

Ranking Possible Carcinogenic Hazards

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

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

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

Extrapolation from the results of rodent cancer tests done at high

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

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

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

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

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Ranking of Possible Carcinogenic Hazards

Since carcinogens differ enormously in potency, a comparison of possible hazards from various carcinogens ingested by humans must take this into account. The measure of potency that we have developed, the TD_{50} , is the daily dose rate (in milligrams per kilogram) to halve the percent of tumor-free animals by the end of a standard lifetime (14). Since the TD_{50} (analogous to the LD_{50}) is a dose rate, the lower the TD_{50} value the more potent the carcinogen. To calculate our index of possible hazard we express each human exposure (daily lifetime dose in milligrams per kilogram) as a percentage of the rodent TD_{50} dose (in milligrams per kilogram) for each carcinogen. We call this percentage HERP [Human Exposure dose/Rodent Potency 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 $\mu\text{g/day}$. 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 TD₅₀ 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 TD₅₀; (?) = is not adequately tested for carcinogenicity. TD₅₀ values shown are averages calculated by taking the harmonic mean of the TD₅₀'s of the positive tests in that species from the Carcinogenic Potency Database. Results are similar if the lowest TD₅₀ value (most potent) is used instead. For each test the target site with the lowest TD₅₀ value has been used. The average TD₅₀ has been calculated separately for rats and mice, and the more sensitive species is used for calculating the possible hazard. The database, with references to the source of the cancer tests, is complete for tests published through 1984 and for the National Toxicology Program bioassays through June 1986 (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 TD₅₀ dose in the rodent (in milligrams per kilogram) to calculate the Human Exposure/Rodent Potency 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) (<i>Agaricus bisporus</i>)	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 μM 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 potentially 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 μM hydrogen peroxide and 0.3 μM 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 LD₅₀) 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 TD₅₀ 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 TD₅₀ (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 $\mu\text{g}/\text{day}$) (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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48. Estragole, one of numerous saffrole-like compounds in plants, is present in the volatile oils of many edible plants, including basil, tarragon, bay, anise, and fennel, as well as in pine oil and turpentine [A. Y. Leung, *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics* (Wiley, New York, 1980)]. Dried basil has a volatile oil content of about 1.5 to 3.0%, which contains (on average) 25% estragole [H. B. Heath, *Source Book of Flavors* (AVI, Westport, CT, 1981), pp. 222-223]. Estragole is used commercially in spice, anise, licorice, and fruit flavors. It is added to beverages, candy, baked goods, chewing gums, ice creams, and condiments at average levels ranging from 2 to 150 ppm [NAS/NRC Food Protection Committee, Food and Nutrition Board, *Chemicals Used in Food Processing* (NAS/NRC Publ. No. 1274, National Academy of Sciences, Washington, DC, 1965), p. 114].
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50. The average daily adult dose of phenobarbital for sleep induction is 100 to 320 mg (HERP = 26 to 83%), though its use is declining [AMA Division of Drugs, *AMA Drug Evaluations* (American Medical Association, Chicago, IL, ed. 5, 1983), pp. 201-202]. The TD₅₀ data in the table is for phenobarbital, which, so far, has been shown to be carcinogenic only in mice; the sodium salt of phenobarbital is carcinogenic in both rats and mice. Human studies on phenobarbital and cancer are reviewed in A. E. M. McLean, H. E. Driver, D. Lowe, I. Sutherland, *Toxicol. Lett.* **31** (suppl.), 200 (1986).
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52. The human dose of clofibrate is 2 g per day for many years [R. J. Havel and J. P. Kane, *Annu. Rev. Med.* **33**, 417 (1982)]. The role of clofibrate as a peroxisome proliferator is reviewed in J. K. Reddy and N. D. Lalwani [CRC Crit. Rev. Toxicol. **12**, 1 (1983)]. An epidemiologic study is in World Health Organization Report, *Lancet* **1984-II**, 600 (1984).
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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. Vondusz, 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 TD₅₀ 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-acetylcytisine, 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 TD₅₀ 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. Saffrole 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, saffrole and saffrole-containing sassafras oils were banned from use in foods in the United States [*Fed. Regist.* **25**, 12412 (1960)]. Saffrole 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. Roc.

Perception of Risk

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Studies of risk perception examine the judgments people make when they are asked to characterize and evaluate hazardous activities and technologies. This research aims to aid risk analysis and policy-making by (i) providing a basis for understanding and anticipating public responses to hazards and (ii) improving the communication of risk information among lay people, technical experts, and decision-makers. This work assumes that those who promote and regulate health and safety need to understand how people think about and respond to risk. Without such understanding, well-intended policies may be ineffective.

THE ABILITY TO SENSE AND AVOID HARMFUL ENVIRONMENTAL conditions is necessary for the survival of all living organisms. Survival is also aided by an ability to codify and learn from past experience. Humans have an additional capability that allows them to alter their environment as well as respond to it. This capability both creates and reduces risk.

In recent decades, the profound development of chemical and nuclear technologies has been accompanied by the potential to cause catastrophic and long-lasting damage to the earth and the life forms that inhabit it. The mechanisms underlying these complex technologies are unfamiliar and incomprehensible to most citizens. Their most harmful consequences are rare and often delayed, hence difficult to assess by statistical analysis and not well suited to management by trial-and-error learning. The elusive and hard to manage qualities of today's hazards have forced the creation of a new intellectual discipline called risk assessment, designed to aid in identifying, characterizing, and quantifying risk (1).

Whereas technologically sophisticated analysts employ risk assessment to evaluate hazards, the majority of citizens rely on intuitive risk judgments, typically called "risk perceptions." For these people,

experience with hazards tends to come from the news media, which rather thoroughly document mishaps and threats occurring throughout the world. The dominant perception for most Americans (and one that contrasts sharply with the views of professional risk assessors) is that they face more risk today than in the past and that future risks will be even greater than today's (2). Similar views appear to be held by citizens of many other industrialized nations. These perceptions and the opposition to technology that accompanies them have puzzled and frustrated industrialists and regulators and have led numerous observers to argue that the American public's apparent pursuit of a "zero-risk society" threatens the nation's political and economic stability. Wildavsky (3, p. 32) commented as follows on this state of affairs.

How extraordinary! The richest, longest lived, best protected, most resourceful civilization, with the highest degree of insight into its own technology, is on its way to becoming the most frightened.

Is it our environment or ourselves that have changed? Would people like us have had this sort of concern in the past? . . . Today, there are risks from numerous small dams far exceeding those from nuclear reactors. Why is the one feared and not the other? Is it just that we are used to the old or are some of us looking differently at essentially the same sorts of experience?

During the past decade, a small number of researchers has been attempting to answer such questions by examining the opinions that people express when they are asked, in a variety of ways, to evaluate hazardous activities, substances, and technologies. This research has attempted to develop techniques for assessing the complex and subtle opinions that people have about risk. With these techniques, researchers have sought to discover what people mean when they say that something is (or is not) "risky," and to determine what factors underlie those perceptions. The basic assumption underlying these efforts is that those who promote and regulate health and safety need to understand the ways in which people think about and respond to risk.

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