Ranking Possible Cancer Hazards from Rodent Carcinogens, Using the Human Exposure/Rodent Potency Index (HERP)

Ranking possible carcinogenic hazards from average US exposures to rodent carcinogens

Chemicals that occur naturally are in blue.

Possible hazard HERP (%) (Column 1) is calculated using the information in columns 2, 3, and 4. **Average daily US human exposure** (Column 2) indicates a daily dose for a lifetime for drugs, the air in the workplace or home, food, water, residues etc. **Human dose of rodent carcinogen** (Column 3) is divided by 70 kg to give a mg/kg/day of human exposure. The **Human Exposure/Rodent Potency index (HERP**) in Column 1 expresses this human dose as a percentage of the **TD_{50}** in the rodent (mg/kg/day), which is reported in Column 4. TD_{50} values used in the HERP calculation are averages calculated by taking the harmonic mean of the TD_{50}s of the positive tests in that species from the Carcinogenic Potency Database (CPDB). Average TD_{50} values have been calculated separately for rats and mice, and the more potent value is used for calculating possible hazard. (See **Appendix**, below for more details.) "." = no data in CPDB; a number in parentheses indicates a TD_{50} value not used in the HERP calculation because TD_{50} is less potent than in the other species. (–) = negative in cancer tests; (+) = positive cancer test(s) not suitable for calculating a TD_{50}.

Possible hazard: HERP (%)	Average daily U.S. exposure	Human dose of rodent carcinogen	Potency TD_{50} (mg/kg/day) Rats	Mice	References for Exposure Estimates
140	EDB: production workers (high exposure) (before 1977)	Ethylene dibromide, 150 mg	1.52	(7.45)	(Ott *et al.*, 1980; Ramsey *et al.*, 1978)
17	Clofibrate	Clofibrate, 2 g	169	.	(Havel and Kane, 1982)
12	Phenobarbital, 1 sleeping pill	Phenobarbital, 60 mg	(+)	7.38	(American Medical Association Division of Drugs, 1983)
6.9	Gemfibrozil	Gemfibrozil, 1.2 g	247	(–)	(Arky, 1998)
6.8	Styrene-butadiene rubber industry workers (1978-86)	1,3-Butadiene, 66.0 mg	(261)	13.9	(Matanoski *et al.*, 1993)
6.2	Comfrey-pepsin tablets, 9 daily (no longer recommended)	Comfrey root, 2.7 g	626	.	(Culvenor *et al.*, 1980; Hirono *et al.*, 1978)
6.1	Tetrachloroethylene: dry cleaners with dry-to-dry units (1980-90)	Tetrachloroethylene, 433 mg	101	(126)	(Andrasik and Cloutet, 1990)
4.0	Formaldehyde: production workers (1979)	Formaldehyde, 6.1 mg	2.19	(43.9)	(Siegal *et al.*, 1983)
3.6	Alcoholic beverages, all types	Ethyl alcohol, 22.8 ml	9110	(–)	(Nephew *et al.*, 2000)
2.4	Acrylonitrile: production workers (1960-1986)	Acrylonitrile, 28.4 mg	16.9	.	(Blair *et al.*, 1998)
2.2	Trichloroethylene: vapor degreasing (before 1977)	Trichloroethylene, 1.02 g	668	(1580)	(Page and Arthur, 1978)
1.8	Beer, 229 g	Ethyl alcohol, 11.7 ml	9110	(–)	(Beer Institute, 1999)
1.4	Mobile home air (14 hours/day)	Formaldehyde, 2.2 mg	2.19	(43.9)	(Connor *et al.*, 1985)
1.3	Comfrey-pepsin tablets, 9 daily (no longer recommended)	Symphytine, 1.8 mg	1.91	.	(Culvenor *et al.*, 1980; Hirono *et al.*, 1978)
0.9	Methylene chloride: workers, industry average (1940s-80s)	Methylene chloride, 471 mg	724	(1100)	(CONSAD Research Corporation, 1990)
0.6	Wine, 20.8 g	Ethyl alcohol, 3.67 ml	9110	(–)	(Wine Institute, 2001)
0.5	Dehydroepiandrosterone (DHEA)	DHEA supplement, 25 mg	68.1	.	
0.4	Conventional home air (14 hours/day)	Formaldehyde, 598 µg	2.19	(43.9)	(McCann *et al.*, 1987)

0.2	Fluvastatin	Fluvastatin, 20 mg	125	.	(Arky, 1998)
0.1	*d*-Limonene in food	*d*-Limonene, 15.5 mg	204	(–)	(Stofberg and Grundschober, 1987)
0.1	Coffee, 11.6 g	Caffeic acid, 20.8 mg	297	(4900)	(Clarke and Macrae, 1988; Coffee Research Institute, 2001)
0.06	Lovastatin	Lovastatin, 20 mg	(–)	515	(Arky, 1998)
0.04	Lettuce, 14.9 g	Caffeic acid, 7.90 mg	297	(4900)	(Herrmann, 1978; Technical Assessment Systems, 1989)
0.03	Safrole in spices	Safrole, 1.2 mg	(441)	51.3	(Hall *et al.*, 1989)
0.03	Orange juice, 138 g	*d*-Limonene, 4.28 mg	204	(–)	(Schreier *et al.*, 1979; Technical Assessment Systems, 1989)
0.03	Comfrey herb tea, 1 cup (1.5 g root) (no longer recommended)	Symphytine, 38 µg	1.91	.	(Culvenor *et al.*, 1980)
0.03	Tomato, 88.7 g	Caffeic acid, 5.46 mg	297	(4900)	(Schmidtlein and Herrmann, 1975a; Technical Assessment Systems, 1989)
0.03	Furfural in food	Furfural, 3.64 mg	(683)	197	(Adams *et al.*, 1997)
0.02	Coffee, 11.6 g	Catechol, 1.16 mg	84.7	(244)	(Coffee Research Institute, 2001; Rahn and König, 1978; Tressl *et al.*, 1978)
0.02	Mushroom (*Agaricus bisporus* 2.55 g)	Mixture of hydrazines, etc. (whole mushroom)	(–)	20,300	(Matsumoto *et al.*, 1991; Stofberg and Grundschober, 1987; Toth and Erickson, 1986)
0.02	Apple, 32.0 g	Caffeic acid, 3.40 mg	297	(4900)	(Mosel and Herrmann, 1974; U.S. Environmental Protection Agency. Office of Pesticide Programs, 1989)
0.01	BHA: daily U.S. avg (1975)	BHA, 4.6 mg	606	(5530)	(U.S. Food and Drug Administration, 1991a)
0.01	Beer (before 1979), 229 g	Dimethylnitrosamine, 646 ng	0.0959	(0.189)	(Beer Institute, 1999; Fazio *et al.*, 1980; Preussmann and Eisenbrand, 1984)
0.008	Aflatoxin: daily U.S. avg (1984-89)	Aflatoxin, 18 ng	0.0032	(+)	(U.S. Food and Drug Administration, 1992)
0.007	Celery, 14 g	Caffeic acid, 1.51 mg	297	(4900)	(Smiciklas-Wright *et al.*, 2002; Stöhr and Herrmann, 1975)
0.007	*d*-Limonene	Food additive, 1.01 mg	204	(–)	(Lucas *et al.*, 1999)
0.007	Cinnamon, 21.9 mg	Coumarin, 65.0 µg	13.9	(103)	(Poole and Poole, 1994)
0.006	Coffee, 11.6 g	Furfural, 783 µg	(683)	197	(Coffee Research Institute, 2001; Stofberg and Grundschober, 1987)
0.005	Coffee, 11.6 g	Hydroquinone, 290 µg	82.8	(225)	(Coffee Research Institute, 2001; Heinrich and Baltes, 1987; Tressl *et al.*, 1978)
0.005	Saccharin: daily U.S. avg (1977)	Saccharin, 7 mg	2140	(–)	(National Research Council, 1979)
0.005	Carrot, 12.1 g	Aniline, 624 µg	194 [a]	(–)	(Neurath *et al.*, 1977; Technical Assessment Systems, 1989)
0.004	Bread, 79 g	Furfural, 584 µg	(683)	197	(Smiciklas-Wright *et al.*, 2002; Stofberg and Grundschober, 1987)
0.004	Potato, 54.9 g	Caffeic acid, 867 µg	297	(4900)	(Schmidtlein and Herrmann, 1975b; Technical Assessment Systems, 1989)
0.004	Methyl eugenol in food	Methyl eugenol, 46.2 µg	(19.7)	18.6	(Smith *et al.*, 2002)
0.003	Conventional home air (14 hour/day)	Benzene, 155 µg	(169)	77.5	(McCann *et al.*, 1987)
0.002	Coffee, 11.6 g	4-Methylcatechol, 378 µg	248	.	(Coffee Research Institute, 2001; Heinrich and Baltes, 1987; International Agency for Research on Cancer, 1991)
0.002	Nutmeg, 17.6 mg	*d*-Limonene, 299 µg	204	(–)	(Bejnarowicz and Kirch, 1963; U.S. Department of Agriculture, 2000)
0.002	Carrot, 12.1 g	Caffeic acid, 374 µg	297	(4900)	(Stöhr and Herrmann, 1975; Technical Assessment Systems, 1989)
0.002	Ethylene thiourea: daily U.S. avg (1990)	Ethylene thiourea, 9.51 µg	7.9	(23.5)	(U.S. Environmental Protection Agency, 1991a)
0.002	BHA: daily U.S. avg (1987)	BHA, 700 µg	606	(5530)	(U.S. Food and Drug Administration, 1991a)

