Misconceptions About Environmental Pollution, Pesticides and the Causes of Cancer

By

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Executive Summary

1. The major causes of cancer are:

   a) Smoking: About a third of U.S. cancer (90 percent of lung cancer);

   b) Dietary imbalances, e.g., lack of dietary fruits and vegetables: The quarter of the population eating the least fruits and 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; and

   d) Hormonal factors: primarily influenced by life style.

2. There is no epidemic of cancer, except for lung cancer due to smoking. Cancer mortality rates have declined 16 percent since 1950 (excluding lung cancer).

3. Regulatory policy that focuses on traces of synthetic chemicals is based on misconceptions about animal cancer tests. Recent research indicates that:

   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 rodent cancer tests that are not relevant to low-dose human exposures and that contribute to the high proportion of chemicals that test positive;

   c) The focus of regulatory policy is on synthetic chemicals, although 99.9 percent of the chemicals humans ingest are natural. More than 1,000 chemicals have been described in coffee: 28 have been tested and 19 are rodent carcinogens. Plants in the human diet contain thousands of natural pesticides that protect them from insects and other predators: 63 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: The Environmental Protection Agency has estimated that environmental regulations cost society $140 billion per year. Others have estimated that the median toxic control program costs 146 times more per life year saved than the median medical intervention. Attempting to reduce tiny hypothetical risks also has costs; for example, if reducing synthetic pesticides makes fruits and vegetables more expensive, thereby decreasing consumption, then cancer will be increased, particularly for the poor.

5. Prevention of cancer will come from knowledge obtained from biomedical research, education of the public and lifestyle changes by individuals. A re-examination of priorities in cancer prevention, both public and private, seems called for.

Clearing Up Cancer Misconceptions

Various misconceptions about the relationship between environmental pollution and human disease, particularly cancer, drive regulatory policy. In this paper, we highlight 10 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. (excluding lung cancer due to smoking) have declined 16 percent since 1950.[1] If lung cancer is included, mortality rates have increased over time, but recently have declined in men due to decreased smoking.

- The types of cancer deaths that have decreased are primarily stomach, cervical, uterine and colorectal.

- The types that have increased are primarily lung cancer (90 percent is due to smoking, as are 35 percent of all cancer deaths in the U.S.), melanoma (probably due to sunburns) and non-Hodgkin's lymphoma.

The rise in incidence rates in older age groups for some cancers, e.g., prostate, can be explained by known factors such as improved screening.[2] As one study noted, "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."[3] Life expectancy has continued to rise since 1950.

"Cancer death rates overall (excluding lung cancer) have declined 16 percent since 1950."

Misconception #2:
Environmental Synthetic Chemicals
Are an Important Cause of Human Cancer

Neither the study of patterns of disease in humans (epidemiology) nor experimental studies on laboratory animals (toxicology) support this idea.[4] Epidemiological studies have identified the factors that are likely to have a major effect on lowering rates of cancer: reduction of smoking, improving diet (e.g., increased consumption of fruits and vegetables), hormonal factors and control of infections. 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, exposures to synthetic pollutants are tiny and rarely seem toxicologically plausible as a

causal factor, particularly when compared to the background of natural chemicals that are rodent carcinogens.[5]

Even assuming that worst-case risk estimates for synthetic pollutants are true risks, the proportion of cancer that the Environmental Protection Agency (EPA) could prevent by regulation would be tiny.[6] Occupational exposures to some carcinogens cause cancer, though how much has been a controversial issue: a few percent seems a reasonable estimate,[7] much of this from 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; however, current permitted workplace exposures are sometimes close to the carcinogenic dose in rodents.[8]

"The proportion of cancer that regulation could prevent would be tiny."

