POLLUTION, PESTICIDES, AND CANCER: MISCONCEPTIONS

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Summary

1. The major causes of cancer are:
   a) Smoking: About a third of U.S. cancer (90% of lung cancer);
   b) Dietary imbalances, e.g., lack of dietary fruits & vegetables: The quarter of the population eating the least fruits & vegetables has double the cancer rate for most types of cancer compared to the quarter eating the most;
   c) Chronic infections: mostly in developing countries;
   d) Hormonal factors influenced by life style.
2. There is no epidemic of cancer, except for lung cancer due to smoking. Cancer mortality rates have declined 15% since 1950 (excluding lung cancer and adjusted for the increased lifespan of the population).
3. Regulatory policy focused on traces of synthetic chemicals is based on misconceptions about animal cancer tests. Recent research contradicts these ideas:
   a) 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";
   b) There are high-dose effects in these rodent cancer tests that are not relevant to low-dose human exposures and which can explain the high proportion of carcinogens;
   c) Though 99.9% of the chemicals humans ingest are natural, the focus of regulatory policy is on synthetic chemicals.
   * Over 1000 chemicals have been described in coffee: 27 have been tested and 19 are rodent carcinogens.
   * Plants we eat contain thousands of natural pesticides, which protect plants from insects and other predators: 64 have been tested and 35 are rodent carcinogens.
4. There is no convincing evidence that synthetic chemical pollutants are important for human cancer. Regulations that try to eliminate minuscule levels of synthetic chemicals are enormously expensive: EPA estimates its regulations cost $140 billion/year. The U.S. spends 100 times more to prevent one hypothetical, highly uncertain, death from a synthetic chemical than it spends to save a life by medical intervention. Attempting to reduce tiny hypothetical risks also has costs, e.g., if reducing synthetic pesticides makes fruits and vegetables more expensive, thereby decreasing consumption, then cancer will be increased, particularly for the poor.
5. Improved health will come from knowledge due to biomedical research, and from lifestyle changes by individuals. Little money is spent on biomedical research or on educating the public about lifestyle hazards, compared to the costs of regulations.

Myths And Facts About Synthetic Chemicals and Human Cancer

Various misconceptions about the relationship between environmental pollution and human disease, particularly cancer, drive regulatory policy. We highlight nine such misconceptions and briefly present the scientific evidence that undermines each.

Misconception #1: Cancer rates are soaring. Cancer death rates overall in the U.S. (after adjusting for age and excluding lung cancer due to smoking) have declined 15% since 1950 (1,2). The types of cancer deaths that have been decreased since 1950 are primarily stomach, cervical, uterine, and rectal. The types 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. (Cancer incidence rates are also of interest, although, they should not be taken in isolation, because trends in the recorded incidence rates are biased by improvements in registration and diagnosis (2,3)).

Cancer is one of the degenerative diseases of old age, increasing exponentially with age in both rodents and humans. External factors, however, can markedly increase cancer rates (e.g., cigarette smoking in humans) or decrease them (e.g., caloric restriction in rodents). Life expectancy has continued to rise since 1950. Thus the increases in cancer deaths are due to the delayed effect of increases in smoking and to increasing life expectancy (2,3).

Misconception #2: Environmental synthetic chemicals are an important cause of human cancer. Neither epidemiology nor toxicology supports the idea that synthetic industrial chemicals are important for human cancer. Epidemiological studies have identified the factors that are likely to have a major effect on reducing rates of cancer: reduction of smoking, improving diet (e.g., increased consumption of fruits and vegetables), and control of infections (4). Although some epidemiologic 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 like diet. Moreover, the exposure to synthetic pollutants are tiny and rarely seem plausible as a causal factor when compared to the background of natural chemicals that are rodent carcinogens (5). Even assuming that the EPA's worst-case risk estimates for synthetic pollutants are true risks, the proportion of cancer that EPA could prevent by regulation would be tiny (6). Occupational exposure to carcinogens can cause cancer, though how much has been a controversial issue: a few percent seems a reasonable estimate (4). The main contributor was asbestos in smokers. Exposures to substances in the workplace can be high in comparison with other chemical exposures in food, air, or water. Past occupational exposures have sometimes been high and therefore comparatively little quantitative extrapolation may be required for risk assessment from high-dose rodent tests to high-dose occupational exposures. Since occupational cancer is concentrated among small groups exposed at high levels, there is an opportunity to control or eliminate risks once they are identified. We (4) estimate that diet accounts for about one-third of cancer risk in agreement with the earlier estimate of Doll and Peto(2). Other factors are lifestyle influencing hormones, avoidance of intense sun exposure, increased physical activity, and reduced consumption of alcohol.

