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# Ranking Possible Carcinogenic Hazards

BRUCE N. AMES,* RENAE MAGAW, LOIS SWIRSKY GOLD

**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.

B. N. Ames is associated with the Department of Biochemistry, University of California, Berkeley, CA 94720. R. Magaw and L. Swirsky Gold are associated with the Biology and Medicine Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720.

*To whom reprint requests should be sent.

## 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) | 506 | *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.

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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.

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# Letters

## 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.

LEONARD STOLOFF
*13208 Bellevue Street, Silver Spring, MD 20904*

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*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.

BRUCE N. AMES
RENAE MAGAW
*Department of Biochemistry,*
*University of California,*
*Berkeley, CA 94720*
LOIS SWIRSKY GOLD
*Lawrence Berkeley Laboratory,*
*Berkeley, CA 94720*

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*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.

RICHARD WILSON
E. A. C. CROUCH
*Department of Physics* and *Energy and*
*Environmental Policy Center,*
*Harvard University,*
*Cambridge, MA 02138*

# Letters

## 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.

ELLEN K. SILBERGELD
*Environmental Defense Fund, 1616 P Street, NW, Washington, DC 20036*

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*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.

BRUCE N. AMES
*Department of Biochemistry, University of California, Berkeley, CA 94720*
LOIS SWIRSKY GOLD
*Biology and Medicine Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720*
RENAE MAGAW
*Department of Biochemistry, University of California, Berkeley*

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*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%.

RICHARD WILSON
E. A. C. CROUCH
*Department of Physics and Energy and Environmental Policy Center, Harvard University, Cambridge, MA 02138*

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# 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!

RAYMOND NEUTRA
*956 Evelyn Avenue, Albany, CA 94706*

*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.

BRUCE N. AMES
RENAE MAGAW
*Department of Biochemistry, University of California, Berkeley, CA 94720*
LOIS S. GOLD
*Biology and Medicine Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720*

## 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.

DEVRA LEE DAVIS
*Board on Environmental Studies and Toxicology, National Research Council, 2101 Constitution Avenue, NW, Washington, DC 20418*

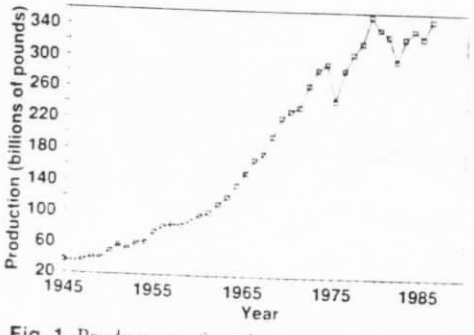


Fig. 1. Production of synthetic organic chemicals, including tar and primary products from petroleum and natural gas, 1945 to 1986.

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SCIENCE 240, 1045-1047 (1988)

## Technical Comments

# Carcinogenic Risk Estimation

In their widely publicized and popularized article "Ranking possible carcinogenic hazard," Bruce N. Ames *et al.* (17 Apr. 1987, p. 271) conclude that "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" and thus that the "high costs of regulation" of such environmental carcinogens are unwarranted. These conclusions reflect both flawed science and public policy.

Although Ames *et al.* challenge the validity of animal carcinogenicity data for quantitative estimation of human risk, they nevertheless use such extrapolations, based on the percentage *H*uman *E*xposure dose/*R*odent *P*otency dose (HERP), for ranking carcinogenic hazards. Apart from the fact that HERP rankings are based on average population exposures excluding sensitive subgroups, such as pregnant women, the derived potencies of Ames *et al.*, doses inducing tumors in half the tumor-free animals, are misleading. Potencies for "synthetic pollutants," such as trichloroethylene, are derived from bioassays in which lowest doses are large fractions of the maximally tolerated dose (MTD), whereas potencies for more extensively studied "natural carcinogens," such as aflatoxins, are generally derived from titrated doses, orders of magnitude below the MTD. Since dose-response curves are usually flattened near the MTD (*1*), potencies derived from high-dose testing yield artificially low risk estimates; HERPs for "synthetic" carcinogens are thus substantially underestimated compared with many "natural carcinogens."

Compounding this misconception, Ames *et al.* maintain that carcinogenic dose-response curves rise more steeply than linear curves and that tumor incidences increase more rapidly than proportional to dose. At high doses, dose-response curves are usually less steep than linear curves (*1*), as also recognized elsewhere by Ames and his colleagues (*2*). Thus at MTD doses, large further dose increases may induce only small increases in tumor incidence, perhaps reflecting competition between transformation and cytotoxicity (*3*); linear extrapolations from high-dose tests thus underestimate low-dose risks.

For Ames *et al.*, the term "carcinogen" heterogeneously includes direct and indirect influences, including promoting and modifying factors and mutagens. Caloric intake is considered "the most striking rodent carcinogen." However, no correlations have been established between food intake and tumor incidence among animals eating ad libitum, despite wide variations in caloric intake and body weight (*4*), nor have correlations been established between obesity and most human cancers. In the statement by Ames *et al.*, "at the MTD a high percentage of all chemicals might be classified as 'carcinogens'," toxicity and carcinogenicity are confused. However, among some 150 industrial chemicals selected as likely carcinogens and tested neonatally at MTD levels, fewer than 10% were carcinogenic (*5*). Many highly toxic chemicals are noncarcinogenic, and carcinogen doses in excess of the MTD often inhibit tumor yields. While Ames *et al.* revive the discredited theory that chronic irritation causes cancer, most irritants are noncarcinogenic, and there is no correlation between nonspecific cell injury and carcinogenic potency (*6*).

