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Cancer Prevention and the Environmental Chemical Distraction

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Entering a new millennium seems a good time to challenge some old ideas about cancer cause and prevention, which in our view

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are implausible, have little supportive evidence, and might best be left behind. In this chapter, we summarize data and conclusions from fifteen years of work, raising five issues that involve toxicology, nutrition, public health, and government regulatory policy:

1. *There is no cancer epidemic other than that due to smoking.*
2. *The dose makes the poison.* Half of all chemicals tested, whether natural or synthetic, cause cancer in high-dose rodent cancer tests. Evidence suggests that this high rate is due primarily to effects that are unique to high doses. The results of these high-dose tests have been used to regulate low-dose human exposures, but are not likely to be relevant.
3. *Even Rachel Carson was made of chemicals: natural vs. synthetic chemicals.* Human exposure to naturally occurring rodent carcinogens is ubiquitous and dwarfs the exposure of the general public to synthetic rodent carcinogens.
4. *Errors of omission.* The major causes of cancer (other than smoking) do not involve exposures to exogenous chemicals that cause cancer in high-dose tests; rather, the major causes are dietary imbalances, hormonal factors, infection and inflammation, and genetic factors. Insufficiency of many vitamins and minerals, which is preventable by supplementation, causes DNA damage by a mechanism similar to radiation.
5. *Damage by distraction: regulating low hypothetical risks.* Regulatory policy places unwarranted emphasis on reducing low-level exposures to synthetic chemicals. Putting large amounts of money into small hypothetical risks can damage public health by diverting resources and distracting the public from major risks.

The Dose Makes the Poison

The main rule in toxicology is that "the dose makes the poison." At some level, every chemical becomes toxic, but there are safe levels below that.

In contrast to that rule, a scientific consensus evolved in the 1970s that we should treat carcinogens differently, that we should assume that even low doses might cause cancer, even though we lacked the methods for measuring carcinogenic effects at low levels. In large part, this assumption was based on the idea that mutagens—chemicals that cause changes in DNA—are carcinogens and that the risk of mutations was directly related to the number of mutagens introduced into a cell. It was also assumed that (1) only a small proportion of chemicals would have carcinogenic potential, (2) testing at a high dose would not produce a carcinogenic effect unique to the high dose, and (3) carcinogens were likely to be synthetic industrial chemicals. As we enter the new century, it is time to take account of information indicating that all three assumptions are wrong.

Laws and regulations directed at synthetic chemicals got a big push from the widely publicized "cancer epidemic," which supposedly stemmed from exposures to those chemicals. In fact, there is not now and there never was a cancer epidemic, and cancer mortality, excluding lung cancer mortality, has declined 19 percent since 1950.[1] Lung cancer mortality began dropping about 1990 as a result of reduced smoking rates, and that trend is likely to continue. Regardless of the absence of evidence for a cancer epidemic, the "epidemic" has left a long-lasting legacy—a regulatory focus on synthetic chemicals.

1. L. A. G. Ries et al., *SEER Cancer Statistics Review, 1973–1997* (Bethesda, Md.: National Cancer Institute, 2000).

Table 1. Proportion of Tested Chemicals Classified as Carcinogenic

Chemicals tested in both rats and mice[a]	
Chemicals in the CPDB	350/590 (59 percent)
Naturally occurring chemicals in the CPDB	79/139 (57 percent)
Synthetic chemicals in the CPDB	271/451 (60 percent)
Chemicals tested in rats and/or mice	
Chemicals in the CPDB	702/1348 (52 percent)
Natural pesticides in the CPDB	38/72 (53 percent)
Mold toxins in the CPDB	14/23 (61 percent)
Chemicals in roasted coffee in the CPDB	21/30 (70 percent)
Commercial pesticides	79/194 (41 percent)
Innes negative chemicals retested[b]	17/34 (50 percent)
Physician's Desk Reference (PDR):	
drugs with reported cancer tests[c]	117/241 (49 percent)
FDA DATABASE OF DRUG SUBMISSIONS[d]	125/282 (44 percent)

Notes: a. L. S. Gold and E. Zeiger, eds., *Handbook of Carcinogenic Potency and Genotoxicity Databases* (Boca Raton, Fla.: CRC Press, 1997), http://potency.berkeley.edu/crcbook.html (Gold and Zeiger, *Handbook of Carincogenic Potency*).

b. J. R. M. Innes et al., "1969 Tested 120 Chemicals for Carcinogenicity," *Journal of the National Cancer Institute* 42 (1969): 1110–14. They reported that only eleven of the chemicals were carcinogens, and that observation was important to the idea that only a small proportion, say 10 percent, of all chemicals were carcinogens. To date, fully half the negative chemicals from the Innes study, when retested, have been shown to be carcinogenic.

c. T. S. Davies and A. Monro, "Marketed Human Pharmaceuticals Reported to be Tumorigenic in Rodents," *J. Am. Coll. Toxicol.* 14 (1995): 90–107.

d. J. Contrera, A. Jacobs, and J. DeGeorge, "Carcinogenicity Testing and the Evaluation of Regulatory Requirements for Pharmaceuticals," *Regul. Toxicol. Pharmacol.* 25 (1997): 130–45.

