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Misconceptions About the Causes of Cancer

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Summary

The major causes of cancer are: 1) smoking, which accounts for 31% of U.S. cancer deaths and 87% of lung cancer deaths; 2) dietary imbalances which account for about another third, e.g., lack of sufficient amounts of dietary fruits and vegetables. 3) chronic infections, mostly in developing countries; and 4) hormonal factors, which are influenced primarily by lifestyle. There is no cancer epidemic except for cancer of the lung due to smoking. Cancer mortality rates have declined 19% 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: 30 have been tested and 21 are rodent carcinogens. Plants in the human diet contain thousands of natural "pesticides" produced by plants to protect themselves from insects and other predators: 71 have been tested and 37 are rodent carcinogens.

There is no convincing evidence that synthetic chemical pollutants are important as a cause of human cancer. Regulations targeted to eliminate low levels of synthetic chemicals are 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 re-examination of priorities in cancer prevention, both public and private, seems called for.

In this chapter we highlight nine misconceptions about pollution, pesticides, and the causes of cancer. We briefly present the scientific evidence that undermines each misconception.

Misconception #1: Cancer rates are soaring.

Overall cancer death rates in the U.S. (excluding lung cancer due to smoking) have declined 19% 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 (87% is due to smoking, as are 31% of all cancer deaths in the U.S. (*2*)), 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 (*1*). For some cancers, mortality rates have begun to decline due in part to early detection, treatment and improved survival (*2, 3*), e.g., breast cancer in women (*4*). The rise in incidence rates in older age groups for some cancers, 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" (*4-7*). Life expectancy has continued to rise since 1950 (*8*).

Misconception #2: Environmental synthetic chemicals are an important cause of human cancer.

Neither epidemiology nor toxicology supports the idea that exposures to environmental levels of synthetic industrial chemicals are important as a cause of human cancer (*7, 9, 10*). Epidemiological studies have identified several factors that are 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 (*10*). 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 (*10, 11*). Moreover, exposures to synthetic pollutants are very low and rarely seem toxicologically plausible as a causal factor, particularly when compared to the background of natural chemicals that are rodent carcinogens (*9, 12, 13*). Even assuming that worst-case risk estimates for synthetic pollutants are true risks, the proportion of cancer that the U.S. Environmental Protection Agency (EPA) could prevent by regulation would be tiny (*14*). Occupational exposures to some carcinogens cause cancer, though exactly how much has been a controversial issue: a few percent seems a reasonable estimate (*10*), much of this from asbestos in smokers. Exposures to substances in the workplace can be much higher than the exposure to chemicals in food, air, or water. Past occupational exposures have sometimes been high, and in risk assessment little quantitative extrapolation may be required from high-dose rodent tests to high-dose occupational exposures. 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 U.S. Permissible Exposure Limits in the workplace are sometimes close to the carcinogenic dose in rodents (*15*).

Cancer is due, in part, to normal aging and increases exponentially with age in both rodents and humans (*16*). 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 part to oxidative damage to DNA and other macromolecules (*16, 17*). 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 (*18*): old rats have about 66,000 oxidative DNA lesions per cell (*19*). DNA is oxidized in normal metabolism because antioxidant defenses, though numerous, are not perfect. Antioxidant defenses against oxidative damage include vitamins C and E (*20*), most of which come from dietary fruits and vegetables.

Smoking contributes to 31% of U.S. cancer, about one-quarter of heart disease, and about 430,000 premature deaths per year in the U.S. (*1, 2, 10*). Tobacco is a known cause of cancer of the lung, mouth, pharynx, larynx, bladder, pancreas, esophagus, and possibly colon. Tobacco causes even more deaths by diseases other than cancer (*21*). 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 non-smokers to achieve the same level in blood, but they rarely do. An inadequate concentration of vitamin C in plasma is more common among smokers (*22*). 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 2.5 times (*23, 24*). Male smokers have more oxidative lesions in sperm DNA (*24*) and more chromosomal abnormalities in sperm (*25*) than do nonsmokers. It is plausible, therefore, that fathers who smoke may increase the risk of birth defects and childhood cancer in offspring (*25, 26*). One epidemiological study suggests that the rate of childhood cancers is increased in offspring of male smokers: acute lymphocytic leukemia, lymphoma, and brain tumors were increased three to four times (*27*). Risk increased as pack-years of paternal smoking increased before conception [Ji, 1997 #2691].

We (*10*) estimate that unbalanced diets account for about one-third of cancer deaths, in agreement with an earlier estimate of Doll and Peto (*1, 2, 6*). Low intake of fruits and vegetables is an important 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 lowers the cancer rate and increases the life span in rodents (*10, 28, 29*).

Chronic inflammation from chronic infection results in the release of oxidative mutagens from phagocytic cells and contributes to cancer (*10, 30*). 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 (*31, 32*); thus they contribute to the carcinogenic process. Antioxidants appear to inhibit some of the pathology of chronic inflammation. Chronic infections are estimated to cause about 21% of new cancer cases in developing countries and 9% in developed countries (*33*).

Endogenous reproductive hormones play a large role in cancer, including that of the breast, prostate, ovary, and endometrium (*34, 35*), contributing to about 20% of all cancer. Many lifestyle factors such as reproductive history, lack of exercise, obesity, and alcohol influence hormone levels and therefore affect risk (*10, 34-36*).

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, which are the source of most pesticide residue exposures to humans, are of major importance for *reducing* cancer; moreover, pesticide residues in food are low and frequently not detected (see Misconception 6). Less use of synthetic pesticides would increase costs of fruits and vegetables and thus reduce consumption, especially among people with low incomes, who eat fewer fruits and vegetables and spend a higher percentage of their income on food.

Dietary fruits and vegetables and cancer prevention. High consumption of fruits and vegetables is associated with a lowered rate of degenerative diseases including cancer, cardiovascular disease, cataracts, and brain dysfunction (*10, 16*). A review of about 200 epidemiological studies reported a consistent association between low consumption of fruits and vegetables and cancer incidence at many target sites (*37-39*) (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 (*40, 41*) 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, such as pesticide residues, can result in a loss of perspective on what is important: half the U.S. population did not name fruit and vegetable consumption as protective against cancer (*42*).

Some micronutrients in fruits and vegetables are anticarcinogens. Antioxidants such as vitamin C (whose dietary source is fruits and vegetables), vitamin E, and selenium protect against oxidative damage caused by normal metabolism (*19*), smoking (*11*), and inflammation (*16*) (See Misconception #2). Micronutrient deficiency can mimic radiation in damaging DNA by causing single- and double-strand breaks, or oxidative lesions, or both (*11*). Those micronutrients whose deficiency appears to mimic radiation are folic acid, B12, B6, niacin, C, E, iron, and zinc, with the laboratory evidence ranging from likely to compelling. The percentage of the population that consumes less than half the RDA for five of these eight micronutrients is zinc (18%), iron (19% of menstruating women), C (15%), E (20+%), and niacin (2%). These deficiencies combined with folate, B12, and B6 (discussed below) may comprise *in toto* a considerable percentage of the U.S. population (*11*).

Folic acid deficiency, one of the most common vitamin deficiencies in the population consuming few dietary fruits and vegetables, causes chromosome breaks in humans (*43*). The mechanism of chromosome breaks has been shown to be deficient methylation of uracil to thymine, and subsequent incorporation of uracil into human DNA (4 million/cell) (*43*). Uracil in DNA is excised by a repair glycosylase with the formation of a transient single-strand break in the DNA; two op-

posing single-strand breaks cause a double-strand chromosome break, which is difficult to repair. Both high DNA uracil levels and chromosome breaks in humans are reversed by folate administration (*43*). Folate supplementation above the RDA minimized chromosome breakage (*44*). Folate deficiency has been associated with increased risk of colon cancer (*45, 46*): in the Nurses' Health Study women who took a multivitamin supplement containing folate for 15 years had a 75% lower risk of colon cancer (*47*). Folate deficiency also damages human sperm (*48, 49*), causes neural tube defects in the fetus and an estimated 10% of U.S. heart disease (*50*). Diets low in fruits and vegetables are commonly low in folate, antioxidants, (e.g., vitamin C) and many other micronutrients (*10, 37, 51*). Approximately 10% of the US population (*52*) had a lower folate level than that at which chromosome breaks occur (*43*). Nearly 20 years ago, two small studies of low-income (mainly African-American) elderly (*53*) and adolescents (*54*) showed that about half the people in both groups studied had folate levels that low; this issue should be reexamined. Recently in the U.S., flour, rice, pasta, and cornmeal have been supplemented with folate (*55*).