Ames *et al.* classify ethanol as carcinogenic, "[one of the two] largest identified causes

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*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.

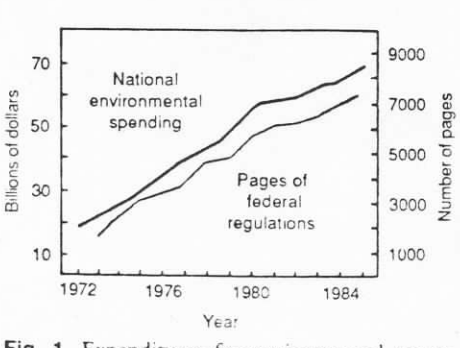


**Fig. 1.** Expenditures for environmental protection (*8*).

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.

BRUCE N. AMES
*Department of Biochemistry, University of California, Berkeley, CA 94720*
LOIS SWIRSKY GOLD
*Lawrence Berkeley Laboratory, Berkeley, CA 94720*

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## Definition Required

Concerning "Science and mutual self-interest" by David Dickson and Colin Nor-

of neoplastic death in the United States" along with tobacco; their HERP indices for a daily glass of wine and "average" occupational exposure to formaldehyde are similar. In four rodent tests cited by Ames *et al.*, alcohol was noncarcinogenic; in the fifth, an experiment with alcohol of undefined purity, carcinogenicity was "extremely low." While epidemiologic studies have incriminated alcohol—particularly in promoting or synergizing tobacco smoke, in upper digestive tract cancers, and also in inducing cirrhosis, a risk factor for liver cancer (*7*)—there is no evidence incriminating alcohol per se as a potent carcinogen for the general population, particularly nonsmokers. Although two cohort studies not cited by Ames *et al.* demonstrate weak associations between breast cancer and alcohol consumption (*8*), their significance is limited by minimal dose-response relationships, several contrary studies, and the contamination of alcoholic beverages with carcinogens including urethane, methylglyoxal, nitrosamines, and pesticide residues.

While diffusely defining carcinogens, Ames *et al.* artificially categorize them as "natural" or "industrial," saying that the former hazards should somehow limit concerns on the latter. However, dietary levels of "natural carcinogens" such as aflatoxins and dimethylnitrosamine are influenced by harvesting and storage technologies and nitrite additives, respectively. Moreover, predominant exposure to other "natural carcinogens" results from industrial activity; examples include asbestos, heavy metals, uranium, and formaldehyde. While emphasizing "natural carcinogens" and "nature's pesticides" in food as major carcinogenic exposures, Ames *et al.* ignore natural dietary anticarcinogens and antimutagens, such as porphyrins, phenolics, and retinoids (*9*). Although risks from aflatoxin and alcohol, described as two most important and potent carcinogens, depend on synergism with hepatitis B virus and tobacco smoke, respectively, risk estimates for most synthetic carcinogens are based on single-agent exposures only. While "natural carcinogens" have long played a role in human cancer, concerns must also focus on recent incremental effects of increased production of and exposure to nonsynthetic carcinogens, such as asbestos and heavy metals, and on the novel and escalating production and exposure to "synthetic carcinogens" (*10*). Although some petrochemicals have been proved to be carcinogenic, most have not been tested; moreover, much industrial data is at best suspect or unavailable (*11*).

The National Institute for Occupational Safety and Health estimates that 11 million workers are exposed to ten high volume industrial carcinogens (*12*). Up to tenfold increases in organ-specific cancer rates are reported among those who work with asbestos, uranium, and arsenic and in coke plants and among those exposed to specific petrochemicals and to some 20 less well-defined processes, such as dry cleaning, spray painting, and plumbing (*12*); excess childhood leukemia is also associated with parental occupational exposures to organic solvents and related chemicals (*13*). Just one of the few well-studied occupational carcinogens, asbestos, responsible for up to 10,000 annual cancer deaths (*14*), is second only to tobacco of all known causes of human cancer.

Growing evidence demonstrates that pervasive contamination of air, water, soil, and food with a wide range of industrial carcinogens, generally without public knowledge and consent, is important in causation of modern preventable cancer. Even if hazards posed by any industrial carcinogen are small, their cumulative, possibly synergistic, effects are likely substantial. Eating food contaminated with residues at maximum legal tolerances of only 28 of 53 known carcinogenic pesticides, excluding numerous other carcinogenic pesticides and incremental exposure in drinking water, is estimated to be potentially responsible for 1.5 million excess lifetime U.S. cancers (*15*). Trichloroethylene is a common contaminant of drinking water, generally resulting from improper disposal of industrial wastes; lifetime consumption levels of 250 parts per billion found in contaminated wells in Woburn, Massachusetts, together with other related carcinogens not considered by Ames, *et al.*, is associated with excess risks of cancer (*16*), childhood leukemia, perinatal deaths, and birth defects (*17*). Some 20 retrospective and case control studies have associated trihalomethane-contaminated water with gastrointestinal and urinary tract cancers (*18*). As only a few organic drinking water contaminants are characterized (*19*), and as inhalation and cutaneous exposures may be as important as ingestion (*16*), risk estimates, excluding possible interactive effects, are likely to be misleadingly low. Nevertheless, Ames *et al.* ignore these limitations and also the substantive epidemiologic data and assert that "the animal evidence provides no good reason to expect that chlorination of water or current levels of man-made pollution of water pose significant carcinogenic hazards," and that the risk from contaminated Woburn water is 1/10,000 that of a glass of wine.