Source: Carcinogenic Potency Database (http://potency.berkeley.edu)

About 50 percent of chemicals, both natural and synthetic, that have been tested in standard, high-dose, animal cancer tests are rodent carcinogens (Table 1).[2] What explains the high per-

2. L. S. Gold et al., *Misconceptions About the Causes of Cancer*, L. S. Gold and E. Zeiger, eds., *Handbook of Carcinogenic Potency and Genotoxicity Databases* (Boca Raton, Fla.: CRC Press, 1997); L. S. Gold et al., "Supplement to the Carcinogemic Potency Database (CPDB): Results of Animal Bioassays Published in the General Literature in 1993–1994 and by the National Toxi-

centage? In standard cancer tests, rodents are given a near-toxic dose of the test substance over their lifetime, the maximum tolerated dose (MTD), to maximize the chance of detecting any carcinogenicity. Evidence is accumulating that cell division caused by the high dose itself, rather than the chemical per se, contributes to cancer in these tests.[3]

High doses can cause chronic wounding of tissues, cell death, and consequent chronic cell division of neighboring cells, which would otherwise not divide. Cell division is a risk factor for cancer because there is some probability that a mutation will occur each time DNA is replicated, and some of those mutations can lead to cancer. A high proportion (41 percent) of chemicals that are carcinogens in rodent tests are not mutagenic, and their carcinogenicity may result from cell killing and consequent division at the high doses tested. Such increased cell division does not occur at the low levels of synthetic chemicals to which humans are usually exposed.

Defenders of rodent tests argue that the high rate of positive tests results from selecting more suspicious chemicals to test, and this seems a likely bias because cancer testing is both expensive and time-consuming, making it prudent to test suspicious compounds. One argument against such a selection bias is the high rate of positive tests for drugs (Table 1) because drug development favors chemicals that are not mutagens or expected carcinogens.[4]

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cology Program in 1995–1996," *Environ. Health Perspect.* 107 (Suppl. 4, 1999): 527–600.

3. B. N. Ames and L. S. Gold, "Chemical Carcinogenesis: Too Many Rodent Carcinogens," *Proc. Natl. Acad. Sci. U.S.A.* 87 (1990): 7772–76; S. M. Cohen, "Cell Proliferation and Carcinogenesis," *Drug Metab. Rev.* 30 (1998): 339–57.

4. See L. S. Gold, T. H. Slone, and B. N. Ames, "What Do Animal Cancer Tests Tell Us About Human Cancer Risk?: Overview of Analyses of the Carcinogenic Potency Database," *Drug Metab. Rev.* 30 (1998): 359–404.

A second argument against selection bias is that the knowledge needed to predict carcinogenicity in rodent tests is highly imperfect, even now, after decades of test results have become available on which to base predictions. For example, in 1990, there was wide disagreement among experts about which chemicals would be carcinogenic when subsequently tested by the National Toxicology Program.[5] Moreover, if the primary basis for selection of chemicals to test were suspicion of carcinogenicity, selection would focus on mutagens (80 percent are carcinogenic compared to 50 percent of nonmutagens). In fact, a majority of tested chemicals, 55 percent, are nonmutagens.

It seems likely that a high proportion of all chemicals, whether synthetic or natural, would be "carcinogens" if administered in the standard rodent bioassay at the MTD, primarily because of the effects of high doses on cell death and division and DNA damage and repair.[6] Without additional data about 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 and have no predictive value about what might occur at lower doses.

The processes of mutagenesis and carcinogenesis are complicated because of many factors, which are dose-dependent.[7] For instance, normal cells contain an appreciable level of DNA lesions, and they contain enzymes that repair the lesions with high

5. G. S. Omenn, S. Stuebbe, and L. B. Lave, "Predictions of Rodent Carcinogenicity Testing Results: Interpretation in Light of the Lave-Omenn Value-of-Information Model," *Mol. Carcinog.* 14 (1995): 37–45.

6. B. Butterworth, R. Conolly, and K. Morgan, "A Strategy for Establishing Mode of Action of Chemical Carcinogens as a Guide for Approaches to Risk Assessment," *Cancer Lett.* 93 (1995): 129–46.

7. J. G. Christensen, T. L. Goldsworthy, and R. C. Cattley, "Dysregulation of Apoptosis by C-myc in Transgenic Hepatocytes and Effects of Growth Factors and Nongenotoxic Carcinogens," *Mol. Carcinog.* 25 (1999): 273–84.

efficiency.[8] The number of those lesions increases in tissues injured by high doses of chemicals[9] and may overwhelm the capacity of the repair enzymes. The far lower levels of chemicals to which humans are exposed through water pollution or synthetic pesticide residues on food are not sufficient to increase the number of DNA lesions in any appreciable way and may pose no or minimal cancer risks.

Regulatory agencies do not consider the great uncertainties in extrapolating from the effects observed in high-dose rodent tests to predictions of possible effects in humans at far lower doses. Instead, they assume that the effects are directly proportional to dose—that there is a linear relationship between dose and cancer—and they calculate the "virtually safe dose" (VSD), which corresponds to a maximum, hypothetical risk of one additional cancer in a million exposed people, and set the VSD as the acceptable exposure level. To the extent that high doses of nonmutagens are the cause of carcinogenicity in rodent bioassays, the linear model is inappropriate.[10] Linearity of dose response seems unlikely in any case even for chemicals that are mutagens because of the inducibility of the numerous defense enzymes that deal with the thousands of exogenous chemicals that we encounter in our diets (see below), and protect us against the natural world of mutagens as well as the small amounts of synthetic chemicals.[11]

8. H. J. Helbock et al., "DNA Oxidation Matters: The HPLC-EC Assay of 8-oxo-deoxyguanosine and 8-oxo-guanine," *Proc. Natl. Acad. Sci. U.S.A.* 95 (1998): 288–93.