Recent evidence indicates that vitamin B6 deficiency works by the same mechanism as folate deficiency and causes chromosome breaks (Ingersoll, Shultz & Ames, unpublished). 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 (*56*). As a result, dietary insufficiencies of niacin (15% of some populations are deficient) (*57*), 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, result in DNA damage, and are associated with higher cancer rates (*10, 11, 37, 51*).

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 (*11*). Deficiency of vitamin B12 causes a functional folate deficiency, accumulation of homocysteine (a risk factor for heart disease) (*58*), and misincorporation of uracil into DNA (*59*). B12 supplementation above the RDA was necessary to minimize chromosome breakage (*44*). Strict vegetarians are at increased risk for developing vitamin B12 deficiency since the dietary source is animal products(*58*).

Optimizing micronutrient intake can have a major effect on health at a low cost (*11*). More research in this area, as well as efforts to increase micronutrient intake and improve diets, should be high priorities for public policy.

Misconception #4: Human exposures to carcinogens and other potential hazards are primarily 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 tiny compared to the amount of natural "pesticides" produced by plants themselves (*12, 13, 60-62*). 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 (*12, 60*). 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 day, which is about 10,000 times more than they consume of synthetic pesticide residues (*60*). Even though only a small proportion of natural pesticides has been tested for carcinogenicity, half of those tested (37/71) are rodent carcinogens; naturally occurring pesticides that are rodent carcinogens are ubiquitous in fruits, vegetables, herbs, and spices (*9, 13*) (Table 2). Cooking of foods produces burnt material (about 2,000 mg per person per day) that contains many rodent carcinogens.

In contrast, the residues of 200 synthetic chemicals measured by Federal Drug Administration, including the synthetic pesticides thought to be of greatest importance, average only about 0.09 mg per person per day (*9, 12, 13*). 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 (*9*) (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 (*13, 61, 62*).

Misconception #5: Cancer risks to humans can be assessed by standard high-dose animal cancer tests.

Approximately half of all chemicals that have been tested in standard animal cancer tests, whether natural or synthetic, are rodent carcinogens (Table 4) (*61-64*). 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 (*65*). 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. The process of mutagenesis and carcinogenesis is complicated because many factors are involved: e.g., DNA lesions, DNA repair, cell division, clonal instability, apoptosis, and p53 (a cell cycle control gene that is mutated in half of human tumors) (*66, 67*). The normal endogenous level of oxidative DNA lesions in somatic cells is appreciable (*19*). In addition, tissues injured by high doses of chemicals have an inflammatory immune response involving activation of white cells in response to cell death (*68-75*). Activated white cells release mutagenic oxidants (including peroxynitrite, hypochlorite, and H_2O_2). Therefore, 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 (*76*) 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, making it 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 uncertain (*77*). Moreover, if the main basis for selection were suspicion rather than human exposure, then one should select mutagens (80% are positive compared to 49% of nonmutagens), yet 55% of the chemicals tested are nonmutagens (*76*).

A 1969 study by Innes *et al*. (*78*) has frequently been cited (*79, and Letters*) as evidence that the positivity rate is low, because only 9% of 119 chemicals tested (primarily pesticides) were positive. However, the Innes tests were only in mice, had only 18 animals per group, and were terminated at 18 months. This protocol lacked the power of modern experiments, in which both rats and mice are tested, with 50 animals per group for 24 months. Of the 34 Innes negative chemicals that have been retested using modern protocols, 17 were positive (Table 4) (*62, 64*).

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 primarily due to the effects of high doses; for mutagens, it would result from a synergistic effect between cell division at high doses and DNA damage (*80-84*). 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. Analyses of apoptosis and cell proliferation in recent bioassays can help assess the mode of action of a chemical and can be used in risk assessment (*85-87*).

Linearity of dose-response seems unlikely in any case due to the inducibility of the numerous defense enzymes which deal with exogenous chemicals as groups, e.g., oxidants, electrophiles, and thus protect us against the natural world of mutagens as well as the small amounts of synthetic chemicals (*60, 88-90*).

There are validity problems associated with the use of the limited data from animal cancer tests for human risk assessment (*76, 91, 92*). Standard practice in regulatory risk assessment for a given rodent carcinogen has been to extrapolate from the high doses of rodent bioassays to the low doses of most human exposures by multiplying carcinogenic potency in rodents by human exposure. Strikingly, due to the relatively narrow range of doses in 2-year rodent bioassays, the small number of animals, and the limited range of tumor incidence rates that could be statistically significant, measures of potency obtained from 2-year bioassays are constrained to a relatively narrow range of values about the MTD, (the high dose used in a rodent bioassay). The range of possible values is similarly limited for the EPA potency measure (q_1^*) and the TD_{50} (Tumorigenic Dose-rate for 50% of test animals). If induced tumors occurred in 100% of dosed animals then the possible values could be more potent, but 100% tumor incidence rarely occurs (*64, 91, 93-95*). For example, the dose usually estimated by regulatory agencies to give one cancer in a million, can be approximated simply by using the MTD as a surrogate for carcinogenic potency. The "virtually safe dose" (VSD) can be approximated from the MTD. Gaylor and Gold (*94*) used the ratio MTD/TD_{50} and the relationship between q_1^* and TD_{50} (1993), to estimate the VSD. The VSD was approximated by the MTD/740,000 for rodent carcinogens (*94*). For 90% of the carcinogens, the MTD/740,000 was within a factor of 10 of the VSD (Table 5). This is similar to the finding that in near-replicate experiments of the same chemical, potency

estimates vary by a factor of 4 around a median value (*63, 96, 97*). Thus, there may be little gain in precision of cancer risk estimates derived from a 2-year bioassay, compared to the estimate based on the MTD from a 90-day study (*98, and Letters*).

Recently, the EPA proposed new carcinogen guidelines (*99*) that employ a benchmark dose as a point-of-departure (POD) for low-dose risk assessment. If information on the carcinogenic mode of action for a chemical supports a nonlinear dose-response curve below the POD, a margin-of-exposure ratio between the POD and anticipated human exposure would be considered (*87, 99*). The POD would be divided by uncertainty (safety) factors to arrive at a reference dose that is likely to produce no, or at most negligible, cancer risk for humans. If nonlinearity below the POD is not supported by sufficient evidence, then linear extrapolation from the incidence at the POD to zero would be used for low-dose cancer risk estimation. The carcinogen guidelines suggest that the lower 95% confidence limit on the dose estimated to produce an excess of tumors in 10% of the animals (LTD_{10}) be used for the POD.

We have shown that, like the TD_{50} or q_1^*, the estimate of the LTD_{10} obtained from 2-year bioassays is constrained to a relatively narrow range of values (*95*). Because of this constraint, a simple, quick, and relatively precise determination of the LTD_{10} can be obtained by MTD/7. All that is needed is a 90-day study to establish the MTD. Thus, if the anticipated human exposure were estimated to be small relative to the MTD/7, there may be little value in conducting a chronic 2-year study in rodents because the estimate of cancer risk would be low regardless of the results of a 2-year bioassay. Either linear extrapolation to a risk of less than 1 in 100,000 or use of an uncertainty factor of 10,000 would give the same regulatory "safe dose" (Table 5). Linear extrapolation to a VSD associated with a cancer risk estimate of less than one in a million would be 10 times lower than the reference dose based on the LTD_{10}/10,000. Thus, whether the procedure involves a benchmark dose or a linearized model, cancer risk estimation is constrained by the bioassay design.

