Ranking Possible Carcinogenic Hazards

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This review discusses reasons why animal cancer tests cannot be used to predict absolute human risks. Such tests, however, may be used to indicate that some chemicals might be of greater concern than others. Possible hazards to humans from a variety of rodent carcinogens are ranked by an index that relates the potency of each carcinogen in rodents to the exposure in humans. This ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances, though one cannot say whether these natural exposures are likely to be of major or minor importance.

EPIDEMIOLOGISTS ESTIMATE THAT AT LEAST 70% OF HUMAN cancer would, in principle, be preventable if the main risk and antirisk factors could be identified (*1*). This is because the incidence of specific types of cancer differs markedly in different parts of the world where people have different life-styles. For example, colon and breast cancer, which are among the major types of cancer in the United States, are quite rare among Japanese in Japan, but not among Japanese-Americans. Epidemiologists are providing important clues about the specific causes of human cancer, despite inherent methodological difficulties. They have identified tobacco as an avoidable cause of about 30% of all U.S. cancer deaths and of an even larger number of deaths from other causes (*1, 2*). Less specifically, dietary factors, or their absence, have been suggested in many studies to contribute to a substantial proportion of cancer deaths, though the intertwined risk and antirisk factors are being identified only slowly (*1, 3, 4*). High fat intake may be a major contributor to colon cancer, though the evidence is not as definitive as that for the role of saturated fat in heart disease or of tobacco in lung cancer. Alcoholic beverage consumption, particularly by smokers, has been estimated to contribute to about 3% of U.S. cancer deaths (*1*) and to an even larger number of deaths from other causes. Progress in prevention has been made for some occupational factors, such as asbestos, to which workers used to be heavily exposed, with delayed effects that still contribute to about 2% of U.S. cancer deaths (*1, 5*). Prevention may also become possible for hormone-related cancers such as breast cancer (*1, 6*), or virus-related cancers such as liver cancer (hepatitis B) and cancer of the cervix (papilloma virus HPV16) (*1, 7*).

Animal bioassays and in vitro studies are also providing clues as to which carcinogens and mutagens might be contributing to human cancer. However, the evaluation of carcinogenicity in rodents is expensive and the extrapolation to humans is difficult (*8–11*). We will use the term "possible hazard" for estimates based on rodent cancer tests and "risk" for those based on human cancer data (*10*).

Extrapolation from the results of rodent cancer tests done at high doses to effects on humans exposed to low doses is routinely attempted by regulatory agencies when formulating policies attempting to prevent future cancer. There is little sound scientific basis for this type of extrapolation, in part due to our lack of knowledge about mechanisms of cancer induction, and it is viewed with great unease by many epidemiologists and toxicologists (*5, 9–11*). Nevertheless, to be prudent in regulatory policy, and in the absence of good human data (almost always the case), some reliance on animal cancer tests is unavoidable. The best use of them should be made even though few, if any, of the main avoidable causes of human cancer have typically been the types of man-made chemicals that are being tested in animals (*10*). Human cancer may, in part, involve agents such as hepatitis B virus, which causes chronic inflammation; changes in hormonal status; deficiencies in normal protective factors (such as selenium or β-carotene) against endogenous carcinogens (*12*); lack of other anticarcinogens (such as dietary fiber or calcium) (*4*); or dietary imbalances such as excess consumption of fat (*3, 4, 12*) or salt (*13*).

There is a need for more balance in animal cancer testing to emphasize the foregoing factors and natural chemicals as well as synthetic chemicals (*12*). There is increasing evidence that our normal diet contains many rodent carcinogens, all perfectly natural or traditional (for example, from the cooking of food) (*12*), and that no human diet can be entirely free of mutagens or agents that can be carcinogenic in rodent systems. We need to identify the important causes of human cancer among the vast number of minimal risks. This requires knowledge of both the amounts of a substance to which humans are exposed and its carcinogenic potency.

Animal cancer tests can be analyzed quantitatively to give an estimate of the relative carcinogenic potencies of the chemicals tested. We have previously published our Carcinogenic Potency Database, which showed that rodent carcinogens vary in potency by more than 10 millionfold (*14*).

This article attempts to achieve some perspective on the plethora of possible hazards to humans from exposure to known rodent carcinogens by establishing a scale of the possible hazards for the amounts of various common carcinogens to which humans might be chronically exposed. We view the value of our calculations not as providing a basis for absolute human risk assessment, but as a guide to priority setting. One problem with this type of analysis is that few of the many natural chemicals we are exposed to in very large amounts (relative to synthetic chemicals) have been tested in animals for carcinogenicity. Thus, our knowledge of the background levels of human exposure to animal carcinogens is fragmentary, biased in favor of synthetic chemicals, and limited by our lack of knowledge of human exposures.

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Ranking of Possible Carcinogenic Hazards

Since carcinogens differ enormously in potency, a comparison of possible hazards from various carcinogens ingested by humans must take this into account. The measure of potency that we have developed, the TD_{50}, is the daily dose rate (in milligrams per kilogram) to halve the percent of tumor-free animals by the end of a standard lifetime (*14*). Since the TD_{50} (analogous to the LD_{50}) is a dose rate, the lower the TD_{50} value the more potent the carcinogen. To calculate our index of possible hazard we express each human exposure (daily lifetime dose in milligrams per kilogram) as a percentage of the rodent TD_{50} dose (in milligrams per kilogram) for each carcinogen. We call this percentage HERP [*H*uman *E*xposure dose/*R*odent *P*otency dose]. The TD_{50} values are taken from our ongoing Carcinogenic Potency Database (currently 3500 experiments on 975 chemicals), which reports the TD_{50} values estimated from experiments in animals (*14*). Human exposures have been estimated from the literature as indicated. As rodent data are all calculated on the basis of lifetime exposure at the indicated daily dose rate (*14*), the human exposure data are similarly expressed as lifelong daily dose rates even though the human exposure is likely to be less than daily for a lifetime.

It would be a mistake to use our HERP index as a direct estimate of human hazard. First, at low dose rates human susceptibility may differ systematically from rodent susceptibility. Second, the general shape of the dose-response relationship is not known. A linear dose response has been the dominant assumption in regulating carcinogens for many years, but this may not be correct. If the dose responses are not linear but are actually quadratic or hockey-stick shaped or show a threshold, then the actual hazard at low dose rates might be much less than the HERP values would suggest. An additional difficulty is that it may be necessary to deal with carcinogens that differ in their mechanisms of action and thus in their dose-response relationship. We have therefore put an asterisk next to HERP values for carcinogens that do not appear to be active through a genotoxic (DNA damaging or mutagenic) mechanism (*15*) so that comparisons can be made within the genotoxic or nongenotoxic classes.

Table 1 presents our HERP calculations of possible cancer hazards in order to compare them within several categories so that, for example, pollutants of possible concern can be compared to natural carcinogens in the diet. A convenient reference point is the possible hazard from the carcinogen chloroform in a liter of average (U.S.) chlorinated tap water, which is close to a HERP of 0.001%. Chloroform is a by-product of water chlorination, which protects us from pathogenic viruses and bacteria.

Contaminated water. The possible hazards from carcinogens in contaminated well water [for example, Santa Clara ("Silicon") Valley, California, or Woburn, Massachusetts] should be compared to the possible hazard of ordinary tap water (Table 1). Of 35 wells shut down in Santa Clara Valley because of their supposed carcinogenic hazard, only two have HERP values greater than ordinary tap water. Well water is not usually chlorinated and typically lacks the chloroform present in chlorinated tap water. Water from the most polluted well (HERP = 0.004% per liter for trichloroethylene), as indicated in Table 1, has a HERP value orders of magnitude less than for the carcinogens in an equal volume of cola, beer, or wine. Its HERP value is also much lower than that of many of the common natural foods that are listed in Table 1, such as the average peanut butter sandwich. Caveats for any comparisons are given below. Since the consumption of tap water is only about 1 or 2 liters per day, the animal evidence provides no good reason to expect that chlorination of water or current levels of man-made pollution of water pose a significant carcinogenic hazard.

Pesticide residues. Intake of man-made pesticide residues from food in the United States, including residues of industrial chemicals such as polychlorinated biphenyls (PCBs), averages about 150 μg/day. Most (105 μg) of this intake is composed of three chemicals (ethylhexyl diphenyl phosphate, malathion, and chlorpropham) shown to be noncarcinogenic in tests in rodents (*16*). A carcinogenic pesticide residue in food of possible concern is DDE, the principal metabolite (>90%) of DDT (*16*). The average U.S. daily intake of DDE from DDT (HERP = 0.0003%) is equivalent to the HERP of the chloroform in one glass of tap water and thus appears to be insignificant compared to the background of natural carcinogens in our diet (Table 1). Even daily consumption of 100 times the average intake of DDE/DDT or PCBs would produce a possible hazard that is small compared to other common exposures shown in Table 1.

Nature's pesticides. We are ingesting in our diet at least 10,000 times more by weight of natural pesticides than of man-made pesticide residues (*12*). These are natural "toxic chemicals" that have an enormous variety of chemical structures, appear to be present in all plants, and serve to protect plants against fungi, insects, and animal predators (*12*). Though only a few are present in each plant species, they commonly make up 5 to 10% of the plant's dry weight (*12*). 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. Only a few dozen of the thousands present in the human diet have been tested in animal bioassays, and only some of these tests are adequate for estimating potency in rodents (*14*). A sizable proportion of those that have been tested are carcinogens, and many others have been shown to be mutagens (*12*), so it is probable that many more will be found to be carcinogens if tested. Those shown in Table 1 are: estragole (HERP = 0.1% for a daily 1 g of dried basil), safrole (HERP = 0.2% for a daily natural root beer), symphytine (a pyrrolizidine alkaloid, 0.03% for a daily cup of comfrey tea), comfrey tablets sold in health food stores (6.2% for a daily dose), hydrazines in mushrooms (0.1% for one daily raw mushroom), and allyl isothiocyanate (0.07% for a daily 5 g of brown mustard).

Plants commonly produce very much larger amounts of their natural toxins when damaged by insects or fungi (*12*). For example, psoralens, light-activated carcinogens in celery, increase 100-fold when the plants are damaged by mold and, in fact, can cause an occupational disease in celery-pickers and in produce-checkers at supermarkets (*12, 17*).

Molds synthesize a wide variety of toxins, apparently as antibiotics in the microbiological struggle for survival: over 300 mycotoxins have been described (*18*). They are common pollutants of human food, particularly in the tropics. A considerable percentage of those tested have been shown to be mutagens and carcinogens: some, such as aflatoxin and sterigmatocystin, are among the most potent known rodent carcinogens. The potency of aflatoxin in different species varies widely; thus, a bias may exist as the HERP uses the most sensitive species. The aflatoxin content of U.S. peanut butter averages 2 ppb, which corresponds to a HERP of 0.03% for the peanut butter in an average sandwich (Table 1). The Food and Drug Administration (FDA) allows ten times this level (HERP = 0.3%), and certain foods can often exceed the allowable limit (*18*). Aflatoxin contaminates wheat, corn (perhaps the main source of dietary aflatoxin in the United States), and nuts, as well as a wide variety of stored carbohydrate foodstuffs. A carcinogenic, though less potent, metabolite of aflatoxin is found in milk from cows that eat moldy grain.

There is epidemiologic evidence that aflatoxin is a human carcinogen. High intake in the tropics is associated with a high rate of liver cancer, at least among those chronically infected with the hepatitis B

virus (*19, 20*). Considering the potency of those mold toxins that have been tested and the widespread contamination of food with molds, they may represent the most significant carcinogenic pollution of the food supply in developing countries. Such pollution is much less severe in industrialized countries, due to refrigeration and modern techniques of agriculture and storage, including use of synthetic pesticides and fumigants.

Preparation of foods and beverages can also produce carcinogens. Alcohol has been shown to be a human carcinogen in numerous epidemiologic studies (*1, 21*). Both alcohol and acetaldehyde, its

Table 1. Ranking possible carcinogenic hazards. *Potency of carcinogens*: A number in parentheses indicates a TD_{50} value not used in HERP calculation because it is the less sensitive species; (−) = negative in cancer test. (+) = positive for carcinogenicity in test(s) not suitable for calculating a TD_{50}; (?) = is not adequately tested for carcinogenicity. TD_{50} values shown are averages calculated by taking the harmonic mean of the TD_{50}'s of the positive tests in that species from the Carcinogenic Potency Database. Results are similar if the lowest TD_{50} value (most potent) is used instead. For each test the target site with the lowest TD_{50} value has been used. The average TD_{50} 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 (*14*). 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, and we give the value for the worst found and indicate pertinent information in the References and Notes. The calculations assume a daily dose for a lifetime; where drugs are normally taken for only a short period we have bracketed the HERP value. For inhalation exposures we assume an inhalation of 9,600 liters per 8 hours for the workplace and 10,800 liters per 14 hours 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 TD_{50} dose in the rodent (in milligrams per kilogram) to calculate the *H*uman *E*xposure/*R*odent *P*otency index (HERP).

