Misconception 7—Synthetic chemicals pose greater carcinogenic hazards than natural chemicals

An analysis of synthetic chemicals against the vast array of natural chemicals shows that synthetic rodent carcinogens are a tiny fraction of the total. In several papers (Ames & al. 1995; Ames & al. 1987; Ames & al. 1990a; Gold & al. 1999; Gold & al. 1992), we have emphasized the importance of setting research and regulatory priorities by gaining a broad perspective about the vast number of chemicals to which humans are exposed. A comparison of potential hazards using a simple index can be helpful in efforts to communicate what might be important factors in cancer prevention and when selecting chemicals for ***chronic bioassay***, mechanistic, or ***epidemiologic*** studies (Ames & al. 1987; Ames & al. 1990b; Gold & al. 1992; Gold & Zeiger 1997). There is a need to identify what might be the important cancer hazards among the ubiquitous exposures to rodent carcinogens in everyday life.

Human Exposure/Rodent Potency index (HERP)—ranking possible human cancer hazards from rodent carcinogens

One reasonable strategy for setting priorities 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 & al. 1999; Gold & al. 1997a; Gold & 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 the mechanism of carcinogenesis for a given chemical is needed to interpret the possible human risk. The ranking of possible hazards is in table 5, pp. 71–85. A description of the fields is on p. 71. 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 dose when exposed over a lifetime (mg/kg/day) (Gold & Zeiger 1997). The method for calculating the HERP index, including an example, is described in the **Appendix** (p. 97). TD_{50} values in our CPDB span a 10 million-fold range across chemicals (Gold & 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 has shown 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. This background of natural chemical results casts doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides (Ames & al. 1987; Gold & al. 1994a; Gold & al.

1992). A committee of the National Research Council recently reached similar conclusions when they compared natural and synthetic chemicals in the diet and called for further research on natural chemicals (National Research Council 1996). The rank order of possible hazards by HERP is similar to the order that would be based on a linear model.

The ranking of possible hazards (HERP values in %) in table 5 (pp. 71–85) is for average exposures in the United States to all rodent carcinogens in the CPDB 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 exposure in the workplace they are past averages for an industry or a high-exposure occupation. The 94 exposures in the ranking (table 5) are ordered by possible carcinogenic hazard (HERP) and natural chemicals in the diet are reported in boldface. Several HERP values make convenient reference points for interpreting table 5. The median HERP value is 0.002% and the background HERP for the average chloroform level in a liter of United States tap water is 0.0008%. Chloroform is formed as a by-product of water chlorination and the HERP value reflects exposure to chloroform from both drinking water and breathing indoor air, for example, when showering (chloroform is volatile.). 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 & al. 1992). The rank order in table 5 would be the same for a Margin of Exposure (MOE) from the TD_{50} because the MOE is inversely related to HERP.

Table 5 indicates that, if the same methodology were used for both naturally occurring and synthetic chemicals, 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 table, even though natural chemicals are markedly

under-represented because so few have been tested in rodent bioassays. The ranking of HERP values maximizes possible hazards from synthetic chemicals because it includes historically high exposure values that are now much lower, for example, exposure to DDT and saccharin as well as to occupational chemicals.

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 the mechanistic data suggesting 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 & Bartsch 1990). HERP values rank at or near the top of table 5 for highly exposed occupational groups, mostly from the past: ethylene dibromide, 1,3-butadiene, tetrachloroethylene, formaldehyde, acrylonitrile, trichloroethylene, and methylene chloride. The assessment of exposure in occupational settings is often difficult because workers are often exposed occupationally to more than one chemical at a time or 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 is in-

adequate (International Agency for Research on Cancer 1971–2002). Unlike the IARC, the National Toxicology Program (US National Toxicology Program 2000b) considered 1,3-butadene to be a human carcinogen; the two agencies differed with respect to their evaluation of the strength of evidence for leukemia in workers exposed to butadiene 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; US 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 & 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 workers most heavily exposed to ethylene dibromide (EDB) is the highest in table 5 (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 tested the study lacked the statistical power to detect a small effect (California Department of Health Services 1985; Ott & al. 1980; Ramsey & al. 1978). Ethylene dibromide is no longer produced in the United States 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 (vapor degreasers) who cleaned equipment with

TCE prior to 1977. We recently conducted an analysis (Bogen & 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's 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 & Gold 1997).