0.002	DDT: daily U.S. avg (before 1972 ban) [b]	DDT, 13.8 µg	(84.7)	12.8	(Duggan and Corneliussen, 1972)
0.001	Estragole in spices	Estragole, 54.0 µg	.	51.8	(Smith *et al.*, 2002)
0.001	Pear, 3.7 g	Caffeic acid, 270 µg	297	(4900)	(Mosel and Herrmann, 1974; U.S. Environmental Protection Agency, 1997)
0.001	Toxaphene: daily U.S. avg (before 1982 ban) [c]	Toxaphene, 6.43 µg	(–)	7.51	(Podrebarac, 1984)
0.001	Mushroom (*Agaricus bisporus* 5.34 g)	Glutamyl-*p*-hydrazinobenzoate, 224 µg	.	277	(Chauhan *et al.*, 1985; U.S. Food and Drug Administration, 2002)
0.001	Plum, 1.7 g	Caffeic acid, 235 µg	297	(4900)	(Mosel and Herrmann, 1974; U.S. Environmental Protection Agency, 1997)
0.001	[UDMH: daily U.S. avg (1988)]	[UDMH, 2.82 µg (from Alar)]	(–)	3.96	(U.S. Environmental Protection Agency. Office of Pesticide Programs, 1989)
0.001	Bacon, 19 g	Diethylnitrosamine, 19 ng	0.0266	(+)	(Sen *et al.*, 1979; Smiciklas-Wright *et al.*, 2002)
0.0008	Bacon, 19 g	Dimethylnitrosamine, 57.0 ng	0.0959	(0.189)	(Smiciklas-Wright *et al.*, 2002; Tricker and Preussmann, 1991)
0.0008	DDE: daily U.S. avg (before 1972 ban) [b]	DDE, 6.91 µg	(–)	12.5	(Duggan and Corneliussen, 1972)
0.0007	TCDD: daily U.S. avg (1994)	TCDD, 12.0 pg	0.0000235	(0.000156)	(U.S. Environmental Protection Agency, 2000)
0.0007	Bacon, 19 g	*N*-Nitrosopyrrolidine, 324 ng	(0.799)	0.679	(Stofberg and Grundschober, 1987; Tricker and Preussmann, 1991)
0.0006	Methyl eugenol	Food additive, 7.7 µg	(19.7)	18.6	(Smith *et al.*, 2002)
0.0004	EDB: Daily U.S. avg (before 1984 ban) [b]	EDB, 420 ng	1.52	(7.45)	(U.S. Environmental Protection Agency. Office of Pesticide Programs, February 8, 1984 1984 1984 1984)
0.0004	Tap water, 1 liter (1987-92)	Bromodichloromethane, 13 µg	(72.5)	47.7	(American Water Works Association. Government Affairs Office, 1993)
0.0004	Celery, 14 g	8-Methoxypsoralen, 8.56 µg	32.4	(–)	(Beier *et al.*, 1983; Smiciklas-Wright *et al.*, 2002)
0.0003	Mango, 1.0 g	*d*-Limonene, 40.0 µg	204	(–)	(Engel and Tressl, 1983; U.S. Environmental Protection Agency, 1997)
0.0003	Furfural	Food additive, 36.4 µg	(683)	197	(Lucas *et al.*, 1999)
0.0003	Carbaryl: daily U.S. avg (1990)	Carbaryl, 2.6 µg	14.1	(–)	(U.S. Food and Drug Administration, 1991b)
0.0003	Mustard, 18.9 mg	Allyl isothiocyanate, 17.4 µg	96	(–)	(Krul *et al.*, 2002; Lucas *et al.*, 1999; Tsao *et al.*, 2002)
0.0002	Beer (1994-95), 229 g	Dimethylnitrosamine, 16 ng	0.0959	(0.189)	(Beer Institute, 1999; Glória *et al.*, 1997)
0.0002	Mushroom (*Agaricus bisporus*, 5.34 g)	*p*-Hydrazinobenzoate, 58.6 µg	.	454 [a]	(Chauhan *et al.*, 1985; U.S. Food and Drug Administration, 2002)
0.0002	Estragole	Food additive, 5.79 µg	.	51.8	(Lucas *et al.*, 1999)
0.0002	Allyl isothiocyanate	Food additive, 10.5 µg	96	(–)	(Lucas *et al.*, 1999)
0.0002	Hamburger, pan fried, 85 g	PhIP, 176 ng	1.64 [a]	(28.6 [a])	(Knize *et al.*, 1994; Technical Assessment Systems, 1989)
0.0001	Toxaphene: daily U.S. avg (1990) [b]	Toxaphene, 595 ng	(–)	7.51	(U.S. Food and Drug Administration, 1991b)
0.00008	PCBs: daily U.S. avg (1984-86)	PCBs, 98 ng	1.74	(9.58)	(Gunderson, 1995)
0.00008	Toast, 79 g	Urethane, 948 ng	(41.3)	16.9	(Canas *et al.*, 1989; Smiciklas-Wright *et al.*, 2002)
0.00008	DDE/DDT: daily U.S. avg (1990) [b]	DDE, 659 ng	(–)	12.5	(U.S. Food and Drug Administration, 1991b)
0.00007	Beer, 229 g	Furfural, 9.50 µg	(683)	197	(Beer Institute, 1999; Lau and Lindsay, 1972; Tressl, 1976; Wheeler *et al.*, 1971)
0.00006	Parsnip, 48.8 mg	8-Methoxypsoralen, 1.42 µg	32.4	(–)	(Ivie *et al.*, 1981; U.S. Environmental Protection Agency,

					1997)
0.00004	Parsley, fresh, 257 mg	8-Methoxypsoralen, 928 ng	32.4	(–)	(Chaudhary *et al.*, 1986; U.S. Environmental Protection Agency, 1997)
0.00003	Hamburger, pan fried, 85 g	MeIQx, 38.1 ng	1.66	(24.3)	(Knize *et al.*, 1994; Technical Assessment Systems, 1989)
0.00002	Dicofol: daily U.S. avg (1990)	Dicofol, 544 ng	(–)	32.9	(U.S. Food and Drug Administration, 1991b)
0.00001	Hamburger, pan fried, 85 g	IQ, 6.38 ng	0.921 [a]	(19.6)	(Knize *et al.*, 1994; Technical Assessment Systems, 1989)
0.000009	Beer, 229 g	Urethane, 102 ng	(41.3)	16.9	(Beer Institute, 1999; Canas *et al.*, 1989)
0.000005	Hexachlorobenzene: daily U.S. avg (1990)	Hexachlorobenzene, 14 ng	3.86	(65.1)	(U.S. Food and Drug Administration, 1991b)
0.000001	Lindane: daily U.S. avg (1990)	Lindane, 32 ng	(–)	30.7	(U.S. Food and Drug Administration, 1991b)
0.0000004	PCNB: daily U.S. avg (1990)	PCNB (Quintozene), 19.2 ng	(–)	71.1	(U.S. Food and Drug Administration, 1991b)
0.0000001	Chlorobenzilate: daily U.S. avg (1989) [b]	Chlorobenzilate, 6.4 ng	(–)	93.9	(U.S. Food and Drug Administration, 1991b)
0.00000008	Captan: daily U.S. avg (1990)	Captan, 115 ng	2080	(2110)	(U.S. Food and Drug Administration, 1991b)
0.00000001	Folpet: daily U.S. avg (1990)	Folpet, 12.8 ng	(–)	1550	(U.S. Food and Drug Administration, 1991b)
<0.00000001	Chlorothalonil: daily U.S. avg (1990)	Chlorothalonil, <6.4 ng	828 [c]	(–)	(U.S. Environmental Protection Agency, 1987; U.S. Food and Drug Administration, 1991b)

[a] TD_{50} harmonic mean was estimated for the base chemical from the hydrochloride salt.
[b] No longer contained in any registered pesticide product (U.S. Environmental Protection Agency, 1998).
[c] Additional data from the EPA that is not in the CPDB were used to calculate this TD_{50} harmonic mean.

