REVIEW

Perspectives on Comparing Risks of Environmental Carcinogens[1]

Frederica Perera, Paolo Boffetta*[2,3]

In 1987, investigators (Ames et al.) concluded that the risks of man-made industrial carcinogens and pesticides (outside of the workplace) are trivial compared with the risks of naturally occurring carcinogens found mostly in the diet. They used a ranking system based on human exposure and rodent potency (HERP) data to arrive at this conclusion. As a result, they recommend that regulatory agencies, such as the Environmental Protection Agency and the Food and Drug Administration, base their priorities in this area on their HERP system. We analyzed the assumptions and data set upon which the HERPs were based, concluding that such a simplified approach to set public health policy is inappropriate given the underlying uncertainties. However, we note that when comparisons are consistently based on estimates of average daily exposure to common carcinogens, the HERP scores of many man-made pollutants are comparable to those of naturally occurring carcinogens in the diet. [J Natl Cancer Inst 1988;80:1282-1293]

Background

The majority (an estimated 60%-90%) of human cancer is considered to be attributable to environmental factors, broadly defined to include cigarette smoking, industrial pollutants, radiation, diet, and perhaps other life-style factors and viruses (*1*). Thus, in theory most cancer is preventable through the identification and control of causative factors, including exposure to carcinogens. For decades, policymakers concerned with the assessment and regulation of environmental carcinogens have searched for a systematic way to set priorities among the many candidates. This paper critically evaluates the most recent proposal for such a ranking scheme (*2*).

Identification of specific etiologic factors and estimation of their relative importance constitute a formidable task. Few cancers are attributable to single factors or exposures; rather, complex interactions between environmental and host factors are generally involved (*3-5*). Moreover, because of the limitations of epidemiology (*6*), only rarely are human data available that directly link an environmental agent to human cancer. For example, epidemiological studies strongly suggest, although they do not conclusively establish, an association between organic chemical carcinogens in drinking water (such as chloroform) and cancers at several sites, including the rectum, colon, and bladder (*7-11*). Certain dietary and nutritional factors (such as dietary fat and fiber) have been implicated in cancer of the breast, colon, rectum, and stomach (*12,13*), but here too a direct causal association has not been established for specific dietary constituents. In addition to active cigarette smoking and a significant number of pollutants in the workplace, established to be human lung carcinogens (*14*), there is growing evidence that passive smoking (*15*) and pollutants in the ambient air (*16,17*) contribute significantly to lung cancer mortality. However, because of cost and feasibility constraints and the difficulty in identifying an appropriate study population, the vast majority of animal carcinogens, both naturally occurring and man-made, have neither been the subject of epidemiological investigation nor are they likely to be (*18*). Thus, for practical purposes, as a matter of long-standing policy, regulatory agencies accept the use of positive animal data as predictive of carcinogenic hazard in human beings (*19*). The alternative, awaiting positive evidence of carcinogenicity in humans,

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[2]Division of Environmental Sciences, Columbia University School of Public Health, New York, NY.

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**Correspondence to:* Dr. Frederica Perera, Division of Environmental Sciences, Columbia University School of Public Health, 60 Haven Ave., B-109, New York, NY 10032.

traditionally has been rejected as morally and socially unacceptable.

A major limitation of epidemiology (and risk assessment) is that reliable data on human exposure to specific chemicals are frequently lacking. Therefore, by necessity, most epidemiological studies have relied on crude or indirect measures of exposure. A significant number of carcinogens have been detected in drinking water, ambient air, and the food supply; however, reliable monitoring data exist for only a small fraction of these chemicals. For example, while dozens of pesticides and industrial chemical carcinogens have been measured routinely in surface water, groundwater, and drinking water, they represent only a small percentage of chemical pollutants present (*10,20–23*). Over 700 organic chemicals have been found to be present in the U.S. drinking water supply, including 40 known or suspected carcinogens (*24*). Numerous carcinogenic air pollutants (trace metals, polycyclic aromatic hydrocarbons, and volatile organic chemicals) have been detected in ambient air; again, there are little or no reliable monitoring data on the majority of airborne carcinogens (*25*). Similarly, many carcinogenic pesticide residues have been identified in the food supply, but reliable exposure data are lacking for most (*26*). Testifying to the pervasiveness of environmental contamination are studies showing significant concentrations of synthetic organic chemicals in the blood, urine, and/or adipose tissue of the U.S. population. These include 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT), dieldrin, heptachlor epoxide, polychlorinated biphenyls (PCBs), and dioxin (*27,28*). Again, data are far from comprehensive; however, they do show a decline in the concentrations of DDT and PCBs as a result of regulation.

Despite their limitations, available exposure and epidemiologic data have served as the basis for a number of widely varying estimates of the proportion of human cancer in the U.S. population that can be attributed to life-style, occupational exposures, or other environmental pollution. These exercises have generated significant debate, as much over the underlying assumptions as the data used to generate them (*17,29–35*). Unfortunately, various such estimates (ranging, for example, from 4% to >20% for occupational exposures) have been cited as a basis for setting priorities for public health protection. This approach ignores both the underlying uncertainties, the relative preventability of various risk factors (*36*), and the disproportionate impact on some segments of the population. For example, once recognized, most chemical pollutant hazards can be reduced or eliminated by practical means. Moreover, the involuntary nature of these exposures necessitates control at the source, in contrast to exposures related to life-style (e.g., diet and smoking), which can be addressed more effectively through public education regarding personal behavioral choices. Another inherent problem with the approach of estimates is that it obscures the much higher risks to certain subpopulations. For example, if the contribution of occupational carcinogens to all cancer deaths in the United States were as low as 3%, for male industrial workers as a group, workplace carcinogens would account for at least 25% of all identified causes of cancer (*33*).

