Does Nature Know Best?

Natural Carcinogens and Anticarcinogens in America's Food

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Executive Summary

• A large number of substances that occur naturally in foods are carcinogenic (cancer-causing) when evaluated by the criteria scientists customarily use to assess the cancer-causing potential of synthetic substances. Other carcinogens are produced by cooking and by the actions of microorganisms. These natural carcinogens are more numerous, more widespread and in some cases more potent than synthetic carcinogens in food.

• It is not necessary or practical for consumers to stop eating foods that contain natural carcinogens—indeed, nearly every food type contains them, and it is impossible to completely avoid them.

• The occurrence of natural carcinogens in foods, particularly plant foods, does not justify changes in Americans' eating habits. Many cancer researchers and nutri-

tionists now recommend that Americans not only increase their intake of fruits and vegetables but also reduce their intake of red meat, alcoholic beverages and fatty foods and reduce their overall caloric intake.

- Eating a wide variety of foods is desirable for nutritional reasons, and increasing fruits and vegetables in the diet has always been recognized as good nutritional advice. Fruits and vegetables are beneficial in that they are now known to contain many protective “anticarcinogens”—compounds that have been shown to counteract the cancer process initiated by carcinogens.
- The common assumption that “natural” is safe and “synthetic” is toxic is contrary to current scientific knowledge. Synthetic chemicals are present in foods at much lower levels than are many naturally occurring carcinogens and toxins. Also, in many cases the synthetic chemicals are less potent carcinogens than the ones that are a natural part of our food. The dose makes the poison.
- There is a need for a new perspective on carcinogens—one that emphasizes both a substance’s carcinogenic potency and the level of human exposure to it rather than whether it is natural or synthetic.
- There is a need to distinguish between real and hypothetical hazards and between functional and unnecessary substances when setting regulatory priorities.
- More research is needed on natural food components. We need to strike a more even balance between our evaluations of natural substances and synthetic substances in the food supply.

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Introduction

American agriculture produces the world's safest and most nutritious food supply. Even with the highest measure of safety, however, our food contains naturally present chemical compounds that are known or strongly suspected to cause cancer in laboratory animals. Many of these compounds, of which thousands have been identified, are commonly termed "nature's pesticides": They are often toxic to competing organisms and can confer a "competitive edge" to the plants or microbes that produce them. There are also other natural chemicals in plants that have no known role. In any event, these chemicals are nothing new; all are "100 percent natural" and have been with us since the beginning of mankind's existence.

These chemicals are in every meal we eat, but thus far they have received little attention. In fact, our food supply contains natural toxins and carcinogens in amounts *greater than 10,000 times* the levels of synthetic or "man-made" chemicals such as pesticides and PCB residues.

Significantly, our bodies handle all chemicals in the same way, regardless of their origin. Yet the popular notion remains that the greatest health threat is posed by the synthetic chemicals in our food. And this fallacy is often encouraged by newspaper headlines and television reports warning of the danger posed by some additive or pesticide in our food.

Witness the growing popularity of "organic" produce grown without the aid of synthetic pesticides or fertilizers. Most people believe the adage, "if it's natural, it's good for you"; and many consumers will willingly pay higher prices for this kind of specialty food in an attempt to avoid

adding synthetic toxic substances to their diets. As we will see, however, "natural" doesn't mean "toxin free." In fact, *most* of the pesticides in our foods are natural ones: They are chemicals thought to be produced by plants as protection against insects and other predators.

Scientists now recognize the falseness of the belief that the majority of cancer-causing chemicals in our food are both rare and synthetic. In this report the American Council on Science and Health (ACSH) summarizes the scientific evidence regarding the overlooked natural carcinogens in our food and discusses the implications for both human health and public safety of their presence. In the interest of balance the report also introduces another set of compounds—the naturally occurring anticarcinogens found in common foods—and evaluates the current state of our knowledge about these possibly important chemicals.

Background: Cancer and the Environment

In 1996, the American Cancer Society estimates, there will be approximately 555,000 deaths from cancer in the United States (American Cancer Society. *Cancer Facts & Figures—1996*). One person in four will probably develop some form of cancer over the course of his or her lifetime. Four major cancers (lung, colon-rectum, breast and prostate) account for over half the cancer deaths, and cancer is second only to heart disease (stroke is third) as a cause of death.

But what are the major causes of cancer? Years ago the World Health Organization (WHO) concluded that the majority of cancers occur largely due to lifestyle and other environmental sources and that they therefore are, in principle, avoidable. This conclusion provided the chief impetus for research into identifying environmental risk factors that might contribute to cancer—research that was regarded as a necessary first step toward reducing the incidence of cancer in our society.

One thing that led to the WHO's view of an environmental origin for certain cancers was the observation that the incidence of these cancers had changed rapidly in recent decades. Stomach cancer, for example, was one of the most common causes of cancer death in the U.S. in the early 20th century, but today it occurs far less frequently. Lung cancer, on the other hand, was uncommon at the beginning of the century but is now the leading cause of cancer death among men and since 1987 has also been the leading cause of cancer death among women. These changes in incidence have occurred far too rapidly to be explained by genetic changes in the U.S. population.

A second body of evidence supporting an environmental origin for certain cancers is the fact that the incidences of specific types of cancer vary widely from country to country and are probably not due to the genetic variance that may exist between population groups.

Descendants of immigrants often acquire, within a generation or two, the cancer incidence pattern characteristic of their adopted country. The best example of this comes from a retrospective study of the descendants of Japanese immigrants who arrived in California in the early part of the 20th century. Within one or two generations the Japanese-American descendants were shown to develop stomach and breast cancers at incidence rates similar to those of other Americans. Yet, in Japan today stomach cancer is common and breast cancer is comparatively rare—the reverse of the pattern in the United States.

There are other examples of this sort, all of which show that, on the whole, the dramatic differences in cancer incidence patterns evident around the world are not attributable to innate genetic differences among populations but rather to potentially alterable environmental factors.

However, with the outstanding exception of cigarette smoking (a primary contributor to lung cancer in the U.S.), and despite a lengthy and assiduous search by scientists, the dominant factors affecting the common cancers responsible for most deaths have not yet been conclusively identified.

Of the major causes of cancer, diet is thought to be an important single cause; it may contribute to as much as one third of all cancer cases. Identifying individual dietary risk factors has been a very slow process, however. And it is important to point out that, contrary to the view of some people, we are not experiencing an epidemic of human cancer. With a few exceptions, cancer mortality is actually declining. The apparent increases in the incidences of some cancers, such as cancer of the prostate, are probably due to improved screening and diagnosis.

What is a carcinogen, and how are carcinogens identified?

A carcinogen is a substance or agent that can cause cancer. That sounds simple, but in fact there continues to be a substantial debate among researchers as to what constitutes sufficient evidence to call a chemical substance a carcinogen, and especially one that poses a cancer threat to humans. The results of epidemiological studies in humans can provide evidence that a substance poses a cancer hazard to humans, of course; but epidemiology has its limitations. Epidemiological studies may not detect weak carcinogenic effects or effects masked by confounding variables or

effects caused by exposures occurring after prolonged latency periods. Moreover, for obvious reasons epidemiologists are confined to conducting studies on substances to which substantial human exposure has *already* occurred.

The recent development of cancer "biomarkers"—chemical substances that can be detected in urine or blood and that can accurately reflect recent carcinogen exposure and / or biological effect—is strengthening cancer epidemiology by eliminating some of these limitations.

The most reliable method of identifying dietary human carcinogens is animal testing. Scientists have concerns about animal testing, however: The main concerns relate, first, to the inherent uncertainty over whether the responses of animals are relevant to humans and, second, to whether laboratory testing conditions are adequate representations of the conditions of human exposure.

Scientists have not yet reached a consensus about these basic questions. But for the purpose of governmental regulation, these questions have been resolved on the policy basis of "prudence": Uncertainties are handled by means of "worst-case" assumptions so as to provide the maximum amount of protection to the public. Thus, any substance that significantly increases the incidence of any type of tumor in any one animal species at any dose level is considered to be a carcinogen.