Community air pollution from industrial emissions, and thus proximity of residence to certain industries, is a recognized cancer risk factor. Numerous studies, controlled or stratified for smoking, demonstrate associations between excess lung cancer rates and heavy metal and aromatic hydrocarbon emissions (*20*); exposure to benzo[*a*]pyrene, a conventional combustion index, increased lung cancer mortality by 5% per nanogram per cubic meter of air (*21*). Others estimate that "the proportion of lung cancer deaths in which air pollution is a factor is 21%" (*22*). Concerns have recently focused on defined industrial emissions, including arsenicals, benzene, chloroform, vinyl chloride, and acrylonitrile, which in both sexes are associated with excess overall and organ-specific, standardized community cancer rates; carcinogenic trace metals and volatile organic community air pollutants, have been incriminated in some 0.6 to 2.3 per 1000 excess lifetime cancers (*23*). Ames *et al.*, however, trivialize risks from "general outdoor air pollution."

Ames *et al.* state that cancer mortality rates "have mostly been steady for 50 years" apart from "lung cancer due to tobacco and melanoma due to ultraviolet light." This is based on analyses that exclude people over 65 and blacks of all ages (*24*) and which ignore the following: effects on mortality rates of the approximately 70% reduction in gastric and cervical cancer mortality since the 1940s which have been masked by increasing mortality from cancers at other sites; probability estimates that have projected marked increases in mortality rates for a wide range of malignancies for those born in 1985 compared with those born in 1975 (*25*); very recent increases in premenopausal breast cancer mortality (*26*); the role of nonsolar causes of melanoma (*26*); and the role of other major causes of lung cancer besides smoking (*27*). While smoking is a major cause of lung cancer, the importance of other causes is evidenced by increasing rates in highly urbanized and highly industrialized communities; disproportionately increasing rates for black males not attributable to smoking pattern differences; increasing rates in nonsmokers while rates for other tobacco-related cancers, such as those of the buccal cavity and pharynx, are declining; increasing rates in some groups of nonsmoking workers; increasing rates in women, greater than can be accounted for by increased smoking; and, increasing proportions of lung cancers that are adenocarcinomas, which are less closely associated with tobacco smoking (*12, 27*). Incidence rates, not considered by Ames *et al.* and which can "reveal changes in cancer occurrence that are not apparent in the mortality data" (*26*), from 1950 through 1985 increased overall by 37%; by 20% or over for pancreas cancer; by 51% for urinary bladder cancers; by over 100% for non-Hodgkins lymphoma, multiple myeloma, and malignant mela-

noma in both sexes; by 31% for female breast cancer; by 92% for testis cancer; by 67% for prostate cancer; and by 63% for colorectal and 142% for kidney cancers in males (*26, 28*).

Apart from fundamental problems inherent in Ames's views on carcinogenesis and his dismissal of concerns about industrial carcinogens as "chemophobia," positions editorially endorsed (*29*), his current views and recommendations contrast strikingly with those previously and strenuously propounded (*30*).

Besides proper concerns about naturally occurring carcinogens and tobacco, prudent policy must reflect overwhelming data on incremental exposure to industrial carcinogens and their association with increasing cancer rates, besides reproductive, neurotoxic, and other toxic effects (*31*). The existence of natural hazards clearly does not absolve industry and government from the responsibility for controlling industrial hazards. From public health, ethical, and policy perspectives, the important distinction is not between "natural" and "synthetic" carcinogens, but between preventable and nonpreventable cancers.

SAMUEL S. EPSTEIN
*University of Illinois Medical Center, Chicago, IL 60680*
JOEL B. SWARTZ*
*University of Quebec, Montreal H3C-3P8, Canada*

*Cosigners: John Bailar, McGill University, Montreal; Eula Bingham, University of Cincinnati Medical School; Donald L. Dahlsten, University of California, Berkeley; Peter Infante, Washington, DC; Philip Landrigan and William Nicholson, Mount Sinai School of Medicine, New York; Marc Lappé and Michael Moreno, University of Illinois Medical Center; Marvin Legator, University of Texas Medical Branch, Galveston; Franklin Mirer, Rafael Moure, and Michael Silverstein, United Auto Workers, Detroit; David Ozonoff, Boston University Medical School; Beverly Paigen, Oakland Children's Hospital, Oakland, CA; and Jacqueline Warren, Natural Resources Defense Council, New York.

