcinogenic hazards from average U.S. exposures (50)*[a]

Possible hazard: HERP (%)	Average daily U.S. exposure	Human dose of rodent carcinogen	Potency, TD_{50} (mg/kg/day)[b] Rats	Mice
140	Ethylene dibromide (EDB): workers (high exposure) (before 1977)	EDB, 150 mg	1.52	(7.45)
17	Clofibrate	Clofibrate, 2 g	169	.
14	Phenobarbital, 1 sleeping pill	Phenobarbital, 60 mg	(+)	6.09
6.8	1,3-Butadiene: rubber workers (1978–1986)	1,3-Butadiene, 66.0 mg	(261)	13.9
6.1	Tetrachloroethylene: dry cleaners with dry-to-dry units (1980–1990)[c]	Tetrachloroethylene, 433 mg	101	(126)
4.0	Formaldehyde: workers	Formaldehyde, 6.1 mg	2.19	(43.9)
2.1	**Beer, 257 g**	**Ethyl alcohol, 13.1 ml**	9110	(—)
1.4	Mobile home air (14 h/day)	Formaldehyde, 2.2 mg	2.19	(43.9)
0.9	Methylene chloride: workers (1940s–1980s)	Methylene chloride, 471 mg	724	(918)
0.5	**Wine, 28.0 g**	**Ethyl alcohol, 3.36 ml**	9110	(—)
0.4	Conventional home air (14 h/day)	Formaldehyde, 598 mg	2.19	(43.9)
0.1	**Coffee, 13.3 g**	**Caffeic acid, 23.9 mg**	297	(4900)
0.04	**Lettuce, 14.9 g**	**Caffeic acid, 7.90 mg**	297	(4900)
0.03	**Safrole in spices**	**Safrole, 1.2 mg**	(441)	51.3
0.03	**Orange juice, 138 g**	***d*-Limonene, 4.28 mg**	204	(—)
0.03	**Pepper, black, 446 mg**	***d*-Limonene, 3.57 mg**	204	(—)
0.02	**Mushroom (*Agaricus bisporus*, 2.55 g)**	**Mixture of hydrazines, etc. (whole mushroom)**	—	20,300
0.02	**Apple, 32.0 g**	**Caffeic acid, 3.40 mg**	297	(4900)
0.02	**Coffee, 13.3 g**	**Catechol, 1.33 mg**	118	(244)
0.02	**Coffee, 13.3 g**	**Furfural, 2.09 mg**	(683)	197
0.009	Butylated hydroxyanisole (BHA): daily U.S. avg (1975)	BHA, 4.6 mg	745	(5530)
0.008	**Beer (before 1979), 257 g**	**Dimethylnitrosamine, 726 ng**	0.124	(0.189)
0.008	**Aflatoxin: daily U.S. avg (1984–89)**	**Aflatoxin, 18 ng**	0.0032	(+)
0.007	**Cinnamon, 21.9 mg**	**Coumarin, 65.0 mg**	13.9	(103)
0.006	**Coffee, 13.3 g**	**Hydroquinone, 333 mg**	82.8	(225)
0.005	Saccharin: daily U.S. avg (1977)	Saccharin, 7 mg	2140	(—)
0.005	**Carrot, 12.1 g**	**Aniline, 624 mg**	194[d]	(—)
0.004	**Potato, 54.9 g**	**Caffeic acid, 867 mg**	297	(4900)
0.004	**Celery, 7.95 g**	**Caffeic acid, 858 mg**	297	(4900)
0.004	**White bread, 67.6 g**	**Furfural, 500 mg**	(683)	197
0.003	**Nutmeg, 27.4 mg**	***d*-Limonene, 466 mg**	204	(—)
0.003	Conventional home air (14 h/day)	Benzene, 155 mg	(169)	77.5
0.002	**Carrot, 12.1 g**	**Caffeic acid, 374 mg**	297	(4900)
0.002	Ethylene thiourea: daily U.S. avg (1990)	Ethylene thiourea, 9.51 mg	7.9	(23.5)
0.002	[DDT: daily U.S. avg (before 1972 ban)]	[DDT, 13.8 mg]	(84.7)	12.3
0.001	**Plum, 2.00 g**	**Caffeic acid, 276 mg**	297	(4900)
0.001	BHA: daily U.S. avg (1987)	BHA, 700 mg	745	(5530)
0.001	**Pear, 3.29 g**	**Caffeic acid, 240 mg**	297	(4900)
0.001	[Unsymmetric 1,1-dimethylhydrazine (UDMH): daily U.S. avg (1988)]	[UDMH, 2.82 mg (from Alar)]	(—)	3.96
0.0009	**Brown mustard, 68.4 mg**	**Allyl isothiocyanate, 62.9 mg**	96	(—)
0.0008	[DDE: daily U.S. avg (before 1972 ban)]	[DDE, 6.91 mg]	(—)	12.5
0.0007	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD): daily U.S. avg (1994)	TCDD, 12.0 pg	0.0000235	(0.000156)
0.0007	Bacon, 11.5 g	Diethylnitrosamine, 11.5 ng	0.0237	(+)