But studies designed to identify carcinogens—and particularly those studies designed to identify carcinogens to which humans are exposed through their diet—most commonly are conducted by feeding the substance under investigation at very high doses—doses at or near the highest quantities tolerable without causing death—to laboratory animals, usually rats or mice, for a lifetime. Cancer studies are also performed by administering the test substance in drinking water or through inhalation, injection or skin painting; but these methods lack relevance for substances found in food.

A substance is considered carcinogenic, and hence a potential human carcinogen, if a statistically significant increase in tumors occurs in animals given the substance compared to animals not given it. For regulatory purposes, a single finding of increased incidence of tumors in one species is all that is needed for a substance to be judged a carcinogen. Negative results in other animal species, even when the studies are conducted under identical conditions of lifetime administration at maximal doses, are discounted on the assumption that humans might be as sensitive as the most sensitive animal species.

This, then, is the operational definition of a carcinogen currently used by U.S. government regulatory agencies to protect the public from the implied cancer hazard of synthetic chemicals. And we will adopt the same definition in this report: That is, we will refer to a substance as a carcinogen as long as there is at least one animal study showing a carcinogenic effect for that substance. It is well to keep in mind, however, that there is usually little or no confirming evidence from direct observations on humans to show that a substance in question is a *human* carcinogen.

This method of defining a carcinogen was adopted in the recent past when our limited scientific understanding suggested that carcinogens were few in number and almost always synthetic, rather than natural, in origin. With this understanding, a prudent and sensible response to the discovery that a substance to which humans were exposed showed carcinogenic activity in animal tests was to eliminate all human exposure to that substance. But this approach grew out of a simplistic view of the cancer problem and held out a vain hope that we could achieve substantial reductions in cancer incidence by the simple means of banning a comparatively small number of synthetic carcinogenic chemicals.

We are now learning that carcinogens are many rather than few and that a substantial number of naturally occurring substances are capable of producing a carcinogenic response in laboratory animals when evaluated under the same guidelines used by regulatory agencies to identify carcinogens of synthetic origin. As we now know, many of these natural carcinogens are present in our daily diets—and human exposure to these natural substances cannot in general be readily eliminated.

Over 80 percent of the chemicals tested in animal cancer tests are synthetic industrial chemicals. Half of those are carcinogens in rodents at the maximum tolerated dose (MTD) used for testing. (The MTD is the highest dose of a chemical that can be given to an animal—generally in a long-term study—that suppresses body weight gain slightly—i.e., by 10 percent.)

But humans are exposed to thousands of times more natural chemicals than synthetic ones. And toxicologists do not expect a different proportion of the natural chemicals to be carcinogens, as our defenses are general and do not distinguish between synthetic and natural chemicals. In fact, according to the definition the government regulatory agencies are using, fully half of the natural chemicals tested are carcinogens.

Dr. Bruce Ames and some other toxicologists believe that high-dose testing is flawed and that

the cell division triggered by high-dose testing is itself a risk factor for cancer. Thus, it is not correct to call something a carcinogen without taking dose into account. Other toxicologists believe that because of the possible existence of a small population of genetically susceptible individuals, a very small dose—theoretically, only one molecule—of a carcinogen is sufficient to cause cancer.

What is a mutagen? How are mutagens related to carcinogens?

A mutagen is a substance that can produce heritable genetic changes, or mutations, in the genetic material of an organism. (Except for some viruses, this genetic material is always DNA.) Mutagenic changes are often determined *in vitro*—that is, in some organism contained in a test tube. Most such changes resulting from chemical exposures are injurious to the organism *per se* and are also accompanied by a substantial amount of additional damage to DNA, which can potentially result in cell death. Occasionally, however, rather than a mutagen's being injurious to a cell, that mutation can convert a normal cell into a cancerous one—a cell that grows out of control and produces a tumor.

Not all cancers are known to result from such alterations in DNA, but it has been observed in experiments that a majority of all natural and synthetic chemicals that have been shown in animal tests to produce a carcinogenic effect are also capable of producing mutations. This observation has led to the proposal that perhaps any substance capable of causing mutations will also be a carcinogen, but evidence supporting this inference is not conclusive.

Nevertheless, the fact that tests for mutability are much easier, quicker and less expensive to perform than animal cancer tests has led to the widespread adoption of mutational tests for the initial screening of suspect carcinogens. While a full-scale animal cancer test can take several years and easily cost a million dollars or more to perform, the most rapid mutational tests require only a few thousand dollars and a few days to perform. A growing number of substances now known to be carcinogenic in animals were first identified as mutagens.

The mutational test in widest use at the present time is the Ames test (so called after its discoverer, Dr. Bruce Ames), which uses special strains of the bacterium *Salmonella typhimurium.* Substances described in this report as "mutagens" have usually been so identified by means of the Ames test and often by other mutational assays as well.

Natural Carcinogens and Toxicants in Foods

Many people find it unsettling to think that carcinogens and other potent, harmful substances may be present in their food. Upon hearing that foods contain hazardous substances, their reaction would probably be to obtain a list of the implicated foods and avoid eating them. But such avoidance is neither necessary nor possible. No human diet can be free from all naturally occurring carcinogens or toxic substances. Indeed, it is hard to find *any* food that does not contain *some* harmful chemical that either occurs naturally or is produced during cooking or by microbial decomposition.

This fact was demonstrated most dramatically by Dr. Richard Hall in a classic 1977 article published in *Nutrition Today*. Dr. Hall examined the menu for a sumptuous, multicourse restaurant luncheon, analyzing the naturally occurring ingredients in each food using the same criteria of safety applied in the U.S. to synthetic substances that are added deliberately to foods.

Dr. Hall looked at all the evidence on adverse health effects that scientists had derived from both animal testing and human experience and then eliminated from the menu all foods containing ingredients that would not satisfy the criteria for food additives. At the end of this exercise Dr. Hall was left with just one food: hearts of palm salad. And he noted that this particular food had survived the examination process only because so little was known about its composition. Had hearts of palm been studied in greater detail, it, too, would most likely have been found to have potentially toxic ingredients.

The foods eliminated from Dr. Hall's luncheon menu included carrots, radishes, onions, olives, melons, ham, shrimp Newburg (the shrimp and two different ingredients in the sauce failed the test), potatoes, butter, parsley, rolls, broccoli, Hollandaise sauce (four offending ingredients), watercress, avocado, lemon-herb salad dressing (nine offending ingredients), four types of cheese, bananas, apples, oranges, coffee, tea, milk, wine—and water. Some items were eliminated from the menu because they contained carcinogens; others contained other types of toxic substances.

ACSH has modernized Dr. Hall's approach: We have produced a Holiday Dinner Menu complete with a listing of potentially toxic natural components. The purpose of the menu is not to alarm the public but to emphasize that humans have been exposed to all these natural toxic substances and have thrived in spite of that constant exposure.

Neither Dr. Hall nor ACSH would urge you to stop eating or drinking any of these foods or

beverages. Nor would ACSH urge you to stop eating any of the foods discussed later in this report—foods that also contain naturally occurring carcinogens. The point here is not to alarm you, but rather to help you put scientific information about carcinogens into perspective.

Natural Carcinogens in Foods: A Survey

Examples of naturally occurring carcinogens in food include the following:

Nitrosamines and Their Precursors

High amounts of nitrate are a normal component of vegetables. Beets, celery, lettuce, spinach, radishes and rhubarb all contain about 200 milligrams (mg) of nitrate per 100 gram (g) portion (100 g is roughly equal to a quarter of a pound; 200 mg / 100g is the same as 2,000 parts per million, or 2,000 ppm).

Cruciferous vegetables such as mustard, kale, turnips and cabbage are also high in nitrate. Nitrate itself has not been shown to produce a carcinogenic effect in animals, but it can be converted by bacteria in human saliva and in the intestine into nitrite, a substance that can react chemically with certain other chemicals normally present in the body (amines and amides) to produce compounds called nitrosamines. There are many different nitrosamines. About 300 of them have been tested in animal cancer tests, and roughly 90 percent of them have been found to be carcinogenic under the conditions of those tests—many of them highly so.

Nitrite can also be ingested directly: It is used to cure fish, poultry and meat. But this is a relatively small source of exposure: The National Academy of Sciences estimates that 72 percent of the nitrite exposure to the mouth and esophagus results from the conversion of the nitrates contained in vegetables and only about nine percent results from the ingestion of cured meats, primarily bacon. Adult Americans' average daily intake of nitrate is estimated to be nearly 100 mg per person while their intake of nitrite is estimated at nearly 1 mg per person and their intake of preformed nitrosamines is estimated at only about one microgram (µg) per person.