In regulatory policy, the VSD has been 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 the nonmutagens and a synergistic effect of cell division at high doses with DNA damage for the mutagens, then this model is inappropriate and markedly overestimates risk.

Misconception #6: 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 (*79, and Letters*). This assumption is flawed for several reasons (*13, 60, 65*):

Humans have many natural defenses that buffer against normal exposures to toxins (*60*); these usually 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 -- the surface layers of the mouth, esophagus, stomach, intestine, colon, skin, and lungs are discarded every few days; DNA repair enzymes, which re-

pair 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 (*60, 62, 64, 100*). 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 is associated 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.

Since no plot of land is free from 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 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) psoralens instead of the 800 ppb present in common celery (*13, 62*).

Misconception #7: Synthetic chemicals pose greater carcinogenic hazards than natural chemicals.

Gaining a broad perspective about the vast number of chemicals to which humans are exposed is important when assessing relative hazards and setting research and regulatory priorities (*9, 10, 12, 62, 79*). Rodent bioassays have provided little information about the mechanisms of carcinogenesis that is needed to estimate low-dose risk. The assumption that synthetic chemicals are hazardous, even at the very low levels of human exposure to pollutants in the environment, has led to a bias in testing so that synthetic chemicals account for 76% (451/590) of the chemicals tested chronically in both rats and mice even though the vast proportion of human exposures are

to naturally-occurring chemicals (Table 4). The background of natural chemicals has never been systematically tested for carcinogenicity.

One reasonable strategy for setting priorities 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 (*9, 62, 64*). 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. 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, 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 average daily dose for a lifetime exposure (mg/kg/day) (*61*) (Table 6). A ranking based on standard regulatory risk assessment and using the same exposures 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 that are present in average consumption or typical portions of common foods, which cast doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides (*9, 15, 62, 64*). 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 (*101*).

The HERP ranking in Table 6 is for *average* U.S. exposures to all rodent carcinogens in the Carcinogenic Potency Database for which concentration data and average exposure or consumption data were both available, and for which human exposure could be chronic for a lifetime. For pharmaceuticals the doses are recommended doses, and for workplace they are past industry or occupation averages. The 87 exposures in the ranking (Table 6) are ordered by possible carcinogenic hazard (HERP), and natural chemicals in the diet are reported in boldface.

Several HERP values make convenient reference points for interpreting Table 6. The median HERP value is 0.002%, and the background HERP for the average chloroform level in a liter of U.S. tap water is 0.0003%. Chloroform is formed as a by-product of chlorination. A HERP of 0.00001% is approximately equal to a regulatory VSD risk of 10^{-6} (*9*). Using the benchmark dose approach recommended in the new EPA guidelines with the LTD_{10} as the point of departure (POD), linear extrapolation would produce a similar estimate of risk at 10^{-6} and hence a similar HERP value (*95*). If information on the carcinogenic mode of action for a chemical supports a nonlinear dose-response curve, then the EPA guidelines call for a margin of exposure approach with the LTD_{10} as the POD. The reference dose using a safety or uncertainty factor of 1000 (i.e. LD_{10}/1000) would be equivalent to a HERP value of 0.001%. If the dose-response is judged to be nonlinear, then the cancer risk estimate will depend on the number and magnitude of safety factors used in the assessment.

The HERP ranking maximizes possible hazards to synthetic chemicals because it includes historically high exposure values that are now much lower, e.g., DDT, saccharin, and some occupational exposures. Additionally, the values for dietary pesticide residues are averages in the *total diet*, whereas for most natural chemicals the exposure amounts are for concentrations of a chemical in an individual food (i.e. foods for which data are available on concentration and average U.S. consumption).

Table 6 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. We discuss several categories of exposure below and indicate that mechanistic data are available for some chemicals, which suggest that the possible hazard may not be relevant to humans or would be low if nonlinearity or a threshold were taken into account in risk assessment.

Occupational Exposures. Occupational and pharmaceutical exposures to some chemicals have been high, and many of the single chemical agents or industrial processes evaluated as human carcinogens have been identified by historically high exposures in the workplace (*102*). HERP values rank at the top of Table 6 for chemical exposures in some occupations to ethylene dibromide, 1,3-butadiene, tetrachloroethylene, formaldehyde, acrylonitrile, trichloroethylene, and methylene chloride. When exposures are high, the margin of exposure from the carcinogenic dose in rodents is low. The issue of how much human cancer can be attributed to occupational exposure has been controversial, but a few percent seems a reasonable estimate (*10*).

In another analysis, we used Permissible Exposure Limits (PELs) recommended in 1989 by the U.S. Occupational Safety and Health Administration (OSHA), as surrogates for actual exposures and compared the permitted daily dose-rate for workers with the TD_{50} in rodents (PERP index, Permissible Exposure/Rodent Potency) (*15*). We found that PELs for 9 chemicals were greater than 10% of the rodent carcinogenic dose and for 27 they were between 1% and 10% of the rodent dose. The highest ranking chemicals should be priorities for regulatory scrutiny. In recent years, for two of the top chemicals, 1,3-butadiene and methylene chloride, the PELs have been lowered substantially, and the current PERP values are below 1%.

For trichloroethylene (HERP is 2.2% for vapor degreasers before 1977), we recently conducted an analysis based on an assumed cytotoxic mechanism of action and using PBPK-effective dose estimates defined as peak concentrations. Our estimates indicate that for occupational respiratory exposures, the PEL for trichloroethylene would produce metabolite concentrations that exceed an acute no observed effect level for hepatotoxicity in mice. On this basis the PEL is not expected to be protective. In contrast, the EPA maximum concentration limit (MCL) in drinking water of 5 µg/liter based on a linearized multistage model, is more stringent than our MCL based on a 1000-fold safety factor, which is 210 µg/liter (*103*).

Pharmaceuticals. Some pharmaceuticals that are used chronically are also clustered near the top of the HERP ranking, e.g. phenobarbital, clofibrate, and fluvastatin. In Table 3 we reported that half the drugs in the PDR with cancer test data are positive in rodent bioassays (*104*). Most drugs, however, are used for only short periods, and the HERP values for the rodent carcinogens

would not be comparable to the chronic, long-term administration used in HERP. The HERP values for less than chronic administration at typical doses would produce high HERP values, e.g., phenacetin (0.3%), metronidazole (5.6%), and isoniazid (14%).

Herbal supplements have recently developed into a large market in the U.S. based in part on the idea that if it's natural it's good. They have not been a focus of carcinogenicity testing. The FDA regulatory requirements for safety and efficacy that are applied to pharmaceuticals do not pertain to herbal supplements under the 1994 Dietary Supplement and Health Education Act (DSHEA), and few have been tested for carcinogenicity. Those that are rodent carcinogens tend to rank high in HERP because, like some pharmaceutical drugs, the recommended dose is high relative to the rodent carcinogenic dose. Moreover, under DSHEA the safety criteria that have been used for decades by FDA for food additives that are "Generally Recognized As Safe" (GRAS) are not applicable to dietary supplements (*105*) even though supplements are used at higher doses. 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%. Pyrrolizidine alkaloids are unusual constituents of herbal supplements tested for carcinogenicity; several are positive in chronic bioassays (lasiocarpine, clivorine, monocrotaline, senkirkine and riddelliine) (*61*). Symphytine, a pyrrolizidine alkaloid 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. Recently the FDA issued an advisory to manufacturers of comfrey products to remove them from the market. Comfrey roots and leaves can be bought at health food stores and on the World Wide Web and can thus be used for tea, although comfrey is recommended for topical use only in the *PDR for Herbal Medicines* (*106*). 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 (*107*).