Another tool that has been used increasingly by regulatory agencies to set priorities and even to determine acceptable levels of exposure to individual environmental contaminants has been quantitative risk assessment. Here, also, the lack of good information on human exposure as well as the usual paucity of epidemiological data are compounded by uncertainties regarding the proper way to extrapolate from high to low dose and from experimental animals to humans (*37*). To offset these uncertainties, the four major U.S. regulatory agencies, including the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), the Consumer Product Safety Commission, and the Food and Drug Administration (FDA), have traditionally preferred conservative models that incorporate an assumption of low-dose linearity, regardless of the presumed mechanism of action of the chemical carcinogen (*19*). However, in certain instances, these conservative models may underestimate cancer risk. For example, the widely accepted linearized multistage model (*38*), considered to be one of the most conservative of the biologically plausible risk-assessment models, works on the assumption that the exposed population is of uniform susceptibility and that interactions do not occur between chemical exposures and other risk factors. Yet significant intraindividual variability has been demonstrated for human metabolism and binding of drugs and carcinogens (*39–45*) as well as for repair of DNA damage (*46*). Moreover, a number of epidemiological studies have demonstrated synergism between chemical exposures and host factors, such as cigarette smoking and air pollutants in the workplace and urban air (*47,48*). To further complicate the situation, although nonlinear (both superlinear and sublinear) dose-response relationships have been observed experimentally and epidemiologically, the available data do not allow low-dose linearity to be ruled out in any of these cases (*49*). Given these uncertainties, it is reassuring that, in a number of cases, risks observed in humans have been consistent with those calculated from high-dose animal experiments with the use of models that incorporated linearity at low dose. These include benzene, ethylene dibromide (EDB), gasoline, asbestos, and ethylene oxide (*50–56*). Therefore, there is general agreement that the use of quantitative risk assessment, performed with appropriate and consistent assumptions and models, affords the possibility of comparing risks for the purpose of setting priorities among selected candidates for regulation. However, most scientists do not view quantitative risk assessment as capable of providing precise estimates of human risk from individual chemicals; general sources of chemical exposures are considered even less likely candidates for risk estimation by this method.

Human Exposure/Rodent Potency (HERP) Index

Most recently, researchers at the University of California at Berkeley and Lawrence Berkeley Laboratory have suggested still another approach to priority setting (*2*). They have calculated a possible hazard index for selected carcinogens by expressing the human exposure (in milligrams/kilogram) as a percentage of the rodent TD_{50} dose

(also in milligrams/kilogram).[4] They have compared the resultant HERP indices for four pollutants found in drinking water and indoor air, three man-made pesticides and other residues, 10 natural pesticides and dietary toxins, two food additives, five drugs, and two occupational exposures (*see* table 1). The authors conclude that man-made environmental pollutants, such as pesticide residues and contaminants in drinking water, are "likely to be of minimal carcinogenic hazard" relative to the background of natural carcinogens (found largely in the diet). They recommend that regulatory agencies that traditionally have emphasized control of exposures to man-made or industrial carcinogens (in addition to those in the occupational setting) revise their priorities.

The authors acknowledge several major limitations of the HERP system, such as the possibility of interspecies (rodent and human) variation in susceptibility to carcinogens and quantitative uncertainties regarding the general shape of the dose-response curve, including the possibility of synergistic effects and thresholds for nongenotoxic carcinogens, such as promoters (*see* discussion below). They caution that it would be a mistake to use the HERP index as a direct estimate of human hazard, but they conclude that the scale provides "a way of setting priorities for concern."

Although this is an innovative approach, it suffers from several inherent flaws. First, as we will show in table 2, the results are influenced strongly by the selection of chemicals and whether one classifies them as "man-made" or "natural." The rationale for selection of the individual compounds in table 1 was not provided by the authors, but presumably it was dictated by the nature and availability of both exposure and rodent potency data. As mentioned, the rodent potency data base is not comprehensive. For example, it omits a number of carcinogenic pesticides including alachlor, which is of current concern as a food contaminant (*26*) and has been found in water supply wells at significant concentrations (*61*). Certainly, the four selected drinking water and air pollutants and the pesticides listed cannot represent the large number of industrial chemicals and pesticides that have been detected frequently in the U.S. drinking water, air, and food supply and that also have evidence of carcinogenicity in humans and/or laboratory animals (*62,63*).

Moreover, although we are aware that there are many potential dietary hazards, the majority of which also are not well characterized (*2,64*), the 10 natural dietary carcinogens in table 1 include a number of exotic foods to which the U.S. general population has limited exposure (sake, comfrey

Table 1. Possible carcinogenic hazards, as ranked by Ames et al. (*2*)*

Possible hazard (HERP %)	Carcinogenic exposure
	Man-made chemicals in foods and beverages
0.0002	PCBs,† U.S. average daily dietary intake
0.0003	DDE/DDT,† average daily dietary intake
0.0004	EDB, average daily dietary intake from grains/grain products
0.0002	Furylfuramide in 2-fluorenamine, daily dietary intake before banning
0.06	Saccharin† in 12-oz diet cola
	Natural carcinogens in foods and beverages
0.003	DMN in 100 g of cooked bacon
0.006	DEN in 100 g of cooked bacon
0.003	Urethane in 250 mL of sake
0.03	Symphytine in 1 cup of comfrey herb tea
0.03	Aflatoxin in 1 peanut butter sandwich
0.06	DEN in dried squid, broiled in gas oven
0.07	Allyl isothiocyanate in 5 g of brown mustard
0.1	Estragole in 1 g of dried basil leaf
0.1	Hydrazines in 1 raw mushroom
0.2	Safrole in natural root beer, before ban
0.008	DMN in 12-oz beer, before 1979
2.8	Ethyl alcohol† in 12-oz beer
4.7	Ethyl alcohol† in 250 mL of wine
6.2	Comfrey root in comfrey-pepsin tablets, 9 daily
1.3	Symphytine in comfrey-pepsin tablets, 9 daily
	Indoor air pollutants
0.6	Formaldehyde in conventional home air, 14 hr/day
0.004	Benzene in conventional home air, 14 hr/day
2.1	Formaldehyde in mobile home air, 14 hr/day
	Water pollutants
0.001	Chloroform† in tap water, 1 L U.S. average
0.004	Tetrachloroethylene† in well water, 1 L, highly contaminated
0.0002	Chloroform† in well water, 1 L, contaminated
0.0003	Tetrachloroethylene† in well water, 1 L, contaminated
0.008	Chloroform† in average swimming pool, 1 hr
	Drugs
0.3	Phenacetin, average dose
5.6	Metronidazole, therapeutic dose
14	Isoniazid, prophylactic dose
16	Phenobarbital, 1 sleeping pill
17	Clofibrate,† average daily dose
	Occupational exposure
5.8	Formaldehyde, worker's average daily exposure
140	EDB, worker's daily intake, high exposure

*DMN = *N*-nitrosodimethylamine, and DEN = *N*-nitrosodiethylamine.
†Carcinogens characterized by Ames et al. as nongenotoxic and likely to have thresholds.

