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What Are the Major Carcinogens in the Etiology of Human Cancer?

Environmental Pollution, Natural Carcinogens, and the Causes of Human Cancer: Six Errors

14a

Introduction ■

Arguments that industrial pollutants are present in significant amounts or contribute substantially to cancer rates share several mistaken assumptions. These are discussed in the following sections, as is the danger inherent in diverting our attention away from tobacco and dietary, hormonal, occupational, and viral carcinogens to industrial pollutants.

Error 1: Cancer Rates Are Soaring ■

Overall, US cancer death rates are staying at the same levels or decreasing, the major exception being smoking-related cancer. A recent update from the National Cancer Institute (February 1988)¹ indicates that "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" (13% decrease overall, 44,000 deaths below expected; 0.1% increase in the over-85 group). The types of cancer deaths that have been decreasing during this period are primarily those of the stomach (by 75%, 37,000 deaths below expected), cervix (73%, 11,000 deaths below expected), uterus (60%, 9,000 deaths below expected), and rectum (65%, 13,000 deaths below expected). The types of cancer deaths that are increasing

are primarily lung cancer (by 247%, 91,000 deaths above expected), which is caused by smoking (as is 30% of U.S. cancer) and non-Hodgkin's lymphoma (by 100%, 8,000 deaths above expected). The overall cancer mortality trends can be seen in the latest plot from the American Cancer Society (Fig. 14a-1).

Clearly, changes in survival rates and incidence rates are also relevant in interpreting those changes.^{1,2} Incidence rates have been increasing for some types of cancer. Doll and Peto,² in their definitive study on cancer trends, pointed out that although incidence rates are of interest, they should not be taken in isolation because of the substantial extent to which trends in recorded incidence rates are biased by improvements in the level of registration and diagnosis, as appears to be the case with breast cancer. Even if particular types of cancer are shown to increase or decrease, establishing a causal relation among the many changing aspects of our lives remains difficult.³⁻¹⁴ There is no convincing evidence that there is a general increase in cancer related to the conditions of the modern industrial world.^{2,9,12}

Life expectancy is steadily increasing in the United States and other industrial countries; infant mortality is decreasing; and, although the statistics are not good, there is no evidence that birth defects are increasing. Thus, the conclusion is that Americans are healthier than they have ever been.

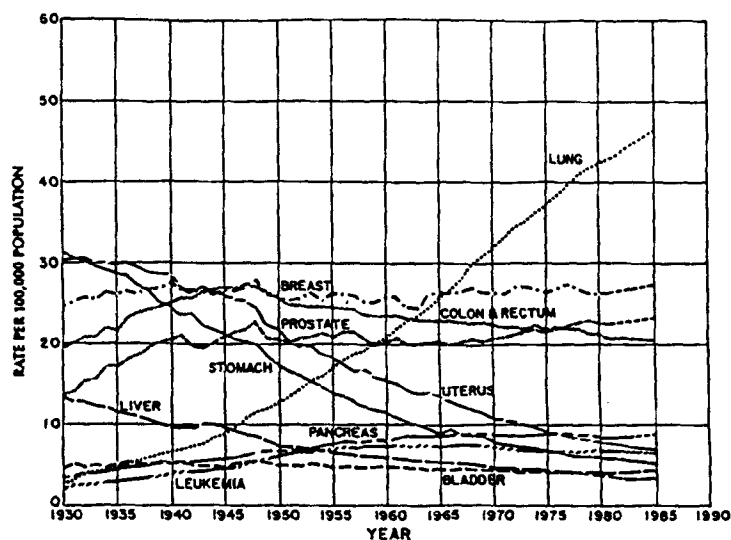


FIG. 14a-1 Cancer death rates by site, United States, 1930-1985. All figures are age-adjusted. Rate for the population standardized for age on the 1970 U.S. population. Sources of data: National Center for Health Statistics and Bureau of the Census, United States. Rates are for both sexes combined except breast and uterus, female population only, and prostate, male population only. (Reprinted with permission from *Cancer Facts and Figures*—1988, New York, American Cancer Society, 1988)

Error 2: Only a Small Number of Chemicals Are Carcinogenic or Teratogenic, and We Can Eliminate Them ■

More than 50% of the chemicals tested to date in rats and mice have been found to be carcinogens at the high doses administered,^{3,15} the maximum tolerated dose (MTD). The exhaustive database of animal cancer tests developed by me and my colleagues^{16,17} listed 392 chemicals tested in both rats and mice at the MTD. Of these, 58% of the synthetic chemicals and 45% of the natural chemicals were carcinogens in at least one species.^{3,15} We concluded that the proportion of chemicals found to be carcinogens is strikingly high, a conclusion reached by others on the basis of smaller compilations. The earlier Innes and colleagues study¹⁸ is sometimes cited to support the conclusion that the proportion of carcinogens is low. However, that study used a much smaller dataset (120 chemicals, 11 positive), and the tests, although appropriate for their time, used only one species and were less thorough than modern tests.¹⁵

