In: Chemical Risk Assessment and Occupational Health: Current Applications, Limitations, and Future Prospects
(C. M. Smith *et al.*, eds., Westport, CT: Auburn House, 1994)

9.

Setting Priorities Among Possible Carcinogenic Hazards in the Workplace

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Historically, many of the 55 chemicals and industrial processes that have been found to cause cancer in humans (Vainio, Coleman, and Wilbourn 1991) were identified in the workplace under high exposure conditions. The U.S. Occupational Safety and Health Administration (OSHA) establishes permissible exposure limits (PELs) in workplace air. The PEL is the maximum allowable concentration of an airborne contaminant in workplace air on a time-weighted average basis over an eight-hour day and thus represents the maximum allowable dose for a worker per day. In 1989, OSHA set new PELs for hundreds of chemicals, chiefly by adopting the threshold limit values (TLVs) of the American Conference of Governmental Industrial Hygienists (ACGIH). Under this new Air Contaminants Standard, more than 400 chemicals are regulated with PELs; however, the PEL for a particular chemical does not usually reflect consideration of carcinogenicity data. In contrast to the limited regulation of occupational exposure on the basis of potential carcinogenic effects, more than 1,100 chemicals have been tested for carcinogenicity in long-term, chronic rodent bioassays, and about half of these are positive in at least one experiment. Other regulatory agencies such as the Environmental Protection Agency (EPA) routinely use such animal cancer test results in the regulatory process.

It is not known whether, or at what exposure levels, rodent carcinogens will turn out to have carcinogenic effects in humans. Thus, it is not clear how best to make use of the animal data. For a variety of reasons, we have argued that rodent bioassays do not provide sufficient information to assess the risks to humans at the low doses of most human exposures; however, occupational exposures can be high. Evidence is lacking as to which mathematical model is appropriate for making a quantitative assessment of human risk by extrapolation across doses. The high doses used in rodent tests may increase the mutagenic and therefore the carcinogenic response, due to increases in cell division (e.g., through cell death and consequent cell replacement [Ames and Gold 1990; Ames, Shigenaga, and Gold, 1993]). Mechanisms of carcinogenesis are only beginning to be understood, and efforts at quantitative human risk assessment based on animal data suffer from both random and systematic errors (Peto 1985).

One reasonable strategy for gaining a broad perspective on possible carcinogenic hazards in the workplace is to use a rough index to compare and rank possible hazards for chemicals that workers are exposed to that have been demonstrated to be rodent carcinogens. Ranking allows research and regulatory priorities to be set by focusing attention on those exposures that are highest in possible hazard. In the occupational context, ranking provides a role for carcinogenesis bioassays in setting priorities among chemicals for medical surveillance, exposure assessment, epidemiological research, and regulatory policy. Additionally, consideration of chemicals that rank high in possible hazard requires little extrapolation from the high doses of rodent bioassays to worker exposure levels, since permitted exposures for chemicals that rank high are close to the doses administered to rodents.

We have used rodent carcinogenicity data in two analyses. First, we have ranked possible carcinogenic hazards among chemicals on the basis of an index that compares the dose at which workers are permitted to be exposed to a given chemical (at the OSHA PEL) with the dose rate that induces a standard tumor rate in laboratory animals (carcinogenic potency). We call this index the Permitted Exposure/Rodent Potency, or PERP. PERP expresses the worker permitted lifetime exposure (in mg/kg/day) to a rodent carcinogen as a percentage of the lifetime dose that induces tumors in 50 percent of animals (the TD_{50} in mg/kg/day). A similar rank order would be expected using standard risk assessment methodology for the same permitted exposures. The ratio of the human versus animal dose rates may well be correlated with occupational carcinogenic hazards; if it is, then by computing this ratio for many chemicals with PELs, potential carcinogenic hazards to workers can be ranked and compared. This index is a rough measure that may be useful for prioritizing on an ordinal scale. It is not, however, intended as a direct estimate of human hazard.

In 1987, we performed a similar ranking by PERP using the OSHA PEL values prior to the 1989 Air Contaminants Standard and for a smaller data set of rodent carcinogenicity results (Gold et al. 1987a). The analysis presented here reflects the reductions in OSHA PEL values, the addition of new PELs for chemicals not previously regulated, and the results of additional animal cancer tests. In our earlier ranking (Gold et al. 1987a), we showed that the possible carcinogenic hazards (PERP) for 41 rodent carcinogens differed by more than 100,000-fold from each other, and that for some substances workers were permitted to be exposed to doses close to those that induce tumors in test animals.

In a second analysis, we have identified chemicals that workers are exposed to and that are carcinogenic in rodents but that currently have no OSHA PEL. The National Occupational Exposure Survey (NOES) (NIOSH 1990) conducted by the National Institute for Occupational Safety and Health (NIOSH) was used to identify the chemicals to which workers are exposed. In both of these analyses, we report for each rodent carcinogen the estimated number of exposed workers according to the NOES, carcinogenicity in rats and mice, carcinogenic potency in rats and mice, and positivity in the *Salmonella* mutagenicity test if results are available.

Our ranking of potential carcinogenic hazards is for *permitted* exposures in the workplace. In a previous analysis, we ranked estimated actual human exposures from a variety of sources, including naturally occurring plant pesticides, the products of cooking, medicinal drugs, workplace exposures, indoor air, and synthetic pesticide residues, using a similar index, HERP (Human Exposure/Rodent Potency) (Gold, Manley, and Ames 1992). This approach may help to formulate sensible priorities for research and regulatory action among the large number of rodent carcinogens already identified.

In summary, we find that the PERP values for 75 rodent carcinogens to which workers are exposed differ by more than 100,000-fold from each other. For 9 chemicals, the permitted worker exposure is greater than 10 percent of the tumorigenic dose rate in rodents (TD_{50}), and for 27, it is between 1 and 10 percent. We have also identified 120 chemicals that require further attention because they have no OSHA PEL, workers are exposed to them, and they are rodent carcinogens.

ANALYTICAL APPROACH

Dose Rates

Two factors are required for the determination of a PERP: worker exposure limits and carcinogenic potency in laboratory animals. For both humans and rodents, we use standard values to estimate an average daily dose rate in milligrams per kilogram body weight per day for a lifetime as follows: Dose rate = dose × exposure per day as a proportion of body weight × proportion of life during which exposure occurs.

Worker Exposure Levels

Exposure assessments for chemicals in the workplace are frequently incomplete or uneven, so the actual average daily dose levels that workers receive are not accurately known. Workplace exposures vary substantially by occupation, type of plant, and even from one particular plant to another. We have studied instead not actual exposures but the PELs set by OSHA, which are based primarily on across-the-board adoption in 1989 of the TLVs of the ACGIH.

PELs are specified in parts per million or milligrams per cubic meter of workplace air. To convert these levels to a maximal average daily dose rate in milligrams per kilogram body weight, we assume that a worker inhales 9.6 m^3 of air per day, weighs 70 kg, works five days per week 50 weeks per year for 40 years, and has a standard life span of 70 years.

Carcinogenic Potency Values in Laboratory Animals

Our group has developed a large database of the results of chronic animal cancer tests, the Carcinogenic Potency Database (CPDB) (Gold et al. 1984; Gold et al. 1986; Gold et al. 1987b; Gold et al. 1990; Gold et al. 1993). TD_{50} values have been estimated from all long-term, chronic experiments that meet a set of standard inclusion criteria, for example, administration by an oral route or by inhalation, a dosing period at least one-fourth the standard life span of two years for rodents, an experiment length of at least one year, and the presence of a control group (Gold et al. 1984). The CPDB excludes particulates, and consequently, some important substances regulated by OSHA such as asbestos and heavy metals are not included in the CPDB. Currently, the CPDB includes results on more than 1,150 chemicals tested in rats or mice, about half of which are positive in at least one experiment. TD_{50} is defined as the chronic dose rate in milligrams per kilogram body weight per day that would halve the proportion of tumorless test animals by the end of a standard lifetime (Sawyer et al. 1984; Peto et al. 1984). The estimation procedure for TD_{50} standardizes the results of rodent experiments by taking into account the spontaneous tumor rate, using lifetable data when available, and adjusting for early termination of dosing or observation period. Our standard values for animal weight; intake of food, air, and water; and life spans are given in Gold et al. (1984). We have found that the TD_{50} values of rodent carcinogens vary more than 10 million–fold (Gold et al. 1984). The availability of a numerical description of the tumorigenic dose rate for a large number of test agents makes it possible to calculate PERP values for a great many human exposures.

In the analysis below, we define a compound as carcinogenic if the author of at least one published paper in the CPDB evaluated it as positive and if, in addition, the *p*-value for at least one experiment is less than 0.01 (Gold et al. 1984; Gold et al. 1986; Gold et al. 1987b; Gold et al. 1990; Gold et al. 1993). For each rodent carcinogen, the TD_{50} value reported for rats and for mice is the harmonic mean of the most potent TD_{50} values from each positive test in that species; the most potent TD_{50} for an experiment is selected from among the positive target sites identified by the author of the published paper. For chemicals positive in both rats and mice, the TD_{50} used in PERP is from the species with the more potent value. For chemicals tested in both species, but positive in only one, we make no adjustment in the PERP for the lack of a carcinogenic effect in the second species. TD_{50} values would be similar if we had selected the most potent value in each species rather than the harmonic mean (Gold et al. 1987a; Gold, Slone, and Bernstein 1989). (Our 1987 PERP analysis [Gold et al. 1987a] used the most potent site rather than a harmonic mean to characterize TD_{50}, whereas here we use the harmonic mean as we did in our recent HERP analysis [NIOSH 1990]).

Selection of Chemicals

The chemicals included in our ranking of potential carcinogenic hazards to workers are all those that have both a PEL in OSHA's 1989 Air Contaminants Standard (OSHA 1989a, 1989d) and also a positive experiment in the CPDB in which the chemical was administered by an oral or inhalation route (Gold et al. 1984; Gold et al. 1986; Gold et al. 1987b; Gold et al. 1990; Gold et al. 1993). The strength of evidence of carcinogenicity in rodents differs among the compounds selected, in terms of number of positive sex-species groups, number of target organs, lethality of tumors, and proportion of tests that are positive. For six of these rodent carcinogens, there is only one positive experiment in the CPDB (e.g., styrene). The shape of the dose response and mechanisms of carcinogenesis are also variable across chemicals, and none of these differences are reflected in the PERP value. For some chemicals with data indicating a markedly upward curvature in the dose response (e.g., formaldehyde), the PERP value may exaggerate potential carcinogenic hazards compared with chemicals with a more linear dose response, since PERP is a simple ratio.

From among approximately 500 carcinogens in the CPDB that were evaluated as tumorigenic in at least one experiment by our criteria above, and more than 400 chemicals that are regulated with PELs by OSHA, only 75 compounds are common to both. We did not calculate PERP values for 11 additional compounds that have no allowable exposure level because they are regulated by OSHA as *carcinogenic hazards* (Table 9.2 footnote).

Estimated Number of Exposed Workers

Estimates of the number of workers exposed to rodent carcinogens are taken from the NIOSH NOES survey conducted in 1981–1983 (Seta, Sundin, and Pedersen 1988). For our listing of rodent carcinogens with no PEL, we include all chemicals in the CPDB with a positive experiment that are also listed in the NOES. The NOES surveyed 4,490 facilities, excluding mining, agriculture, government, military, and major sectors of the financial system. The number of exposed workers includes those exposed at least 30 minutes per week on an annual average or at least one time per week for 90 percent of the year (NIOSH 1990).

RANKING POTENTIAL CARCINOGENIC HAZARDS BY PERP

Table 9.1 lists alphabetically the 75 rodent carcinogens with PELs and the TD_{50} values in rats and/or mice from the CPDB. For each of the 75 chemicals,

Table 9.1
Carcinogenic Potency of 75 Rodent Carcinogens with OSHA PELs

CAS[a]	Chemical	TD_{50} in mg/kg/day[b]		CAS[a]	Chemical	TD_{50} in mg/kg/day[b]	
		Rats	Mice			Rats	Mice
75-07-0	Acetaldehyde	153	NT	50-00-0	Formaldehyde	2.19	43.9
79-06-1	Acrylamide	6.15	NT	98-01-1	Furfural	683	197
107-13-1	Acrylonitrile	16.9	NT	556-52-5	Glycidol	4.28	34.7
309-00-2	Aldrin	?	1.27	76-44-8	Heptachlor	-	1.21
61-82-5	Amitrole	9.94	25.3	87-68-3	Hexachlorobutadiene	65.8	NT
142-04-1	Aniline[c]	194	-	67-72-1	Hexachloroethane	55.4	338
134-29-2	*o*-Anisidine [c]	23.0	748	302-01-2	Hydrazine	0.31	2.93
71-43-2	Benzene	169	77.5	7722-84-1	Hydrogen peroxide	NT	9,010
100-44-7	Benzyl chloride	-	61.5	123-31-9	Hydroquinone	59.9	122
111-44-4	*bis*-2-Chloroethylether	NT	11.7	78-59-1	Isophorone	1,210	-
74-96-4	Bromoethane	149	535	58-89-9	Lindane	-	25.3
75-25-2	Bromoform	648	-	75-09-2	Methylene chloride	724	918
106-99-0	1,3-Butadiene	261	26.2	101-14-4	4,4'-Methylene-*bis*-(2-chloroaniline)	19.3	NT
10108-64-2	Cadmium[c]	0.00625	-	60-34-4	Methylhydrazine	NT	7.55
2425-06-1	Captafol	NT	108	100-00-5	*p*-Nitrochlorobenzene	-	473
56-23-5	Carbon tetrachloride	449	150	27323-18-8	PCB-54%	-	9.58
57-74-9	Chlordane	-	2.99	87-86-5	2,3,4,5,6-Pentachlorophenol	-	23.0
75-00-3	Chloroethane	-	1,810	122-60-1	Phenylglycidyl ether	44.0	NT
67-66-3	Chloroform	262	90.3	59-88-1	Phenylhydrazine [c]	NT	53.5
123-73-9	Crotonaldehyde	4.20	NT	78-87-5	Propylene dichloride	-	276
96-12-8	DBCP	0.259	2.72	75-56-9	Propylene oxide	74.4	912
50-29-3	DDT	84.7	12.3	7446-34-6	Selenium compounds[d]	8.01	69.3
7572-29-4	Dichloroacetylene	3.58	0.57	100-42-5	Styrene	23.3	-
106-46-7	*p*-Dichlorobenzene	644	398	79-34-5	1,1,2,2-Tetrachloroethane	-	38.3
542-75-6	1,3-Dichloropropene	94.0	49.6	127-18-4	Tetrachloroethylene	101	126
62-73-7	Dichlorvos	4.16	70.4	509-14-8	Tetranitromethane	0.447	1.19
60-57-1	Dieldrin	?	1.01	26471-62-5	Toluene diisocyanate	33.7	250
121-69-7	*N,N*-Dimethylaniline	125	-	638-03-9	*m*-Toluidine	-	1,080
57-14-7	1,1-Dimethylhydrazine	NT	2.64	636-21-5	*o*-Toluidine [c]	32.6	629
	Dinitrotoluene	8.02	NT	540-23-8	*p*-Toluidine	-	62.5
123-91-1	Dioxane	334	838	8001-35-2	Toxaphene	-	5.57
106-89-8	Epichlorohydrin	2.96	-	79-00-5	1,1,2-Trichloroethane	-	55.0
140-88-5	Ethyl acrylate	120	324	79-01-6	Trichloroethylene	668	1,578
64-17-5	Ethyl alcohol	9,110	-	108-05-4	Vinyl acetate	201	NT
106-93-4	Ethylene dibromide	1.52	7.45	593-60-2	Vinyl bromide	18.5	NT
107-06-2	Ethylene dichloride	8.04	101	75-01-4	Vinyl chloride	19.1	20.9
75-21-8	Ethylene oxide	21.3	63.7	75-35-4	Vinylidene chloride	-	34.6
117-81-7	di(2-Ethylhexyl)phthalate[c]	798	894				

[a]CAS= Chemical Abstracts Service registry number. [b]NT = No test in the CPDB in this species. - = all tests in this species were negative; ? = in only one report, did the author evaluate the chemical as carcinogenic to rats, but there was no identified target site; for the category "all tumor-bearing animals" there was no dose-related effect (p=1).
[c]The TD_{50} is for the free-base and the CAS is for the hydrochloride salt. For cadmium, the TD_{50} is for the free-base and the CAS is for cadmium chloride; both cadmium chloride and cadmium sulfate were used in calculating the TD_{50}.
[d]The TD_{50} and the CAS are for selenium sulfide.