Dehydroepiandrosterone (DHEA), a natural hormone manufactured as a dietary supplement, has a HERP value of 0.5% for the recommended dose of 1 daily capsule containing 25 mg DHEA. DHEA is widely taken in hope of delaying aging and increasing muscle mass, and a 1997 survey reported that it was the fastest-selling product in health food stores (*108*). The mechanism of liver carcinogenesis in rats is peroxisome proliferation (*109*), like clofibrate (*110*). Recent work on the mechanism of peroxisome proliferation in rodents indicates that it is a receptor-mediated response (*111*), suggesting a threshold below which tumors are not induced. This mechanism is unlikely to be relevant to humans at any anticipated exposure level (*112, 113*). Recent analyses of the molecular basis of peroxisome proliferation conclude that there is an apparent lack of a peroxisome proliferative response in humans (*114*). A recent review of clinical, experimental, and epidemiological studies concluded that late promotion of breast cancer in postmenopausal women may be stimulated by prolonged intake of DHEA (*115*).

Natural Pesticides. Natural pesticides, because few have been tested, are markedly underrepresented in our HERP analysis. Importantly, for each plant food listed, there are about 50 additional untested natural pesticides. Although about 10,000 natural pesticides and their break-down products occur in the human diet (*12*), only 71 have been tested adequately in rodent bioassays (Table 2). Average exposures to many natural-pesticide rodent carcinogens in common foods rank above or close to the median in the HERP Table, ranging up to a HERP of 0.1%. These include caffeic acid (in coffee, lettuce, tomato, apple, potato, celery, carrot, plum and pear); safrole

(in spices and formerly in natural root beer before it was banned), allyl isothiocyanate (mustard), *d*-limonene (mango, orange juice, black pepper); coumarin in cinnamon; and hydroquinone, catechol, and 4-methylcatechol in coffee. Some natural pesticides in the commonly eaten mushroom (*Agaricus bisporus*) are rodent carcinogens (glutamyl-*p*-hydrazinobenzoate, *p*-hydrazinobenzoate), and the HERP based on feeding whole mushrooms to mice is 0.02%. For *d*-limonene, no human risk is anticipated because tumors are induced only in male rat kidney tubules with involvement of α_{2u}-globulin nephrotoxicity, which does not appear to be relevant for humans (*116-119*).

Synthetic Pesticides. Synthetic pesticides currently in use that are rodent carcinogens in the CPDB and that are quantitatively detected by the FDA Total Diet Study as residues in food, are all included in Table 6. Many are at the very bottom of the ranking; however, HERP values are about at the median for ethylene thiourea (ETU), unsymmetrical dimethylhydrazine (UDMH, from Alar) before its discontinuance, and DDT before its ban in the U.S. in 1972. These 3 synthetic pesticides rank below the HERP values for many naturally occurring chemicals that are common in the diet. The HERP values in Table 6 are for residue intake by females 65 and older, since they consume higher amounts of fruits and vegetables than other adult groups, thus maximizing the exposure estimate to pesticide residues. We note that for pesticide residues in the TDS, the consumption estimates for children (mg/kg/day from 1986-1991) are within a factor of 3 of the adult consumption (mg/kg/day) (*120*).

DDT and similar early pesticides have been a concern because of their unusual lipophilicity and persistence, even though there is no convincing epidemiological evidence of a carcinogenic hazard to humans (*121*), and although natural pesticides can also bioaccumulate. In a recently completed 24-year study in which DDT was fed to rhesus and cynomolgus monkeys for 11 years, DDT was not evaluated as carcinogenic (*122, 123*) despite doses that were toxic to both liver and central nervous system. However, the protocol used few animals and dosing was discontinued after 11 years, which may have reduced the sensitivity of the study (*62*).

Current U.S. exposure to DDT and its metabolites is in foods of animal origin, and the HERP value is low, 0.00008%. DDT is often viewed as the typically dangerous synthetic pesticide because it concentrates in adipose tissue and persists for years. DDT was the first synthetic pesticide; it eradicated malaria from many parts of the world, including the U.S., and 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 fresh, nutritious foods, thus making them accessible to more people. DDT was also of low toxicity to humans. A 1970 National Academy of Sciences report concluded: “In little more than two decades DDT has prevented 500 million deaths due to malaria, that would otherwise have been inevitable” (*124*). There is no convincing epidemiological evidence, nor is there much toxicological plausibility, that the levels of DDT normally found in the environment or in human tissues are likely to be a significant contributor to human 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 (*125*). Natural pesticides can also bioconcentrate if they are fat-soluble. Potatoes, for ex-

ample, naturally contain the fat soluble neurotoxins solanine and chaconine (*12, 13*), 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 (*60*).

For ETU the HERP value would be about 10 times lower if the potency value of the EPA were used instead of our TD_{50}; EPA combined rodent results from more than one experiment, including one in which ETU was administered *in utero*, and obtained a weaker potency (*126*). (The CPDB does not include *in utero* exposures.) Additionally, EPA has recently discontinued some uses of fungicides for which ETU is a breakdown product, and exposure levels are therefore lower.

In 1984 the EPA banned the agricultural use of ethylene dibromide (EDB) the main fumigant in the U.S., because of the residue levels found in grain, HERP = 0.0004%. This HERP value ranks low, whereas the HERP of 140% for the high exposures to EDB that some workers received in the 1970s, is at the top of the ranking (*9*). Two other pesticides in Table 6, toxaphene (HERP=0.0002%) and chlorobenzilate (HERP=0.0000001%), have been cancelled (*127*).

Most residues of synthetic pesticides have HERP values below the median. In descending order of HERP these are carbaryl, toxaphene, dicofol, lindane, pentachloronitrobenzene (PCNB), chlorobenzilate, captan, folpet, and chlorothalonil. Some of the lowest HERP values in Table 6 are for the synthetic pesticides, captan, chlorothalonil, and folpet, which were also evaluated in 1987 by the National Research Council (NRC) and were considered by NRC to have a human cancer risk above 10^{-6} (*128*). Why were the EPA risk estimates reported by NRC so high when our HERP values are so low? We have investigated this disparity in cancer risk estimation for pesticide residues in the diet by examining the two components of risk assessment: carcinogenic potency estimates from rodent bioassays and human exposure estimates (*129*). We found that potency estimates based on rodent bioassay data are similar whether calculated, as in the NRC report, as the regulatory q_1^* or as the TD_{50} in the CPDB. In contrast, estimates of dietary exposure to residues of synthetic pesticides vary enormously, depending on whether they are based on the Theoretical Maximum Residue Contribution (TMRC) calculated by the EPA vs. the average dietary residues measured by the FDA in the Total Diet Study (TDS). The EPA's TMRC is the theoretical maximum human exposure anticipated under the most severe field application conditions, which is often a large overestimate compared to the measured residues. For several pesticides, the NRC risk estimate was greater than one in a million whereas the FDA did not detect any residues in the TDS even though the TDS measures residues as low as 1 ppb (*129, 130*).

Cooking and Preparation of Food. Cooking and preparation of food can also produce chemicals that are rodent carcinogens. Alcoholic beverages are a human carcinogen, and the HERP values in Table 6 for alcohol in beer (2.1%) and wine (0.5%) are high in the ranking. Ethyl alcohol is one of the least potent rodent carcinogens in the CPDB, but the HERP is high because of high concentrations in alcoholic beverages and high U.S. consumption. Another fermentation product, urethane (ethyl carbamate), has a HERP value of 0.00001% for average beer consumption; and 0.00007% for average bread consumption (as toast).