The intakes of persons with nonstandard diets may, of course, differ from these averages. Vegetarians, for example, are estimated to ingest an average of 268 mg per day of nitrate, mostly from vegetables. And the nitrate content of vegetables can be substantially increased by the use of

nitrate-containing fertilizers, both “organic” and synthetic.

The proportion of dietary nitrate that ends up in the body in the form of nitrosamines is believed to be minimal. Some nitrosamines, however, have been shown in animal tests to be potent carcinogens; and some scientists believe that human exposure to nitrosamines resulting from the dietary ingestion of nitrate and nitrite may be a factor in cancer of the esophagus and stomach. This hypothesis has not been proved, however; indeed, a recent report found an *inverse* relation between the incidence of stomach cancer and the nitrate / nitrite content of the patient’s saliva.

Carcinogens Produced by Cooking

The burned and browned matter produced when meats are char broiled, smoked or fried is highly mutagenic. Some of this matter comes from the smoke of burned material deposited on the meat by the cooking process, but much of it originates from the breakdown of the meat protein itself. This charred material has been analyzed, and several of its chemicals have been identified as both mutagenic and carcinogenic.

One important class of such chemicals are the heterocyclic amines, formed when certain amino acids (the building blocks of proteins) in foods are heated. The heterocyclic amines include compounds with abbreviated names such as TrpP1, TrpP2, PhIP, IQ, and MeIQ. These compounds have been shown in some bacterial tests to be highly mutagenic, rivaling or exceeding some of the most potent mutagens known, such as aflatoxin B_1 (see below). All are carcinogenic in animal tests. Heterocyclic amines can be found in such burnt foods as broiled beef and fish, toast, bread crusts, coffee, fried potatoes and a variety of other foods, and the amounts of them in the foods appear to be related to cooking temperatures. More heterocyclic amines are formed when meat is broiled than when it is cooked at lower temperatures, such as by boiling or microwaving.

Another class of compounds formed in cooked foods are the polycyclic aromatic hydrocarbons, of which benzo(a)pyrene is a notable representative. Not only is this substance carcinogenic in its own right, but under laboratory conditions it can “promote” (i.e., enhance) the carcinogenic action of other chemicals.

Aflatoxins and Other Mold Toxins

Aflatoxins are a group of closely related toxic substances produced by the fungi *Aspergillus*

flavus and *Aspergillus parasiticus,* which grow on peanuts, corn and other grains, particularly under hot, humid conditions. Some contamination can occur before harvest, but the main source of human exposure to this toxin is improper postharvest storage conditions that foster mold growth.

The most toxic and carcinogenic member of this family, aflatoxin B_1, is acutely poisonous, highly mutagenic and intensely carcinogenic. It has been shown to cause cancer in mice, rats, hamsters, rainbow trout, ducks, marmosets, tree shrews, guinea pigs, sheep and monkeys. Aflatoxin B_1 mainly causes liver tumors and, in fact, is the most potent animal liver carcinogen known.

Aflatoxins have been found in the milk of cows that have been fed aflatoxin-contaminated grains. They have also been found in peanut butter, cereals, coconuts, nuts and other foods. Aflatoxin B_1 and its major animal metabolite, aflatoxin M_1, are the only natural toxins regulated by the Food and Drug Administration (FDA). Their presence in foods is now routinely monitored. The "action level" (the concentration above which it is illegal to sell the food) of aflatoxin B_1 is set at 20 parts per billion (ppb) in all foods; the action level of aflatoxin M_1 in milk (its main source) is set at 0.5 ppb.

In the U.S. aflatoxins are typically found in amounts of one to three ppb in foods susceptible to such contamination. This is a very small concentration (to put it in perspective, one part per billion is the equivalent of one family of four as compared to the current entire population of the earth), and it is currently believed to be virtually without hazard to humans. But even this minute amount is carcinogenic in rainbow trout, the animal most susceptible to the effects of aflatoxin B_1.

A high level of liver cancer in West Africa and Southern China has been correlated with aflatoxin contamination in the food of those regions, but persuasive proof of a causal relationship has not been obtained. Exposure to hepatitis B virus, a known risk factor for liver cancer, is also endemic in these regions; and the relative contribution each factor may make to liver cancer incidence has not yet been sorted out.

Sterigmatocystin, a toxin produced by several mold species (and particularly by molds in the genera *Aspergillus* and *Penicillium*) is sometimes found in country-cured ham, salami, green coffee beans and wheat. Sterigmatocystin is a liver carcinogen in rats and is between one tenth and one one-hundredth as potent a carcinogen as aflatoxin B_1.

Corn is often contaminated with fumonisins, which are produced by the fungi in the genus *Fusaria.* Fumonisins are carcinogenic in animals and are thought to be a cause of human liver cancer

in some geographical locations.

Other mold toxins sometimes found in specific foods include ochratoxin A, T-2 toxin (thought by some scientists to be the toxic component of so-called “yellow rain”), patulin, penicillic acid and griseofulvin. All have shown some form of carcinogenic activity in animal tests.

Hydrazines in Edible Mushrooms

The three most commonly eaten mushrooms are the false morel *(Gyromitra esculenta),* the common cultivated mushroom *(Agaricus bisporus)* and the shiitake mushroom *(Cortinellus shiitake).* All contain substantial amounts of compounds in the hydrazine family. Many of these are potent carcinogens in animal tests.

The false morel contains 11 identified hydrazines, three of which are carcinogenic. One of these, N-methyl-N formylhydrazine, is found in concentrations of 50 mg per 100 g portion (500 ppm) and causes lung tumors in mice when administered at a low daily rate of 0.02 mg per mouse per day. It has also shown a carcinogenic effect in hamsters. Humans eating a 100 g serving, and therefore ingesting 50 mg, would be getting very nearly the same dose on a per-kilogram (kg) body weight basis (mice weigh about 30 g; humans, about 70 kg) as the dose that gives cancer to mice upon sustained daily exposure. Unlike many other toxins, however, the amounts of many of these carcinogenic compounds in mushrooms is reduced in cooking.

Another carcinogenic hydrazine, gyromitrin, is also present in the false morel in similar concentrations. Methylhydrazine, yet another carcinogen, is present in smaller concentrations (14 ppm).

The shiitake mushroom and the cultivated mushroom both contain agaritine, another hydrazine, at a level of 300 mg / 100 g portion (3,000 ppm). A metabolic product of agaritine has been shown to be mutagenic to bacteria and highly carcinogenic. Ingestion of a single dose of 400 µg of this derivative produced stomach tumors in 30 percent of mice tested. The comparable human dose would be (70 kg / 30 g) x (400 µg) = 920 mg, or about three 100 g portions of these mushrooms, assuming that all of the agaritine was converted to the diazonium derivative (fortunately, an unlikely assumption). The most common cultivated mushroom also contains para-hydrazinobenzoic acid at a level of 10 ppm. It, too, is a carcinogen.

Allyl Isothiocyanate

This substance is a major, naturally occurring pungent flavor ingredient in mustard and horseradish, where it is present at about 50–100 ppm. It is also present at much lower levels in broccoli, cabbage and rocket (arugula). It has been shown to be a carcinogen in tests on rats.

Pyrrolizidine Alkaloids

These chemicals, many of which are present in herbal teas and traditional herbal "remedies," are often carcinogenic, mutagenic, teratogenic (capable of causing birth defects) and chronically toxic. Pyrrolizidine alkaloids form irreversible "cross-links" with DNA, thereby preventing cell division. Deadly human diseases such as liver cirrhosis (scarring of the liver), veno-occlusive disease and liver cancer are linked to consumption of pyrrolizidine alkaloid–containing plants.

Pyrrolizidine alkaloids are present in hundreds of plant species, and at very high levels—as much as 5 percent of the plant's dry weight. Human intoxication by pyrrolizidine alkaloid–containing plants is well recognized and reported in the medical literature. Hispanic and Native American populations in the western and southwestern U.S. are at high risk for pyrrolizidine alkaloid intoxications because of their traditional, widespread use of herbs, their occasional lack of confidence in traditional medicine and, more commonly, their lack of access to medical care.