Table 9.2 reports the PERP value, expressed as the milligram per kilogram daily permitted dose to workers as a percentage of the rodent TD_{50}. PERP values are listed in descending order, with the highest potential hazards at the top. PERP values range more than 100,000-fold for exposures to different substances at the current PEL. For 9 chemicals the permitted exposures are more than 10 percent of the rodent TD_{50}; for 17, they are between 1 and 10 percent of the rodent TD_{50}; and for 39, they are less than 1 percent. The nine substances with PERP

Table 9.2
Ranking by PERP of 75 Rodent Carcinogens with OSHA PELs[a]

PERP %	Chemical	OSHA PEL ppm	OSHA PEL mg/m^3	TD_{50} in mg/kg/day	Estimated no. workers(NOES)
540	*Ethylene dibromide [s][b,+]	20	153	1.52	8,562
456	*1,3-Butadiene[b,+]	1,000	2,200	26.2	51,973
94	Tetranitromethane[+]	1	8	0.447	1,445
96	Glycidol[+]	25	75	4.28	4,871
50	Styrene[+]	50	215	23.3	333,210
32	Bromoethane[+]	200	890	149	12,285
15	*Epichlorohydrin [s][+]	2	8	2.96	80,167
14	*bis*-2-Chloroethylether [s][+]	5	30	11.7	-
13	*Methylene chloride [b,+]	500	1,737	724	1,438,207
9.1	*Tetrachloroethylene [-]	25	170	101	688,099
7.7	Chloroethane[+]	1,000	2,600	1,810	49,212
7.7	Crotonaldehyde	2	6	4.20	-
6.8	Propylene dichloride[+]	75	350	276	2,947
6.3	*Acetaldehyde[-]	100	180	153	216,534
6.1	**p*-Dichlorobenzene[-]	75	450	398	33,977
5.8	*Vinyl bromide	5	20	18.5	1,821
4.4	1,1,2-Trichloroethane [s] [-]	10	45	55.0	1,036
4.0	*Cadmium [c,-]	-	0.005	0.00625	88,966
3.9	Dichloroacetylene	0.1[c]	0.4[c]	0.57	61
3.6	*Propylene oxide[+]	20	50	74.4	421,143
3.6	**o*-Toluidine [s]	5	22	32.6	356
2.7	*Ethylene dichloride[+]	1	4	8.04	83,249
2.3	*Formaldehyde [c,+]	0.75	0.923	2.19	1,329,332
2.2	Heptachlor [s][-]		0.5	1.21	1,033
2.2	Phenylhydrazine [s][+]	5	22	53.5	212
2.2	Trichloroethylene[-]	50	270	668	401,366
2.0	*1,1-Dimethylhydrazine [s][+]	0.5	1	2.64	2,917
1.6	*Hydrazine [s][+]	0.1	0.1	0.31	60,499
1.5	*Dioxane [s][-]	25	90	334	429,314
1.4	*Acrylonitrile [s][c,+]	2	4.5	16.9	81,686
1.3	Dichlorvos [s][+]	-	1	4.16	24,204
1.3	Dieldrin [s][-]	-	0.25	1.01	-
1.1	Ethyl alcohol[-]	1,000	1,900	9,110	2,069,131
1.1	*N,N*-Dimethylaniline [s][-]	5	25	125	30,480
1.0	Aldrin [s][-]	-	0.25	1.27	42
1.0	Dinitrotoluene [s][+]	-	1.5	8.02	-
0.98	1,1,2,2-Tetrachloroethane[s][-]	1	7	38.3	4,143
0.97	Hexachloroethane [s][-]	1	10	55.4	8,515
0.90	Chlordane [s][-]	-	0.5	2.99	3,832
0.90	*Ethyl acrylate [s][-]	5	20	120	44,603
0.80	Vinyl acetate[-]	10	30	201	129,022
0.77	*p*-Toluidine	2	9	62.5	-
0.73	Phenylglycidyl ether[+]	1	6	44.0	10,554
0.73	*Vinyl chloride [c,+]	1	2.6	19.1	81,318
0.62	Vinylidene chloride[+]	1	4	34.6	2,675
0.58	*Chloroform[-]	2	9.78	90.3	95,778
0.54	*1,3-Dichloropropene[+]	1	5	49.6	2,159
0.48	*Toxaphene [s][+]	-	0.5	5.57	-
0.45	*Ethylene oxide [c,+]	1	1.8	21.3	270,684
0.45	*Carbon tetrachloride [s][-]	2	12.6	150	104,172
0.44	*DDT[s][-]	-	1	12.3	-
0.44	Benzyl chloride[+]	1	5	61.5	41,072
0.39	*DBCP[c,+]	0.001	0.01	0.259	-
0.28	*PCB-54%[s][-]	-	0.5	9.58	23
0.25	Methylhydrazine [s][+]	0.2[c]	0.35[c]	77.5	1,473
0.22	Aniline [s][-]	2	8	194	41,991
0.22	*Benzene [c,d-]	1	3.2	77.5	272,286
0.22	Furfural [s][+]	2	8	197	135,914
0.18	Hydroquinone[-]	-	2	59.9	442,744
0.14	Selenium compounds[+]	-	0.2	8.01	2,965
0.12	2,3,4,5,6-Pentachlorophenol [s][-]	-	0.5	23.0	26,805

Table 9.2 (Continued)

0.12	*o-Anisidine [s]+	-	0.5	23.0	1,108
0.11	*Amitrole-	-	0.2	9.94	694
0.11	Lindane [s]-	-	0.5	25.3	15,035
0.10	Isophorone-	4	23.0	1,210	47,099
0.062	*4,4'-Methylene-*bis* (2-chloroaniline) [s]+	0.02	0.22	19.3	114
0.045	*m*-Toluidine	2	9	1,080	-
0.042	Bromoform [s]+	0.5	5	648	1,473
0.034	*di(2-Ethylhexyl)phthalate-	-	5	798	340,797
0.033	*Acrylamide [s]-	-	0.03	6.15	10,653
0.020	Hexachlorobutadene-	0.02	0.24	65.8	1,010
0.011	*p*-Nitrochlorobenzene [s]+	-	1	473	2,950
0.006	*Toluene diisocyanate+	0.005	0.04	33.7	38,883
0.005	Captafol-	-	0.1	108	-
0.001	Hydrogen peroxide +	1	1.4	9,010	1,006,736

[a]PERP: Permitted Exposure/Rodent Potency. The following chemicals have no PERP values because they are suspected human carcinogens with no allowable exposure level: 2-actylaminofluorene, 4-aminodiphenyl, benzidine, *bis*-(chloromethyl)ether, chloromethyl methyl ether, 3,3'-dichlorobenzidine, 4-dimethylaminoazobenzene, ethylene imine, ß-naphthylamine, *N*-nitrosodimethylamine, and ß-propiolactone.
[b]In process of OSHA 6(b) rule-making.
[c]Final OSHA 6(b) rule, comprehensive standard.
[d]Workers exposed to benzene from gasoline are not included in estimate of number of exposed workers.
+ = Mutagenic in *Salmonella*.
- = Nonmutagenic in *Salmonella*.
[c]=Dichloroacetylene and methylhydrazine are both ceiling values.
[s]=OSHA indicates that thése substances may be absorbed into the bloodstream through the skin, mucous membranes and/or eyes, as well as by inhalation.
* = International Agency for Research on Cancer's evaluation of the chemical is "sufficient evidence" of carcinogenicity in animals.

greater than 10 percent are ethylene dibromide (PERP = 540 percent), 1,3-butadiene (456 percent), tetranitromethane (96 percent), glycidol (94 percent), styrene (50 percent), bromoethane (32 percent), epichlorohydrin (15 percent), *bis*-2-chloroethylether (14 percent), and methylene chloride (13 percent). Three of the chemicals with highest PERP values (ethylene dibromide, 1,3-butadiene, and methylene chloride) have been addressed individually by OSHA, and 6(b) rulemakings are in progress. The PERP values for these chemicals would rank much lower if the new recommended values were used instead of the current PELs. Estimates of the PERP for various chemicals span several orders of magnitude, whereas the TD_{50} values for the same compounds estimated from various experiments are generally within one order of magnitude; therefore, we would expect little difference in the ranking of chemicals by PERP if we had used the most potent site per chemical instead of the average of the various TD_{50}s.

Among the nine chemicals that rank highest in potential carcinogenic hazard at the PEL (PERP > 10 percent) are eight that have been tested in both rats and mice, of which six are positive in both species. All nine are mutagenic in *Salmonella* (Table 9.2), and four of the nine have been evaluated by the International Agency for Research on Cancer (IARC) as having sufficient evidence of çarcinogenicity in laboratory animals (Table 9.2).

It is relevant to consider, even if it is not explicitly used, information about the size of the exposed population, as well as information about the ratio of the permitted exposure levels in humans to the carcinogenic potency in rodents. The number of U.S. workers exposed to different chemicals varies widely, and it changes over time due to alterations in markets, production techniques, and product substitution. Crude estimates of the numbers of workers who might be exposed to each compound are reported in Table 9.2 based on estimates from the NOES. These numbers include workers who might be exposed only 30 minutes per week annually, whereas the PEL is based on a time-weighted average of eight hours per day.

IDENTIFICATION OF RODENT CARCINOGENS THAT HAVE NO PEL

OSHA has indicated that a high regulatory priority is the establishment of PELs for chemicals for which no exposure limits exist (OSHA 1989d). Table 9.3 reports 120 chemicals that are rodent carcinogens lacking PELs, to which workers are exposed (based on NOES); the chemicals are ordered by the number of workers estimated to be exposed. This list is a first step toward identifying chemicals that OSHA may want to investigate further. For each chemical, we report the TD_{50} values in rats and mice, the estimated number of workers exposed, mutagenicity results in *Salmonella,* and whether IARC evaluates the compound as having sufficient evidence of carcinogenicity in laboratory animals. Among the 120 chemicals, 33 have the IARC sufficient evaluation, and 43 are mutagenic in *Salmonella* (Table 9.3).

DISCUSSION

The PERP is a rough measure that is useful for prioritizing potential carcinogenic hazards on an ordinal scale. It is not intended as a direct estimate of human carcinogenic hazard because rodent bioassays (for several reasons, including lack of data on cell division [Ames and Gold 1990; Gold et al. 1992]) do not provide enough information about mechanisms of carcinogenesis or shape of the dose response to assess the risks to humans. Our results indicate that it is reasonable to give special consideration to reduction of allowable worker exposures to those chemicals that rank highest in PERP, particularly since their PELs are so close to the tumorigenic dose rate in rodents. Thus, little quantitative extrapolation (across doses) is required. Further work on the top-ranked chemicals might include evaluation of mechanisms of carcinogenesis, particularly data on increased cell division at the high doses administered to rodents (Ames and Gold 1990), strength of evidence of carcinogenicity in rodents, further exposure assessment, and epidemiological studies.

Our ranking by PERP of 75 rodent carcinogens with PELs under the 1989 OSHA Air Contaminants Standard indicates that possible carcinogenic hazards vary widely, more than 100,000-fold across chemicals. We found a similar range

Table 9.3
Numbers of U.S. Workers Exposed to 120 Rodent Carcinogens with No OSHA PEL

CAS[a]	Chemical	TD50 in mg/kg/day[b]		Estimated no. workers(NOES)
		Rats	Mice	
7632-00-0	Nitrite, sodium	167	-	928,528
111-46-6	Diethylene glycol⁻	1,660	NT	890,123
90-43-7	*o*-Phenylphenol+	232	-	617,393
63449-39-8	Chlorinated paraffins	222	113	573,164
140-11-4	Benzyl acetate⁻	-	1,440	275,797
106-88-7	1,2-Epoxybutane+	220	-	261,646
828-00-2	Dimethoxane	716	NT	183,977
5989-27-5	*d*-Limonene⁻	204	-	138,293
5160-02-1	D & C Red No. 9+	146	-	122,320
25013-16-5	*Butylated hydroxyanisole⁻	719	-	89,675
149-30-4	2-Mercaptobenzothiazole⁻	344	-	86,505
548-62-9	Gentian Violet⁻	NT	90.5	75,635
128-44-9	*Saccharin, sodium⁻	2,140	-	68,407
100-52-7	Benzaldehyde⁻	-	1,690	67,717
103-90-2	Acetaminophen⁻	495	1,620	65,110
1897-45-6	Chlorothalonil⁻	2,270	-	62,724
132-27-4	**o*-Phenylphenate, sodium⁻	487	-	56,548
842-07-9	1-Phenylazo-2-naphthol+	29.4	-	44,359
2475-45-8	C.I. Disperse Blue 1+	156	-	43,520
108-78-1	Melamine⁻	735	-	43,104
62-56-6	*Thiourea⁻	98.5	-	37,577
137-30-4	Zinc dimethyldithiocarbamate+	40.7	-	34,595
1163-19-5	Decabromodiphenyl oxide⁻	3,341	-	32,656
50-18-0	*Cyclophosphamide+	2.21	5.96	30,028
5307-14-2	2-Nitro-*p*-phenylenediamine+	-	614	29,422
7758-01-2	*Bromate, potassium	9.81	-	26,562
139-13-9	Nitrilotriacetic acid⁻	1,770	2,660	25,216
517-28-2	Hematoxylin⁻	1,000	NT	24,190
50-06-6	*Phenobarbital+	-	5.52	22,928
6373-74-6	C.I. Acid Orange 3+	1,710	-	22,237
18662-53-8	Nitrilotriacetic acid, trisodium salt, monohydrate⁻	370	-	21,594
924-42-5	*N*-(Hydroxymethyl)acrylamide⁻	-	26.6	20,666
2832-40-8	C.I.Disperse Yellow 3+	380	1,020	20,479
99-57-0	2-Amino-4-nitrophenol+	839	-	20,255
62-44-2	*Phenacetin+	1,250	2,140	19,676
2465-27-2	Auramine-*0*⁻	11	62.7	19,093
4342-03-4	*Dacarbazine+	0.71	0.97	17,274
98-85-1	α-Methylbenzyl alcohol⁻	458	-	15,990
103-23-1	di(2-Ethylhexyl)adipate⁻	-	3,880	15,635
114-83-0	1-Acetyl-2-phenylhydrazine+	NT	51.2	15,429
121-88-0	2-Amino-5-nitrophenol+	111	-	14,512
54-31-9	Furosemide⁻	-	732	14,100
915-67-3	FD & C Red No. 2⁻	1,470	NT	13,794
99-55-8	5-Nitro-*o*-toluidine+	-	277	13,741
57-30-7	*Phenobarbital, sodium⁻	86.0	51.2	13,061
119-34-6	4-Amino-2-nitrophenol+	309	-	11,981
105-55-5	*N,N'*-Diethylthiourea⁻	24.0	-	11,481
96-45-7	*Ethylene thiourea+	16.5	16.9	10,749
51-79-6	*Urethane⁻	41.3	22.1	9,458