Cooking food is plausible as a contributor to cancer. A wide variety of chemicals are formed during cooking. Rodent carcinogens formed include furfural and similar furans, nitrosamines,

polycyclic hydrocarbons, and heterocyclic amines. Furfural, a chemical formed naturally when sugars are heated, is a widespread constituent of food flavor. The HERP value for naturally-occurring furfural in average consumption of coffee is 0.02% and in white bread is 0.004%. Furfural is also used as a commercial food additive, and the HERP for total average U.S. consumption as an additive is 0.00006% (Table 6). Nitrosamines are formed from nitrite or nitrogen oxides (NO_x) and amines in food. In bacon the HERP for diethylnitrosamine is 0.0006%, and for dimethylnitrosamine it is 0.0005%.

A variety of mutagenic and carcinogenic heterocyclic amines (HA) are formed when meat, chicken or fish are cooked, particularly when charred. Compared to other rodent carcinogens, there is strong evidence of carcinogenicity for HA in terms of positivity rates and multiplicity of target sites; however, concordance in target sites between rats and mice for these HA is generally restricted to the liver (*131*). Under usual cooking conditions, exposures to HA are in the low ppb range, and the HERP values are low: for HA in pan fried hamburger, the HERP value for 2-amino-1-methyl-6-phenylimidazo[4, 5-*b*]-pyridine (PhIP) is 0.00006%, for 2-amino-3,8-dimethylimidazo[4, 5-*f*]-quinoxaline (MeIQx) 0.00003%. and for 2-amino-3-methylimidazo[4, 5-*f*]-quinoline (IQ) 0.000006%. Carcinogenicity of the 3 HA in the HERP table, IQ, MeIQx, and PhIP, has been investigated in studies in cynomolgus monkeys. IQ administered by gavage rapidly induced a high incidence of hepatocellular carcinoma; if the HERP value were based on the TD_{50} in monkeys, the value would be 0.00002% (*132*). MeIQx, which induced tumors at multiple sites in rats and mice (*133*), did not induce tumors in monkeys (*134*). The PhIP study is in progress. Metabolism studies indicate the importance of *N*-hydroxylation in the carcinogenic effect of HA in monkeys (*135*). IQ is activated via *N*-hydroxylation and forms DNA adducts; the *N*-hydroxylation of IQ appears to be carried out largely by hepatic CYP3A4 and/or CYP2C9/10, and not by CYP1A2; whereas the poor activation of MeIQx appears to be due to a lack of expression of CYP1A2 and an inability of other cytochromes P450, such as CYP3A4 and CYP2C9/10, to *N*-hydroxylate the quinoxalines. PhIP is activated by *N*-hydroxylation in monkeys and forms DNA adducts, suggesting that it may have a carcinogenic effect (*134, 135*).

Food Additives. Food additives that are rodent carcinogens can be either naturally-occurring (e.g., allyl isothiocyanate, furfural, and alcohol) or synthetic (butylated hydroxyanisole [BHA] and saccharin, Table 6). The highest HERP values for average dietary exposures to synthetic rodent carcinogens in Table 6 are for exposures in the 1970s to BHA (0.01%) and saccharin (0.005%). Both are nongenotoxic rodent carcinogens for which data on mechanism of carcinogenesis strongly suggest that there would be no risk to humans at the levels found in food.

BHA is a phenolic antioxidant that is Generally Regarded as Safe (GRAS) by the FDA. By 1987, after BHA was shown to be a rodent carcinogen, its use declined six fold (HERP=0.002%) (*136*); this was due to voluntary replacement by other antioxidants, and to the fact that the use of animal fats and oils, in which BHA is primarily used as an antioxidant, has consistently declined in the U.S. The mechanistic and carcinogenicity results on BHA indicate that malignant tumors were induced only at a dose above the MTD at which cell division was increased in the forestomach, which is the only site of tumorigenesis; the proliferation is only at high doses, and is dependent on continuous dosing until late in the experiment (*137*). Humans do not have a forestomach. We note that the dose-response for BHA curves sharply upward, but the potency value used in HERP is based on a linear model; if the California EPA potency value (which is based on

a linearized multistage model) were used in HERP instead of TD_{50}, the HERP values for BHA would be 25 times lower (*138*).

Saccharin, which has largely been replaced by other sweeteners, has been shown to induce tumors in rodents by a mechanism that is not relevant to humans. Recently, both National Toxicology Program (NTP) and International Agency for Research on Cancer (IARC) re-evaluated the potential carcinogenic risk of saccharin to humans. NTP delisted saccharin in its *Report on Carcinogens* (*139*), and IARC downgraded its evaluation to Group 3, "not classifiable as to carcinogenicity to humans" (*140*). There is convincing evidence that the induction of bladder tumors in rats by sodium saccharin requires a high dose and is related to development of a calcium phosphate-containing precipitate in the urine (*81*), which is not relevant to human dietary exposures. In a recently completed 24-year study by NCI, rhesus and cynomolgus monkeys were fed a dose of sodium saccharin that was equivalent to 5 cans of diet soda daily for 11 years (*122*). The average daily dose-rate of sodium saccharin was about 100 times lower than the dose that was carcinogenic to rats (*62, 133*). There was no carcinogenic effect in monkeys. There was also no effect on the urine or urothelium, no evidence of increased urothelial cell proliferation or of formation of solid material in the urine (*141*). One would not expect to find a carcinogenic effect under the conditions of the monkey study. Additionally, there may be a true species difference because primate urine has a low concentration of protein and is less concentrated (lower osmolality) than rat urine (*141*). Human urine is similar to monkey urine in this respect (*81*).

For three naturally-occurring chemicals that are also produced commercially and used as food additives, average exposure data were available and they are included in Table 6. The HERP values are as follows: For furfural the HERP value for the natural occurrence is 0.02% compared to 0.00006% for the additive; for *d*-limonene the natural occurrence HERP is 0.1% compared to 0.003% for the additive; and for estragole the HERP is 0.00005% for both the natural occurrence and the additive.

Safrole is the principle component (up to 90%) of oil of sassafras. It was formerly used as the main flavor ingredient in root beer. It is also present in the oils of basil, nutmeg, and mace (*142*). The HERP value for average consumption of naturally-occurring safrole in spices is 0.03%. In 1960 safrole and safrole-containing sassafras oils were banned from use as food additives in the U.S. (*143*). Before 1960, for a person consuming a glass of sassafras root beer per day for life, the HERP value would have been 0.2% (*79*). Sassafras root can still be purchased in health food stores and can therefore be used to make tea; the recipe is on the World Wide Web.

Mycotoxins. Of the 23 fungal toxins tested for carcinogenicity, 14 are positive (61%) (Table 3). The mutagenic mold toxin, aflatoxin, which is found in moldy peanut and corn products, interacts with chronic hepatitis infection in human liver cancer development (*144*). There is a synergistic effect in the human liver between aflatoxin (genotoxic effect) and the hepatitis B virus (cell division effect) in the induction of liver cancer (*145*). The HERP value for aflatoxin of 0.008% is based on the rodent potency. If the lower human potency value calculated by FDA from epidemiological data were used instead, the HERP would be about 10-fold lower (*146*). Biomarker measurements of aflatoxin in populations in Africa and China, which have high rates of hepatitis B and C viruses and liver cancer, confirm that those populations are chronically exposed to high levels of aflatoxin (*147, 148*). Liver cancer is rare in the U.S. Hepatitis viruses

can account for half of liver cancer cases among non-Asians and even more among Asians in the U.S. (*149*).

Ochratoxin A, a potent rodent carcinogen (*61*), has been measured in Europe and Canada in agricultural and meat products. An estimated exposure of 1 ng/kg/day would have a HERP value at about the median of Table 6 (*150, 151*).

Synthetic Contaminants. Polychlorinated biphenyls (PCBs) and tetrachlorodibenzo-*p*-dioxin (TCDD), which have been a concern because of their environmental persistence and carcinogenic potency in rodents, are primarily consumed in foods of animal origin. In the U.S. PCBs are no longer used, but some exposure persists. Consumption in food in the U.S. declined about 20-fold between 1978-1986 (*152, 153*). The HERP value for PCB in Table 6 for the most recent reporting in the FDA Total Diet Study (1984-86) is 0.00008%, towards the bottom of the ranking, and far below many values for naturally occurring chemicals in common foods. It has been reported that some countries may have higher intakes of PCBs than the U.S. (*154*).