9. D. L. Laskin and K. J. Pendino, "Macrophages and Inflammatory Mediators in Tissue Injury," *Annu. Rev. Pharmacol. Toxicol.* 35 (1995): 655–77.

10. D. W. Gaylor and L. S. Gold, "Regulatory Cancer Risk Assessment Based on a Quick Estimate of a Benchmark Dose Derived from the Maximum Tolerated Dose," *Regul. Toxicol. Pharmacol.* 28 (1998): 222–25.

11. T. D. Luckey, "Nurture with Ionizing Radiation: A Provocative Hypothesis," *Nutr. Cancer* 34 (1999): 1–11; Ames and Gold, "Paracelsus to Parascience."

Regulatory agencies are moving to take nonlinearity and questions about mechanisms of carcinogenicity into account; for example, the U.S. Environmental Protection Agency (EPA) recently concluded that chloroform (a by-product of disinfecting water with chlorine) was not likely to be carcinogenic to humans unless the exposures were high enough to cause cell toxicity and increased cell division. The chloroform levels in drinking water are low and do not produce such effects.[12]

Even Rachel Carson Was Made of Chemicals: Natural vs. Synthetic Chemicals

About 99.9 percent of the chemicals humans ingest are natural, and the amounts of synthetic pesticide residues in foods are insignificant compared to the amount of natural pesticides that are always in our diet because of the plants we eat.[13] Of all dietary pesticides that humans eat, 99.99 percent are natural chemicals produced by plants to defend themselves against fungi, insects, and other animal predators. The natural pesticides come in great variety because each plant produces a different array of such chemicals.

We have estimated that on average Americans ingest roughly 5,000 to 10,000 different natural pesticides and their breakdown

12. U.S. Environmental Protection Agency, "Integrated Risk Information System (IRIS)" (Cincinnati: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, 2002).

13. B. N. Ames, M. Profet, and L. S. Gold, "Nature's Chemicals and Synthetic Chemicals: Comparative Toxicology," *Proc. Natl. Acad. Sci. U.S.A.* 87 (1990): 7782–86; B. N. Ames, M. Profet, and L. S. Gold, "Dietary Pesticides 99.99 Percent All Natural," ibid., 7777–81; L. S. Gold, T. H. Slone, and B. N. Ames, "Prioritization of Possible Carcinogenic Hazards in Food," in D. Tennant, ed., *Food Chemical Risk Analysis* (London: Chapman & Hall, 1997), pp. 267–95.

products. Each day, the average American eats about 1,500 milligrams (mg = 1/1000th of a gram) of natural pesticides, which is about 10,000 times more than the 0.09 mg they consume of synthetic pesticide residues.[14]

Only a small proportion of natural pesticides have been tested for carcinogenicity, but 38 of the 72 tested are rodent carcinogens. As shown in Table 2, naturally occurring pesticides that are rodent carcinogens are ubiquitous in common fruits, vegetables, herbs, and spices. The widespread distribution of such chemicals means that no diet can be free of natural chemicals that are rodent carcinogens.

The average American eats about 2,000 mg of burnt material, which is produced in usual cooking practices, each day. That burnt material contains many rodent carcinogens and mutagens, swamping, again, the 0.09 mg of 200 synthetic chemicals, primarily synthetic pesticides, that are ingested each day and that are classified as rodent carcinogens.

The natural chemicals that are known rodent carcinogens in a single cup of coffee are about equal in weight to a year's worth of ingested synthetic pesticide residues that are rodent carcinogens. This is so, even though only 3 percent of the natural chemicals in roasted coffee have been adequately tested for carcinogenicity (Table 3). This does not mean that coffee or natural pesticides are dangerous; rather, assumptions about high-dose animal cancer tests for assessing human risk at low doses need reexamination.

14. E. L. Gunderson, "Chemical Contaminants Monitoring: FDA Total Diet Study, April 1982–April 1984, Dietary Intakes of Pesticides, Selected Elements, and Other Chemicals," *J. Assoc. Off. Anal. Chem.* 71 (1988):1200–9.

Table 2. Carcinogenicity Status of Natural Pesticides Tested in Rodents

Occurrence: *Natural pesticides that are 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, citronella, 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, oregano, 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.

Carcinogens and Noncarcinogens among Tested Natural Pesticides:

Carcinogens: N=38	acetaldehyde methylformylhydrazone, allyl isothiocyanate, arecoline.HCl, benzaldehyde, benzyl acetate, caffeic acid, capsaicin, catechol, clivorine, coumarin, crotonaldehyde, 3,4-dihydrocoumarin, estragole, ethyl acrylate, *N*2-λ-glutamyl-*p*-hydrazinobenzoic acid, hexanal methylformylhydrazine, *p*-hydrazinobenzoic acid.HCl, hydroquinone, 1-hydroxyanthraquinone, lasicarpine, *d*-limonene, 3-methoxycatechol, 8-methoxypsoralen, *N*-methyl-*N*-formylhydrazine, α-methylbenzyl alcohol, 3-methylbutanal methylformylhydrazone, 4-methylcatechol, methyl eugenol, 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*-[β-*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

Source: Carcinogenic Potency Database (http://potency.berkeley.edu); Gold and Zeiger, *Handbook of Carincogenic Potency*.