Table 9.3 (Continued)

140-67-0	Estragole⁻	NT	51.8	9,128
95-80-7	*2,4-Diaminotoluene+	2.47	26.7	8,513
59-87-0	5-Nitro-2-furaldehyde semicarbazone+	8.39	30.8	6,653
94-59-7	*Safrole⁻	441	56.2	6,475
389-08-2	Nalidixic acid⁻	201	-	6,187
615-28-1	*o*-Phenylenediamine[C]	177	526	6,083
4680-78-8	FD & C Green No. 1	6,060	-	5,997
50-55-5	Reserpine⁻	0.306	5.02	5,610
139-05-9	Cyclamate, soidum	-	667	5,267
443-48-1	*Metronidazole+	542	507	5,263
1694-09-3	*FD & C Violet No. 1⁻	612	-	4,330
94-52-0	Nitrobenzimidazole+	-	372	4,273
101-61-1	4,4'-Methylenebis (*N,N*-dimethyl)benzenamine⁻	16.4	207	4,140
67-20-9	Nitrofurantoin+	698	1,400	3,755
305-03-3	*Chlorambucil+	0.896	0.133	3,718
51-52-5	*Propylthiouracil	13.7	409	3,331
75-27-4	Bromodichloromethane+	72.5	47.7	3,266
54-85-3	Isoniazid+	150	27.1	2,924
88-73-3	1-Chloro-2-nitrobenzene+	-	157	2,897
563-41-7	Carbamyl hydrazine [C,-]	NT	169	2,814
593-70-4	Chlorofluoromethane	27.5	NT	2,705
136-40-3	*Phenazopyridine [C,-]	265	62.1	2,547
301-04-2	Lead acetate⁻	28.4	-	2,145
756-79-6	Dimethyl methylphosphonate⁻	700	-	2,135
60-35-5	*Acetamide⁻	180	3,010	2,073
90-94-8	Michler's Ketone+	5.64	84.1	2,025
101-90-6	*Diglycidyl resorcinol ether, technical grade+	3.78	24.3	1,857
868-85-9	Dimethyl hydrogen phospite+	139	-	1,821
105-11-3	*p*-Quinone dioxime+	106	-	1,810
141-90-2	Thiouracil	NT	55.0	1,776
135-23-9	Methapyrilene [C,-]	8.15	NT	1,698
2432-99-7	11-Aminoundecanoic acid⁻	1,100	-	1,534
2489-77-2	Trimethylthiourea⁻	25.8	-	1,522
80-08-0	Dapsone⁻	22.4	-	1,510
56-53-1	*Diethylstilbestrol⁻	0.114	0.0407	1,492
97-56-3	**o*-Aminoazotoluene+	4.04	-	1,449
23031-25-6	Terbutaline	410	NT	1,406
78-42-2	Tris(2-ethylhexyl)phosphate⁻	-	2,560	1,209
3761-53-3	*D & C Red No.5⁻	386	716	1,200
118-74-1	*Hexachlorobenzene⁻	8.03	65.1	1,038
11096-82-5	*Aroclor 1260	1.74	NT	991
122-66-7	Hydrazobenzene+	5.59	26	977
10034-93-2	Hydrazine sulfate+	40.8	7.59	946
13292-46-1	Rifampicin	-	33.6	927
624-84-0	Formylhydrazine	NT	36	919
569-61-9	*p*-Rosaniline[C,+]	35.5	46.4	908
88-06-2	*2,4,6-Trichlorophenol⁻	405	1,070	851
62-55-5	*Thioacetamide-	11.5	5.36	787
18559-94-9	Salbutamol	40.0	NT	744
60-56-0	Methimazole⁻	1.14	NT	708
3165-93-3	*4-Chloro-*o*-toluidine[C,-]	-	21.5	682
82-68-8	Pentachloronitrobenzene⁻	-	71.1	575

Table 9.3 (Continued)

70-25-7	*N-Methyl-N-Nitrosoguanidine+	0.817	NT	522
96-09-3	*Styrene oxide+	55.4	118	457
57-97-6	7,12-Dimethylbenz (a)anthracene+	NT	0.084	448
156-51-4	Phenylethylhydrazine sulfate+	NT	14.6	438
117-10-2	Chrysazin	245	201	357
637-07-0	Clofibrate	169	NT	323
536-33-4	Ethionamide-	-	69.3	307
76-01-7	Pentachloroethane-	-	57.3	231
91-93-0	3,3'-Dimethoxybenzidine-4,4'-diisocyanate+	1,630	-	227
590-21-6	1-Chloropropene	NT	5.05	145
135-20-6	Cupferron+	8.35	585	136
331-39-5	Caffeic acid-	284	4,970	80
86-74-8	Carbazole-	NT	164	78
115-28-6	Chlorendic acid-	40.8	141	55
3564-09-8	*FD & C Red No. 1-	521	NT	36
613-94-5	Benzoyl hydrazine	NT	9.59	28
2243-62-1	1,5-Naphthalenediamine+	69.6	162	28
72-54-8	*p,p'*-DDD-	-	30.7	14
1746-01-6	*2,3,7,8-Tetrachlorodibenzo-p-dioxin-	0.000023	0.000156	14

[a]CAS = Chemical Abstracts Service registry number.
[b]NT = No Test in the CPDB in this group. If no value is given the chemical was evaluated as a carcinogen in at least one test in the CPDB, but all tests in the specific group were negative.
[c]The TD_{50} is for the free-base, and the CAS is for the hydrochloride salt.
* = International Agency for Research on Cancer's evaluation of the chemical is "sufficient evidence" of carcinogenicity in animals.
\+ = Mutagen in *Salmonella*. - = Nonmutagen in *Salmonella*.

of PERP values in our 1987 paper based on the then-current OSHA PELs (Gold et al. 1987a). In general, we would expect a similar rank order of "cancer risk estimates" using current regulatory risk assessment methodology for the same permitted exposure values, since linear extrapolation from the TD_{50} generally leads to low-dose slope estimates similar to those based on the linearized multistage model (Krewski, Szyszkowicz, and Rosenkranz 1990).

The wide variation in PERP values reflects in part the fact that carcinogenic effects are rarely the basis for establishment of PEL values. OSHA reports that among the hundreds of chemicals with PELs, only 15 were set on the basis of cancer: 7 of these are among the 75 chemicals in our analysis (OSHA 1989b). In contrast, NIOSH has recommended that 53 of the 75 be treated as potential occupational carcinogens (NIOSH 1992). Additionally, NIOSH has recommended that exposures to 34 of the 75 be lower than the PEL (NIOSH 1992).

The wide range in PERP values based on rodent carcinogenicity data is consistent with an analysis by Roach and Rappaport of the ACGIH TLVs (which OSHA used to set most of its PEL values) (Roach and Rappaport 1990). Those authors examined the epidemiological data referenced in the documentation for the TLVs and suggested that TLVs were generally set at levels that were prevalent in industry rather than at levels that were below those reported to have adverse health effects in the workplace.

We have examined actual exposure estimates in the workplace for a few of the chemicals that rank highest in PERP. The conclusion of Roach and Rappaport is consistent with our finding that for the chemicals we examined (ethylene dibromide, methylene chloride, styrene, tetrachloroethylene, and 1,3-butadiene), estimates of actual average exposures for high exposure occupations were within an order of magnitude of the PEL (data to appear in a future paper). For some of the chemicals with highest PERP values, OSHA has performed a substance-specific rulemaking, using carcinogenicity data. The newly recommended PEL values would result in much lower PERP values for 1,3-butadiene, methylene chloride, and ethylene dibromide (nearly all uses of ethylene dibromide have now been discontinued in the United States).

ADDENDUM AT TIME OF PUBLICATION

The federal courts have overturned OSHA's Air Contaminants Standard that we have used in our analyses because the chemicals did not go through a chemical-by-chemical (6b) rulemaking process. The generic approach used by OSHA to base PELs on TLVs could still be authorized by future legislation.

NOTE

Supported by Department of Energy contract DE-AC-03-76SF00098 and National Institute of Environmental Health Sciences Center grant ESO1896. We thank Bonnie Stern and Bruce Ames for suggestions on the manuscript, and David S. Sundin, David H. Pedersen, and the late Joseph A. Seta for assistance with the NOES. Parisa Farvid, Lars Rohrbach, and Ken Chow provided much valued technical assistance.

References

ACGIH (American Conference of Governmental Industrial Hygienists). 1990–91. *Threshold limit values for chemical substances and physical agents and biologic exposure indices.* Cincinnati, Ohio: ACGIH.

Ad Hoc Working Group on Risk Assessment. Federal Coordinating Council for Science, Engineering and Technology (FCCSET). 1992. Draft report: A cross-species scaling factor for carcinogen risk assessment based on equivalence of mg/kg$^{3/4}$/day. *Federal Register* 57 (June 5):24152–73.

Alavanja, M. C. R., A. Blair, and M. N. Masters. 1990. Cancer mortality in the U.S. flour industry. *J. & Natl. Cancer Inst.* 82:840–48.

Allen, B. C., A. M. Shipp, K. S. Crump, B. Kilian, M. L. Hogg, J. Tudor, and B. Keller. 1987. *Investigations of cancer risk assessment methods.* Report no. PB88-1271113. 3 vols. Washington, D.C.: National Technical Information Service.

Altham, P. 1978. Two generalizations of the binomial distribution. *Appl. Stat.* 27:162–67.

American Federation of Labor-Congress of Industrial Organisation v. OSHA, 965 F.2d. 962 (1991).

American Petroleum Institute v. OSHA, 581 F. 2d 493 (5th Cir., 1978).

American Smelting and Refining Co. v. OSHA, 746 F. 2nd 483 (9th Cir. 1984).

American Textile Manufacturers Institute v. Donovan, 452 U.S. 490, 495 (1981).

Ames, B. 1971. The detection of chemical mutagens with enteric bacteria. In *Chemical mutagens,* ed. A. Hollaender. New York: Plenum Press.

Ames, B. N., and L. S. Gold. 1990. Chemical carcinogenesis: Too many rodent carcinogens. *Proc. Natl. Acad. Sci. U.S.A.* 87:7772–76.

Ames, B. N., and L. S. Gold. 1990. Too many rodent carcinogens: Mitogenesis increases mutagenesis [published erratum]. *Science* 249:1487.

Ames, B. N., R. Magaw, and L. S. Gold. 1987. Ranking possible carcinogenic hazards. *Science* 236:271–80.

Ames, B. N., M. K. Shigenaga, and L. S. Gold. 1993. DNA lesions, inducible DNA repair, and cell division: Three key factors in mutagenesis and carcinogenesis. *Environ. Health Perspect.* 101 Suppl 5:35–44.

Anderson, M. E., H. J. Clewell III, M. L. Gargas, F. A. Smith, and R. H. Reitz. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol. Appl. Pharmacol.* 87:185–205.

Anderson, M. E., J. J. Mills, M. L. Gargas, L. Kedderis, L. S. Birnbaum, D. Neubert, and W. F. Greelee. 1993. Modeling receptor-mediated processes with dioxin: Implications for pharmacokinetics and risk assessment. *Risk Anal.* 12(1):25–36.

Andjelkovich, A., M. Mathew, B. Richardson, and J. Levine. 1990. Mortality of Oron Foundry workers: I. Overall findings. *J. Occup. Med.* 32:529–40.

Apostolou, A. 1990. Relevance of maximum tolerated dose to human carcinogenic risk. *Regul. Toxicol. Pharmacol.* 11:68–80.

Armitage, P. and R. Doll. 1954. The age distribution of cancer and a multistage theory of carcinogenesis. *Brit. J. Cancer* 18:1–12.

Ashby, J., N. G. Doerrer, G. Flamm, J. E. Harris, D. H. Hughes, F. R. Johannsen, S. C. Lewis, N. D. Krivanek, J. F. McCarthy, R. J. Moolenaar, G. K. Raabe, R. C. Reynolds, J. M. Smith, J. T. Stevens, M. J. Teta, and J. D. Wilson. 1990. A scheme for classifying carcinogens. *Regul. Toxicol. Pharmacol.* 12(3):270–95.

Ashford, N. A. 1988. Science and values in the regulatory process. *Statistical Science* 3: 377–83.

Ashford, N. A., and C. C. Caldart. eds. 1991. *Technology, law and the working environment.* New York: Van Nostrand Reinhold.

Ashford, N. A., W. C. Ryan, and C. C. Caldart. 1983. Law and science policy in federal regulation of formaldehyde. *Science* 222:94–900.

Automobile Workers v. Johnson Controls, 111 S. Ct. 1196 (1991).

Bailar III, J. C., E. A. C. Crouch, R. Shaikh, and D. Spiegelman. 1988. One-hit models of carcinogenesis: Conservative or not? *Risk Anal.* 8:485–97.

Bailar III, J. C., E. A. C. Crouch, D. Spiegelman, and R. Shaikh. 1990. Response to Park. *Risk Anal.* 10:211–12.

Baker, E. L. 1988. Neurologic and behavioral disorders. In *Occupational health: Recognizing and preventing work-related disease,* ed. B. S. Levy and D. H. Wegman. Boston: Little, Brown.

Baker, R. J., and J. A. Nelder. 1978. *Generalized linear interactive modeling* (GLIM). Release 3. Oxford, England: Numerical Algorithms Group.

Ballew, M., and D. Hattis. 1989. *Reproductive effects of glycol ethers in females—a quantitative analysis.* CTPID 89–7. Cambridge, Mass.: MIT Center for Technology, Policy, and Industrial Development.

Beir, V. 1990. *Health effects of exposure to low levels of ionizing radiation.* Washington, D.C.: National Academy Press.

Beirne, G. J., and J. T. Brennan. 1972. Glomerulonephritis associated with hydrocarbon solvents. *Arch. Environ. Health* 25:365–69.

Berkson, J. 1950. Are there two regressions? *J Am. Stat. Assoc.* 45:164–80.

Blair, A., P. Decoufle, and D. Grawman. 1979. Causes of death among laundry and dry cleaning workers. *Am. J. Public Health* 69:508–11.

