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Ranking the Potential Carcinogenic Hazards to Workers from Exposures to Chemicals That Are Tumorigenic in Rodents

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For 41 chemicals there exist both reasonable data on carcinogenic potency in experimental animals and also a defined Permissible Exposure Level (PEL), which is the upper limit of legally permissible chronic occupational exposure for U.S. workers. These 41 agents are ranked by an index that compares the permitted chronic human exposure to the chronic dose rate that induces tumors in 50% of laboratory animals. This index, the Permitted Exposure/Rodent Potency index, or PERP, does not estimate absolute risks directly, but rather suggests the relative hazards that such substances may pose. The PERP values for these 41 substances differ by more than 100,000-fold from each other. The PERP does not take into account the actual level of exposure or the number of exposed workers. Nevertheless, it might be reasonable to give priority attention to the reduction of allowable worker exposures to substances that appear most hazardous by this index and that some workers may be exposed to full-time near the PEL. Ranked by PERP, these chemicals are: ethylene dibromide, ethylene dichloride, 1,3-butadiene, tetrachloroethylene, propylene oxide, chloroform, formaldehyde, methylene chloride, dioxane, and benzene.

Introduction

Hundreds of chemicals have been shown to induce tumors in rodents in controlled laboratory experiments, but more evidence is needed about the relevance of these laboratory results for human populations. Unfortunately, epidemiologic data on cancer causation are not readily obtainable, and only about 40 chemicals and chemical mixtures have thus far been reliably identified as human carcinogens (*1,2*). We know that most chemicals that have been identified as human carcinogens have been shown to yield a positive carcinogenic response in at least one rodent species, but we do not know whether the large number of other rodent carcinogens will turn out to have any substantial carcinogenic effect on humans. Nor do we have evidence indicating that one or another mathematical model is appropriate for making a quantitative assessment of human risk by extrapolation across doses and species, from the high doses administered in animal bioassays to the lower doses of most human exposures. 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 (*3–5*). Therefore, it is not clear how best to make use of the animal data.

In this paper we propose the use of animal results to rank possible occupational hazards to people from exposures to those chemicals that are known to be carcinogenic in rodents. This approach has been suggested elsewhere (*3–6*) but without as much data as we now use. We propose a comparison between the dose rate at which workers are allowed to be exposed to a given chemical and the dose rate that induces a standard tumor rate in laboratory animals. The ratio of these two dose rates may well be correlated with occupational carcinogenic hazards; if it is, then by computing this ratio for a great many chemicals to which people may be exposed, a scale can be constructed to help rank possible human carcinogenic hazards from chemicals in the workplace. This Permitted Exposure/Rodent Potency index (PERP) can be calculated for very small exposures of large numbers of people (e.g., to things such as pesticide residues in food), or for larger exposures of smaller numbers of people (e.g., to things such as inhalation of solvents by factory workers). In this paper we examine PERP values for permitted exposures in the workplace, while in an earlier paper we reported a similar index (HERP or Human Exposure/Rodent Potency) for actual exposures in food, drugs,

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air, and water (*5*). This approach may help to formulate sensible priorites for concern among the large number of rodent carcinogens already identified.

Our group has developed a large database of the results of chronic animal cancer tests, the Carcinogenic Potency Database (CPDB) (*7–9*). Currently the CPDB includes results on approximately 1000 chemicals, about half of which are positive in at least one animal experiment. To describe the dose rate that produces tumors in an animal experiment, this database estimates the 50% tumorigenic dose-rate, or TD_{50}. The 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 (*10,11*). We have found that the TD_{50} values of rodent carcinogens vary more than 10 million-fold.

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 present analysis of workplace exposure limits we use TD_{50} values in the calculation of the PERP to compare the rodent dose rate with the Permissible Exposure Limit (PEL) set by the U.S. Occupational Safety and Health Administration (OSHA) for the occupational exposure level (*12*).