One reasonable strategy for setting priorities in cancer prevention is to use a rough index to compare and rank possible carcinogenic hazards from a wide variety of chemical exposures at levels that humans typically receive, and then to focus on those that rank highest (Gold *et al.*, 1999; Gold *et al.*, 1997a; Gold *et al.*, 1992). Ranking is thus a critical first step. Although one cannot say whether the ranked chemical exposures are likely to be of major or minor importance in human cancer, it is not prudent to focus attention on the possible hazards at the bottom of a ranking if, by using the same methodology to identify hazard, there are numerous common human exposures with much greater possible hazards. Research on mechanism of carcinogenesis for a given chemical is needed to interpret the possible human risk.

Our analyses are based on the Human Exposure/Rodent Potency index (HERP) which indicates what percentage of the rodent carcinogenic potency (TD_{50} in mg/kg/day) a person receives from a given average daily exposure over a lifetime (mg/kg/day) (Gold and Zeiger, 1997). The method for calculating the HERP index, including an example, is described in the Appendix at the end of this file, and an example is given. TD_{50} values in our CPDB span a 10 million-fold range across chemicals (Gold *et al.*, 1997c). Human exposures to rodent carcinogens range enormously as well, from historically high workplace exposures in some occupations or pharmaceutical dosages to very low exposures from residues of synthetic chemicals in food or water. Consideration of both these values for a chemical is necessary for ranking possible hazard.

Overall, our HERP ranking shows that synthetic pesticide residues rank low in possible carcinogenic hazard compared to many common exposures. HERP values for some historically high exposures in the workplace and some pharmaceuticals rank high, and there is an enormous background of naturally-occurring rodent carcinogens in average consumption of common foods. Results on this background of natural chemicals cast doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides (Ames *et al.*, 1987; Gold *et al.*, 1994a; Gold *et al.*, 1992). The rank order of possible hazards by HERP is similar to the order that would be based on risk assessment using a linear model.

The ranking of possible hazards (HERP values in %) in the HERP table is for *average* United States exposures to each rodent carcinogen in our Carcinogenic Potency Database (http://potency.berkeley.edu/chemicalsummary.html) for which concentration data and average United States exposure or consumption data were both available, and for which human exposure could be chronic for a lifetime. For pharmaceuticals the doses are recommended doses, and for workplace they are past industry or occupation averages for high-exposure occupations. The 93 exposures in the ranking are ordered by possible carcinogenic hazard (HERP), and natural chemicals in the diet are reported in blue. Two HERP values make convenient reference points for interpreting the HERP table. The median HERP value is 0.002%. A HERP of 0.00001% is approximately equal to a regulatory risk level of 1-in-a-million based on a linear model, i.e. the Virtually Safe Dose (VSD) (Gold *et al.*, 1992). The rank order in the HERP table would be the same for a Margin of Exposure from the TD_{50} because the MOE is inversely related to HERP. The HERP table indicates that if the same methodology is used for both naturally-occurring and synthetic chemicals, without additional data on mechanism for each chemical, most ordinary foods would not pass the default regulatory criteria that have been used for synthetic chemicals. For many natural chemicals the HERP values are in the top half of the HERP table, even though natural chemicals are markedly underrepresented because so few have been tested in rodent bioassays. The ranking of HERP values maximizes possible hazards from synthetic chemicals be-

cause it includes historically high exposure values that are now much lower: for example, exposure to DDT and saccharin in food and to several chemicals in the workplace.

For readers who are interested in the results for particular categories of exposure or particular chemicals, we discuss below several categories of exposure and selected chemicals. We indicate for some chemicals that recent mechanistic data suggests that the rodent results may not be relevant to humans or that possible hazards would be lower if nonlinearity or a threshold in the dose-response were taken into account in risk assessment.

Occupational exposures

Occupational exposures to some chemicals have been high, and many of the single chemical agents or industrial processes evaluated as human carcinogens have been identified by historically high exposures in the workplace (International Agency for Research on Cancer, 1971-2002; Tomatis and Bartsch, 1990). HERP values rank at or near the top of HERP table for highly exposed occupations, mostly from the past: ethylene dibromide, 1,3-butadiene, tetrachloroethylene, formaldehyde, acrylonitrile, trichloroethylene, and methylene chloride. The estimation of average daily exposure in occupational settings is often difficult because workers are often exposed to more than one chemical at a time or for different lengths of time over the course of a worklife. Epidemiological studies are often small and lack information on potentially confounding factors such as smoking and alcohol consumption. The International Agency for Research on Cancer (IARC) has evaluated the evidence in humans as limited for butadiene, trichloroethylene, tetrachloroethylene, and formaldehyde; for ethylene dibromide, acrylonitrile, and methylene chloride the evidence in humans is inadequate (International Agency for Research on Cancer, 1971-2002). Unlike the IARC, the National Toxicology Program (NTP) (U.S. National Toxicology Program, 2000b) considered 1,3-butadiene to be a human carcinogen; the two agencies differed with respect to their evaluation of the strength of evidence for leukemia in butadiene-exposed workers and in whether an increased risk in the styrene-butadiene industry may have been due to exposures other than butadiene (International Agency for Research on Cancer, 1999a; U.S. National Toxicology Program, 2000b). The rodent carcinogens listed in the HERP table as occupational exposures also occur naturally, with the exception of ethylene dibromide; for example, butadiene occurs in forest fires, environmental tobacco smoke, and heated cooking oils (Shields *et al.*, 1995); acrylonitrile occurs in cigarette smoke; formaldehyde is ubiquitous in food, is generated metabolically in animals, and is present in human blood.

The possible hazard estimated for past actual exposure levels of the most heavily exposed EDB workers is the highest in the table (HERP=140%). We testified in 1981 that our calculations showed that the workers were allowed to breathe in a dose higher than the dose that gave half of the test rats cancer, although the level of human exposure may have been somewhat overestimated (California Department of Health Services, 1985). An epidemiologic study of these workers, who inhaled EDB for over a decade, did not show any increase in cancer; however, because of the relatively small numbers of people the study lacked the statistical power to detect a small effect (California Department of Health Services, 1985; Ott *et al.*, 1980; Ramsey *et al.*, 1978). Ethylene dibromide is no longer produced in the U.S., and nearly all of its uses have been discontinued (the primary use was as an antiknock agent in leaded gasoline).

For trichloroethylene (TCE), the HERP is 2.2% for workers who cleaned equipment with TCE prior to 1977 (vapor degreasers). We recently conducted an analysis (Bogen and Gold, 1997) based on the assumption that carcinogenic effects are due to toxic effects from peak doses

to the liver, the target organ for trichloroethylene carcinogenicity in mice. Our estimates indicate that for occupational respiratory exposures, the Permissible Exposure Limit (PEL) for trichloroethylene would produce concentrations of TCE metabolites that are higher than the no observed effect level (NOEL) for liver toxicity in mice. On this basis, the PEL is not expected to be protective. In contrast, the EPA maximum concentration limit (MCL) in drinking water of 5 µg/liter based on a linearized multistage model, is more stringent than our safe dose estimate based on a 1000-fold safety factor, which is 210 µg/liter (Bogen and Gold, 1997).