Petasitenine, a pyrrolizidine alkaloid, is found in *Petasites japonicus* (a kind of coltsfoot), a medicinal herb used as an expectorant and cough suppressant. The flower stalks of this herb are used as a food and a herbal remedy. When dried, ground and mixed in the diet of rats, stalks of *Petasites japonicus* cause a high incidence of liver tumors. Purified petasitenine also causes liver cancer in rats and is mutagenic in bacterial tests.

Coltsfoot (*Tussilago farfara*) is a common herb used for similar medicinal purposes in Japan. It contains the pyrrolizidine alkaloid senkirkine at concentrations as high as 0.015 percent (150 ppm) and also contains high concentrations of senecionine, another very toxic and carcinogenic pyrrolizidine alkaloid. The dried buds of coltsfoot (when ground and mixed in the diet) and purified senkirkine or senecionine cause liver tumors in rats, and all are mutagenic to bacteria.

Comfrey is a nearly universal herb commonly sold not only in health food stores and by herbalists but also in supermarkets. Both leaves and roots are used to make teas and compress pastes to treat a variety of external and internal diseases. Numerous vegetarian recipes call for com-

frey leaves to make soufflés, salads and breads.

Comfrey leaves and roots contain up to 0.29 percent pyrrolizidine alkaloids such as intermedine, lycopsamine, symphytine and others. A powder made by mixing and milling dried comfrey leaves and roots caused liver tumors in rats when mixed in their diet. Additionally, these pure pyrrolizidine alkaloids are both animal carcinogens and bacterial mutagens. There are also several cases cited in the medical literature of comfrey-related intoxications in people.

Comfrey's well-demonstrated reported toxicity and carcinogenicity is such a significant cause for concern that the governments of four countries (Australia, Canada, Great Britain and Germany) either restrict comfrey's availability or have banned its sale entirely. The U.S. Food and Drug Administration has not yet acted to restrict the sale of pyrrolizidine alkaloid-containing foods, however.

Substances in Bracken Fern

This fern *(Pteridium esculentum* and *aquilinum*) is eaten by humans as greens or in salads in New Zealand, Australia, the U.S. (fiddlehead greens), Canada and, especially, Japan. It is also a forage plant for sheep and cattle. Yet bracken fern is the only known higher plant shown to cause cancer in animals. It is strongly carcinogenic to the bladder and intestine when fed to rats. It causes bladder cancer in cattle, sheep and guinea pigs; lung tumors in mice; and intestinal tumors in Japanese quail. Lactating cows fed bracken fern produced milk that was carcinogenic to rats, showing that human exposure might also occur through cows' milk. Human consumption of bracken fern has been linked to an increased incidence of esophageal cancer in Japan.

The major carcinogen in bracken is ptaquiloside, a potent sesqiterpenoid glucoside. The plant also contains quercetin, kaempferol and other mutagenic compounds of the flavonoid family (see page XX) that may contribute to its carcinogenicity. It also contains carcinogenic tannins (see page XX).

Safrole, Estragole, Beta-Asarone and Isosafrole

These are closely related compounds (all are alkenylbenzenes) found in many spices and herbs and in a limited number of vegetables. All are carcinogenic in the rat, mouse or both.

Safrole causes liver cancer when administered to rodents. It is found in sassafras tea and

makes up 75 percent of oil of sassafras, which was once used to flavor root beer. Safrole has been banned as a flavor additive since 1960 but is a minor, natural component of nutmeg, mace, star anise, cinnamon and black pepper. Black pepper also contains piperine (a closely related compound) in much larger amounts (about 10 percent by weight). Extracts of black pepper have caused cancer in mice at several sites in skin-painting tests.

Estragole is found in tarragon, basil and fennel. It causes liver cancer in mice.

Beta-asarone is a major component of oil of calamus and has been used to flavor bitters and vermouth. It causes intestinal tumors in rats.

Isosafrole, a component of ylang-ylang oil, a flavorant and scent, is carcinogenic in mice.

Tannins

Tannins occur in coffee, tea, red wines, bracken fern and many other foods derived from plants. In injection studies, tannins cause liver cancer in rats and mice. People who are habitual chewers of betel nut (primarily in India, Pakistan and Southeast Asia) have a high incidence of carcinoma of the mouth that has been linked to the high tannin content (10 to 25 percent) of this nut, although other components may be involved as well. An extract of betel nut causes cancer in hamsters. A high incidence of esophageal cancer in Transkei, South Africa, has been associated with the consumption of high-tannin varieties of sorghum.

Somewhat paradoxically, some tannins are also anticarcinogenic (see page XX).

Psoralens

This family of substances is widespread in umbelliferous plants such as celery, parsnips and parsley. Psoralens are present in parsnips, for example, at a level of 4 mg / 100 g portion (40 ppm). In celery they are present at 10 µg / 100 g portion (100 ppb).

These compounds are mutagenic when activated by sunlight. Many members of this chemical family are carcinogenic as well, including 5-methoxypsoralen and 8-methoxypsoralen. At one time psoralens were a component of European suntanning oil.

Ethyl Carbamate

This chemical is found in naturally fermented foods and beverages, including bread, yogurt,

soy sauce, beer and wine. The amounts are small, roughly one to five µg/kg (1 to 5 ppb). Ethyl carbamate produces tumors in a wide variety of tissues in rats and mice whether administered orally, by inhalation or by injection.

Estrogenic Substances

One of the newest and most controversial subjects in food safety and toxicology centers on environmental estrogens: compounds that interact with estrogen receptors, thereby mimicking the effects of natural estrogen in the body. One provocative theory is that environmental estrogens may contribute to various cancers by increasing cell division in estrogen-sensitive tissues such as the breast and uterus. Increased cell division occurs normally as part of the sexual maturation process, but prolonged estrogenic stimulation and subsequent cell division in postmenopausal women is thought to be a risk factor for these types of cancers.

So far, much of the available data argues that our exposure to phytoestrogens (estrogens from plants) is so minute and their estrogenic activity so much less potent than that of endogenous estrogens (the circulating hormones in our bodies) that the cancer risk posed by phytoestrogens is not significant.

Several phytoestrogens—such as genestein, coumestrol, estrone and mirestrol—are found in many plants, including hops, soybeans and alfalfa. There is no evidence at present showing that estrogens of plant origin are carcinogenic. However, estrogens of animal origin administered to rodents in high amounts can cause (or promote) cancer in hormonally sensitive organs. As this carcinogenic capability is believed to be inherent in the estrogenic property itself, plant estrogens would be expected to be carcinogenic as well.

Paradoxically, many phytoestrogens have been demonstrated to have anticarcinogenic activity (see page XX) in that they can actually reduce the incidence of cancer in animals that have been challenged with a chemical carcinogen. One well-studied anticarcinogenic phytoestrogen is indole 3-carbinol, a substance that is present in *Brassica* vegetables such as cauliflower and broccoli. Phytoestrogens may also reduce the risk of breast cancer, because their weak estrogenic activity may compete with the more potent endogenous estrogens. It is clear that much more work needs to be done to define the adverse and/or beneficial effects of phytoestrogens in our diet.

Zearalenone, a toxin produced by *Fusarium* molds, also has estrogenic activity. Zearalenone is

an almost universal contaminant in corn and can frequently be found in soybeans, wheat, barley, oats and sorghum, particularly if these have been improperly stored. In exposed female animals it causes vaginal prolapse, swollen vulva and mammae and enlargement of the uterus; in males it causes signs of feminization, such as shrunken testicles and enlarged nipples. Zearalenone also has demonstrated carcinogenic activity in mice.

Coumarin

This substance is widely distributed in a number of natural flavoring agents such as cassia, lovage, lavender and woodruff. The first three are used to flavor candy and liqueurs; the last is used to flavor May wine and a popular German summer beer called “Berliner Weisse.” Purified coumarin was once used as a food additive, but this use was discontinued in 1954 after it was found that high doses caused liver damage in test animals. Coumarin is a powerful anticoagulant and as such is the active ingredient in many brands of rodent baits. It is also used in human medicines as a blood-thinning agent. Coumarin has been reported to cause bile duct carcinomas in rats.