Even when one considers that some chemicals are selected for testing based on a high index of suspicion, the large proportion of positive findings is disturbing. From considerations of carcinogenesis mechanisms, it is plausible that a large proportion of all chemicals we test in the future, both natural and man-made, will prove to be carcinogens (see "Error 4" below).³

Large proportions of positives are also reported for teratogenesis tests. Fully one-third of the 2800 chemicals tested in laboratory animals have been shown to induce birth defects at the MTD.¹⁹ Thus, it seems

likely that a sizable percentage of both natural and man-made chemicals will be reproductive toxins when tested at these doses. The world is full of carcinogens and reproductive toxins, and it always has been. The important issue is the human exposure dose, and, fortunately, this is almost always miniscule.

The major preventable risk factors for cancer causation, such as tobacco, dietary imbalances,^{11,13,14, 20-23} hormones,¹⁰ and viruses,^{24,25} have been discussed by us^{3-8,26} and others.^{2,9-12}

Error 3: Man-made Chemical Pollutants Are Present in Significant Amounts ■

We have attempted to address the issue of priority setting among possible carcinogenic hazards.³ Carcinogens differ enormously in potency in rodent tests and comparisons of possible hazards from various carcinogens ingested by humans must take this into account. Our analysis makes use of an exhaustive database of carcinogenic potency (currently 3500 experiments on 975 chemicals)^{16,17} that analyzes animal cancer tests and calculates the TD₅₀, essentially: the dose of the carcinogen sufficient to cause cancer in half of the animals. The TD₅₀ is close to the high dose (MTD) actually given, and thus involves a minimal extrapolation. To calculate our index of possible hazard, we express each human exposure (daily life time dose, in mg/kg) as a percentage of the rodent TD₅₀ dose (mg/kg) for each carcinogen. We call this percentage HERP (human exposure dose/rodent potency dose). Because rodent data are all calculated on the basis of lifetime exposure at the indicated daily dose rate,^{16,17} the human exposure data are similar

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Table 14a-1
Ranking of Possible Carcinogenic Hazards*

Possible Hazard: HERP (%)	Daily Human Exposure	Carcinogen Dose per 70-kg Person	Potency of Carcinogen: TD ₅₀ (mg/kg)	
			Rats	Mice
Environmental Pollution				
0.001†	Tap water 1 L	Chloroform, 83 µg (US average)	(119)	90
0.004†	Well water, 1 L contaminated (worst well in Silicon Valley)	Trichloroethylene, 2800 µg	(-)	941
0.0004†	Well water, 1 L contaminated, Woburn	Trichloroethylene, 267 µg	(-)	941
0.0002†		Chloroform, 12 µg	(119)	90
0.0003†		Tetrachloroethylene, 21 µg	101	(126)
0.008†	Swimming pool, 1 h (for child)	Chloroform, 250 µg (average pool)	(119)	90
0.6	Conventional home air (14 h/d)	Formaldehyde, 598 µg	1.5	(44)
0.004		Benzene, 155 µg	(157)	53
2.1	Mobile home air (14 h/d)	Formaldehyde, 2.2 mg	1.5	(44)
Pesticide and Other Residues				
0.0002†	PCBs: daily dietary intake	PCBs, 0.2 µg (US average)	1.7	(9.6)
0.0003†	DDE/DDT: daily dietary intake	DDE, 2.2 µg (US average)	(-)	13
0.0004	EDB: daily dietary intake (from grains and grain products)	Ethylene dibromide, 0.42 µg (US average)	1.5	(5.1)
Natural Pesticides and Dietary Toxins				
0.003	Bacon, cooked (100 g)	Dimethylnitrosamine, 0.3 µg	(0.2)	0.2
0.006		Diethylnitrosamine, 0.1 µg	0.02	(+)
0.003	Sake (250 ml)	Urethane, 43 µg	(41)	22
0.03	Comfrey herb tea (1 cup)	Symphytine, 38 µg (750 µg of pyrrolizidine alkaloids)	1.9	(?)
0.03	Peanut butter (32 g; one sandwich)	Aflatoxin, 64 ng (US average, 2 ppb)	0.003	(+)
0.06	Dried squid, broiled in gas oven (54 g)	Dimethylnitrosamine, 7.9 µg	(0.2)	0.2
0.07	Brown mustard (5 g)	Allyl isothiocyanate, 4.6 mg	96	(-)
0.1	Basil (1 g of dried leaf)	Estragole, 3.8 mg	(?)	52
0.1	Mushroom, one raw (<i>Agaricus bisporus</i> ; 15 g)	Mixture of hydrazines, etc.	(?)	20,300
0.2	Natural root beer (12 ounces; 354 ml; now banned)	Safrole, 6.6 mg	(436)	56
0.008	Beer, before 1979 (12 ounces; 354 ml)	Dimethylnitrosamine, 1 µg	(0.2)	0.2
2.8†	Beer (12 ounces; 354 ml)	Ethyl alcohol, 18 ml	9110	(?)
4.7†	Wine (250 ml)	Ethyl alcohol, 30 ml	9110	(?)
6.2†	Comfrey-pepsin tablets (nine daily)	Comfrey root, 2700 mg	626	(?)
1.3	Comfrey-pepsin tablets (nine daily)	Symphytine, 1.8 mg	1.9	(?)
Food Additives				
0.0002	AF-2: daily dietary intake before banning	AF-2 (furylfuramide), 4.8 µg	29	(131)
0.06†	Diet cola (12 ounces; 354 ml)	Saccharin, 95 mg	2143	(-)
Drugs				
[0.3]	Phenacetin pill (average dose)	Phenacetin, 300 mg	1246	(2137)
[5.6]	Metronidazole (therapeutic dose)	Metronidazole, 2000 mg	(542)	506
[14]	Isoniazid pill (prophylactic dose)	Isoniazid, 300 mg	(150)	30
16†	Phenobarbital, one sleeping pill	Phenobarbital, 60 mg	(+)	5.5
17†	Clofibrate (average daily dose)	Clofibrate, 2000 mg	169	(?)
Occupational Exposure				
3.8	Formaldehyde: workers' average daily intake	Formaldehyde, 6.1 mg	1.5	(44)
140	EDB: workers' daily intake (high exposure)	Ethylene dibromide, 150 mg	1.5	(5.1)