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29. P. H. Abelson, *Science* **237**, 473 (1987); further illustrations of the relationship between Ames and the editors of *Science* is provided in B. Ames, *ibid.* **226**, 1396 (1984).
30. In 1977, Blum and Ames warned that the synthetic carcinogenic pesticide ethylene dibromide (EDB) is a "potent carcinogen" whose structural similarity to the flame retardant tris is one of the reasons why the synthetic chemical tris "should not be used." They also pointed to "enormous possible [carcinogenic] risks" from using an untested chemical in [a fire retardant in] pajamas, predicted that a "steep increase in the human cancer rate from these suspect . . . chemicals may soon occur" "as the 20- to 30-year lag time of chemical carcinogenesis in humans is almost over," [A. Blum and B. Ames, *Science* **195**, 17 (1977)]. Blum and Ames also emphasized the need for high-dose testing in an effort to compensate for the "inherent statistical limitation in animal cancer tests" and expressed concerns about "the effects of the large-scale human exposure to the halogenated carcinogens [including] vinyl chloride, Strobane-toxaphene, aldrin-dieldrin, DDT, trichloroethylene . . . [and] heptachlor-chlordane." In 1979, Ames and his colleagues demonstrated that carcinogenesis dose-response curves usually rise less steeply than linear curves and criticized the view that many carcinogens have activity only at very high doses [W. Hooper, R. Harris, B. Ames, *ibid.* **203**, 602 (1979)]. Ames also stressed the need to establish "priorities for trying to minimize human exposure to these [synthetic] chemicals" [B. Ames, *ibid.* **204**, 587 (1979)]. Four years later, however, he reversed himself and concluded that cancer rates were not rising, that synthetic carcinogens posed only trivial risks, and that the real culprits were natural carcinogens and faulty life-styles, tobacco, and high-fat diets, citing Doll and Peto (*24*), who "guestimated" that diet, particularly fat, is incriminated in 35% of all cancer deaths, as the basis for this statement [B. Ames, *ibid.* **221**, 1256 (1983)]. Now, the carcinogenic hazards of high-fat diets are virtually dismissed in a few parenthetic words "[a possible risk factor in colon cancer . . .]," presumably reflecting Peto's recent reversal on the role of fat [R. Peto, *ibid.* **235**, 1562 (1987)], and in its place alcohol now emerges, alongside tobacco, as [one of the two] "largest indentified cause of neoplastic death in the United States."
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*Response*: We agree with only the last two sentences of the letter of Epstein *et al.* Correcting each of their errors would require lengthy explanations and would duplicate previous detailed analyses (*1–3*), so here we cover only the main issues.

■ *Half the chemicals tested in animals are carcinogens.* Our exhaustive database of animal cancer tests listed 392 chemicals tested in *both* rats and mice at or near the maximum tolerated dose (MTD). Of these, 60% of the synthetic chemicals and 45% of the natural chemicals were carcinogens in at least one species (*1*). The finding that about half of tested chemicals are positive in rodents has been reported for many sets of data; we cited among others the studies of the National Toxicology Program (NTP). We concluded that the proportion of chemicals found to be carcinogens is strikingly high. Epstein *et al.* ignore our data and citations and cite the early Innes *et al.* study to support their conclusion that the proportion of carcinogens is low. This misrepresents the facts. The Innes tests (120 chemicals, not 150 as stated by Epstein *et al.*, 11 positive) used only one species and were much less thorough than modern tests: they therefore were less likely to detect a carcinogenic effect (*4*).

The proportion of carcinogens is about as high for natural chemicals as for industrial chemicals. Therefore, our diet is likely to be

very high in natural carcinogens, since more than 99.99% of the pesticides we ingest are "nature's pesticides," chemicals that plants produce to defend themselves against insects, fungi, and other pests (*1*, *2*). These are present in all plants and in enormous variety, and their concentration is commonly in parts per thousand (*1*, *2*, *5*) rather than the parts per billion level of synthetic pesticide residues or water pollution (*1*, *2*). The known natural carcinogens in mushrooms, parsley, basil, parsnips, celery, figs, mustard, pepper, fennel, and citrus oil are just a beginning, since so few of "nature's pesticides" have yet been tested (*5*). Cooking food produces carcinogens (*1*, *2*) and so does our normal metabolism (*2*, *6*). A high proportion of the chemical elements tested are carcinogens. Epstein *et al.* do not address this problem. They do not acknowledge that at the MTD about one-third of all chemicals tested are teratogens (*1*), half of all chemicals are carcinogens, and many chemicals are mutagens; and these categories are not completely overlapping. Even when one considers that some chemicals are selected for testing because they are suspicious, these are strikingly high proportions (*1*, *4*).

■ *Extrapolating rodent cancer test results to humans.* The key issue, given the above facts, is how to identify *significant* preventable exposures to carcinogens (*1*, *7*, *8*). It is reasonable to assume that if a chemical is a carcinogen in rats and mice it is likely to be a carcinogen in humans at the same (MTD) dose. However, until we understand more about mechanisms, knowing the shape of the dose response in the dose range tested in laboratory animals provides little scientific basis for predicting the risk to humans at low doses, often hundreds of thousands of times below the dose at which an effect is observed in rodents (*9*). Thus, quantitative risk assessment is currently not scientifically possible (*1*, *7–10*).

Our HERP index uses the same toxicological information from animal bioassays that is generally used to estimate human risk, but is instead a relative ranking of the possible hazards of a variety of natural and synthetic chemical exposures to humans. We stated clearly that our HERP value should not be used to assess risks, because we do not know how to extrapolate to low doses. The HERP scale may be a way of putting possible hazards in perspective and of setting priorities for epidemiological testing and regulatory policy. Our ranking uses the same criteria for all exposures and indicates that there is a large background of natural and everyday exposures that rank high in possible hazard compared with exposures to pesticide residues or water pollutants. As we indicated in our article, one cannot say whether such natural exposures are likely to be of major or minor importance in human cancer. Our database of carcinogenic potency analyzes animal cancer tests and calculates the $TD_{50}$, essentially the dose of the carcinogen to give half of the animals cancer; the $TD_{50}$ is close to the dose range tested in the laboratory animal. Our HERP is the dose (in milligrams per kilogram) to which humans are exposed, as a percentage of the $TD_{50}$ dose.