Alcohol

The excessive consumption of alcoholic beverages, particularly in conjunction with tobacco use, has been associated with cancer of the mouth, esophagus, pharynx and larynx in humans. Alcoholic beverages also have been implicated in liver cancer, usually as a result of cirrhosis. Furthermore, alcohol has been shown to cause birth defects in the offspring of chronically alcoholic women.

There is some question, however, whether alcohol itself or other constituents of alcoholic beverages are responsible for alcohol’s association with human cancer. So far there is only limited evidence that pure ethyl alcohol is an animal carcinogen. The combination of alcohol abuse with smoking multiplies the incidence of tumors of the mouth and throat several times above that seen among smokers who do not drink alcohol.

Alcohol when abused and/or used excessively has, in fact, been described as “the most dangerous toxin of all”—a phrase that refers to its total social impact, however, and not merely to its role as a probable carcinogen.

Substances in Coffee

Hundreds of mutagenic substances have been found in coffee, and coffee has been found to be highly mutagenic *in vitro.* Just one cup of coffee has fifty times the mutagenic activity of the smoke absorbed from smoking a single cigarette. A variety of mutagenic constituents have been identified in the beverage, although many more are still unknown. The aromatic component diacetyl has been identified as an *in vitro* mutagen, as have the closely related compounds glyoxal and methyl glyoxal.

Methyl glyoxal has been identified as a potent mutagen in bacteria, and a cup of freshly brewed coffee contains 0.5 mg of that compound. (Instant coffee contains only about one fifth as much as fresh brewed coffee.) Preliminary evidence also indicates that methyl glyoxal is a carcinogen in rats. Methyl glyoxal can also be found in bourbon whiskey, wine, apple brandy, sake, roasted bread, soy sauce, tomatoes, boiled potatoes and roast turkey. A cup of coffee also contains 150 mg of chlorogenic acid, another bacterial mutagen. This substance has not been tested for carcinogenicity.

Also found in coffee are small amounts of benzo(a)pyrene, a strong mutagen and carcinogen, and carcinogenic tannins. Caffeine, which in laboratory animals can promote the growth of tumors caused by other substances, can also cause birth defects in animals tested at high doses (doses much higher than typical human ingestion levels).

Diacetyl

Diacetyl, mentioned above (see page XX) as a component of coffee, can also be found in butter. It is, in fact, the substance that gives butter its characteristic aroma. Diacetyl is a bacterial mutagen but has not yet been tested for carcinogenicity.

Quercetin, Kaempferol, Rutin and Other Flavonoids

This family of chemicals is widespread in plant-derived foods, including fruits and fruit juices, vegetables, buckwheat, tea, cocoa, red wine, dill, soybeans, bracken fern and others. The estimated average daily intake of flavonoids is one gram. None of these has yet been conclusively shown to be carcinogenic, but both quercetin and kaempferol are highly mutagenic. Rutin is not mutagenic in itself, but it can be metabolized by intestinal bacteria to yield quercetin. Quercetin also has some anticarcinogenic properties (see page XX).

Other Toxins in Common Foods

While the emphasis in this report has been on carcinogens and presumptive carcinogens (i.e., mutagens), it is worth noting that many other deleterious substances—some of them quite surprising—occur naturally in food. Only a few will be mentioned here.

Think sprouts are the ultimate health food? Think again! Alfalfa sprouts contain a substance called canavanine in a concentration of 1.5 percent by weight (15,000 ppm). This highly toxic substance is chemically similar to the amino acid arginine; and canavanine can displace arginine in cellular proteins, thereby rendering them inactive.

Canavanine has not been tested for carcinogenicity, but feeding alfalfa sprouts to monkeys causes a severe toxic syndrome resembling the human disease lupus erythematosus. In humans this disease arises from a defect in the immune system resulting in a degree of autoimmunity; i.e., the immune system attacks certain of the body's own tissues. In monkeys the syndrome may result from the body's immune response to canavanine-containing protein.

Cyanogenetic glycosides are compounds that can produce hydrogen cyanide upon food structure disruption, such as occurs through chewing or digestion: Thus, the very act of eating foods containing these compounds causes the cyanide to be released. Cyanogenetic glycosides are distributed widely in plants and their products; they are found (primarily in the seeds) in apples, apricots, cherries, peaches, pears, plums and quinces and are also found in almonds, sorghum, lima beans, cassava, corn, yams, chickpeas, cashew nuts and kirsch (cherry brandy).

Cyanogenetic compounds are extremely toxic substances; cattle and other range animals have died from eating plants containing them. Cases of human poisoning from the cyanide released from certain varieties of lima beans, cassava and bitter almonds have been reported.

Potatoes contain solanine and chaconine, which are teratogens (substances that cause fetal malformations) and highly toxic cholinesterase inhibitors (i.e., they affect nerve transmission much like the most toxic chemical-warfare agents). Solanine and chaconine are present in potatoes at 15 mg per 200 g (75 ppm). Bruised potatoes and potatoes that have begun to sprout have substantially higher levels and can be lethal.

Anticarcinogens; or, Now the Good News!

Fortunately, our food also contains chemicals that can counteract the adverse effects of many of the above-cited carcinogens and mutagens. While much more work is needed, the research results are very encouraging, indicating that some foods can actually reduce the incidence of certain types of cancer.

Animal studies have identified several foods or specific compounds that offer protection against the carcinogenic effects of a wide variety of natural and synthetic chemicals. (In animal studies, anticarcinogens are generally identified by their ability to reduce or completely inhibit the incidence of cancer when given either before, after, or along with a chemical carcinogen.) A few compounds have been shown actually to reverse the carcinogenic process in animals. As might be imagined, the field of anticarcinogenesis is one of the most exciting areas of cancer research today.

Natural Anticarcinogens in Foods: A Brief Survey

Foods contain both major constituents (protein, fat, carbohydrate and fiber) and minor constituents (vitamins, minerals and nonessential compounds). Most of the major types of anticarcinogenic substances that scientists have identified so far have been minor, nonnutritive components of foods—that is, compounds with no known nutritive value.

Some of the more versatile anticarcinogens, those that have been shown in animal studies to inhibit cancers induced by a variety of chemical carcinogens, include:

Organosulfur compounds. One class of organosulfur compounds, the aromatic isothiocyanates (such as benzyl and phenethyl isothiocyanates), are present in cruciferous vegetables—cabbage, brussels sprouts, broccoli and cauliflower. Sulforaphane is a powerful anticarcinogen recently discovered in broccoli. Other allylsulfur compounds, such as diallyl sulfide—which is present in *Allium* plants such as garlic, onions, leeks and shallots—may also have anticarcinogenic properties.

Indoles. Indoles such as indole-3-carbinol are also present in cruciferous vegetables.

Monoterpenes. Monoterpenes such as d-limonene and d-carvone are present in oils from citrus fruits, nuts and seeds.

Flavonoids. Apigenin, quercetin, myricetin, three flavonoids, are widely distributed in fruits.

Tannins. An excellent example of a tannin is ellagic acid; strawberries are a particularly good

source of ellagic acid.

There are also various minor food constituents of known nutritive value that have demonstrated anticarcinogenic effects in either animal studies or in model systems that use bacteria or cultured cells. These include carotenoids (vitamin A and its precursors, particularly beta-carotene), vitamin C, vitamin E, chlorophyllin, conjugated linolenic acid and selenium salts.

In addition to these natural protective agents, some synthetic compounds have also shown promising results. For example, three antioxidant food additives—butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and ethoxyquin—have been shown to have anticarcinogenic effects in some animal studies.

How do these anticarcinogens work?

Nearly all of the foodborne carcinogens discussed above require metabolic activation; that is, these "procarcinogens," (such as aflatoxin B_1, polycyclic aromatic hydrocarbons, hydrazines and heterocyclic amines) are not carcinogenic *per se* but must first be "activated" into chemically reactive and carcinogenic intermediates by enzymes that occur naturally in our bodies. These chemical intermediates then react with DNA and cause mutations, thereby initiating the cancer process. (This same process has been identified for many synthetic compounds as well.)