Table 3. Rodent Carcinogens in the Natural Chemicals Present in Roasted Coffee

Carcinogens: 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
Noncarcinogens: N=8	acrolein, biphenyl, choline, eugenol, nicotinamide, nicotinic acid, phenol, piperidine
Uncertain:	caffeine
Yet to test:	~1,000 chemicals

Source: Carcinogenic Potency Database (http://potency.berkeley.edu); Gold and Zieger, *Handbook of Carcinogenic Potency*.

Ranking Risks

Gaining a broad perspective about the vast number of chemicals to which humans are exposed can be helpful when setting research and regulatory priorities. Rodent cancer tests by themselves 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, and such chemicals account for 76 percent (451 of 590) of the chemicals tested chronically in both rats and mice (Table 1). The world of natural chemicals has never been tested systematically.

One reasonable strategy to use the available information about cancer risk is to construct an index to compare and rank possible carcinogenic hazards from a wide variety of chemical exposures at levels typically experienced by humans, and then to focus research and regulatory efforts on those that rank highest.[15]

15. L. S. Gold et al., *Misconceptions About the Causes of Cancer;* B. N. Ames,

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 risks at the bottom of a ranking if the same methodology identifies numerous, common human exposures that pose much greater possible risks. Our rankings are based on the human exposure/rodent potency (HERP) index, which is the ratio between the average human exposure to a chemical and the dose that caused cancer in 50 percent of exposed rodents.

Overall, our analyses have shown that HERP values for some historically high exposures in the workplace—to butadiene and tetrachloroethylene—and to some pharmaceuticals—clofibrate—rank high, and that there is an enormous background of naturally occurring rodent carcinogens in typical portions of common foods. The background of natural exposures casts doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides. (A committee of the National Research Council of the National Academy of Sciences reached similar conclusions about natural vs. synthetic chemicals in the diet, and called for further research on natural chemicals.)[16]

The possible carcinogenic hazards from synthetic pesticides are minimal compared to the background of nature's pesticides, though neither may be a hazard at the low doses consumed. Analysis also indicates that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. Caution is necessary in drawing conclusions about the occurrence in the diet of natural chemicals that are rodent carcinogens. These di-

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R. Magaw, and L. S. Gold, "Ranking Possible Carcinogenic Hazards," *Science* 236 (1987): 271–80.

16. National Research Council, C*arcinogens and Anticarcinogens in the Human Diet: A Comparison of Naturally Occurring and Synthetic Substances* (Washington, D.C.: National Academy Press, 1996).

etary exposures are not necessarily of much relevance to human cancer. The data call for a reevaluation of the utility of animal cancer tests in protecting the public against minor hypothetical risks without understanding how the chemical causes tumors.

Cellular Defenses Against Chemical Carcinogens Work Against Natural and Synthetic Chemicals

It is often assumed that because natural chemicals are part of human evolutionary history, whereas synthetic chemicals are recent, the mechanisms 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.

1. Human defenses to ward off effects of exposures to toxins are usually general, directed at classes of similar chemicals, rather than tailored for specific chemicals, and they work against both natural and synthetic chemicals.[17] 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 repair DNA damage regardless of the source of the damage. Detoxification enzymes of the liver and other organs generally react with classes of chemicals rather than individual chemicals.

General defense mechanisms make good evolutionary sense for animals, such as humans, which eat plants and encounter a diverse and ever-changing array of plant toxins in an evolving world. A herbivore that had defenses against only a specific set of toxins would be at great disadvantage in obtaining new food when favored foods became scarce or evolved new chemical defenses.

17. Ames, Profet, and Gold, "Nature's Chemicals and Synthetic Chemicals."

2. Various natural toxins, which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates. Mold toxins, such as aflatoxin, have been shown to cause cancer in rodents (Table 1) and other species including humans. Many common elements are carcinogenic to humans at high doses—for example, 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 ingested natural substances may be carcinogenic risks to humans. Naturally occurring arsenic in drinking water causes cancer of the lung, bladder, and skin,[18] and the chewing of betel nut with tobacco causes oral cancer.

3. 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, such as 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.

4. DDT is often viewed as the typically dangerous synthetic pesticide because it concentrates in adipose tissues and persists for years. DDT, the first synthetic pesticide, eradicated malaria from many parts of the world, including the United States. It was effective against many vectors of disease such as mosquitoes, tsetse flies, lice, ticks, and fleas and against many crop pests, significantly increasing the supply and lowering the cost of food, making fresh, nutritious foods more accessible to poor people. DDT was also of low toxicity to humans. DDT prevented many

18. National Research Council, *Arsenic in Drinking Water: 2001 Update* (Washington, D.C.: National Academy Press, 2001).

millions of deaths due to malaria.[19] (See also Bate chapter, this volume.)