Methods

Two factors are required for the 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 Permissible Exposure Limits (PELs) set by OSHA. The PEL is the maximum allowable concentration of an airborne contaminant in workplace air on a time-weighted average basis over an 8-hr day and thus represents the maximum allowable dose for a worker per day. 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 (*13*), works 5 days per week 50 weeks per year for 40 years, and has a standard lifespan of 70 years. We call this value the Maximum Occupational Dose Rate (MOD). The calculation for the MOD, assuming 100% absorption, is therefore:

$$\frac{\text{PEL (in mg/m}^3\text{)} \times 9.6\ \text{m}^3\text{/day}}{\text{70 kg body weight person}} \times \frac{\text{5 days/week}}{\text{7 days}} \times \frac{\text{50 weeks/year}}{\text{52 weeks}} \times \frac{\text{40 years work life}}{\text{70 year life}}$$

Estimation of Carcinogenic Potency in Laboratory Animals

TD_{50} values have been estimated from all long-term, chronic experiments that meet a set of standard inclusion criteria, e.g., administration by an oral route or by inhalation, a dosing period at least one-fourth the standard lifespan of 2 years for rodents, an experiment length of at least 1 year, and the presence of a control group (*7,10,11*). The TD_{50} is the estimated daily dose rate in milligrams per kilogram body weight per day to halve the proportion of tumorless survivors at the end of a standard lifespan. The estimation procedure 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 of the period of observation. Our standard values for animal weight, intake of food, air, and water, and standard lifespans are given in Gold et al., 1984 (*7*). Since the TD_{50} is subject to the usual statistical uncertainties, we have estimated confidence limits for it, and report these values in Gold et al. (*7–9*).

The TD_{50} can be calculated for any particular neoplasm or group of neoplasms, so our database often contains several TD_{50} values for each experiment (i.e., for one sex in one strain of one species from a single research report). In the analysis below we define a compound as carcinogenic if the author of at least one published paper evaluated it as positive, and if, in addition, the p value for at least one experiment is less than 0.01. For each carcinogen, we use the most potent TD_{50} (i.e., the lowest numerical value, since a low TD_{50} corresponds to a potent carcinogen) for any target site(s) identified by the author of the published paper. We use TD_{50} values only from tests that used an oral or inhalation route of administration.

Calculation of the Permitted Exposure Rodent Potency Index

The PERP is defined as MOD/TD_{50} × 100:

$$\frac{\text{Occupational exposure-rate to workers (mg/kg/day)}}{\text{Tumorigenic dose rate for 50\% of rodents (mg/kg/day)}} \times 100$$

Thus, the PERP is the daily human exposure as a percentage of the tumorigenic dose rate for 50% of the animals. 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.

Selection of Compounds

The present study is of chemicals for which PELs for workers have been set by OSHA and for which our CPDB contains at least one experiment in rats or mice in which the compound was evaluated as carcinogenic. From among approximately 500 compounds in the CPDB that were evaluated as tumorigenic in at least one experiment, and about 500 chemicals that are regulated with PELs by OSHA, only 41 compounds are common to both. An additional 12 compounds in the CPDB are regulated by OSHA as "toxic and hazardous" substances but have no PELs, e.g., benzidine and β-napthalamine. These are not included in our analysis.

In Table 1 we list the 41 chemicals and the most potent TD$_{50}$ values in rats and/or mice from the CPDB. Twenty-one chemicals have been found by the International Agency for Research on Cancer (IARC) to have "sufficient" evidence for carcinogenicity in animal experiments and 15 have been found to have "limited" evidence (*1*), as indicated in the table.

When the database contains more than one positive experiment for a chemical, the value reported in Table 1 for each species is the most potent TD$_{50}$ in any experiment, rather than some average of values. To determine how much lower the PERP would be if we were to use an average of TD$_{50}$ values, we compared the most potent value in any experiment to the harmonic mean obtained by using a TD$_{50}$ from each positive experiment in the CPDB. For 83% of the chemicals, the two estimates of potency differ by a factor less than 2, and for only two chemicals did they differ by more than a factor of 3: ethylene oxide (by 4) and vinyl chloride (by 6). Since these differences are small compared with the wide range of potency among different carcinogens, we conclude that overall the values in Table 1 adequately reflect carcinogenic potency in rodents. Our earlier paper (*5*) used the harmonic mean of TD$_{50}$ values in the HERP index.

Seventeen of the substances are carcinogenic in both rats and mice (Table 1), and we calculate the PERP using the more potent TD$_{50}$ value regardless of which species it represents. 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.