Epstein *et al.* have three erroneous objections to our comparisons.

1) They say our HERP values are overestimates for natural chemicals relative to synthetic chemicals because (i) dose-response curves flatten out at high doses and therefore linear extrapolations underestimate low-dose risks, and (ii) natural chemicals are more thoroughly studied (at lower doses) than are synthetic chemicals. Neither (i) nor (ii) is true. As we discussed in our article, there is no way to calculate a low-dose risk from the two dose levels tested in an animal bioassay. In addition, our analysis of the animal dose-response curves indicated a better fit with a quadratic model (upward curving) than with a linear model, and that flat dose-response curves (supralinear) are a rarity. Synthetic chemicals are not less well studied than natural chemicals, as can be seen from our published database: 80% of the studies are on synthetic chemicals; most of the studies referred to were National Cancer Institute (NCI)–NTP tests done at the MTD and at half the MTD; the few chemicals tested at a wider range of doses are not biased toward natural chemicals.

2) Epstein *et al.* say we ignore the fact that plants contain anticarcinogens. We do discuss this fact (*1*, *2*), and it does not support their argument that this affects our comparisons: plant antioxidants, the major known type of ingested anticarcinogens, help to protect us against oxidant carcinogens *whether synthetic or natural in origin.*

3) Epstein *et al.* say natural carcinogens can be synergistic with other substances. However, this is also true of synthetic chemicals, and it is also irrelevant to our argument that synthetic pesticide residues in food or water pollution appear to be a trivial increment over the background of natural carcinogens.

■ *Carcinogenesis mechanisms and the dose-response curve.* We discussed the rapidly developing field of mechanisms in carcinogenesis because this understanding is essential for rational risk assessment. Cell proliferation (promotion) and mutation are involved in carcinogenesis, with a basal spontaneous rate for each step (*6*, *11*, *12*). Thus, increasing either rate increases the chance of cancer. In addition, several mutations appear necessary, and we have many layers of defense against carcinogens. These considerations of mechanism suggest a sublinear dose-response relation, which is consistent with both the animal and human data (*1*). It also suggests that multiplicative relationships may be the norm in human cancer causation. Administering chemicals in cancer tests at near-toxic doses (the MTD) commonly causes cell proliferation (*9*). If a chemical is nonmutagenic, but is carcinogenic because of its toxicity, then it should have no effect at low doses. This is a major point (*1*). Epstein *et al.* raise two points concerning the above that we find erroneous.

1) They say we should not call promoting agents carcinogens. However, well-studied promoting agents have been shown to cause cancer by themselves, as do those hormones that cause cell proliferation (*11*). In fact, this class of carcinogens may well include the most important risk factors for human cancer (*1*, *8*, *11*, *12*).

2) Chronic irritation as a risk factor for cancer is not "a discredited theory," but is supported by rodent and human evidence, and by recent evidence on cancer mechanisms indicating that cell-killing causes both cell proliferation and a mutagenic burst of oxygen radicals (*1*).

■ *Factors important in causing human cancer.* The major risk factors of tobacco (30% of U.S. cancer), dietary imbalances, hormones, and viruses appear to account for the bulk of human cancer (*1*, *3*, *7*, *8*, *11–13*). In our article we analyzed the evidence from animal cancer tests that was relevant to some of these risk factors and to occupational exposures and pollution.

Epstein *et al.* distort our discussion of the role of dietary fat and calories in cancer causation. Limiting calories in rats or mice (compared with ad libitum consumption) *reproducibly* extends life-span and decreases spontaneous tumor rates. Caloric intake is likely to be a significant risk factor in human cancer causation (*11*, *14*). Excess saturated fat consumption is a clear risk factor for heart disease. Excess fat consumption is a plausible, but not proved, risk factor in several types of human cancer, a view supported by extensive animal evidence (*1*, *3*, *12–14*). However, disentangling the effect of excess fat from excess calories is difficult in both rodents and humans (*14*).

Alcohol consumption is certainly the major known chemical risk factor for birth defects and is thought to account for 3% of U.S. cancer (*15*). Epstein *et al.* discount the importance of alcohol because it is synergistic with smoking. They are inconsistent, because they do not discount the effects of radon, asbestos, or other occupational exposures that are also synergistic with smoking.

For example, they attribute deaths to asbestos (exaggerated), but do not mention that the risk of lung cancer for asbestos workers would be an order of magnitude less if workers did not smoke. It is more reasonable to apportion, rather than to dismiss, these risks.

Occupational exposures to chemicals and possible hazards can be high, as we showed in our article. But the sweeping statements made by Epstein *et al.*, without a discussion of dose, do not clarify matters. In a separate analysis (*16*) we have ranked the potential carcinogenic hazards to U.S. workers using the PERP index (analogous to the HERP index except that Occupational Safety and Health Administration Permitted Exposure Levels replace actual exposures). The PERP values differ by more than 100,000-fold. For 12 substances, the permitted levels for workers are greater than 10% of the rodent $TD_{50}$ values. Priority should be given to reduction of the allowable worker exposures that appear most hazardous in the PERP ranking.