Reprinted with permission from Ames BN, Magaw R, Gold LS: Ranking possible carcinogenic hazards. Science 236: 271-280, 1987.

* *Potency of carcinogens:* A number in parentheses indicates a TD₅₀ value not used in HERP calculation because it is the less sensitive species: (-) = negative in cancer test; (+) = positive for carcinogenicity in tests not suitable for calculating a TD₅₀; (?) = not adequately tested for carcinogenicity. TD₅₀ values shown are averages calculated by taking the harmonic mean of the TD₅₀ of the positive tests in that species from the Carcinogenic Potency Database. Results are similar if the lowest TD₅₀ value (most potent) is used instead. For each test the target site with the lowest TD₅₀ value has been used. The average TD₅₀ has been calculated separately for rats and mice, and the more sensitive species is used for calculating the possible hazard. The database, with references to the source of the cancer tests, is complete for tests published through 1984 and for the National Toxicology Program bioassays through June 1986. We have not indicated the route of exposure or target sites or other particulars of each test, although these are reported in the database. *Daily human exposure:* We have tried to use average or reasonable daily intakes to facilitate comparisons. In several cases, such as contaminated well water or factory exposure to EDB, this is difficult to determine; these are assigned the value for the worst levels found. The calculations assume a daily dose for a lifetime; where drugs are normally taken only for a short period, we have bracketed the HERP value. For inhalation exposures, we assume an inhalation of 9600 L per 8 h for the workplace and 10,800 L per 14 h for indoor air at home. *Possible hazard:* The amount of rodent carcinogen indicated under carcinogen dose is divided by 70 kg to give a milligram per kilogram of human exposure, and this human dose is given as the percentage of the TD₅₀ dose in the rodent (mg/kg) to calculate the HERP.

† HERP from carcinogens thought to be nongenotoxic.

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expressed, although the human exposure is likely to be less than daily for a lifetime. The HERP values are not risk assessments, because it is impossible to extrapolate to low doses (see "Error 4"), but provide a way to compare possible hazards of exposures so as to put them in perspective and set priorities (see Table 14a-1).

This analysis suggests that the amounts of pollution humans ingest from pesticide residues or water pollution appear to be trivial relative to the background of natural or traditional (e.g., from cooking food) carcinogens.^{3,26}

Nature's Pesticides ■

Americans ingest in their diet at least 10,000 times more natural pesticides (by weight) than man-made pesticide residues.²⁶ These natural "toxic chemicals" have an enormous variety of chemical structures, appear to be present in all plants, and serve as protection against fungi, insects, and animal predators.^{8,26} Although only a few dozen are found in each plant species, they commonly make up 5% to 10% of the plant's dry weight.²⁶ There has been relatively little interest in the toxicology or carcinogenicity of these compounds until quite recently, although they are by far the main source of "toxic chemicals" ingested by humans.

Although most chemicals tested for carcinogenicity in rodent bioassays are synthetic compounds, the proportion of positive tests is about as high for natural pesticides as for synthetic chemicals. Because more than 99.99% of the pesticides we ingest are "nature's pesticides,"^{3,8,26} our diet is likely to be very high in natural carcinogens. Their concentration is usually in parts per thousand or more, rather than parts per billion, as is usual for synthetic pesticide residues or water pollution.³ The known natural carcinogens in mushrooms, parsley, basil, parsnips, fennel, pepper, celery, figs, mustard, and citrus oil are no doubt just the beginning of the list because so few of nature's pesticides have been tested.^{3,8,26} For example, a recent analysis²⁷ of lima beans showed an array of 23 natural alkaloids (those tested have biocidal activity) that ranged in concentration in stressed plants from 0.2 to 33 parts per thousand fresh weight. None appears to have been tested for carcinogenicity or teratogenicity.