[4]Here the TD_{50} is the average daily dose rate to halve the percent of tumor-free animals by the end of a standard lifetime (*57*). The average TD_{50} is calculated by taking the harmonic mean of the TD_{50}s of the positive tests in the most sensitive species. From each test, the target site with the lowest TD_{50} value was used. In general, the harmonic mean and the lowest TD_{50} differ by a factor of ≈2 (*58*). The source of TD_{50} values is the Carcinogenic Potency Data Base (CPDB) (*57-60*). The data base is a compilation of results from >3,500 experiments on 975 chemicals. It includes results from the Carcinogenesis Bioassay Program of the National Cancer Institute/National Toxicology Program (through May of 1986) as well as studies published in the literature (through December of 1984). The data base is restricted to tests that meet very stringent methodologic criteria. Thus certain human carcinogens (such as asbestos and tobacco smoke) are excluded; seven chemicals regarded by the International Agency for Research on Cancer (IARC) as having sufficient evidence of carcinogenicity in animals (cadmium chloride, cadmium sulfate, epichlorohydrin, glycidaldehyde, isosafrole, mestranole, and 2-nitropropane) are recorded in the CPDB as having only negative tests. The CPDB is a useful tool, but its limitations should be kept in mind.

herb tea, dried squid, brown mustard, and comfrey-pepsin tablets). Therefore, comparisons between drinking 1 L of water containing average concentrations of chloroform and eating a daily serving of dried squid ignore the fact that the average American adult ingests an estimated 2 L or more of water a day (*65*)[5] and rarely, if ever, eats dried squid.

An additional problem is that several "natural pesticides and dietary toxins" in table 1 are misclassified in that they can result from harvesting, manufacturing, or cooking processes and therefore cannot be considered to be strictly natural. For example, aflatoxin in nuts and grains is partially attributable to improper harvesting and storage procedures, whereas, as the authors acknowledge, nitrosamines are formed in cured meats through the reaction of secondary amines with nitrites added as preservatives. Carcinogenic nitropyrenes and nitrosamines occur in browned or burned meats as a result of cooking with gas flames that generate NO_2 (*2*).

Moreover, a number of natural substances or food additives in table 1 have been banned (safrole in natural root beer and AF-2, a Japanese food additive never used in the United States) (*67*), so that there is no current exposure to the U.S. population. Several of the environmental pollutants have been regulated (chloroform, PCBs, and EDB) or even banned (DDT), so that postregulatory exposures (and HERPs) are predictably low, testifying to the effectiveness of regulation.

A second major limitation of the approach of Ames et al. derives from the fact that, as can be seen in table 1, varying exposure indices were used. For waterborne and airborne contaminants, daily exposure was calculated; for pesticides and other residues in food, daily average dietary intake was provided; for "natural" carcinogens in food, one serving was assumed to occur daily; for food additives and drugs, several different measures were used.

To illustrate the effect of chemical selection and of assumptions regarding levels of exposure, we have constructed table 2; it includes all of the chemicals/exposures in table 1, except for those dietary constituents not widely consumed in the United States and those that have been banned and have no current U.S. exposure. We have also omitted drugs because exposure is generally of short duration; drugs are a special case because they are prescribed when benefits are thought to outweigh risks to the individual. Finally, we have included in table 2 several chemicals or sources of exposure that are encountered commonly by the U.S. population and for which rodent potency (*58-60*) and exposure data are available. Unfortunately, in several cases environmental chemicals of concern were in the rodent potency data base, but we could not find reliable exposure data for specific media. This was true for dioxin or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). However, according to the EPA, a crude estimate of total daily intake of dioxin by sizeable segments of industrialized populations is 1 pg/kg (*28*), which corresponds to a HERP of 0.004.

To avoid the problems of inconsistent exposure indices, we have adopted in table 2 the standard approach of uniformly providing average daily dose to the U.S. adult. We recognize both the uncertainties in available exposure data (*143*) and the fact that the average estimates mask wide interindividual variation in exposure depending on geographical, cultural, economic, social, and host factors. For example, a child's exposure to pollutants in drinking water is proportionally greater than exposure of the adult, because children ingest an estimated 1 L of water per 10 kg of body weight compared with 2 L or more per 70 kg of body weight for the adult (*65*). Children may also consume more of a contaminated food than adults. In the case of the pesticide daminozide, the daily dose to the U.S. child (1-6 yr) from consumption of apples, apple juice, and peanut butter is from fivefold to 15-fold higher than the daily dose to the U.S. adult (*70,71.*)

Thus, there are obvious drawbacks to using each of the possible exposure indices (average, worst case, general population, or sensitive subpopulation). However, it is imperative in making comparisons that the same measure of exposure be used consistently. This is demonstrated by table 3 in which we compared HERPs from tables 1 and 2 for the same compound.

As mentioned above, postregulatory exposures (and HERPs) for environmental carcinogens such as DDT/DDE (1,1-dichloro-2,2′-bis(*p*-chlorophenyl)ethylene) are low. Therefore, in a number of cases we have included preregulatory and postregulatory values for purposes of comparison.

Unfortunately, any listing of chemicals such as in tables 1-3 cannot convey the reality of cumulative exposures to different carcinogens in the same medium. Also, it does not reflect the possibility of interactions among them or the need to consider exposures to the same chemical via several different media. For example, the individual has exposure to synthetic volatile organic compounds in the drinking water from ingestion, from dermal absorption while bathing or showering, and from inhalation of the volatilized compound (*144*). Humans may be exposed concurrently to the same carcinogenic substance via a number of different sources and media. For example, in considering the risk of EDB in grain, the New York Department of Health reasonably chose to sum the potential risks of the pesticide in food, ambient air (from use of unleaded gas), and drinking water (*145*).

Finally, an important distinction not conveyed by either table 1 or table 2 is that between voluntary and involuntary exposure. As discussed in the introduction, individuals are capable of voluntarily reducing exposure to substances in diet and cigarette smoke that have been identified as carcinogenic hazards. By contrast, individuals cannot feasibly control their exposure to air, water, and workplace pollution.

In tables 2 and 3, we have attempted to demonstrate the susceptibility of the HERP system (or any such simplified approach) to the effects of selection of both chemicals and exposure estimates. As is clear from table 3, the differences between tables 1 and 2 are largely because of these two factors. In contrast to that of Ames et al. (*2*), our approach, incorporating a representative set of exposures to the U.S.

[5]In fact, the results of a recent water consumption survey show that for 5% of adults 20-64 yr old, the average daily consumption of tap water is 2.71 L/day, whereas the average daily total water intake is 3.79 L (*66*).