Table 1. Carcinogenic potency (TD$_{50}$) in rats and mice of 41 rodent carcinogens regulated by OSHA PELs.[a]

	Most potent TD$_{50}$, mg/kg/day	
Chemical	Rats	Mice
** Acrylonitrile	5.31	NT
* Aldrin	?	0.741
* Aniline[b]	88.0	—
** *o*-Anisidine[b]	27.8	935
* Benzene	51.1	15.1
* *bis*-2-Chloroethylether	NT	8.19
** 1,3-Butadiene	NT	65.9
Carbaryl	14.1	—
** Carbon tetrachloride	390	127
* Chlordane	—	2.15
** Chloroform	119	48.0
** DBCP	0.106	1.28
** DDT	57.2	4.55
* Dieldrin	?	0.547
** 1,1-Dimethylhydrazine	NT	2.09
** Dioxane	126	594
** Ethylene dibromide	1.10	2.34
** Ethylene dichloride	5.49	61.2
* Ethylene imine	NT	0.283
** Ethylene oxide	7.43	NT
** Di(2-ethylhexyl)phthalate	2280	3400
** Formaldehyde	0.798	43.9
* Heptachlor	—	1.09
* Hexachloroethane	—	359
** Hydrazine	NT	2.20
* Hydrogen peroxide (90%)	NT	9010
* Lindane	—	15.4
** Methylene chloride	598	817
Methylhydrazine	—	4.58
p-Nitrochlorobenzene	—	430
** PCB-54%	—	9.58
Phenylhydrazine[b]	NT	70.6
** Propylene oxide	35.1	732
Selenium compounds[c]	6.14	46.8
* 1,1,2,2-Tetrachloroethane	—	35.4
* Tetrachloroethylene	90.8	75.6
** *o*-Toluidine[b]	23.3	646
** Toxaphene	—	4.08
* 1,1,2-Trichloroethane	—	47.6
* Trichloroethylene	—	421
** Vinyl chloride	3.69	10.6

[a] Symbols: NT, no test in CPDB; ?, in one report, author evaluated the chemical as carcinogenic to rats without identifying a target site. For the category "all tumor-bearing animals" there was no dose-related effect ($p = 1$); —, no experiment in CPDB was evaluated by the published author as evidence for carcinogenicity; **, IARC evaluation is sufficient evidence of carcinogenicity in experimental animals; *, IARC evaluation is limited evidence of carcinogenicity.

[b] The TD$_{50}$ is for the hydrochloride salt.

[c] The TD$_{50}$ is for selenium sulfide.

Results

Ranking Potential Carcinogenic Hazards to Workers

For each chemical, the PERP value in Table 2 expresses the permitted milligram per kilogram daily dose to workers as a percentage of the rodent TD$_{50}$. The table presents the PERP values in descending order for the 41 rodent carcinogens in the CPDB that have OSHA PELs. In Figure 1 the compounds are ordered alphabetically, and PERP values are presented graphically. The PERP ranges more than 100.000-fold for exposures to different substances at the current PEL. For 12 of the chemicals the permitted exposures are more than 10% of the rodent TD$_{50}$, for 18 they are between 1% and 10% of the rodent TD$_{50}$, and for 11 they are less than 1%. Three chemicals have PELs greater than the TD$_{50}$, i.e., PERP greater than 100.

The 12 substances with PERP greater than 10 are ethylene dibromide (PERP 749), ethylene dichloride (199), 1,3-butadiene (179), *bis*-2-chloroethylether (59), tetrachloroethylene (perchloroethylene) (48), propylene oxide (37), chloroform (27), formaldehyde (25), ethylene imine (19), methylene chloride (16), dioxane (15), and

Table 2. Forty-one rodent carcinogens regulated by OSHA PELs ranked by PERP: carcinogenic potency in rodents (TD_{50}), OSHA PEL, and MOD.