In earlier papers, Gold et al used PELs of the United States Occupational Safety and Health Administration (OSHA), as surrogates for actual exposures and compared the permitted daily dose-rate for workers with the TD_{50} in rodents (PERP index, Permissible Exposure/Rodent Potency) (Gold *et al.*, 1987; Gold *et al.*, 1994a) For current permitted levels, PERP values for 14 chemicals are greater than 10% indicating that workers are permitted to receive doses that are only 10 times lower than the dose to give tumors to half of laboratory animals. Because workers can be exposed chronically to high doses of chemicals, it is important to have protective exposure limits (Gold *et al.*, 1994a). In recent years the permitted exposures for 1,3-butadiene and methylene chloride have been lowered substantially in the U.S., and the current PERP values are below 1%.

Pharmaceuticals and herbal supplements

Half the drugs in the Physician's Desk Reference (PDR) that have reported cancer test data, are carcinogens in rodent bioassays (Davies and Monro, 1995), as are 44% of new drug submissions to United States Food and Drug Administration (FDA) (Contrera *et al.*, 1997). Most drugs, however, are used for only short periods, and therefore we have not calculated HERP values for them. Pharmaceuticals are evaluated by the FDA using mechanistic data as well as tumor incidence, and taking benefits into account.

The HERP ranking includes pharmaceuticals that can be used chronically; some are high in the HERP ranking. Phenobarbital (HERP =12%) is a sedative and anticonvulsant that has been investigated in humans who took it for decades; there is no convincing evidence that it caused cancer (American Medical Association Division of Drugs, 1983; Freidman and Habel, 1999; McLean *et al.*, 1986). Mechanistic data suggest that the dose-response curve for tumors induced in rodents is nonlinear and perhaps exhibits a threshold. Four cholesterol-lowering drugs have evidence of carcinogenicity in rodent tests; they are not mutagenic or genotoxic, and long-term epidemiological studies and clinical trials have not provided evidence of an association with fatal or non-fatal cancers in humans (Bjerre and LeLorier, 2001; Childs and Girardot, 1992; Havel and Kane, 1982; International Agency for Research on Cancer, 1996; Pfeffer *et al.*, 2002; Reddy and Lalwani, 1983; World Health Organization, 1984). Two of these drugs, clofibrate (HERP = 17%) which was used as a cholesterol lowering agent primarily before the 1970s, and gemfibrozil (HERP = 6.9%) which is currently used, increase liver tumors in rodents by the mechanism of peroxisome proliferation, suggesting that they would not be expected to be carcinogenic in humans (Cattley *et al.*, 1996; Havel and Kane, 1982; Reddy and Lalwani, 1983; World Health Organization, 1984). The two other cholesterol-lowering drugs in the HERP table are statins: fluvastatin (HERP=0.2%) and the widely-used drug, lovastatin (HERP=0.06%). Large clinical trials of statins have shown no carcinogenic effects in humans, although there were limitations in the studies: the follow-up period of 5 years is short for observing carcinogenic effects, and the trials were not designed to measure cancer risk (Bjerre and LeLorier, 2001; Guallar and Goodman, 2001; Pfeffer *et al.*, 2002). A meta-analysis of 5 clinical trials examined

only the combination of all cancers rather than specific types of cancer (Guallar and Goodman, 2001).

Herbal supplements have recently developed into a large market in the United States; they have not been a focus of carcinogenicity testing. The FDA regulatory requirements for safety and efficacy that are applied to pharmaceuticals do not pertain to herbal supplements under the 1994 Dietary Supplement Health and Education Act (DSHEA), and few have been tested for carcinogenicity. The relevant regulatory requirements in Canada are under review, and current regulations treat non-prescription ingredients of botanical origin separately from pharmaceuticals (Health Canada, 1995; Volpe, 1998). Those that are rodent carcinogens tend to rank high in HERP because, like some pharmaceutical drugs, the recommended dose is high relative to the rodent carcinogenic dose. Moreover, under DSHEA the safety criteria that have been used for decades by FDA for food additives that are "Generally Recognized As Safe" (GRAS) are not applicable to dietary supplements (Burdock, 2000) even though supplements are used at higher doses. The NTP is currently testing several medicinal herbs or chemicals that are present in herbs.

Comfrey

Recently the FDA issued a warning about comfrey and asked manufacturers to withdraw their comfrey products after several people became ill from taking comfrey as a supplement or as tea. Comfrey is banned from distribution in Canada (Stickel and Seitz, 2000). Comfrey is a medicinal herb whose roots and leaves have been shown to be carcinogenic in rats. For the dose of 9 daily comfrey-pepsin tablets, formerly recommended on the bottle, HERP=6.2%. Symphytine, a pyrrolizidine-alkaloid which is a natural plant pesticide, is a rodent carcinogen present in comfrey-pepsin tablets and comfrey tea. The HERP value for symphytine is 1.3% in the formerly recommended dosage in comfrey pills and 0.03% in a daily cup of comfrey herb tea. Comfrey pills are no longer widely sold, but are available on the World Wide Web. Comfrey roots and leaves can be bought at health food stores and on the Web and can thus be used for tea, although comfrey is recommended only for topical use in the *PDR for Herbal Medicines* (Gruenwald *et al.*, 1998). Poisoning epidemics by pyrrolizidine alkaloids have occurred in the developing world. In the United States, poisonings, including deaths, have been associated with use of herbal teas containing comfrey (Huxtable, 1995). Several other pyrrolizidine-containing medicinal plants are rodent carcinogens, including coltsfoot, *Senecio longilobus* and *S. nemorensis*, *Petasites japonicus*, and *Farfugium japonicum*. Over 200 pyrrolizidine alkaloids are present in more than 300 plant species. Up to 3% of flowering plant species contain pyrrolizidine alkaloids (Prakash *et al.*, 1999). Several pyrrolizidine alkaloids have been tested chronically in rodent bioassays and are carcinogenic e.g., senkirkine, lasiocarpine, petasitenine and riddelliine (Gold *et al.*, 1997c).

Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) and DHEA sulfate are the major secretion products of adrenal glands in humans and are precursors of androgenic and estrogenic hormones (Oelkers, 1999; van Vollenhoven, 2000). DHEA is manufactured as a dietary supplement, and sold widely for a variety of purposes including the delay of aging. DHEA is a controlled drug in Canada (Health Canada, 2000). In rats, DHEA induces liver tumors (Hayashi *et al.*, 1994; Rao *et al.*, 1992), and the HERP value for the dose on the bottle of one daily capsule containing 25 mg DHEA is 0.5%. Peroxisome proliferation is the mechanism of liver carcinogenesis in rats for DHEA, suggesting that the carcinogenicity may not be relevant to humans (Hayashi *et al.*, 1994). DHEA has also

been shown to inhibit the development of tumors of the rat testis (Rao, 1992) and the rat and mouse mammary gland (McCormick *et al.*, 1996; Schwartz *et al.*, 1981). A recent review of clinical, experimental, and epidemiological studies concluded that late promotion of breast cancer in postmenopausal women may be stimulated by prolonged intake of DHEA (Stoll, 1999); however the evidence for a positive association in postmenopausal women between serum DHEA levels and breast cancer risk is conflicting (Bernstein *et al.*, 1990; Stoll, 1999).

Aristolochic acid

Herbal medicinal products containing aristolochic acid (AA) have induced urinary tract cancer in humans, and the FDA issued warnings in 2000 and 2001 about supplements and traditional medicines that contain aristolochic acid (Schwetz, 2001, http://www.cfsan.fda.gov/%20~dms/ds-bot.html). *Aristolochia* species, which are the source of aristolochic acid, are listed in the Chinese pharmacopoeia (Reid, 1993). AA has recently been evaluated by the World Health Organization as a human carcinogen (International Agency for Research on Cancer, 2002). In a diet clinic in Belgium, aristolochic acid was unintentionally administered to patients in pills which purportedly contained a different plant species (*Stephania tetandra*). Many of the patients who took aristolochic acid developed kidney disease (Chinese-herb nephropathy), and the cumulative dose of aristolochic acid was related to the progression of the disease. Thirty nine patients suffered terminal renal failure, and of these, 18 developed urothelial tract carcinoma (Nortier *et al.*, 2000). The average treatment time in the diet clinic was only 13.3 months. The mutagenicity of aristolochic acid and the carcinogenic effects in rodent bioassays, were demonstrated two decades ago (Mengs, 1982; Mengs, 1988; Robisch *et al.*, 1982). In rats, malignant tumors were induced unusually rapidly (26 weeks) after dosing for 13 weeks. AA is also a potent carcinogen in mice (Mengs, 1988) and rabbits (Cosyns *et al.*, 2001) and forms DNA adducts in humans (Bieler *et al.*, 1997; Schmeiser *et al.*, 1996). In rabbits AA induces acute nephrotoxicity, the same DNA adducts in the kidney as in humans, and induces urothelial tumors (Cosyns *et al.*, 2001). No HERP is reported because the human exposures in the diet clinic were for a short time only.