Bloomfield, C. D., D. C. Arthur, G. Frizzera, and E. G. Levine. 1983. Nonrandom chromosome abnormalities in lymphoma. *Cancer Res.* 43:2975–84.

Board, P., M. Coggan, P. Johnston, V. Ross, T. Suzuki, and G. Webb. 1990. Genetic heterogeneity of the human glutathione transferases: A complex of gene families. *Pharmac. Ther.* 48:357–69.

Bohning, D. E., H. L. Atkins, and S. H. Cohn. 1982. Long-term particle clearance in man: Normal and impaired. *Ann. Occup. Hyg.* 26:259–71.

Brain, J. D., B. Beck, A. J. Warren, and R. A. Shaikh, eds. 1988. *Variations in susceptibility to inhaled pollutants: Identification, mechanisms and policy implications.* Baltimore: Johns Hopkins University Press.

Brandt, E. N., Jr., Assistant Secretary for Health, Department of Health and Human Services. 1983a. Personal communication based on notes recorded at the meeting. Washington, D.C., February 11.

Brandt, E. N., Jr., Assistant Secretary for Health, Department of Health and Human Services. 1983b. *Testimony before the Subcommittee on Department Operations, Research, and Foreign Agriculture.* Committee on Agriculture, House of Representatives. Washington, D.C.: GPO, February 22.

Brandt-Rauf, P. W. 1987. Preface. In *Occupational cancer and carcinogenesis: Occupational medicine, state of the art review,* ed. P. W. Brandt-Rauf. Philadelphia: Hanley and Belfus.

Brent, R. L., and R. P. Jensh. 1967. Intra-uterine growth retardation. *Adv. Teratol.* 2: 139–227.

Breslin, J. A., J. Strazisar, and R. L. Stein. 1976. *Size distribution and mass output of particulates from diesel engine exhausts.* Report of Investigation 8141r. Washington, D.C.: U.S. Bureau of Mines.

Breslow, N. E., and N. E. Day. 1987. *Statistical methods in cancer research. Volume II-The design and analysis of cohort studies.* United Kingdom: Oxford University Press.

Bressac, B., M. Kew, J. Wands, and M. Ozturk. 1991. Selective G to T mutations of p53 gene in hepatocellular carcinoma in southern Africa. *Nature* 350:429–31.

Brown, C. C., and K. C. Chu. 1983. Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. *J. Natl. Cancer Inst.* 70:455–63.

Brown, D. P., and S. D. Kaplan. 1987. Retrospective cohort mortality study of dry cleaner workers using perchloroethylen. *J. Occup. Med.* 29:535–41.

Busch, K. A., T. J. Meinhardt, and M. A. Ballew. 1986. Statistical approach to quantitative risk assessment: Discussion of the underlying assumptions in quantitative risk assessment. In *Quantitative Risk Assessment: Biomedical Ethics Reviews,* ed. James M. Humber and Robert F. Almeder, 9–55. Clifton, N.J.: Humana Press.

Butterworth, B. E., T. J. Slaga, W. Farland, and M. McClain. 1989. *Chemically induced cell proliferation. Implications for risk assessment.* Proceedings of the Chemically Induced Cell Proliferation Conference, Austin, Texas, November 29–December 2. New York: Wiley-Liss.

Carr, G. J., and C. J. Portier. 1991. An evaluation of the Rai and Van Ryzin dose-response model in teratology. *Risk Anal.* 11:111–20.

Casanova, M., K. T. Morgan, W. H. Steinhagen, J. I. Everitt, J. A. Popp, and H. d/A. Heck. 1991. Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of rhesus monkeys: Pharmacokinetics, rat-to-monkey interspecies scaling and extrapolation to man. *Fundam. Appl. Toxicol.* 17:409–28.

Catalano, P. J., and L. M. Ryan. 1992. Bivariate latent variable models for clustered discrete and continuous outcomes. *J. Am. Stat. Assoc.* 87: 651–658.

Catalano, P. J., D. O. Scharfstein, L. M. Ryan, C. A. Kimmel, and G. L. Kimmel. 1992. *A statistical model for fetal death, fetal weight, and malformation in developmental toxicity studies.* Harvard School of Public Health Technical Report. Harvard University.

Catalano, P. J., D. O. Scharfstein, L. M. Ryan, C. A. Kimmel, and G. L. Kimmel. 1993. Statistical model for fetal death, fetal weight, and malformation in development toxicity studies. *Teratology* 47:281–90.

Chappel, C. I. 1992. A review and biological risk assessment of sodium saccharin. *Regul. Toxicol. Pharmacol.* 15(3):352–70.

Checkoway, H., Pearce, J. L. S. Hickey, and J. M. Dement. 1990. Latency analysis in occupational epidemiology. *Arch. of Environ. Health* 45:95–100.

Chemical Substances TLV Committee. 1992. *Notice of intended changes for 1992–1993.* Annual reports of the Committee on Threshold Limit Values and Biological Exposure Indices. Boston: Chemical Substances TLV Committee, June 2.

Chen, J. J., and R. J. Kodell. 1989. Quantitative risk assessment for teratologic effects. *J. Am. Stat. Assoc.* 84:966–71.

Chen J. J., R. L. Kodell, R. B. Howe, and D. W. Gaulor. 1991. Analysis of trinomial responses from reproductive and developmental toxicity experiments. *Biometrics* 47:1049–58.

Chesson, J. 1986. *Battelle Columbus Laboratories—Washington Operations. Developmental and reproductive toxicity data analysis. Draft final report Task 2–6.* Washington, D.C.: Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency Contract 68–02–4246.

Chester, E. H., D. G. Gillespe, and F. D. Kranse. 1969. The prevalence of chronic obstruction pulmonary disease in chlorine gas workers. *Am. Rev. Respir. Dis.* 99: 365–73.

CIMARPH (Committee on the Institutional Means for Assessment of Risks to Public Health). 1983. *Risk assessment in the federal government: Managing the process.* Washington, D.C.: National Academy Press.

Clayson, D. B. 1981. Specific aromatic amines as occupational bladder carcinogens. *Natl. Cancer Inst. Monogr.* 58:15–19.

Clayson, D. B. 1983. Trans-species and trans-tissue extrapolation of carcinogenicity assays. *Basic Life Sci.* 24:637–51.

CMA (Chemical Manufacturers Association). Epidemiology Task Group. 1991. Guidelines for good epidemiology practices. *J. Occup. Med.* 33:1221–29.

Cochran W. G. 1968. Errors of measurement in statistics. *Technometrics* 10:637–66.

Cohen, S. M., and L. B. Ellwein. 1991. Genetic errors, cell proliferation and carcinogenesis. *Cancer Res.* 15(24):6493–6505.

Cole, P. 1977. Cancer and occupation: Status and needs of epidemiologic research. *Cancer* 39:1788–91.

Committee on the Biological Effects of Ionizing Radiations. 1990. *Health effects of exposure to low levels of ionizing radiation, BEIRV.* Washington, D.C.: National Academy Press.

Comstock, K. E., B. J. Sanderson, G. Claflin, and W. D. Henner. 1990. GST1 Gene deletion determined by polymerase chain reaction. *Nucleic Acids Res.* 18:3670.

Costello, J., and W. Graham. 1988. Vermont granite workers' mortality study. *Am. J. Ind. Med.* 13:26–31.

Cox, D. R. 1972. Regression models and life tables. *J. of Royal Statis. Soc.* B34:187–202.

Cox, D. R., and D. V. Hinkley. 1974. *Theoretical statistics.* London: Chapman and Hall.

Crane, M. M., M. J. Keating, and J. M. Trujillo, 1989. Environmental exposures in cytogenetically defined subsets of acute nonlymphocytic leukemia. *J.A.M.A.* 262: 634–39.

Crane, M. M., M. J. Keating, J. M. Trujillo, D. R. Labarthe, and R. F. Frankowski. 1989. Environmental exposures in cytogenetically defined subsets of acute nonlymphocytic leukemia. *J. Am. Med. Assc.* 262:634–39.

Crane, M. M., M. J. Keating, J. M. Trujillo, D. R. Labarthe, and R. F. Frankowski. 1989. Environmental exposures in cytogenetically defined subsets of acute nonlymphocytic leukemia [published erratum]. *J. Am. Med. Assc.* 263:662.

Crouch, E. A. C., and R. Wilson. 1979. Interspecies comparison of carcinogenic potency. *J. Toxicol. Environ. Health* 5:1095–1118.

Crump, K. S. 1984. An improved procedure for low-dose carcinogenic risk assessment from animal data. *J. Environ. Pathol. Toxicol.* 5:339–46.

Crump, K. S. 1984. A new method for determining allowable daily intakes. *Fundam. Appl. Toxicol.* 4:854–71.

Crump, K. S., and B. C. Allen. 1985. Methods for quantitative risk assessment using occupational studies. *The Am. Statis.* 39:442–50.

Crump, K. S., D. G. Hoel, C. H. Langley, and R. Peto. 1976. Fundamental carcinogenic processes and their implications for low dose risk assessment. *Cancer Res.* 36: 2973–979.

Crump, K. S., H. A. Guess, and K. L. Deal. 1977. Confidence intervals and test of hypothesis concerning dose response relations inferred from animal carcinogenicity data. *Biometrics* 33:437–51.

Crump, K. S., and R. B. Howe. 1985. Review of methods for calculating confidence limits in low dose extrapolation. In *Toxicological risk assessment,* ed. D. B. Clayson, D. R. Krewski, and I. C. Munroe. Boca Raton, Fla: CRC Press.

Cumming, R. G., J. L. Kelsey, and M. S. Nevitt. 1990. Methodological issues in the study of frequent and recurrent health problems: Falls in the elderly. *Ann. Epidemiol.* 1:49–56.

Curran, W. J. 1985. Dangers for pregnant women in the workplace. *N. Engl. J. Med.* 312:164–65.

Daly, A. K., M. Armstrong, S. G. Monkman, M. E. Idle, and J. R. Idle. 1991. Genetic and metabolic criteria for the assignment of debrisoquine 4-hydroxylation cytochrome P-4502D6 phenotypes. *Pharmacogenetics* 1:133–41.

Dankovic, D. A., R. J. Smith, J. Seltzer, A. J. Bailer, and L. T. Stayner. 1991. *A quantitative assessment of the risk of cancer associated with exposure to 1,3-butadiene, based on a low dose inhalation study in B6C3F1 mice.* U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, September 27.

Davidson, I. W. F., J. C. Parker, and R. P. Beliles. 1986. *Biological basis for extrapolation across mammalian species.* 6:211–37. Regul: Toxicol. Pharmacol.

de Fromentel, C. C. and T. Soussi. 1992. TP53 Tumor suppressor gene: A model for investigating human mutagenesis. *Genes Chromosom. Cancer* 4:1–15.

Dedrick, R. L., and P. F. Morrison. 1992. Carcinogenic potency for alkylating agents in rodents and humans. *Cancer Res.* 52:2464–67.

Deguchi, T., M. Mashimo, and T. Suzuki. 1990. Correlation between acetylator phenotypes and genotypes of polymorphic arylamine *N*-acetyltransferase in human liver. *J. Biol. Chem.* 265:12757–60.

Department of Labor, Occupational Safety and Health Administration. 1989. Occupational exposure to 4.4-methylenedianilline (MDA): Proposed rule. *Federal Register* 29 CFR Parts 1910, 1926, 54:20672–744.

Department of Labor, Occupational Safety and Health Administration. 1990. Occupational exposure to 1.3 butudrene: Proposed rule and notice of hearing. *Federal Register* 29 CFR Part 1910, 55:32736–2826.

Devereux T. R., J. F. Foley, R. R. Maronpot, F. Kari, and M. W. Anderson. 1993. Ras proto-oncogene activation in liver and lung tumors from B6C3F1 mice exposed chronically to methylene chloride. *Carcinogenesis.* May; 14(5):795–801.

Dietrich, D. R., and J. A. Swenberg. 1991. The presence of alpha 2u-globulin is necessary for d-limonene promotion of male rat kidney tumors. *Cancer Res.* 51:3512–521.

Dlouhy, S. R., P. Wheeler, J. A. Trofatter, P. J. Stambrook, and J. A. Tischfield. 1991. Detection of point mutations by denaturing-gradient gel electrophoresis. In *Methods in molecular biology.* Vol. 9, *Protocols in human molecular genetics,* ed. C. G. Mathew, 95–110. Clifton, N.J.: Humana Press.

Doll, R., and R. Peto. 1982. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst.* 66:1191–1308.

Dominick, D. D. 1975. HCB tolerances: An example of risk-benefit decision making. In *Decision making for regulating chemicals in the environment.* Washington, D.C.: U.S. National Academy of Sciences.

Dosemeci, M., S. Wacholder, and J. Lubin. 1990. Does nondifferential misclassification of exposure always bias a true effect toward the null value? *Am. J. Epidemiol.* 132:746–48.

Doull, J., and M. C. Bruce. 1986. Origin and scope of toxicology. In *Toxicology: The basic science of poisons,* ed. C. D. Klaassen, M. O. Amdur, and J. Doull. New York: Macmillan.

Dourson, M. L., and J. F. Stara. 1983. Regulatory history and experimental support of uncertainty safety factors. *Regul. Toxicol. Pharmacol.* 3:224–38.

Drake, K., and A. Wildavsky. 1990. Theories of risk perception: Who fears what and why. *Daedalus* 119:41–60.

Duh, R. W., and N. R. Asal. 1984. Mortality among laundry and dry cleaning workers in Oklahoma. *Am. J. Public Health* 74:1278–80.

EC (European Community). 1983. Commission Directive. *Off. J. Eur. Community* 26 N. L. 257/22.

Eisen, E. A., D. H. Wegman, D. Kriebel, S. R. Woskie, and X. Hu. 1991. Epidemiologic approach to the study of acute reversible health effects in the workplace. *Epidemiology* 2:263–70.

EPA (Environmental Protection Agency), Office of Health and Environmental Assessment. 1984. *Updated assessment of mutagenicity and carcinogenicity assessment of cadmium.* EPA 600/8-83-025B.

EPA (Environmental Protection Agency). 1986. Guidelines for carcinogenic risk assessment. *Federal Register* 51: (September 24):33992–34003.

EPA (Environmental Protection Agency). 1991. Guidelines for developmental toxicity and risk assessment. *Federal Register* 56:63798–63826.

Evans, J. S., J. D. Graham, G. M. Gray, A. Hollis, B. Ryan, A. Smith, M. Smith, and A. Taylor. 1992. Summary of workshop to review an OMB report on regulatory risk assessment and management. *Risk Issues Health Safety* 3:77–83.

Fabro, S., G. Shull, and N. A. Brown. 1982. The relative teratogenic potency: Proposed components of developmental toxicity rish assessment. *Teratogenesis Carcinog. Mutagen.* 2:61–76.

FCCSET (Federal Coordinating Council on Scientific Engineering and Technology) Ad Hoc Working Group on Risk Assessment. 1992. Draft Report: A cross-species scaling factor for carcinogen risk assessment based on equivalence of mg/kg$^{3/4}$/day. *Federal Register* 57:24152–4173.

Fingerhut, M. A., W. E. Halpern, D. A. Marlow, L. A. Piacitelli, P. A. Honchar, M. H. Sweeney, A. L. Greife, P. A. Dill, K. Steenland, and A. J. Suruda. 1991. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *N. Engl. J. Med.* 324:212–18.