Chemical	PERP $MOD/TD_{50} \times 100$[a]	OSHA PEL ppm	 mg/m^3	TD_{50}, mg/kg[b]	MOD, mg/kg[c]
Ethylene dibromide (s)[d]	749	20	153	1.10	8.24
Ethylene dichloride	199	50	202	5.49	10.9
1,3-Butadiene	179	1000	2200	65.9	118
bis-2-Chloroethylether (s)	59.1	15	90	8.19	4.84
Tetrachloroethylene	48.3	100	678	75.6	36.5
Propylene oxide	36.8	100	240	35.1	12.9
Chloroform	26.9	50	240	48.0	12.9
Formaldehyde	24.9	3	3.7	0.798	0.199
Ethylene imine (s)	19.1	0.5	1	0.283	0.054
Methylene chloride	15.6	500	1737	598	93.5
Dioxane (s)	15.4	100	360	126	19.4
Benzene (s)	11.4	10	32	15.1	1.72
Trichloroethylene	6.91	100	540	421	29.1
1,1,2,2-Tetrachloroethane (s)	5.31	5	35	35.4	1.88
1,1,2-Trichloroethane (s)	5.08	10	45	47.6	2.42
o-Toluidine (s)	5.06	5	22	23.3	1.18
Acrylonitrile (s)	4.56	2	4.5	5.31	0.242
Vinyl chloride (s)	3.79	1	2.6	3.69	0.140
Hydrazine (s)	3.18	1	1.3	2.20	0.070
Carbon tetrachloride (s)	2.67	10	63	127	3.39
1,1-Dimethylhydrazine (s)	2.58	0.5	1	2.09	0.054
Heptachlor (s)	2.48		0.5	1.09	0.027
Dieldrin (s)	2.37		0.25	0.547	0.013
Carbaryl	1.91		5	14.1	0.269
Aldrin (s)	1.75		0.25	0.741	0.013
Phenylhydrazine (s)	1.67	5	22	70.6	1.18
Ethylene oxide	1.31	1	1.8	7.43	0.097
Chlordane (s)	1.26		0.5	2.15	0.027
DDT (s)	1.19		1	4.55	0.054
Aniline (s)	1.16	5	19	88.0	1.02
Toxaphene (s)	0.662		0.5	4.08	0.027
DBCP	0.509	0.001	0.01	0.106	0.001
Methylhydrazine (s)	0.415	0.2	0.35	4.58	0.019
PCB-54% (s)	0.282		0.5	9.58	0.027
Selenium compounds	0.179		0.2	6.14	0.011
Lindane (s)	0.175		0.5	15.4	0.027
Hexachloroethane (s)	0.150	1	10	359	0.538
o-Anisidine (s)	0.097		0.5	27.8	0.027
p-Nitrochlorobenzene (s)	0.013		1	430	0.054
Di(2-ethylhexyl)phthalate	0.012		5	2280	0.269
Hydrogen peroxide, 90%	0.001	1	1.4	9010	0.075

[a] PERP, Permitted Exposure/Rodent Potency.

[b] Most potent TD_{50}, calculated to three significant figures.

[c] MOD, maximum occupational dose.

[d] (s): OSHA indicates that these substances may be absorbed into the bloodstream through the skin, mucous membranes and/or eyes, as well as by inhalation. For *bis*-2-chloroethylether, chloroform and methylhydrazine, OSHA PELs are ceiling values.

benzene (11). For many of these substances, skin absorption may occur at the PEL in addition to inhalation (Table 2), and this is not reflected in the PERP.

Because estimates of the PERP span several orders of magnitude, whereas the TD_{50} values estimated from various experiments of the same compound are generally within one order of magnitude, we would expect little difference in the ranking of chemicals by PERP values if we had used instead some average of the various TD_{50}s for a given chemical instead of the most potent TD_{50} value. (We calculated the Spearman rank correlation coefficient between PERPs obtained from the most potent TD_{50} value and PERPs obtained from the harmonic mean of TD_{50}s from all positive experiments in a species. The correlation is 0.98, indicating that the ranking is not importantly dependent upon the choice of the most potent TD_{50}.)

Bioassay results indicate that these 12 chemicals are high on other measures of hazard as well (*14*). For example, among the 9 of these chemicals that have been tested in both rats and mice, all 9 are positive in both species. By comparison, among the 226 carcinogens in the entire CPDB that were tested in two species, only 130 (58%) are positive in both (chi square, $p = 0.01$). In addition, a higher proportion of these chemicals induced tumors at multiple target sites than was the case in the entire CPDB, although the difference is not statistically significant. All of these 12 top-ranked substances have been tested in mice, and 7 (58%) induced tumors at multiple sites in mice; 9 have been tested in