Natural pesticides

Natural pesticides, because few have been tested, are markedly underrepresented in our HERP analysis. Importantly, for each plant food listed, there are about 50 additional untested natural pesticides. Although about 10,000 natural pesticides and their break-down products occur in the human diet (Ames *et al.*, 1990a), only 72 have been tested adequately in rodent bioassays. Half are carcinogens in these tests as are half of all chemicals tested.

Average exposures in common foods to many natural pesticides that are carcinogenic in rodents rank above or close to the median in the HERP table, ranging up to a HERP of 0.1%. These include caffeic acid (in coffee, lettuce, tomato, apple, potato, celery, carrot, plum and pear); safrole (in spices and formerly in natural root beer before it was banned), allyl isothiocyanate (mustard), *d*-limonene (mango, orange juice, black pepper); coumarin in cinnamon; and hydroquinone, catechol, and 4-methylcatechol in coffee. Some natural pesticides in the commonly eaten mushroom (*Agaricus bisporus*) are rodent carcinogens (glutamyl-*p*-hydrazinobenzoate, *p*-hydrazinobenzoate), and the HERP based on feeding whole mushrooms to mice is 0.02%. For *d*-limonene, no human risk is anticipated because tumors are induced only in male rat kidney tubules with involvement of α_{2u}-globulin nephrotoxicity, which does not appear to be

relevant for humans (Hard and Whysner, 1994; International Agency for Research on Cancer, 1993; Rice *et al.*, 1999; U.S. Environmental Protection Agency, 1991b).

Synthetic pesticides

Synthetic pesticides currently in use that are rodent carcinogens in the CPDB and that are quantitatively detected as residues in food by the FDA Total Diet Study (TDS), are all included in the HERP table. Several are at the very bottom of the ranking; however, HERP values are about at the median for 3 exposures prior to their discontinuance or reduction in use: ethylene thiourea (ETU) in 1990, toxaphene before its cancellation in the United States in 1982, and DDT before its ban in the United States in 1972. These 3 synthetic pesticides rank below the HERP values for many naturally occurring chemicals that are common in the diet. The values in the HERP table are for residue intake by females 65 and older, since they consume higher amounts of fruits and vegetables than other adult groups, thus maximizing the exposure estimate to pesticide residues. We note that for pesticide residues in the TDS, the consumption estimates for children (mg/kg/day in 1986-1991) are within a factor of 3 of the adult consumption (mg/kg/day), greater in adults for some pesticides and greater in children for others (U.S. Food and Drug Administration, 1993b).

DDT and similar early pesticides have been a concern because of their unusual lipophilicity and persistence; however, natural pesticides can also bioaccumulate. There is no convincing epidemiological evidence of a carcinogenic hazard of DDT to humans (Agency for Toxic Substances and Disease Registry, 2002; Key and Reeves, 1994). In a recently completed 24-year study in which DDT was fed to rhesus and cynomolgus monkeys for 11 years, DDT was not evaluated as carcinogenic (Takayama *et al.*, 1999; Thorgeirsson *et al.*, 1994) despite doses that were toxic to both liver and central nervous system. However, the experimental protocol used few animals, and dosing was discontinued after 11 years, which may have reduced the sensitivity of the study (Gold *et al.*, 1999).

Current United States exposure to DDT and its metabolites is in foods of animal origin, and the HERP value is low, 0.00008%. DDT is often viewed as the typically dangerous synthetic pesticide because it concentrates in adipose tissue and persists for years. DDT was the first synthetic pesticide; it eradicated malaria from many parts of the world, including the United States, and was effective against many vectors of disease such as mosquitoes, tsetse flies, lice, ticks and fleas. DDT prevented many millions of deaths from malaria (Jukes, 1974). It was also lethal to many crop pests, and significantly increased the supply and lowered the cost of fresh, nutritious foods, thus making them accessible to more people. There is no convincing epidemiological evidence, nor is there much toxicological plausibility, that the levels of DDT normally found in the environment or in human tissues are likely to be a significant contributor to human cancer (Laden *et al.*, 2001). A recent study of breast cancer on Long Island found no association between breast cancer and blood levels of DDT, DDE, dieldrin or chlordane (Gammon *et al.*, 2002).

DDT is unusual with respect to bioconcentration, and because of its chlorine substituents it takes longer to degrade in nature than most chemicals; however, these are properties of relatively few synthetic chemicals. In addition, many thousands of chlorinated chemicals are produced in nature (Gribble, 1996). Natural pesticides can also bioconcentrate if they are fat-soluble. Potatoes, for example, naturally contain the fat soluble neurotoxins solanine and chaconine (Ames *et al.*, 1990a; Gold *et al.*, 1997b), which can be detected in the bloodstream of all potato

eaters. High levels of these potato neurotoxins have been shown to cause birth defects in rodents (Ames *et al.*, 1990b).

The HERP value for ethylene thiourea (ETU), a breakdown product of certain fungicides, is the highest among the synthetic pesticide residues (0.002%); it is at the median of the ranking. The HERP value would be about 10 times lower if the potency value of the EPA were used instead of our TD_{50}; EPA combined rodent results from more than one experiment, including one in which ETU was administered *in utero*, and obtained a weaker potency (U.S. Environmental Protection Agency, 1992). (The CPDB does not include *in utero* exposures.) Additionally, EPA has recently discontinued some uses of fungicides for which ETU is a breakdown product, and exposure levels are therefore lower.

In 1984 the EPA banned the agricultural use of ethylene dibromide (EDB) the main fumigant in the U.S., because of the residue levels found in grain, HERP = 0.0004%. This HERP value ranks low, whereas the HERP of 140% for the high exposures to EDB that some workers received in the 1970s, is at the top of the ranking (Gold *et al.*, 1992). Two other pesticides in the HERP table, toxaphene (HERP = 0.001% in 1982 and 0.0001% in 1990) and chlorobenzilate (HERP=0.0000001%), have been cancelled (Ames and Gold, 1991; U.S. Environmental Protection Agency, 1998).

HERP values for other pesticide residues are all below the median of 0.002%. In descending order of HERP these are DDE (before the 1972 ban of DDT), ethylene dibromide, carbaryl, toxaphene (after cancellation), DDE/DDT (after the ban), dicofol, lindane, PCNB, chlorobenzilate, captan, folpet, and chlorothalonil. Some of the lowest HERP values in the HERP table are for the synthetic pesticides, captan, chlorothalonil, and folpet, which were also evaluated in 1987 by the National Research Council (NRC) and were considered by NRC to have a human cancer risk above 10^{-6} (National Research Council, 1987).

Why were the EPA risk estimates reported by NRC so high when the HERP values are so low? We have investigated this disparity in cancer risk estimation for pesticide residues in the diet by examining the two components of risk assessment: carcinogenic potency estimates from rodent bioassays and human exposure estimates (Gold *et al.*, 2001; Gold *et al.*, 1997d). We found that potency estimates based on rodent bioassay data are similar whether calculated, as in the NRC report, as the regulatory q_1^* or as the TD_{50} in the CPDB. In contrast, estimates of dietary exposure to residues of synthetic pesticides vary enormously, depending on whether they are based on the Theoretical Maximum Residue Contribution (TMRC) calculated by the EPA vs. the average dietary residues measured by the FDA in the Total Diet Study (TDS). The EPA's TMRC is the theoretical maximum human exposure anticipated under the most severe field application conditions, which is often a large overestimate compared to the measured residues. For several pesticides, the NRC risk estimate was greater than one in a million whereas the FDA did not detect any residues at all in the TDS even though the TDS measures residues as low as 1 ppb in the diet (Gold *et al.*, 1997d).

In the 1980s enormous attention was given in the media to Alar, a chemical used to regulate the growth of apples while on the tree (not a pesticide). UDMH, a rodent carcinogen, is the breakdown product of Alar in apples, applesauce, and apple juice (Ames and Gold, 1989). The HERP value in the average total diet before use of Alar was discontinued, was 0.001%, just below the median of the HERP table. Many natural dietary chemicals that are rodent carcinogens have higher HERP values, e.g. caffeic acid in lettuce, tomato, apple, and celery; safrole in spices, and catechol in coffee. Apple juice contains 353 natural volatile chemicals (Nijssen *et*

al., 1996) of which only 12 have been tested for carcinogenicity in the CPDB; 9 of these have been found to be carcinogenic.