Man-made Pesticide Residues ■

The intake of man-made pesticide residues from food in the United States, including residues of industrial chemicals such as polychlorinated biphenyls (PCBs),

has been estimated by the Food and Drug Administration (FDA). They assayed food for residues of the 70 compounds thought to be of greatest importance.²⁸ The human intake averages about 150 $\mu\text{g}/\text{day}$. Most of this intake (105 μg) is composed of three chemicals (ethylhexyl diphenyl phosphate, malathion, and chlorpropham), shown to be noncarcinogenic in tests in rodents.³ Thus, the intake of carcinogens from residues (45 $\mu\text{g}/\text{day}$ if all the other residues are carcinogenic, which is unlikely) is extremely small relative to the background of natural substances.^{3,26}

The latest figures from the FDA about actual exposures do not include every known man-made pesticide, but represent a reasonable attempt to do so. In a recent National Research Council/National Academy of Sciences (NRC/NAS) report, *Regulating Pesticides in Food*,²⁹ it is suggested that some of the pesticides not covered by the FDA sampling, particularly those used on tomatoes, should have their allowable limits lowered and presumably should be added to the FDA sampling program. Nevertheless, the estimate of 45 μg of possibly carcinogenic pesticide residues consumed in a day is likely to be a reasonable one, as is our conclusion that the possible hazards from these residues are minimal compared to the background of nature's pesticides. For comparison,³ there are about 500 μg of carcinogens in a cup of coffee (hydrogen peroxide and methylglyoxal), 185 μg of carcinogenic formaldehyde in a slice of bread, about 2000 μg of formaldehyde in a cola, 760 μg of carcinogenic estragole in a basil leaf, a gram of burnt material from cooking our food, plus nitrosamines formed in gas ovens.

An alternative to synthetic pesticides is to raise the level of natural plant toxins by breeding. However, it is not clear that this approach, even where feasible, is preferable. One consequence of disproportionate concern about tiny traces of synthetic pesticide residues, such as ethylene dibromide,³ is that plant breeders are developing highly insect-resistant plants, thus creating other risks. Two recent cases are instructive. A major grower introduced a new variety of highly insect-resistant celery into commerce. There was soon a flurry of complaints to the Centers for Disease Control (CDC) from all over the country, because people who handled the celery developed a severe rash when they were subsequently exposed to sunlight. Some detective work revealed that the pest-resistant celery contained 9000 parts per billion (ppb) psoralens (light-activated mutagenic carcinogens) instead of the level of 900 ppb psoralens in normal celery.^{30,31} It is unclear whether other natural pesticides in the celery were increased as well.

Solanine and chaconine (the main natural alkaloids in potatoes) are cholinesterase inhibitors that were

widely introduced into the human diet about 400 years ago with the dissemination of the potato from the Andes. They can be detected in the blood of all potato eaters. Total alkaloids are present in potatoes at a level of 15,000 μg per 200 g potato, which is only about a sixfold safety margin from the toxic level for humans.³ Neither alkaloid has been tested for carcinogenicity. By contrast, the pesticide malathion, the main synthetic organophosphate cholinesterase inhibitor present in our diet (17 $\mu\text{g}/\text{day}$), has been thoroughly tested and is not a carcinogen in rodents. Plant breeders produced an insect-resistant potato that had to be withdrawn from the market because of its acute toxicity to humans, a consequence of higher levels of solanine and chaconine.

There is a tendency for laymen to think of chemicals as being only man-made, and to characterize them as toxic, as if every natural chemical were not also toxic at some dose. Even a recent NRC/NAS report states that "Advances in classical plant breeding . . . offer some promise for nonchemical pest control in the future. Nonchemical approaches will be encouraged by tolerance revocations if more profitable chemical controls are not available. . . ."²⁹ The report was particularly concerned with some pesticides used on tomatoes. Of course, tomatine, one of the alkaloids in tomatoes, is a chemical too, and was introduced from the New World 400 years ago. It has not been tested in rodent cancer bioassays, is present at 36,000 $\mu\text{g}/100$ g tomato, and is orders of magnitude closer to the toxic level than are man-made pesticide residues.