Epstein *et al.* misrepresent the conclusions of the NRC-NAS committee report on pesticides, which did not say there would be 1.5 million deaths from pesticide use; the report did not predict deaths from pesticide use at all (*17*). Our article showed that the actual levels of synthetic pesticide residues eaten in the United States are tiny relative to the background of natural pesticides in plants. The end result of disproportionate concern about tiny traces of synthetic pesticide residues, such as ethylene dibromide (*1*), is that plant breeders are breeding highly insect-resistant plants: this may create other risks (*18*).

Our conclusion that water pollution did not make toxicological sense as a significant cause of cancer (or birth defects) because the amounts involved were extremely small compared with the background levels, is not contradicted by the epidemiological studies cited by Epstein *et al.* It is almost always beyond the power of epidemiology to provide convincing evidence that clusters of cancer or birth defects are due to pollution or to chance, bias, or confounding variables (*7*). Epstein *et al.* discuss Woburn, Massachusetts, without mentioning severe criticisms of the study they cite (*19*). Our analysis showed that the polluted water in Woburn or in Silicon Valley was less of a possible hazard than the chloroform in average U.S. tap water, a minimal possible hazard itself compared with the background. Comparative toxicological analyses such as ours can help epidemiologists to set priorities in their efforts and to distinguish causal correlations from the myriad of chance correlations. For example, the intake of burnt material from outdoor air pollution is so tiny compared with that from smoking (or from cooking food) that it seems implausible as a major source of cancer, a view consistent with the epidemiology cited, and indicates that epidemiologists must rigorously control for smoking (*20*).

■ *Cancer trends.* In our article we discussed cancer trends only in passing, but others have dealt with them in greater depth than do Epstein *et al.* (*3, 21*). Our statement that cancer death rates were not increasing except for those due to tobacco (mainly lung) and ultraviolet light (melanoma) was based mainly on analyses by Doll and Peto (*3*). Their analysis did take into account blacks and people over 65: Doll and Peto also pointed out that although incidence rates are of interest, they should not be taken in isolation because of the substantial extent to which trends in the recorded incidence rates are biased by improvements in the level of *registration* and *diagnosis*, as appears to be the case with breast cancer. Even if particular types of cancer will be shown to increase or decrease (stomach, liver, and uterine cancer are decreasing), establishing a causal relation among the many changing aspects of our lives remains difficult (*3, 7, 11–13*). There is no good evidence that there is any general increase in cancer due to the modern industrial world (*3*).

Epstein *et al.* complain that one of us (B.N.A.) has modified his views in the last decades. In the rapidly changing and difficult area of cancer cause and prevention, not modifying one's views to keep up with new facts is a sure way to lose scientific credibility (*22*).

BRUCE N. AMES
*Department of Biochemistry, University of California, Berkeley, CA 94720*
LOIS SWIRSKY GOLD
*Biology and Medicine Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720*

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3. R. Doll and R. Peto, *The Causes of Cancer* (Oxford Univ. Press, Oxford, England, 1981).
4. J. R. M. Innes *et al.* [*J. Natl. Cancer Inst.* **42**, 1101 (1969)] used two mouse strains (versus two species for NCI-NTP), had only 17 animals per group (versus 50 for NCI-NTP), had only one dose level (versus two for NCI-NTP), and were 18-month experiments (versus 24-month for most NCI-NTP); the dose was likely below the MTD (among 19 Innes chemicals also tested by another laboratory, the Innes dose was usually lower, sometimes by more than tenfold). We have discussed positivity in animal cancer tests in detail, including the Innes design (L. S. Gold *et al.*, *Environ. Health Perspect.*, in press).
5. For example, a recent analysis of lima beans showed an array of 23 natural alkaloids (those tested have biocidal activity) that ranged in concentrations in stressed plants from 0.2 to 33 parts per thousand fresh weight. None appear to have been tested for carcinogenicity or teratogenicity [J. B. Harborne, in *Natural Resistance of Plants to Pests. Roles of Allelochemicals*, M. B. Green and P. A. Hedin, Eds. (ACS Symposium 296, American Chemical Society, Washington, DC, 1986), pp. 22–35].
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15. Ethyl alcohol itself (15 grams per drink) is the likely teratogen and carcinogen in alcoholic beverages [B. N. Ames, "Review of evidence for alcohol-related carcinogenesis" (report for Proposition 65 meeting, Sacramento, CA, 11 December 1987)]. The dose response in humans is of considerable interest: four drinks per day is associated with increased cancer and birth defects, yet one drink per day (the U.S. average) has not clearly been associated with increased risk. Both orange juice and bread naturally contain considerable amounts of alcohol.
16. L. S. Gold *et al.*, *Environ. Health Perspect.* **76**, 211 (1987).
17. At the press conference on the report, Arthur Upton, speaking for the committee, responded to a question by saying that the worst-case scenario possible might implicate pesticides in 400 cases of cancer per year at the present time. The worst-case scenario pictures every farmer using the maximum possible amount of every pesticide allowed, the public consuming this food for a lifetime, and a worst-case linearized multistage model for predicting risk. Since all of these worst cases appear much too pessimistic, an actual risk close to zero is more likely.
18. A recent case is instructive. A major grower introduced a new variety of highly insect-resistant celery into commerce. A flurry of complaints to the Centers for Disease Control from all over the country soon resulted when people who handled the celery developed a severe rash when they were exposed to sunlight. Some detective work uncovered that, instead of the normal level of 900 parts per billion of psoralens (light-activated carcinogens and mutagens), the pest-resistant variety contained 9000 ppb of psoralens. It is unclear whether other natural pesticides in the celery were increased as well [S. F. Berkley *et al.*, *Ann. Intern. Med.* **105**, 351 (1986); P. J. Seligman *et al.*, *Arch. Dermatol.* **123**, 1478 (1987).]
19. W. Lagakos *et al.*, *J. Am. Stat. Assoc.* **81**, 583 (1986). The same issue contains articles by other epidemiologists critical of this study.
20. Epstein *et al.* cite an estimate that air pollution is a causal factor in 21% of lung cancer. This is not supported by other epidemiology. The cited study was not peer-reviewed and did not take into account important confounding variables [see (*3*)].
21. *Annual Cancer Statistics Review Including Cancer Trends: 1950–1985* (National Cancer Institute, Bethesda, MD, January 1988).
22. In this context the comments of two eminent epidemiologists on Epstein's writings are enlightening [C. K. Peto, *Nature* **284**, 297 (1980).]