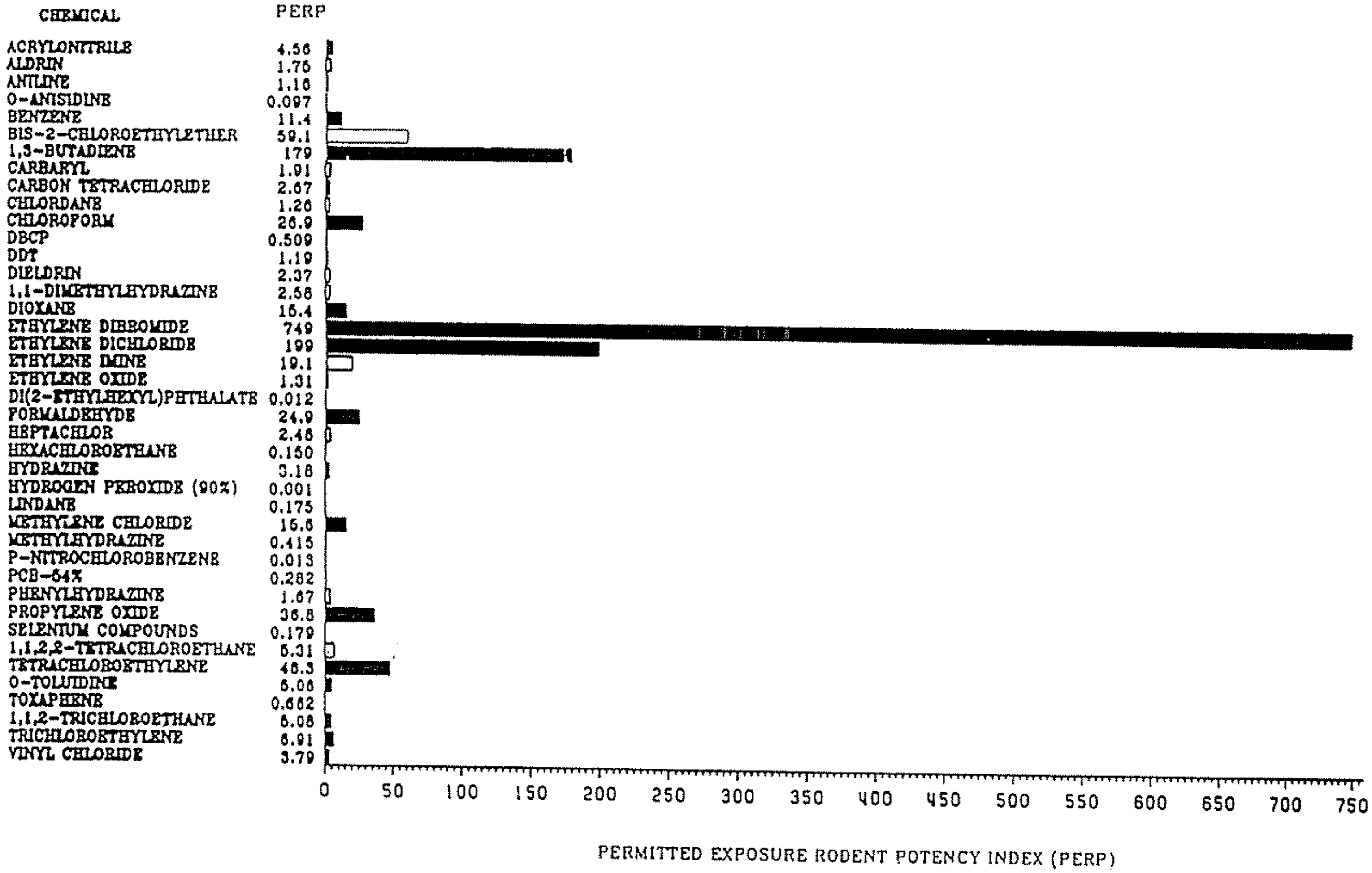

FIGURE 1. Comparison of permitted worker exposure levels to the dose that induces tumors in 50% of rodents (TD_{50}). Shaded bars indicate that some workers are potentially exposed full-time to the chemical. White bars indicate that no workers are potentially exposed full-time.

rats, and 6 (67%) induced tumors at multiple sites. This compares with 42% for mice and 47% for rats in the CPDB. All 12 chemicals have been evaluated by IARC as having evidence (either sufficient or limited) of carcinogenicity in laboratory animals.

Consideration of the Route of Administration in the Rodent Test

Worker exposure to chemicals for which PELs have been defined is primarily by inhalation, whereas exposure to test animals is usually by diet or gavage and only infrequently by inhalation. This difference raises the question whether inhalation bioassays should be used for comparisons to human exposures whenever they are available, regardless of the results of bioassays by other routes. Ten of the 41 chemicals with PELs have been tested in rodents by inhalation as well as by another route (gavage in 9 cases, drinking water in 1), and in Table 3 we compare the results. There is good concordance in positivity between routes among the 10 chemicals: all but one (ethylene dichloride) have at least one positive test by both routes. This concordance is similar for each species separately, whenever two routes have been tested. Benzene is an exception, causing tumors by gavage in both species but by inhalation only in mice. [A discussion of the discordance by route for ethylene dichloride can be found in (*15*).]

