POLLUTION, PESTICIDES, AND CANCER

by Bruce N. Ames and Joseph Krovoza, ed.

Editor's note: On February 8, 1992 Dr. Ames delivered the keynote address "Understanding the Causes of Aging and Cancer" at the U.C. Davis Environmental Law Society's conference ***Toxics Law In Transition: Emerging Issues of the 1990's.*** *Introducing Dr. Ames, Professor Harrison C. Dunning mentioned that environmental lawyers are typically well aware of how the law prevents toxic accidents and apportions liability, but that lawyers are too often not as knowledgeable with respect to scientific debates concerning when a problem of public health exists. Hence he welcomed Dr. Ames to further an important policy-oriented debate on the ultimate effect of pesticide use.*

Dr. Ames discussed the causes of aging, how they relate to cancer, the causes of cancer, and why the world is full of synthetic and natural carcinogens "that really don't matter." He also questioned the necessity of much of the Environmental Protection Agency's regulatory structure. This paper encompasses most of the themes from Dr. Ames' February address.[1]

In the last several decades there has been a persistent widespread belief among many groups in this country that nature is benign and that man-made things—i.e., modern technology—have destroyed our benevolent relationship with nature. This yearning for a time when humans were happily in harmony with nature is a yearning for a time that never existed: in reality, life before the modern industrial era was for most people, even in Thomas Hobbes' time, "nasty, brutish, and short". Disease and malnutrition ensured a very short average life expectancy, an early end to the misery of life in a natural world.

The history of agriculture is one of a nonending contest with pests such as insects and fungi. Fields of crops, which often have been bred to have low levels of natural plant defensive chemicals in order to be more edible for human consumption, are easy sources of food for thousands of species of insects and fungi. Infestation of crops by pests can have dramatic impacts on human life: last century, the potato fungus *Phytophthora infestans* wiped out the potato crop of Ireland, which led to the deaths of over a million people due to malnutrition (which made people susceptible to disease) and starvation. The relationship between pesticides and disease is significant. DDT, the first synthetic pesticide, eradicated malaria from many parts of the world, including the U.S. It was so effective against many diseases because (1) it was lethal to many vectors of disease, e.g., mosquitoes, tsetse flies, lice, ticks, and fleas; and (2) it was lethal to many crop pests, and so significantly increased the supply of food and lowered the cost of food, making fresh nutritious foods accessible even to relatively poor people. In Ceylon, for example, in less than 20 years of DDT use, the number of cases of malaria decreased from 2,800,000 per year to 17.[2]

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Some ideologists have twisted the story of pesticides: instead of pesticides freeing us from disease, they assert, pesticides are bringing us disease. There are many misconceptions about the relationship between environmental pollution and human disease, particularly cancer, and these can lead to errors in risk perception, which in turn can lead to counterproductive regulatory policies. Accurate science is crucial for assessing public risk from environmental hazards. As scientific information about a subject increases, public risks often need to be reassessed and public policy refined.

The attempt to prevent cancer by regulating low levels of synthetic chemicals by "risk assessment", using worst-case, one-in-a-million risk scenarios is not scientifically justified. Testing chemicals for carcinogenicity at near-toxic doses in rodents does not provide enough information to predict the excess numbers of human cancers that might occur at low-dose exposures. In addition, this cancer prevention strategy is enormously costly, is counterproductive because it diverts resources from much more important risks, and, in the case of synthetic

pesticides, makes fruits and vegetables more expensive, thus serving to decrease consumption of foods that help to prevent cancer.

The regulatory process does not take into account: 1) that the natural world of chemicals makes up the vast bulk of chemicals humans are exposed to; 2) that the toxicology of synthetic and natural toxins is not fundamentally different; 3) that about half of the natural chemicals tested chronically in rats and mice at the maximum tolerated dose are carcinogens; 4) that testing at the maximum tolerated dose frequently can cause chronic cell killing and consequent cell replacement (a risk factor for cancer

that can be limited to high doses), and that ignoring this greatly exaggerates risks; 5) that an extrapolation from high to low doses should be based on an understanding of the mechanisms of carcinogenesis.