TCDD, the most potent rodent carcinogen, is produced naturally by burning when chloride ion is present, e.g. in forest fires or wood burning in homes. EPA (*155*) proposes that the source of TCDD is primarily from the atmosphere directly from emissions, e.g. incinerators , or indirectly by returning dioxin to the atmosphere(*155, 156*). TCDD bioaccumulates through the food chain because of its lipophilicity, and more than 95% of human intake is from animal fats in the diet (*155*). Dioxin emissions decreased by 80% from 1987-1995, which EPA attributes to reduced medical and municipal incineration emissions (*155*).

The HERP value of 0.0004% for average U.S. intake of TCDD (*155*) is below the median of the values in Table 6. Recently, EPA has re-estimated the potency of TCDD based on a body burden dose-metric in humans (rather than intake) (*155*) and a re-evaluation of tumor data in rodents (which determined 2/3 fewer liver tumors) (*157*). Using this EPA potency for HERP would put TCDD at the median of HERP values in Table 6, 0.002%.

TCDD exerts many of its harmful effects in experimental animals through binding to the Ah receptor (AhR), and does not have effects in the AhR knockout mouse (*158, 159*). A wide variety of natural substances also bind to the Ah receptor (e.g., tryptophan oxidation products), and insofar as they have been examined, they have similar properties to TCDD (*60*) including inhibition of estrogen-induced effects in rodents (*160*). For example, a variety of flavones and other plant substances in the diet, and their metabolites also bind to the Ah receptor, e.g. indole-3-carbinol (I3C). I3C is the main breakdown compound of glucobrassicin, a glucosinolate that is present in large amounts in vegetables of the *Brassica* genus, including broccoli, and gives rise to the potent Ah binder, indole carbazole (*161*). The binding affinity (greater for TCDD) and amounts consumed (much greater for dietary compounds) both need to be considered in comparing possible harmful effects. Some studies provide evidence of enhancement of carcinogenicity of I3C (*162*). Additionally, both I3C and TCDD, when administered to pregnant rats, resulted in reproductive abnormalities in male offspring (*163*). Currently, I3C is in clinical trials for prevention of breast cancer (*164-166*) and also is being tested for carcinogenicity by NTP (*166*). I3C is marketed as a dietary supplement at recommended doses about 30 times higher (*167*) than present in the average Western diet (*166*).

TCDD has received enormous scientific and regulatory attention, most recently in an ongoing assessment by the U.S. EPA (*155, 156, 168, 169*). Some epidemiologic studies suggest an association with cancer mortality, but the evidence is not sufficient to establish causality. IARC evaluated the epidemiological evidence for carcinogenicity of TCDD in humans as limited (*170*). The strongest epidemiological evidence was among highly exposed workers for overall cancer mortality. There is a lack of evidence in humans for any specific target organ. Estimated blood levels of TCDD in studies of those highly exposed workers were similar to blood levels in rats in positive cancer bioassays (*170*). In contrast, background levels of TCDD in humans are about 100 to 1000 fold lower than in the rat study. The similarity of worker and rodent blood levels and mechanism of the Ah receptor in both humans and rodents, were considered by IARC when they evaluated TCDD as a Group 1 carcinogen in spite of only limited epidemiological evidence. IARC also concluded that "Evaluation of the relationship between the magnitude of the exposure in experimental systems and the magnitude of the response, (i.e. dose-response relationships) do not permit conclusions to be drawn on the human health risks from background exposures to 2,3,7,8-TCDD." The NTP *Report on Carcinogens* recently evaluated TCDD as "reasonably anticipated to be a human carcinogen," i.e., rather than as a known human carcinogen (*139*). The EPA draft final report (*155*) characterized TCDD as a "human carcinogen" but concluded that "there is no clear indication of increased disease in the general population attributable to dioxin-like compounds." (*155*) Possible limitations of data or scientific tools were given by EPA as possible reasons for the lack of observed effects.

In sum, the HERP ranking in Table 6 indicates that when synthetic pesticide residues in the diet are ranked on possible carcinogenic hazard and compared to the ubiquitous exposures to rodent carcinogens, they rank low. Widespread exposures to naturally-occurring rodent carcinogens cast doubt on the relevance to human cancer of low-level exposures to synthetic rodent carcinogens. In regulatory efforts to prevent human cancer, the evaluation of low-level exposures to synthetic chemicals has had a high priority. Our results indicate, however, that a high percentage of both natural and synthetic chemicals are rodent carcinogens at the MTD, that tumor incidence data from rodent bioassays are not adequate to assess low-dose risk, and that there is an imbalance in testing of synthetic chemicals compared to natural chemicals. There is an enormous background of natural chemicals in the diet that rank high in possible hazard, even though so few have been tested in rodent bioassays. In Table 6, 90% of the HERP values are above the level that would approximate a regulatory virtually safe dose of 10^{-6}.

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. In fact, epidemiological results indicate that adequate consumption of fruits and vegetables reduces cancer risk at many sites, and that protective factors like intake of vitamins such as folic acid are important, rather than intake of individual rodent carcinogens (See Misconception #3).

The HERP ranking also indicates the importance of data on mechanism of carcinogenesis for each chemical. For several chemicals, data has recently been generated which indicates that exposures would not be expected to be a cancer risk to humans at the levels consumed in food (e.g. saccharin, BHA, chloroform, *d*-limonene). Standard practice in regulatory risk assessment for

chemicals that induce tumors in high-dose rodent bioassays, has been to extrapolate risk to low dose in humans by multiplying potency by human exposure. Without data on mechanism of carcinogenesis, however, the true human risk of cancer at low dose is highly uncertain and could be zero (*9, 84, 171, 172*). Adequate risk assessment from animal cancer tests requires more information for a chemical, about pharmacokinetics, mechanism of action, apoptosis, cell division, induction of defense and repair systems, and species differences.

Misconception #8: Pesticides and other synthetic chemicals are disrupting hormones.

Synthetic hormone mimics such as organochlorine pesticides, have become an environmental issue (*173*), which was recently addressed by NAS (*174*). We discussed in Misconception #2 that hormones factors are important in human cancer and that lifestyle factors can markedly change the levels of endogenous hormones. The trace exposures to estrogenic organochlorine residues are tiny compared to the normal dietary intake of naturally occurring endocrine-active chemicals in fruits and vegetables (*175-177*). These low levels of human exposure seem toxicologically implausible as a significant cause of cancer or of reproductive abnormalities (*175-178*). Synthetic hormone mimics have been proposed as a cause of declining sperm counts, even though it has not been shown that sperm counts are declining (*174, 179-183*). A recent analysis for the U.S. examined all available data on sperm counts and found that mean sperm concentrations were higher in New York than all other U.S. cities (*183*). When this geographic difference was taken into account, there was no significant change in sperm counts for the past 50 years (*183*). Even if sperm counts were declining, there are many more likely causes, such as smoking and diet (Misconception #2).

Some recent studies have compared estrogenic equivalents (EQ) of dietary intake of synthetic chemicals vs. phytoestrogens in the normal diet, by considering both the amount humans consume and estrogenic potency. Results support the idea that synthetic residues are orders of magnitude lower in EQ and are generally weaker in potency. One study used a series of *in vitro* assays and calculated the EQs in extracts from 200 ml of red cabernet wine and the EQs from average intake of organochlorine pesticides (*184*). EQs for a single glass of wine ranged from 0.15 to 3.68 µg/day compared to 1.24 ng/day for organochlorine pesticides (*184*). Another study (*185*) compared plasma concentrations of the phytoestrogens genistein and daidzein in infants fed soy-based formula vs. cow milk formula or human breast milk. Mean plasma levels were hundreds of times higher for the soy fed infants than others.