Cancer is due in part to normal aging and increases exponentially with age in both rodents and humans.[9] To the extent that the major external risk factors for cancer are diminished, cancer will occur at 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 oxidative damage to DNA and other macromolecules.[10] Oxidant by-products of normal metabolism — superoxide, hydrogen peroxide and hydroxyl radical — are the same mutagens (agents that alter DNA) produced by radiation. Mitochondria from old animals leak oxidants;[11] old rats have about 66,000 oxidative DNA lesions per cell.[12] DNA is oxidized in normal metabolism because antioxidant defenses, though numerous, are not perfect. Antioxidant defenses against oxidative damage include Vitamins C and E and perhaps carotenoids,[13] most of which come from dietary fruits and vegetables.

"Smoking contributes to about 35 percent of cancer."

Smoking contributes to about 35 percent of U.S. cancer, about one-quarter of heart disease and about 400,000 premature deaths per year in the United States.[14] 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 the poor and smokers.

Men with inadequate diets or who smoke may damage the DNA of their sperm as well as the DNA in the rest of their cells. 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 percent.[15] Male smokers, compared to non-smokers, have more oxidative lesions in sperm DNA[16] and more chromosomal abnormalities in sperm.[17] Smoking by fathers, therefore, may plausibly increase the risk of birth defects and childhood cancer in offspring.[18] A new epidemiological study suggests that the rate of childhood cancers is increased in offspring of male smokers, e.g., acute lymphocytic leukemia, lymphoma, and brain tumors are increased three to four times.[19]

"Unbalanced diets, with a low intake of fruits and vegetables, account for about one-third of cancer risk."

The authors estimate that unbalanced diets (e.g., low intake of fruits and vegetables) account for about one-third of cancer risk, in agreement with the earlier estimate of researchers R. Doll and R. Peto.[20] [See Misconception #3.] There has been considerable interest in calories (and dietary fat) as a risk factor for cancer, in part because caloric restriction markedly lowers the cancer rate and increases life span in rodents.[21]

Chronic inflammation from chronic infection, a major contributor to cancer,[22] results in release from white cells of oxidants that are mutagens. 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, chronic cell killing with compensatory cell division, and mutation[23] and thus contribute to the carcinogenic process. Antioxidants appear to inhibit some of the pathology of chronic inflammation. Chronic infections cause about 21 percent of new cancer cases in developing countries and 9 percent in developed countries.[24]

Reproductive hormones play a large role in cancer, including breast, prostate, ovary and endometrium (the inner lining of the uterus),[25] contributing to as much as 20 percent of all cancer. Many lifestyle factors such as reproductive history, lack of exercise, obesity and alcohol intake influence hormone levels and therefore increase risk.[26]

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

"If fruits and vegetables become more expensive because of reduced synthetic pesticides then cancer, especially among the poor, is likely to increase."

On the contrary, fruits and vegetables are of major importance for reducing cancer; if they become more expensive because of reduced use of synthetic pesticides, then cancer is likely to increase. People with low incomes eat fewer fruits and vegetables and spend a higher percentage of their income on food.

High consumption of fruits and vegetables is associated with a lowered risk of degenerative diseases including cancer, cardiovascular disease, cataracts and brain dysfunction.[27]

- Over 200 studies in the epidemiological literature have been reviewed that show, with great consistency, an association between low consumption of fruits and vegetables and cancer incidence.[28] [See Appendix Table I].

- The quarter of the population with the lowest dietary intake of fruits and vegetables has roughly twice the cancer rate of the quarter with the highest intake for most types of cancer (lung, larynx, oral cavity, esophagus, stomach, colorectal, bladder, pancreas, cervix and ovary).

- 80 percent of U.S. children and adolescents[29] and 68 percent of adults did not meet the intake recommended by the National Cancer Institute and the National Research Council: five servings of fruits and vegetables per day.

Publicity about hundreds of minor hypothetical risks, such as pesticide residues (see Misconception #7), can cause loss of perspective on what is important: half the public does not know that fruit and vegetable consumption is a major protection against cancer.[30]

"Publicity about hypothetical risks, such as pesticide residues can cause the public to miss important health concerns, for instance half the public does not know that fruit and vegetable consumption is a major protection against cancer."