The Idea That Nature Is Benign ■

The notion that evolution has allowed us to cope with the toxic chemicals in the natural world³² is not compelling⁷ for several reasons: First, there is no reason to think that natural selection should eliminate the carcinogenic hazard of a plant toxin that causes cancer past the reproductive age, although there could be selection for resistance to the acute effects of particular carcinogens. For example, aflatoxin, a mold toxin that presumably arose early in evolution, causes cancer in trout, rats, mice, monkeys, and probably people, although the species are not equally sensitive.^{5,33} Many of the common metal salts are carcinogens (e.g., lead, cadmium, beryllium, nickel, chromium, selenium, and arsenic) despite their presence during all of evolution. Second, it is argued by some that humans, as opposed to rats or mice, may have developed resistance to each specific plant toxin or chemical in cooked food.³² This is unlikely, because both rodents and humans have developed many types

of general defenses against the large amounts and enormous variety of nature's pesticides.^{3,8,26} These defenses include the constant shedding of the surface layer of cells of the digestive system, the detoxification of alkylating agents by glutathione transferases, the active excretion of hydrophobic toxins out of liver or intestinal cells, numerous defenses against oxygen radicals, and DNA excision repair. The fact that defenses usually are general, rather than specific for each chemical, makes good evolutionary sense and is supported by various studies. Experimental evidence indicates that these general defenses are effective against both natural and synthetic compounds,³⁴ since basic mechanisms of carcinogenesis are not unique to either. Third, the human diet has changed drastically in the last few thousand years, and most of us are eating recently introduced plants (coffee, potatoes, tomatoes, and kiwi fruit) that our ancestors did not eat. Fourth, the argument that plants contain anticarcinogens which protect us against plant carcinogens is irrelevant: plant antioxidants, the major known type of ingested anticarcinogens, do not distinguish whether oxidant carcinogens are synthetic or natural in origin, and thus help to protect us against both. Fifth, it has been argued that synthetic carcinogens can be synergistic. However, this is also true of natural chemicals and is irrelevant to the argument that synthetic pesticide residues in food or water pollution appear to be a trivial increment over the background of natural carcinogens.

Dioxin Compared to Alcohol and Broccoli ■

Common sense suggests that a chemical pollutant should not be treated as a significant hazard if its possible hazard level is far below that of common food items. Dioxin (TCDD) is a substance of great public concern, because it is an extremely potent carcinogen and teratogen in rodents, yet the doses humans are exposed to are very low relative to the effective level in rodents. TCDD can be compared to alcohol, as an example. Alcohol is an extremely weak carcinogen and teratogen, yet the doses humans are exposed to are very high relative to the effective dose in rodents (or humans). Indeed, alcoholic beverages are the most important known human teratogen, and the effective dose level of alcohol in humans (in milligrams per kilogram) is similar to the level that causes birth defects in mice. By contrast, there is no convincing evidence that TCDD is carcinogenic or teratogenic in man, although it is in rodents. If one compares the teratogenic potential of TCDD to that of alcohol for causing birth defects, after adjusting

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for their potency in rodents,³ then a daily consumption of the Environmental Protection Agency (EPA) "reference dose" (formerly "acceptable dose limit") of TCDD, 6 pg/kg per day, is equivalent in teratogenic potential to the amount of alcohol ingested daily from 1/3000 of a beer, the equivalent of drinking one beer (15 g ethyl alcohol) over a period of 8 years. A daily slice of bread or glass of orange juice contains much more natural alcohol than this.

Alcoholic beverages are clearly carcinogenic in man (at a daily dose of about 5 drinks), although only one of several tests on ethyl alcohol in rats was positive.^{22,23} This test should be replicated as confirmation that ethyl alcohol is the active ingredient, although the evidence for that is fairly strong.²² A comparison of the carcinogenic potential of TCDD with that of alcohol, adjusting for potency in rodents, shows that the equivalence for the TCDD reference dose of 6 pg/kg per day is 1 beer every 5 months. Since the average *per capita* consumption of alcohol in the United States is equivalent to more than one beer per day, the great concern over TCDD at levels in the range of the reference dose seems unreasonable.

The assumption of a worst-case linear dose-response, often used for carcinogens, is not plausible for TCDD, yet extrapolations to man using such assumptions have generated great concern. TCDD binds to a receptor in mammalian cells, the Ah receptor, and the evidence suggests strongly that all of TCDD's effects are mediated through this binding.³⁵ Moreover, a wide variety of natural substances bind to the Ah receptor, and, as far as they have been examined, they have all of the properties of TCDD. A cooked steak contains polycyclic hydrocarbons, which bind to the Ah receptor and mimic TCDD. In addition, our diet contains a variety of flavones and other substances from plants, which bind to the Ah receptor. The most interesting of such substances is indole carbinol (IC), which is present in large amounts in broccoli (500 mg/kg), cabbage, cauliflower, and other members of the *Brassica* family.³⁶ The two substances induce the same set of enzymes.³⁷ When given before aflatoxin or other carcinogens, IC protects against carcinogenesis, as does TCDD.³⁸ However, when it is given after aflatoxin or other carcinogens, IC is a strong promoter of carcinogenesis, as is TCDD.³⁹ This stimulation of carcinogenesis has also been shown for cabbage itself.⁴⁰ When IC is exposed to acid pH (equivalent to that of the stomach), it is converted to a series of dimers and trimers that are similar to TCDD in size and shape, bind to the Ah receptor, and induce the set of TCDD-inducible enzymes, thus mimicking TCDD.^{37,41} The 360 pg/day TCDD EPA reference dose should be compared with 50 million pg of IC per 100 g of broccoli (one

portion); the affinity of the indole derivatives in binding to the Ah receptor is less by a factor of about 8000, suggesting that the broccoli portion might be roughly 20 times the possible hazard. Although these IC derivatives appear to be much more of a possible hazard than TCDD, it is not clear whether, at these low doses, either represents any danger.