Possible hazard: HERP (%)	Daily human exposure	Carcinogen dose per 70-kg person	Potency of carcinogen: TD_{50} (mg/kg)		References
			Rats	Mice	
		Environmental pollution			
0.001*	Tap water, 1 liter	Chloroform, 83 μg (U.S. average)	(119)	90	*96*
0.004*	Well water, 1 liter contaminated (worst well in Silicon Valley)	Trichloroethylene, 2800 μg	(−)	941	*97*
0.0004*	Well water, 1 liter contaminated, Woburn	Trichloroethylene, 267 μg	(−)	941	*98*
0.0002*		Chloroform, 12 μg	(119)	90	
0.0003*		Tetrachloroethylene, 21 μg	101	(126)	
0.008*	Swimming pool, 1 hour (for child)	Chloroform, 250 μg (average pool)	(119)	90	*99*
0.6	Conventional home air (14 hour/day)	Formaldehyde, 598 μg	1.5	(44)	*100*
0.004		Benzene, 155 μg	(157)	53	
2.1	Mobile home air (14 hour/day)	Formaldehyde, 2.2 mg	1.5	(44)	*28*
		Pesticide and other residues			
0.0002*	PCBs: daily dietary intake	PCBs, 0.2 μg (U.S. average)	1.7	(9.6)	*101*
0.0003*	DDE/DDT: daily dietary intake	DDE, 2.2 μg (U.S. average)	(−)	13	*16*
0.0004	EDB: daily dietary intake (from grains and grain products)	Ethylene dibromide, 0.42 μg (U.S. average)	1.5	(5.1)	*102*
		Natural pesticides and dietary toxins			
0.003	Bacon, cooked (100 g)	Dimethylnitrosamine, 0.3 μg	(0.2)	0.2	*40*
0.006		Diethylnitrosamine, 0.1 μg	0.02	(+)	
0.003	Sake (250 ml)	Urethane, 43 μg	(41)	22	*24*
0.03	Comfrey herb tea, 1 cup	Symphytine, 38 μg (750 μg of pyrrolizidine alkaloids)	1.9	(?)	*103*
0.03	Peanut butter (32 g; one sandwich)	Aflatoxin, 64 ng (U.S. average, 2 ppb)	0.003	(+)	*18*
0.06	Dried squid, broiled in gas oven (54 g)	Dimethylnitrosamine, 7.9 μg	(0.2)	0.2	*37*
0.07	Brown mustard (5 g)	Allyl isothiocyanate, 4.6 mg	96	(−)	*47*
0.1	Basil (1 g of dried leaf)	Estragole, 3.8 mg	(?)	52	*48*
0.1	Mushroom, one raw (15 g) (*Agaricus bisporus*)	Mixture of hydrazines, and so forth	(?)	20,300	*104*
0.2	Natural root beer (12 ounces; 354 ml) (now banned)	Safrole, 6.6 mg	(436)	56	*105*
0.008	Beer, before 1979 (12 ounces; 354 ml)	Dimethylnitrosamine, 1 μg	(0.2)	0.2	*38*
2.8*	Beer (12 ounces; 354 ml)	Ethyl alcohol, 18 ml	9110	(?)	*23*
4.7*	Wine (250 ml)	Ethyl alcohol, 30 ml	9110	(?)	*23*
6.2	Comfrey-pepsin tablets (nine daily)	Comfrey root, 2700 mg	626	(?)	*103*
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)	*44*
0.06*	Diet Cola (12 ounces; 354 ml)	Saccharin, 95 mg	2143	(−)	*106*
		Drugs			
[0.3]	Phenacetin pill (average dose)	Phenacetin, 300 mg	1246	(2137)	*51*
[5.6]	Metronidazole (therapeutic dose)	Metronidazole, 2000 mg	(542)	306	*107*
[14]	Isoniazid pill (prophylactic dose)	Isoniazid, 300 mg	(150)	30	*108*
16*	Phenobarbital, one sleeping pill	Phenobarbital, 60 mg	(+)	5.5	*50*
17*	Clofibrate (average daily dose)	Clofibrate, 2000 mg	169	(?)	*52*
		Occupational exposure			
5.8	Formaldehyde: Workers' average daily intake	Formaldehyde, 6.1 mg	1.5	(44)	*109*
140	EDB: Workers' daily intake (high exposure)	Ethylene dibromide, 150 mg	1.5	(5.1)	*55*

*Asterisks indicate HERP from carcinogens thought to be nongenotoxic.

major metabolite, are carcinogens in rats (*22, 23*). The carcinogenic potency of ethyl alcohol in rats is remarkably low (*23*), and it is among the weakest carcinogens in our database. However, human intake of alcohol is very high (about 18 g per beer), so that the possible hazards shown in Table 1 for beer and wine are large (HERP = 2.8% for a daily beer). The possible hazard of alcohol is enormous relative to that from the intake of synthetic chemical residues. If alcohol (*20*), trichloroethylene, DDT, and other presumptive nongenotoxic carcinogens are active at high doses because they are tumor promoters, the risk from low doses may be minimal.

Other carcinogens are present in beverages and prepared foods. Urethane (ethyl carbamate), a particularly well-studied rodent carcinogen, is formed from ethyl alcohol and carbamyl phosphate during a variety of fermentations and is present in Japanese sake (HERP = 0.003%), many types of wine and beer, and in smaller amounts in yogurt and bread (*24*). Another fermentation product, the dicarbonyl aldehyde methylglyoxal, is a potent mutagen and was isolated as the main mutagen in coffee (about 250 μg in one cup). It was recently shown to be a carcinogen, though not in a test suitable for calculating a TD_{50} (*25*). Methylglyoxal is also present in a variety of other foods, such as tomato puree (*25, 26*). Diacetyl (2,3-butanedione), a closely related dicarbonyl compound, is a fermentation product in wine and a number of other foods and is responsible for the aroma of butter. Diacetyl is a mutagen (*27*) but has not been tested for carcinogenicity.

Formaldehyde, another natural carcinogenic and mutagenic aldehyde, is also present in many common foods (*22, 26–28*). Formaldehyde gas caused cancer only in the nasal turbinates of the nose-breathing rodents and even though formaldehyde is genotoxic, the dose response was nonlinear (*28, 29*). Hexamethylenetetramine, which decomposes to formaldehyde in the stomach, was negative in feeding studies (*30*). The effects of oral versus inhalation exposure for formaldehyde remain to be evaluated more thoroughly.

As formaldehyde is almost ubiquitous in foods, one can visualize various formaldehyde-rich scenarios. Daily consumption of shrimp (HERP = 0.09% per 100 g) (*31*), a sandwich (HERP of two slices of bread = 0.4%) (*22*), a cola (HERP = 2.7%) (*32*), and a beer (HERP = 0.2%) (*32*) in various combinations could provide as much formaldehyde as living in some mobile homes (HERP = 2.1%; Table 1). Formaldehyde is also generated in animals metabolically, for example, from methoxy compounds that humans ingest in considerable amounts from plants. The level of formaldehyde reported in normal human blood is strikingly high (about 100 μ*M* or 3000 ppb) (*33*) suggesting that detoxification mechanisms are important.

The cooking of food generates a variety of mutagens and carcinogens. Nine heterocyclic amines, isolated on the basis of their mutagenicity from proteins or amino acids that were heated in ways that occur in cooking, have now been tested; all have been shown to be potent carcinogens in rodents (*34*). Many others are still being isolated and characterized (*34*). An approximate HERP of 0.02% has been calculated by Sugimura *et al.* for the daily intake of these nine carcinogens (*34*). Three mutagenic nitropyrenes present in diesel exhaust have now been shown to be carcinogens (*35*), but the intake of these carcinogenic nitropyrenes has been estimated to be much higher from grilled chicken than from air pollution (*34, 36*). 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 air pollution (*12*).

Gas flames generate NO_2, which can form both the carcinogenic nitropyrenes (*35, 36*) and the potently carcinogenic nitrosamines in food cooked in gas ovens, such as fish or squid (HERP = 0.06%; Table 1) (*37*). We suspect that food cooked in gas ovens may be a major source of dietary nitrosamines and nitropyrenes, though it is not clear how significant a risk these pose. Nitrosamines were ubiquitous in beer and ale (HERP = 0.008%) and were formed from NO_2 in the gas flame–heated air used to dry the malt. However, the industry has switched to indirect heating, which resulted in markedly lower levels (<1 ppb) of dimethylnitrosamine (*38*). The dimethylnitrosamine found in human urine is thought to be formed in part from NO_2 inhaled from kitchen air (*39*). Cooked bacon contains several nitrosamines (HERP = 0.009%) (*40*).

Oxidation of fats and vegetable oils occurs during cooking and also spontaneously if antioxidant levels are low. The result is the formation of peroxides, epoxides, and aldehydes, all of which appear to be rodent carcinogens (*8, 12, 27*). Fatty acid hydroperoxides (present in oxidized oils) and cholesterol epoxide have been shown to be rodent carcinogens (though not in tests suitable for calculating a TD_{50}). Dried eggs contain about 25 ppm of cholesterol epoxide (a sizable amount), a result of the oxidation of cholesterol by the NO_2 in the drying air that is warmed by gas flames (*12*).

Normal oxidation reactions in fruit (such as browning in a cut apple) also involve production of peroxides. Hydrogen peroxide is a mutagenic rodent carcinogen that is generated by oxidation of natural phenolic compounds that are quite widespread in edible plants. A cup of coffee contains about 750 μg of hydrogen peroxide (*25*); however, since hydrogen peroxide is a very weak carcinogen (similar in potency to alcohol), the HERP for drinking a daily cup of coffee would be very low [comparable to DDE/DDT, PCBs, or ethylene dibromide (EDB) dietary intakes]. Hydrogen peroxide is also generated in our normal metabolism; human blood contains about 5 μ*M* hydrogen peroxide and 0.3 μ*M* of the cholesterol ester of fatty acid hydroperoxide (*41*). Endogenous oxidants such as hydrogen peroxide may make a major contribution to cancer and aging (*42*).

Caloric intake, which could be considered the most striking rodent carcinogen ever discovered, is discussed remarkably little in relation to human cancer. It has been known for about 40 years that increasing the food intake in rats and mice by about 20% above optimal causes a remarkable decrease in longevity and a striking increase in endocrine and mammary tumors (*43*). In humans, obesity (associated with high caloric intake) leads to increased levels of circulating estrogens, a significant cause of endometrial and gall bladder cancer. The effects of moderate obesity on other types of human cancer are less clear (*1*).

Food additives are currently screened for carcinogenicity before use if they are synthetic compounds. AF-2 (HERP = 0.0002%), a food preservative, was banned in Japan (*44*). Saccharin (HERP = 0.06%) is currently used in the United States (the dose-response in rats, however, is clearly sublinear) (*45*). The possible hazard of diethylstilbestrol residues in meat from treated farm animals seems miniscule relative to endogenous estrogenic hormones and plant estrogens (*46*). Some natural carcinogens are also widely used as additives, such as allyl isothiocyanate (*47*), estragole (*48*), and alcohol (*23*).

Air pollution. A person inhales about 20,000 liters of air in a day; thus, even modest contamination of the atmosphere can result in inhalation of appreciable doses of a pollutant. This can be seen in the possible hazard in mobile homes from formaldehyde (HERP = 2.1%) or in conventional homes from formaldehyde (HERP = 0.6%) or benzene (HERP = 0.004%; Table 1). Indoor air pollution is, in general, worse than outdoor air pollution, partly because of cigarette smoke. The most important indoor air pollutant may be radon gas. 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 for humans (*49*). It has been estimated that in 1 million homes in the United States the level of exposure to products of radon decay may be higher than that

received by today's uranium miners. Two particularly contaminated houses were found that had a risk estimated to be equivalent to receiving about 1200 chest x-rays a day (*49*). Approximately 10% of the lung cancer in the United States has been tentatively attributed to radon pollution in houses (*49*). Many of these cancers might be preventable since the most hazardous houses can be identified and modified to minimize radon contamination.

General outdoor air pollution appears to be a small risk relative to the pollution inhaled by a smoker: one must breathe Los Angeles smog for a year to inhale the same amount of burnt material that a smoker (two packs) inhales in a day (*12*), though air pollution is inhaled starting from birth. It is difficult to determine cancer risk from outdoor air pollution since epidemiologists must accurately control for smoking and radon.

Some common drugs shown in Table 1 give fairly high HERP percentages, primarily because the dose ingested is high. However, since most medicinal drugs are used for only short periods while the HERP index is a daily dose rate for a lifetime, the possible hazard would usually be markedly less. We emphasize this in Table 1 by bracketing the numbers for these shorter exposures. Phenobarbital (HERP = 16%) was investigated thoroughly in humans who had taken it for decades, and there was no convincing evidence that it caused cancer (*50*). There is evidence of increased renal cancer in long-term human ingestion of phenacetin, an analgesic (*51*). Acetaminophen, a metabolite of phenacetin, is one of the most widely used over-the-counter pain killers. Clofibrate (HERP = 17%) is used as a hypolipidemic agent and is thought to be carcinogenic in rodents because it induces hydrogen peroxide production through peroxisome proliferation (*52*).

Occupational exposures can be remarkably high, particularly for volatile carcinogens, because about 10,000 liters of air are inhaled in a working day. For formaldehyde, the exposure to an average worker (HERP = 5.8%) is higher than most dietary intakes. For a number of volatile industrial carcinogens, the ratio of the permitted exposure limit [U.S. Occupational Safety and Health Administration (OSHA)] in milligrams per kilogram to the TD_{50} has been calculated; several are close to the TD_{50} in rodents and about two-thirds have permitted HERP values >1% (*53*). The possible hazard estimated for the actual exposure levels of the most heavily exposed EDB workers is remarkably high, HERP = 140% (Table 1). Though the dose may have been somewhat overestimated (*54*), it was still comparable to the dose causing cancer in half the rodents. An epidemiologic study of these heavily exposed EDB workers who inhaled EDB for over a decade did not show any increase in cancer, though because of the limited duration of exposure and the relatively small numbers of people monitored the study would not have detected a small effect (*54, 55*). OSHA still permits exposures above the TD_{50} level. California, however, lowered the permitted level over 100-fold in 1981. In contrast with these heavy workplace exposures, the Environmental Protection Agency (EPA) has banned the use of EDB for fumigation because of the residue levels found in grain (HERP = 0.0004%).

Uncertainties in Relying on Animal Cancer Tests for Human Prediction

Species variation. Though we list a possible hazard if a chemical is a carcinogen in a rat but not in a mouse (or vice versa), this lack of agreement raises the possibility that the risk to humans is nonexistent. Of 392 chemicals in our database tested in both rats and mice, 226 were carcinogens in at least one test, but 96 of these were positive in the mouse and negative in the rat or vice versa (*56*). This discordance occurs despite the fact that rats and mice are very closely related and have short life-spans. Qualitative extrapolation of cancer risks from rats or mice to humans, a very dissimilar long-lived species, is unlikely to be as reliable. Conversely, important human carcinogens may not be detected in standard tests in rodents; this was true for a long time for both tobacco smoke and alcohol, the two largest identified causes of neoplastic death in the United States.

For many of the chemicals considered rodent carcinogens, there may be negative as well as positive tests. It is difficult to deal with negative results satisfactorily for several reasons, including the fact that some chemicals are tested only once or twice, while others are tested many times. The HERP index ignores negative tests. Where there is species variation in potency, use of the more sensitive species, as is generally done and as is done here, could introduce a tendency to overestimate possible hazards; however, for most chemicals that are positive in both species, the potency is similar in rats and mice (*57*). The HERP may provide a rough correlate of human hazard from chemical exposure; however, for a given chemical, to the extent that the potency in humans differs from the potency in rodents, the relative hazard would be different.

Quantitative uncertainties. Quantitative extrapolation from rodents to humans, particularly at low doses, is guesswork that we have no way of validating (*1, 5, 10, 11, 58*). It is guesswork because of lack of knowledge in at least six major areas: (i) the basic mechanisms of carcinogenicity; (ii) the relation of cancer, aging, and life-span (*1, 10, 42, 59*); (iii) the timing and order of the steps in the carcinogenic process that are being accelerated; (iv) species differences in metabolism and pharmacokinetics; (v) species differences in anticarcinogens and other defenses (*1, 60*); and (vi) human heterogeneity—for example, pigmentation affects susceptibility to skin cancer from ultraviolet light. These sources of uncertainty are so numerous, and so substantial, that only empirical data will resolve them, and little of this is available.