Table 2. Ranking possible carcinogenic hazards with the use of the methodology of Ames et al. (2)*

Possible hazard (HERP %)	Carcinogenic exposure	Average daily carcinogen dose (70-kg adult)	Potency of carcinogen TD_{50} (mg/kg)	Comment†
	Man-made chemicals in foods/beverages			
0.02	Daminozide in treated apples and apple juice (1987)	20 μg	1.2	(1)
0.002	Daminozide in peanuts and peanut butter (1987)	1.9 μg	1.2	(1)
0.03	DBCP in treated carrots (preregulatory, 1976)	5.1 μg	0.24	(2)
0.003	DDT, DDD, and DDE in food (preregulatory, 1968-1969)	29.0 μg	13	(3)
0.0003	DDT, DDD, and DDE in food (postregulatory, (1980-1982)	2.3 μg	13	(3)
0.002	Dieldrin in food (preregulatory, 1968-1969)	1.5 μg	1.1	(4)
0.001	Dieldrin in food (postregulatory, 1980-1982)	1.1 μg	1.1	(4)
0.004	EDB in treated apples (preregulatory)	4.1 μg	1.5	(5)
0.0004	EDB in grain products (preregulatory, 1983)	0.42 μg	1.5	(5)
0.01	PCBs in food (preregulatory, 1971)	15 μg	1.7	(6)
0.0002	PCBs in food (postregulatory, 1980-1982)	0.2 μg	1.7	(6)
0.003	Sodium saccharin in diet soda (1977-1978)	4.9 ng	2,100	(7)
	Natural carcinogens in foods and beverages			
0.003	Aflatoxins in peanuts and peanut butter (1977)	5.8 ng	0.0026	(8)
<0.0001	Estragole in basil	<3.8 μg	52	(9)
1.6	Ethyl alcohol in beer (1981)	10.2 g	9,100	(10)
0.4	Ethyl alcohol in wine (1981)	2.7 g	9,100	(10)
1.3	Ethyl alcohol in hard liquor (1981)	8.1 g	9,100	(10)
0.01	Hydrazines in mushrooms (1977)	0.16 g	20,000	(11)
0.001	DMN in cured meat and bacon (1980)	0.12 μg	0.16	(12)
0.002	DEN in cured meat and bacon (1980)	0.034 μg	0.021	(12)
	Ambient air pollutants			
0.03	Benzene (Los Angeles, preregulatory, 1968)	1.0 mg	53	(13)
0.009	Benzene (Los Angeles, postregulatory, 1984)	0.32 mg	53	(13)
0.0005	Carbon tetrachloride (U.S. urban and surburban areas, 1973-1974)	48 μg	140	(14)
0.0004	Carbon tetrachloride (U.S. urban areas, 1980)	42 μg	140	(14)
0.0002	DDT (U.S. rural areas, preregulatory, 1972)	2.0 μg	13	(15)
0.00003	DDT (U.S. rural areas, postregulatory, 1974)	0.24 μg	13	(15)
0.004	EDB (U.S. urban areas, 1980-1981)	4.3 μg	1.5	(16)
1.8	Formaldehyde (Los Angeles, 1966)	1.9 mg	1.5	(17)
0.4	Formaldehyde (Los Angeles, 1979)	370 μg	1.5	(17)
0.002	PCBs (U.S. suburban areas, preregulatory, 1975)	2 μg	1.7	(18)
0.0001	PCBs (U.S. urban areas, postregulatory, 1979)	150 ng	1.7	(18)
0.003	Tetrachloroethylene (Bayonne, NJ, 1973)	220 μg	100	(19)
0.001	Tetrachloroethylene (Bayonne, NJ, 1983)	92 μg	100	(19)
0.001	Toxaphene (U.S. rural areas, 1972)	5.2 μg	5.8	(20)
	Indoor air pollutants			
0.005	Benzene (personal average, New Jersey, 1981)	173 μg	53	(21)
0.0002	Carbon tetrachloride (personal average, New Jersey, 1981)	16.2 μg	140	(22)
0.01	Chlordane (average in treated homes, 1976-1982)	20.5 μg	2.4	(23)
0.6	Formaldehyde in conventional homes (average of all reported U.S. data)	600 μg	1.5	(24)
2.1	Formaldehyde in mobile homes (U.S. average, 1984)	2.2 mg	1.5	(24)
0.02	Heptachlor (average in treated homes, 1982)	13.9 μg	1.2	(25)
0.001	Tetrachloroethylene (personal average, New Jersey, 1981)	80 μg	100	(26)
	Water pollutants			
0.0001	Chlordane (Kansas City drinking water, preregulatory, 1965-1967)	0.14 μg	2.4	(27)
0.003	Chloroform (average U.S. drinking water, 1976)	170 μg	90	(28)
0.01	DBCP (California, postregulatory, 1984)	2.0 μg	0.24	(29)
0.007	EDB (Florida, groundwater, 1983)	7.8 μg	1.5	(30)
0.03	Heptachlor (South Carolina rural drinking water, preregulatory, 1977)	24 μg	1.2	(31)
0.0003	PCBs (U.S. surface water, preregulatory, 1971-1974)	0.4 μg	1.7	(32)
0.0002	Tetrachloroethylene (New Jersey water supplies, 1985)	12 μg	100	(33)
0.00002	TCE (U.S. water supplies, 1985)	14 μg	940	(34)
0.0002	Vinylidine chloride (New Jersey water supplies, 1985)	4 μg	24	(35)

Table 2. Continued

Possible hazard (HERP %)	Carcinogenic exposure	Average daily carcinogen dose (70-kg adult)	Potency of carcinogen TD_{50} (mg/kg)	Comment†
	Occupational exposures			
32.3	Benzene (rubber industry, preregulatory, 1942)	1.2 g	53	(36)
0.06	Benzene (rubber industry, postregulatory, 1980s)	2.4 mg	53	(36)
105.0	Formaldehyde (resin and paper manufacture, 1961)	110 mg	1.5	(37)
3.0	Formaldehyde (resin and plastic manufacture, 1980s)	3.2 mg	1.5	(37)
6.2	TCE (small factories, preregulatory, 1940s)	4.1 g	940	(38)
0.2	TCE (postregulatory, 1980s)	0.1 g	940	(38)

*The selection of chemicals and the estimates of exposure differ somewhat from those in Ames et al., as described in the text. To calculate average daily dose over an individual lifetime, we assumed: *a*) food consumption according to nationwide surveys; *b*) water consumption: 2 L/day; *c*) ambient air: inhalation of 20,000 L/day; *d*) indoor air: inhalation of 10,800 L/14-hr day; *e*) workplace air: inhalation of 9,600 L/day, 5 days/wk, 50 wk/yr, 40/70 yr (i.e., 3,768 L/day over an average lifetime) (*68*). For carcinogens listed as ambient and indoor air pollutants, the respective HERPs cannot be considered additive, since the 20,000 L/day may include both types of exposure. We also calculated exposure for a 70-kg male adult, although a 60-kg adult is more reasonable (*69*). When only a range of values was reported in the literature, their geometric mean was used as the average exposure. The HERP is derived by dividing the daily carcinogen dose by 70 kg to provide a milligram-per-kilogram value, which is then given as the percentage of the TD_{50} dose in the rodent (also in mg/kg).