Another study⁴² also shows that when sunlight oxidizes tryptophan, a normal amino acid, it converts it to a variety of indoles (similar to the broccoli IC dimers), which bind to the Ah receptor and mimic the action of TCDD. It seems likely that many more of these "natural dioxins" will be discovered in the future.

Water Pollution ■

The possible hazards from carcinogens in contaminated well water (e.g., the Santa Clara, or "Silicon," Valley, in California, and Woburn, Massachusetts) should be compared to the possible hazards of ordinary tap water (see Table 14a-1).³ Of the 35 wells shut down in Santa Clara Valley because of a supposed carcinogenic hazard—low traces of trichloroethylene—only two were of a possible hazard greater than ordinary tap water. Well water is not usually chlorinated and therefore lacks the 83 ppb chloroform present in average chlorinated tap water.³ Water from the most polluted well had a relative hazard that was orders of magnitude less than that for the carcinogens in an equal volume of cola, beer, or wine, or many natural carcinogens in our daily diet. The consumption of tap water is only about 1 or 2 liters/day, and the animal evidence cited³ provides no good reason to expect that chloroform in water or current levels of man-made pollution of water would pose a significant carcinogenic hazard.

The trace amounts of chemicals found in polluted wells should be a negligible cause of birth defects, when compared to the background level of known teratogens such as alcohol. Most agents causing birth defects would also be expected to be harmless at low doses. Important risk factors for birth defects in humans include age of mother, alcohol ingestion, smoking, and rubella virus.

Air Pollution ■

A person inhales about 20,000 liters of air in a day. Thus, even modest contamination of the atmosphere results in inhalation of appreciable doses of a pollutant. Indoor air pollution is, in general, considerably more of a health hazard than outdoor air pollution, partly because of cigarette smoke, formaldehyde, benzene, and radon.^{3,43} The most important indoor

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air pollutant is radon gas.⁴³ Radon is a natural radioactive gas that is present in the soil, gets trapped in houses, and gives rise to radioactive decay products that are known to be carcinogenic in humans.⁴³ It has been estimated that one million homes in the United States have a level of exposure to products of radon decay higher than that received by today's uranium miners. Two particularly contaminated houses had a risk estimated to be equivalent to receiving about 1200 chest x-rays a day. Approximately 10% of the lung cancer in the United States has been tentatively attributed to radon pollution in houses.⁴³ Many of these cancers may be preventable, because the most hazardous houses can be identified and modified to minimize radon contamination.⁴³

General outdoor air pollution is a small risk relative to indoor air pollution or to the pollution inhaled by a smoker: a person breathing Los Angeles smog for a year inhales the same amount of burnt material that a smoker does in one day (two packs).^{3,26} It is difficult for epidemiologists to determine cancer risk from outdoor air pollution because smoking and radon exposure must be accurately controlled.

Cooking Food ■

The cooking of food generates a variety of mutagens and carcinogens. The total amount of browned and burnt material eaten in a typical day is at least several hundred times more than that inhaled from severe outdoor air pollution.²⁶ Nine heterocyclic amines, isolated on the basis of their mutagenicity from proteins or amino acids that were heated in ways that reproduce cooking methods, have now been tested; all have been shown to be potent carcinogens in rodents.^{44,45} Many others are still being isolated and characterized.^{44,45} Three mutagenic nitropyrenes present in diesel exhaust have been shown to be carcinogens,⁴⁶ but the intake of these carcinogenic nitropyrenes from grilled chicken is estimated to be much higher than that from air pollution.^{44,45-47}

Gas flames generate NO₂, which can form both the carcinogenic nitropyrenes^{23,24} and the potentially carcinogenic nitrosamines in food, such as fish, cooked in gas ovens. It seems likely that food cooked in gas ovens may be a major source of dietary nitrosamines and nitropyrenes.

Occupational Exposures ■

Occupational exposures to chemicals are often significant.^{3,48} The potential carcinogenic hazards to US workers has been ranked using the PERP index (analogous to the HERP index,³ except that the Oc-

cupational Safety and Health Administration permitted exposure levels replace actual exposures).⁴⁸ The PERP values differ by more than 100,000-fold. For 12 substances, the permitted levels for workers are greater than 10% of the rodent TD₅₀ dose. Priority attention should be given to reduction of the allowable worker exposures that appear most hazardous in the PERP ranking.