Misconception #4:
Identification of Carcinogenic Chemicals Should Be the Primary Strategy for Preventing Human Cancer

Hormonal factors, dietary imbalances, infection and inflammation and genetic factors, none of which involve a carcinogenic chemical, are major contributors to cancer.

Deficiency of micronutrients, many of which come from fruits and vegetables, can cause cancer. Antioxidants may account for some of the beneficial effect of fruits and vegetables, as discussed in Misconception #2. However, the effects of deficiency of dietary antioxidants are difficult to disentangle by epidemiological studies from that of other important vitamins and ingredients present in fruits and vegetables.[31]

Folate deficiency, one of the most common vitamin deficiencies, causes extensive chromosome breaks in human genes.[32] Approximately 10 percent of the US population[33] has a lower folate level than that at which chromosome breaks occur.[34] In two small studies of low income (mainly African-American) elderly[35] and adolescents[36] nearly half had folate levels that low. The rate of chromosome breaks in humans is reduced by folate administra-

tion.[37] Chromosome breaks could contribute to the increased risk of cancer and cognitive defects associated with folate deficiency in humans.[38] Folate deficiency also damages human sperm,[39] causes neural tube defects in the fetus and about 10 percent of U.S. heart disease.[40] Diets deficient in fruits and vegetables are commonly low in folate, antioxidants, (e.g., vitamin C) and many other micronutrients, and result in DNA damage and higher cancer rates.[41]

Many other micronutrients whose main dietary sources are other than fruits and vegetables, also 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 B_{12} (found in 5 percent of the U.S. population) causes a functional folate deficiency, accumulation of homocysteine (a risk factor for heart disease)[42] and probably causes chromosome breaks.[43] Strict vegetarians are at increased risk of developing a vitamin B_{12} deficiency.[44] Niacin contributes to the repair of DNA breaks.[45] As a result, dietary insufficiencies of niacin (15 percent of some populations are deficient)[46], folate and antioxidants may act together to increase DNA damage. There is also some evidence that deficiencies of zinc, copper, iron, selenium and vitamin B_6 (each deficiency occurs in 5 to 20 percent of the population), can lead to DNA damage.[47] Optimizing micronutrient intake (through better diets, fortification of foods or multivitamin-mineral pills) can have a major impact on health at low cost. Increasing research in this area, and efforts to increase micronutrient intake and more balanced diets, should be high priorities for public policy.

Misconception #5:
Human Exposures to Carcinogens and Other Potential Hazards Are Nearly All Due to Synthetic Chemicals

On the contrary, 99.9 percent 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.[48] Of all dietary pesticides that humans eat, 99.99 percent are natural: they are chemicals produced by plants to defend themselves against fungi, insects, and other animal predators.[49] Each plant produces a different array of such chemicals.

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- 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 have been tested for carcinogenicity, 35 of the 63 tested are rodent carcinogens. Naturally occurring pesticides that are rodent carcinogens are ubiquitous in fruits, vegetables, herbs, and spices.[50] [See Appendix Table II.]

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.[51] In a single cup of coffee the natural chemicals that are *known* rodent carcinogens are about equal in weight to a year's worth of synthetic pesticide residues that are rodent carcinogens, even though only 3 percent of the natural chemicals in roasted coffee have been adequately tested for carcinogenicity.[52] [See Appendix Table III.] 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.[53]

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Misconception #6:
Cancer Risks to Humans Can Be Assessed By Standard High-Dose Animal Cancer Tests

About 50 percent of all chemicals — whether natural or synthetic — that have been tested in standard, high-dose, animal cancer tests are rodent carcinogens.[54] [See Appendix Table IV.] What are the explanations for this high percentage? 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, can contribute to cancer in these tests. 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.[55] Each time a cell divides, the probability increases that a mutation will occur, thereby increasing the risk for cancer. At the low levels to which humans are usually exposed, such increased cell division does not occur. In addition, tissues injured by high doses of chemicals have an inflammatory immune response involving activation of white cells in response to cell death.[56] Activated white cells release mutagenic oxidants (including peroxynitrite, hypochlorite, and hydrogen peroxide). Therefore, the very low levels of chemicals to which humans are exposed through water pollution or synthetic pesticide residues may pose no or minimal cancer risks.