[a] **Chemicals that occur naturally in foods are in boldface.** Daily human exposure: The calculations assume an average daily dose for a lifetime. Possible hazard: The human exposure to a 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 Human Exposure/Rodent Potency index (HERP); 100% means that the human exposure in mg/kg/day is equal to the dose estimated to give 50% of the rodents tumors. TD_{50} values used in the HERP calculation are averages calculated by taking the harmonic mean of the TD_{50}s of positive tests with species from the Carcinogenic Potency Database. Average TD_{50} values have been calculated separately for rats and mice; the more potent value is used to calculate possible hazard. The less potent value is in parentheses. Exposures in brackets are for chemicals that have been banned or discontinued. [b] Period (.) = no data in CPDB; (—) = negative in cancer test; (+) = positive cancer test(s) not suitable for calculating a TD_{50}. [c] This is not an average, but a reasonably large sample (1027 workers). [d] TD_{50} harmonic mean was estimated for the base chemical from the hydrochloride salt. [e] Additional data from EPA that is not in the CPDB were used to calculate these TD_{50} harmonic means.

continued on next page

TABLE 5. (*continued*)

Possible hazard: HERP (%)	Average daily U.S. exposure	Human dose of rodent carcinogen	Potency, TD_{50} (mg/kg/day)[b] Rats	Mice
0.0006	**Mushroom (*Agaricus bisporus*, 2.55 g)**	**Glutamyl-*p*-hydrazinobenzoate, 107 mg**	.	277
0.0004	**Bacon, 11.5 g**	***N*-Nitrosopyrrolidine, 196 ng**	(0.799)	0.679
0.0004	**Bacon, 11.5 g**	**Dimethylnitrosamine, 34.5 ng**	0.124	(0.189)
0.0004	[EDB: Daily U.S. avg (before 1984 ban)]	[EDB, 420 ng]	1.52	(7.45)
0.0004	Tap water, 1 liter (1987–1992)	Bromodichloromethane, 13 mg	(72.5)	47.7
0.0003	**Mango, 1.22 g**	***d*-Limonene, 48.8 mg**	204	(—)
0.0003	**Beer, 257 g**	**Furfural, 39.9 mg**	(683)	197
0.0003	Tap water, 1 liter (1987–1992)	Chloroform, 17 mg	(262)	90.3
0.0003	Carbaryl: daily U.S. avg (1990)	Carbaryl, 2.6 mg	14.1	(—)
0.0002	**Celery, 7.95 g**	**8-Methoxypsoralen, 4.86 mg**	32.4	(—)
0.0002	Toxaphene: daily U.S. avg (1990)	Toxaphene, 595 ng	(—)	5.57
0.00009	**Mushroom (*Agaricus bisporus*, 2.55 g)**	***p*-Hydrazinobenzoate, 28 mg**	.	454[d]
0.00008	PCBs: daily U.S. avg (1984–86)	PCBs, 98 ng	1.74	(9.58)
0.00008	DDE/DDT: daily U.S. avg (1990)	DDE, 659 ng	(—)	12.5
0.00007	**Parsnip, 54.0 mg**	**8-Methoxypsoralen, 1.57 mg**	32.4	(—)
0.00007	**Toast, 67.6 g**	**Urethane, 811 ng**	(41.3)	16.9
0.00006	**Hamburger, panfried, 85 g**	**2-Amino-1-methyl-6-phenylimidazo[4,5-b]-pyridine (PhIP), 176 ng**	4.29[d]	(28.6)[d]
0.00005	**Estragole in spices**	**Estragole, 1.99 mg**	.	51.8
0.00005	**Parsley, fresh, 324 mg**	**8-Methoxypsoralen, 1.17 mg**	32.4	(—)
0.00003	**Hamburger, panfried, 85 g**	**2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 38.1 ng**	1.99	(24.3)
0.00002	Dicofol: daily U.S. avg (1990)	Dicofol, 544 ng	(—)	32.9
0.00001	**Cocoa, 3.34 g**	**α-Methylbenzyl alcohol, 4.3 mg**	458	(—)
0.00001	**Beer, 257 g**	**Urethane, 115 ng**	(41.3)	16.9
0.000005	**Hamburger, panfried, 85 g**	**2-Amino-3-methylimidazo[4,5-f]quinoline (IQ), 6.38 ng**	1.89[d]	(19.6)
0.000001	Lindane: daily U.S. avg (1990)	Lindane, 32 ng	(—)	30.7
0.0000004	Pentachloronitrobenzene (PCNB): daily U.S. avg (1990)	PCNB (Quintozene), 19.2 ng	(—)	71.1
0.0000001	Chlorobenzilate: daily U.S. avg (1989)	Chlorobenzilate, 6.4 ng	(—)	93.9
<0.00000001	Chlorothalonil: daily U.S. avg (1990)	Chlorothalonil, <6.4 ng	828[e]	(—)
0.000000008	Folpet: daily U.S. avg (1990)	Folpet, 12.8 ng	.	2280[e]
0.000000006	Captan: daily U.S. avg (1990)	Captan, 11.5 ng	2690[e]	(2730)[e]