Although the number of chemicals is small, a comparison of carcinogenic potency values suggests that there are no consistent or large differences by route of administration. For about half the chemicals the more potent route is inhalation, and for the other half it is gavage. In addition, these differences are within an order of magnitude, with the exception of benzene. Such differences must be viewed within the context of the usual variation in TD_{50} that we have found in other analyses of the CPDB. Only five of the route comparisons in Table 3 involve experiments using the same strain within a species, and all of these are concordant in positivity. For these cases we have also compared potency values for males and females separately, and found that the variation in potency is comparable with the variation obtained in our large database for experiments using the same route, species, strain, and sex (*16*). Therefore, although the number of cases is small, route of administration in the rodent bioassay does not appear to have a large or consistent effect on positivity or potency, and the use of results from tests using routes other than inhalation is reasonable. We note that of the nine rodent carcinogens positive by two routes of administration, five have a common target site by the two routes.

Table 3. Comparison of inhalation and oral routes of administration by species: positivity and most potent TD_{50}.[a]

	Rats		Mice	
Chemicals[b]	Inhalation	Gavage	Inhalation	Gavage
Acrylonitrile	32.4*	5.31*[c]	NT	NT
Benzene	—	51.1	441	15.1
DBCP	0.106	0.855	1.28*	4.29*
Ethylene dibromide	1.10	1.26	9.60*	2.34*
Ethylene dichloride	—	5.49	—	61.2
Ethylene oxide	30.8	7.43	NT	NT
Propylene oxide	35.1	39.5	732	NT
Tetrachloroethylene	90.8	I	190*	75.6*
Trichloroethylene	—	—	3380	421
Vinyl chloride	3.69*	14.2*	10.6	NT

[a] Symbols: *, TD_{50} values are estimated from experiments by different routes using the same species and strain of test animal; NT, no test in CPDB; —, no experiment in CPDB was evaluated by the published author as evidence of carcinogenicity in experimental animals; I, The National Cancer Institute evaluated its experiment as inadequate.

[b] The large Carcinogenic Potency Database contains data for two additional chemicals that were tested by inhalation and an oral route: Dichlorvos was not positive by either inhalation or diet; vinylidine chloride was negative in rats by inhalation, water, and diet; it was negative in mice by diet and positive by inhalation.

[c] Route of administration by water.

Consideration of the Number of Exposed Workers

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 alteration in markets, production techniques, and product substitution. Crude estimates of the numbers of workers who might by exposed to various compounds are available from the National Occupational Hazard Survey (NOHS) of 1972–1974, updated during 1981–1983. The survey is representative of 38 million workers, but excludes such industries as mining and agriculture (and the military). Estimates (which are subject both to systematic errors and to sizable statistical errors) are included for full-time exposure, i.e., an average of more than 4 hr per working day; and for part-time exposure, i.e., an average of more than 27 min per working week.

In Table 4 we report the updated exposure estimates for the 39 of the 41 carcinogens with PELs that were identified in the NOHS survey; the chemicals are ranked by PERP value. There are strikingly fewer workers exposed full-time than part-time, but this is less true for many of the top 12 chemicals than for the other 29. In Figure 1, the PERP values for those chemicals to which no workers are exposed full-time are indicated with unshaded bars.

To include the number of workers in our prioritization, we considered multiplying the PERP by the number potentially exposed full-time or part-time. This method had, however, little effect on which chemicals would be ranked as appearing most important: of the top 12 chemicals, all except *bis*-2-chloroethylether and ethylene imine (which have no full-time exposures and few part-time exposures) remain ranked among the highest in possible hazard. Two additional compounds, trichloroethylene and carbon tetrachloride, to which

Table 4. Estimated number of workers potentially exposed full-time and/or part-time to rodent carcinogens with OSHA PELs ranked by PERP.