Uncertainties due to mechanism in multistage carcinogenesis. Several steps (stages) are involved in chemical carcinogenesis, and the dose-response curve for a carcinogen might depend on the particular stage(s) it accelerates (*58*), with multiplicative effects if several stages are affected. This multiplicative effect is consistent with the observation in human cancer that synergistic effects are common. The three steps of carcinogenesis that have been analyzed in most detail are initiation (mutation), promotion, and progression, and we discuss these as an aid to understanding aspects of the dose-response relation.

Mutation (or DNA damage) as one stage of the carcinogenic process is supported by various lines of evidence: association of active forms of carcinogens with mutagens (*61*), the changes in DNA sequence of oncogenes (*62*), genetic predisposition to cancer in human diseases such as retinoblastoma (*63*) or DNA-repair deficiency diseases such as xeroderma pigmentosum (*64*). The idea that genotoxic carcinogens might show a linear dose-response might be plausible if only the mutation step of carcinogenesis was accelerated and if the induction of repair and defense enzymes were not significant factors (*65*).

Promotion, another step in carcinogenesis, appears to involve cell proliferation, or perhaps particular types of cell proliferation (*66*), and dose-response relations with apparent thresholds, as indicated by various lines of evidence: (i) The work of Trosko *et al.* (*67*) on promotion of carcinogenesis due to interference with cell-cell communication, causing cell proliferation. (ii) Rajewsky's and other work indicating initiation by some carcinogenic agents appears to require proliferating target cells (*68*). (iii) The work of Farber *et al.* (*69*) on liver carcinogenesis supports the idea that cell proliferation (caused by partial hepatectomy or cell killing) can be an important aspect of hepatocarcinogenesis. They have also shown for several chemicals that hepatic cell killing shows a toxic threshold with dose. (iv) Work on carcinogenesis in the pancreas, bladder and stomach

(*70*), and other tissues (*58*) is also consistent with results on the liver (*71, 72*) though the effect of cell proliferation might be different in tissues that normally proliferate. (v) The work of Mirsalis *et al.* (*71*) suggests that a variety of nongenotoxic agents are hepatocarcinogens in the B6C3F1 mouse (commonly used in cancer tests) because of their toxicity. Other studies on chloroform and trichloroethylene also support this interpretation (*72, 73*). Cell proliferation resulting from the cell killing in the mouse liver shows a threshold with dose (*71*). Also relevant is the extraordinarily high spontaneous rates of liver tumors (21% carcinomas, 10% adenomas) in the male B6C3F1 mouse (*74*). These spontaneous tumors have a mutant *ras* oncogene, and thus the livers in these mice appear to be highly initiated (mutated) to start with (*75*). (vi) Oncogenes: As Weinberg (*62*) has pointed out, "Oncogene-bearing cells surrounded by normal neighbors do not grow into a large mass if they carry only a single oncogene. But if the normal neighbors are removed . . . by killing them with a cytotoxic drug . . . then a single oncogene often suffices." (vii) Cell killing, as well as mutation, appears to be an important aspect of radiation carcinogenesis (*76*).

Promotion has also been linked to the production of oxygen radicals, such as from phagocytic cells (*77*). Since chronic cell killing would usually involve inflammatory reactions caused by neutrophils, one would commonly expect chemicals tested at the maximally tolerated dose (MTD) to be promoters because of the chronic inflammation.

Progression, another step in carcinogenesis, leading to selection for invasiveness and metastases, is not well understood but can be accelerated by oxygen radicals (*78*).

Chronic cell toxicity caused by dosing at the MTD in rodent cancer bioassays thus not only could cause inflammation and cell proliferation, but also should be somewhat mutagenic and clastogenic to neighboring cells because of the release of oxygen radicals from phagocytosis (*12, 79, 80*). The respiratory burst from phagocytic neutrophils releases the same oxidative mutagens produced by radiation (*77, 79*). Thus, animal cancer tests done at the MTD of a chemical might commonly stimulate all three steps in carcinogenesis and be positive because the chemical caused chronic cell killing and inflammation with some mutagenesis. Some of the considerable human evidence for chronic inflammation contributing to carcinogenesis and also some evidence for and against a general effect of inflammation and cytotoxicity in rodent carcinogenesis have been discussed (*81*).

Another set of observations may also bear on the question of toxicity and extrapolation. Wilson, Crouch, and Zeise (*82*) have pointed out that among carcinogens one can predict the potency in high-dose animal cancer experiments from the toxicity (the LD_{50}) of the chemical, though one cannot predict whether the substance is a carcinogen. We have shown that carcinogenic potency values are bounded by the MTD (*57*). The evidence from our database suggests that the relationship between TD_{50} and MTD has a biological as well as a statistical basis (*57*). We postulate that a just sublethal level of a carcinogen causes cell death, which allows neighboring cells to proliferate, and also causes oxygen radical production from phagocytosis and thus chronic inflammation, both important aspects of the carcinogenic process (*57*). The generality of this relationship and its basis needs further study.

If most animal cancer tests done at the MTD are partially measuring cell killing and consequent cell proliferation and phagocytic oxygen radical damage as steps in the carcinogenic process, one might predict that the dose-response curves would generally be nonlinear. For those experiments in our database for which life table data (*14*) were available, a detailed analysis (*83*) shows that the dose-response relationships are more often consistent with a quadratic (or cubic) model than with a linear model.

Experimentally, it is very difficult to discriminate between the various extrapolation models at low doses (*11, 58*). However, evidence to support the idea that a nonlinear dose-response relationship is the norm is accumulating for many nongenotoxic and some genotoxic carcinogens. Dose-response curves for saccharin (*45*), butylated hydroxyanisole [BHA (*84*)], and a variety of other nongenotoxic carcinogens appear to be nonlinear (*85*). Formaldehyde, a genotoxic carcinogen, also has a nonlinear dose response (*28, 29*). The data for both bladder and liver tumors in the large-scale study on acetylaminofluorene, a genotoxic chemical, could fit a hockey stick–shaped curve, though a linear model, with a decreased effect at lower dose rates when the total dose is kept constant (*86*), has not been ruled out.

Carcinogens effective at both mutating and killing cells (which includes most mutagens) could be "complete" carcinogens and therefore possibly more worrisome at doses far below the MTD than carcinogens acting mainly by causing cell killing or proliferation (*15*). Thus, all carcinogens are not likely to be directly comparable, and a dose of 1/100 the TD_{50} (HERP = 1%) might be much more of a carcinogenic hazard for the genotoxic carcinogens dimethylnitrosamine or aflatoxin than for the apparently nongenotoxic carcinogens trichloroethylene, PCBs, or alcohol (HERP values marked with asterisks in Table 1). Short-term tests for mutagenicity (*61, 87*) can have a role to play, not only in understanding mechanisms, but also in getting a more realistic view of the background levels of potential genotoxic carcinogens in the world. Knowledge of mechanism of action and comparative metabolism in rodents and humans might help when estimating the relative importance of various low-dose exposures.

Human cancer, except in some occupational or medicinal drug exposures, is not from high (just subtoxic) exposures to a single chemical but is rather from several risk factors often combined with a lack of antirisk factors (*60*); for example, aflatoxin (a potent mutagen) combined with an agent causing cell proliferation, such as hepatitis B virus (*19*). High salt [a possible risk factor in stomach cancer (*13*)] and high fat [a possible risk factor in colon cancer (*4*)] both appear to be effective in causing cell killing and cell proliferation.

Risk from carcinogenesis is not linear with time. For example, among regular cigarette smokers the excess annual lung cancer incidence is approximately proportional to the fourth power of the duration of smoking (*88*). Thus, if human exposures in Table 1 are much shorter than the lifetime exposure, the possible hazard may be markedly less than linearly proportional.

A key question about animal cancer tests and regulatory policy is the percentage of tested chemicals that will prove to be carcinogens (*89*). Among the 392 chemicals in our database that were tested in both rats and mice, 58% are positive in at least one species (*14*). For the 64 "natural" substances in the group, the proportion of positive results is similar (45%) to the proportion of positive results in the synthetic group (60%). One explanation offered for the high proportion of positive results is that more suspicious chemicals are being tested (for example, relatives of known carcinogens), but we do not know if the percentage of positives would be low among less suspicious chemicals. If toxicity is important in carcinogenicity, as we have argued, then at the MTD a high percentage of all chemicals might be classified as "carcinogens."

The Background of Natural Carcinogens

The object of this article is not to do risk assessment on naturally occurring carcinogens or to worry people unduly about an occasional raw mushroom or beer, but to put the possible hazard of man-made carcinogens in proper perspective and to point out that we

lack the knowledge to do low-dose "risk assessment." We also are almost completely ignorant of the carcinogenic potential of the enormous background of natural chemicals in the world. For example, cholinesterase inhibitors are a common class of pesticides, both man-made and natural. Solanine and chaconine (the main alkaloids in potatoes) are cholinesterase inhibitors and were introduced generally 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 almost all people (*12, 90*). Total alkaloids are present at a level of 15,000 μg per 200-g potato with not a large safety factor (about sixfold) from the toxic level for humans (*91*). Neither alkaloid has been tested for carcinogenicity. By contrast, malathion, the main synthetic organophosphate cholinesterase inhibitor in our diet (17 μg/day) (*16*), is not a carcinogen in rodents.

The idea that nature is benign and that evolution has allowed us to cope perfectly with the toxic chemicals in the natural world is not compelling for several reasons: (i) there is no reason to think that natural selection should eliminate the hazard of carcinogenicity of a plant toxin that causes cancer in old age past the reproductive age, though 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, and monkeys, and probably people, though the species are not equally sensitive. Many of the common metal salts are carcinogens (such as lead, cadmium, beryllium, nickel, chromium, selenium, and arsenic) despite their presence during all of evolution. (ii) Given the enormous variety of plant toxins, most of our defenses may be general defenses against acute effects, such as shedding the surface lining of cells of our digestive and respiratory systems every day; protecting these surfaces with a mucin layer; having detoxifying enzymes that are often inducible, such as cytochrome P-450, conjugating enzymes, and glutathione transferases; and having DNA repair enzymes, which would be useful against a wide variety of ingested toxic chemicals, both natural and synthetic. Some human cancer may be caused by interfering with these normal protective systems. (iii) The human diet has changed drastically in the last few thousand years, and most of us are eating plants (such as coffee, potatoes, tomatoes, and kiwi fruit) that our ancestors did not. (iv) Normal metabolism produces radiomimetic mutagens and carcinogens, such as hydrogen peroxide and other reactive forms of oxygen. Though we have defenses against these agents, they still may be major contributors to aging and cancer. A wide variety of external agents may disturb this balance between damage and defense (*12, 42*).

Implications for Decision-Making

For all of these considerations, our scale is not a scale of risks to humans but is only a way of setting priorities for concern, which should also take into account the numbers of people exposed. It should be emphasized that it is a linear scale and thus may overestimate low potential hazards if, as we argue above, linearity is not the normal case, or if nongenotoxic carcinogens are not of very much concern at doses much below the toxic dose.

Thus, it is not scientifically credible to use the results from rodent tests done at the MTD to directly estimate human risks at low doses. For example, an EPA "risk assessment" (*92*) based on a succession of worst case assumptions (several of which are unique to EDB) concluded that EDB residues in grain (HERP = 0.0004%) could cause 3 cases of cancer in 1000 people (about 1% of all U.S. cancer). A consequence was the banning of the main fumigant in the country. It would be more reasonable to compare the possible hazard of EDB residues to that of other common possible hazards. For example, the aflatoxin in the average peanut butter sandwich, or a raw mushroom, are 75 and 200 times, respectively, the possible hazard of EDB. Before banning EDB, a useful substance with rather low residue levels, it might be reasonable to consider whether the hazards of the alternatives, such as food irradiation, or the consequences of banning, such as increased mold contamination of grain, pose less risk to society. Also, there is a disparity between OSHA not regulating worker exposures at a HERP of 140%, while the EPA bans the substance at a HERP of 0.0004%. In addition, the FDA allows a possible hazard up to a HERP of 0.3% for peanut butter (20 ppb), and there is no warning about buying comfrey pills.

Because of the large background of low-level carcinogenic and other (*93*) hazards, and the high costs of regulation, priority setting is a critical first step. It is important not to divert society's attention away from the few really serious hazards, such as tobacco or saturated fat (for heart disease), by the pursuit of hundreds of minor or nonexistent hazards. Our knowledge is also more certain about the enormous toll of tobacco—about 350,000 deaths per year (*1, 2*).

There are many trade-offs to be made in all technologies. Trichloroethylene and tetrachloroethylene (perchloroethylene) replaced hazardous flammable solvents. Modern synthetic pesticides displaced lead arsenate, which was a major pesticide before the modern chemical era. Lead and arsenic are both natural carcinogens. There is also a choice to be made between using synthetic pesticides and raising the level of plants' natural toxins by breeding. It is not clear that the latter approach, even where feasible, is preferable. For example, plant breeders produced an insect-resistant potato, which has to be withdrawn from the market because of its acute toxicity to humans due to a high level of the natural plant toxins solanine and chaconine (*12*).

This analysis on the levels of synthetic pollutants in drinking water and of synthetic pesticide residues in foods suggests that this pollution is likely to be a minimal carcinogenic hazard relative to the background of natural carcinogens. This result is consistent with the epidemiologic evidence (*1*). Obviously prudence is desirable with regard to pollution, but we do need to work out some balance between chemophobia with its high costs to the national wealth, and sensible management of industrial chemicals (*94*).

Human life expectancy continues to lengthen in industrial countries, and the longest life expectancy in the world is in Japan, an extremely crowded and industrialized country. U.S. cancer death rates, except for lung cancer due to tobacco and melanoma due to ultraviolet light, are not on the whole increasing and have mostly been steady for 50 years. New progress in cancer research, molecular biology, epidemiology, and biochemical epidemiology (*95*) will probably continue to increase the understanding necessary for lengthening life-span and decreasing cancer death rates.