Cooking and preparation of food

Cooking and preparation of food, e.g. fermentation, also produce chemicals that are rodent carcinogens. Alcoholic beverages cause cancer in humans in the liver, esophagus and oral cavity. Epidemiological studies indicate that all types of alcoholic beverages are associated with increased cancer risk, suggesting that ethyl alcohol itself causes the effect rather than any particular type of beverage. The HERP values in the table for alcohol are high in the ranking: HERP=3.6% for average U.S. consumption of all alcoholic averages combined, 1.8% in beer, and 0.6% in wine.

Cooking food is plausible as a contributor to cancer. A wide variety of chemicals are formed during cooking. Rodent carcinogens formed include furfural and similar furans, nitrosamines, polycyclic hydrocarbons, and heterocyclic amines. Furfural, a chemical formed naturally when sugars are heated, is a widespread constituent of food flavor. The HERP value for naturally-occurring furfural in average consumption of coffee is 0.006% and in white bread is 0.004%.

Recently, an industrial chemical that is also formed in cigarette smoke, was identified as a common constituent in the human diet. Acrylamide is formed when carbohydrate is cooked at high temperatures and is found in common foods; the highest concentrations are in potato chips and French fries (Tareke *et al.*, 2002). Epidemiological studies in workers (Collins *et al.*, 1989; Marsh *et al.*, 1999) and studies of dietary exposure to acrylamide have not shown an association with cancer (Mucci *et al.*, 2003; Pelucchi *et al.*, 2003). Acrylamide is carcinogenic at several target sites in rat bioassays, and the TD_{50} in rats is 8.89 mg/kg/day. No estimates are available for average U.S. consumption; therefore, it is not included in the HERP table. The estimate for average consumption of dietary acrylamide in Sweden is 40 µg/day (Tareke *et al.*, 2002, http://www.slv.se/engdefault.asp), and the HERP value would be 0.01%. This HERP value is similar to other natural constituents of food such as safrole and furfural. Smokers are estimated to take in four times as much acrylamide as nonsmokers in the general population (Schettgen *et al.*, 2003). Acrylamide is genotoxic, and the HERP value is above the median, suggesting that further work is needed to assess its potential hazard to humans, e.g. on formation and fate of acrylamide in food during cooking and processing, on the absorption, metabolism, and disposition in humans of acrylamide from food, on the mode of action in the animal cancer tests, and on the mechanisms of action and dose-response characteristics.

Nitrosamines are formed in food from nitrite or nitrogen oxides (NO_x) and amines in food. Tobacco smoking and smokeless tobacco are a major source of non-occupational exposure to nitrosamines that are rodent carcinogens [*N´*-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-(butanone)] (Hecht and Hoffmann, 1998). Most exposure to nitrosamines in the diet is for chemicals that are not carcinogenic in rodents (Hecht and Hoffmann, 1998; Lijinsky, 1999). The nitrosamines that are carcinogenic are potent carcinogens, and it has been estimated that in several countries humans are exposed to about 0.3–1 µg per day (Tricker and Preussmann, 1991) (National Academy of Sciences, 1981), primarily *N*-nitrosodimethylamine (DMN), *N*-nitrosopyrrolidine (NPYR) and *N*-nitrosopiperidine. The largest exposure was to DMN in beer: concentrations declined more than 30-fold after 1979 (HERP=0.01%) when it was reported that DMN was formed by the direct-fired drying of malt, and the industry modified the process to indirect firing (Glória, Barbour and Scanlan, 1997). By the 1990s, the HERP value for DMN in

beer was 0.0002% (Glória *et al.*, 1997). The HERP values for average consumption of bacon are: DMN=0.0008%, *N*-Nitrosodiethylamine (DEN)=0.001%, and NPYR=0.0007%. DEN induced liver tumors in rhesus and cynomolgus monkeys and tumors of the nasal mucosa in bush babies (Gold *et al.*, 1999; Thorgeirsson *et al.*, 1994). In a study of DMN in rhesus monkeys, no tumors were induced; however the administered doses produced toxic hepatitis, and all animals died early. Thus, the test was not sensitive because the animals may not have lived long enough to develop tumors (Gold *et al.*, 1999; Thorgeirsson *et al.*, 1994).

A variety of mutagenic and carcinogenic heterocyclic amines (HA) are formed when meat, chicken or fish is cooked, particularly when charred. HA are potent mutagens with strong evidence of carcinogenicity in terms of positivity rates, multiplicity of species and target sites; however, concordance in target sites between rats and mice for these HA is generally restricted to the liver (Gold *et al.*, 1994b). Some of the target sites of HA in rats are among the more common cancer sites in humans: colon, prostate and breast. Prostate tumors were induced by PhIP at only the highest dose tested (400 ppm) and not by other HA. Under usual cooking conditions, exposures to HA are in the low ppb range, and the HERP values are low. The values in the HERP table, which rank below the median, are based on hamburger consumption because hamburger has the best available concentration estimates based on various levels of doneness. A recent estimate of HA in the total diet was about 2-fold higher than our consumption estimates for hamburger (Bogen and Keating, 2001; Keating and Bogen, 2001).

For HA in pan fried hamburger, the HERP value is highest for PhIP, 0.0002%, compared to 0.00003% for MeIQx and 0.00001% for IQ. Carcinogenicity of the three HA in the HERP table, IQ, MeIQx, and PhIP, has been investigated in studies in cynomolgus monkeys. IQ rapidly induced a high incidence of hepatocellular carcinoma (Adamson *et al.*, 1994) and the HERP value would be 2.5 times higher than rats. MeIQx, which induced tumors at multiple sites in rats and mice (Gold *et al.*, 1997c), did not induce tumors in monkeys (Ogawa *et al.*, 1999). The PhIP study is still in progress. Metabolism studies indicate the importance of *N*-hydroxylation in the carcinogenic effect of HA in monkeys (Ogawa *et al.*, 1999; Snyderwine *et al.*, 1997).

Food Additives

Food additives that are rodent carcinogens can be either naturally-occurring (e.g., allyl isothiocyanate, furfural) or synthetic (e.g., butylated hydroxyanisole [BHA], saccharin). The highest HERP values for average dietary exposures to synthetic rodent carcinogens in the HERP table are for exposures in the early 1970s to BHA (0.01%) and saccharin in the 1970s (0.005%). Both are nongenotoxic rodent carcinogens for which data on mechanism of carcinogenesis strongly suggest that there would be no risk to humans at the levels found in food.

Naturally-occurring food additives

For five naturally-occurring rodent carcinogens that are also produced commercially and used as food additives, average exposure data were available and they are included in the HERP table. The HERP value for the natural occurrence of each chemical is greater than for use as a commercial additive because the average consumption by naturally-occurring exposures is greater. For furfural (a product of cooking discussed above) the HERP value for intake from the natural occurrence is 0.03% compared to 0.0003% for the additive; for *d*-limonene the natural occurrence (e.g. in citrus and other common foods) HERP is 0.1% compared to 0.007% for the additive; for estragole (in spices) the natural occurrence HERP is 0.001% compared to 0.0002% for the additive; for methyleugenol intake from natural occurrence (in spices) HERP is 0.004%

compared to 0.0006% for the additive. For allyl isothiocyanate the natural occurrence HERP in mustard is 0.0003% compared to 0.0002% for the additive; the natural value only includes mustard (Krul *et al.*, 2002; Tsao *et al.*, 2002), but allyl isothiocyanate is also present in other *Brassica* vegetables, e.g., cabbage, cauliflower, and Brussels sprouts (Nijssen *et al.*, 1996).

Safrole is the principle component of oil of sassafras (up to 90%). It was formerly used as the main flavor ingredient in root beer. It is also present in the oils of basil, nutmeg, and mace (Nijssen *et al.*, 1996). The HERP value for average consumption of naturally-occurring safrole in spices is 0.03%. Safrole and safrole-containing sassafras oils were banned from use as food additives in the U.S. and Canada (Canada Gazette, 1995; U.S. Food and Drug Administration, 1960). Before the 1964 ban in the U.S., a person consuming a glass of sassafras root beer per day for life, would have had a HERP value of 0.2% (Ames *et al.*, 1987). Sassafras root can still be purchased in health food stores and can therefore be used to make tea; the recipe is on the World Wide Web.