Misconception #9: Regulation of low, hypothetical risks is effective in advancing public health.

Since there is no risk-free world and resources are limited, society must set priorities in order to save the greatest number of lives (*186, 187*). 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 Gross National Product) (*188*). 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 (*189*). For example, the median toxin control program costs 146 times more per life-year

saved than the median medical intervention (*189*). 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 (*9, 76, 94*) (Misconception #5). Some economists have argued that costly regulations intended to save lives may actually increase the number of deaths (*190*), in part because they divert resources from important health risks and in part because higher incomes are associated with lower mortality (*191-193*). 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 lifestyle.

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

Cancer site	Fraction of studies with 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 Block *et al.* (*37*).

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

Carcinogens: 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

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.

[a] Fungal toxins are not included. From the Carcinogenic Potency Database (*61, 62*).

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

Positive: N=21	acetaldehyde, benzaldehyde, benzene, benzofuran, benzo(*a*)pyrene, caffeic acid, catechol, 1,2,5,6-dibenzanthracene, ethanol, ethylbenzene, formaldehyde, furan, furfural, hydrogen peroxide, hydroquinone, isoprene, limonene, 4-methylcatechol, 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 the Carcinogenic Potency Database (*61, 62*).

Table 4. Proportion of chemicals evaluated as carcinogenic [a]

Chemicals tested in both rats and mice [a]	
Chemicals in the Carcinogenic Potency Database (CPDB)	350/590 (59%)
Naturally-occurring chemicals in the CPDB	79/139 (57%)
Synthetic chemicals in the CPDB	271/451 (60%)
Chemicals tested in rats and/or mice [a]	
Chemicals in the CPDB	702/1348 (52%)
Natural pesticides in the CPDB	37/71 (52%)
Mold toxins in the CPDB	14/23 (61%)
Chemicals in roasted coffee in the CPDB	21/30 (70%)
Commercial pesticides	79/194 (41%)
Innes negative chemicals retested[a]	17/34 (50%)
Physician's Desk Reference (PDR): drugs with reported cancer tests [b]	117/241 (49%)
FDA database of drug submissions [c]	125/282 (44%)

[a] From the Carcinogenic Potency Database (*61, 62*).
[b] From Davies and Monro (*104*).
[c] From Contrera *et al.* (*194*).
140 drugs are in both the FDA and PDR databases.

Table 5. Cancer Risk Assessment without Conducting a 2-Year Bioassay [a]

Approach to Risk Assessment	Estimated Regulatory "Safe Dose"
Low-dose linear extrapolation based on the multistage model [b]	
risk < 10^{-6}	MTD [c]/740,000
risk < 10^{-5}	MTD/74,000
risk < 10^{-4}	MTD/7,400
Benchmark dose point-of-departure = LTD_{10} [d] with linear extrapolation	
risk < 10^{-6}	MTD/700,000
risk < 10^{-5}	MTD/70,000
risk < 10^{-4}	MTD/7,000
Reference dose for nonlinear dose-response curve based on uncertainty factors	
LTD10/1000 [e]	MTD/7,000
LTD10/10,000 [f]	MTD/70,000

[a] From Gaylor and Gold (*95*)
[b] From Gaylor and Gold (*94*)
[c] MTD = Maximum tolerated dose (high dose in rodent test)
[d] LTD_{10} = lower confidence limit on dose to produce 10% of rodents with tumors
[e] Combined uncertainty factors of 10 for animal to human extrapolation, 10 for sensitive humans, and 10 since the LTD_{10} represents a low-observed-adverse-effect-level (*195*).
[f] Additional uncertainty factor of 10 would be considered to account for possible extra sensitivity of children per the Food Quality Protection Act of 1996 or because of the severity of cancer even from low doses (*196, 197*).

Table 6. Ranking Possible Carcinogenic Hazards from Average U.S. Exposures to Rodent Carcinogens
[Chemicals that occur naturally in foods are in bold.] *Daily human exposure:* Reasonable daily intakes are used to facilitate comparisons. The calculations assume a daily dose for a lifetime. *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.

Possible hazard: HERP (%)	Average daily US exposure	Human dose of rodent carcinogen	Potency TD_{50} (mg/kg/day) [a] Rats	Mice	Exposure references
140	EDB: production workers (high exposure) (before 1977)	Ethylene dibromide, 150 mg	1.52	(7.45)	(*198*, *199*)
17	Clofibrate	Clofibrate, 2 g	169	.	(*200*)
14	Phenobarbital, 1 sleeping pill	Phenobarbital, 60 mg	(+)	6.09	(*201*)
6.8	1,3-Butadiene: rubber industry workers (1978-86)	1,3-Butadiene, 66.0 mg	(261)	13.9	(*202*)
6.2	**Comfrey-pepsin tablets, 9 daily (no longer recommended)**	**Comfrey root, 2.7 g**	626	.	(*203*, *204*)
6.1	Tetrachloroethylene: dry cleaners with dry-to-dry units (1980-90)	Tetrachloroethylene, 433 mg	101	(126)	(*205*)
4.0	Formaldehyde: production workers (1979)	Formaldehyde, 6.1 mg	2.19	(43.9)	(*206*)
2.4	Acrylonitrile: production workers (1960-1986)	Acrylonitrile, 28.4 mg	16.9	.	(*207*)
2.2	Trichloroethylene: vapor degreasing (before 1977)	Trichloroethylene, 1.02 g	668	(1580)	(*208*)
2.1	**Beer, 257 g**	**Ethyl alcohol, 13.1 ml**	9110	(-)	(*209*)
1.4	Mobile home air (14 hours/day)	Formaldehyde, 2.2 mg	2.19	(43.9)	(*210*)
1.3	**Comfrey-pepsin tablets, 9 daily (no longer recommended)**	**Symphytine, 1.8 mg**	1.91	.	(*203*, *204*)
0.9	Methylene chloride: workers, industry average (1940s-80s)	Methylene chloride, 471 mg	724	(1100)	(*211*)
0.5	**Wine, 28.0 g**	**Ethyl alcohol, 3.36 ml**	9110	(-)	(*209*)
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)	(*212*)
0.2	Fluvastatin	Fluvastatin, 20 mg	125	.	(*213*)
0.1	**Coffee, 13.3 g**	**Caffeic acid, 23.9 mg**	297	(4900)	(*209*, *214*)
0.1	***d*-Limonene in food**	***d*-Limonene, 15.5 mg**	204	(-)	(*209*)
0.04	**Lettuce, 14.9 g**	**Caffeic acid, 7.90 mg**	297	(4900)	(*215*, *216*)
0.03	**Safrole in spices**	**Safrole, 1.2 mg**	(441)	51.3	(*217*)
0.03	**Orange juice, 138 g**	***d*-Limonene, 4.28 mg**	204	(-)	(*215*, *218*)
0.03	**Comfrey herb tea, 1 cup (1.5 g root) (no longer recommended)**	**Symphytine, 38 µg**	1.91	.	(*204*)
0.03	**Tomato, 88.7 g**	**Caffeic acid, 5.46 mg**	297	(4900)	(*215*, *219*)
0.03	**Pepper, black, 446 mg**	***d*-Limonene, 3.57 mg**	204	(-)	(*209*, *220*)
0.02	**Coffee, 13.3 g**	**Catechol, 1.33 mg**	88.8	(244)	(*209*, *221*, *222*)
0.02	**Furfural in food**	**Furfural, 2.72 mg**	(683)	197	(*209*)