†*See* appendix for comments.

Table 3. Comparison of possible carcinogenic hazards (HERPs) as estimated by Ames et al. and with the use of average exposure estimates*,†

Carcinogenic exposure	Ames et al. estimate		Our estimate, average exposure
	Average exposure	Worst-case exposure	
	Man-made chemicals in foods and beverages		
DDE/DDT in food			
Preregulatory	—	—	0.003
Postregulatory	0.0003	—	0.0002
EDB in grains	0.0004	—	0.0004
PCBs in food			
Preregulatory	—	—	0.01
Postregulatory	0.0002	—	0.0002
Sodium saccharin in diet sodas	—	0.06	0.003
	Natural carcinogens in foods and beverages		
Aflatoxins in peanuts and peanut butter	—	0.03	0.003
DMN in cured meat and bacon	—	0.003	0.001
DEN in cured meat and bacon	—	0.006	0.002
Estragole in basil	—	0.1	<0.0001
Ethyl alcohol in beer	—	2.8	1.6
Ethyl alcohol in wine	—	4.7	0.4
Hydrazines in mushrooms	—	0.1	0.01
	Ambient air pollutants		
Formaldehyde in conventional home air	0.6	—	0.6
Formaldehyde in mobile home air	2.1	—	2.1
	Water pollutants		
Chloroform in water	0.001	—	0.003
Tetrachloroethylene in water	—	0.0003	0.0002‡
TCE in water	—	0.004	0.00002§
	Occupational exposures		
Formaldehyde in workplace air	5.8	—	3.0

*DMN = *N*-nitrosodimethylamine, DEN = *N*-nitrosodiethylamine, and TCE = trichloroethylene.

†*See* tables 1 and 2 for details on daily carcinogenic dose and TD_{50}.

‡Worst-case assumption: HERP % = 0.007.

§Worst-case assumption: HERP % = 0.1.

population, shows that the selected man-made or industrial pollutants generally are comparable in terms of HERP scale to naturally occurring carcinogens in the diet. Because of the limitations in the HERP approach, however, we stress that regulatory agencies would be unwise to base public health policies principally on comparisons such as these.

Finally, Ames et al. (*2*) asserted that nine of the 26 carcinogens listed in table 1 "are thought to be nongenotoxic" and are therefore likely to have nonlinear dose-response curves or a decreased risk at lower dose. This subject has been discussed frequently (*146–149*). The general consensus on the part of regulatory agencies and expert groups has been that such policy distinctions are premature because they are supported inadequately by scientific data (*19,63,147,150,151*).

There are few, if any, clear-cut promoters and initiators; rather, there is evidence that under different conditions the same carcinogen can operate as a complete carcinogen, an initiator, or a promoter (*147*). For example, TCDD has demonstrated the ability to act both as a complete carcinogen and a promoter (*152–155*). It is just as difficult to distinguish between genotoxic and nongenotoxic agents because in most cases short-term tests for genetic toxicity have generated a mixture of positive and negative results. This phenomenon has been observed with a variety of chemicals regarded up to this time as model "epigenetic, late stage" carcinogens: asbestos, the phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate, diethylstilbestrol, and DDT. These compounds have induced a variety of genetic effects, either indirectly or directly, in experimental systems or in humans (*149*).

The nine so-called nongenotoxic carcinogens in table 1 illustrate the difficulty of making such categorical distinctions. Although in most instances the majority of short-term test results have been negative, each of the compounds (with the exception of clofibrate) has tested positive in at least one assay for each of several different genetic toxicity end points

(*156*).[6] For eight of the nine chemicals, although the evidence of genetic toxic effects is generally limited, it cannot be dismissed. Therefore, it is not possible to conclude definitively that these are nongenotoxic carcinogens that do not act at some stage and under some conditions, either directly or indirectly, by damaging the genetic material. Viewed in a larger context, the proposed distinction among carcinogens on the basis of presumed mechanism or stage at which they act is belied by the observation that control of late-stage carcinogens that may not be genotoxic may lead to the most rapid reduction in risk, as has been seen with postmenopausal estrogen therapy and cigarette smoking (*158*).

In summary, there is no question that both occupational and food carcinogens are real concerns. However, while the hazards of the workplace are relatively well characterized (*68*), there is clearly a need for more research on dietary carcinogens. At the same time, there is evidence from epidemiologic, experimental, and monitoring sources that the cumulative risks of environmental pollution are important. Despite its limitations, the HERP analysis for a selection of exposures prevalent in the U.S. environment tends to support this conclusion. Although it is not possible to estimate the magnitude of these risks with certainty, it is prudent to continue to reduce involuntary exposures to carcinogens. The dramatic decrease in estimated cancer risk following regulation of a number of industrial chemicals illustrates this point. Controlling exposures to carcinogens such as those listed in table 2 has important side benefits in that many carcinogens are mutagenic, teratogenic, reproductive, or neurological toxicants (*36*).

[6]As summarized by the IARC, chloroform has been positive in only one of many assays for gene mutation in bacteria and has been largely negative in other systems used. However, it has tested positive in lower eukaryotic systems (inducing differential toxic effects in DNA repair-deficient strains, gene conversion, and/or recombination and reverse mutation). Trichloroethylene has been positive in a number of assays. It has induced genetic toxic effects in bacteria (mutation), in yeast (gene conversion or recombination and mutation), in *Tradescantia* (mutation), in rodent cells (transformation), in human cells in vitro [unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs)], in animals in vitro (DNA damage), and in animal cells in vivo (mutation and micronuclei). Tetrachloroethylene, PCBs, and DDT have been largely negative in assays for genetic toxic effects; however, for tetrachloroethylene there have been positive results in yeast (recombination or gene conversion), in *Tradescantia* (mutation), and in animal cells (transformation and DNA damage). PCBs have induced DNA damage in animal cells in vitro and UDS in rat primary hepatocytes. DDT has been positive in insect systems (dominant lethal mutation and aneuploidy), animal cells in vitro (chromosome aberrations), and animal cells in vivo (chromosome aberrations and dominant lethal mutation). Ethyl alcohol has been studied extensively; a significant number of positive results were found. Evidence of genetic toxic effects includes gene conversion or recombination, mutation, and aneuploidy in lower eukaryotic systems; SCE, micronuclei, and chromosome aberrations in plant systems; SCE, chromosome aberrations, and aneuploidy in animal cells in vitro; SCE, chromosome aberrations, micronuclei, dominant lethal mutations, and aneuploidy in animal cells in vivo; and SCE and chromosome aberrations in human cells in vivo. Alcoholism is associated with increased incidence of chromosome aberrations (*157*). For phenobarbitol, the preponderance of results has been negative. However, there is evidence for the induction of gene mutation in bacteria and aneuploidy in yeast; gene mutation, SCE, and chromosome aberrations in rodent cells in vitro; cell transformation in rodent cells; as well as gene mutation and chromosome aberrations in human cells in vitro. Clofibrate has only been tested in two assays, both of which were negative. Finally, sodium saccharin has evidence of genetic toxic effects in lower eukaryotic systems (gene conversion or recombination and mutation), in insects (mutation), in animal and human cells in vitro (SCE and chromosome aberrations), and in animals in vivo (SCE and mutation).