Error 4: Extrapolating Risks Without Understanding Mechanisms of Carcinogenesis ■

Rodent Carcinogenesis Tests ■

It is prudent to assume that if a chemical is a carcinogen in rats and mice at the MTD, it is also likely to be a carcinogen in humans at the MTD. However, until we understand more about mechanisms of carcinogenesis, we cannot reliably predict risk to humans at low doses, often hundreds of thousands of times below the dose where an effect is observed in rodents. Thus, quantitative risk assessment currently is not scientifically possible.^{3,4,7}

Carcinogenesis Mechanisms and the Dose-Response Curve ■

The study of mechanisms of carcinogenesis is a rapidly developing field and is essential for rational risk assessment. Both mutations and cell proliferation (i.e., promotion) are required in carcinogenesis.^{3,49,50} There is an enormous spontaneous rate of damage to DNA from endogenous oxidants, which we have discussed in relation to cancer and aging.^{51,52} There is also a basal spontaneous rate for cell proliferation in some organs, e.g., colon, but not others, e.g., liver.^{10,11} Thus, increasing either mutation or cell proliferation should be carcinogenic. Additional complications are that several mutations appear necessary for carcinogenesis, and there are many layers of defense against carcinogens. These considerations suggest a sublinear dose-response relationship, which is consistent with both the animal and human data,³⁻⁷ and indicate that multiplicative interactions will be common in human cancer causation. Administering chemicals in cancer tests at the MTD commonly causes cell proliferation and inflammatory reactions.^{3,49,50,53} Inflammatory reactions with release of oxygen radicals from phagocytic cells are equivalent to irradiating the tissue. If a chemical is nonmutagenic and its carcinogenicity is due to cell proliferation resulting from near-toxic doses, one might commonly expect a threshold.^{3,49,50}

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The fact that high doses of a chemical cause tumors does not necessarily mean that small doses will. Most chemicals may, in fact, be harmless at low levels. A list of carcinogens is not enough. The main rule in toxicology is that the "dose makes the poison:" at some level, every chemical becomes toxic, but there are safe levels below that. A scientific consensus evolved in the 1970s that we should treat carcinogens differently—that we should assume that even low doses could possibly cause some harm, even though we do not have the methods to measure effects at low levels. This idea evolved because most carcinogens appeared to be mutagens (agents that damage the DNA). The precedent of radiation, which is both a mutagen and carcinogen, gave credence to the idea that there could be effects of chemicals even at low doses. Some recent work on radiation, however, suggests that low doses may be of no harm or even protective.^{54,54a,55,55a}

The idea that most of the classical carcinogens were mutagens that damaged DNA (about 90% in our studies),^{56,57} along with work on oncogenes,⁵⁸ reinforced the mutagen-carcinogen connection. However, in recent years there has been a change in the picture. About half of all chemicals tested in animals are carcinogens, but only about half of these appear to be mutagenic. It is now standard in cancer tests to be rigorous about giving the MTD of the chemical for the lifetime of the animal, and this may be a factor. It seems quite reasonable that nonmutagens cause cancer, and mutagens in part cause cancer, because dosing at the MTD accelerates the promotional step of carcinogenesis.^{59,60}

Promotion, or cell proliferation, can also be accelerated by viruses, such as the human carcinogenic hepatitis B viruses, a major cause of liver cancer around the world,²⁵ or human papilloma virus 16 (HPV-16), a contributor to cancer of the cervix.²⁴ Both cause chronic cell killing and consequent cell proliferation. Promotion can also be induced by hormones, which cause cell proliferation. Hormones appear to be major risk factors for certain human cancers, such as breast cancer, and appear to only increase cell proliferation.¹⁰ The promotional step of cancer causation can also be accelerated by chemicals. Alcohol, for example, causes cirrhosis of the liver, leading to cancer. The classical chemical promoters, such as phenobarbital and tetradecanoyl phorbol acetate, would be expected to be, and are, carcinogens when tested in thorough animal tests at the MTD.⁶⁰ There is increasing evidence to show that low doses of promoters are not active.^{49,50} It seems likely, therefore, that a high percentage of all chemicals, both man-made and natural, will cause cell proliferation at the MTD and be classified as carcinogens, but most of

these may be acting as promoters and therefore may not be of interest at doses much below the toxic dose.³

Thus, the common water pollutants, such as trichloroethylene (TCE) and perchloroethylene (PCE), are unlikely to be of public health significance because [a] the amounts we are exposed to in pollution are trivial relative to the background of natural carcinogens, and [b] the evidence is that they are likely to be acting as promoters, not as DNA-damaging carcinogens, and therefore should be ignored at low concentrations.