0.02	**Mushroom (*Agaricus bisporus* 2.55 g)**	**Mixture of hydrazines, etc. (whole mushroom)**	-	20,300	(*209*, *223*, *224*)
0.02	**Apple, 32.0 g**	**Caffeic acid, 3.40 mg**	297	(4900)	(*225*, *226*)
0.02	**Coffee, 13.3 g**	**Furfural, 2.09 mg**	(683)	197	(*209*)
0.01	BHA: daily US avg (1975)	BHA, 4.6 mg	606	(5530)	(*136*)
0.01	**Beer (before 1979), 257 g**	**Dimethylnitrosamine, 726 ng**	0.0959	(0.189)	(*209*, *227*, *228*)
0.008	**Aflatoxin: daily US avg (1984-89)**	**Aflatoxin, 18 ng**	0.0032	(+)	(*229*)
0.007	**Cinnamon, 21.9 mg**	**Coumarin, 65.0 µg**	13.9	(103)	(*230*)
0.006	**Coffee, 13.3 g**	**Hydroquinone, 333 µg**	82.8	(225)	(*209*, *221*, *231*)
0.005	Saccharin: daily US avg (1977)	Saccharin, 7 mg	2140	(-)	(*232*)
0.005	**Carrot, 12.1 g**	**Aniline, 624 µg**	194 [b]	(-)	(*215*, *233*)
0.004	**Potato, 54.9 g**	**Caffeic acid, 867 µg**	297	(4900)	(*215*, *234*)
0.004	**Celery, 7.95 g**	**Caffeic acid, 858 µg**	297	(4900)	(*235*, *236*)
0.004	**White bread, 67.6 g**	**Furfural, 500 µg**	(683)	197	(*209*)
0.003	*d*-Limonene	Food additive, 475 µg	204	(-)	(*237*)
0.003	**Nutmeg, 27.4 mg**	***d*-Limonene, 466 µg**	204	(-)	(*209*, *238*)
0.003	Conventional home air (14 hour/day)	Benzene, 155 µg	(169)	77.5	(*212*)
0.002	**Coffee, 13.3 g**	**4-Methylcatechol, 433 µg**	248	.	(*209*, *231*, *239*)
0.002	**Carrot, 12.1 g**	**Caffeic acid, 374 µg**	297	(4900)	(*215*, *236*)
0.002	Ethylene thiourea: daily US avg (1990)	Ethylene thiourea, 9.51 µg	7.9	(23.5)	(*240*)
0.002	BHA: daily US avg (1987)	BHA, 700 µg	606	(5530)	(*136*)
0.002	DDT: daily US avg (before 1972 ban) [c]	DDT, 13.8 µg	(84.7)	12.8	(*241*)
0.001	**Plum, 2.00 g**	**Caffeic acid, 276 µg**	297	(4900)	(*226*, *242*)
0.001	**Pear, 3.29 g**	**Caffeic acid, 240 µg**	297	(4900)	(*209*, *226*)
0.001	[UDMH: daily US avg (1988)]	[UDMH, 2.82 µg (from Alar)]	(-)	3.96	(*225*)
0.0009	**Brown mustard, 68.4 mg**	**Allyl isothiocyanate, 62.9 µg**	96	(-)	(*209*, *243*)
0.0008	DDE: daily US avg (before 1972 ban) [d]	DDE, 6.91 µg	(-)	12.5	(*241*)
0.0006	**Bacon, 11.5 g**	**Diethylnitrosamine, 11.5 ng**	0.0266	(+)	(*209*, *244*)
0.0006	**Mushroom (*Agaricus bisporus* 2.55 g)**	**Glutamyl-*p*-hydrazino-benzoate, 107 µg**	.	277	(*209*, *245*)
0.0005	**Bacon, 11.5 g**	**Dimethylnitrosamine, 34.5 ng**	0.0959	(0.189)	(*209*, *244*)
0.0004	**Bacon, 11.5 g**	***N*-Nitrosopyrrolidine, 196 ng**	(0.799)	0.679	(*209*, *246*)
0.0004	EDB: Daily US avg (before 1984 ban) [d]	EDB, 420 ng	1.52	(7.45)	(*247*)
0.0004	Tap water, 1 liter (1987-92)	Bromodichloromethane, 13 µg	(72.5)	47.7	(*248*)
0.0004	TCDD: daily US avg (1994)	TCDD, 6.0 pg	0.0000235	(0.000156)	(*155*)
0.0003	**Mango, 1.22 g**	***d*-Limonene, 48.8 µg**	204	(-)	(*242*, *249*)
0.0003	**Beer, 257 g**	**Furfural, 39.9 µg**	(683)	197	(*209*)
0.0003	Tap water, 1 liter (1987-92)	Chloroform, 17 µg	(262)	90.3	(*248*)
0.0003	Carbaryl: daily US avg (1990)	Carbaryl, 2.6 µg	14.1	(-)	(*250*)
0.0002	**Celery, 7.95 g**	**8-Methoxypsoralen, 4.86 µg**	32.4	(-)	(*235*, *251*)

0.0002	Toxaphene: daily US avg (1990) [c]	Toxaphene, 595 ng	(-)	5.57	(*250*)
0.00009	**Mushroom (Agaricus bisporus, 2.55 g)**	***p*-Hydrazinobenzoate, 28 µg**	.	454 [b]	(*209*, *245*)
0.00008	PCBs: daily US avg (1984-86)	PCBs, 98 ng	1.74	(9.58)	(*153*)
0.00008	DDE/DDT: daily US avg (1990) [c]	DDE, 659 ng	(-)	12.5	(*250*)
0.00007	**Parsnip, 54.0 mg**	**8-Methoxypsoralen, 1.57 µg**	32.4	(-)	(*252*, *253*)
0.00007	**Toast, 67.6 g**	**Urethane, 811 ng**	(41.3)	16.9	(*209*, *254*)
0.00006	**Hamburger, pan fried, 85 g**	**PhIP, 176 ng**	4.22 [b]	(28.6 [b])	(*215*, *255*)
0.00006	Furfural	Food additive, 7.77 µg	(683)	197	(*237*)
0.00005	**Estragole in spices**	**Estragole, 1.99 µg**	.	51.8	(*209*)
0.00005	**Parsley, fresh, 324 mg**	**8-Methoxypsoralen, 1.17 µg**	32.4	(-)	(*252*, *256*)
0.00005	Estragole	Food additive, 1.78 µg	.	51.8	(*237*)
0.00003	**Hamburger, pan fried, 85 g**	**MeIQx, 38.1 ng**	1.66	(24.3)	(*215*, *255*)
0.00002	Dicofol: daily US avg (1990)	Dicofol, 544 ng	(-)	32.9	(*250*)
0.00001	**Beer, 257 g**	**Urethane, 115 ng**	(41.3)	16.9	(*209*, *254*)
0.000006	**Hamburger, pan fried, 85 g**	**IQ, 6.38 ng**	1.65 [b]	(19.6)	(*215*, *255*)
0.000005	Hexachlorobenzene: daily US avg (1990)	Hexachlorobenzene, 14 ng	3.86	(65.1)	(*250*)
0.000001	Lindane: daily US avg (1990)	Lindane, 32 ng	(-)	30.7	(*250*)
0.0000004	PCNB: daily US avg (1990)	PCNB (Quintozene), 19.2 ng	(-)	71.1	(*250*)
0.0000001	Chlorobenzilate: daily US avg (1989) [c]	Chlorobenzilate, 6.4 ng	(-)	93.9	(*250*)
0.00000008	Captan: daily US avg (1990)	Captan, 115 ng	2080	(2110)	(*250*)
0.00000001	Folpet: daily US avg (1990)	Folpet, 12.8 ng	(-)	1550	(*250*)
<0.00000001	Chlorothalonil: daily US avg (1990)	Chlorothalonil, <6.4 ng	828 [d]	(-)	(*250*, *257*)

[a] "." = no data in CPDB; a number in parentheses indicates a TD_{50} value not used in the HERP calculation because TD_{50} is less potent than in the other species. (-) = negative in cancer tests; (+) = 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] No longer contained in any registered pesticide product (*127*).

[d] Additional data from the EPA that is not in the CPDB were used to calculate this TD_{50} harmonic mean.

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