Finkel, A. M. 1987. Uncertainty, variability and the value of information in cancer risk assessment. Ph.D. diss., Harvard University.

Finkel, A. M. 1989. Is risk assessment really too conservative?: Revising the revisionists. *Columbia J. Environ. Law* 14:427–67.

Finkel, A. M. 1990. *Confronting uncertainty in risk management: A guide for decision makers.* Washington, D.C.: Center for Risk Management, Resources for the Future.

FIWCLL (Fifth International Workshop on Chromosomes in Leukemia-Lymphoma). 1987. Correlation of chromosome abnormalities with histologic and immunologic characteristics in non-Hodgkin's lymphoma and adult T-cell leukemia-lymphoma. *Blood* 70:1554.

Flamm, W. G., and L. D. Lehman-McKeeman. 1991. The human relevance of the renal tumor-inducing potential of d-limonene in male rats: Implications for risk assessment. *Regul. Toxicol. Pharmacol.* 13:70–86.

Fox, A. J., and P. F. Collier. 1976. Low mortality rates industrial cohort studies due to selection for work and survival in the industry. *Brit. J. of Prev. Soc. Med.* 30:25.

Franchini, I., A. Cavatorta, M. Falzoi, S. Lucertini, and A. Mutti. 1984. Early indicators of renal damage in workers exposed to organic solvents. *Int. Arch. Occup. Environ. Health* 52:1–9.

Frome, E. L., and H. Checkoway. 1985. Use of poisson regression models in estimating incidence rates and ratios. *Am. J. of Epidemio.* 121:309–22.

Gail, M. 1975. Measuring the benefits of reduced exposure to environmental carcinogens. *J. Chron. Dis.* 28:135–147.

Gail, M. 1986. Adjusting for covariates that have the same distribution in exposed and unexposed cohorts. In *Modern statistical methods in chronic disease epidemiology,* ed. S. H. Moolgavkar and R. L. Prentice, 3–18. New York: John Wiley & Sons.

Garabrant, D. H., L. Bernstein, J. M. Peters, T. J. Smith, and W. E. Wright. 1985. Respiratory effects of borax dust. *Br. J. Ind. Med.* 42:831–37.

Gardner, M. J., D. Coggon, B. Pannett, and E. C. Harris. 1989. Workers exposed to ethylene oxide: A follow-up study. *Br. J. Ind. Med.* 46:860–65.

Garry, V. F., T. J. Danzl, R. Tarone, J. Griffith, J. Cervenka, L. Krueger, E. B. Whorton, and R. L. Nelson. 1992. Chromosome rearrangements in fumigant appliers: Possible relationship to non-Hodgkin's lymphoma risk. *Cancer Epidemiol. Biomark. Prevent.* 1:287–91.

Garshick, E., M. B. Schenken, A. Munoz, M. Segal, T. J. Smith, S. R. Woskie, S. K. Hammond, and F. E. Speizer. 1988a. A case control study of lung cancer and diesel exhaust exposure in railroad workers. *Am. Rev. Respir. Dis.* 135:1242–48.

Garshick, E., M. B. Schenker, A. Munoz, M. Segal, T. J. Smith, S. R. Woskie, S. K. Hammond, and F. E. Speizer. 1988b. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. *Am. Rev. Resp. Dis.* 137:820–25.

Gart, J. J., D. Krewski, P. N. Lee, R. E. Tarone, and J. Wahrendorf. 1986. *Statistical methods in cancer research.* Vol. 3, *The design and analysis of long-term animal experiments.* Oxford: Oxford University Press.

Gaylor, D. W. 1983. The use of safety factors in controlling risk. *J. Toxicol. Environ. Health* 11:329–36.

Gaylor, D. W. 1989. Quantitative risk analysis for quantal reproductive and developmental effects. *Environ. Health Perspect.* 79:243–46.

Gaylor, D., and W. Slikker. 1992. Risk assessment for neurotoxicants. In *Neurotoxicology,* ed. Hugh Tilson and Clifford Mitchell, 331–43. New York: Raven Press.

Geddes, A. A., D. T. Bowen, and A. Jacobs. 1990. Clonal karyotype abnormalities and clinical progress in the myelodysplastic syndrome. *Br. J. Haematol.* 76:194–202.

George, J. D., C. J. Price, C. A. Kimmel, and M. C. Marr. 1987. The developmental toxicity of triethylene glycol dimethyl ether in mice. *Fundam. Appl. Toxicol.* 9: 173–181.

Gibson M. 1986. Quantified risk assessment: Values in, values out? In *Quantitative Risk Assessment, Biomedical Ethics Reviews,* ed. J. M. Humber, and R. F. Almeder 171–204. Clifton, N.J.: Humana Press.

Gilbert, E. 1991. Does nondifferential misclassification of exposure always bias true effect toward the null value? *Am. J. Epidemiol.* 134(4)440–441.

Gold, L. S., N. B. Manley, T. H. Slone, G. B. Garfinkel, L. Rohrbach, and B. N. Ames. 1993. The fifth plot of the carcinogenic potency database: Results of animal bioassays published in the general literature through 1988 and by the National Toxicology Program through 1989. *Environ. Health Persp.* 100:65–169.

Gold, L. S., G. M. Backman, N. K. Hooper, and R. Peto. 1987. Ranking the potential carcinogenic hazards to workers from exposures to chemicals that are tumorigenic in rodents. *Environ. Health Perspect.* 76:211–19.

Gold, L. S., M. de Veciana, G. M. Backman, R. Magaw, P. Lopipero, M. Smith, M. Blumenthal, R. Levinson, L. Bernstein, and B. N. Ames. 1986. Chronological supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1982. *Environ. Health Perspect.* 74:237–329.

Gold, L. S., N. B. Manley, and B. N. Ames. 1992. Extrapolation of carcinogenesis between species: Qualitative and quantitative factors. *Risk Anal.* 12:579–88.

Gold, L. S., C. B. Sawyer, R. Magaw, G. M. Backman, M. de Veciana, R. Levinson, N. K. Hooper, W. R. Havender, L. Bernstein, R. Peto, M. C. Pike, and B. N. Ames. 1984. A carcinogenic potency database of the standardized results of animal bioassays. *Environ. Health Perspect.* 58:9–319.

Gold, L. S., T. H. Slone, G. M. Backman, S. Eisenberg, M. Da Costa, M. Wong, N. B. Manley, L. Rohrbach, and B. N. Ames. 1990. Third chronological supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1986 and by the National Toxicology Program through June 1987. *Environ. Health Perspect.* 84:215–86.

Gold, L. S., T. H. Slone, G. M. Backman, R. Magaw, M. Da Costa, P. Lopipero, M. Blumenthal, and B. N. Ames. 1987b. Second chronological supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1984 and by the National Toxicology Program through May 1986. *Environ. Health Perspect.* 74:237–329.

Gold, L. S., T. H. Slone, and L. Bernstein. 1989. Summary of carcinogenic potency TD_{50} and positivity for 492 rodent carcinogens in the Carcinogenic Potency Database. *Environ. Health Perspect.* 79:259–72.

Gold, L. S., T. H. Slone, B. R. Stern, N. B. Manley, and B. N. Ames. 1992. Rodent carcinogens: Setting priorities. *Science* 258:261–65.

Goldman, L. R., D. Hayward, D. M. Siegel, and R. A. Stephens. 1991. Letter to the editor. *N. Engl. J. Med.* 324(25):1811.

Golomb, H. M., G. Alimena, J. D. Rowley, J. W. Vardman, J. R. Testa, and C. Sovik. 1982. Correlation of occupation and karyotype in adults with acute nonlymphocytic leukemia. *Blood* 60:404–11.

Goodman, G., and R. Wilson. 1991. Quantitative prediction of human cancer risk from rodent carcinogenic potencies: A closer look at the epidemiological evidence for some chemicals not definitively carcinogenic in humans. *Regul. Toxicol. Pharmacol.* 142:118–46.

Greenberg, H. L., M. G. Ott, and R. E. Shore. 1990. Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: A mortality study. *Br. J. Ind. Med.* 47:221–30.

Greene, M. 1982. Non-Hodgkin's lymphoma and mycosis fungoides. In *Cancer epidemiology and prevention,* ed. D. Schottenfeld and J. F. Fraumeni, 754–78. Philadelphia: W. B. Saunders.

Greife, A. L., R. W. Hornung, L. G. Stayner, and K. N. Steenland. 1988. Development of a model for use in estimating exposure to ethylene oxide in a retrospective cohort mortality study. *J. Work Environ. Health* 12:1, 29–30.

Hagmar, H., H. Welinder, K. Linden, R. Attewell, S. Osterman-Golkar, and M. Tornquist. 1991. An epidemiologic study of cancer risk among workers exposed to ethylene oxide using hemoglobin adducts to validate environmental exposure assessments. *Int. Arch. Occup. Environ. Health* 63:271–77.

Haluska, F. G., L. R. Finger, J. Kagan, and C. M. Croce. 1990. Molecular genetics of chromosomal translocations in B- and T-lymphoid malignancies. In *Molecular genetics in cancer diagnosis,* ed. J. Crossman, 143–62. New York: Elsevier.

Hammer, W., and F. Sjoquist. 1976. Plasma levels of tricyclic antidepressants. *Life Sci.* 6:1895–1903.

Harris, C. C. 1991. Molecular epidemiology and the genetics of environmental cancer. *J.A.M.A.* 266:681–87.

Haseman, J. K., 1985. Issues in carcinogenicity testing: Dose selection. *Fundam. Appl. Toxicol.* 5:66–78.

Haseman, J. K., and L. L. Kupper. 1979. Analysis of dichotomous response data from certain toxicological experiments. *Biometrics* 35:281–93.

Haseman, J. K., and S. K. Seilkop. 1992. An examination of the association between maximum-tolerated dose and carcinogenicity in 326 long-term studies in rats and mice. *Fundam. Appl. Toxicol.* 19:207–13.

Hashimoto, D. H., T. Brennan, and D. C. Christiani. 1991. Should exposure to asbestos in buildings be regulated on an occupational or environmental basis 643:609–14. *Ann. N. Y. Acad. Sci.*

Hass, J. F., and R. Schottenfeld. 1979. Risks to the offspring from parental occupational exposures. *J. Occup. Med.* 21:607–15.

Hatch, M. C., and Z. A. Stein. 1988. Reproductive disorders. In *Occupational health: Recognizing and preventing work-related disease,* ed. B. S. Levy and D. H. Wegman. Boston: Little, Brown.

Hattis, D. 1987. *A pharmacokinetic/mechanism-based analysis of the carcinogenic risk of ethylene oxide.* CTPID 87–1. Washington, D.C.: National Technical Information Service No. NTIS/PB88–188784, MIT Center for Technology, Policy and Industrial Development.

Hattis, D., S. Abdollahzadeh, and C. A. Franklin. 1990. Strategies for testing the 'irritation-signaling' model for chronic lung effects of fine acid particles. *J. Air. Poll. Cont. Assoc.* 40:322–30.

Hattis, D., L. Erdreich and M. Ballew. 1987. Human variability in susceptibility to toxic chemicals—a preliminary analysis of pharmacokinetic data from normal volunteers. *Risk Anal.* 7:415–426.

Hattis, D., and K. Shapiro. 1990. Analysis of dose/time/response relationships for chronic tc :ic effects—the case of acrylamide. *Neurotoxicology* 11:219–36.

Hattis, D., and K. Silver. 1991. Projection of human lung cancer risks for diesel particulates from animal data—effects of using measures of internal *vs.* external dose and possible interactions with smoking. Cambridge, Mass.: Report to the United Mine Workers by Ashford Associates, July.

Hattis, D., and J. A. Smith, Jr. 1986. What's wrong with quantitative risk assessment? In *Quantitative risk assessment, Biomedial ethics reviews, 1986,* ed. J. M. Humber and R. F. Almeder. Clifton, N.J.: Humana Press.

Hattis, D., S. Tuler, L. Finkelstein, and Z. Luo. 1986. *A pharmacokinetic/mechanism-based analysis of the carcinogenic risk of perchloroethylene.* CTPID 86–7. Washington, D.C.: National Technical Information Service, No. NTIS/PB88–163209, Report to the National Institute for Occupational Safety and Health and the National Institute for Environmental Health Sciences; MIT Center for Technology, Policy and Industrial Development.

Hattis, D., and J. Wasson. 1987. *A pharmacokinetic/mechanism-based analysis of the carcinogenic risk of butadiene.* CTPID 87–3. Washington, D.C.: National Technical Information Service No. NTIS/PB88-202817, MIT Center for Technology, Policy and Industrial Development.

Hattis, D., L. S. Welch, and S. M. Schrader. 1988. *Male fertility effects of glycol ethers—a quantitative analysis.* CTPID 88–3. Cambridge, Mass.: MIT Center for Technology, Policy and Industrial Development.

Hearne, F. T. 1991. Response to Tollefson, et al. *Risk Anal.* 11:569–71.

Hoel, D. G., J. K. Haseman, M. D. Hogan, J. Huff, and E. E. McConnell. 1988. The impact of toxicity on carcinogenicity studies: Implications for risk assessment. *Carcinogenesis* 9:2045–52.

Hoel, D. G., N. C. Kaplan, and M. W. Andersen. 1983. Implications of non-linear kinetics on risk estimation in carcinogenesis. *Science* 219:1032–37.

Hogstedt, C., L. Avinger, and A. Gustavsson. 1984. Ethylene oxide and cancer—a review and follow-up of two epidemiological studies. *Work and Health* 49:1–37.

Hogstedt, C., L. Aringer, and A. Gustavsson. 1986. An epidemiologic support for ethylene oxide as a cancer-causing agent. *J.A.M.A.* 255:1575–78.

Hogstedt, C., N. Malmqvist, and B. Wadman. 1979. Leukemia in workers exposed to ethylene oxide. *J.A.M.A.* 241:1132–33.

Hogstedt, C., O. Rohlen, B. D. Berndtsson, O. Axelson, and L. Ehrenbert. 1979. A cohort study of mortality and cancer incidence in ethylene oxide production workers. *Br. J. Ind. Med.* 36:766–80.

Hogstedt, C. S. 1988. Epidemiologic studies of ethylene oxide. *IARC Sci. Publ.* 89:265–70.

Hollstein, D. Sidransky, and B. Vogelstein. 1991. p53 Mutations in human cancers. *Science* 253:49–53.

Holmes, L. B. 1992. Fetal environmental toxins. *Pediatr. Rev.* 13(10):364–69.

Hornung, R. 1985. Modeling occupational mortality data with applications to U.S. uranium miners. Ph.D. diss., University of North Carolina.

Hsu, I. C., R. A. Metcalf, T. Sun, J. A. Welsh, N. J. Wang, and C. C. Harris. 1991. Mutational hotspot in the p53 gene in human hepatocellular carcinoma. *Nature* 350:427–28.

Hu, X., D. H. Wegman, E. A. Eisen, S. R. Woskie, and R. G. Smith. 1992. Dose-related acute irritant symptom responses to occupational exposure to sodium borate dusts. *Br. J. Ind. Med.* 49:706–11.