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# Letters

## Pesticides, Risk, and Applesauce

The tremendous attention in the media to the growth-regulator Alar raises important issues about the nation's efforts to prevent human cancer by regulating chemicals that are carcinogenic in animal studies. Leslie Roberts, in her Research News articles "Pesticides and kids" (10 Mar., p. 1280) and "Is risk assessment conservative?" (24 Mar., p. 1553), did not address several points that we think are important for putting possible risks in perspective.

1) *Pesticides, 99.99% all natural.* Although regulatory efforts are focused on identifying and controlling synthetic chemicals that are estimated to pose a possible carcinogenic risk to society greater than one in a million (such as Alar), we are ingesting about 10,000 times more natural than synthetic pesticides (*1*). All plants produce toxins to protect themselves against fungi, insects, and predators such as man (*2, 3*). Tens of thousands of these natural pesticides have been discovered, and every species of plant contains its own set of different toxins, usually a few dozen. When plants are stressed or damaged, such as during a pest attack, they increase their natural pesticide levels manyfold, occasionally to levels that are acutely toxic to humans (*4*). Very few of these plant toxins have been tested in animal cancer bioassays, but among those tested, about half (20/42) are carcinogenic (*4, 5*).

It is probable that almost every plant product in the supermarket contains natural carcinogens. The following foods contain natural pesticides that cause cancer in rats or mice and are present at levels ranging from a few parts per billion to 4 million parts per billion (ppb) (*3, 4*): anise, apples, bananas, basil, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, celery, cinnamon, cloves, cocoa, comfrey tea, fennel, grapefruit juice, honeydew melon, horseradish, kale, mushrooms, mustard, nutmeg, orange juice, parsley, parsnips, peaches, black pepper, pineapples, radishes, raspberries, tarragon, and turnips. Of the pesticides we eat, 99.99% are all natural, and, like man-made pesticides, most are relatively new to the modern diet because of the exchange of plant foods among the Americas, Europe, Asia, and Africa within the last 1000 years. It is reassuring, however, that the many layers of general defenses in humans and other animals (*1, 6, 7*) protect against toxins, without distinguishing whether they are synthetic or natural.

2) *Trade-offs.* In response to fears about residues of man-made pesticides, plant breeders are active in developing varieties that are naturally pest-resistant. Such varieties contain increased amounts of natural pesticides. It should be no surprise, then, that a newly introduced variety of insect-resistant potato had to be withdrawn from the market, due to acute toxicity to humans caused by much higher levels of the teratogens solanine and chaconine than are normally present in potatoes (*8*). Similarly, a new variety of insect-resistant celery recently introduced widely in the United States is causing outbreaks of dermatitis in produce workers due to a concentration of the carcinogen 8-methoxypsoralen (and related psoralens) of 9000 ppb, rather than the usual 900 ppb (*9*). Many more such cases are likely to crop up. Thus, there is a fundamental trade-off between nature's pesticides and man-made pesticides. The Environmental Protection Agency (EPA) has strict regulatory requirements for new synthetic pesticides and is steadily weeding out old substances such as Alar that are thought to pose a significant hazard; however, natural pesticides are almost completely neglected. Natural pesticides that are possibly hazardous to humans could easily be decreased by plant breeding.

Given the background of human exposures to natural carcinogens (*1–7*), the finding that about half the chemicals tested in rodents (whether synthetic or natural) are carcinogenic (*1, 5*), and the difficulties in risk assessment (discussed below), we have ranked possible hazards on a HERP index (daily *H*uman *E*xposure dose/*R*odent *P*otency dose, as a percent) in order to achieve some perspective on human exposure to the plethora of carcinogens (*1*). Our ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be minimal relative to the background levels of natural substances.