Butylated hydroxyanisole (BHA)

BHA is a phenolic antioxidant that is Generally Regarded as Safe (GRAS) by the FDA. By 1987, after BHA was shown to be a rodent carcinogen, its use declined six fold (HERP=0.002%) (U.S. Food and Drug Administration, 1991a); this was due to voluntary replacement by other antioxidants, and to the fact that the use of animal fats and animal oils, in which BHA is primarily used as an antioxidant, has consistently declined in the U.S. The mechanistic results on BHA indicate that malignant tumors were induced only at a dose above the MTD at which cell division was increased in the forestomach, which is the only site of tumorigenesis; the proliferation is only at high doses, and is dependent on continuous dosing until late in the experiment (Clayson *et al.*, 1990). Humans do not have a forestomach. We note that the dose-response for BHA curves sharply upward, but the potency value used in HERP is based on a linear model; if the California EPA potency value were used in HERP instead of TD_{50}, the HERP values for BHA would be 25 times lower (California Environmental Protection Agency. Standards and Criteria Work Group, 1994). A recent epidemiological study in the Netherlands found no association between BHA consumption and stomach cancer in humans (Botterweck *et al.*, 2000).

Saccharin

Saccharin, which has largely been replaced by other sweeteners, has been shown to induce tumors in rodents by a mechanism that is not relevant to humans. Recently, both NTP and IARC re-evaluated the potential cancer risk of saccharin to humans. NTP delisted saccharin in its *Report on Carcinogens* (U.S. National Toxicology Program, 2000b), and IARC downgraded its evaluation to Group 3, “not classifiable as to carcinogenicity to humans” (International Agency for Research on Cancer, 1999b). There is convincing evidence that the induction of bladder tumors in rats by sodium saccharin requires a high dose and is related to development of a calcium phosphate-containing precipitate in the urine (Cohen, 1995), which is not relevant to human dietary exposures. In a 24-year study by National Cancer Institutte, rhesus and cynomolgus monkeys were fed a dose of sodium saccharin that was equivalent to 5 cans of diet soda daily for 11 years (Thorgeirsson *et al.*, 1994). The average daily dose-rate of sodium saccharin administered to monkeys was about 100 times lower than the dose that was carcinogenic to rats (Gold *et al.*, 1999; Gold *et al.*, 1997c). There was no carcinogenic effect in monkeys. There was also no effect on the urine or urothelium, no evidence of increased urothelial-cell proliferation or of formation of solid material in the urine (Takayama *et al.*, 1998). One would not expect to find a carcinogenic effect under the conditions of the monkey study because of the low dose

administered (Gold *et al.*, 1999). Additionally, however, there may be a true species difference because primate urine has a low concentration of protein and is less concentrated (lower osmolality) than rat urine (Takayama *et al.*, 1998). Human urine is similar to monkey urine in this respect (Cohen, 1995).

Mycotoxins

Of the 23 fungal toxins tested for carcinogenicity, 14 are positive (61%). The mutagenic mold toxin, aflatoxin, which is found in moldy peanut and corn, interacts with chronic hepatitis infection in human liver cancer development (Qian *et al.*, 1994), i.e., there is a synergistic effect in the human liver between aflatoxin (genotoxic effect) and the hepatitis B virus (cell division effect) in the induction of liver cancer (Wu-Williams *et al.*, 1992). The HERP value for aflatoxin in the average U.S. diet in the 1980s is 0.008% based on the rodent potency. If the lower human potency value calculated by FDA from epidemiological data were used instead, the HERP would be about 10-fold lower (U.S. Food and Drug Administration, 1993a). Aflatoxin also induced liver tumors in cynomolgus and rhesus monkeys, and the HERP value using TD_{50} in monkeys would be between the value based on results in rodents results in humans. Biomarker measurements of aflatoxin in populations in Africa and China, which have high rates of hepatitis B and C viruses and liver cancer, confirm that those populations are chronically exposed to high levels of aflatoxin (Groopman *et al.*, 1992; Pons, 1979). Liver cancer is unusual in the U.S. and Canada (about 2% of cancer deaths), and is more common among men than women (National Cancer Institute of Canada, 2001; Ries *et al.*, 2000). In the U.S. an increase in liver cancer in the early 1990s was most likely due to the spread of hepatitis virus infection transmitted by transfusions (before screening of blood products for the hepatitis C virus) use of intravenous drugs, and sexual practices ten to 30 years earlier (El-Serag and Mason, 1999; Ince and Wands, 1999). One study estimated that in the U.S., hepatitis viruses can account for half of liver cancer cases among non-Asians and even more among Asians (Yu *et al.*, 1991).

Ochratoxin A, a potent rodent carcinogen (Gold and Zeiger, 1997), has been measured in Europe and Canada in agricultural and meat products. An estimated exposure of 1 ng/kg/day would have a HERP value at about the median of the table (International Life Sciences Institute, February 1996; Kuiper-Goodman and Scott, 1989).

The Persistent Contaminants PCBs and TCDD

Polychlorinated biphenyls (PCBs) and tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin), which have been a concern because of their environmental persistence and carcinogenic potency in rodents, are primarily consumed in foods of animal origin. In the U.S. PCBs are no longer used, but some exposure persists. Consumption in food in the U.S. declined about 20-fold between 1978-1986 (Gartrell *et al.*, 1986; Gunderson, 1995). PCBs, which are not flammable, were formerly used as coolants and lubricants in electrical equipment. The HERP value for PCB for the most recent reporting in the FDA Total Diet Study (1984-86) is 0.00008%, towards the bottom of the ranking, and far below many values for naturally occurring chemicals in common foods. It has been reported that some countries may have higher intakes of PCBs than the U.S. (World Health Organization, 1993). A recent epidemiological study found no association between PCBs and breast cancer, in which PCBs were measured in the blood of women on Long Island (Gammon *et al.*, 2002).

TCDD, the most potent rodent carcinogen, is produced naturally by burning when chloride ion is present, e.g. in forest fires or wood burning in homes. EPA (U.S. Environmental Protection Agency, 2000) estimates that the source of TCDD is primarily from the atmos-

phere — either directly from emissions, e.g. incinerators or burning trash, or indirectly by returning dioxin that is already in the environment to the atmosphere (U.S. Environmental Protection Agency, 1994a; U.S. Environmental Protection Agency, 2001). TCDD bioaccumulates through the food chain because of its lipophilicity, and more than 95% of human intake is from animal fats in the diet (U.S. Environmental Protection Agency, 2001). Dioxin emissions decreased by 75% from 1987-1995, which EPA primarily attributes to reduced medical and municipal incineration emissions. The decline continues (U.S. Environmental Protection Agency, 2001). Estimates of dietary intake can vary because TCDD is often not detected in samples of animal products (about 60% of such samples have no detectable TCDD). Intake estimates are based on an assumption that dioxin is present in food at one-half the limit of detection when no dioxin is detected; the intake estimate would be lower by about half if zero were assumed instead (Schecter *et al.*, 2001).

TCDD, which is not genotoxic (U.S. Environmental Protection Agency, 2000), exerts many of its harmful effects in experimental animals through binding to the Ah receptor (AhR), and does not have effects in the AhR knockout mouse (Birnbaum, 1994; Fernandez-Salguero *et al.*, 1996). A wide variety of natural substances also bind to the Ah receptor (e.g., tryptophan oxidation products), and insofar as they have been examined, they have similar properties to TCDD (Ames *et al.*, 1990b) including inhibition of estrogen-induced effects in rodents (Safe *et al.*, 1998). For example, a variety of flavones and other plant substances in the diet and their metabolites bind to the receptor or are converted in the stomach to chemicals that bind to the Ah receptor e.g. indole-3-carbinol (I3C). I3C is the main metabolite of glucobrassicin, a natural chemical that is present in large amounts in vegetables of the *Brassica* genus, including broccoli, and gives rise to the potent Ah binder, indole carbazole (Bradfield and Bjeldanes, 1987). In comparing possible harmful effects, the binding affinity (greater for TCDD) and amounts in the diet (much greater for dietary compounds) both need to be considered. Some studies provide evidence that I3C enhances carcinogenicity (Dashwood, 1998). Additionally, both I3C and TCDD, when administered to pregnant rats, resulted in reproductive abnormalities in male offspring (Wilker *et al.*, 1996). Currently, I3C is in clinical trials for prevention of breast cancer (Kelloff *et al.*, 1996a; Kelloff *et al.*, 1996b; U.S. National Toxicology Program, 2000a) and is also being tested by NTP (U.S. National Toxicology Program, 2000a). I3C is marketed as a dietary supplement at recommended doses about 30 times higher (Theranaturals, 2000) than present in the average Western diet (U.S. National Toxicology Program, 2000a).