Error 5: Storks Bring Babies, and Pollution Causes Cancer and Birth Defects ■

The number of storks in Europe has been decreasing for decades. At the same time, the European birth rate has also been decreasing. We would be foolish to accept this high correlation⁶¹ as evidence that storks bring babies. The science of epidemiology tries to sort out from the myriad chance correlations those that are meaningful and involve cause and effect. However, it is not easy to obtain convincing evidence by epidemiologic methods because of inherent methodologic difficulties.⁹ There are many sources of bias in observational data, and chance variation is also an important factor. For example, because there are so many different types of cancer or birth defects, by chance alone one might expect some of them to occur at a high frequency in a small community. Toxicology provides evidence to help decide whether an observed correlation might be causal or accidental.

There is no convincing evidence from epidemiology or toxicology that pollution is a significant source of birth defects and cancer. For example, the epidemiologic studies of Love Canal, dioxin in Agent Orange,^{62,63} Contra Costa County refineries,^{64,65} Silicon Valley,⁶⁶ Woburn,^{3,8} and the use of DDT provide no convincing evidence that pollution was the cause of human harm in any of these well-publicized exposures. Even in Love Canal, where people were living next to a toxic waste dump, the epidemiologic evidence for an effect on public health is equivocal. Analysis of the toxicology data on many of these cases suggests that the amounts of the chemicals involved were much too low relative to the background of natural and traditional carcinogens to be credible sources of increased cancer risk to humans.³ A comparative analysis of teratogens using a HERP-type index expressing the human exposure level as a percentage of the dose level effective in rodents would be of interest (see Error 3), but this has not been done in a systematic way.

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Environmental exposure to TCE, PCE, trichloroethane, ethylene dibromide (EDB), and other pollutants is thousands of times lower than the exposure to these same agents in the workplace.^{3,48} Thus, if parts per billion of these pollutants were causing cancer or birth defects, one might expect to see an effect in the workplace. The studies on these chemicals to date do not provide any evidence for a causal association,³³ although epidemiologic studies are inherently insensitive. Historically, cases of cancer due to workplace exposure resulted mainly from exposures to chemicals at very high levels. For example, the permissible and actual EDB levels for workers were shockingly high (see Table 14a-1). (I testified in California in 1981 that our calculations showed that the workers were allowed to breathe in a dose higher than the TD₅₀ in rats.) California lowered the permissible worker exposure by more than 100-fold. Despite the fact that the epidemiology of EDB in highly exposed workers does not show any significant effect, the uncertainties in our knowledge make it important to have strict rules because workers can be exposed to extremely high doses.

Error 6: Technology Is Doing Us In ■

Modern technologies are almost always replacing older, more hazardous technologies. The reason that billions of pounds of TCE (one of the most important industrial nonflammable solvents) and PCE (the main dry-cleaning solvent in the United States) are used is that they have low toxicity and are not flammable. Is it advisable to go back to the age when industry and dry cleaners used flammable solvents and fires were frequent? Eliminating a carcinogen may not always be a good idea. For example, EDB, the main fumigant in the United States before it was banned, was present in trivial amounts in our food: the average daily intake was about one-tenth of the possible carcinogenic hazard of the aflatoxin in the average peanut butter sandwich, a trivial risk in itself (see Table 14a-1).³ Elimination of fumigation results in insect infestation and subsequent contamination of grain by carcinogen-producing molds. This might result in a regression in public health, not an advance, and would also greatly increase costs. The proposed alternatives, such as irradiating food, could possibly be more hazardous than EDB, as well as more expensive. Similarly, modern pesticides replaced more hazardous substances such as lead arsenate, one of the major pesticides before the modern era. Lead and arsenic are both natural, highly toxic, and carcinogenic. Pesticides have increased crop yields and brought down the price of foods, a major public health advance.

Every living thing and every industry "pollutes" to some extent. How much does society wish to spend to get the last part per billion of TCE out of the wells in Silicon Valley, or to remove PCE from dry-cleaning plants? We are currently spending enormous amounts of money trying to eliminate lower and lower levels of pollution; one estimate is about \$80 billion annually.⁷ The fact that scientists have developed methods to measure parts per billion (one part per billion is equivalent to one person in all of China) of carcinogens and are developing methods to measure parts per trillion does not mean that significant pollution is increasing, or that the pollution found is a cause of human harm.

Conclusion ■

Everyone knows that spending all of one's effort on trivia without focusing on important problems is counterproductive. If we divert too much of our attention to traces of pollution and away from important public health concerns such as smoking (400,000 deaths per year), alcohol (100,000 deaths per year), unbalanced diets (*e.g.*, too much saturated fat and cholesterol), acquired immunodeficiency syndrome, radioactive radon in our homes, and high-dose occupational exposure, we do not improve public health, and the important hazards are lost in the confusion. It is the inexorable progress of modern technology and scientific research that will continue to provide the knowledge resulting in steady progress to decrease cancer and birth defects and lengthen life span.

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