There is no convincing epidemiological evidence,[20] 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 cancer. Two chemical properties of DDT were important in focusing attention on it. DDT, once ingested, is stored in fatty tissues, and the DDT in an insect, when eaten by a small bird, will be concentrated and stored in the bird's fat. If a larger bird, such as an eagle, eats the small bird, it will ingest the concentrated DDT and each additional meal of DDT-containing prey will increase the concentration. The chlorine components (substituents) of DDT cause it to be resistant to degradation in nature, and, as a result, it persists longer than most chemicals. Few synthetic chemicals share these properties.

These properties are not unique to synthetic chemicals. Many thousands of chlorinated chemicals are produced in nature,[21] and natural pesticides can bioconcentrate if they are fat-soluble. Potatoes, for example, contain solanine and chaconine, which are fat-soluble, neurotoxic, natural pesticides that can be detected in the blood of all potato eaters. High levels of these potato neurotoxins have been shown to cause birth defects in rodents,[22] though they have not been tested for carcinogenicity.

5. Because no plot of land is immune to attack by insects,

19. National Academy of Sciences, U.S.A., *The Life Sciences: Recent Progress and Application to Human Affairs, the World of Biological Research, Requirement for the Future* (Washington, D.C.: Committee on Research in the Life Sciences, 1970).

20. T. Key and G. Reeves, "Organochlorines in the Environment and Breast Cancer," *Br. Med. J.* 308 (1994): 1520–21.

21. G. W. Gribble, "The Diversity of Natural Organochlorines in Living Organisms," *Pure Appl. Chem.* 68 (1996): 1699–1712.

22. Ames, Profet, and Gold, "Nature's Chemicals and Synthetic Chemicals."

plants need chemical defenses—either natural or synthetic—to survive, and trade-offs between naturally occurring and synthetic pesticides are possible. One consequence of disproportionate concern about synthetic pesticide residues is that some plant breeders develop plants to be more insect-resistant, which sometimes increases their levels of natural pesticides, which can bring its own hazards. When a major grower introduced a new variety of highly insect-resistant celery into commerce, people who handled the celery developed rashes when they went out into the 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.[23]

Errors of Omission

High consumption of fruits and vegetables is associated with a lowered risk of degenerative diseases including cancer, cardiovascular disease, cataracts and brain dysfunction.[24] More than 200 studies in the epidemiological literature show, with consistency, an association between low consumption of fruits and vegetables and high cancer incidence (Table 4). The evidence of a protective effect of fruits and vegetables is most convincing for cancers of the oral cavity, esophagus, stomach, and lung. The median relative risk of cancer of the lung, larynx, oral cavity, esophagus, stomach, bladder, pancreas, and cervix was about double for the quarter of the population with the lowest dietary intake of fruits

23. S. F. Berkley et al., "Dermatitis in Grocery Workers Associated with High Natural Concentrations of Furanocoumarins in Celery," *Ann. Intern. Med.* 105 (1986): 351–55.

24. B. N. Ames, L. S. Gold, and W. C. Willett, "The Causes and Prevention of Cancer," *Proc. Natl. Acad. Sci. U.S.A.* 92 (1995): 5258–65; B. N. Ames, M. K. Shigenaga, and T. M. Hagen, "Oxidants, Anti-Oxidants, and the Degenerative Diseases of Aging," ibid. 90 (1993): 7915–22.

Table 4. Review of Epidemiological Studies on Association Between Fruit and Vegetable Consumption and Cancer Risk at Various Sites

Cancer site	*Proportion of Studies with Statistically Significant Protective Effect of Fruits and/or Vegetables*[a]	*Percent of Studies with Protective Effect*
Larynx	6/6	100
Stomach	28/30	93
Mouth, oral cavity, and pharynx	13/15	87
Bladder	6/7	86
Lung	11/13	85
Esophagus	15/18	83
Pancreas	9/11	82
Cervix	4/5	80
Endometrium	4/5	80
Rectum	8/10	80
Colon	15/19	79
Colon/rectum	3/5	60
Breast	8/12	67
Thyroid	3/5	60
Kidney	3/5	60
Prostate	1/6	17
Nasal and nasopharynx	2/4	—[b]
Ovary	3/4	—
Skin	2/2	—
Vulva	1/1	—
Mesothelium	0/1	—
TOTAL	144/183	79

Notes: a. Based on standard statistical tests; see the source publication for further information.

b. — = fewer than 5 studies; no percent was calculated.

Source: World Cancer Research Fund (1997). *Food, Nutrition and the Prevention of Cancer: A Global Perspective* (Washington, D.C.: American Institute for Cancer Research, 1997).

and vegetables when compared to the quarter with the highest intake.[25] The median relative risk, although elevated, was not as

25. G. Block, B. Patterson, and A. Subar, "Fruit, Vegetables, and Cancer Prevention: A Review of the Epidemiologic Evidence," *Nutr. Cancer* 18 (1992): 1–29.

high for the hormonally related cancers of breast, prostate, and ovary, or for the colon.

Inadequate diets, with too few fruits and vegetables, are a cancer risk, and they are common. Fully 80 percent of children and adolescents[26] and 68 percent of adults[27] do not eat the five servings of fruits and vegetables per day recommended by the National Cancer Institute and the National Research Council. Publicity about hundreds of minor hypothetical risks, such as pesticide residues, can cause a loss of perspective about what is important. In a survey, half the U.S. public did not name fruit and vegetable consumption as protective against cancer.[28]

Fascination with the hypothetical risks from pesticides may increase cancer risks. Fruits and vegetables are of major importance for reducing cancer; if they become more expensive because of reduced use of synthetic pesticides then consumption is likely to decline and cancer to increase. The effects of such policies will be most notable on people with low incomes who must spend a higher percentage of their income on food, and who already eat fewer fruits and vegetables.