REFERENCES AND NOTES

1. R. Doll and R. Peto, *The Causes of Cancer* (Oxford Univ. Press, Oxford, England, 1981).
2. *Smoking and Health: A Report of the Surgeon General*, Department of Health, Education and Welfare Publication No. (PHS) 79-50066 (Office of the Assistant Secretary for Health, Washington, DC, 1979).
3. G. J. Hopkins and K. K. Carroll, *J. Environ. Pathol. Toxicol. Oncol.* **5**, 279 (1985); J. V. Joossens, M. J. Hill, J. Geboers, Eds., *Diet and Human Carcinogenesis* (Elsevier, Amsterdam, 1985); I. Knudsen, Ed., *Genetic Toxicology of the Diet* (Liss, New York, 1986); Committee on Diet, Nutrition and Cancer, Assembly of Life Sciences, National Research Council, *Diet, Nutrition and Cancer* (National Academy Press, Washington, DC, 1982).
4. R. P. Bird, R. Schneider, D. Stamp, W. R. Bruce, *Carcinogenesis* **7**, 1657 (1986); H. L. Newmark *et al.*, in *Large Bowel Cancer*, vol. 3 in *Cancer Research Monographs*, A. J. Mastromarino and M. G. Brattain, Eds. (Praeger, New York, 1985), pp. 102–130; E. A. Jacobson, H. L. Newmark, E. Bright-See, G. McKeown-Eyssen, W. R. Bruce, *Nutr. Rep. Int.* **30**, 1049 (1984); M. Buset, M. Lipkin, S. Winawer, S. Swaroop, E. Friedman, *Cancer Res.* **46**, 5426 (1986).
5. D. G. Hoel, R. A. Merrill, F. P. Perera, Eds., *Banbury Report 19. Risk Quantitation and Regulatory Policy* (Cold Spring Laboratory, Cold Spring Harbor, NY, 1985).
6. B. E. Henderson *et al.*, *Cancer Res.* **42**, 3232 (1982).

7. R. Peto and H. zur Hausen, Eds., *Banbury Report 21. Viral Etiology of Cervical Cancer* (Cold Spring Harbor Laboratory, Cold Spring Habor, NY, 1986); F.-S. Yeh *et al.*, *Cancer Res.* **45**, 872 (1985).
8. International Agency for Research on Cancer, *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* (International Agency for Research on Cancer, Lyon, France, 1985), vol. 39.
9. D. A. Freedman and H. Zeisel, *From Mouse to Man: The Quantitative Assessment of Cancer Risks* (Tech. Rep. No. 79, Department of Statistics, University of California, Berkeley, 1987).
10. R. Peto, in *Assessment of Risk from Low-Level Exposure to Radiation and Chemicals*, A. D. Woodhead, C. J. Shellabarger, V. Pond, A. Hollaender, Eds. (Plenum, New York and London, 1985), pp. 3–16.
11. S. W. Samuels and R. H. Adamson, *J. Natl. Cancer Inst.* **74**, 945 (1985); E. J. Calabrese, *Drug Metab. Rev.* **15**, 505 (1984).
12. B. N. Ames, *Science* **221**, 1256 (1983); *ibid.* **224**, 668, 757 (1984).
13. H. Ohgaki *et al.*, *Gann* **75**, 1053 (1984); S. S. Mirvish, *J. Natl. Cancer Inst.* **71**, 630 (1983); J. V. Joossens and J. Geboers, in *Frontiers in Gastrointestinal Cancer*, B. Levin and R. H. Riddell, Eds. (Elsevier, Amsterdam, 1984), pp. 167–183; T. Hirayama, *Jpn. J. Clin. Oncol.* **14**, 159 (1984); C. Furihata *et al.*, *Biochem. Biophys. Res. Commun.* **121**, 1027 (1984).
14. R. Peto, M. C. Pike, L. Bernstein, L. S. Gold, B. N. Ames, *Environ. Health Perspect.* **58**, 1 (1984); L. S. Gold *et al.*, *ibid.*, p. 9; L. S. Gold *et al.*, *ibid.* **67**, 161 (1986); L. S. Gold *et al.*, *ibid.*, in press.
15. G. M. Williams and J. H. Weisburger, in *Casarett and Doull's Toxicology. The Basic Science of Poisons*, C. D. Klaassen, M. O. Amdur, J. Doull, Eds. (Macmillan, New York, ed. 3, 1986), chap. 5, pp. 99–172; B. E. Butterworth and T. J. Slaga, Eds., *Banbury Report 25. Non-Genotoxic Mechanisms in Carcinogenesis* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1987).
16. The FDA has estimated the average U.S. dietary intake of 70 pesticides, herbicides, and industrial chemicals for 1981/1982 [M. J. Gartrell, J. C. Craun, D. S. Podrebarac, E. L. Gunderson, *J. Assoc. Off. Anal. Chem.* **69**, 146 (1986)]. The negative test on 2-ethylhexyl diphenyl phosphate is in J. Treon, F. Dutra, F. Cleveland, *Arch. Ind. Hyg. Occup. Med.* **8**, 170 (1953).
17. R. C. Beier *et al.*, *Food Chem. Toxicol.* **21**, 163 (1983).
18. L. Stoloff, M. Castegnaro, P. Scott, I. K. O'Neill, H. Bartsch, Eds., *Some Mycotoxins*, vol. 5 in *Environmental Carcinogens. Selected Methods of Analysis* (IARC Scientific Publ. No. 44, International Agency for Research on Cancer, Lyon, France, 1982); H. Mori *et al.*, *Cancer Res.* **44**, 2918 (1984); R. Röschenthaler, E. E. Creppy, G. Dirheimer, *J. Toxicol.-Toxin Rev.* **3**, 53 (1984); W. F. O. Marasas, N. P. J. Kriek, J. E. Fincham, S. J. van Rensburg, *Int. J. Cancer* **34**, 383 (1984); *Environmental Health Criteria 11: Mycotoxins* (World Health Organization, Geneva, Switzerland, 1979), pp. 21–85; W. F. Busby *et al.*, in *Chemical Carcinogens*, C. E. Searle, Ed. (ACS Monograph 182, American Chemical Society, Washington, DC, ed. 2, 1984), vol. 2, pp. 944–1136.
19. S. J. Van Rensburg *et al.*, *Br. J. Cancer* **51**, 713 (1985); S. N. Zaman *et al.*, *Lancet* **1985-I**, 1357 (1985); H. Austin *et al.*, *Cancer Res.* **46**, 962 (1986).
20. A. Takada, J. Nei, S. Takase, Y. Matsuda, *Hepatology* **6**, 65 (1986).
21. J. M. Elwood *et al.*, *Int. J. Cancer* **34**, 603 (1984).
22. Aldehydes and ketones are largely responsible for the aroma and flavor of bread [Y. Y. Linko, J. A. Johnson, B. S. Miller, *Cereal Chemistry* **39**, 468 (1962)]. In freshly baked bread, formaldehyde (370 μg per two slices of bread) accounts for 2.5% of the total carbonyl compounds [K. Lorenz and J. Maga, *J. Agric. Food Chem.* **20**, 211 (1972)]. Acetaldehyde, which is present in bread at about twice the level of formaldehyde, is a carcinogen in rats [R. A. Woutersen, L. M. Appelman, V. J. Feron, C. A. Vanderheijden, *Toxicology* **31**, 123 (1984)] and a DNA cross-linking agent in human cells [B. Lambert, Y. Chen, S.-M. He, M. Sten, *Mutat. Res.* **146**, 301 (1985)].
23. Ethyl alcohol contents of wine and beer were assumed to be 12% and 5%, respectively. The TD_{50} calculation is based on M. J. Radike, K. L. Stemmer, E. Bingham, *Environ. Health Perspect.* **41**, 59 (1981). Rats exposed to 5% ethyl alcohol in drinking water for 30 months had increased incidences of endocrine and liver tumors.
24. C. S. Ough, *J. Agric. Food Chem.* **24**, 323 (1976). Urethane is also carcinogenic in hamsters and rhesus monkeys.
25. Y. Fujita, K. Wakabayashi, M. Nagao, T. Sugimura, *Mutat. Res.* **144**, 227 (1985); M. Nagao, Y. Fujita, T. Sugimura, in *IARC Workshop*, in press.
26. M. Petro-Turza and I. Szarfoldi-Szalma, *Acta Alimentaria* **11**, 75 (1982).
27. L. J. Marnett *et al.*, *Mutat. Res.* **148**, 25 (1985).
28. Formaldehyde in air samples taken from all the mobile homes examined ranged from 50 to 660 ppb (mean, 167 ppb) [T. H. Connor, J. C. Theiss, H. A. Hanna, D. K. Monteith, T. S. Matney, *Toxicol. Lett.* **25**, 33 (1985)]. The important role of cell toxicity and cell proliferation in formaldehyde carcinogenesis is discussed in T. B. Starr and J. E. Gibson [*Annu. Rev. Pharmacol. Toxicol.* **25**, 745 (1985)].
29. J. A. Swenberg *et al.*, *Carcinogenesis* **4**, 945 (1983).
30. G. Della Porta, M. I. Colnaghi, G. Parmiani, *Food Cosmet. Toxicol.* **6**, 707 (1968).
31. Formaldehyde develops postmortem in marine fish and crustaceans, probably through the metabolism of trimethylamine oxide. The average level found in shrimp from four U.S. markets was 94 mg/kg [T. Radford and D. E. Dalsis, *J. Agric. Food Chem.* **30**, 600 (1982)]. Formaldehyde is found in remarkably high concentrations (300 ppm, HERP = 29% per 100 g) in Japanese shrimp that have been bleached with a sulfite solution [A. Yoshida and M. Imaida, *J. Food Hygienic Soc. Japan* **21**, 288 (1980)].
32. J. F. Lawrence and J. R. Iyengar, *Int. J. Environ. Anal. Chem.* **15**, 47 (1983).
33. H. d'A. Heck *et al.*, *Am. Ind. Hyg. Assoc. J.* **46**, 1 (1985).
34. T. Sugimura *et al.*, in *Genetic Toxicology of the Diet*, I. Knudsen, Ed. (Liss, New York, 1986), pp. 85–107; T. Sugimura, *Science* **233**, 312 (1986).
35. H. Ohgaki *et al.*, *Cancer Lett.* **25**, 239 (1985).
36. T. Kinouchi, H. Tsutsui, Y. Ohnishi, *Mutat. Res.* **171**, 105 (1986).
37. T. Kawabata *et al.*, in *N-Nitroso Compounds: Analysis, Formation and Occurrence*, E. A. Walker, L. Griciute, M. Castegnaro, M. Borzsonyi, Eds. (IARC Scientific Publ. No. 31, International Agency for Research on Cancer, Lyon, France, 1980), pp. 481–490; T. Maki, Y. Tamura, Y. Shimamura, and Y. Naoi [*Bull. Environ. Contam. Toxicol.* **25**, 257 (1980)] have surveyed Japanese food for nitrosamines.
38. T. Fazio, D. C. Havery, J. W. Howard, in *N-Nitroso Compounds: Analysis, Formation and Occurrence*, E. A. Walker, L. Griciute, M. Castegnaro, M. Borzsonyi, Eds. (IARC Scientific Publ. No. 31, International Agency for Research on Cancer, Lyon, France, 1980), pp. 419–435; R. Preussmann and G. Eisenbrand, in *Chemical Carcinogenesis*, C. E. Searle, Ed. (ACS Monograph 182, American Chemical Society, Washington, DC, ed. 2, 1984), vol. 2, pp. 829–868; D. C. Havery, J. H. Hotchkiss, T. Fazio, *J. Food Sci.* **46**, 501 (1981).
39. W. A. Garland *et al.*, *Cancer Res.* **46**, 5392 (1986).
40. E. A. Walker, L. Griciute, M. Castegnaro, M. Borzsonyi, Eds., *N-Nitroso Compounds: Analysis, Formation and Occurrence* (IARC Scientific Publ. No. 31, International Agency for Research on Cancer, Lyon, France, 1980), pp. 457–463; B. Spiegelhalder, G. Eisenbrand, R. Preussmann, *Oncology* **37**, 211 (1980); R. A. Scanlan and S. R. Tannenbaum, Eds., *N-Nitroso Compounds* (ACS Symposium Series No. 174, American Chemical Society, Washington, DC, 1981), pp. 165–180. Nitrosamines are formed in cured meats through reactions of secondary amines with nitrites added during the manufacturing process. One survey of bacon commercially available in Canada identified *N*-nitrosodimethylamine (DMN), *N*-nitrosodiethylamine (DEN), and *N*-nitrosopyrrolidine (NPYR) in most samples tested, with average levels of 3.4, 1.0, and 9.3 ppb, respectively. The cooked-out fat from the bacon samples contained DMN and NPYR at average levels of 6.4 and 21.9 ppb, respectively [N. P. Sen, S. Seaman, W. F. Miles, *J. Agric. Food Chem.* **27**, 1354 (1979); R. A. Scanlan, *Cancer Res.* **43**, 2435s (1983)]. The average levels of NPYR in cooked bacon have decreased since 1971 because of reduced levels of nitrite and increased levels of ascorbate used in bacon curing mixtures [D. C. Havery, T. Fazio, J. W. Howard, *J. Assoc. Off. Anal. Chem.* **61**, 1379 (1978)].
41. Y. Yamamoto *et al.*, *Anal. Biochem.* **160**, 7 (1987).
42. B. N. Ames and R. L. Saul, in *Theories of Carcinogenesis*, O. H. Iversen, Ed. (Hemisphere, New York, in press); R. Cathcart, E. Schwiers, R. L. Saul, B. N. Ames, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 5633 (1984).
43. B. P. Yu, E. J. Masoro, I. Murata, H. A. Bertrand, F. T. Lynd, *J. Gerontol.* **37**, 130 (1982); F. J. C. Roe, *Proc. Nutr. Soc.* **40**, 57 (1981); *Nature (London)* **303**, 657 (1983); M. J. Tucker, *Int. J. Cancer* **23**, 803 (1979).
44. Y. Tazima, *Environ. Health Perspect.* **29**, 183 (1979); M. Kinebuchi, T. Kawachi, N. Matsukura, T. Sugimura, *Food Cosmet. Toxicol.* **17**, 339 (1979).
45. F. W. Carlborg, *Food Chem. Toxicol.* **23**, 499 (1985).
46. T. H. Jukes, *Am. Stat.* **36**, 273 (1982); *J. Am. Med. Assoc.* **229**, 1920 (1974).
47. Allyl isothiocyanate (AITC) is the major flavor ingredient, and natural pesticide, of brown mustard and also occurs naturally in varying concentrations in cabbage, kale, broccoli, cauliflower, and horseradish [Y. M. Ioannou, L. T. Burka, H. B. Matthews, *Toxicol. Appl. Pharmacol.* **75**, 173 (1984)]. It is present in the plant's volatile oil as the glucoside sinigrin. (The primary flavor ingredient of yellow mustard is *p*-hydroxybenzyl isothiocyanate.) The AITC yield from brown mustard is approximately 0.9% by weight, assuming all of the sinigrin is converted to AITC [A. Y. Leung, *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics* (Wiley, New York, 1980), pp. 238–241]. Synthetic AITC is used in nonalcoholic beverages, candy, baked goods, meats, condiments, and syrups at average levels ranging from 0.02 to 88 ppm [T. E. Furia and B. Nicolo, Eds., *Fenaroli's Handbook of Flavor Ingredients*, (CRC Press, Cleveland, OH, 2 ed., 1975), vol. 1, p. 19].
48. Estragole, one of numerous safrole-like compounds in plants, is present in the volatile oils of many edible plants, including basil, tarragon, bay, anise, and fennel, as well as in pine oil and turpentine [A. Y. Leung, *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics* (Wiley, New York, 1980)]. Dried basil has a volatile oil content of about 1.5 to 3.0%, which contains (on average) 25% estragole [H. B. Heath, *Source Book of Flavors* (AVI, Westport, CT, 1981), pp. 222–223]. Estragole is used commercially in spice, anise, licorice, and fruit flavors. It is added to beverages, candy, baked goods, chewing gums, ice creams, and condiments at average levels ranging from 2 to 150 ppm [NAS/NRC Food Protection Committee, Food and Nutrition Board, *Chemicals Used in Food Processing* (NAS/NRC Publ. No. 1274, National Academy of Sciences, Washington, DC, 1965), p. 114].
49. The estimation of risk is from human data on uranium miners and estimates of intake. E. P. Radford, *Environ. Health Perspect.* **62**, 281 (1985); A. V. Nero *et al.*, *Science* **234**, 992 (1986); A. V. Nero, *Technol. Rev.* **89**, 28 (1986); R. Hanley, *The New York Times*, 10 March 1986, p. 17.
50. The average daily adult dose of phenobarbital for sleep induction is 100 to 320 mg (HERP = 26 to 83%), though its use is declining [AMA Division of Drugs, *AMA Drug Evaluations* (American Medical Association, Chicago, IL, ed. 5, 1983), pp. 201–202]. The TD_{50} data in the table is for phenobarbital, which, so far, has been shown to be carcinogenic only in mice; the sodium salt of phenobarbital is carcinogenic in both rats and mice. Human studies on phenobarbital and cancer are reviewed in A. E. M. McLean, H. E. Driver, D. Lowe, I. Sutherland, *Toxicol. Lett.* **31** (suppl.), 200 (1986).
51. Phenacetin use has gradually decreased following reports of urinary bladder and kidney tumors in heavy users [J. M. Piper, J. Tonascia, G. M. Matanoski, *N. Engl. J. Med.* **313**, 292 (1985)]. Phenacetin also induces urinary bladder and kidney tumors in rats and mice.
52. The human dose of clofibrate is 2 g per day for many years [R. J. Havel and J. P. Kane, *Annu. Rev. Med.* **33**, 417 (1982)]. The role of clofibrate as a peroxisome proliferator is reviewed in J. K. Reddy and N. D. Lalwani [*CRC Crit. Rev. Toxicol.* **12**, 1 (1983)]. An epidemiologic study is in World Health Organization Report, *Lancet* **1984-II**, 600 (1984).
53. L. S. Gold, G. Backman, N. K. Hooper, R. Peto, *Lawrence Berkeley Laboratory Report 23161* (1987); N. K. Hooper and L. S. Gold, in *Monitoring of Occupational Genotoxicants*, M. Sorsa and H. Norppa, Eds. (Liss, New York, 1986), pp. 217–228; K. Hooper and L. S. Gold, in *Cancer Prevention: Strategies in the Workplace*, C. Becker, Ed. (Hemisphere, Washington, DC, 1985), pp. 1–11.
54. California Department of Health Services, *EDB Criteria Document* (1985).
55. M. G. Ott, H. C. Scharnweber, R. R. Langner, *Br. J. Ind. Med.* **37**, 163 (1980); J. C. Ramsey, C. N. Park, M. G. Ott, P. J. Gehring, *Toxicol. Appl. Pharmacol.* **47**, 411 (1978). This has been disputed (*54*). The carcinogen dose reported in the table assumes a time-weighted average air concentration of 3 ppm and an 8-hour workday 5 days per week for 50 weeks per year for life.