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APPENDIX: TABLE 2 COMMENTS

(1) Daminozide is a plant growth retardant. In 1986, the EPA adopted interim measures to reduce its use, and a ban has been proposed. The estimated residues are 0.86 ppm in peanuts, 0.47 ppm in peanut butter, 1.02 ppm in apples, and 0.38 ppm in apple juice (*70*). The estimated average adult daily consumption of these foods is: apples, 18.1 g; apple juice, 4.4 g; and peanuts and peanut butter, 2.9 g (*71*).

(2) 1,2,-Dibromo-3-chloropropane (DBCP), a soil fumigant for the control of nematodes, was widely used on a variety of vegetable, fruit, and nut crops until the ban in 1979. Concentrations were highest in root crops. The DBCP concentration in peeled raw carrots 9 wk after treatment at seeding was 0.607 mg/kg; the concentration of DBCP was 60% lower after 5 min of boiling in water (*72*). The average daily consumption of carrots is 8.4 g/day (*71*).

(3) The dose calculation for DDT, 1,1-dichloro-2,2'-bis(*p*-chlorophenyl)ethane (DDD), and DDE is based on FDA's Total Diet Study, which yielded estimates of daily intakes of 29 μg/day in 1968–1969 (*73*). DDD and DDE are the major metabolites of DDT and are therefore present mainly in meat, fish, and dairy products (*74*). The TD_{50}s of the three chemicals are similar. DDT was phased out from use on many food crops in the late 1960s and was banned in 1972. According to an FDA study on pesticide intake from the diet in 1980–1982, the average daily intake of DDT was <40 ng/day; for DDE it was 2.2 μg/day (*75*). The higher levels of DDE reflect the fact that long after the DDT ban, significant residues of DDT were available for metabolic conversion to DDE by animals used for food consumption.

(4) Dieldrin is a cyclodiene pesticide that was banned in 1974, as was aldrin, another pesticide that was oxidized in the environment to yield residues of dieldrin. The estimates of average daily intake of dieldrin are derived from Duggan and Corneliussen (*73*) and Gartell et al. (*75*).

(5) EDB residue (0.23 ppm) was estimated 12 days after fumigation, the average interval between spraying and consumption (*76*). Daily apple consumption is estimated at 18 g/day for a 70-kg adult (*71*). Citrus fruits, plums, peaches, and cherries were also fumigated with EDB prior to its being banned for this use in 1984. In 1983, EPA estimated the average adult consumption of EDB in grain products at 0.006 μg/kg/day (*77*). The EDB residues in these foods are lower than in fruits, reflecting the relatively long interval between fumigation and consumption of grain and grain products. Fumigation of grains with EDB was banned in 1984.

(6) The dose calculation is based on FDA's Total Diet Study, which yielded estimates of average daily PCB intake of 15.0 μg/day in 1971, falling to 8.7 μg/day in 1975 (*78*). Although PCBs were used in pesticide manufacture, the main source of dietary exposure was the widespread environmental contamination from industrial uses. Fish, cheese, and eggs were the foods most significantly contaminated with PCBs. A number of regulatory and other actions were taken in 1971–1972 to reduce food contamination, and PCBs were banned from use in nonclosed systems in 1979. Although manufacture was discontinued in 1977, residues persist in the environment. The 1980–1982 estimate of daily intake was 0.196 μg (*75*).

(7) Consumption of saccharin increased substantially after cyclamates were banned in 1970. In recent years, other artificial sweeteners have become more popular. In 1976, an estimated 45% of all saccharin consumed in the United States was in soft drinks (*79*). A U.S. Department of Agriculture nutritional survey in 1977–1978 reported an average intake of artificially sweetened soft drinks at 14.7 g/day for males aged 19 and over (*80*). The average concentration of sodium saccharin is 33.5 mg/100 g of diet soda (*79*). A survey during 1977–1978 indicated an average daily intake of saccharin from all sources of 9.24 mg for males aged 18 and over (*81*).

(8) Aflatoxins are substances produced by molds that contaminate nuts, cereals, and other foods. Although they are naturally occurring, their concentration is inversely proportional to the quality of food storage techniques. Thus, they are, in part, man-made carcinogens, and exposures can be appreciably controlled by improvements in commercial processes. The average consumption of peanuts and peanut butter is 2.9 g/day (*71*), and the U.S. average concentration of aflatoxins in peanuts and peanut butter is assumed to be 2 ppb (*82,83*).

(9) The average concentration of estragole in dried basil is 3.8 mg/g (*84*). The EPA reports "zero" average daily consumption of basil (*71*). However, since EPA reports no daily intake <1 mg, we are assuming basil intake to be <1 mg. Other herbs (anise, fennel, bay, and marjoram) are considered to be the most important sources of estragole. They are also reported to have zero average daily consumption in the United States (*71*).

(10) Ethyl alcohol is the best known human dietary carcinogen. It has been associated with cancers of the oral cavity, larynx, esophagus, and liver (*85*). Health and societal effects of alcohol consumption other than carcinogenesis are more important in terms of mortality, morbidity, and costs. Valid estimates of alcoholic beverage consumption are difficult to obtain. Data from household surveys, estimated consumption based on tax revenues, and estimates by producers do not cover all aspects of drinking patterns. The dose calculation is based on estimates by the Distilled Spirits Council of the United States and by the Economic Department of the Wine Institute (*86*): 116.56 L/yr of beer (3.2% alcohol by weight), 10.36 L/yr of wine (9.6% alcohol by weight), and 9.26 L/yr of hard liquor (32% alcohol by weight).

(11) The TD_{50} is derived from data on dry *Agaricus bisporus* (*2,87*). The average daily consumption of mushrooms has been estimated as 1.6 g (*71*). The HERP is calculated assuming 90% of mushroom weight to be water and that all eaten mushrooms have the carcinogenic potency of *A. bisporus*, the most commonly eaten mushroom in the United States (*88*). No data are available concerning possible transformation of hydrazines, the principal carcinogens, during the cooking process.