Huff, J., J. Haseman, and D. Rall. 1991. Scientific concepts, value, and significance of chemical carcinogenesis studies. *Ann. Rev. Pharmacol. Toxicol.* 31:621–52.

Humber, J., and R. Almeder. 1986. Risk assessment and the notion of an acceptable risk. In *Quantitative risk assessment: Biomedical ethics and reviews,* ed. J. Humber and R. Almeder, 171–204. Clifton, N.J.: Humana Press.

IARC (International Agency for Research on Cancer). 1978. *International agency for research on cancer on the evaluation of the carcinogenic risk of chemicals to humans. Volume 17.* Lyon, France: IARC.

IARC (International Agency for Research on Cancer). 1979. *International agency for research on cancer on the evaluation of the carcinogenic risk of chemicals to humans. Volume 17. Suppliment 1.* Lyon, France: IARC.

IARC (International Agency for Research on Cancer). 1981. *Wood, leather and some associated industries.* International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risk to Humans, vol. 25. Lyon: World Health Organization, IARC.

IARC (International Agency for Research on Cancer). 1982a. *Overall evaluations of carcinogenicity: An updating of IARC monographs vols 1–42.* International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risk to Humans, supp. 7. Lyon: World Health Organization, IARC.

IARC (International Agency for Research on Cancer). 1982b. *The rubber industry.* International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risk to Humans, vol. 28. Lyon: World Health Organization, IARC.

IARC (International Agency for Research on Cancer). 1982c. *International agency for research on cancer on the evaluation of the carcinogenic risk of chemicals to humans. Volume 17. Suppliment 4.* Lyon, France: IARC.

IARC (International Agency for Research on Cancer). 1987a. *International agency for research on cancer on the evaluation of the carcinogenic risk of chemicals to humans. Volume 17. Suppliment 6.* Lyon, France: IARC.

IARC (International Agency for Research on Cancer). 1987b. *International agency for research on cancer on the evaluation of the carcinogenic risk of chemicals to humans. Volume 17. Suppliment 7.* Lyon, France: IARC.

IARC (International Agency for Research on Cancer). 1987c. *Silica.* IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, vol. 42. Lyon: World Health Organization, IARC.

IARC (International Agency for Research on Cancer). 1989. *Diesel and gasoline exhausts and some nitroarenes.* International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 46. Lyon: World Health Organization, IARC.

ICRP (International Commission of Radiological Protection). 1975. *Report of the task group on reference man.* Vol. 23. Oxford, England: Pergamon Press.

Industrial Union Department AFL-CIO v. American Petroleum Institute, 448 U.S. 607 (1980).

Johansson, B., F. Martens, and F. Mitelman. 1991. Geographic heterogeneity of neoplasia-associated chromosome aberrations. *Genes Chromosom. Cancer* 3:1–7.

Jonveaux, P., and R. Berger. 1991. Infrequent mutations in the p53 gene in primary human T-cell acute lymphoblastic leukemia. *Leukemia* 5:839–40.

Kadlubar, F. F., K. L. Dooley, C. H. Teitel, D. W. Roberts, R. W. Benson, M. A. Butler, J. R. Bailey, J. F. Young, P. W. Skipper, and S. R. Tannenbaum. 1991. Frequency of urination and its effects on metabolism, pharmacokinetics, blood hemoglobin adduct formation, and liver and urinary bladder DNA adduct levels in beagle dogs given the carcinogen 4-aminobiphenyl. *Cancer Res.* 51:4371–377.

Kaplan, N., D. Hoel, C. Portier, and M. Hoagan. 1987. An evaluation of the safety factor approach in risk assessment. *Banbury Report 26: Developmental toxicology: Mechanisms and risk.* Cold Spring Harbor Laboratory.

Kari, F. W., R. R. Marenpot, and M. W. Anderson. 1992. *Submission of the OSHA hearing on the proposed occupational standard for methylene chloride.* September 16.

Katz, R. M., and D. Jowett. 1981. Female laundry and dry cleaning workers in Wisconsin: A mortality analysis. *Am. J. Public Health* 71:305–7.

Kawajiri, K., K. Nakachi, K. Imai, K. Yoshii, A. Shinoda, and J. Watanabe. 1990. Identification of genetically high risk individuals to lung cancer by DNA polymorphisms of the cytochrome P4501A1 gene. *Fed. Eur. Biol. Soc. Lett.* 263:131–33.

Kennedy, S. M., D. A. Enarson, R. G. Jansen, and M. Chan-Yeung. 1991. Lung health consequences of reported accidental chlorine exposures among pulp mill workers. *Am. Rev. Respir. Dis.* 143:74–79.

Keohavong, P., V. F. Liu, and W. G. Thilly. 1991. Analysis of point mutations induced by ultraviolet light in human cells. *Mutat. Res.* 249:147–59.

Kimmel, C. A. 1990. Quantitative approaches to human risk assessment for noncancer health effects. *Neurotoxicology* 11:201–10.

Kimmel, C. A., and D. W. Gaylor. 1988. Issues in qualitative and quantitative risk analysis for development toxicology. *Risk Anal.* 8:15–20.

Kimmel, C. A., and C. J. Price. 1990. Developmental toxicity studies. *Handbook of in vivo toxicity testing,* ed. D. L. Arnold, H. C. Grice, D. R. Krewski. San Diego: Academic Press. 271–300.

Kiesselbach, N., R. Ulm, H.-J. Lange and U. Korallus. 1990. A multicentre mortality study of workers exposed to ethylene oxide. *Br. J. Ind. Med.* 47:182–88.

Kline, J., Z. Stein, and M. Susser. 1989. *From conception to birth: Epidemiology of prenatal development.* New York: Oxford University Press.

Kotin, P., H. L. Flak, and M. Thomas. 1955. Aromatic hydrocarbons. III. Presence in the particulate phase of diesel engine exhausts and the carcinogenicity of exhaust extracts. *Arch. Ind. Health* 11:113–20.

Krewski, D., M. Szyszkowicz, and H. Rosenkranz. 1990. Quantitative factors in chemical carcinogenesis: Variation in carcinogenic potency. *Regul. Toxicol. Pharmacol.* 12: 13–29.

Krewski, D., K. S. Crump, J. Farmer, D. W. Gaylor, R. Howe, C. Portier, D. Salsburg, R. L. Sielken, and J. Van Ryzin. 1983. A comparison of statistical methods for low dose extrapolation utilizing time-to-tumor data. *Fundam. and Appl. Toxicol.* 3:140–60.

Krewski, D., and J. Van Ryzin. 1981. Dose-response models for quantal response toxicity data. In *Statistics and related topics,* ed. J. Sxorgo, D. Dawson, J. N. K. Rao, and E. Saleh. New York: North-Holland.

Kupper, L. L., C. Portier, M. D. Hogan, and E. Yamamoto. 1986. The impact of litter effects on dose-response modeling in teratology. *Biometrics* 42:85–98.

Kupper, L. L., and J. K. Haseman. 1978. The use of a correlated binomial model for the analysis of certain toxicological experiments. *Biometrics* 38:810–15.

LaBeau, M. M., and R. A. Larson. 1991. Cytogenetics and neoplasia. In *Hematology, basic principles and practice,* ed. R. Hoffman, E. J. Benz, Jr., S. J. Shattil, B. Furie, and H. J. Cohen, 638–55. New York: Churchill Livingstone.

Laird, N. M, and J. H. Ware. 1982. Random effects models for longitudinal data. *Biometrics* 38:963–74.

Lauwerys, R., A. Bernard, C. Viav, and J. P. Buchet. 1985. Kidney disorders and hematotoxicity from organic solvent exposure. *Scand. J. Work Environ. Health.* 11 (supp. 1):83–90.

Lefkopoulou, M., D. Moore, and L. Ryan. 1989. The analysis of multiple correlated binary outcomes: Application to rodent teratology experiments. *J. Am. Stat. Assoc.* 84:810–15.

Leisenring, W., and L. M. Ryan. 1992. Statistical properties of the NOAEL. *Regul. Toxicol. Pharmacol.* 15:161–71.

Lemen, R. A., J. S. Lee, J. K. Wagoner, and H. P. Blejer. 1976. Cancer mortality among cadmium production workers. *Ann. N.Y. Acad. Sci.* 271:273–79.

Levine, E. G., D. C. Arthur, G. Frizzera, B. A. Peterson, and others. 1985. There are differences in cytogenetic abnormalities among histological subtypes of the non-Hodgkin's lymphomas. *Blood* 66:1414.

Levy, B. S., and D. H. Wegman. 1988. Occupational health in the United States: An overview. In *Occupational health; recognizing and preventing work-related disease,* ed. B. S. Levy and D. H. Wegman. Boston: Little, Brown.

Lewtas, J. 1982. Mutagenic activity of diesel emissions. In *Toxicological effects of emissions from diesel engines,* ed. J. Lewtas. Developments in Toxicology and Environmental Science, vol. 10. New York: Elsevier Biomedical.

Liang, K. Y., and S. L. Zeger. 1986. Longitudinal data analysis using generalized linear models. *Biometrika* 73:13–22.

Liber, H. L., K. Benforado, R. M. Crosby, D. Simpson, and T. B. Skopek. 1989. Formaldehyde-induced and spontaneous alterations in human *hprt* DNA sequence and mRNA expression. *Mutat. Res.* 226:31–37.

Lipokowitz, S., V. F. Garry, and I. R. Kirsch. 1992. Interlocus V-J recombination measures: Genomic instability in agriculture workers at risk for lymphoid malignancies. *Proc. Nat. Acad. Sci.* U.S.A. 89:5301–5.

Lower, G. M., Jr. 1983. Arylamines and bladder cancer causality: Application of conceptual and operational criteria. *Clin. Pharmacol. Ther.* 34:129–35.

Lutz, W. K. 1991. Dose-response relationships in chemical carcinogenesis: From DNA adducts to tumor incidence. *Adv. Exp. Med. Biol.* 283:151–56.

Lyons, M. J. 1962. Comparison of aromatic polycyclic hydrocarbons from gasoline engine and diesel engine exhausts, general atmospheric dust, and cigarette-smoke condensate. *NCI Monogr.* 9:193–99.

MacFarland, H. N., C. E. Ulrich, C. E. Holdsworth, D. N. Kitchen, W. H. Halliwell, and S. C. Blum. 1984. A chronic inhalation study with unleaded gasoline vapor. *J. Am. Coll. Toxicol.* 3:231–48.

Malkin, D. F., P. Li, L. C. Strong, J. F. Fraumeni, C. E. Nelson, D. H. Kim, J. Kassel, M. A. Gryka, F. Z. Bischoff, M. A. Tamsky, and S. H. Friend. 1990. Germ-line p53 mutations in a familial syndrome of breast cancer, sarcomas and other neoplasms. *Science* 250:1233–50.

Matula, T. I., and E. Somers. 1989. The classification of chemical carcinogens. *Regul. Toxicol. Pharmacol.* 10:174–82.

Mauderly, J. I., R. K. Jones, W. C. Griffith, R. F. Henderson, and R. O. McClellan. 1987. Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. *Fundam. Appl. Toxicol.* 9:208–21.

Mazumdar, S., C. K. Redmond, P. E. Enterline, G. E. Marsh, J. P. Costantino, Z. Y. J. Zhou, and R. N. Patwardhan. 1989. Multistage modeling of lung cancer mortality among arsenic-exposed copper-smelter workers. *Risk Anal.* 9:51–563.

McCullagh, P., and J. A. Nelder. 1989. *Generalized linear models.* London: Chapman and Hall.

McMichaels, A. J. 1976. Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. *J. Occ. Med.* 18:165–68.

Melnick, R. L., J. Huff, B. J. Chow, and R. A. Miller. 1990. Carcinogenicity of 1,3-butadiene in C57BL/C3H F1 mice at low exposure concentrations. *Cancer Res.* 50:6592–99.

Melnick, R. L., R. E. Morrissey, and K. E. Tomaszewski. 1987. Studies by the national toxicology program on di (2-ethylhexyl) phthalate. *Toxicol. Ind. Health* 3:99–118.

Mertes, I., R. Fleischmann, H. R. Glatt, and F. Oesch. 1985. Interindividual variations in the activities of cytosolic and microsomal epoxide hydrolase in human liver. *Carcinogenesis* 6:219–23.

Meyer, U. D., U. M. Zanger, D. Grant, and M. Blum. 1989. Genetic polymorphisms of drug metabolism. In *Advances in drug research,* ed. B. Testa, 197–241. London: Academic Press.

Michalopoulos, G. K., P. M. Eckl, J. L. Cruise, D. L. Novicki, and R. L. Jirtle. 1987. Mechanisms of rodent liver carcinogenesis. *Toxicol. Ind. Health* 3:119–28.

Millar, J. D. 1988. Summary of proposed national strategies for the prevention of leading work-related diseases and injuries, part I. *Am. J. Ind. Med.* 13:223.

Millar, J. D. 1990. Risk assessment: A tool to be used responsibly. Presented to the American Mining Congress session on Occupational Safety and Health, New Orleans.

Mirer, F. E. 1991. Comments on EPA's proposed risk assessment for formaldehyde. EPA Science Advisory Board, Washington, D.C., July 17.

Mirer, F. E., R. M. Park, and M. A. Silverstein. 1989. Epidemiological and toxicologic evidence of occupational cancer in metalworking and transportation equipment industries. *Ann. N. Y. Acad. Sci.* 572:10–16.

Mitchell, B. D., M. P. Stern, S. M. Haffner, H. P. Hazuda, and J. K. Patterson. 1990. Risk factors for cardiovascular mortality in Mexican Americans and non-Hispanic whites. *Am. J. Epidemio.* 131:423–33.

Mitelman, F. 1981. Tumor etiology and chromosome pattern: Evidence from human and experimental neoplasms. In *Genes, chromosomes, and neoplasia,* ed. F. E. Arrighi, P. N. Rao, and E. Stubblefield, 335–50. New York: Raven Press.

Mitelman, F., L. Brandt, and P. G. Nilsson. 1978. Relation among occupational exposure to potential mutagenic/carcinogenic agents, clinical findings, and bone marrow chromosomes in acute nonlymphocytic leukemia. *Blood* 52:1229.

Mitelman, F., P. G. Nilsson, L. Brandt, G. Alimena, R. Gastaldi, and B. Dallapicocola. 1981. Chromosome pattern, occupation, and clinical features in patients with acute nonlymphocytic leukemia. *Cancer Genet. Cytogenet.* 4:197–214.

Monson, R. R. 1990. *Occupational epidemiology.* Boca Raton, Fla.: CRC Press.

Moolgavkar, S. H., and A. G. Knudson. 1981. Mutation and cancer: A model for human carcinogenesis. *J. Nat. Cancer Inst.* 66:1037–52.

Moolgavkar, S. H. 1986. Carcinogenesis modeling: From molecular biology to epidemiology. *Ann. Rev. Pub. Health* 7:151–69.

Moolgavkar, S. H., and D. J. Venzon. 1987. General relative risk regression models for epidemiological studies. *Am. J. Epidemio.* 126:949–61.

Morgan, R. W., K. W. Claxton, B. J. Divine, S. D. Kaplan and V. B. Harris. 1981. Mortality among ethylene oxide workers. *J. Occup. Med.* 23:767–69.