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The authors have discussed in another paper[57] the argument that the high positivity rate is due to selecting more suspicious chemicals to test, which is a likely bias since cancer testing is both expensive and time-consuming, and it is prudent to test suspicious compounds. One argument against selection bias is the high positivity rate for drugs [see Appendix Table IV] 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 two-year NTP bioassays. There was wide disagreement among them on which chemicals would be carcinogenic when tested, and accuracy varied, thus indicating that predictive knowledge is highly uncertain.[58]

"It seems likely that a high proportion of all chemicals, whether synthetic or natural, might be 'carcinogens' if administered in high enough doses."

It seems likely that a high proportion of all chemicals, whether synthetic or natural, might be "carcinogens" if administered in the standard rodent bioassay at the maximum tolerated dose, primarily due to the effects of high doses on cell division and DNA damage.[59] Without additional data on how a chemical causes cancer, the interpretation of a positive result in a rodent bioassay is highly uncertain. The induction of cancer could be the result of the high doses tested.

In regulatory policy, the "virtually safe dose" (VSD), corresponding to a maximum, hypothetical risk of one cancer in a million, is estimated from bioassay results using a linear model, which assumes that cancer causation is directly proportional to dose and that there are no unique effects of high doses. 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. The EPA has recently proposed guidelines that permit the use of non-linear approaches to low dose extrapolation if warranted by mechanistic data and a possible threshold of dose below which effects will not occur.[60]

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 can be helpful when setting research and regulatory priorities.[61] Rodent cancer tests provide little information about how a chemical causes cancer or about low-dose risk. The assumption that synthetic chemicals are hazardous has led to a bias in testing, such that synthetic chemicals account for 77 percent (432 of 559) of the chemicals tested chronically in both rats and mice. [See Appendix Table IV.] 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.[62] Ranking is a critical first step that can

help to set priorities for selecting chemicals for long term cancer tests, studies on mechanism, epidemiological research and 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, 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 (TD50 in mg/kg/day, i.e. dose to give 50 percent of test animals tumors) a human receives from a given daily lifetime exposure (mg/kg/day).[63] [See Appendix Table V.] A ranking based on standard regulatory risk assessment would be similar.

Overall, our analyses have shown that HERP values for some historically high exposures in the workplace (e.g., butadiene and tetrachloroethylene) and some pharmaceuticals (e.g., clofibrate) 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.[64] 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.[65]

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. [See Appendix Table V.] Appendix Table V also indicates that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. For many natural chemicals the HERP values are in the top half of the table, even though natural chemicals are markedly underrepresented because so few have been tested in rodent bioassays. Caution is necessary in drawing conclusions from the occurrence in the diet of natural chemicals that are rodent carcinogens. It is not argued here that these dietary exposures are necessarily of much relevance to human cancer. Our results call for a reevaluation of the utility of animal cancer tests in protecting the public against minor hypothetical risks.

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Misconception #8:
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.[66]

a) Humans have many natural defenses that buffer against normal exposures to toxins,[67] 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 human defenses are usually general, rather than specific for each chemical, makes good evolutionary sense. The reason that predators of plants evolved general defenses is presumably to be prepared to counter a diverse and ever-changing array of plant toxins in an evolving world; if a herbivore had defenses against only a set of specific toxins, it would be at a great disadvantage in obtaining new food when favored foods became scarce or evolved new toxins.

b) Various natural toxins, which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates.[68] Mold toxins, such as aflatoxin, have been shown to cause cancer in rodents and other species including humans [see Appendix Table IV.] 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.

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

"Natural selection works far too slowly for humans to have evolved specific resistance to the toxins in many common foods."