(12) N-nitrosamines constitute an important group of carcinogens formed by the reaction of amines with a nitrosating agent, usually nitrous acid. Human exposure to nitrosamines has a complex pattern with four major aspects: *a*) endogenous formation of precursors (from saliva and gastric juice) and endogenous formation of N-nitrosamines, *b*) endogenous formation after uptake of precursors (mainly nitrite and nitrate in foods), *c*) uptake of N-nitrosamines present in food, and *d*) uptake from other sources (tobacco smoke, drugs, cosmetics, and various occupations) (*89*). It has been estimated that 94% of exposure to *N*-nitrosodimethylamine (DMN) is from exogenous sources (*90*). N-nitrosamines are present in cooked bacon, mainly from the frying process, whereas they occur in cured meat from added nitrate (*89,91*). The DMN content of beer, formerly high, has been significantly reduced through technological changes. Levels of N-nitrosamines in cured meat are also decreasing over time. The estimated daily intake is based on average concentrations in both cured meat and bacon of 3.4 μg/kg (DMN) and 1 μg/kg [*N*-nitrosodiethylamine (DEN)] (*91*) and a total consumption of 34 g/day (bacon and cured meat) (*92*). Daily intake of DEN from meat in the Federal Republic of Germany in 1976 was estimated to be 0.1 μg/day (*89*).

(13) Benzene is mainly used as an intermediate in the synthesis of numerous chemicals, as a solvent, and as a gasoline component. The major source of ambient air concentration is from gasoline, both from refueling and motor operation (*93*). The average concentration of benzene in Los Angeles ambient air in 1968 was 0.05 mg/m^3 (*94*), corresponding to a daily intake of 1.0 mg. In 1980, the average intake from the ambient air of a number of U.S. cities was estimated to be 0.6 mg/day (*95*). The 1984 Los Angeles estimate is 16 μg/m^3 (*96*). The average 1979–1982 concentration from five urban areas was 12.3 μg/m^3 (*25*).

(14) Carbon tetrachloride is used as a solvent and in the production of freons. It was used as a grain fumigant until banned for that use in 1985. The major sources of ambient air contamination are solvent emissions; the use of carbon tetrachloride is declining because of the concern about its toxic effects (*97*). The mean of eight measurements in urban and suburban areas in the Northeastern United States in the early 1970s was 2.4 μg/m^3 (*98*). Other measurements during the same period ranged between 0.45 and 9.1 μg/m^3 (*99–101*). A decade later, the average concentration in five urban areas (2.1 μg/m^3) was comparable (*25*).

(15) The estimates derive from a 1972–1974 ambient air survey in the Mississippi Delta area where DDT was widely used on cotton crops until its ban in January of 1973. The average concentrations were 0.1 μg/m^3 in 1972 and 0.012 μg/m^3 in 1974 (*102*). A previous estimate from nine urban and agricultural areas in the United States had an upper estimate of 1.56 μg/m^3, corresponding to a HERP% of 0.003 (*103*).

(16) The average ambient air concentration of EDB in 10 U.S. cities was 213 ng/m^3 (*104,105*), largely from its use as a scavenger in leaded gas. Regulations to reduce the use of leaded gas have been in effect since 1975.

(17) Formaldehyde is an important industrial chemical used as an intermediate in the production of resins for the construction, automotive, and appliance industries. It is also used in the manufacture of fungicides and bactericides, various textiles, paper, and a number of consumer products, such as cosmetics, air fresheners, and drugs (*93*). Formaldehyde is a component of tobacco smoke. There is no major environmental (other than occupational) regulation of formaldehyde on the basis of its carcinogenicity. Data from 1966 are derived from a survey that showed a range of daily average concentrations in Los Angeles ambient air between 60 and 148 $\mu g/m^3$ (geometric mean, 94 $\mu g/m^3$) (*106*). Other estimates in the same period were similar (*107*). The 1979 estimate (18.5 $\mu g/m^3$) is considerably lower (*108*). Other investigators have also reported a decline in formaldehyde levels over time (*109*).

(18) The average ambient air concentration of PCBs in suburban areas of Florida, Mississippi, and Colorado in 1975 was 100 ng/m^3 (*110*). The most significant reduction in PCB air concentrations followed the production ban in 1979. The average urban air concentration in 1979 was estimated to be 5–10 $\mu g/m^3$ (*111*); the HERP is based on the midpoint. A 1979 study in Minneapolis reported an average ambient air concentration of 7.1 $\mu g/m^3$ (*112*).

(19) Tetrachloroethylene is used largely in the textile (processing and finishing) and dry cleaning industries, in vapor degreasing and cold cleaning of metals, and as an intermediate in the chemical industry. In 1975, it constituted >65% of the total dry cleaning solvent usage (*113*). Both exposure estimates refer to Bayonne, NJ, ambient air. The average daily ambient concentrations were 11.1 $\mu g/m^3$ in 1973 (*98*) and 4.6 $\mu g/m^3$ in 1983 (*23*). Studies of other urban areas reported similar average daily concentrations: Los Angeles 1976, 4.6 $\mu g/m^3$ (*114*); Baltimore 1978–1983, 4.0 $\mu g/m^3$; and Philadelphia 1979–1982, 5.9 $\mu g/m^3$ (*25*).

(20) Use of toxaphene has increased in the last decade, partly because of the ban on DDT. It is mainly used for the control of cotton insect pests. The average concentration measured in 1972 in the Mississippi Delta area was 0.26 $\mu g/m^3$ (*102*).

(21) The dose calculation for benzene is based on personal air samplers carried by ~600 New Jersey residents in the fall of 1981. These samplers would have integrated outdoor and indoor exposure, but in all cases outdoor concentrations were lower than personal average concentrations; hence, the personal samples would have underestimated indoor exposure. Tobacco smoke was thought to be the main source of indoor concentrations of benzene (*23*).

(22) The dose calculation for carbon tetrachloride is based on personal air sampling in New Jersey (*23*). *See* comment 21.

(23) Chlordane and heptachlor are chlorinated cyclodiene insecticides, structurally similar to dieldrin. Chlordane was widely applied to the soil below and around the foundations of buildings to control subterranean termites until this use was terminated by agreement with the EPA in 1987. The dose calculation is based on a survey of military housing (*115*). Data for nonmilitary housing in the same period suggested higher average doses of 28–48 μg/day (*116,117*). Chlordane is a complex mixture. The methods of measurement used in the cited studies would not have included the more volatile fractions and hence would have underestimated total exposures. Local data for 1983–1985 suggest a substantial reduction in exposure levels, perhaps resulting from improved application techniques introduced in the 1980s (*118*).