Narod, S. A., and I. D. Dube. 1989. Occupational history and involvement of chromosomes 5 and 7 in acute nonlymphocytic leukemia. *Cancer Genet. Cytogenet.* 38:261–69.

NAS NRC (National Academy of Sciences, National Research Council). 1975. *Pest control volume 1: An assessment of present and alternative technologies.* Washington, D.C.: National Academy Press.

NAS NRC (National Academy of Sciences, National Research Council). 1983. *Risk assessment in the federal government: Managing the process.* Washington, D.C.: National Academy Press.

NAS NRC (National Academy of Sciences, National Research Council). 1985. *Toxicology testing needs.* Washington, D.C.: National Academy Press.

NAS NRC (National Academy of Sciences, National Research Council). Environmental Studies Board. 1975. *Contemporary pesticide practices: Report of the Executive Committee.* Washington, D.C.: National Academy Press. 66–83.

Nebert, D. W., D. R. Nelson, M. Adesnik, M. J. Coon, R. W. Estabrook, F. J. Gonzalez, F. P. Guengerich, I. C. Gunsalus, E. F. Johnson, B. Kemper, W. Levin, I. R. Phillips, R. Sato, and M. R. Waterman. 1989. The P450 gene superfamily: Update on listing of all genes and recommended nomenclature of chromosomal loci. *DNA* 8:1–13.

Nichols, A. L., and R. Zeckhauser. 1988. The perils of prudence: How conservative risk assessments distort regulation. *Regul. Toxicol. Pharmacol.* 8:61–75.

NIOSH (National Institute for Occupational Safety and Health). 1987. *Criteria for a* *recommended standard: Occupational exposure to radon progeny in underground mines.* DHHS Publication No. 88–101. Cincinnati, Ohio: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, NIOSH.

NIOSH (National Institute for Occupational Safety and Health). 1990. NIOSH national occupational exposure survey 1981–1983. Unpublished provisional data as of July 1, 1990. Cincinnati, Ohio: National Institute for Occupational Safety and Health.

NIOSH (National Institute for Occupational Safety and Health). 1992. *NIOSH Recommendations for occupational safety and health: Compendium of policy documents and statements.* Cincinnati, Ohio: National Institute for Occupational Safety and Health.

NTP (National Toxicology Program). 1986. *Toxicology and carcinogenesis studies of dichloromethane (methylene chloride) (CAS No. 75-09-2) in F344/N rats and B6C3F1 mice (inhalation studies).* Technical Report Series No. 306. Research Triangle Park, N.C.: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institutes of Health.

NTP (National Toxicology Program). 1989. *Toxicology and carcinogenesis studies of chloroethane (ethyl chloride) (CAS No. 75–00–3) in F344/N rats and B6C3F1 mice (inhalation studies).* Technical Report Series No. 346. NIH Publication No. 90–2801. Washington, D.C.: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, October.

O'Brien, P. 1984. Procedures for comparing samples with multiple endpoints. *Biometrics* 40:1079–87.

Occupational exposure to 1,3-butadiene: Proposed rule and notice of hearing. 1990. *Federal Register* SS, no 155 (August 10): 32736.

Occupational exposure to methylene chloride: Proposed rule. 1991. *Federal Register* 56 (November 7): 57036.

Ochi, Y., and R. L. Prentice. 1984. Likelihood inference in a correlated probit regression model. *Biometrika* 71:531–43.

Okumura, M., R. Hasegawa, T. Shirai, and M. Ito. 1992. Relationship between calculus formation and carcinogenesis in the urinary bladder of rats administered the non-genotoxic agents thymine or melamine. *Carcinogenesis* 12(6):1043–45.

Orita, M. Y., T. Suzuki, K. Sekiya, and K. Hayashi. 1989. Rapid and sensitive detection of point mutations and DNA polymorphisms using the polymerase chain reaction. *Genomics* 5:874–79.

OSHA (Occupational Safety and Health Administration). 1978. Occupational exposure to lead. *Federal Register* 43:54353.

OSHA (Occupational Safety and Health Administration). 1989a. Air contaminants. *Federal Register* 54:12792–12868.

OSHA (Occupational Safety and Health Administration). 1989b. Air contaminants; corrections. *Federal Register* 54:28054–61.

OSHA (Occupational Safety and Health Administration). 1989c. Occupational exposure to 4,4'-methylenedianiline (MDA): Proposed rule. *Federal Register* 54 (May 12): 20672–20744.

OSHA (Occupational Safety and Health Administration). 1989d. OSHA revises standards on air contaminants. *Federal Register* 54:2332–2983.

OSHA (Occupational Safety and Health Administration). 1990. Occupational exposure

to 1,3-butadiene: Proposed rule and notice of hearing. *Federal Register* 55 (August 10).

OSHA (Occupational Safety and Health Administration). 1992. Occupational exposure to cadmium: Final rule. *Federal Register* 57 CFR, Parts 1910, 1915, 1926:42102.

OTA (Office of Technology Assessment). Congress of the United States. 1987. *Identifying and regulating carcinogens.* Washington, D.C.: OTA, November.

Park, C. N. 1990. Underestimation of linear models. *Risk Anal.* 10:209–10.

Park, R. M., N. A. Maizlish, L. Punnett, R. Moure-Eraso, and M. Silverstein. 1991. A comparison of PMRs and SMRs as estimators of occupational mortality. *Epidemiology* 2:49–59.

Paul, S. R. 1982. Analysis of affected fetuses in teratological experiments. *Biometrics* 38:361–70.

Paul, S. R. 1987. On the beta-correlated binomial (bcb) distribution—a three parameter generalization of the binomial distribution. *Commun. Stat. Theory Methods* 16: 1473–78.

Paustenbach, D. J. 1989. Important recent advances in the practice of health risk assessment: Implications for the 90's. *Regul. Toxicol. Pharmacol.* 10:204–43.

Paustenbach, D. J., J. D. Jernigan, B. L. Finley, S. R. Ripple, and R. E. Keenan. 1990. The current practice of risk assessment: Potential impact on standards for toxic air contaminants. *J. Air Waste Mgmt. Assoc.* 40:1620–30.

Paxman, D. G., and J. C. Robinson. 1990. Regulation of occupational carcinogens under OSHA's air contaminants standard. *Regul. Toxicol. Pharmacol.* 12:296–308.

Pearce, N. 1988. Multistage modelling of lung cancer mortality in asbestos textile workers. *Int. J. Epidemio.* 17:747–52.

Pearce, N., and J. S. Reif. 1990. Epidemiologic studies of cancer in agricultural workers. *Am. J. Ind. Med.* 18:133–48.

Pedersen-Bjergaard, J., and P. Philip. 1987. Cytogenetic characteristics of therapy-related acute nonlymphocytic leukemia, preleukemia and acute myeloproliferative syndrome: Correlation with clinical data for 61 consecutive cases. *Br. J. Haematol.* 66:199–207.

Pelicci, P. G., D. M. Knowles, I. Magrath, and R. Dalla-Favera. 1986. Chromosomal breakpoints and structural alterations of the c-myc locus differ in endemic and sporadic forms of Burkitt's lymphoma. *Proc. Natl. Acad. Sci. U.S.A.* 83:2984–88.

Pepe, M., S. Self, and R. Prentice. 1989. Further results on covariate measurement errors in cohort studies with time to response data. *Stat. Med.* 8:1168–78.

Peters, R. 1989. *Red army.* New York: Simon & Schuster, 32.

Peto, R. 1985. Epidemiological reservations about risk assessment. In *Assessment of risk from low-level exposure to radiation and chemicals,* ed. A. D. Woodhead, C. J. Shellabarger, V. Pond, and A. Hollaender, 16–30. New York: Plenum Press.

Peto, R., M. C. Pike, L. Bernstein, L. S. Gold, and B. N. Ames. 1984. The TD_{50}: A proposed general convention for the numerical description of the carcinogenic potency of chemicals in chronic-exposure animal experiments. *Environ. Health Perspect.* 58:1–8.

Piegorsch, W. W., and J. K. Haseman. 1991. Statistical methods for analyzing developmental toxicity data. *Teratogenesis Carcinog. Mutagen.* 11:115–33.

Pirkle, J. L., J. Schwartz, R. Landis, and W. R. Harlan. 1985. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. *Am. J. Epidemiol.* 121:246–58.

Pitot, H. C., Y. P. Dragan, and M. J. Neveu. 1991. Chemicals, cell proliferation, risk estimation and multistage carcinogenesis. *Prog. Clin. Biol. Res.* 369:517–32.

Pocock, S. J., N. L. Geller, and A. A. Tsiatis. 1987. The analysis of multiple endpoints in clinical trials. *Biometrics* 43:487–98.

Portier, C. J., and N. J. Kaplan. (1989). Variability of safe dose estimates when using complicated models of the carcinogenic process: A case study: Methylene chloride. *Fundam. Appl. Toxicol.* 13:533–44.

Portier, C., A. Tritscher, M. Kohn, C. Sewall, G. Clark, L. Edler, D. Hoel, and G. Lucier. 1993. Ligand/receptor binding for 2,3,7,8-TCDD: Implications for risk assessment. *Fundam. Appl. Toxicol.* 20:48–56.

Prentice, R. L. 1982. Covariate measurement errors and parameters estimation in a failure time regression model. *Biometrika* 69:331–42.

Prentice, R. L. 1986. Binary regression using an extended beta-binomial distribution, with discussion of correlation induced by covariate measurement errors. *J. Am. Stat. Assoc.* 81:321–27.

Prentice, R. L. 1988. Correlated binary regression with covariates specific to each binary observation. *Biometrics* 44:1033–48.

Prentice, R. L., and L. P. Zhao. 1991. Estimating equations for parameters in means and covariances of multivariate discrete and continuous responses. *Biometrics* 47:825–39.

Price, C. J., C. A. Kimmel, J. D. George, and M. C. Marr. 1987. The developmental toxicity of diethylene glycol dimethyl ether in mice. *Fundam. Appl. Toxicol.* 8: 115–26.

Price, C. J., C. A. Kimmel, R. W. Tyl, and M. C. Marr. 1985. The developmental toxicity of ethylene glycol in rats and mice. *Toxicol. Appl. Pharmacol.* 81:113–27.

Radich, J. P., K. J. Kopecky, F. Appelbaum, C. L. William, and S. J. Collins. 1992. N-ras mutations in acute myelogenous leukemia: A review of the current literature and an update of the Southwest Oncology Group Experience. *Leukem. Lymphom.* 6:325–34.

Rai, K., and J. Van Ryzin. 1985. A dose-response model for teratological experiments involving quantal responses. *Biometrics* 41:1–9.

Rao, M. S., and J. K. Reddy. 1991. An overview of peroxisome proliferator-induces hepatocarcinogenesis. *Environ. Health Perspect.* 93:205–9.

Rappaport, S. M., and T. J. Smith, eds. 1991. *Exposure assessment for epidemiology and hazard control.* Chelsea, Mass.: Lewis Publishers.

Ravnskov, U., B. Forsberg, and S. Skerfring. 1979. Glomerulonephritis and exposure to organic solvents. *Acta Med. Scand.* 205:575–79.

Rawls, J. 1971. *A theory of justice.* Cambridge, Mass.: Belknap Press of Harvard University Press.

Recio, L., D. Simpson, J. Cochrane, H. Liber, and T. R. Skopek. 1990. Molecular analysis of *hprt* mutants induced by 2-cyanoethylene oxide in human lymphoblastoid cells. *Muta. Res.* 242:195–208.

Reddy, J. K. 1990. Carcinogenicity of peroxisomes proliferators: Evaluation and mechanisms. *Biochem. Soc. Trans.* 18:92–94.

Reitz, R. H., A. L. Mendrala, and F. P. Guengerich. 1989. *In vitro* metabolism of methylene chloride in human and animal tissues: Use in physiologically based pharmacokinetic models. *Toxicol. Appl. Pharmacol.* 97:230–46.

Reynolds, S. D., S. J. Stoers, R. R. Marenpot, and M. W. Anderson. 1987. Activated oncogenes in B6C3F1 mouse liver tumors: Implications for risk assessment. *Science* 237:1309–17.

Roach, S. A., and S. M. Rappaport. 1990. But they are not thresholds; a critical analysis of the documentation of threshold limit values. *Am. J. Ind. Med.* 17:727–53.

Robins, J. M., P. J. Landrigan, T. G. Robins, and L. J. Fine. 1985. Decision-making under uncertainty in the setting of environmental health regulations. *J. Public Health Policy* 63:322–28.

Rodricks, J. V., S. M. Brett, and G. C. Wrenn. 1987. Significant risk decisions in federal regulatory agencies. *Regul. Toxicol. Pharmacol.* 7:307–20.

Rodricks, J. V., R. G. Tardiff, S. M. Brett, R. M. Putzrath, and C. St. Hilaire. 1986. *Elements of toxicology and chemical risk assessment.* Washington, D.C.: Environ Corporation.

Rosenberg, M. J., P. J. Feldblum, and E. G. Marshall. 1987. Occupational influences on reproduction: A review of the recent literature. *J. Occup. Med.* 29:584–98.

Rosner, B. 1982. Statistical methods in ophthalmology: An adjustment for the intraclass correlation between eyes. *Biometrics* 38:105–14.

Rosner, B. 1984. Multivariate methods in ophthalmology with applications to other paired data situations. *Biometrics* 40:1025–35.

Rosner, D., and G. Markowitz. 1991. *Deadly dust. Silicosis and the politics of occupational disease in twentieth-century America.* Princeton, N.J.: Princeton University Press.

Rothman, K. J. 1986. *Modern epidemiology.* Boston: Little, Brown and Co.

Rowley, J. D. 1974. Do human tumors have a chromosome pattern specific for each etiologic agent? *J. Nat. Cancer Ins.* 52:315–20.

Rowley, J. D., and M. M. Le Beau. 1989. Cytogenetic and molecular analysis of therapy-related leukemia. *Ann. N. Y. Acad. Sci. U.S.A.* 567:130–40.

Rushefsky, M. E. 1985. Assuming the conclusions: Risk assessment in the development of cancer policy. *Politics Life Sci.* 4:31–44.

Rushefsky, M. E. 1986. *Making cancer policy.* Albany: State University of New York Press.

Ryan, L. M. 1992a. Quantitative risk assessment for developmental toxicity. *Biometrics* 48:215–23.

Ryan, L. M. 1992b. The use of generalized estimating equations for risk assessment in developmental toxicity. *Risk Anal.* 12:439–47.

Ryan, L. M., P. J. Catalano, C. A. Kimmel, and G. L. Kimmel. 1991. Relationship between fetal weight and malformation in developmental toxicity studies. *Teratology* 44:215–23.

Salisbury, D. A., D. A. Emarson, M. Chan-Yeung, and S. M. Kennedy. 1991. First aid reports of acute chlorine gassing among pulp mill workers as indicators of lung health consequences. *Am. J. Ind. Med.* 20:71–81.

Samet, J. M., C. R. Key, D. M. Kutvirt, and C. L. Wiggins. 1980. Respiratory disease mortality in New Mexico Indians and Hispanics. *Am. J. Pub. Health* 70:492–97.