Since cancer is due, in part, to normal aging, to the extent that the major external risk factors for cancer are diminished (smoking, unbalanced diet, chronic infection and hormonal factors) cancer will occur at a later age, 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 the accumulation of oxidative damage to DNA and other macromolecules (7). By-products of normal metabolism -- superoxide, hydrogen peroxide, and hydroxyl radical -- are the same oxidative mutagens produced by radiation. Oxidative lesions in DNA accumulate with age, so that by the time a rat is old it has about a million oxidative DNA lesions per cell (7). Mutations also accumulate with age. 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 carotenoids, most of which come from dietary fruits and vegetables.

Smoking contributes to about 35% of U.S. cancer, about one-quarter of heart disease, and about 400,000 premature deaths per year in the United States (8). Tobacco is a known cause of cancer of the lung, bladder, mouth, pharynx, pancreas, stomach, larynx, esophagus and possibly colon. Tobacco causes even 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 non-smokers to achieve the same level in blood, but they rarely do. Inadequate concentration of Vitamin C in plasma is more common among single males, the poor, and smokers (7). 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% (9-11). Paternal smoking, therefore, may plausibly increase the risk of birth defects and appears to increase childhood cancer in offspring (9,10,12).

Chronic inflammation from chronic infection results in release of oxidative mutagens from phagocytic cells and is a major contributor to cancer (4,13). 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. The oxidants protect humans from immediate death from infection, but they also cause oxidative damage to DNA, mutation, and chronic cell killing with compensatory cell division (14,15) and thus contribute to the carcinogenic process. Antioxidants appear to inhibit some of the pathology of chronic inflammation. We estimate that chronic infections contribute to about one-third of the world's cancer, mostly in developing countries.

Endogenous reproductive hormones play a large role in cancer, including breast, prostate, ovary and endometrium (16,17), contributing to as much as 20% of all cancer. Many lifestyle factors such as lack of exercise, obesity and reproductive history influence hormone levels and therefore risk.

Genetic factors play a significant role in cancer 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. On the contrary, fruits and vegetables are of major importance for reducing cancer: if they become more expensive by reducing 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 and Cancer Prevention. Consumption of adequate fruits and vegetables is associated with a lowered risk of degenerative diseases including cancer, cardiovascular disease, cataracts, and brain dysfunction (7). Over 200 studies in the epidemiological literature have been reviewed that show, with great consistency, an association between lack of adequate consumption of fruits and vegetables and cancer incidence (18-20) (Table 1). The quarter of the population with the lowest dietary intake of fruits and vegetables compared to the quarter with the highest intake has roughly twice the cancer rate for most types of cancer (lung, larynx, oral cavity, esophagus, stomach, colon and rectum, bladder, pancreas, cervix, and ovary). Only 22% of Americans met the intake recommended by the NCI and the National Research Council (21-23): 5 servings of fruits and vegetables per day. When the public is told about hundreds of minor hypothetical risks, they lose perspective on what is important: half the public does not know that fruits and vegetables protect against cancer (24).

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, the effects of dietary antioxidants are difficult to disentangle by epidemiological studies from other important vitamins and ingredients in fruits and vegetables (19,20,22,25).