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. 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."[69]   There is no convincing epidemiological evidence, nor is there much toxicological plausibility, that the levels of DDT 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[70] 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.[71]

e) Since no plot of land is immune to attack by insects, plants need chemical defenses — either natural or synthetic — 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.[72]

Misconception #9:
Pesticides and Other Synthetic Chemicals Are Disrupting Hormones

Synthetic hormone mimics have become an environmental issue. Hormonal factors are important in cancer, as mentioned in Misconception #2. The 1996 book *Our Stolen Future*[73] claims 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[74] and that lifestyle factors can markedly change the levels of endogenous hormones [see 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.[75] In addition, it has not been shown convincingly that sperm counts are declining,[76] and even if they were, there are many more likely causes, such as smoking and diet.

Misconception #10:
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 based on cost-effectiveness in order to save the most lives.[77] The EPA projected in 1991 that the cost to society of environmental regulations in 1997 would be about $140 billion per year (about 2.6 percent of gross national product).[78] Most of this cost is to the private sector. Several economic analyses have concluded that current expenditures are not cost-effective; that is, resources are not being utilized so as to save the most lives per dollar. One estimate is that the U.S. could prevent 60,000 deaths per year by redirecting the same dollar resources to more cost-effective programs.[79] For example, the median toxin control program costs 146 times more per year of life saved than the median medical intervention.[80] This difference is likely to be 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.[81] [See Misconception #6.] Some economists have argued that costly regulations intended to save lives may actually lead to increased deaths,[82] in part because they divert resources from important health risks and in part because higher incomes are associated with lower mortality.[83] 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. 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.

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Regulatory efforts to reduce low-level human exposures to synthetic chemicals because they are rodent carcinogens 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 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.

Why has the government focused on minor hypothetical risks at huge cost? A recent article in *The Economist*[84] had a fairly harsh judgment: "Predictions of ecological doom, including recent ones have such a terrible track record that people should take them with pinches of salt instead of lapping them up with relish. For reasons of their own, pressure groups, journalists and fameseekers will no doubt continue to peddle ecological catastrophes at an undiminishing speed.... Environmentalists are quick to accuse their opponents in business of having vested interests. But their own incomes, their fame and their very existence can depend on supporting the most alarming versions of

every environmental scare. "The whole aim of practical politics" said H.L. Mencken, "is to keep the populace alarmed — and hence clamorous to be led to safety — by menacing it with a series of hobgoblins, all of them imaginary. Mencken's forecast, at least, appears to have been correct."

Dr. Aaron Wildavsky discusses worst-case risk assessment in his book *But Is It True: A Citizen's Guide to Environmental Health and Safety Issues.*[85] "We should be guided by the probability and extent of harm, not by its mere possibility. The search for possibilities is endless and it trivializes the subject. There is bound to be great diversion of resources without reducing substantial sources of harm. Consternation is created but health is not enhanced.... Weak causes are likely to have weak effects. Our search should be for strong causes with palpable effects, like cigarette smoking. They are easier to find and their effects are much more important to control.... The past necessity of proving harm has been replaced by a reversal of causality: now the individuals and businesses must prove that they will do no harm. My objection to this...is profound: our liberties are curbed and our health is harmed."

APPENDIX TABLE I

Review of Epidemiological Studies on Cancer Showing Protection by Consumption of Fruits and Vegetables[86]

Cancer site	Fraction of Studies Showing Significant Cancer Protection	Median Relative risk of Lowest Quarter vs. Highest Quarter 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	

APPENDIX TABLE II

Carcinogenicity of Natural Plant Pesticides Tested in Rodents (Fungal Toxins Are Not Included)[87]

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, N2-gamma-glutamyl-p-hydrazinobenzoic acid, hexanal methylformylhydrazine, p-hydrazinobenzoic acid.HCl, hydroquinone, 1-hydroxyanthraquinone, lasiocarpine, d-limonene, 8-methoxypsoralen, N-methyl-N-formylhydrazine, α-methylbenzyl alcohol, 3-methylbutanal methylformylhydrazone, methylhydrazine, monocrotaline, pentanal methylformylhydrazone, petasitenine, quercetin, reserpine, safrole, senkirkine, sesamol, symphytine

Noncarcinogens:

N=28   atropine, benzyl alcohol, biphenyl, d-carvone, deserpidine, disodium glycyrrhizinate, emetine.2HCl, ephedrine sulphate, eucalyptol, eugenol, gallic acid, geranyl acetate, β-N-[gamma-l(+)-glutamyl]-4-hydroxy-methylphenylhydrazine, glycyrrhetinic acid, p hydrazinobenzoic acid, isosafrole, kaempferol, dl-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, chili pepper, chocolate milk, cinnamon, cloves, cocoa, coffee, collard greens, comfrey herb tea, corn, corriander, 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.