56. R. Magaw, L. S. Gold, L. Bernstein, T. H. Slone, B. N. Ames, in preparation.
57. L. Bernstein, L. S. Gold, B. N. Ames, M. C. Pike, D. G. Hoel, *Fundam. Appl. Toxicol.* **5**, 79 (1985); L. Bernstein, L. S. Gold, B. N. Ames, M. C. Pike, D. G. Hoel, *Risk Anal.* **5**, 263 (1985).
58. D. B. Clayson, *Toxicol. Pathol.* **13**, 119 (1985); D. B. Clayson, *Mutat. Res.*, in press.
59. R. Peto, S. E. Parish, R. G. Gray, in *Age-Related Factors in Carcinogenesis*, A. Likhachev, V. Anisimov, R. Montesano, Eds. (IARC Scientific Publ. No. 58, International Agency for Research on Cancer, Lyon, France, 1985), pp. 43–53.
60. D. M. Shankel, P. Hartman, T. Kada, A. Hollaender, Eds., *Antimutagenesis and Anticarcinogenesis: Mechanisms* (Plenum, New York, 1986).
61. B. N. Ames and J. McCann, *Cancer Res.* **41**, 4192 (1981).
62. R. A. Weinberg, *Science* **230**, 770 (1985).
63. A. G. Knudson, Jr., *Cancer Res.* **45**, 1437 (1985).
64. J. E. Cleaver, in *Genes and Cancer*, J. M. Bishop, J. D. Rowley, M. Greaves, Eds. (Liss, New York, 1984), pp. 117–135.
65. A. D. Woodhead, C. J. Shellabarger, V. Pond, A. Hollaender, Eds., *Assessment of Risk from Low-Level Exposure to Radiation and Chemicals: A Critical Overview* (Plenum, New York, 1985).
66. J. Cairns, *Nature (London)* **255**, 197 (1975); C. C. Harris and T. Sun, *Carcinogenesis* **5**, 697 (1984); A. M. Edwards and C. M. Lucas, *Biochem. Biophys. Res. Commun.* **131**, 103 (1985); H. Tsuda *et al.*, *Cancer Res.* **39**, 4491 (1979); W. H. Haese and E. Bueding, *J. Pharmacol. Exp. Ther.* **197**, 703 (1976).
67. J. E. Trosko and C. C. Chang, in *Methods for Estimating Risk of Chemical Injury: Human and Non-Human Biota and Ecosystems*, V. B. Vouk, G. C. Butler, D. G. Hoel, D. B. Peakall, Eds. (Wiley, New York, 1985), pp. 181–200; J. E. Trosko and C. C. Chang, in *Assessment of Risk from Low-Level Exposure to Radiation and Chemicals: A Critical Overview*, A. D. Woodhead, C. J. Shellabarger, V. Pond, A. Hollaender, Eds. (Plenum, New York, 1985), pp. 261–284; H. Yamasaki, *Toxicol. Pathol.* **14**, 363 (1986).
68. M. F. Rajewsky, in *Age-Related Factors in Carcinogenesis*, A. Likhachev, V. Anisimov, R. Montesano, Eds. (IARC Scientific Publ. No. 58, International Agency for Research on Cancer, Lyon, France, 1985), pp. 215–224; V. Kinsel, G. Furstenberger, H. Loehrke, F. Marks, *Carcinogenesis* **7**, 779 (1986).
69. E. Farber, *Cancer Res.* **44**, 5463 (1984); E. Farber, S. Parker, M. Gruenstein, *ibid.* **36**, 3879 (1976).
70. A. Denda, S. Inui, M. Sunagawa, S. Takahashi, Y. Konishi, *Gann* **69**, 633 (1978); R. Hasegawa and S. M. Cohen, *Cancer Lett.* **30**, 261 (1986); R. Hasegawa, S. M. Cohen, M. St. John, M. Cano, L. B. Ellwein, *Carcinogenesis* **7**, 633 (1986); B. I. Ghanayem, R. R. Maronpot, H. B. Matthews, *Toxicology* **6**, 189 (1986).
71. J. C. Mirsalis *et al.*, *Carcinogenesis* **6**, 1521 (1985); J. C. Mirsalis *et al.*, *Environ. Mutag.* **8** (suppl. 6), 55 (1986); J. Mirsalis *et al.*, Abstract for Fourth International Conference on Environmental Mutagens, held 24–28 June in Stockholm, Sweden (1985).
72. W. T. Stott, R. H. Reitz, A. M. Schumann, P. G. Watanabe, *Food Cosmet. Toxicol.* **19**, 567 (1981).
73. D. H. Moore, L. F. Chasseaud, S. K. Majeed, D. E. Prentice, F. J. C. Roe, *ibid.* **20**, 951 (1982).
74. J. K. Haseman, J. Huff, G. A. Boorman, *Toxicol. Pathol.* **12**, 126 (1984); R. E. Tarone, K. C. Chu, J. M. Ward, *J. Natl. Cancer Inst.* **66**, 1175 (1981).
75. S. H. Reynolds, S. J. Stowers, R. R. Maronpot, M. W. Anderson, S. A. Aaronson, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 33 (1986); T. R. Fox and P. G. Watanabe, *Science* **228**, 596 (1985).
76. T. D. Jones, *Health Phys.* **4**, 533 (1984); J. B. Little, A. R. Kennedy, R. B. McGandy, *Radiat. Res.* **103**, 293 (1985).
77. T. W. Kensler and B. G. Taffe, *Adv. Free Radical Biol. Med.* **2**, 347 (1986); P. A. Cerutti, in *UCLA Symposium on Molecular and Biology Growth Factors, Tumor Promoters and Cancer Genes*, in press; P. A. Cerutti, in *Biochemical and Molecular Epidemiology of Cancer*, vol. 40 of UCLA Symposium on Molecular and Cellular Biology, C. Harris, Ed. (Liss, New York, 1986), p. 167; in *Theories of Carcinogenesis*, O. H. Iversen, Ed. (Hemisphere, New York, in press); H. C. Birnboim, *Carcinogenesis* **7**, 1511 (1986); K. Frenkel and K. Chrzan, *ibid.* **8**, 455 (1987).
78. J. Rotstein, J. O. O'Connell, T. Slaga, *Proc. Assoc. Cancer Res.* **27**, 143 (1986); J. S. O'Connell, A. J. P. Klein-Szanto, J. DiGiovanni, J. W. Fries, T. J. Slaga, *Cancer Res.* **46**, 2863 (1986); J. S. O'Connell, J. B. Rotstein, T. J. Slaga, in *Banbury Report 25. Non-Genotoxic Mechanisms in Carcinogenesis*, B. E. Butterworth and T. J. Slaga, Eds. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1987).
79. M. A. Trush, J. L. Seed, T. W. Kensler, *Proc. Natl. Acad. Sci. U.S.A.* **82**, 5194 (1985); A. I. Tauber and B. M. Babior, *Adv. Free-Radical Biol. Med.* **1**, 265 (1985); G. J. Chellman, J. S. Bus, P. K. Working, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 8087 (1986).
80. I. U. Schraufstatter *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **83**, 4908 (1986); M. O. Bradley, in *Basic and Applied Mutagenesis*, A. Muhammed and R. C. von Borstel, Eds. (Plenum, New York, 1985), pp. 99–109.
81. L. Diamond, T. G. O'Brien, W. M. Baird, *Adv. Cancer Res.* **32**, 1 (1980); D. Schmahl, *J. Cancer Res. Clin. Oncol.* **109**, 260 (1985); O. H. Iversen and E. G. Astrup, *Cancer Invest.* **2**, 51 (1984); A. Hagiwara and J. M. Ward, *Fundam. Appl. Toxicol.* **7**, 376 (1986); J. M. Ward, in *Carcinogenesis and Mutagenesis Testing*, J. F. Douglas, Ed. (Humana, Clifton, NJ, 1984), pp. 97–100.
82. L. Zeise, R. Wilson, E. Crouch, *Risk Analysis* **4**, 187 (1984); L. Zeise, E. A. C. Crouch, R. Wilson, *ibid.* **5**, 265 (1985); L. Zeise, E. A. C. Crouch, R. Wilson, *J. Am. College Toxicol.* **5**, 137 (1986).
83. D. Hoel, personal communication.
84. N. Ito, S. Fukushima, A. Hagiwara, M. Shibata, T. Ogiso, *J. Natl. Cancer Inst.* **70**, 343 (1983).
85. F. W. Carlborg, *Food Chem. Toxic.* **20**, 219 (1982); *Food Cosmet. Toxicol.* **19**, 255 (1981).
86. K. G. Brown and D. G. Hoel, *Fundam. Appl. Toxicol.* **3**, 470 (1983); N. A. Littlefield and D. W. Gaylor, *J. Toxicol. Environ. Health* **15**, 545 (1985).
87. J. Ashby, *Mutagenesis* **1**, 3 (1986).
88. R. Doll, *Cancer Res.* **38**, 3573 (1978); ——— and R. Peto, *J. Epidemiol. Community Health* **32**, 303 (1978).
89. J. E. Huff, E. E. McConnell, J. K. Haseman, *Environ. Mutagenesis* **7**, 427 (1985); H. S. Rosenkranz, *ibid.*, p. 428.
90. M. H. Harvey, B. A. Morris, M. McMillan, V. Marks, *Human Toxicol.* **4**, 503 (1985).
91. S. J. Jadhav, R. P. Sharma, D. K. Salunkhe, *CRC Crit. Rev. Toxicol.* **9**, 21 (1981).
92. Environmental Protection Agency, *Position Document 4* (Special Pesticide Review Division, Environmental Protection Agency, Arlington, VA, 1983).
93. R. Wilson and E. Crouch, *Risk/Benefit Analysis* (Ballinger, Cambridge, MA, 1982); W. F. Allman *Science 85* **6**, 30 (1985).
94. P. Huber, *Regulation*, **33** (March/April 1984); C. Whipple, *ibid.* **9**, 37 (1985).
95. B. A. Bridges, B. E. Butterworth, I. B. Weinstein, Eds., *Banbury Report 13. Indicators of Genotoxic Exposure.* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1982); P. E. Enterline, Ed., Fifth Annual Symposium on Environmental Epidemiology, *Environ. Health Perspect.* **62**, 239 (1985).
96. A national survey of U.S. drinking water supplies identified the concentrations of about 20 organic compounds. The mean total trihalomethane concentration was 117 μg/liter, with the major component, chloroform, present at a mean concentration of 83 μg/liter (83 ppb). Raw water that is relatively free of organic matter results in drinking water relatively free of trihalomethanes after chlorination. These studies are reviewed in S. J. Williamson, *The Science of the Total Environment* **18**, 187 (1981).
97. Public and private drinking water wells in Santa Clara Valley, California, have been found to be contaminated with a variety of halogenated hydrocarbons in small amounts. Among 19 public water system wells, the most commonly found contaminants were 1,1,1-trichloroethane (TCA), and 1,1,2-trichloro-1,2,2-trifluoroethane (Freon-113). TCA was found in 15 wells generally at concentrations of less than 30 ppb, though one well contained up to 8800 ppb, and Freon-113 was found in six wells at concentrations up to 12 ppb. Neither chemical has been adequately tested for carcinogenicity in long-term bioassays. In addition to these compounds, three wells also contained carcinogenic compounds at low concentrations. Water from public supply wells may be mixed with treated surface water before delivery, thus the concentrations of these compounds that people actually receive may be somewhat reduced. Thirty-five private drinking water supply wells were examined; the major contaminant was the carcinogen trichloroethylene (TCE), at levels up to 2800 ppb. TCA and Freon-113 were also found in some wells, at maximum levels of 24 ppb and 40 ppb, respectively. Though fewer people drink from private water wells, the contaminant concentrations may be higher because the water is not mixed with water from other sources [California Department of Health Services, California Regional Water Quality Control Board 2, Santa Clara County Public Health Department, Santa Clara Valley Water District, U.S. Environmental Protection Agency, *Ground Water and Drinking Water in the Santa Clara Valley: A White Paper* (1984), table 8]. Trichloroethylene may not be a carcinogen in humans at low doses [R. D. Kimbrough, F. L. Mitchell, V. N. Houk, *J. Toxicol. Environ. Health* **15**, 369 (1985)].
98. Contaminated drinking water in the area of Woburn, Massachusetts, was found to contain 267 ppb trichloroethylene, 21 ppb tetrachloroethylene, 12 ppb chloroform, 22 ppb trichlorotrifluoroethane, and 28 ppb 1,2-*trans*-dichloroethylene [S. W. Lagakos, B. J. Wessen, M. Zelen, *J. Am. Stat. Assoc.* **81**, 583 (1986)].
99. The amount of chloroform absorbed by a 6-year-old child in a chlorinated freshwater swimming pool has been estimated [J. A. Beech, *Med. Hypotheses* **6**, 303 (1980)]. Table 1 refers to the chloroform in an average pool (134 μg/liter) and for a 37-kg child. Three other trihalomethanes were identified in these freshwater pools: bromoform, bromodichloromethane and chlorodibromomethane. U. Lahl, J. Vondusze, B. Gabel, B. Stachel, W. Thiemann [*Water Res.* **15**, 803 (1981)] have estimated absorption in covered swimming pools.
100. J. McCann, L. Horn, J. Girman, A. V. Nero, in *Short-Term Bioassays in the Analysis of Complex Environmental Mixtures*, V. S. Sandhu, D. M. De Marini, M. J. Mass, M. M. Moore, J. L. Mumford, Eds. (Plenum, New York, in press). This estimate (Table 1) for formaldehyde in conventional homes, excludes foam-insulated houses and mobile homes. The figure is a mean of the median or mean of the reported samples in each paper. For benzene, the figure is a mean of all reported median or mean samples. The level of benzene in Los Angeles outdoor air is similar (U.S. EPA Office of Air Quality Planning and Standards, EPA 450/4-86-012, 1986).
101. The average adult daily PCB intake from food estimated by the FDA in fiscal years 1981/1982 was 0.2 μg/day (*16*). Many slightly different PCB mixtures have been studied in long-term animal cancer bioassays; the calculation of TD_{50} was from a test of Aroclor 1260 which was more potent than other PCBs (*14*).
102. The average consumption of EDB residues in grains has been estimated by the EPA for adults as 0.006 μg kg^{-1} day^{-1} and for children as 0.013 μg kg^{-1} day^{-1} [U.S. EPA Office of Pesticide Programs, *Ethylene Dibromide (EDB) Scientific Support and Decision Document for Grain and Grain Milling Fumigation Uses* (8 February 1984)].
103. The leaves and roots of Russian comfrey are widely sold in health food stores and are consumed as a medicinal herb or salad plant or are brewed as a tea. Comfrey leaf has been shown to contain 0.01 to 0.15%, by weight, total pyrrolizidine alkaloids, with an average level of 0.05% for intermediate size leaves [C. C. J. Culvenor, J. A. Edgar, J. L. Frahn, L. W. Smith, *Aust. J. Chem.* **33**, 1105 (1980)]. The main pyrrolizidine alkaloids present in comfrey leaves are echimidine and 7-acetyllycopsamine, neither of which has been tested for carcinogenicity. Almost all tested 1,2-unsaturated pyrrolizidine alkaloids have been shown to be genotoxic and carcinogenic [H. Mori *et al.*, *Cancer Res.* **45**, 3125 (1985)]. Symphytine accounts for 5% of the total alkaloid in the leaves and has been shown to be carcinogenic [C. C. J. Culvenor *et al.*, *Experientia* **36**, 377 (1980)]. We assume that 1.5 g of intermediate size leaves are used per cup of comfrey tea (Table 1). The primary alkaloids in comfrey root are symphytine (0.67 g per kilogram of root) and echimidine (0.5 g per kilogram of root) [T. Furuya and M. Hikichi, *Phytochemistry* **10**, 2217 (1971)]. Comfrey-pepsin tablets (300 mg of root per tablet) have a recommended dose of one to three tablets three times per day. Comfrey roots and leaves both induce liver tumors in rats [I. Hirono, H. Mori, M. Haga, *J. Natl. Cancer Inst.* **61**, 865 (1978)], and the TD_{50} value is based on these results. Those pyrrolizidine alkaloids tested have been found to be at least