Laboratory studies of vitamin and mineral inadequacy associate such deficiencies with DNA damage, which indicates that the vitamin and mineral content of fruits and vegetables may explain the observed association between fruit and vegetable intake and cancer risk. Antioxidants such as vitamin C (whose dietary source is fruits and vegetables), vitamin E, and selenium

26. S. M. Krebs-Smith et al., "Fruit and Vegetable Intakes of Children and Adolescents in the United States," *Arch. Pediatr.* 150 (1996): 81–86.

27. S. M. Krebs-Smith et al., "U.S. Adults" Fruit and Vegetable Intakes, 1989 to 1991: A Revised Baseline for the Healthy People 2000 Objective," *Am. J. Public Health* 85 (1995): 1623–29.

28. National Cancer Institute Graphic, "Why Eat Five?" *J. Natl. Cancer Inst.* 88 (1996): 1314.

protect against oxidative damage caused by normal metabolism,[29] smoking,[30] and inflammation.[31]

Laboratory evidence ranging from likely to compelling indicates that deficiency of some vitamins and minerals—folic acid, vitamins B_{12}, B_6, C, and E, niacin, iron, and zinc—causes damage to DNA that mimics the damage caused by radiation.[32] In the United States, the percentage of the population that consumes less than half the Recommended Daily Allowance (RDA) in the diet (that is, ignoring supplement use) for five of these eight vitamins or minerals is estimated to be: zinc (10 percent of women/men older than 50), iron (25 percent of menstruating women, and 5 percent of women over 50), vitamin C (25 percent of women/men), folate (50 percent of women; 25 percent of men), vitamin B_6 (10 percent of women/men), vitamin B_{12} (10 percent of women; 5 percent of men). These deficiencies may constitute a considerable percentage to the cancer risk of the United States population.[33]

Folic acid (or folate) deficiency, one of the most common vitamin deficiencies in the population consuming few dietary fruits and vegetables, causes chromosome breaks in humans,[34] analogous to those caused by radiation. Folate supplementation above

29. H. J. Helbock et al., "DNA Oxidation Matters: The HPLC-Electrochemical Detection Assay of 8-oxo-deoxyguanosine and 8-oxo-guanine," *Proc. Natl. Acad. Sci. USA* 95 (1998): 288–93.

30. B. N. Ames, "Micronutrients Prevent Cancer and Delay Aging," *Toxicol. Lett.* 103 (1998): 5–18.

31. Ames, Shigenaga, and Hagen, "Oxidants, Antioxidants, and the Degenerative Diseases of Aging."

32. Ames, "Micronutrients Prevent Cancer and Delay Aging."

33. B. N. Ames and P. Wakimoto, "Are Vitamin and Mineral Deficiencies a Major Cancer Risk?" *Nature Rev. Cancer* 2 (2002): 694–704.

34. B. C. Blount et al., "Folate Deficiency Causes Uracil Misincorporation into Human DNA and Chromosome Breakage: Implications for Cancer and Neuronal Damage," *Proc. Natl. Acad. Sci. USA* 94 (1997): 3290–95.

the RDA has been shown to minimize chromosome breakage.[35] Researchers conducting a long-term study of women's health, the Nurses' Health Study, associated folate deficiency with increased risk of colon cancer.[36] They also reported that women who took a multivitamin supplement containing folate for fifteen years had a 75 percent lower risk of colon cancer.[37] Folate deficiency also damages human sperm,[38] causes neural tube defects in the fetus, and an estimated 10 percent of United States heart disease.[39]

Approximately 10 percent of the U.S. population[40] had a lower folate level than that at which chromosome breaks occur.[41] The recent decision in the United States to supplement flour, rice, pasta, and cornmeal with folate[42] may reduce the percentage of the population with the deficiency.

Other vitamins—vitamin B_6 and niacin—complement folic acid. Vitamin B_6 deficiency apparently causes chromosome breaks by the same mechanism as folate deficiency.[43] Niacin is

35. M. Fenech, C. Aitken, and J. Rinaldi, "Folate, Vitamin B12, Homocysteine Status and DNA Damage in Young Australian Adults," *Carcinogenesis* 19 (1998): 1163–71.

36. E. Giovannucci et al., "Folate, Methionine, and Alcohol Intake and Risk of Colorectal Adenoma," *J. Natl. Cancer Inst.* 85 (1993): 875–84.

37. E. Giovannucci et al., "Multivitamin Use, Folate, and Colon Cancer in Women in the Nurses' Health Study" *Ann. Intern. Med.* 129 (1998): 517–24.

38. L. M. Wallock et al., "Low Seminal Plasma Folate Concentrations Are Associated with Low Sperm Density and Count in Male Smokers and Nonsmokers," *Fertil. Steril.* 75 (2001): 252–59.

39. C. J. Boushey et al., "A Quantitative Assessment of Plasma Homocysteine as a Risk Factor for Vascular Disease: Probable Benefits of Increasing Folic Acid Intakes," *J. Am. Med. Assoc.* 274 (1995): 1049–57.