Folate deficiency, one of the most common vitamin deficiencies, causes extensive chromosome breaks in human genes (26). Approximately 10% of the US population (27) is deficient at the level causing chromosome breaks. In two small studies of low income (mainly African-American) elderly (28) and adolescents (29) nearly half were folate deficient to this level. The mechanism is deficient methylation of uracil to thymine, and subsequent incorporation of uracil into human DNA (4 million/cell) (26). During repair of uracil in DNA, transient nicks are formed; two opposing nicks causes a chromosome break. Both high DNA uracil levels and chromosome breaks in humans are reversed by folate administration (26). Chromosome breaks could contribute to the increased risk of cancer and cognitive defects associated with folate deficiency in humans (26). Folate deficiency also damages human sperm (30), causes neural tube defects in the fetus, and 10% of U.S. heart disease (26).

Other micronutrients are 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 B12 causes a functional folate deficiency, accumulation of homocysteine (a risk factor for heart disease) (31), and misincorporation of uracil into DNA (32). Strict vegetarians are at increased risk of developing a Vitamin B12 deficiency (31). 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 (33). As a result, dietary insufficiencies of niacin (15% of some populations are deficient (34)), folate, and antioxidants may act 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 significant amounts of DNA damage and higher cancer rates (4,18,35).

Optimizing micronutrient intake can have a major impact on health. Increasing research in this area and efforts to improve micronutrient intake and balanced diet should be a high priority for public policy.

Misconception #4: Human exposures to carcinogens and other potential hazards are nearly all to synthetic chemicals. On the contrary, 99.9% of the chemicals humans ingest are natural. The amounts of synthetic pesticide residues in plant foods are insignificant compared to the amount of natural pesticides produced by plants themselves (36,37). Of all dietary pesticides that humans eat, 99.99% are natural: they are chemicals produced by plants to defend themselves against fungi, insects, and other animal predators (36,37). 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.

Even though only a small proportion of natural pesticides has been tested for carcinogenicity, half of those tested (35/64) are rodent carcinogens, and naturally occurring pesticides that are rodent carcinogens are ubiquitous in fruits, vegetables, herbs, and spices (38) (Table 2).

Cooking foods produces about 2,000 mg per person per day of burnt material that contains many rodent carcinogens and many mutagens. By contrast, the residues of 200 synthetic chemicals measured by FDA, including the synthetic pesticides thought to be of greatest importance, average only about 0.09 mg per person per day (36,38). The known natural rodent carcinogens in a single cup of coffee are about equal in weight to an entire year's worth of carcinogenic synthetic pesticide residues, even though only 3% of the natural chemicals in roasted coffee have been tested for carcinogenicity (5) (Table 3). This does not mean that coffee is 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 (38).

Misconception #5: Cancer risks to humans can be assessed by standard high-dose animal cancer tests. Approximately half of all chemicals -- whether natural or synthetic -- that have been tested in standard animal cancer tests are rodent carcinogens (39,40) (Table 4). What are the explanations for the high positivity rate? In standard cancer tests rodents are given chronic, near-toxic doses, the maximum tolerated dose (MTD). Evidence is accumulating that it may be cell division caused by the high dose itself, rather than the chemical per se, that is increasing the cancer 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 (39). Each time a cell divides it increases the probability 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. Therefore, the very low levels of chemicals to which humans are exposed through water pollution or synthetic pesticide residues are likely to pose no or minimal cancer risks.

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, but this will be primarily due to the effects of high doses for the non-mutagens, and a synergistic effect of cell division at high doses with DNA damage for the mutagens (41-43). Without additional data on 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 does tested. The recent report

of the National Research Council, *Science and Judgment in Risk Assessment* (44) supports these ideas. The EPA's draft document *Working Paper for Considering Draft Revisions to the U.S. EPA Guidelines for Cancer Risk Assessment* (44) is a step toward improvement in the use of animal cancer test results.

In regulatory policy, the "virtually safe dose" (VSD), corresponding to a maximum, hypothetical cancer risk of one in a million, is estimated from bioassay results using a linear model. To the extent that carcinogenicity in rodent bioassays is due to the effects of high doses for the non-mutagens, and a synergistic effect of cell division at high doses with DNA damage for the 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 (45). This is about as precise as the estimate obtained from conducting near-replicate cancer tests of the same chemical (45).