as potent as carcinogens such as symphytine. If the other pyrrolizidine alkaloids in comfrey were as potent carcinogens as symphytine, the possible hazard of a daily cup of tea would be HERP = 0.6% and that of a daily nine tablets would be HERP = 7.3%.

104. *Agaricus bisporus* is the most commonly eaten mushroom in the United States with an estimated annual consumption of 340 million kilograms in 1984–85. Mushrooms contain various hydrazine compounds, some of which have been shown to cause tumors in mice. Raw mushrooms fed over a lifetime to male and female mice induced bone, forestomach, liver, and lung tumors [B. Toth and J. Erickson, *Cancer Res.* **46**, 4007 (1986)]. The 15-g raw mushroom is given as wet weight. The TD_{50} value based on the above report is expressed as dry weight of mushrooms so as to be comparable to other values for TD_{50} in Table 1; 90% of a mushroom is assumed to be water. A second mushroom, *Gyromitra esculenta*, has been similarly studied and found to contain a mixture of carcinogenic hydrazines [B. Toth, *J. Environ. Sci. Health* **C2**, 51 (1984)]. These mushrooms are eaten in considerable quantities in several countries, though less frequently in the United States.
105. Safrole is the main component (up to 90%) of oil of sassafras, formerly used as the main flavor ingredient in root beer [J. B. Wilson, *J. Assoc. Off. Anal. Chem.* **42**, 696 (1959); A. Y. Leung, *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics* (Wiley, New York, 1980)]. In 1960, safrole and safrole-containing sassafras oils were banned from use in foods in the United States [*Fed. Regist.* **25**, 12412 (1960)]. Safrole is also naturally present in the oils of sweet basil, cinnamon leaf, nutmeg, and pepper.
106. Diet cola available in a local market contains 7.9 mg of sodium saccharin per fluid ounce.
107. Metronidazole is considered to be the drug of choice for trichomonal and *Gardnerella* infections [AMA Division of Drugs, *AMA Drug Evaluations* (American Medical Association, Chicago, IL, ed. 5, 1983), pp. 1717 and 1802].
108. Isoniazid is used both prophylactically and as a treatment for active tuberculosis. The adult prophylactic dose (300 mg daily) is continued for 1 year [AMA Division of Drugs, *AMA Drug Evaluations* (American Medical Association, Chicago, IL, ed. 5, 1983), pp. 1766–1777].
109. D. M. Siegal, V. H. Frankos, M. A. Schneiderman, *Reg. Toxicol. Pharmacol.* **3**, 355 (1983).
110. Supported by NCI Outstanding Investigator Grant CA39910 to B.N.A., NIEHS Center Grant ES01896, and NIEHS/DOE Interagency Agreement 222-Y01-ES-10066. We are indebted to numerous colleagues for criticisms, particularly W. Havender, R. Peto, J. Cairns, J. Miller, E. Miller, D. B. Clayson, J. McCann, and F. J. C. Roe.

Letters

Risk Assessment

With regard to the article by Bruce Ames *et al.* (17 Apr., p. 271), consider the following parable: I am steaming in my Berkeley hot tub when my neighbor leans over the redwood fence with a long spoon and sprinkles some TCE (trichloroethylene)into the hot tub. "What are you doing," I ask in some consternation. "It's so expensive to dispose of this legally, I thought I'd dispose of it this way," he replies. When I start to protest he points out that the "HERP" [*H*uman *E*xposure dose/*R*odent *P*otency dose] from the TCE is negligible when compared with the chloroform from the hot tub, the aflatoxin from my half-eaten peanut butter sandwich, and the basil in my herb salad. Although this has a reassuring effect on me, it does not prevent me from sloshing off to call my lawyer to obtain an injunction. This parable illustrates the strength and the weakness of the article by Ames *et al.* It *is* reassuring to assess exposures and risks in a larger context. But the decision to choose between action options (stay in the tub or call the lawyer) is governed by more than mere risk considerations. First, one must also consider the tangible and intangible costs of tolerating or replacing an exposure. This means that my neighbor should not count on convincing me to automatically accept risks comparable to those previously accepted on the basis of specific cost-benefit trade-offs made in other settings. Thus the fact that the Environmental Protection Agency, after considering the benefits of water chlorination, accepted a particular risk from trihalomethanes, does not mean that I or the proverbial rational decision-maker, would allow my neighbor to continue spooning TCE into my hot tub until the risk conveyed the same HERP as did the chlorination! Since there are no benefits from bathing in TCE I will predictably tolerate less risk from it than I would tolerate from the chlorination that prevents skin infection and unsightly algal blooms! There is a second class of considerations that is most important. These are societal and ethical considerations that override cost-benefit-risk considerations. Our society tends to be intolerant of situations in which exposures are involuntary or when one party derives the benefit and the other party bears the risk. We fear some illnesses and some ways of dying more than others. Slovic's article in the same issue of *Science* (17 Apr., p. 280) emphasizes the public concern with dread disease and unknown outcomes. Peter Sandman at Rutgers University has been publicly referring to these intangible constraints as the "outrage factor." It is outrageous for my neighbor to dispose of minute amounts of hazardous waste in my hot tub without my permission. Sophisticated decision analysts know this and take it into consideration as a constraint. Ames *et al.* ignore this factor and the decision-analysis literature that has tried to deal with it. Although helpful in overall perspective, the information in the article by Ames *et al.* provides little guidance in helping us to decide if we should initiate a program to *prevent* underground tanks from leaking or how polluted a well needs to be before we shut it down.

It is one thing to say that the degree of ground-water contamination to date does not warrant the kind of sensational treatment it has received in the press. It is another thing to ignore the "outrage factor" and the potential for worsening groundwater pollution and to imply that scientific data suggest that the problem should be passed over until the last smoker lays down his cigarette!

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Response: Neutra's hot tub parable is not germane to the issues raised by our article. We did not imply that cost-benefit-risk considerations should be the sole basis of public policy. Our intention was not to provide a new regulatory policy but rather to contribute scientific information and perspective.

Neutra's parable leaves out the benefits to everyone (including health) of modern technology. Every industry pollutes to some extent, and reduction of exposure to pollutants usually involves trade-offs, including loss of some benefits. Neutra's car pollutes the air for those of us who walk to work, but modern automotive technology benefits all of us, even those without cars, in many ways. A decision on whether or how much to increase the costs of transportation in order to reduce the pollution of cars and trucks, depends in part on understanding the true health costs of *each* option.

As we pointed out, modern technologies are constantly replacing older, more hazardous technologies. The reason billions of pounds of the solvents TCE and PCE (perchloroethylene—the main dry-cleaning solvent in the United States) are used is because of their low acute toxicity and the dangers of the flammable solvents they replaced. We have also pointed out that consideration of alternative substances and possible preventative measures should be part of the public policy decision-making process.

In the modern context of being able to measure parts-per-billion and parts-per-trillion levels of substances and the realization that there is universal human exposure to rodent carcinogens of natural origin, it is first important to prioritize among the plethora of possible hazards in order to avoid being distracted from working on the more important problems. The enormous uncertainties in the use of animal data to assess human risk and our lack of knowledge about the mechanisms of carcinogenesis make policy-making especially difficult; however, we do not imply that all problems should be passed over until the last smoker lays down his cigarette.

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Carcinogenicity of Aflatoxins

The generally well-presented articles and editorial in the "Risk Assessment" issue of *Science* (17 April) contain, by my count, 12 references to aflatoxin (a mold toxin, or mycotoxin) and one generalization about mycotoxins. Each reference is presented as an illustration of a point, but unfortunately much of the key information given is inaccurate and the reader may be left with an incorrect impression of the risk from aflatoxin and other mycotoxins and the management of that risk.

Richard Wilson and E. A. C. Crouch (p. 267) and Lester B. Lave (p. 291) imply a toxicological basis for the Food and Drug Administration (FDA) "action level" of 20 parts per billion of aflatoxins. In fact, that concentration was established in 1969, with no toxicological basis, as the lowest at which the identity of aflatoxin could be confirmed by the then available methods (*1*). Although improved methods now allow confirmation of identity (a prerequisite for legal action) at much lower concentrations, the "action level" has not been reduced.

Wilson and Crouch (table 3, p. 270), and Bruce N. Ames *et al.* (p. 271) state with varying degrees of certitude that aflatoxin is a human carcinogen, relying on outdated (Wilson and Crouch) or incomplete (Ames *et al.*) information; and Ames *et al.* (table 1, p. 273) list aflatoxin as a carcinogen for mice, an interpretation of the data that is questionable. The positive observations of liver malignancies in mice were from experiments in which large interperitoneal doses were used (*2*). Large doses given orally produced no tumors (*3*) (mice are generally considered to be refractory to aflatoxin carcinogenesis). Ames *et al.* could have discussed the considerable information on aflatoxin metabolism and pharmacodynamics (*4, 5*) in rats, mice, other susceptible and resistant species, and humans (in vitro) that points to between-species differences. The epidemiological evidence on which they rely for their conclusion "that aflatoxin is a human carcinogen" allowed a select committee of the International Agency for Research on Cancer, meeting in 1982, to conclude (*6*) only that the evidence for carcinogenicity in humans was limited, that is "a causal interpretation is credible, but alternate explanations such as chance, bias, or confounding could not be excluded." The studies on which this conclusion was based can be criticized (*4, 7*), and a confounding factor has since been determined to be chronic infection with hepatitis B virus (HBV). There is a strong association—an odds ratio of 223 for liver cancer in HBV carriers (*8*) compared with an odds ratio of 10 for lung cancer in cigarette smokers (*9*)—between liver cancer, the putative hazard from aflatoxin ingestion, and chronic infection with HBV (*10*) in areas of the world where liver cancer is encountered. The conclusion that aflatoxin is not a likely human carcinogen is supported by other independent studies of liver cancer (*7, 11*) and other cancers (*12*) in the United States. The current contention is that aflatoxin intoxication may interact with chronic HBV infection to produce liver cancer (*13*), but the evidence is not persuasive.