40. F. R. Senti and S. M. Pilch, "Analysis of Folate Data from the Second National Health and Nutrition Examination Survey (NHANES II)" *J. Nutr.* 115 (1985): 1398–1402.

41. Blount et al., "Folate Deficiency."

42. P. F. Jacques et al., "The Effect of Folic Acid Fortification on Plasma Folate and Total Homocysteine Concentrations," *N. Engl. J. Med.* 340 (1999): 1449–54.

43. A. C. Huang, T. D. Shultz, and B. N. Ames, unpublished MS.

important to the repair of DNA strand-breaks.[44] As a result, dietary insufficiencies of niacin (15 percent of some populations are deficient),[45] folate, vitamin B_6, and antioxidants, such as vitamin C, may interact synergistically to adversely affect DNA synthesis and repair.

People with diets deficient in fruits and vegetables generally have vitamin and mineral deficiencies. The findings summarized in Table 4, which associate higher cancer rates with such diets, underline the importance of fruits and vegetables and the vitamins and minerals they contain in cancer prevention.

Vitamins and minerals, 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. Vitamin B_{12} is found in animal products, and deficiencies of B_{12} cause a functional folate deficiency, accumulation of the amino acid homocysteine (a risk factor for heart disease),[46] and chromosome breaks. B_{12} supplementation above the RDA was necessary to minimize chromosome breakage.[47] Strict vegetarians are at increased risk for developing vitamin B_{12} deficiency.

Epidemiological studies of supplement usage (vitamin and mineral intake by pill) have shown at most only modest support for an association between intake of these substances and lower cancer rates. Many problems complicate those studies, including

44. J. Z. Zhang, S. M. Henning, and M. E. Swendseid, "Poly(ADP-ribose) Polymerase Activity and DNA Strand Breaks Are Affected in Tissues of Niacin-deficient Rats," *J. Nutr.* 123 (1993): 1349–55.

45. E. L. Jacobson, "Niacin Deficiency and Cancer in Women," *J. Am. Coll. Nutr.* 12 (1993): 412–16.

46. V. Herbert and L. J. Filer, Jr., "Vitamin B-12," in E. E. Ziegler, ed., *Present Knowledge in Nutrition* (Washington, D.C.: ILSI Press, 1996), pp. 191–205.

47. Fenech, Aitken, and Rinaldi, "Folate, Vitamin B12, Homocysteine Status and DNA Damage in Young Australian Adults."

the difficulty in measuring supplement use over a long period of time, and potential confounding of supplement usage with many other aspects of a healthy lifestyle that are related to it, such as more exercise, better diet, and not smoking. Clinical trials of supplements are generally too short to measure cancer risk, since cancers usually develop slowly and the risk increases with age; moreover, such trials cannot measure the potential reduction in risk if supplements are taken throughout a lifetime. Additionally, cancer risks of supplement users may be overestimated because they are more likely to undergo early screening like mammograms or tests for prostate cancer, which are associated with increased diagnosis rates, and can artificially increase the apparent incidence rate. Such confounding factors are not measured in many epidemiological studies.

The strongest effect in clinical trials was for a protective effect of vitamin E against cancers of the prostate and colon.[48] More well-done trials will increase the information about the usefulness of supplements in cancer prevention.

In the meantime, it is clear that intake of adequate amounts of vitamins and minerals may have a major effect on health, and the costs and risks of a daily multivitamin/mineral pill are low.[49] More research in this area, as well as efforts to improve diets, should be high priorities for public policy.

48. R. E. Patterson, A. R. Kristal, and M. L. Neuhouser, "Vitamin Supplements and Cancer Risk: Epidemiologic Research and Recommendations," in A. Bendich and R. J. Deckelbau, eds., *Primary and Secondary Preventive Nutrition* (Totowa, N.J.: Humana Press, 2001), pp. 21–43.

49. Ames and Wakimoto, "Are Vitamin and Mineral Deficiencies a Major Cancer Risk?"

Damage by Distraction: Regulating Low Hypothetical Risks

Synthetic chemicals that mimic hormones—"environmental estrogens" or "endocrine disruptors"—arose as a major environmental issue in the 1990s. Environmental concerns have focused on exposures to estrogenic organochlorine residues (largely plastics and pesticides) that are tiny compared to the normal dietary intake of naturally occurring endocrine-active chemicals in fruits and vegetables.[50] These low levels of human exposure to the synthetic chemicals seem toxicologically implausible as a significant cause of cancer or of reproductive abnormalities.

Recent epidemiological studies have found no association between organochlorine pesticides and breast cancer, including one in which DDT, DDE, dieldrin, and chlordane were measured in blood of women on Long Island.[51] 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.[52] An analysis of U.S. data about sperm counts found distinct geographical differences, with the highest concentrations in New

50. S. H. Safe, "Endocrine Disruptors and Human Health—Is There a Problem? An Update," *Environ. Health Perspect.* 108 (2000): 487–93.

51. M. D. Gammon et al., "Environmental Toxins and Breast Cancer on Long Island. II. Organochlorine Compound Levels in Blood," *Cancer Epidemiol. Biomarkers Prev.* 11 (2002): 686–97.