Chemicals to which workers are exposed[a]	PERP	Full-time and part-time	Part-time	Full-time
Ethylene dibromide	749	108,878	107,939	1,234
Ethylene dichloride	199	1,351,190	1,341,952	23,834
1,3-Butadiene	179	69,555	57,169	14,812
bis-2-Chloroethylether	59.1	42	42	
Tetrachloroethvlene	48.3	1,597,072	1,569,580	44,350
Propylene oxide	36.8	268,433	268,056	1,047
Chloroform	26.9	215,000	211,170	14,757
Formaldehyde	24.9	1,420,588	1.387,416	51,436
Ethylene imine	19.1	1,712	1,712	
Methylene chloride	15.6	2,175,499	2,148,454	42,207
Dioxane	15.4	307,706	303,016	5,722
Benzene	11.4	1,495,706	1,473,236	40,844
Trichloroethylene	6.91	2,782,797	2.726,858	86,587
1,1,2,2-Tetrachloroethane	5.31	7,201	7,201	
1,1,2-Trichloroethane	5.08	72,191	72,196	202
o-Toluidine	5.06	13,058	13,053	143
Acrylonitrile	4.56	374.345	350.239	25,245
Vinyl chloride	3.79	239.375	232,827	8,186
Hydrazine	3.18	11.187	10.528	1,156
Carbon tetrachloride	2.67	1.380.232	1,371.253	21,457
1,1-Dimethylhydrazine	2.58	25	25	
Heptachlor	2.48	566,911	565.780	
Dieldrin	2.37	5,159	5,159	
Carbaryl	1.91	14,117	14,117	
Aldrin	1.75	5,239	5.236	
Phenylhydrazine	1.67	1,120	1,120	
Ethylene oxide	1.31	144,152	142.383	2,767
Chlordane	1.26	21,171	21,171	ND
DDT	1.19	ND[b]	ND	
Aniline	1.16	852.757	847,831	14,941
Toxaphene	0.662	203	203	
DBCP	0.509	9,681	9,597	84
Methylhydrazine	0.415	ND	ND	ND
PCB-54%	0.282	6,540	6.540	
Selenium compounds	0.179	108,695	106,543	3,997
Lindane	0.175	173,240	171,875	1,663
Hexachloroethane	0.150	1,489	1,489	
o-Anisidine	0.097	83	83	
p-Nitrochlorobenzene	0.013	17,725	17,638	84
Di(2-ethylhexyl)phthalate	0.012	612,106	588,488	33,855
Hydrogen peroxide, 90%	0.001	467,089	465,603	11,256

[a] Data on number of exposed workers is derived from National Occupational Hazard Survey (NOHS) of 1972–74. (National Institute of Occupational Safety and Health. personal communication, D. Sundin, 1986.) Exposures include: actual. surveyor observed the agent; tradename, surveyor observed a tradename product known to contain agent; and generic, surveyor observed a product in some type of general use which led NIOSH to suspect that the agent may be in that product. Number of potentially exposed full-time and part-time combined may be lower than the sum of part-time and full-time because of NOHS method of estimation based on actual, trade name, and generic exposures. Numbers represent workers potentially exposed to the substance regulated with a PEL, regardless of whether the TD_{50} is for a salt.

[b] ND, no data in NOHS.

many workers are exposed, replaced these 2 in the top 12. (However, we expect that exposures to trichloroethylene have been reduced in recent years due to product substitution.)

Discussion

The PERP may provide a rough correlate of human hazard from exposures to chemicals that are known to cause tumors in laboratory animals. The PERP is not, however, an exact correlate, and although moderate interspecies differences in metabolism might have little effect on the suggested ranking of the top dozen or so chemicals, it is possible that strikingly large differences could have an effect on the ranking. We have used the PEL as a surrogate for the estimates of exposure levels and have shown that the margin of protection offered by current PEL values varies more than 100,000-fold from exposures to different rodent carcinogens. This wide variation occurs partly because PELs are not generally based on rodent carcinogenicity, but rather on consensus standards adopted in the 1970s to protect workers from other health effects.

For some substances, workers are permitted to be exposed to doses that are close to those that produce tumors in 50% of test animals. The PERP values for 12 compounds are greater than 10% of the TD_{50} estimated from an experiment in rats or mice: ethylene dibromide, ethylene dichloride, 1,3-butadiene, [*bis*-2-chloroethylether], tetrachloroethylene, propylene oxide, chloroform, formaldehyde, [ethylene inime], methylene chloride, dioxane, and benzene. These 12 chemicals also score high on other indices of hazard in rodent bioassays and (with the exception of the two in brackets) in a prioritization that also uses the number of exposed workers; indeed, 8 of these compounds are among the top 50 chemicals by volume produced in the U.S. (*17*). For these 12 chemicals that have permissible worker exposure levels so close to the carcinogenic dose in rodents, we are not extrapolating as far to low doses as is usually the case for human exposures. Therefore, assumptions about linearity in the dose response are less important here.

The PERP is calculated as if exposures to a chemical could occur at a reasonably constant annual level for an entire lifetime, but it remains a valid correlate of potential hazard even though workplace exposures rarely last for an entire working life. In addition, the PERP is based on exposures to individual agents. Some workers may be exposed to several carcinogens, and we have little knowledge about the potential interactions among these agents or, perhaps more importantly, between these agents and the major known causes of human cancer, such as tobacco. The potential hazards from individual substances may also depend on further toxicological factors such as mechanism of action, pharmacokinetics, and shape of the dose response, which we have discussed in an earlier paper (*5*).