The causes of cancer

The main causes of cancer appear to be mutagenesis (DNA damage) and mitogenesis (cell division). Normal rates of mutagenesis in mammals are high. Mutagens (chemicals that damage DNA) cause cancer by mutating the DNA of cells in ways that cause them to proliferate in an uncontrollable fashion. It is generally agreed that several mutations are necessary to convert a normal cell to a cancer cell capable of uncontrolled growth. Mutagens are often assumed to be exogenous agents (coming from outside the body), e.g., synthetic chemicals; however, many endogenous mutagens (produced inside the body) are formed naturally during normal metabolic processes, such as oxygen utilization, which produces DNA-damaging oxidants. Thus, in a sense, breathing oxygen is equivalent to irradiating the body. Studies in our laboratory have shown that normal metabolism causes chronic massive oxidative DNA damage: we estimate that the number of oxidative hits to DNA per cell per day is about 100,000 in rats and 10,000 in humans. All mammals have numerous defenses to counter this damage, such as enzymes that repair damaged DNA, but this repair is imperfect. DNA damage in somatic cells accumulates with time because a considerable proportion of an animal's resources is devoted to reproduction at a cost to maintenance. Proteins can become oxidized as well, and other laboratories have shown that normal protein oxidation is extensive and that oxidized proteins accumulate with age, contributing to brain dysfunction. Thus, oxidative damage appears to be a major contributor to many of the degenerative diseases of aging, including cancer, because not all the DNA damage is repaired.

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Mitogenesis (cell division) increases mutagenesis and carcinogenesis because DNA adducts are converted to mutations when a cell divides. Dividing cells are much more at risk than are non-dividing, quiescent cells. Agents that cause chronic cell division are therefore indirectly mutagenic (and commonly carcinogenic). Saccharin, for example, is not itself a mutagen, but high doses of saccharin given to rodents cause sufficient cell division to be carcinogenic. Low doses, however, would be expected to have no carcinogenic effect. Agents that cause chronic cell division (e.g., by irritation and inflammation of tissues) appear to be important in many of the known causes of human cancer: estrogen, for example, which causes cell proliferation in breast tissue, is a risk factor for breast cancer; hepatitis B and C viruses and alcohol, which induce cell wounding and subsequent cell proliferation in the liver, are risk factors for liver cancer; high salt intake and *Helicobacter* bacterial infection, which induce chronic irritation of the stomach lining, are risk factors for stomach cancer; papilloma virus, which can cause chronic infection and proliferation of cells of the cervix, is a risk factor for cervical cancer; asbestos and tobacco smoke, which irritate the lungs, are risk factors for lung cancer. For the chemicals associated with occupational cancer, worker exposures usually have been at near-toxic doses that would be likely to cause cell proliferation.

A marked decrease in age-specific cancer rates has accompanied the marked increase in life span that has occurred in the last 60 million years of mammalian evolution. For example, cancer rates are high in two-year-old rodents, but extremely low in two-year-old humans. Cancer incidence increases with approximately the fifth power of age, both in short-lived species such as rats and mice and in long-lived species such as humans. Thus, cancer is one of the degenerative diseases of old age, although exogenous factors can substantially increase it (e.g., cigarette smoking in humans) or decrease it (e.g., calorie restriction in rodents). One important factor in longevity appears to be basal metabolic rate, which is much lower in man than in rodents and could markedly affect the level of endogenous mutagens produced by normal metabolism.