Fortunately, carcinogen detoxification reactions also occur in our bodies, and these reactions serve to counteract this natural process. Several groups of anticarcinogens are thought to act either to suppress the chemical activation reactions or to increase carcinogen detoxification. Some anticarcinogens are thought to act through both mechanisms. The net effect of both of these effects is to reduce the amount of activated carcinogens that reach or react with DNA or other important targets in our cells.

Other anticarcinogens, like chlorophyll, are thought to act by other routes, binding to and detoxifying chemically reactive intermediates; still others are thought to act by suppressing the process by which cells become cancerous.

It is important to point out again, first, that our bodies cannot distinguish between natural and synthetic chemicals and, second, that the mechanism of action of natural and synthetic carcinogens is likewise the same. Thus, anticarcinogens would be expected to be active against cancer-causing compounds regardless of their origin.

Are we ready for anticarcinogen therapy?

There are several problems to be addressed before anticarcinogens can truly become a practical and safe protective therapy in people. First, the anticarcinogenic benefits of at least some compounds are seen only when they are a natural part of the foods from which they are derived. Thus, these compounds may not bestow their benefits when given as a supplement. Americans currently are enthralled with the idea of taking supplements as a way to health and, specifically, as a way to reduce risk of cancer. But while some supplements may prove useful, they are no substitute for a good diet.

Second, some anticarcinogens, such as vitamin A and selenium, are toxic at levels not much greater than those found in a normal diet.

Third, animal studies have shown that, under some experimental conditions, some anticarcinogens may actually be carcinogenic in their own right or may *promote* the carcinogenic effects of another chemical. Examples include indole 3-carbinol, quercetin, BHA, caffeic acid and chlorogenic acid.

Fourth, some research has shown that the protective effects of a chemical may be specific to a given carcinogen or a closely related class of carcinogens.

Lastly, of course, there is always the question of extrapolation of animal studies to humans: Will animal anticarcinogens behave the same way in people?

It is clear that much more work is needed in this field; however, we can still benefit from the work that has been done. Despite the fact that many questions remain about the effectiveness and safety of anticarcinogens, there is strong evidence pointing to the protective benefits of increasing the fruits and vegetables in our diet.

Dr. Gladys Block and her coworkers recently conducted a survey of approximately 200 studies examining the relationship between fruit and vegetable intake and the incidence of several cancer types. An overwhelming majority (128 of 156) of these studies showed that eating fruits and vegetables statistically lowered cancer risk. The case was particularly striking for fruits, which in 28 of 29 studies showed a statistically significant protective effect against cancers of the esophagus, oral cavity and larynx and in 24 of 25 studies showed a statistically significant protective effect against lung cancer.

Thus, there is no need to wait for extensive clinical trials to make dietary changes now that will reduce your risk of cancer. Given the strong data already available, organizations such as the National Cancer Institute are recommending that people eat a balanced diet that includes five servings of fruit and vegetables daily (see Appendix I on page XX for serving sizes of different foods).

Is Anything Safe?

If by "safe" you mean absolutely safe, No. As Dr. Bruce Ames has pointed out, "There are large numbers of mutagens and carcinogens in every meal, all perfectly natural and traditional. Nature is not benign. It should be emphasized that no human diet can be entirely free of mutagens and carcinogens."

But why are these carcinogens, mutagens and toxins naturally present in foods?

Plants are not simply foods for humans; they are living, highly complex organisms in their own right. Some of the chemicals that plants synthesize function in the plants' growth and reproductive processes; others may be waste products and metabolites. We do not know all the functions of all the carcinogenic, mutagenic and toxic substances in plants; but one theory is that these substances help plants defend themselves against their enemies, which can include bacteria, molds, nematodes, insects, birds and grazing animals. What we do know is that plants have developed chemical defenses of extraordinary variety and subtlety; Dr. Ames has termed these defensive compounds "nature's pesticides."

How do the amounts of nature's pesticides compare with the amount of synthetic pesticides in food?

Nature's pesticides are present in foods in much larger amounts than the synthetic kind. Most of the concentrations listed for natural pesticides in this report are in the high parts per million or even parts per thousand range, while synthetic pesticides are present in foods in the much smaller low parts per million or even parts per billion ranges. It is estimated that humans typically eat some 10,000 times more of nature's pesticides than they do of synthetic ones. This fact suggests the need, in research efforts, of striking a better balance in evaluating natural versus synthetic pesticides.

How can we compare the possible cancer hazards from natural and synthetic substances?

Scientists consider several factors when evaluating the possible human cancer hazard from any chemical, whether natural or synthetic; and Dr. Bruce Ames and colleagues have proposed an index by which we can estimate such hazards to humans. What follows here is a simplified explanation of that index; for a more detailed explanation see Appendix 2 on page XX.

First, since current estimates of carcinogenicity are often based on animal studies, one must measure the carcinogenic potency of a chemical when it is given to animals—usually to rodents such as rats or mice. The potency is defined in terms of the extent to which the chemical increases the tumor load—the number of tumors the animals develop. Typically, a chemical is given in very high doses over much of the animals' lifespan.

In the normal course of affairs, however, people are not exposed to very high doses of these chemicals over an entire lifespan. Thus, an index of possible hazard should take the typical human exposure into account. This is exactly what Ames' et al.'s HERP (Human Exposure/Rodent Potency) index does: it takes a measure of the human exposure (HE) to a possible carcinogen and divides it by the rodent potency (RP) of that chemical.

The HERP index gives a much clearer picture of a substance's potential effect on humans than do animal test results alone because the HERP index includes an estimated human exposure to the substance. An extremely potent carcinogen may pose little hazard if human exposure is very low, but a weak carcinogen may be a potential hazard if humans consume relatively large amounts of it as a food component. The toxicological principle that "the dose makes the poison" applies to carcinogens, natural or synthetic, just as it does to other substances.

The HERP index puts the risk of cancer in perspective by providing a ranking system for the hundreds of cancer-causing substances people encounter daily. In this way the HERP approach exposes the real potential hazards and allows us to separate them from the trivial risks. With the help of HERP we can concentrate on the substances that are likely to be the worst offenders. Table 1 shows the HERP indices for some natural and synthetic substances that are present in food; Table 2 shows some nonfood substances for comparison.

Table 1.

Ranking of Possible Carcinogenic Hazards from Human Food

Possible Hazard HERP (%)[1]	Food	Carcinogenic Component
0.001	Tap water	Chloroform
0.0002	All food	PCBs
0.0004	Grain products	Ethylene dibromide (EDB)
0.003–0.006	Bacon, cooked	Nitrosamines
0.03	Peanut butter	Aflatoxin
0.06	Diet cola	Saccharin
0.07	Brown mustard	Allylisothiocyanate
0.1	Basil	Estragole
0.1	Mushrooms	Hydrazines
2.8	Beer	Ethyl alcohol
7.5	Comfrey-pepsin tablets	Comfrey root and symphytine

[1]The HERP, or Human Exposure/Rodent Potency dose, is defined as the percentage of the animal TD_{50} dose (see below) that a human would receive as a daily lifetime exposure in mg per kg per day for 70 years. The lower the HERP value, the lower the hazard or risk, based on either the inherent potency of the compound, the typical human exposure to the compound or both.

The TD_{50} dose is the daily dose rate in mg per kg of body weight needed to reduce the number of tumor-free animals by 50 percent at the end of the standard lifetime of that test animal.

Table 2.

Some Nonfood Carcinogenic Hazards

Possible Hazard HERP (%)[1]	Source	Carcinogenic Component
0.008	Swimming-pool water	Chloroform
0.6	Conventional home air	Formaldehyde
5.8	Worker exposed to formaldehyde	Formaldehyde
16	Anticonvulsant medication	Phenobarbital
17	Lipid-lowering drugs	Clofibrate
140	High worker exposure to EDB[2]	EDB

[1]For definition, see Table 1 on page XX.

[2]EDB: ethylene dibromide

But how does the overall carcinogenic hazard from natural substances in food compare with the hazard from synthetic substances? Let's answer this question by first looking at two examples of carcinogenic synthetic food components. One of these is saccharin; the other is ethylene dibromide (EDB), a grain fumigant that the Environmental Protection Agency (EPA) banned early in 1984 after residues were found in a wide variety of grain-derived foods in supermarkets. EDB is carcinogenic in laboratory animals; according to the EPA, it is also one of the most powerfully carcinogenic of all pesticides.