APPENDIX TABLE III

Carcinogenicity in Rodents of Natural Chemicals in Roasted Coffee[88]

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

APPENDIX TABLE IV

Proportion of Chemicals Evaluated as Carcinogenic

Chemicals tested in both rats and mice[a]	330/559	(59%)
Naturally-occurring chemicals	73/127	(57%)
Synthetic chemicals	257/432	(59%)
Chemicals tested in rats and/or mice[a]		
Chemicals in Carcinogenic Potency Database	668/1275	(52%)
Natural pesticides	35/64	(55%)
Mold toxins	14/23	(61%)
Chemicals in roasted coffee	19/28	(68%)
Innes negative chemicals retested[a,b]	16/34	(47%)
Physician's Desk Reference (PDR): drugs with reported cancer tests[c]	117/241	(49%)
FDA database of drug submissions[d]	125/282	(44%)

[a] From the Carcinogenic Potency Database. [89]

[b] The 1969 study by Innes et al.[90] is frequently cited as evidence that the proportion of carcinogens is low, as only 9% of 119 chemicals tested (primarily pesticides) were positive. However, these tests, which were only in mice with few animals per group, lacked the power of modern tests. Of the 34 Innes negative chemicals that have been retested using modern protocols: 16 were positive.

[c] Davies and Monro.[91]

[d] Contrera et al.[92] 140 drugs are in both the FDA and PDR databases.

APPENDIX TABLE V

Ranking Possible Carcinogenic Hazards from Average U.S. Exposures[93]

[Chemicals that occur naturally in foods are in bold.] *Daily human exposure:* The calculations assume an average daily dose for a lifetime. *Possible hazard:* The human exposure to a rodent carcinogen is divided by 70 kg to give a mg/kg/day of human exposure, and this dose is given as the percentage of the TD_{50} in the rodent (mg/kg/day) to calculate the *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. The less potent value is in parentheses.

Possible Hazard: HERP (%)	Average Daily U.S. 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 (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	724	(918)
0.5	**Wine, 28.0 g**	**Ethyl alcohol, 3.36 ml**	9110	(—)
0.4	Conventional home air (14 hours/day)	Formaldehyde, 598 µg	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 µg**	13.9	(103)
0.006	**Coffee, 13.3 g**	**Hydroquinone, 333 µg**	82.8	(225)
0.005	Saccharin: daily US avg (1977)	Saccharin, 7 mg	2140	(—)
0.005	**Carrot, 12.1 g**	**Aniline, 624 µg**	194[c]	(—)
0.004	**Potato, 54.9 g**	**Caffeic acid, 867 µg**	297	(4900)
0.004	**Celery, 7.95 g**	**Caffeic acid, 858 µg**	297	(4900)
0.004	**White bread, 67.6 g**	**Furfural, 500 µg**	(683)	197
0.003	**Nutmeg, 27.4 mg**	**d-Limonene, 466 µg**	204	(—)
0.003	Conventional home air	Benzene, 155 µg	(169)	77.5
0.002	**Carrot, 12.1 g**	**Caffeic acid, 374 µg**	297	(4900)