According to the National Cancer Institute's 1987 statistics review, "The age adjusted mortality rate for all cancers combined except lung cancer has been declining since 1950 for all individual age groups except 85 and above". Although incidence rates for some cancers have been rising, trends in recorded incidence rates may be biased by improved registration and diagnosis. Even though mortality rates for cancers at particular sites can be shown to be increasing (for example, non-Hodgkins lymphoma, melanoma) or decreasing (for example, stomach, cervical, rectal), establishing causes remains difficult because of the many changing aspects of our life-style. Life expectancy continues to increase every year.

Cancer clusters in small geographical areas are expected to occur by chance alone, and epidemiology lacks the power to establish causality in these cases. It is important to show that a pollution exposure that purportedly causes a cancer cluster is significantly greater than the background of exposures to naturally occurring rodent carcinogens.

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Causes of cancer in animal tests

Animal cancer tests are conducted at near toxic doses the maximum tolerated dose (MTD) of the test chemical for long periods of time, which can cause chronic mitogenesis. Chronic dosing at the MTD can be thought of as chronic wounding, which is known to be both a promoter of carcinogenesis in animals and a risk factor for cancer in humans. Thus, a high percentage of all chemicals might be expected to be carcinogenic at chronic, near-toxic doses and this is exactly what is found. About half of all chemicals tested chronically at the MTD are carcinogens.

Synthetic chemicals account for 82% of the 427 chemicals adequately tested for carcinogenicity in both rats and mice. Despite the fact that humans eat vastly more natural than synthetic chemicals, natural chemicals have never been tested systematically. Of the natural chemicals that have been tested, about half are carcinogens, which is about the same as found for synthetic chemicals. It is unlikely that the high proportion of chemicals found to be carcinogens in rodent studies is due simply to selection of suspicious chemical structures. Most chemicals were selected because of their use as industrial compounds, pesticides, drugs, or food additives.

Dietary pesticides: 99.99% natural

Daniel H. Janzen of the University of Pennsylvania wrote, "Plants are not just food for animals... The world is not green. It is colored lectin, tannin, cyanide, caffeine, aflatoxin, and canavanine."

Nature's pesticides are one important subset of natural chemicals. Plants produce toxins to protect themselves against fungi, insects, and animal predators. Tens of thousands

of these natural pesticides have been discovered, and every species of plant analyzed contains its own set of perhaps a few dozen toxins. When plants are stressed or damaged, such as during a pest attack, they may greatly increase their natural pesticide levels, occasionally to levels that can be acutely toxic to humans. We estimate that Americans eat about 1.5 g of natural pesticides per person per day, which is about 10,000 times more than they eat of synthetic pesticide residues.

Cruciferous vegetables, such as broccoli, and cauliflower, were used in ancient times primarily for medicinal purposes.

Concentrations of natural pesticides in plants are usually measured in parts per thousand or per million rather than parts per billion, the usual concentration of synthetic pesticide residues or of pollutants in water. We estimate that the human diet contains roughly 5,000 to 10,000 different natural pesticides and their breakdown products. For example, 49 natural pesticides (and metabolites) are ingested when cabbage is eaten. Only two have been tested for carcinogenicity. Lima beans contain a completely different array of 23 natural toxins that, in stressed plants, range in concentration from 0.2 to 33 parts per thousand fresh weight. None appears to have been tested yet for carcinogenicity or teratogenicity. Many leguminous plants contain canavanine, a toxic arginine analog that, after being eaten by animals, is incorporated into protein in place of arginine. Feeding alfalfa sprouts (1.5 % canavanine dry weight) or canavanine itself to monkeys causes a lupus erythematosus-like syndrome. Lupus in humans is characterized by a defect in the immune system that is associated with autoimmunity, anti-nuclear antibodies, chromosome breaks, and various types of pathology. The toxicity of non-food plants is well known. Plants are among the most commonly ingested poisonous substances for children under 5 years of age.