toxicity to humans. A 1970 NAS report concluded: "In little more than two decades DDT has prevented 500 million deaths due to malaria, that would otherwise have been inevitable (68)." There is no convincing epidemiological evidence, nor is there much toxicological plausibility, that the levels normally found in the environment are likely to contribute significantly to cancer. DDT was unusual with respect to bioconcentration, and because of its chlorine substituents it takes longer to degrade in nature than most chemicals; however, these are properties of relatively few synthetic chemicals. In addition, many thousands of chlorinated chemicals are produced in nature (69), and natural pesticides can also bioconcentrate if they are fat soluble. Potatoes, for example, naturally contain the fat-soluble neurotoxins solanine and chaconine (49), which can be detected in the bloodstream of all potato eaters. High levels of these potato neurotoxins have been shown to cause birth defects in rodents (48).

Since no plot of land is immune to attack by insects, plants need chemical defenses—either natural or synthetic—in order to survive. Thus, there is a trade-off between naturally occurring and synthetic pesticides. One consequence of the 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 6200 parts per billion (ppb) of carcinogenic (and mutagenic) psora-

lens instead of the 800 ppb present in common celery (49).

MISCONCEPTION #8: PESTICIDES AND OTHER SYNTHETIC CHEMICALS ARE DISRUPTING HUMAN HORMONES

Synthetic hormone mimics have become an environmental issue. Hormonal factors are important in cancer (Misconception #2). A recent book (70) states that traces of synthetic chemicals, such as pesticides with weak hormonal activity, may contribute to cancer and reduce sperm count. This book ignores the fact that our normal diet contains natural chemicals that have estrogenic activity millions of times higher than that due to the traces of synthetic estrogenic chemicals (71, 72) and that lifestyle factors can markedly change the levels of endogenous hormones (Misconception #2). The low levels of exposure to residues of industrial chemicals in humans are toxicologically implausible as a significant cause of cancer or reproductive abnormalities, especially when compared to the natural environment (71–74). Moreover, it has not been shown convincingly that sperm counts are declining (75); even if they were, there are many more likely causes, such as smoking and diet (Misconception #2).

MISCONCEPTION #9: REGULATING LOW, HYPOTHETICAL RISKS ADVANCES PUBLIC HEALTH

Since there is no risk-free world and resources are limited, society must set priorities based on cost effectiveness in order to save the greatest number of lives (76, 77). In 1991 the EPA projected that the cost to society of environmental regulations in 1997 would be about $140 billion per year (about 2.6% of the gross national product) (78). Most of this cost would be to the private sector. Several economic analyses have concluded that current expenditures are not cost effective; resources are not being used so as to save the greatest number of lives per dollar. One estimate is that the U.S. could prevent 60,000 deaths per year by redirecting the same dollar resources to more cost-effective programs (79). For example, the median toxin control program costs 146 times more per life-year saved than the median medical intervention (79). This difference is likely to be even greater because cancer risk estimates for toxin control programs are worst-case, hypothetical estimates, and the true risks at low dose are often likely to be zero (5, 6, 50) (Misconception #5). Some economists have argued that costly regulations intended to save lives may actually lead to an increased number of deaths (80), in part because they divert resources from important health risks and in part because higher incomes are associated with lower mortality (81–83). Rules on air and water pollution are necessary (it was a public health benefit to phase lead out of gasoline), and clearly cancer prevention is not the only reason for regulations. However, worst-case assumptions in risk assessment represent a policy decision, not a scientific one, and they confuse attempts to allocate money effectively for risk abatement.

Regulatory efforts to reduce low-level human exposure to synthetic chemicals because they are rodent carcinogens are expensive since they aim to eliminate minuscule concentrations that can now be measured with improved techniques. These efforts distract from the major task of improving public health through increasing scientific understanding about how to prevent cancer (e.g., the role of diet), increasing public understanding of how lifestyle influences health, and improving our ability to help individuals alter their lifestyle.

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