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 (5,37,46,47). Rodent bioassays provide little information about mechanisms of carcinogenesis and low-dose risk. The assumption that synthetic chemicals are hazardous has led to a bias in testing, such that synthetic chemicals account for 77% of the 559 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 to focus on those that rank highest (5,47,48). Ranking is a critical first step that can help to set priorities for 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 off a ranking if, 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 index (Human Exposure/Rodent Potency), which indicates what percentage of the rodent carcinogenic potency (TD_{50} in mg/kg/day) a human receives from a given daily lifetime exposure (mg/kg/day). TD_{50} values in our Carcinogenic Potency Database span a 10-million-fold range across chemicals (49). (Table 5).

Overall, our analyses have shown that HERP values for some historically high exposures in the workplace and some pharmaceuticals rank high, and that there is an enormous background of naturally occurring rodent carcinogens in typical portions of common foods that cast doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides (5,47,50). A committee of the National Research Council/National Academy of Sciences recently reached similar conclusions about natural vs. synthetic chemicals in the diet, and called for further research on natural chemicals (51).

The possible carcinogenic hazards from synthetic pesticides (at average exposures) are minimal compared to the background of nature's pesticides, though neither may be 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 re-evaluation of the utility of animal cancer tests in 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 (37,39).

a) Humans have many natural defenses that make us well buffered against normal exposures to toxins (37), and these are usually general, rather than tailored for each specific chemical. Thus they work against both natural and synthetic chemicals. Examples of general defenses include the continuous shedding of cells exposed to toxins -- the surface layers of the mouth, esophagus, stomach, intestine, colon, skin, and lungs are discarded every few days; DNA repair enzymes, which repair DNA that was damaged from many different sources; and detoxification enzymes of the liver and other organs which generally target classes of 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 is presumably to be prepared to counter a diverse and ever-changing array of plant toxins in an evolving world; if a herbivore had defenses against only a set of specific toxins, it would be at a great disadvantage in obtaining new food when favored foods became scarce or evolved new toxins.

b) Various natural toxins, which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates (37,40). 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 world-wide.

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

d) DDT is often viewed as the typically 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 remarkably non-toxic 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 other wise have been inevitable (52)." There is no convincing epidemiological evidence, nor is there much toxicological plausibility, that the levels normally found in the environment are likely to be a significant contributor 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 and natural pesticides also can bioconcentrate if they are fat soluble. Potatoes, for example, naturally contain the fat soluble neurotoxins solanine and chaconine, 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 (37).

e) Since no plot of land is immune to attack by insects, plants need chemical defenses -- either natural or synthetic -- in order to survive pest attack. Thus, there is a trade-off between naturally occurring pesticides 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 6,200 parts per billion (ppb) of carcinogenic (and mutagenic) psoralens instead of the 800 ppb present in common celery (37).

Misconception #8: Pesticides and other synthetic chemicals are disrupting our hormones. Synthetic hormone mimics are likely to be the next big environmental issue, with accompanying large expenditures. Hormonal factors are important in cancer (Misconception #2). A recent book

(53), holds that traces of synthetic chemicals, such as pesticides with weak hormonal activity, may contribute to cancer and reduce sperm counts. The 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 (54,55) 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 of reproductive abnormalities, especially when compared to the natural background (54-56). In addition, it has not been shown that sperm counts really are declining (57), and even if they were, there are many more likely causes, such as smoking and diet (Misconception # 2).

Misconception #9: Regulation of low hypothetical risks advances public health. There is no risk-free world, and resources are limited; therefore, society must set priorities based on which risks are most important in order to save the most lives. The EPA reports that its regulations cost $140 billion per year. It has been argued that overall these regulations harm public health (58-61), because "wealthier is not only healthier but highly risk reducing." One estimate indicates "that for every 1% increase in income, mortality is reduced by 0.05%" (59). In addition, the median toxin control program costs 58 times more per life-year saved than the median injury prevention program and 146 times more than the median medical program (62). It has been estimated that the U.S. could prevent 60,000 deaths a year by redirecting resources to more cost effective programs (63). The discrepancy is likely to be greater because cancer risk estimates used for toxin control programs are worst-case, hypothetical estimates, and the true risks at low dose are often likely to be zero (5,38,61)(Misconception #5).