Surprisingly few plant toxins have been tested for carcinogenicity. Among 1052 chemicals tested in at least one species in chronic cancer tests, only 52 are naturally occurring plant pesticides. Among these, 27 are carcinogenic. Even though only a tiny proportion of the plant toxins in our diet has been tested so far, the 27 natural pesticides that are rodent carcinogens are present at levels above 10 ppm in the following foods: anise, apple, basil, Brussels sprouts, cabbage, caraway, carrot, cauliflower, celery, cherries, cloves, coffee (brewed), comfrey herb tea, dill, eggplant, endive, fennel, grapefruit juice, grapes, honey, horseradish, lettuce, mango, mushrooms, mustard (brown), nutmeg, orange juice, parsley, parsnip, pear, pepper (black), plum, potato, rosemary, sage, sesame seeds (heated), tarragon, and thyme. In addition, the following foods contain these 27 natural pesticides at levels below 10 ppm: apricot, banana, broccoli, cantaloupe, cinnamon, cloves, cocoa, collard greens, currants, guava, honeydew melon, kale, lentils, peach, peas, pineapple, radish, raspberries, tea, tomato, and turnip.

Thus, it is probable that almost every fruit and vegetable contains natural plant pesticides that are rodent carcinogens. The levels of these 27 rodent carcinogens in the above plants are commonly thousands of times higher than the levels of synthetic pesticides. Caution is necessary in interpreting the implications of ingesting natural pesticides that are rodent carcinogens. It is not argued here that these dietary exposures are necessarily of much relevance to human cancer. What is important in our analysis is that exposures to natural rodent carcinogens may cast doubt on the relevance of far lower levels of exposures to synthetic rodent carcinogens. Particular natural pesticides that are carcinogenic in rodents can be bred out of crops if studies of mechanism indicate that they may be significant hazards to humans.

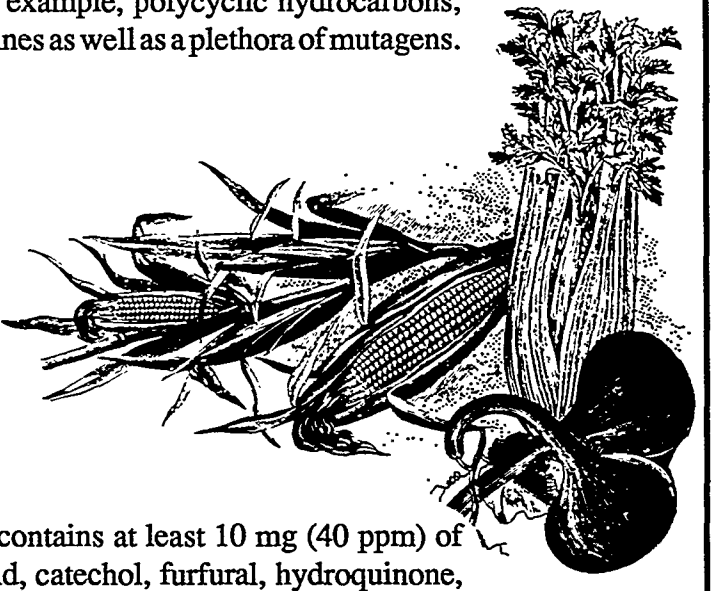
Residues of pesticides

The Food and Drug Administration has assayed food for 200 chemicals, including the synthetic pesticide residues thought to be of greatest importance, and the residues of some

industrial chemicals, such as polychlorinated biphenyls. FDA found residues for 105 of these chemicals. The U.S. intake of the sum of these 105 chemicals averages about 0.09 mg per person per day, which we compare with an intake of 1500 mg of natural pesticides. Thus, the average intake of pesticides is 99.99% natural. Other analyses of synthetic pesticide residues are similar.

About half (0.04 mg) of this daily intake of synthetic pesticides is composed of four chemicals that are not carcinogenic in rodent tests: ethylhexyl diphenyl phosphate, chlorpropham, malathion, and dicloran. Thus, the intake of known or potential rodent carcinogens from synthetic residues is only about 0.05 mg a day.