Saccharin, on the other hand, is one of the weakest carcinogens ever detected in animal tests, and it is very strain- and sex-specific. Whether saccharin is, in fact, carcinogenic at all is a matter of debate. All of the naturally occurring carcinogens discussed in this report that have been tested in animals in experimental designs that permit comparisons of relative carcinogenic potency with saccharin (that is, administration of the chemical for a lifetime and by the oral route rather than by skin painting or injection) are more powerful—and often far more powerful—carcinogens than saccharin.

Aflatoxin B_1, for example, is roughly one million times more potent as a carcinogen than saccharin. Thus, one million times as much saccharin as aflatoxin B_1 would be needed to induce the same incidence of tumors in rats; or, to put it in another way, a single gram of aflatoxin B_1 would have the same carcinogenic hazard, based on animal tests, as one million grams—a little more than a ton—of saccharin.

On the same potency scale EDB is just about in the middle of the range between aflatoxin B_1 and saccharin. That is, EDB is about 1,000 times more potent than saccharin and about 1/1,000 as potent as aflatoxin B_1. In 1984, on the basis of extensive food testing, the EPA estimated that the average level of EDB contamination in grain-based foods was 2 to 3 ppb and that the average pre-ban dietary intake from all sources by an adult was about 0.5 micrograms (µg) per person.

It is worth comparing this amount and potency of EDB with several of the natural carcinogens described above. Aflatoxin B_1 is about 1,000 times more potent than EDB, yet it is allowed in foods at levels as high as 20 ppb—nearly ten times higher than the average level of EDB found pre-ban in grain-based food products.

One of the mushroom hydrazines, N-methyl-N-formylhydrazine, has a carcinogenic potency similar to that of EDB, yet it is present in such large amounts in the false morel that a person eating a single 100 g serving of those mushrooms would ingest 50 mg of this chemical alone. This is about 100,000 times (50 mg/0.5µg) the amount of a single day's pre-ban ingestion of EDB, or the equivalent of nearly 300 years of such ingestion.

The methyl hydrazine present in the same mushroom at 14 ppm is about one tenth as potent as EDB. A 100 g serving of false morels would therefore contain 1,400 µg of methyl hydrazine. This would be equivalent in carcinogenic risk (1,400 mg/0.5 µg)(10) to 280 days, or about 9 months, of average pre-ban EDB ingestion.

Symphytine is about as potent a carcinogen as EDB, but a cup of comfrey tea contains 130 mg of it, or some 260 times as much as a typical pre-ban day's EDB ingestion. The carcinogenic risk from this one substance in that one cup of comfrey tea would thus be equivalent to about 8 months of EDB ingestion at the average daily pre-ban rate.

These examples indicate clearly that nature's pesticides—considering both their potency and the amounts in which they appear in food—are substantially more hazardous than the trace amounts of synthetic pesticides found in food. Obviously, research on the substances found in food

needs to be balanced more evenly between natural and synthetic substances.

Reducing our exposure to pesticides in foods may, in fact, actually increase the incidence of cancer. How? As we have seen, fruits and vegetables are important for reducing cancer. But by reducing our use of pesticides, we will cause fruits and vegetables to become more expensive—and fewer consumers will be able to afford to include them as important components of their diets.

Recently, Dr. Ames and his coworkers have modified the HERP index to utilize more readily available LD_{50} data (the *lethal* dose in 50 percent of test animals), rather than the relatively scarce TD_{50} values from animal cancer tests. While derived from short-term, or acute, studies, LD_{50} values are often correlated with carcinogenic potency. The new index, termed HERT (for Human Exposure/Rodent *Toxicity*), may prove to be a useful surrogate for the HERP index because acute toxicity values are available for many more chemicals.

What about other man-made chemicals in food?

The great bulk of our food—more than 99 percent by weight—consists of natural ingredients. Food additives make up less than one percent, and pesticide residues and other "introduced" contaminants (such as those from packaging materials) cannot even usefully be measured at percent levels. When these contaminants occur, they are present in "trace" amounts in low ppm range or less. Thus, human exposure to "chemicals" consists overwhelmingly of exposure to chemicals of natural, not synthetic, origin. Even a cup of coffee is estimated to contain more than 2,000 natural chemical components, few of which have been adequately studied toxicologically and many of which have never been identified. At least 150 distinct naturally occurring chemicals have been identified in potatoes, with many more unknown substances also present. Other natural food sources are similarly complex, and the majority of chemical substances contained in them are unidentified. Substances presently unknown will be discovered in familiar foods with each advance in analytical techniques.

Moreover, the synthetic chemicals that appear in the food supply are tightly monitored and carefully controlled in the U.S. and in other countries. Their use is permitted in foods only at levels that ensure a large margin of safety (typically, at least 100-fold) between the levels of human exposure and the highest level at which no harm of any sort is evident in test animals.

The margins of safety of many natural substances—what we might term "nature's margins"—are often much smaller. For a person who drinks five or six cups a day, nature's safety mar-

gin for the caffeine in coffee is only about twenty. The safety margin is about ten to twenty for the solanine in potatoes; about ten for the cyanide-generating compounds in lima beans; and about five for salt before hypertensive effects become evident, although this is also affected by genetic factors and disease. Nature's margins for vitamins A and D are about 25 to 40. And nature's margin for energy intake—calories—is far less than two: A person who consistently eats double the amount of calories needed will soon be at risk of obesity and its many related health problems—health problems that may (according to a recent report by the National Academy of Sciences) include cancer.

In addition, the toxicological properties of the synthetic chemicals in food have been studied far more thoroughly (even while leaving much to be discovered) than those of most of the natural components in food. Furthermore, relatively little effort has been put into determining the carcinogenicity of natural compounds. The weight of cancer prevention efforts in the past has been directed toward identifying synthetic carcinogens. Thus, when we seriously start screening the natural components of food for carcinogenicity in a systematic way, it is likely that many more carcinogens of natural origin will be recognized. Even now, however, it is apparent that the known carcinogenic risks from the natural substances in food markedly outweigh those arising from synthetic chemicals.

What about the argument that synthetic chemicals are particularly dangerous because they are new, and thus humans have not had a chance to adapt genetically to them?

This position seems to have little merit. If the argument were valid, then rats and mice, which have adapted to the presence of natural carcinogens just as we have, should not develop cancer when exposed to them. But, of course, rats and mice do: Animal tests, after all, are our main means of identifying carcinogens, whether synthetic or natural. And there is no way to distinguish the carcinogenic response of animals to natural chemicals from their response to synthetic ones. A natural substance giving a carcinogenic response in such a test can be presumed to be as hazardous as a synthetic substance of the same potency.

Moreover, the volume and variety of toxic, teratogenic, mutagenic and carcinogenic substances in nature is clearly so large that animals and people have most likely adapted to them by developing a generalized capability to handle dangerous chemicals. Humans are, after all, unusually omnivorous; and as omnivores we are exposed to a very large variety of chemical substances as a natural part of our diet. Consequently, we would have been subject throughout time to constant

(albeit gradual) changes in our dietary chemical components. Indeed, the human liver is an extremely versatile organ in its ability to detoxify an array of foreign chemicals, both natural and synthetic. The capacity to deal flexibly with chemicals in general would thus appear to be favored and would give us a substantial degree of protection against new synthetic chemicals as well. If this were not the case, the human race would have disappeared long ago.

This defense capacity need not, of course, be perfect to be highly useful. It would be optimal for dealing with normal—i.e., comparatively low—exposures, be they synthetic or natural. What it would likely not be adapted to handle well would be abnormally high exposures. And, in fact, most of the instances in which human cancer has been traced to a specific, chemical cause seem to have involved high levels of exposure over long periods, such as are seen in some occupational settings, in medical therapies and in personal habits such as smoking or drinking alcoholic beverages.

Yet another consideration arguing that biochemical mechanisms for coping with novel synthetic chemicals either preexist or are readily developed is the ease with which insects develop resistance to new pesticides. Increased resistance is usually already evident within a few generations after the introduction of a new pest control agent.

What about the interactions of these synthetic chemicals? Couldn't some type of deleterious synergism result from these combinations? After all, we have hardly tested the interactions at all.