Regulatory efforts to reduce low-level human exposures to synthetic chemicals are expensive because they aim to eliminate minuscule concentrations that now can be measured with improved techniques. These efforts are distractions from the major task of improving public health through increasing knowledge, public understanding of how lifestyle influences health, and effectiveness in incentives and spending to maximize health. Basic biomedical research is the basis for improved public health and longevity, yet its cost is less than 10% the cost to society of EPA regulations.

Rules on air and water pollution are necessary (e.g., it was a public health advance to phase lead out of gasoline) and clearly, cancer prevention is not the only reason for regulations. But worst case scenarios, with their concomitant large costs to the economy, are not in the interest of public health and can be counterproductive.

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

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	

Source: Block *et al.* (18)

Table 2. Carcinogenicity of natural plant pesticides tested in rodents (Fungal toxins are not included.)

Carcinogens: 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-g-glutamyl-*p*-hydrazinobenzoic acid, hexanal methylformylhydrazine, *p*-hydrazinobenzoic acid.HCl, hydroquinone, 1-hydroxyanthraquinone, lasiocarpine, *d*-limonene, 8-methoxypsoralen, *N*-methyl-*N*-formylhydrazine, a-methylbenzyl alcohol, 3-methylbutanal methylformylhydrazone, methylhydrazine, monocrotaline, pentanal methyl-formylhydrazone, petasitenine, quercetin, reserpine, safrole, senkirkine, sesamol, symphytine
Noncarcinogens: N=29	atropine, benzyl alcohol, biphenyl, *d*-carvone, deserpidine, disodium glycyr-rhizinate, emetine.2HCl, ephedrine sulphate, eucalyptol, eugenol, gallic acid, geranyl acetate, b-*N*-[g-*l*(+)-glutamyl]-4-hydroxy-methylphenylhydrazine, glycyrrhetinic acid, glycyrrhizinate, disodium, *p*-hydrazinobenzoic acid, isosafrole, kaempferol, *d*-menthol, nicotine, norharman, pilocarpine, piperidine, protocatechuic acid, rotenone, rutin sulfate, sodium benzoate, 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, chilli pepper, chocolate milk, cinnamon, cloves, cocoa, coffee, collard greens, comfrey herb tea, corriander, currants, dill, eggplant, endive, fennel, garlic, grapefruit, grapes, guava, honey, honeydew melon, horseradish, kale, lemon, lentils, lettuce, licorice, lime, mace, mango, marjoram, 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.

Source: Gold *et al.* (38)

Table 3. Carcinogenicity in rodents of natural chemicals in roasted coffee.

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

Source: Gold *et al.* (40).

Table 4. Proportion of chemicals evaluated as carcinogenic.

Chemicals tested in both rats and mice	330/559	(59%)
Naturally-occurring chemicals	73/127	(57%)
Synthetic chemicals	257/432	(59%)
Chemicals tested in rats and/or mice		
Natural pesticides	35/64	(55%)
Mold toxins	14/23	(61%)
Chemicals in roasted coffee	19/28	(68%)
Innes negative chemicals retested[a]	16/34	(47%)
Drugs in the Physician's Desk Reference	117/241	(49%)

[a] The 1969 study by Innes et al (64) is frequently cited as evidence that the proportion of carcinogens is low, as only 9% of 119 chemicals tested (primarily pesticides) were positive in cancer tests on mice. However, these tests lacked the power of modern tests (40). We have found 34 of the Innes negative chemicals that have been retested using modern protocols: 16 were positive (40), again about half.

Source: Gold *et al.* (40).