To put Alar in perspective, we estimate that the possible hazard from UDMH (the carcinogenic breakdown product of Alar) in a daily lifetime glass (6 ounces) of apple juice is HERP = 0.0017% (*10*). This possible hazard is less than that from the natural carcinogenic hydrazines consumed in one daily mushroom (HERP = 0.1%) (*1*) or that from aflatoxin in a daily peanut butter sandwich (HERP = 0.03%) (*1*). It is also less than other possible hazards from natural carcinogens in food, although few have been tested. These include 8-methoxypsoralen in a daily portion (100 grams) of celery (*3, 11*), allyl isothiocyanate in a daily portion of cabbage or Brussels sprouts (*3, 12*), and alcohol in a daily glass of orange juice (*13*). The possible hazard of UDMH in a daily apple is 1/10 that of a daily glass of apple juice. Other HERP comparisons are shown in (*1*). Apple juice has been reported to contain 137 natural volatile chemicals (*14*), of which only five have been tested for carcinogenicity (*5*); three of these—benzyl acetate, alcohol, and acetaldehyde—have been found to be carcinogenic.

The EPA has proposed cancellation hearings on Alar, and the Natural Resources Defense Council (NRDC) is trying to speed this process up by a year or two. The trade-offs must be considered in efforts to prevent hypothetical carcinogenic risks of $10^{-6}$ or $10^{-5}$, because the results could be counterproductive if the risks of the alternatives are worse. What risks might we incur by banning Alar? Alar is a growth regulator that delays ripening of apples so that they do not drop prematurely, and it also delays overripening in storage. Alar plays a role in reducing pesticide use for some types of apples, particularly in the Northeast (*15*).

For example, without Alar, the danger of fruit fall from leafminers is greater, and more pesticides are required to control them. Also, when apples fall prematurely, pests on the apples remain in the orchard to attack the crop the next summer, and more pesticides must be used. Since Alar produces firmer apples, and results in fewer falling to the ground, treated fruit may be less susceptible to molds. Therefore, it is possible that the amounts and variety of mold toxins present in apple juice, for example, patulin (*16*), will be higher in juice made from untreated apples. The carcinogenicity of patulin has not been adequately examined (*17*). The EPA should, as NRDC emphasizes, also take into consideration that children consume large amounts of apple juice. Another trade-off is that fewer domestically grown, fresh apples would be available throughout the year, and the price would be higher; thus, consumers might substitute less healthy foods.

3) *Risk assessment*. Currently, neither theory nor experimental evidence is adequate to guide scientists in extrapolating from rodent cancer tests at the maximum tolerated dose (MTD) to human exposures that are thousands or millions of times lower. Therefore, for prudence's sake, federal regulatory agencies routinely make worst-case assumptions to estimate the upper limit on risk for low doses; however, the real risks at low doses may well be zero. Conventional risk assessments at the low levels of human exposure thus are really quite speculative (*1*) and should not be viewed as if they were real risks. Accumulating scientific evidence (*1, 6, 7, 18*) suggests that chemicals administered in animal cancer tests at the MTD are causing cancer in quiescent tissues primarily by increasing cell proliferation, an essential aspect of carcinogenesis for both mutagens and nonmutagens. Because endogenous rates of DNA damage are enormous (*6*), cell proliferation alone is likely to be tumorigenic. Cell proliferation converts DNA adducts (either spontaneous or exogenous) to mutations or to epimutations (such as loss of 5-methylC) and exposes single-stranded DNA, a much more sensitive target for mutagens. It also allows mutant cells to escape from growth inhibition signals coming from surrounding cells (*1, 6, 7*).

If animal cancer tests are primarily measuring cell proliferation, then the dose-response curve should fall off sharply with dose, even for mutagens [as with diethylnitrosamine (*18*)] and should have a threshold for nonmutagens. Thus, the hazards at low doses could be minimal. Furthermore, humans have numerous inducible defense systems against mutagenic carcinogens, such as DNA repair, antioxidant defenses, glutathione transferases, and so forth, which may make low doses of mutagens protective in some circumstances. Even radiation—the classical DNA-damaging agent and carcinogen—may be protective in small doses against DNA damage at higher doses, as shown by recent work in human cells (*19*). Also, recent radiation experiments in mice show a dose threshold for the latency of tumor appearance (*20*). Thus, low doses of carcinogens appear to be both much more common and less hazardous than is generally thought. These scientific questions about mechanisms of carcinogenesis and the preventable causes of human cancer, in any case, are being resolved by the scientific community as quickly as resources allow.

Regulation of low-dose exposures to chemicals based on animal cancer tests may not result in significant reduction of human cancer, because we are exposed to millions of different chemicals—almost all natural—and it is not feasible to test all of them. Most exposures, with the exception of some occupational, medical, or natural pesticide exposures, are at low doses. The selection of chemicals to test, a critical issue, should reflect human exposures that are at high doses relative to their toxic doses and the numbers of people exposed. Epidemiology has been reasonably successful in identifying risk factors for human cancer, such as smoking, hormonal and dietary imbalances, asbestos, and several occupational chemicals; the data suggest that pesticide residues are unlikely to be a significant risk factor (*6, 21*). Epidemiology, with molecular approaches, is becoming more sophisticated and will continue to be our main tool in analyzing causes of cancer. In order to minimize cancer and the other degenerative diseases of aging [which are associated with our constantly increasing life expectancy (*6, 7*)], we need to obtain the knowledge that will come from further basic scientific research.

BRUCE N. AMES
*Department of Biochemistry, University of California, Berkeley, CA 94720*
LOIS SWIRSKY GOLD
*Cell and Molecular Biology Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720*

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