The cooking of food is also a major dietary source of potential rodent carcinogens. Cooking produces about 2000 mg per person per day of mostly untested burnt material that contains many rodent carcinogens for example, polycyclic hydrocarbons, heterocyclic amines, furfural, nitrosamines as well as a plethora of mutagens.



Thus, the number and amount of total synthetic pesticide residues, including those that are carcinogenic, appear to be minimal compared to the background of naturally-occurring chemicals in the diet. Roasted coffee, for example, is known to contain 826 volatile chemicals; 21 have been tested chronically and 16 are rodent carcinogens; caffeic acid, a non-volatile rodent carcinogen, is also present. A typical cup of coffee contains at least 10 mg (40 ppm) of rodent carcinogens (mostly caffeic acid, catechol, furfural, hydroquinone, and hydrogen peroxide). Thus, the 10 mg of known natural rodent carcinogens in a cup of coffee (only a few percent of the chemicals have been tested) would be equivalent in amount ingested to a year's worth of synthetic pesticide residues (assuming half of the untested synthetic residue weight turns out to be carcinogenic in rodents).

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The evidence on coffee and human health has been recently reviewed, and to date it is insufficient to show that coffee is a risk factor for cancer in humans. The same caution discussed above about the implications for humans of natural rodent carcinogens in the diet apply to coffee and the products of cooked food.

Similar toxicology

It is often assumed that because plants are part of human evolutionary history, while synthetic chemicals are recent, the mechanisms that animals have evolved to cope with the toxicity of natural chemicals will fail to protect us against synthetic chemicals. An example of this view is the statement of Rachel Carson: "For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death." We find this assumption flawed for several reasons.

Defenses that animals have evolved are mostly of a general type, as might be expected, because the number of natural chemicals that might have toxic effects is so large. General defenses offer protection, not only against natural but also against synthetic chemicals, making humans well buffered against toxins. These defenses include the following: (a) 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. (b) The induction of a wide variety of general detoxifying mechanisms, such as antioxidant defenses or the Phase II electrophile-detoxifying systems. Cells that are exposed to small doses of an oxidant, such as radiation or hydrogen peroxide, induce antioxidant defenses and become more resistant to higher doses of oxidants, whether synthetic or natural. Natural or synthetic electrophiles induce Phase II detoxifying enzymes that are effective against both. (c) The active excretion of planar hydrophobic molecules (natural or synthetic) out of liver and intestinal cells. (d) DNA repair, which is effective against DNA adducts formed from both synthetic and natural chemicals, and is inducible in response to DNA damage.

Anticarcinogenic chemicals in the diet, such as antioxidants, help to protect humans against carcinogens but do not distinguish between synthetic and natural carcinogens. It has been argued that synergism between synthetic carcinogens could multiply hazards, but this is equally true of natural carcinogens.

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The fact that defenses are usually general, rather than specific, for each chemical makes good evolutionary sense. The reason that predators of plants evolved general defenses against toxins is presumably to be prepared to counter a diverse and ever-changing array of plant toxins in an evolving world. If a herbivore had defenses against only a set of specific toxins, it would be at a great disadvantage in obtaining new foods when favored foods became scarce or evolved new toxins.

Various natural toxins, some of which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates. Mold aflatoxins, for example, have been shown to cause cancer in trout, rats, mice, monkeys and possibly in humans. Eleven mold toxins out of 16 tested have been reported to be carcinogenic. Many of the common elements, such as salts of lead, cadmium, beryllium, nickel, chromium, selenium and arsenic, are carcinogenic or clastogenic (agents that break chromosomes) at high doses, despite their presence throughout evolution. Selenium and chromium, nevertheless, are essential trace elements in animal nutrition.