For some of the chemicals with the highest PERP values, California OSHA has lowered the PEL below that of the U.S. OSHA for ethylene dibromide, methylene chloride, and propylene oxide (*18*), and so in California these would be less extreme than they appear in Figure 1. U.S. OSHA recently lowered the PEL for ethylene oxide by 50-fold, and the new PEL has been used in Figure 1 and Table 2. A PERP for the old PEL would have ranked ethylene oxide fourth among the chemicals in our analysis, while the PERP for the new PEL (1.3) is lower than for most of the other 40 rodent carcinogens. In contrast, the PEL for ethylene dibromide remains much higher than any other agent, for the OSHA proposal (1983) to reduce it from 20 ppm to 0.1 ppm (*19*) has not at present been adopted. For some substances, the numbers of workers exposed have been reduced due to recently curtailed usage, e.g., DDT, DBCP, aldrin, dieldrin, and heptachlor.

The American Conference of Governmental Industrial Hygienists (ACGIH), a nonregulatory group, recommends that exposures to 9 of the 12 top-ranked chemicals be limited to levels lower than designated by the PEL (*20*). Their recommendations, called Threshold Limit Values (TLVs) are three- to fivefold lower for ethylene dichloride, *bis*-2-chloroethylether, tetrachloroethylene, propylene oxide, chloroform, formaldehyde, methylene chloride, and dioxane. The TLV for 1,3-butadiene was recently lowered to a level that is 100-fold lower than the PEL, and actual workplace exposures for butadiene were already below that level. This is not the case for all compounds, however; for some, exposures near to the PEL are common.

We have examined reports of actual concentrations in workroom air for three of the substances that ranked highest by PERP: ethylene dibromide, formaldehyde, and tetrachloroethylene. Exposures to workers vary substantially by job classification, type of plant, and from one particular plant to another. For operators in one ethylene dibromide production plant, average exposures were about one-fifth the PEL (*21*). For machine operators in dry cleaning establishments, average exposures to tetrachloroethylene (perchloroethylene) were also about one-fifth the PEL (*22*). Exposures to formaldehyde were about one-third the PEL for workers in chemical manufacturing plants, plywood production, and wood furniture production. The average for all workers exposed to formaldehyde was about one-fourth the PEL (*23*). In contrast, even for workers with high levels of exposure to 1,3-butadiene, the average exposures were only 1% of the PEL (*24*). These actual exposure estimates indicate that for ethylene dibromide, tetrachloroethylene, and formaldehyde, the PERP values calculated at the PEL are reasonable correlates of the possible hazard to some workers, and the actual exposures are not far from the doses that induce tumors in half of the laboratory animals. That does not necessarily mean, however, that these agents would be the chief priorities for the population, because the intensity of exposure of workers to particular agents may be several orders of magnitude greater than that of the general population.

For example, the actual exposure data for ethylene dibromide, tetrachloroethylene, and formaldehyde illustrate that some workers receive very high levels of these chemicals in comparison to the general population. The daily intake by inhalation for operators in an ethylene dibromide production plant is about 1650 μg/kg/day, while the average American dietary intake of ethylene dibromide from grains and grain products is 0.006μg/kg/day (*25*). Thus, some actual worker exposures are about a quarter of a million times higher than the average population exposures to EDB residues in grain. But, while the OSHA PEL remains high, the EPA banned the use of ethylene dibromide as a grain fumigant. Dry-cleaning operators may actually receive 7300 μg/kg/day of tetrachloroethylene (perchloroethylene). In contrast, people drinking 1 L/day of contaminated Woburn well water would receive only 0.3 μg/kg/day (*26*), which is 20,000 times smaller. Yet, the regulations now being introduced affect water rather than workers. In contrast, for formaldehyde, inhalation exposures from indoor air in homes may be quite high, i.e., 8 μg/kg/day (*27*), which is within an order of magnitude of the 67 μg/kg/day received by workers engaged in formaldehyde production or plywood manufacture.

These comparisons illustrate the potential utility of the PERP as an index to help rank the possible carcinogenic hazards of chemical exposures from a variety of sources. Both the PERP and the numbers of workers exposed are relevant in formulating priorities. We have not made explicit use of any evidence on probable interspecies differences in metabolism because for most of the chemicals studied no reliable such evidence exists. If there are any striking interspecies differences in absorption or metabolic activation, however, these might importantly modify our suggested ranking. The PERP based upon current PELs, combined with the crude estimates of numbers exposed, suggest that it is reasonable to give special consideration to the reduction of allowable worker exposures to ethylene dibromide, ethylene dichloride, 1,3-butadiene, tetrachloroethylene, propylene oxide, chloroform, formaldehyde, methylene chloride, dioxane, and benzene.

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