(24) The release of formaldehyde from urea-formaldehyde foam insulation in mobile homes as well as in conventional homes containing particle board and plywood are the most important sources of indoor exposure to formaldehyde, but it has widespread use in construction materials, wood products, and furniture, textiles, and paper. Sources of indoor contamination for benzene include tobacco smoke and solvents (*93*). The estimate of average daily uptake of formaldehyde in the air in conventional homes is based on the means of all reported median or mean concentrations, as estimated by Ames et al. (*2*). The mean concentration of formaldehyde in the air of mobile homes (0.205 mg/m^3) is derived from Connor et al. (*119*).

(25) Heptachlor is a component of technical chlordane (5.8%) and is often applied with it in a 1:2 mixture. The dose calculation is based on measurements in homes treated with either this mixture or with technical chlordane (*116*). Local data for 1983–1985 suggest a substantial reduction in exposure levels, perhaps resulting from improved application techniques introduced in the 1980s (*118*).

(26) The dose calculation for tetrachloroethylene is based on personal air sampling in New Jersey (*see* comment 21). Dry-cleaned clothes were thought to be a source of indoor concentrations of tetrachloroethylene (*23*).

(27) Chlordane was used on many commercial fruit, vegetable, and grain crops, as well as in private gardening. Chlordane was detected in 21 out of 50 samples of Kansas City drinking water between 1965 and 1967 (*120*). Because only concentrations higher than 0.1 $\mu g/L$ were listed separately in this study, a level of 0.05 $\mu g/L$ was assumed for the remaining positive samples; the average (0.07 $\mu g/L$) is used in the table. The maximum chlordane concentration reported in the same study was 8 $\mu g/L$ (HERP%, 0.01).

(28) The average drinking water concentration of chloroform estimated in a 1976 nationwide study of 113 public water systems was 84 $\mu g/L$ (*121*). It is mainly formed through the reaction of chlorine with organic chemicals in water (*122*). The risk posed by chloroform must be compared with the benefits of chlorination, and its benefits should be compared with those of other water-disinfection technologies.

(29) DBCP concentrations in positive groundwater samples from five states in the 1980s ranged between 0.02 and 20 $\mu g/L$ (*123*). The upper value corresponds to a HERP% of 0.2. A concentration of 137 $\mu g/L$ (HERP% 1.6) has been reported for a single polluted well in Arizona (*10*). Monitoring of wells in both small domestic and large water systems in California showed that ~30% were contaminated with DBCP. The majority had concentrations >1 $\mu g/L$; hence this value is used in the table as an average estimate (*124*).

(30) An EPA groundwater EDB contamination study in four states found >100 contaminated wells. Eighty-six of them were in Florida; the concentration ranged between 1.0 and 15.0 $\mu g/L$. The HERP is based on the geometric mean (3.9 $\mu g/L$). The highest concentration in this study was 100 $\mu g/L$, corresponding to a HERP% of 0.2, and was found in Georgia (*125*).

(31) Before being banned in 1983, heptachlor was mainly used to treat corn crops and seeds. A 1977 study of drinking water in two U.S. rural counties showed mean levels of heptachlor in positive samples of 15 and 9 $\mu g/L$, respectively (*126*). The HERP is based on the average value of 12 $\mu g/L$.

(32) The estimated surface water concentration of PCBs in 17 major U.S. drainage basins during 1971–1974 was 0.1–3.0 $\mu g/L$ (*127*). The HERP is based on the average of positive results for 1974: 0.2 $\mu g/L$.

(33) The median concentration of tetrachloroethylene in NJ public water supplies that tested positive from July to December of 1985 was 6 $\mu g/L$; maximum concentration was 46 $\mu g/L$ (*128*) (HERP%, 0.001). Concentrations as high as 1,500 $\mu g/L$ (HERP%, 0.04) have been detected in polluted wells (*10*).

(34) Trichloroethylene (TCE) is used in the vapor degreasing of lubricated metal parts, as a solvent in the textile, adhesive, and lubricants industry, as well as in some consumer cleaning products. In 1977, FDA prohibited its use as an extraction solvent in the food (coffee and spices) industry (*129*). The major source of environmental contamination by TCE is the metal industry (*129*). The median contamination of TCE in New Jersey public water supplies that tested positive from July to December 1985 was 7 $\mu g/L$ (*128*). The same study showed a maximum concentration of 190 $\mu g/L$ (HERP%, 0.0006). Levels as high as 35,000 $\mu g/L$ (HERP%, 0.1) have also been found in contaminated private drinking water supply wells (*130*).

(35) In the New Jersey study described in comment 33, the median concentration of vinylidine chloride was 2 $\mu g/L$, and the maximum was 9 $\mu g/L$ (HERP%, 0.001). Vinylidene chloride is the basis for the production of copolymers, which are used in food packaging, coatings for paper, fibers, tubes, and pipes (*131*). Vinyl chloride, whose polymers are also used in the production of plastics, is a known human and animal carcinogen and is strictly regulated both in the workplace and in the environment. It has been found in polluted wells at concentrations as high as 20 $\mu g/L$ (*132*) and 10 $\mu g/L$ (*128*). Inasmuch as the TD_{50} is 8.0 mg/kg, the respective HERP% values are 0.007 and 0.004.

(36) Concentrations of 100 ppm of benzene or more were common in the rubber, printing, leather, and shoe industries until the 1970s (*93,133*). The 1942 exposure corresponded to 100 ppm. In 1980, a permissible exposure limit (PEL) of 100 ppm was issued by OSHA; today the limit is 1 ppm or 3.2 mg/m^3. The estimated average postregulatory benzene concentration in the rubber industry is 0.20 ppm (*134*).

(37) The estimated workplace air concentration (28.3 mg/m^3) is the midpoint of values obtained in a 1961 U.S. study on resin manufacture and paper production (*135,136*). In 1980, OSHA set the PEL at 3.7 mg/m^3 (HERP%, 13.3) on the basis of noncarcinogenic effects. In 1987, it was lowered to 1.2 mg/m^3 (HERP%, 4.3). Estimates of the concentration of formaldehyde (0.86 mg/m^3) in the resin and plastic industry during the 1980s indicates a 33-fold decrease (*137–139*).

(38) The HERP is based on an estimated workplace concentration of 200 ppm, which was not uncommon before regulations were imposed (*140*). Concentrations as high as 8,000 ppm, corresponding to a HERP% of 256, have also been measured (*141*). Today, the OSHA PEL is 100 ppm or 538 mg/m^3 (HERP% 3.2), and the HERP is based on an estimated workplace concentration of 5 ppm (*142*).