TCDD has received enormous scientific and regulatory attention, and controversy abounds about possible health risks to humans. It has been speculated that nearly 7000 publications have been written and $3-5 billion US has been spent to assess dioxin exposure and health effects to humans and wildlife (Paustenbach, 2002). The U.S. EPA has been estimating dioxin cancer risk since 1991 (U.S. Environmental Protection Agency, 1994a; U.S. Environmental Protection Agency, 1994b; U.S. Environmental Protection Agency, 1995; U.S. Environmental Protection Agency, 2000), and the EPA Science Advisory Board has recently recommended reconsideration of many issues in the EPA assessment. (Paustenbach, 2002; Science Advisory Board, 2001). A committee of the U.S. National Academy of Sciences has been appointed to evaluate the risks from dioxins in the diet.

The IARC evaluated TCDD as a human carcinogen (Group 1) on the basis of overall cancer mortality, even though no specific type of cancer was found to be increased in the epidemiological studies of formerly highly-exposed workers (International Agency for Research on Cancer, 1997). An IARC evaluation based on overall cancer mortality is unprecedented. With

respect to risks, IARC concluded that "Evaluation of the relationship between the magnitude of the exposure in experimental systems and the magnitude of the response (i.e. dose-response relationships) do not permit conclusions to be drawn on the human health risks from background exposures to 2,3,7,8-TCDD." (International Agency for Research on Cancer, 1997, p. 342) The U.S. NTP *Ninth Report on Carcinogens* concurred with IARC in the human carcinogen evaluation (U.S. National Toxicology Program, 2000b; U.S. National Toxicology Program, 2001). The EPA characterized TCDD as a "human carcinogen" but concluded that "there is no clear indication of increased disease in the general population attributable to dioxin-like compounds." (U.S. Environmental Protection Agency, 2000; U.S. Environmental Protection Agency, 2001) One meta-analysis combined the worker studies and found that there was no increasing cancer mortality, overall or for a specific organ, with increasing exposure to TCDD (Starr, 2001). The most recent meta-analysis, using additional follow-up data, found an increased trend in total cancer mortality with increasing TCDD exposure (Crump *et al.*, 2003).

Worldwide, dioxin has primarily been regulated by many groups on the basis of sensitive reproductive and developmental (noncancer) effects in experimental animals, which have a threshold. In contrast the U.S. EPA estimates have used cancer potency factors and a standard linearized risk assessment model. The level of acceptable intake for humans has been judged similarly by many groups: the World Health Organization (Van den Berg *et al.*, 1998), the U.S. Agency for Toxic Substances and Disease Registry (ATSDR) (Agency for Toxic Substances and Disease Registry, 1998), the European Community (European Commission Scientific Committee on Foods, 2001), Health and Welfare Canada (Ministry of Environment and Energy, 1997), and the Japanese Environmental Agency (Japanese Environmental Agency, 1999). The acceptable level set by these groups differs from the U.S. EPA assessments that are based on cancer: the risks levels that are considered to be safe are 1,000 to 10,000 times higher (less stringent) than the levels that the EPA draft documents would consider to be a negligible risks (one in a million cancer risk). All of the agencies, including the U.S. EPA, have based their evaluations on Toxic Equivalency (TEQ), a method which combines exposures to all dioxins and dioxin-like compounds. These agencies also take into consideration the body burden doses of dioxins in humans due to bioaccumulation in lipid. There are uncertainties in these methods, e.g., the TEQ method assumes that the toxic effects of many compounds are additive; however antagonistic effects have been reported among these chemicals in experimental studies (European Commission Scientific Committee on Foods, 2000). The EPA risk estimates thus provide a worst-case risk; actual risks are unlikely to be greater and may be substantially less. The EPA Science Advisory Board (SAB) has recommended reconsideration of many aspects of the EPA cancer risk assessment, including the issue of classification as a known human carcinogen, methods to estimate cancer potency and noncancer effects, uncertainties in estimation of body burden of dioxins, and consideration of dose-response curves other than a linear one (Agency for Toxic Substances and Disease Registry, 1998; Paustenbach, 2002; Science Advisory Board, 2001).

In the HERP table, the value of 0.0003%, which is for average U.S. intake of TCDD, is below the median of the values in the table. If the exposures to all dioxin-like compounds were used for the exposure estimate (TEQ), then the HERP value would be 10 times greater. If the body burden of these combined dioxins were also considered in HERP, as the EPA has done in its risk assessment, then the combined effect of these two factors would make the HERP value 30 times greater, (HERP would be 0.01%, but would not be comparable to the other HERP values in the table because of combining exposures to several chemicals [TEQ] and considering exposure due to bioaccumulation).

In sum, the HERP analysis demonstrates the ubiquitous exposures to rodent carcinogens in everyday life, and documents that possible hazards to the background of naturally-occurring rodent carcinogens occur throughout the ranking. Widespread exposures to naturally-occurring rodent carcinogens cast doubt on the relevance to human cancer of low-level exposures to synthetic rodent carcinogens. In regulatory efforts to prevent human cancer, the evaluation of low-level exposures to synthetic chemicals has had a high priority. Our results indicate, however, that a high percentage of both natural and synthetic chemicals are rodent carcinogens at the MTD, that tumor incidence data from rodent bioassays are not adequate to assess low-dose risk. Moreover, there is an imbalance in testing of synthetic chemicals compared to natural chemicals. There is a background of natural chemicals in the diet that rank at or near the median HERP value, even though so few natural chemicals have been tested in rodent bioassays. In the table, 90% of the HERP values are above the level that has been used for as the virtually safe dose (VSD at one-in-a-million risk) in regulatory policy for rodent carcinogens.

Caution is necessary in drawing conclusions from the occurrence in the diet of natural chemicals that are rodent carcinogens. It is not argued here that these dietary exposures are necessarily of much relevance to human cancer. The major known causes of human cancer are not single chemicals agents like those studied in rodent bioassays.

Appendix: Calculation of HERP

The HERP index takes into account both human exposures and the carcinogenic dose to rodents and compares them. HERP values indicate what percentage of the rodent carcinogenic daily dose (mg/kg/day) for 50% of test animals, a person receives from an average daily exposure (mg/kg/day).

For example, methyleugenol is a chemical that is carcinogenic in rats and mice and has a HERP value of 0.004% for average daily U.S. consumption in food from its natural occurrence, and 0.0006% for average daily U.S. consumption as a synthetic food additive. Below is an example of the HERP calculation for methyleugenol that occurs naturally.

Data are available indicating that average methyleugenol consumption in the U.S. from natural occurrence in food is 46.2 µg/day (Smith *et al.*, 2002). The calculation of HERP from the values in the HERP table for methyleugenol is as follows:

1. Human dose of rodent carcinogen is 46.2 µg/day / 70 kg body weight = 0.66 µg/kg/day (=0.00066 mg/kg/day).
2. Rodent potency: the TD_{50} in mice is 18.6 mg/kg/day
3. Possible hazard (HERP) is: $\frac{0.00066 \quad \text{mg / kg / day} \quad \text{human} \quad \text{exposure}}{18.6 \quad \text{mg / kg/ day} \quad TD_{50}} = 0.00004;$

$0.00004 \times 100 = 0.004\%$

The TD_{50} values used in HERP are averages for rats and mice separately, calculated by taking the harmonic mean of the TD_{50} values from positive experiments in each species. For methyleugenol the TD_{50} in rats is 19.7 mg/kg/day and in mice 18.6 mg/kg/day. Since the mouse TD_{50} is lower (more potent), this value is used in HERP. Experiments in the CPDB that do not show an increase in tumors are ignored in HERP.

The TD_{50} value for rats or mice in the HERP table is a harmonic mean of the most potent TD_{50} values from each positive experiment. The harmonic mean (T_H) is defined as:

$$T_H = \frac{1}{\frac{1}{n}\sum_{i=1}^{n}\frac{1}{T_i}}$$

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