Table 5. Ranking Possible Carcinogenic Hazards from Average U.S. Exposures. [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), i.e., 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 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
140	EDB: workers (high exposure) (before 1977)	Ethylene dibromide, 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 (1978-86)	1,3-Butadiene, 66.0 mg	(261)	13.9
6.1	Tetrachloroethylene: dry cleaners with dry-to-dry units (1980-90)[b]	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 hours/day)	Formaldehyde, 2.2 mg	2.19	(43.9)
0.9	Methylene chloride: workers (1940s-80s)	Methylene chloride, 471 mg	724	(918)
0.5	**Wine, 28.0 g**	**Ethyl alcohol, 3.36 ml**	9110	(—)
0.4	Conventional home air (14 hours/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	BHA: daily US 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 US 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 US avg (1977)	Saccharin, 7 mg	2140	(—)
0.005	**Carrot, 12.1 g**	**Aniline, 624 mg**	194[c]	(—)
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 hour/day)	Benzene, 155 mg	(169)	77.5
0.002	**Carrot, 12.1 g**	**Caffeic acid, 374 mg**	297	(4900)
0.002	Ethylene thiourea: daily US avg (1990)	Ethylene thiourea, 9.51 mg	7.9	(23.5)
0.002	[DDT: daily US 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 US avg (1987)	BHA, 700 mg	745	(5530)
0.001	**Pear, 3.29 g**	**Caffeic acid, 240 mg**	297	(4900)

Table 5 contd.

0.001	[UDMH: daily US 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 US avg (before 1972 ban)]	[DDE, 6.91 mg]	(—)	12.5
0.0007	TCDD: daily US avg (1994)	TCDD, 12.0 pg	0.0000235	(0.000156)
0.0007	Bacon, 11.5 g	Diethylnitrosamine, 11.5 ng	0.0237	(+)
0.0006	**Mushroom (*Agaricus bisporus* 2.55 g)**	**Glutamyl-*p*-hydrazino-benzoate, 107 mg**	.	277
0.0005	**Jasmine tea, 2.19 g**	**Benzyl acetate, 504 mg**	(—)	1440
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 US avg (before 1984 ban)]	[EDB, 420 ng]	1.52	(7.45)
0.0004	Tap water, 1 liter (1987-92)	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 (1987-92)	Chloroform, 17 mg	(262)	90.3
0.0003	Carbaryl: daily US 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 US avg (1990)	Toxaphene, 595 ng	(—)	5.57
0.00009	**Mushroom (Agaricus bisporus, 2.55 g)**	***p*-Hydrazinobenzoate, 28 mg**	.	454[c]
0.00008	PCBs: daily US avg (1984-86)	PCBs, 98 ng	1.74	(9.58)
0.00008	DDE/DDT: daily US 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, pan fried, 85 g**	**PhIP, 176 ng**	4.29[c]	(28.6[c])
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, pan fried, 85 g**	**MeIQx, 38.1 ng**	1.99	(24.3)
0.00002	Dicofol: daily US avg (1990)	Dicofol, 544 ng	(—)	32.9
0.00001	**Cocoa, 3.34 g**	**a-Methylbenzyl alcohol, 4.3 mg**	458	(—)
0.00001	**Beer, 257 g**	**Urethane, 115 ng**	(41.3)	16.9
0.000005	**Hamburger, pan fried, 85 g**	**IQ, 6.38 ng**	1.89[c]	(19.6)
0.000001	Lindane: daily US avg (1990)	Lindane, 32 ng	(—)	30.7
0.0000004	PCNB: daily US avg (1990)	PCNB (Quintozene), 19.2 ng	(—)	71.1
0.0000001	Chlorobenzilate: daily US avg (1989)	Chlorobenzilate, 6.4 ng	(—)	93.9
<0.00000001	Chlorothalonil: daily US avg (1990)	Chlorothalonil, <6.4 ng	828[d]	(—)
0.000000008	Folpet: daily US avg (1990)	Folpet, 12.8 ng	.	2280[d]
0.000000006	Captan: daily US avg (1990)	Captan, 11.5 ng	2690[d]	(2730[d])

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

[b]This is not an average, but a reasonably large sample (1027 workers).

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

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

Source: Gold *et al.* (40).