Humans have not had time to evolve into a "toxic harmony" with all of the plants in their diet. Indeed, very few of the plants that humans eat would have been present in an African hunter-gatherer's diet. The human diet has changed drastically in the past few thousand years, and most humans are eating many recently introduced plants that their ancestors did not: for example, cocoa, tea, potatoes, tomatoes, corn, avocados, mangoes, olives and kiwi fruit. In addition, cruciferous vegetables, such as cabbage, broccoli, kale, cauliflower, and mustard were used in ancient times primarily for medicinal purposes and spread as foods across Europe only in the Middle Ages. Natural selection works far too slowly for humans to have evolved specific resistance to the food toxins in these newly introduced plants. DDT bioconcentrates in the food chain as a result of its unusual lipid solubility. However, natural toxins can also bioconcentrate.

DDT is often viewed as the typically dangerous synthetic pesticide because it persists for years. It is representative of a class of chlorinated pesticides. Natural pesticides bioconcentrate if lipophilic. For example, the teratogens from potato, solanine (and its aglycone solanidine), and chaconine, are found in the tissues of potato eaters. Although DDT is unusual with respect to bioconcentration, it is remarkably non-toxic to mammals, saved millions of lives, and has not been shown to cause harm to humans.

To a large extent DDT, the first major synthetic insecticide, replaced lead arsenate, a major pesticide used before the modern era. Lead arsenate is even more persistent than DDT, and although natural, both lead and arsenic are carcinogenic.

These arguments undermine many assumptions of current regulatory policy and necessitate a rethinking of policy designed to reduce human cancer. Minimizing pollution is a separate issue and is clearly desirable for reasons other than effects on public health. There is a sizeable literature on why focussing on worst case, one-in-a-million risks, rather than major risks, impedes intelligent risk reduction.

It is by no means clear that many significant risk factors for human cancer will be discovered by screening assays. Dietary imbalances, such as antioxidant and folate deficiencies, are likely to be major contributors to human cancer, and understanding these should be, but is not, a major priority of research. Understanding why caloric restriction dramatically lowers cancer and mitogenesis rates and extends life span in experimental animals should also be a major research priority. More studies on mechanisms of carcinogenesis should also be of high priority.

Synthetic pesticides have markedly lowered the cost of vegetables and fruit, thus increasing consumption. Other than giving up smoking (causing 30% of cancer and 25% of heart disease) eating more fruits and vegetables and less fat may be the best way to lower risks of cancer and heart disease. In conclusion, the attempt to prevent cancer by regulating low levels of synthetic chemicals by traditional "risk assessment", using worst-case, one-in-a-million risk scenarios, is not scientifically justified. This does not mean that chemical regulation per se is undesirable. The question is how best to regulate pollution, such that tradeoffs are efficiently factored into regulatory policy. One way is by putting pollution control in the realm of the free market, for example, by auctioning off pollution licenses or taxing polluters depending on the amount of pollution produced. According to A.S. Blinder "the secret [of the market's success] is the market's unique ability to accommodate individual differences in this case, differences among polluters...the profit motive will automatically assign the task of pollution abatement to the low-cost firms something no regulators can do."[3] This solution would partition economic tradeoffs most efficiently. Firms that can relatively inexpensively reduce their pollution will have a strong incentive to do so to avoid paying the pollution tax. Even if the risks of a particular type of pollution are initially overestimated, it is the firms that can cost-effectively change their pollution habits that have the incentive to do so, inflicting the lowest overall cost on the consumer. As new scientific information leads to the reassessment of these risks, or as the values of a society change, the tax on different types of pollution can be raised or lowered.

It is the inexorable progress of modern technology and scientific research that is likely to lead to a decrease in cancer death rates, a decrease in birth defects, a decrease in pollution, and an increase in the average human life span.

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ENDNOTES

[1] Reprinted from Ames,75 Jrnl.AOAC Int'l #1, 1-5 (1992) with permission of Dr. Ames.

[2] After Ceylon stopped using DDT, the number of malaria cases increased again.

[3] Blinder, Hard Heads, Soft Hearts, Addison-Wesley, Reading, MA (1987).