Savitz, D. 1986. Changes in Spanish surname cancer rates relative to other whites, Denver areas, 1969–71 to 1979–81. *Am. J. Pub. Health* 76:1210–215.

Sawyer, C., R. Peto, L. Bernstein, and M. C. Pike. 1984. Calculation of carcinogenic potency from long-term animal carcinogenesis experiments. *Biometrics* 40:27–40.

Schneiderman, M. 1986. Risk assessment: Where do we want it to go? In *Quantitative risk assessment, biomedical ethics reviews,* ed. J. M. Humber and R. F. Almeder. Clifton, N.J.: Humana Press.

Seidegard, J., J. W. DePierre, and R. W. Pero. 1985. Hereditary interindividual differences in the glutathione transferase activity towards trans-stilbene oxide in resting human mononuclear leukocytes are due to a particular isozyme(s). *Carcinogenesis* 6: 1211–216.

Seta J. A., D. S. Sundin, and D. H. Pedersen. 1988. *National occupational exposure survey field guidelines.* Vol. 1. Cincinnati, Ohio: NIOSH.

Shields, P. G. 1993. Inherited factors and environmental exposures in cancer risk. *J. Occup. Med.* 35:34–41.

Shrader Frechette, K. S. 1991. *Risk and rationality: Philosophical foundations for populist reform.* Berkeley: University of California Press.

Sielken, R. L. 1990. Driving cancer dose-response modeling with data, not assumptions. *Risk Anal.* 10:207–8.

Silbergeld, E. K., P. J. Landrigan, J. R. Froines, and R. M. Pfeffer. 1991. The occupational lead standard: a goal unachieved, a process in need of repair. *New Solutions* 1:20–30.

Silver, K., and D. Hattis. 1991. *Methodology for quantitative assessment of risks from chronic respiratory damage: Lung function decline and associated mortality from coal dust.* CTPID 90–9. Cambridge, Mass: MIT Center for Technology, Policy and Industrial Development.

Skalko, R. G., and E. M. Johnson, mods. 1987. Consensus workshop on the evaluation of maternal and developmental toxicity. Work Group I report: End points of maternal and developmental toxicity. *Teratogenesis Carcinog. Mutagen.* 7:307–10.

Slovic, P. 1987. Perceptions of risk. *Science* 236:280–85.

Smith, A. H. 1988. Epidemiologic input to environmental risk assessment. *Arch. Environ. Health* 43:124–27.

Smith, C. M, D. C. Christiani, and K. T. Kelsey. In press. A possible role for glutathione transferase mu in susceptibility to asbestos related pulmonary disease. Occupational Epidemiology, National Institute for Occupational Safety and Health.

Smith, C. M., K. T. Kelsey, and D. C. Christiani. 1993. Risk assessment and occupational health: Overview and recommendations. *New Solutions* (Winter):26–38.

Smith, M. T., J. Wiemels, N. Rothman, and M. S. Linet. 1992. Chemical exposure, ras oncogene activation and acute myeloid leukemia. *J. Natl. Cancer Inst.* 84:1614–15.

Smith, R., and L. Stayner. 1990. An exploratory assessment of the risk of lung cancer associated with exposure to diesel exhaust based on a study in rats. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio, July 2.

Smith, T. J. 1987. Exposure assessment for occupational epidemiology. *Am. J. Ind. Med.* 12:249–68.

Smith, T. J. 1992. Occupational exposure and dose over time: Limitations of cumulative exposure. *Am. J. Ind. Med.* 21:35–51.

Smith, T. J., S. K. Hammond, S. Hallock, and S. R. Woskie. 1991. Exposure assessment for epidemiology: Characteristics of exposure. *Appl. Occup. Environ. Hyg.* 6:6.

Snellings, W., C. Weil, and R. Maronpot. 1984. A two-year inhalation study of the carcinogenic potential of ethylene oxide in Fischer 344 rats. *Toxicol. Appl. Pharmacol.* 5:105–17.

Sommer, S. S. 1990. Mutagen test. *Nature* 346:22–23.

Sommer, S. S., J. Cunningham, R. M. McGovern, S. Saitoh, J. J. Schroeder, L. E. Wold, and J. S. Kovach. 1992. Patterns of p53 gene mutations in breast cancers of women in the midwestern United States. *J. Natl. Cancer Inst.* 84:246–52.

Sram, R. J., L. Tomatis, J. Clemmesen, and B. A. Bridges. 1981. An evaluation of the genetic toxicity of epichlorohydrin. A report of an expert group of the International Commission for Protection against Environmental Mutagens and Carcinogens. *Mutat. Res.* 87:299–319.

Statistics in Medicine 8. 1989.

Stayner, L., R. Smith, M. Thun, T. Schnorr, and R. Lemen. 1991. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. *Ann. Epidemiol.* 23:177–94.

Stayner, L. T., R. J. Smith, M. T. Thun, T. M. Schnorr, and R. A. Lemen. 1992. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. *Ann. Epidemiol.* 2: 177–94.

Steenland, K., L. Stayner, W. Halperin, A. Griefe, R. Hayes, R. Hornung, and S. Nowlin. 1991. Mortality among workers exposed to ethylene oxide. *N. Engl. J. Med.* 324: 1402–7.

Steward, P. A., A. Blair, D. Mustafa, and G. Manuel. 1991. Collection of exposure data for retrospective occupational epidemiologic studies. *Appl. Occup. Environ. Hyg.* 6:4.

Swenberg, J. A., D. R. Dietrich, R. M. McClain, and S. M. Cohen. 1992. Species-specific mechanisms of carcinogenesis. *IARC Sci. Publ.* 116:477–500.

Taylor, J. A., D. P. Sandler, C. D. Bloomfield, D. L. Shore, E. D. Ball, A. Neubauer, O. R. McIntyre, and E. Lin. 1992. Ras oncogene activation and occupational exposures in acute myeloid leukemia. *J. Natl. Cancer Inst.* 84:1626–32.

Taylor, R. E. 1990. Putting the money where the math is. *Govt. Execut.* 22(April):4, 17.

Temellini, A., L. Giuliani, and G. M. Pacifici. 1991. Interindividual variability in the glucuronidation and sulphation of ethinyloestradiol in human liver. *Br. J. Clin. Pharmacol.* 31:661–64.

Tennant, R. W., B. H. Margolin, M. D. Shelby, E. Zeiger, J. K. Haseman, J. Spalding, W. Caspary, M. Resnick, S. Stasiewicz, B. Anderson, and R. Minor. 1987. Prediction of chemical carcinogenicity in rodents from genetic assays. *Science* 236: 933–41.

Teta, M. J., L. O. Benson, and J. N. Vitale. 1993. Mortality study of ethylene oxide workers in chemical manufacturing. *Br. J. Ind. Med.* 50:704–9.

Theiss, A. M., R. Frentzel-Beyne, R. Link, and W. Stocker. 1981. *Mortality study on employees exposed to alkylene oxides, (ethylene oxide/propylene oxide) and their derivatives.* Prevention of Occupational Cancer (Occupational Safety and Health Series), 46:249–59. Geneva: International Labor Office.

Theriault, G. P. 1988. Cardiovascular disorders. In *Occupational health: Recognizing and preventing work-related disease,* ed. B. S. Levy and D. H. Wegman, 431–41. Boston: Little, Brown.

Thilly, W. G. 1990. Mutational spectrometry in animal toxicity testing. *Ann. Rev. Pharmacol. Toxicol.* 30:369–85.

Thilly, W. G., V. F. Liu, B. J. Brown, N. F. Cariello, A. G. Kat, and P. Keohavong. 1989. Direct measurement of mutational spectra in humans. *Genome* 31:590–93.

Thomas, D. C. 1981. General relative risk functions for survival time and matched case-control studies. *Biometrics* 37:673–86.

Thun, M. T., T. M. Schnorr, A. B. Smith, W. E. Halperin, and R. A. Lemen. 1985. Mortality among a cohort of U.S. cadmium production workers—an update. *J. Nat. Cancer Inst.* 74:325–33.

Thurow, L. E. 1987. *The zero-sum society: Distribution and the possibilities for economic change.* New York: Basic Books.

Tollefson, L., R. J. Lorentzen, R. N. Brown, and J. A. Springer. 1990. Comparison of the cancer risk of methylene chloride predicted from animal bioassay data with the epidemiologic evidence. *Risk Anal.* 10:429–35.

Tomatis, L., A. Aitio, J. Wilbourn, and L. Shuker. 1989. Human carcinogens so far identified. *Jpn. J. Cancer Res.* 80:795–807.

Travis, C. C., ed. 1988. *Carcinogen risk assessment.* New York: Plenum Press.

Travis, C. C., and H. A. Hattemer-Frey. 1988. Determining an acceptable level of risk. *Environ. Sci. Technol.* 22:873–76.

Travis, C. C., S. A. Richter, E. A. C. Crouch, R. Wilson, and E. D. Klema. 1987. Cancer risk management. *Environ. Sci. Technol.* 21:415–20.

Tyl, R. W., C. J. Price, M. C. Marr, and C. A. Kimmel. 1988. Developmental toxicity evaluation of dietary di(2-ethylhexyl)phthalate in Fischer 344 rats and CD-1 mice. *Fundam. Appl. Toxicol.* 10:395–412.

U.S. Department of Labor. MSHA (Mine Safety and Health Administration). 1992. Advance notice of proposed rulemaking. Permissible exposure limit for diesel particulates. *Federal Register* 57 (January 6): 500–503.

U.S. Department of Labor. OSHA (Occupational Safety and Health Administration). 1978a. Part IV: Occupational exposure of lead: Final standard. *Federal Register* 43 (November 14): 54353.

U.S. Department of Labor. OSHA (Occupational Safety and Health Administration). 1978b. Part III: Occupational exposure to cotton dust: Final standard. *Federal Register* 43 (June 23).

U.S. Department of Labor. OSHA (Occupational Safety and Health Administration). 1989. Part III: Air contaminants; Final rule. *Federal Register* (January 19).

U.S. DHHS (U.S. Department of Health and Human Services). 1985. *Risk assessment and risk management of toxic substances: A report to the Secretary of the Department of Health and Human Services* Washington, D.C.: DHHS, April.

U.S. FDA (Food and Drug Administration). 1966. *Guidelines for reproduction and studies for safety evaluation of drugs for human use.* Rockville, M.D.: Bureau of Drugs.

U.S. Office of Management and Budget. 1991. *Current regulatory issues in risk assessment and risk management.* Regulatory Program of the United States. Washington, D.C.: OMB, April 1–March 31.

U.S. Public Law 91–173. *Mine Safety and Health Act of 1977.* Sec. 101(a)(1).

Vahakangas, K., H. Autrup, and C. C. Harris. 1984. Interindividual variation in carcinogen metabolism, DNA damage and DNA repair. *IARC Sci. Publ.* 85–98.

Vahakangas, K. H., J. M. Samet, R. A. Metcalf, J. A. Welsh, W. P. Bennett, D. P. Lane, and C. C. Harris. 1992. Mutations of p53 and ras genes in radon-associated lung cancer from uranium miners. *Lancet* 339:576–80.

Vainio, H., M. Coleman, and J. Wilbourn. 1991. Carcinogenicity evaluations and ongoing studies: The IARC databases. *Environ. Health Perspect.* 96:5–9.

Vogelstein, B., and K. W. Kinzler. 1992. p53 Function and dysfunction. *Cell* 70:523–26.

Vostal, J. J. 1983. Bioavailability and biotransformation of the mutagenic component of particulate emissions present in motor exhaust samples. *Environ. Health Perspect.* 47:267–81.

Wallace, W. E., M. J. Keane, C. A. Hill, X. Jing, and O. Tong-man. 1987. Mutagenicity of diesel exhaust particles and oil shale particles dispersed in lecithin surfactant. *J. Toxicol. Environ. Health* 21:163–71.

Wegman, D. H. 1993. Examination of the effects of certain acute environmental exposures on future respiratory health consequences. In *Veterans at risk.* Washington, D.C.: Institute of Medicine, National Academy Press.

Wegman, D. H., and D. C. Christiani. 1988. Respiratory disorders. In *Occupational health: Recognizing and preventing work-related disease,* ed. B. S. Levy and D. H. Wegman. Boston: Little, Brown.

Wegman, D. H., E. A. Eisen, X. Hu, S. R. Woskie, and R. G. Smith. In press. Acute and chronic respiratory effects of sodium borate particulate exposures. *Environ. Health Perspect.*

Whittemore, A. S. 1977. The age distribution of human cancer for carcinogenic exposures of varying intensity. *Am. J. Epidemio.* 106:418–32.

Whittemore, A. S. 1983. Facts and values in risk analysis for environmental toxicants. *Risk Anal.* 3:23–33.

Williams, D. A. 1975. The analysis of binary responses from toxicology experiments involving reproduction and teratogenicity. *Biometrics* 31:949–52.

Williams, D. A. 1987a. Dose-response models for teratological experiments. *Biometrics* 43:1013–16.

Williams, D. A. 1982b. Extra-binomial variation in logistic linear models. *Appl. Stat.* 31: 144–48.

Wolf, H., G. M. Lower, Jr., and G. T. Bryan. 1980. Role of N-acetyltransferase phenotype in human susceptibility to bladder carcinogenic arylamines. *Scand. J. Urol. Nephrol.* 14:161–65.

Wolff, S. 1982. Chromosome aberrations, sister chromatid exchanges and the lesions that produce them. In *Sister chromatid exchange,* ed. S. Wolff, 41–58. New York: John Wiley and Sons.

Woskie, S. R., P. Shen, M. Finkel, E. A. Eisen, T. J. Smith, R. Smith, and D. H. Wegman. 1993. Calibration of a continuous-reading aerosol monitor, Miniram, to measure borate dust exposures. *Appl. Occup. Environ. Hyg.* 8:1.

Yu, C. P., and G. B. Xu. 1987. Predictive models for deposition of inhaled diesel exhaust particles in humans and laboratory species. *Res. Rep. Health Eff. Inst.* 3–22.

Yu, R. C., T. Wai-Yuan, R. M. Mathen, D. A. Andjelkovich, and R. L. Levine. 1990. A deterministic mathematical model for quantitative estimation of historical exposure. *Am. Ind. Hyg. Assoc. J.* 51(4):194–201.

Yunis, J. J., G. Frizzera, M. M. Oken, J. McKenna, A. Theologides, and M. Arnesen. 1987. Multiple recurrent genomic defects in follicular lymphoma: A possible model for cancer. *N. Engl. J. Med.* 316:79.

Zeger, S. L., and K. Y. Liang. 1986. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 42:121–30.

Zeise, L., E. A. Crouch, and R. Wilson. 1985. On the relationship of toxicity and carcinogenicity [letter]. *Risk Anal.* 5:265–70.

Zeise, L., R. Wilson, and E. A. Crouch. 1987. Dose-response relationships for carcinogens: A review. *Environ. Health Perspect.* 73:259–306.

Ziman, J. 1968. *Public knowledge.* Cambridge, MA: Cambridge U.P.

Ziman, J. 1978. *Reliable knowledge.* Cambridge, MA: Cambridge U.P.

Zimmerman, S. W., K. Groehler, and G. J. Beirne. 1975. Hydrocarbon exposure and chronic glomerulonephritis. *Lancet* 199–201.