There is no way to rule out this possibility. But the same possibility holds for the natural substances as well and, indeed, is more likely to involve them, given their greater number, variety and amount. Given, too, that we now know about anticarcinogens, it is also possible that substances may interact to *lower* the chances of cancer. Furthermore, two carcinogens coadministered in an animal cancer study are just as likely to reduce cancer incidence as to increase it. Very recent evidence indicates that for noncancer toxic endpoints, synergism is not likely unless the doses of each of the chemicals are equal to or greater than their individual threshold levels. (A "threshold" is defined as the dose above which toxic effects of a chemical begin to be observed.) It is not known whether this is true for carcinogens.

But is it really fair to treat natural and synthetic chemicals alike? We can't do much about the natural carcinogens, aside from a partial avoidance; but we can do something about the synthetic

ones, namely, stop adding them. So shouldn't we still focus our primary attention on banning synthetic chemicals that cause cancer in laboratory animals?

It is true that it is easier not to add something than to remove something already there. And if all other things were equal, this reasoning would make sense. But we usually face situations in which all other things are not equal—not even remotely so. As argued above, present evidence indicates that the cancer hazards posed by natural carcinogens in foods substantially outweigh the hazards from synthetic chemicals. In many cases, the cancer risk from synthetic substances in food is small enough to be insignificant against the background risk from the natural substances in the food—small enough that the reduction in total cancer risk that would resulting from banning the synthetics would be the equivalent of trying to clean up a sandy beach by removing one or two grains.

It is against this backdrop that the Delaney clause (the Federal ruling that prohibits the inclusion in food of any food additive that causes any cancer in any animal mode) was modified in 1996—at least insofar as it relates to residues of pesticides in foods—by removing the "zero-risk" provision and replacing it with a new standard of "a reasonable certainty of no harm."

Synthetic pesticides serve a useful function; furthermore, as mentioned above (see page XX), they may actually *reduce* the incidence of human cancer because their use promotes an abundant and economical supply of fruits and vegetables, which are known to reduce cancer risk. Unless alternatives to the synthetic chemicals exist—alternatives that can effectively perform the same function and that also are known not to be carcinogens—then we risk losing the pesticides' beneficial function altogether. This is precisely the situation consumers faced when a saccharin ban was proposed a few years back at a time when no other low-calorie sugar substitute was available. A similar situation prevails at the present time with regard to the grain fumigant EDB, since none of its commonly used substitutes has passed a high-dose, long-term animal cancer test with a clean bill of health.

In situations where the cancer risk posed by a synthetic substance is minute compared to the background of natural substances, much more could be gained in terms of the net lowering of human cancer risk by reducing, even partially, the background level of natural carcinogens than could be gained by exorcising every last molecule of the synthetic chemical. And this reduction of the former could be done without sacrificing the benefits of the latter.

Clearly, we need to learn to distinguish between potent and weak carcinogens, between large and small amounts of carcinogens and between functional and unnecessary chemicals so that we can make intelligent decisions about what we allow in the nation's food supply and what regulatory priorities we need to set.

What, then, would be ACSH's overall recommendations? Is it worthwhile, in health terms, to make an individual effort to minimize one's intake of natural mutagens and carcinogens, to increase one's intake of anticarcinogens or to do both?

While we have been able to identify a substantial number of natural carcinogens in our diet through laboratory tests, we have yet to identify any one natural carcinogen that significantly affects human cancer incidence rates. There are variations in the incidence rates of specific cancers in different countries, and some of these variations have been associated with differences in diet. But simple association does not establish causation. Observations can only suggest (but do not prove) that diet can play a significant role in determining the occurrence of some cancers.

No specific food component, whether natural or synthetic, has yet been identified with certainty as a primary cause of a cancer common in the U.S. in the same manner and to the same extent that cigarette smoking has been shown unequivocally to be the leading cause of lung cancer.

Given the foregoing, however, our specific recommendations would be to consume a diet rich in variety, going easy on any one particular food type. This practice minimizes exposure to any single carcinogen that might overwhelm the body's natural defenses. And speaking of "natural defenses," we also heartily agree with the "five fruits and vegetables a day" recommendation of the National Cancer Institute (as discussed above; see page XX) because of the strong evidence that fruit and vegetable intake is related to reduced risk for several types of cancer.

Conclusions

ACSH's review of the literature on naturally occurring carcinogens leads us to three general conclusions.

First, the best way to minimize the potential hazard posed by naturally occurring carcinogens is to eat a wide variety of foods, including generous helpings of fruits and vegetables. Further, the

National Academy of Sciences has reported that a high-calorie diet may introduce a cancer risk equal to or exceeding that posed by exposure, in a typical American diet, to a majority of the natural carcinogens discussed in this ACSH report. Therefore, ACSH recommends a reduced caloric intake as important to the reduction of cancer incidence. It would be unrealistic to attempt to remove from our food supply every known trace of any naturally occurring cancer-causing agent, or to avoid all exposure to carcinogens, just as it would be unrealistic to seek "zero exposure" to sunlight (a skin carcinogen) or medical radiation (which would mean dispensing with the manifest benefits of diagnosing with X rays and using therapeutic radiology to treat cancer). In any case, at this point there is no evidence that low-level exposure to either natural or synthetic chemicals in the U.S. food supply poses a significant human cancer risk.

Second, although scientists are just now identifying the carcinogens of nature and determining whether they pose hazards to humans, it is already evident that the presumption that "natural" means safe and "synthetic" is suspect should be rejected. There is no scientific evidence to support this superstitious presumption; and, indeed, the information summarized in this report completely refutes it.

Third, the increasing body of evidence documenting the carcinogenicity of common, everyday substances in nature points out the contradiction that we have created in our regulatory approach to carcinogens; that is, the disproportionate emphasis we have placed on synthetic carcinogens and our efforts to purge our land of them, while simply ignoring natural carcinogens even though available information indicates that the latter hazard is far greater than the former.

Our new regulatory emphasis should be on the potency of a carcinogen and the level of human exposure to it rather than on the natural versus artificial origin of the substance. Regulatory priorities must be based on clearly distinguishing the risks that matter from the multitude that don't. We must gain a renewed appreciation, in the context of carcinogens, for that scientifically sound and time-honored principle—the most basic tenet of toxicology—that "the dose makes the poison."

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Appendix 1: Serving Sizes for Different Food Groups*

One Serving Equals:

- **Grain Products Group (bread, cereal, rice and pasta):**
  1 slice bread
  1 ounce ready-to-eat cereal
  1/2 cup cooked cereal, rice or pasta

- **Vegetable Group:**
  1 cup raw leafy vegetables
  1/2 cup other vegetables, cooked or chopped raw
  3/4 cup vegetable juice

- **Fruit Group:**
  1 medium apple, banana or orange
  1/2 cup chopped, cooked or canned fruit
  3/4 cup fruit juice

- **Milk Group (milk, yogurt and cheese):**
  1 cup (8 ounces) milk or yogurt
  1 1/2 ounces natural cheese
  2 ounces processed cheese

- **Meat and Beans Group (meat, poultry, fish, dry beans, eggs and nuts):**
  2–3 ounces cooked lean meat, poultry or fish
  1/2 cup cooked dry beans or 1 egg can substitute for 1 ounce lean meat
  2 tablespoons peanut butter or 1/3 cup nuts can substitute for 1 ounce meat

*From: U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Dietary Guidelines for Americans.* 4th ed. 1995; page 7.

Appendix 2: The HERP (Human Exposure/Rodent Potency) INDEX

1. Determine carcinogenic potency of test substance

a. Estimate the tumorigenic (tumor-producing) dose rate or TD_{50} of the substance: TD_{50} is the daily dose rate—in milligrams (mg) of substance per kilogram (kg) of body weight—to halve the number of tumor-free animals at the end of the standard lifetime for the test animal. The TD_{50} corresponds to the cancer-causing potency of the substance: The lower the TD_{50} (i.e., the less substance needed to cause tumors), the more tumorigenic, or potent the material.

2. Determine the typical exposure of humans to the test substance through food, water or other usual routes of exposure.

a. Express the percentage of the animal TD_{50} dose that a human would experience, measured as a daily lifetime exposure in mg per kg per day for 70 years. This percentage is defined as the Human Exposure dose / Rodent Potency dose, or HERP.