Ames *et al.* state (p. 273) that "[c]onsidering the potency of those mold toxins that have been tested and the widespread contamination of food with molds, they represent the most significant carcinogenic pollution of the food supply in developing countries." This subject has been reviewed (*14*). Of those mycotoxins likely to be contaminants of foods, only aflatoxin, ochratoxin A, patulin, penicillic acid, zearalenone, T-2 toxin, and deoxynivalenol have been studied with any degree of thoroughness. Aflatoxin and T-2 toxin have been implicated in acute human toxicoses; no mycotoxin has been linked with a specific cancer in humans. There has been speculation that one or more trichothecenes (for example, T-2 toxin) may be related to esophageal cancer in some areas of Africa and Asia and that ochratoxin A may be a factor in the endemic nephritis observed in the Balkans. However, the risk of human injury from patulin, penicillic acid, and zearalenone has been found to be insignificant. Another 28 mycotoxins have been shown to produce a cellular aberration by some type of mutagen screening test. I believe that jumping to conclusions from such evidence is hazardous. Interest and enthusiasm can easily affect the unwary to the point that speculation changes to increasing degrees of certainty, with no change in material evidence. Scientists are not immune to this disease.

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REFERENCES

1. L. Stoloff, *J. Assoc. Off. Anal. Chem.* **63**, 1067 (1980).
2. S. D. Vesselinovitch, N. Mihailovich, G. N. Wogan, L. S. Lombard, K. V. N. Rao, *Cancer Res.* **32**, 2289 (1972).
3. G. N. Wogan, *Methods Cancer Res.* **7**, 309 (1973); D. B. Louria, G. Finkel, J. K. Smith, M. Buse, *Sabouraudia* **12**, 371 (1974).
4. L. Stoloff, in *Mycotoxins and Phycotoxins*, P. S. Steyn and R. Vleggaar, Eds. (Elsevier, Amsterdam, 1986), pp. 457–471.
5. W. F. Busby, Jr., and G. N. Wogan, in *Chemical Carcinogens*, C. E. Searle, Ed. (American Chemical Society, Washington, DC, 1984), pp. 945–1136.
6. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 4 to IARC Monographs, Vols. 1–29* (International Agency for Research on Cancer, World Health Organization. Lyon, France, 1982), pp. 11 and 31.
7. D. J. Wagstaff, *Regul. Toxicol. Pharmacol.* **5**, 384 (1985).
8. R. P. Beasley, L-Y. Hwang, C-C. Lin, C-S. Chien, *Lancet* **1981-II**, 1129 (1981).
9. R. Doll and R. Peto, *J. Natl. Cancer Inst.* **66**, 1191 (1981).
10. B. S. Blumberg and W. T. London, *ibid.* **74**, 267 (1985); *Technical Report Series No. 691* (World Health Organization, Geneva, 1983).
11. L. Stoloff, *Nutr. Cancer* **5**, 165 (1983).
12. T. J. Mason, F. W. McKay, R. Hoover, W. J. Blot, J. F. Fraumeni, Jr., *HEW Publ. No. (NIH) 75-780* (Department of Health, Education, and Welfare, Washington, DC, 1975).
13. S. J. Van Rensburg *et al.*, *Br. J. Cancer* **51**, 713 (1985).
14. L. Stoloff, in *Carcinogens and Mutagens in the Environment*, vol. 1, *Food Products*, H. F. Stitzh, Ed. (CRC Press, Boca Raton, FL, 1982), pp. 97–119.

Response: We and Stoloff are apparently in agreement that aflatoxin is a carcinogen in several species, and that species differ in their sensitivity. Although, as we indicated in our table, there are no positive experiments in mice that are suitable for calculation of TD_{50}, our "+" in mice is based on the evaluation of the International Agency for Research on Cancer that aflatoxin induces tumors in that species. The epidemiological data suggest that it is a human carcinogen in combination with hepatitis B virus, although we agree with Stoloff that the evidence is not of the same certainty as that linking smoking and cancer (*1*). What our HERP (*H*uman *E*xposure dose/*R*odent *P*otency dose) ranking points out is that at current levels of human exposure and given the potency in rats, the possible hazard of aflatoxin in a peanut butter sandwich is greater by 10 to 100 times than possible hazards from several environmental pollutants, including trichloroethylene in contaminated well water and ethylene dibromide residues in grain. Yet those synthetic contaminants are given greater regulatory scrutiny on the basis of the results of animal experiments and even in the absence of epidemiological data, indicating that they might be carcinogenic in humans. In extreme cases in the United States HERP values for aflatoxin reached levels of 6% of the TD_{50} dose, which seems to us reason for concern. We also stand by our statement on pollution by molds in developing countries. In addition, new mutagenic mold toxins in food are constantly being found when they are looked for, and it is reasonable to suppose many will be found to be carcinogenic (*2*).

We stress that it is important to view the possible hazard of aflatoxin from the perspective of the many everyday possible hazards of life and with the knowledge that there are a great many uncertainties in the use of animal bioassay data in extrapolation to humans. As we discussed at length, the promotional aspects of cancer are also critical, and it is likely that the hazard from aflatoxin will be much lower in the absence of some toxicity in the liver such as from hepatitis virus, alcoholic cirrhosis, or the maximum tolerated dose in rodents. Since the HERP values for synthetic pollutants, including pesticides, are usually an order of magnitude less than that from aflatoxin, concern over them should be even less.

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REFERENCES

1. H. Autrop, T. Seremet, J. Wakhisi, A. Wasunna, *Cancer Res.* 47, 3430 (1987); S. V. Thomson *et al.*, *J. Appl. Environ. Microbiol.* 35, 1150 (1978); S. J. Cheng *et al.*, *Carcinogenesis* 6, 903 (1985).

Response: We generally agree both with Stoloff's letter and the response of Ames *et al.* However, we *were* aware that the reliability of the connection between human cancers and exposure to aflatoxin B1 has been called into question by the realization that a more important risk factor is infection with hepatitis B virus, which inevitably confounds the data. Nonetheless, we believe that the certainty for human carcinogenesis is high, although not absolute; it is certainly superior to the evidence for cancers caused by dioxin. The 20 parts-per-billion action level for aflatoxin in peanut butter may indeed have been set at a detection limit (although we do not like this practice). However, as Stoloff himself points out, it has *not* been reduced, although a modest, in our view inadequate, proposal to reduce it to 15 ppb was made in 1977 long after more sensitive detection equipment was available. The proposal was abandoned.

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Risk Assessment

Risk assessment may have its funny side, as noted by Daniel E. Koshland, Jr. (Editorial, 17 Apr., p. 241), but current mismanagement of risk by regulatory agencies is no laughing matter. Identifying, controlling, and setting priorities for risks within the areas that Congress has designated for federal activity has been extraordinarily inconsistent and unprotective. Koshland's reaction is not unlike that of most environmentalists, who have long worried that the practice of risk assessment to date has not improved health or advanced policy.

Unfortunately, the special Risk Assessment issue of *Science* (17 April) does not provide a fresh examination of issues, in large part because the authors selected have familiar and entrenched positions. Instead, it reinforces three persistent fallacies: First, that the only primary concern is cancer; second, that the data on exposure are reliable; and third, that bare calculations of health risk can be expected to guide human behavior.

Richard Wilson and E. A. C. Crouch (p. 267) have long lamented the failure of the public to rationalize their "risk portfolios," which suggests that the authors rather than the public are slow to learn that no one makes choices solely on the basis of simple equations or point estimates. Physicist-sociologists of risk need to note that some of the recent work in the study of economic behavior has provided a framework for a more complex analysis of consumer choice in the marketplace in place of simple comparisons of marginal benefit and cost. The proposal by Bruce N. Ames *et al.* (p. 271) for ranking risk of carcinogens, while elegant in structure, is not realistic or implementable. First, as a basis for the HERP (*H*uman *E*xposure dose/*R*odent *P*otency dose), it relies heavily on the assumption that there are reliable data on exposure. Assessment of exposure remains the weakest aspect of evaluating risks for regulatory purposes. The failure to require meaningful information on new chemicals and overreliance on models rather than on monitoring have resulted in a void of information for calculating human exposure. When this lack of data is factored into an equation already burdened by the range of unresolved issues and uncertainties of risk assessment (*1*), it is doubtful how much practical use the approach of Ames *et al.* can be. Second, any comprehensive system ranking risk should be capable of devolution to deal with risk control decisions at the margin. That is, it is important to be able to determine how to deal with, for instance, risks of dioxin from incinerator emissions in populations who smoke, eat certain foods, sunbathe, or otherwise engage in risky business. It is hard to know how to use the approach of Ames *et al.* for this critical assessment.

Finally, the approach of Ames *et al.* and much of the discussion of risk assessment in *Science* and elsewhere continues to confine our national debate to one end point—cancer risk. While evaluating the potential risks of chemicals as carcinogens is important, the human disease and dysfunction that can reasonably be associated with impacts of chemical exposure and environmental modifications are likely to be expressed in many other outcomes. The debate on risk assessment needs to be radically revised; it should start with an assessment of health status in the United States and then move to a consideration of which impairments of health might reasonably be associated with exposure to chemical agents, with the use of such techniques as biological markers to support proposed linkages (*2*). After such an analysis, rational ranking might occur.

This method would revise our current practice of going from the chemical by means of its toxicology to the estimation of health impact, the Environmental Protection Agency dogma of hazard identification, risk characterization, exposure assessment, and then to risk assessment, as explicated by Milton Russell and Michael Gruber (p. 286). Such an approach, while radically different from current science policy, could avoid some of the silliness of current regulatory practice, which provokes not only the amusement of scientists but also the disgust of the public as it observes continued failure to deal efficiently, at the source, with obviously significant environmental risks like lead, sulfur dioxide, radon, formaldehyde, and asbestos.

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REFERENCES

1. E. K. Silbergeld, *Nat. Res. Environ.* **2**, 17 (1986).
2. Board on Environmental Sciences and Toxicology, National Academy of Sciences–National Research Council, *Biological Markers and Environmental Medicine* (National Academy Press, Washington, DC, in press).

Response: Silbergeld does not emphasize the importance of setting priorities in research and regulation, so that efforts to protect public health are not diverted from the most important issues. Since regulation of carcinogens has been based largely on results of rodent bioassays, it is necessary to recognize that about half of all chemicals tested at the maximum tolerated dose are carcinogens in rodents, whether the chemicals are natural or man-made. We believe that our attempts to provide a framework for setting priorities among human exposures to rodent carcinogens is of practical use. One contribution is to show that possible carcinogenic hazards to humans from current levels of pesticide residues or water pollution are likely to be of minimal concern *relative* to the background levels of natural substances, although one cannot say whether these natural exposures are likely to be of major or minor importance. Another contribution is to examine the many uncertainties in relying on animal cancer tests for human prediction given our current understanding of the mechanisms of carcinogenesis.

Silbergeld states that it is a fallacy to treat

cancer as "the only primary concern." We agree: it is also desirable to set priorities for chemicals that cause other toxicological problems. In both cases it is counterproductive to focus on quantities that are minute relative to their toxic level. Although our work focused on cancer, our methods are also relevant to other biological end points, including reproductive damage. Ranking priorities among possible teratogenic hazards is important, especially since fully one-third of the 2800 chemicals tested in laboratory animals have been shown to induce birth defects at maximum tolerated doses (*1*). Humans are ingesting enormous excesses of natural chemicals compared with man-made ones. For example, we ingest about 10,000 times more of nature's pesticides than man-made pesticide residues (*2*). Thus, one priority should be to estimate whether their toxicological effects might be in about the same proportion. There is no convincing evidence, either epidemiological or toxicological, to suggest that pollution is likely to be of great teratogenic interest relative to the background of natural chemicals.

Silbergeld's reference to dioxin pollution seems to imply that new incinerators should not be built until we know that dioxin poses no harm "to people who smoke, eat certain foods, sunbathe, or otherwise engage in risky business." Such an approach is impractical toxicologically and is an invitation to paralysis. To attempt to avoid all exposures that might cause some type of harm to someone under some circumstances ignores the background of natural hazards, the benefits of technology, and the hazardous side effects of the alternatives when some technology is eliminated. Is dioxin of importance at the tiny levels people are exposed to from incinerators when compared with the "risky business" people are already engaged in? Silbergeld's letter has prompted us to compare dioxin and alcohol in terms of the exposures to humans relative to the dose levels that have been shown to be teratogenic to mice in laboratory experiments. Unlike dioxin, alcohol is a known, and important, human teratogen. The teratogenic dose of alcohol for mice is more than a million times greater than the teratogenic dose of dioxin, similar to the difference in carcinogenic doses for the two chemicals. However, because the dose of alcohol in a bottle of beer is very high, drinking a daily beer would pose a possible teratogenic hazard about the equivalent of eating a daily kilogram of dirt contaminated with 1 part per billion of dioxin. Soil ingestion is considered by government regulatory agencies to be the main possible route of exposure (*3*). Given the information available concerning Silbergeld's example, our highest priority should be to warn people about the carcinogenic and teratogenic hazards of smoking and alcohol and of the carcinogenic hazards of sunbathing and to investigate the dietary imbalances that appear likely to be major causes of cancer.

Silbergeld laments the quality of exposure data. Yet our society has made an enormous effort to measure exposures to man-made pollutants and to regulate them at a large economic cost. We have turned up remarkably little of public health interest aside from occupational hazards. Additional measurements of parts per billion or per trillion of man-made pollutants do not seem likely to make a major contribution.

Silbergeld states that the public is concerned with more than "bare" calculations of health risks. That may be, but it is the job of scientists to provide the best estimates that they can about possible hazards. This includes putting worst-case estimates of hypothetical human risks in perspective. Our work suggests that traces of pollutants are likely to be of only minimal concern relative to the background of natural chemicals. Epidemiological evidence indicates that there is no epidemic of cancer (other than that due to smoking) or of birth defects.

The biological understanding of the causes of cancer and birth defects is progressing remarkably rapidly, considering the complexity of the problem. Silbergeld's suggestions are not likely to change the priorities of the many accomplished scientists working in this area.

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REFERENCES

1. J. L. Schardein, B. A. Schwatz, M. F. Kenal, *Environ. Health Perspect.* **61**, 55 (1985).
2. B. N. Ames, R. Magaw, L. S. Gold, *Science* **236**, 271 (1987).
3. D. J. Paustenbach, H. P. Shu, F. J. Murray, *Regul. Toxicol. Pharmacol.* **6**, 284 (1986).