52. S. Becker and K. Berhane, "A Meta-analysis of 61 Sperm Count Studies Revisited," *Fertil. Steril.* 67 (1997): 1103–8; J. Gyllenborg et al., "Secular and Seasonal Changes in Semen Quality Among Young Danish Men: A Statistical Analysis of Semen Samples from 1927 Donor Candidates During 1977–1995," *Int. J. Androl.* 22 (1999): 28–36; National Research Council, *Hormonally Active Agents in the Environment* (Washington, D.C.: National Academy Press, 1999); J. A. Saidi et al., "Declining Sperm Counts in the United States? A Critical Review," *J. Urol.* 161 (1999): 460–62; S. H. Swan, E. P. Elkin, and L. Fenster, "Have Sperm Densities Declined? A Reanalysis of Global Trend Data," *Environ. Health Perspect.* 105 (1997):1228–32.

York City.[53] When geographic differences were taken into account, there was no significant change in sperm counts for the past fifty years. Even if sperm counts were declining, there are many more likely causes, such as smoking and diet.

Some recent studies have compared estrogenic equivalents (EQ) of dietary intake of synthetic chemicals vs. phytoestrogens (estrogens of plant origin) in the normal diet, by considering both the amounts consumed by humans and estrogenic potency. Results support the idea that synthetic residues are orders of magnitude lower in EQ and are generally weaker in potency. Scientists using a series of *in vitro* assays calculated the EQs in 200 ml. of Cabernet Sauvignon wine and the EQs from average daily intake of organochlorine pesticides.[54] EQs in a single glass of wine were about 1,000 times higher. (Safe's chapter, this volume, and a National Academy of Sciences report[55] provide additional information about endocrine disruptors.)

Conclusions

Because 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.[56] The EPA projected in 1991 that the cost to society of U.S. environmental regulations in 1997 would be about US$140 billion per year (about 2.6 percent of gross national prod-

53. Saidi et al., "Declining Sperm Counts in the United States?"

54. K. Gaido et al., "Comparative Estrogenic Activity of Wine Extracts and Organochlorine Pesticide Residues in Food," *Environ. Health Perspect.* 106 (Suppl. 6, 1998): 1347–51.

55. National Research Council, *Hormonally Active Agents in the Environment* (Washington, D.C.: National Academy Press, 1999).

56. R. W. Hahn, *Risks, Costs, and Lives Saved: Getting Better Results from Regulation* (New York: Oxford University Press and Washington, D.C.: AEI Press, 1996); J. Graham and J. Wiener, eds., *Risk versus Risk: Tradeoffs in Protecting Health and the Environment* (Cambridge, Mass.: Harvard University Press, 1995).

uct).[57] Most of this cost is borne by the private sector, which passes much of it along to consumers in higher prices.

Several economic analyses have concluded that current expenditures are not cost-effective; that is, resources are not used so as to save the most lives per dollar. One estimate is that the United States could prevent 60,000 deaths per year by redirecting the same dollar resources to more cost-effective programs.[58] For example, the median toxin control program, such as those administered by EPA, costs 146 times more per year of life saved than the median medical intervention program. The true difference is likely to be greater, because cancer risk estimates for toxin-control programs are worst-case, hypothetical estimates, and there may be no risk at low dose. 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.

The many worst-case assumptions built into cancer risk assessments are there because of policy decisions, not because of scientific ones, and they confuse attempts to allocate money effectively for public health. For example, EPA estimates of synthetic pesticide residues in the diet have used the theoretical maximum human residue that is anticipated under the most severe field application conditions, which is often a large overestimate compared to the measured residues in food. Despite the EPA's estimated high risks from exposures to several pesticides, the U.S. Food and Drug Administration detected no residues of those pesticides in the food samples in its Total Diet Study.[59]

57. U.S. Environmental Protection Agency, *Environmental Investments: The Cost of a Clean Environment* (Washington, D.C.: Office of the Administrator, 1991).

58. T. O. Tengs et al., "Five Hundred Life-saving Interventions and Their Cost-effectiveness," *Risk Anal. Prod. Safe Food* 15 (1995): 369–89.

59. L. S. Gold et al., "Pesticide Residues in Food: Investigation of Dispar-

Regulatory efforts to reduce low-level human exposures to synthetic chemicals because they are rodent carcinogens are expensive, can do nothing but reduce already minuscule chemical concentrations, and are unlikely to have any effect on cancer rates. Moreover, they distract from the major task of improving public health through increasing scientific understanding about how to prevent cancer (e.g., what aspects of diet are important), increasing public understanding of how lifestyle influences health, and improving our ability to help individuals alter their lifestyles.

Why has the government focused on minor hypothetical risks at huge cost? A recent article in *The Economist* 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 fame-seekers 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.[60]

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ities in Cancer Risk Estimates," *Cancer Lett.* 117 (1997): 195–207; L. S. Gold et al., "Pesticide Residues in Food and Cancer Risk: A Critical Analysis," in *Handbook of Pesticide Toxicology*, 2d ed., ed. R. Krieger (San Diego: Academic Press, 2001), pp. 799–842.

60. "Plenty of Gloom: Environmental Scares—Forecasters of Scarcity and Doom Are Not Only Invariably Wrong, They Think that Being Wrong Proves them Right," *The Economist*, December 20, 1997–January 3, 1998, pp. 19–21.