APPENDIX TABLE V continued

Possible Hazard: HERP (%)	Average Daily U.S. Exposure	Human Dose of Rodent Carcinogen	Potency TD50 (mg/kg/day)[a]	
			Rats	Mice
0.002	Ethylene thiourea: U.S. avg (1990)	Ethylene thiourea, 9.51 μg	7.9	(23.5)
0.002	[DDT: US avg (before 1972 ban)]	[DDT, 13.8 μg]	(84.7)	12.3
0.001	**Plum, 2.00 g**	**Caffeic acid, 276 μg**	297	(4900)
0.001	BHA: US avg (1987)	BHA, 700 μg	745	(5530)
0.001	**Pear, 3.29 g**	**Caffeic acid, 240 μg**	297	(4900)
0.001	[UDMH: US avg (1988)]	[UDMH, 2.82 μg (from Alar)]	(—)	3.96
0.0009	**Brown mustard, 68.4 mg**	**Allyl isothiocyanate, 62.9 μg**	96	(—)
0.0008	[DDE: US avg (before 1972 ban)]	[DDE, 6.91 μg]	(—)	12.5
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 μg**		277
0.0004	**Bacon, 11.5 g**	***N*-Nitrosopyrrolidine, 196 ng**	(0.799)	0.679
0.0004	**Bacon, 11.5 g**	**Dimethylnitrosamine, 34.5 ng**	0.124	(0.189)
0.0004	[EDB: US avg (before 1984 ban)]	[EDB, 420 ng]	1.52	(7.45)
0.0004	Tap water, 1 liter (1987-92)	Bromodichloromethane, 13 μg	(72.5)	47.7
0.0004	TCDD: US avg (1994)	TCDD, 12.0 pg	0.0000457	(0.000156)
0.0003	**Mango, 1.22 g**	***d*-Limonene, 48.8 μg**	204	(—)
0.0003	**Beer, 257 g**	**Furfural, 39.9 μg**	(683)	197
0.0003	Tap water, 1 liter (1987-92)	Chloroform, 17 μg	(262)	90.3
0.0003	Carbaryl: US avg (1990)	Carbaryl, 2.6 μg	14.1	(—)
0.0002	**Celery, 7.95 g**	**8-Methoxypsoralen, 4.86 μg**	32.4	(—)
0.0002	Toxaphene: US avg (1990)	Toxaphene, 595 ng	(—)	5.57
0.00009	**Mushroom (Agaricus bisporus, 2.55 g)**	***p*-Hydrazinobenzoate, 28 μg**		454[c]
0.00008	PCBs: US avg (1984-86)	PCBs, 98 ng	1.74	(9.58)
0.00008	DDE/DDT: US avg (1990)	DDE, 659 ng	(—)	12.5
0.00007	**Parsnip, 54.0 mg**	**8-Methoxypsoralen, 1.57 μg**	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 μg**		51.8
0.00005	**Parsley, fresh, 324 mg**	**8-Methoxypsoralen, 1.17 μg**	32.4	(—)
0.00003	**Hamburger, pan fried, 85 g**	**MeIQx, 38.1 ng**	1.99	(24.3)
0.00002	Dicofol: US avg (1990)	Dicofol, 544 ng	(—)	32.9
0.00001	**Cocoa, 3.34 g**	**α-Methylbenzyl alcohol, 4.3 μg**	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: US avg (1990)	Lindane, 32 ng	(—)	30.7
0.0000004	PCNB: US avg (1990)	PCNB (Quintozene), 19.2 ng	(—)	71.1
0.0000001	Chlorobenzilate: US avg (1989)	Chlorobenzilate, 6.4 ng	(—)	93.9
<0.00000001	Chlorothalonil: US avg (1990)	Chlorothalonil, <6.4 ng	828[d]	(—)
0.000000008	Folpet: US avg (1990)	Folpet, 12.8 ng		2280[d]
0.000000006	Captan: US avg (1990)	Captan, 11.5 ng	2690	(2730[d])

[a] " " = no data in CPDB; (—) = negative in cancer test; (+) = positive cancer test(s) not suitable for calculating a TD50.
[b] This is not an average, but a reasonably large sample (1027 workers).
[c] TD50 harmonic mean was estimated for the base chemical from the hydrochloride salt.
[d] For references for exposures see Gold & Zeiger eds. (1997).

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