Response: The criticism by Silbergeld should primarily be addressed to the risk management procedures of the federal government and society in general. One possible reason that risk management has been inconsistent is a failure of regulatory agencies to properly inform the managers in the same agencies. For example, the Office of Drinking Water Standards of the Environmental Protection Agency, in a discussion of risks of organic hydrocarbons (*1*), omits any *mention* of chloroform, thereby withholding from the Administrator and from the public the instructive comparison with risks of trichloroethylene in our table 2 and on page 269 of our article.

We agree that no one makes choices solely on the basis of simple equations or point estimates and have said so in almost all of our writings, including the last paragraph of our article in *Science*. However, that is no excuse for not accurately determining the point estimate—and the uncertainty of that estimate—and for putting these numbers into perspective by comparison.

Public health officials, both in private and public, have in the last century emphasized acute effects that occur as a result of a short, high exposure. For these it is generally assumed that a low exposure means a risk close to zero. Risk assessors follow public demand in addressing the risk of cancer—a chronic effect arising from long exposure, often at lower levels. For these it is often assumed that there is linearity between response (probability of cancer) and dose. However, as we emphasized, the risk calculations for cancer can be a surrogate for other end points also.

Since for chronic effects risk is approximately dose times potency, dose information is vital. When it is available, a direct comparison such as, for example, for the radiation doses in our table 1, is less uncertain, and we find that people are helped by this. Again, however, we find that regulatory agencies and newspapers often omit this comparison, thereby failing to adequately inform the public of the risk and its meaning. This makes the risk assessment useless and any decision less well based than it need be.

We would also like to note, as kindly pointed out by Ernest V. Anderson, that in the discussion in our article of "Expression of risks" (p. 270, paragraph 2, line 24), an arithmetic error occurred: 0.0047% should have been 0.023%.

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REFERENCES

1. *Fed. Regist.* **50**, 46880 (13 November 1985).

Paleolithic Diet, Evolution, and Carcinogens

Philip H. Abelson (Editorial, 31 July, p. 473) and Bruce N. Ames *et al.* (Articles, 17 Apr., p. 271) observe that cancer is a complex of diseases with multiple causes, ranging from carcinogens and hormonal factors to chronic infectious diseases and dietary patterns. Moreover, Ames *et al.* advise that naturally occurring carcinogens in the food supply are generally more toxic than industrial carcinogens, excepting workplace exposures. This interpretation of greater toxicity of food-borne carcinogens derives from the HERP [*H*uman *E*xposure dose/*R*odent *P*otency dose] index of Ames *et al.*, which uses data from animal studies of carcinogenicity and finds alcohol and peanut butter more potent than pesticide residues.

While the work of Ames *et al.* presents an interesting use of toxicological data, it should not be construed as the final word on the role of synthetic organic carcinogens in producing cancer patterns in humans. The relative contribution of different synthetic and natural toxicants to human evolution and to current cancer and other disease patterns is a complex matter. A National Research Council (NRC) report (*1*) noted that many of the nondietary toxicants in foods are not known to be harmful to normal healthy human beings when the foods are prepared in time-honored ways. Adequate cooking reduces or destroys the harmful properties of the cyanogenetic glycosides in the lima bean, the goitrogens in certain vegetables, thiaminase in fish, and avidin in the egg. After ripening, the ackee fruit and grapefruit lose their toxic components.

Some observations from studies of Paleolithic nutrition may also be relevant, as widely varying foods were available to evolving hominids at least 4 million years ago. (*2*). Ames *et al.* note that some pyrolysis products are potent carcinogens. However, fire-cooked wild game meats have been consumed by humans for at least 700,000 years; for example, in Lantian, China (*3*), along with a variety of plants (*4*).

A recent visit with my son Aaron to the expanded exhibit at the Hall of Fossils of the Smithsonian Institution's Museum of Natural History provided some relevant information. Reconstructions of the earliest archeological sites of human ancestors indicate that the larger, more robust form of Australopithecus, *Homo robustus*, died out about 1 million years ago and probably depended on vegetable foods, as its huge molar teeth and massive jaws are well adapted for such a rough diet. A sagittal crest (bony ridge of the top of the skull) and protruding cheek bones anchored the strong chewing muscles. The hominids from which we evolved had teeth that were adapted for an omnivorous diet of vegetables and meat and lived about 1.2 to 3 million years ago. Moreover, the range of early diets was extensive, from protein rich diets of far northern peoples to the vegetable-laden diets of the Australian Kalahari.

To be sure, materials causing chronic illnesses that are commonly expressed in postreproductive persons would not have a selective influence on the evolution of human genotypes. However, such materials could have had major effects on human development. Experimental data suggest that few carcinogens are not also toxic to reproduction (*5*). Thus, exposure to food-borne toxicants in early humans may have selected out genotypes that produced spermatocytes, oocytes, embryos, and fetuses with susceptibility to toxic constituents of foods. Early pregnant humans may have experienced spontaneous abortions due to prenatal and other exposures to carcinogens in the food supply, which would have produced genetic resistance in the human genome.

Nearly four decades ago, J. B. S. Haldane argued that diseases are responsible for much of the observed biochemical and genetic variability of wild populations, insofar as the struggle against disease plays an important evolutionary role (*6*). Reasoning that a small biochemical change provides a host species a substantial degree of resistance, Haldane argued that it is an advantage to a species to be biochemically diverse.

Whatever the role of evolution may prove to be, humans have been eating complex foods far longer than they have been exposed to synthetic, organic carcinogens. Moreover, some cancer patterns in the United States have changed markedly and recently in ways that are unlikely to be related to changes in food consumption. Other cancers, such as breast cancer, appear closely related to patterns of dietary fat consumption (*7*). But several cancers, with no known or suspected nutritional basis, have been increasing. Moreover, some food-related cancers, including stomach cancer have been declining in many industrial countries (*8*). In the United States cancers in persons under age 45 have also declined markedly in recent years (*9*). In contrast, multiple myeloma, lung cancer, and brain cancer have increased at least 50% from 1968 to 1978 in white and nonwhite persons aged 75 to 84. (*9, 10*). From 1975 to 1984, the age-adjusted U.S. cancer mortality rate rose from 162.2 to 170.7 per 100,000 individuals; during this same time, the death rate per 100,000 for nonlung cancer changed from 125.4 to 125.1 (*11*).

In light of these complex patterns, serious research needs to be done on possible changes in the environment in the past that could account for these patterns. Whether recent chemical exposures are linked with changing cancer patterns in the elderly remains an open question. However, in the past three decades, production of synthetic organic chemicals grew exponentially (Fig. 1). This older cohort includes persons who have lived long enough to experience cancers that may be associated with such exposures.

As Ames *et al.* point out, the range of variation in worldwide cancer patterns is substantial, running at least sixfold, and many cancers occur with even greater variation (*8*). Diet alone is unlikely to explain all of this variation, nor are changes in diet likely to be involved with some of the specific changes noted above.

The relative roles of food and nonfood carcinogens are unclear. It is highly likely that the impact of the latter may differ qualitatively from that of the former. Also synergies may occur between them, with newer compounds enhancing the toxicity of longer established compounds. In light of the relatively recent increase in the volume of production of some carcinogenic and other hazardous substances, it is not now possible to determine the extent to which exposures to such chemicals will influence future cancer rates. Prudent public policy dictates that additional research be conducted on the relative potencies of these materials for humans.

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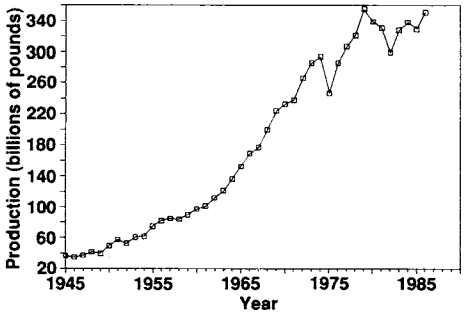

Fig. 1. Production of synthetic organic chemicals, including tar and primary products from petroleum and natural gas, 1945 to 1986.

REFERENCES

1. National Research Council, *Toxicants Occurring*

Naturally in Foods (National Academy of Sciences, Washington, DC, 1966).
2. S. B. Eaton and M. J. Konner, *N. Engl. J. Med.* **312**, 283 (1985).
3. J. D. Clark and J. W. K. Harris, *Afr. Archaeol. Rev.* **3**, 3 (1985).
4. A. B. Stahl, *Curr. Anthropol.* **25**, 151 (1984).
5. D. L. Davis, *Toxic Subst. J.* **1**, 205 (1979).
6. J. B. S. Haldane, *On Being the Right Size and Other Essays* (Oxford Univ. Press, Oxford, England, 1985).
7. National Research Council, *Diet, Nutrition and Cancer* (National Academy of Sciences, Washington, DC, 1983).
8. *Cancer Incidence on Five Continents* (International Agency for Research on Cancer, Lyon, France, 1976), vol. 3.
9. S. S. Devesa *et al. J. Natl. Cancer Inst.* **79**, 701 (1987).
10. D. L. Davis, A. D. Lilienfeld, A. Gittelsohn, M. E. Scheckenbach, *Toxicol. Ind. Health* **2**, 127 (1986).
11. J. C. Bailar, III, *Issues Sci. Technol.* **4**, 16 (1987).

Response: Davis takes issue with our documentation that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances. She indicates that humans, as opposed to rats or mice, may have developed *specific* resistance to these natural chemicals, since we have been selected by evolution to deal with plant toxins or cooked food. This is unlikely, because, as we discussed in our article, both rodents and humans have developed many types of *general* defenses against the large amounts and enormous variety of toxic chemicals in plants (nature's pesticides). These defenses include the constant shedding of the surface layer of cells of the digestive system, the glutathione transferases for detoxifying alkylating agents, the active excretion of hydrophobic toxins out of liver or intestinal cells (*1*), numerous defenses against oxygen radicals (*2*), and DNA excision repair. The fact that defenses appear to be mainly general, rather than specific for each chemical, makes good evolutionary sense and is supported by various studies. Experimental evidence indicates that these general defenses will work against both natural and synthetic compounds, since basic mechanisms of carcinogenesis are not unique to either.

We also pointed out that humans ingest about 10,000 times more of nature's pesticides than man-made pesticides. Relatively few of nature's pesticides that we are eating have been tested for carcinogenicity, but about half of the naturally occurring substances that have been tested in rats and mice are carcinogens. We also pointed out that the modern diet is vastly different from that of a few thousand years ago or of primitive man (*3*). Davis dismisses dietary and other life-style factors too readily as potential causes of cancer that do not change; they do change all of the time. For example, as part of the back-to-nature movement we are eating canavanine in alfalfa sprouts, carcinogenic hydrazines in raw mushrooms, and carcinogens in herb teas. Cooking food does destroy some carcinogens but also makes others, such as the variety of nitrosamines and nitropyrenes formed when food is cooked in gas ovens, a relatively recent invention. Davis' argument that natural selection eliminated all hazards from carcinogens acting late in life because they are reproductive toxins is not supported by good evidence and appears unlikely.

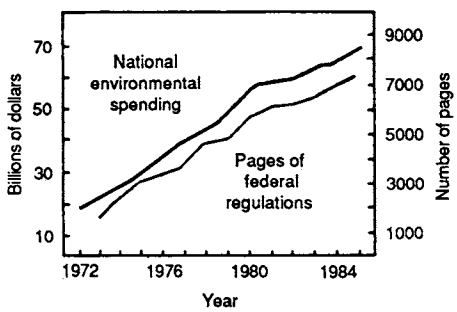

Fig. 1. Expenditures for environmental protection (*8*).

We have discussed why "risk assessment" based on worst-case scenarios may not have much to do with biological reality for either synthetic or natural chemicals. Linear extrapolations from results at the maximum tolerated dose may enormously exaggerate risks at low dose if, as appears to be true, an important aspect of carcinogenesis is cell proliferation, which may frequently result from the high (maximally tolerated) doses of test chemicals administered in rodent bioassays (*4*). Concern with very low doses is even more likely to be misplaced for agents suspected of causing birth defects, because of a threshold effect. In this respect it would be useful to compare rodent data for particular synthetic chemical pollutants with those for a representative set of natural chemicals, analogous to our HERP index comparisons. One important comparison to be made would be that between alcohol and other rodent teratogens. Alcohol is a leading cause of mental retardation in humans (fetal alcohol syndrome), and such a comparison would put possible teratogenic hazards into perspective.

The key issue is not that production of synthetic chemicals has gone up markedly in recent years, but whether the tiny amounts of pesticide residues or water pollutants we are ingesting are likely to be important in human cancer. In our ranking, such exposures are very low compared with the background of natural carcinogens, but we also pointed out that workplace exposures often rank high (*5*).

Davis contends that the incidence of brain tumors and multiple myelomas in the elderly has clearly increased. However, Doll and Peto, in a detailed analysis of the causes of human cancers, convincingly point out why such apparent increases may be due to recent improvements in diagnosis (*6*). Peto concluded, in commenting on this matter (*7*, p. 283), that "Future trends may differ substantially from recent trends, of course, but at present the U.S. data contain no clear evidence for any generalized increase in cancer over and above that due to the delayed effects of tobacco. Opposite conclusions by other commentators appear to derive chiefly from methodological oversights."

From a policy perspective, we discussed in our article that it is prudent to consider the benefits of modern technology and also the alternative substances that might replace regulated compounds. Modern chemicals commonly replaced more hazardous substances, for example, chlorinated solvents replaced flammable solvents. Modern technology, which concomitantly causes the increase in production of synthetic chemicals, has contributed in important ways to our steadily increasing life-span. Currently, as a society our expenditures on pollution abatement and control are more than $80 billion annually (Fig. 1), despite the uncertainty of whether environmental pollutants at parts-per-billion levels have public health significance. We believe that the potential carcinogenic hazards of pollutants should be evaluated in the context of background level exposures to natural substances until science makes the further understanding of mechanisms clearer, as we emphasized in our article.

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REFERENCES

1. F. Thiebaut *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 7735 (1987).
2. B. N. Ames, in *Detection Methods for DNA-Damaging Agents in Man* (International Agency for Research on Cancer, Lyon, France, in press).
3. L. A. Cohen, *Sci. Am.* **257**, 42 (November 1987).
4. J. A. Swenberg *et al.*, *Environ. Health Perspect.*, in press.
5. L. S. Gold, G. M. Backman, N. K. Hooper, R. Peto, *ibid.*, in press.
6. R. Doll and R. Peto, *The Causes of Cancer* (Oxford Univ. Press, Oxford, England, 1981).
7. R. Peto, in *Quantification of Occupational Cancer*, R. Peto and M. Schneiderman, Eds. (Banbury Report 9, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1981), pp. 269–284.
8. J. Hirschhorn, *Serious Reduction of Hazardous Waste* (Office of Technology Assessment, Washington, DC, 1986), figure 1, p. 8.