In other analyses, we 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 & al. 1987a; Gold & al. 1994a) For current permitted levels, PERP values for 14 chemicals are greater than 10%. Because workers can be exposed chronically to high doses of chemicals, it is important to have protective exposure limits (Gold & al. 1994a). In recent years, the permitted exposures for 1,3-butadiene and methylene chloride have been lowered substantially in the United States, and the current PERP values are below 1%.

Pharmaceuticals and herbal supplements

In table 4, we reported that half the drugs in the *Physician's Desk Reference* (PDR) that have reported cancer test data are carcinogens in rodent bioassays (Davies & Monro 1995), as are 44% of drug submissions to United States Food and Drug Administration (FDA) (Contrera & al. 1997). Most drugs, however, are used only for 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, primarily because the dose ingested is high. 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 & Habel 1999; McLean & 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 & LeLorier 2001; Childs & Girardot 1992; Havel & Kane 1982; International Agency for Research on Cancer 1996; Pfeffer & al. 2002; Reddy & 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. This suggests that they would not be expected to be carcinogenic in humans (Cattley & al. 1996; Havel & Kane 1982; Reddy & Lalwani 1983; World Health Organization 1984). The two other cholesterol-lowering drugs in table 5 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 & LeLorier 2001; Guallar & Goodman 2001; Pfeffer & al. 2002). A meta-analysis of 5 clinical trials

examined only the combination of all cancers rather than specific types of cancer (Guallar & 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 apply to herbal supplements under the 1994 Dietary Supplement and Health 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

Comfrey is a medicinal herb whose roots and leaves have been shown to be carcinogenic in rats. For the formerly recommended dose of 9 daily comfrey-pepsin tablets, HERP = 6.2%. Symphytine, a pyrrolizidine-alkaloid that 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 pills and 0.03% in 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 for topical use only in the *PDR for Herbal Medicines* (Gruenwald &

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). Recently, the US 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 & Seitz 2000). Several other medicinal plants containing pyrrolizidine 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 & al. 1999). Several pyrrolizidine alkaloids have been tested chronically in rodent bioassays and are carcinogenic (Gold & 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 & al. 1994; Rao & al. 1992) and the HERP value for the recommended human dose 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 & al. 1994). DHEA inhibited the development of tumors of the rat testis (Rao 1992) and the rat and mouse mammary gland (McCormick & al. 1996; Schwartz & 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 & al. 1990; Stoll 1999).

Aristolochic acid

Herbal medicinal products containing aristolochic acid have been found to induce cancer in the urinary tracts of humans and the FDA has issued warnings 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). In a diet clinic in Belgium, aristolochic acid was unintentionally administered to patients in pills which purportedly contained a chemical from a different plant species. Many of the female 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 & al. 2000). The average treatment time in the diet clinic was 13.3 months. The mutagenicity and the carcinogenic effects of aristolochic acid in rodent bioassays, was demonstrated two decades ago (Mengs 1982; Mengs 1988; Robisch & al. 1982). In rats, malignant tumors were induced unusually rapidly. No HERP is reported because the human exposures 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 natu-

ral pesticides and their break-down products occur in the human diet (Ames & al. 1990a), only 72 have been tested adequately in rodent bioassays (table 2). Average exposures to many natural pesticides that are carcinogenic in rodents found in common foods 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 & Whysner 1994; International Agency for Research on Cancer 1993; Rice & al. 1999; US Environmental Protection Agency 1991c).

Synthetic pesticides

Synthetic pesticides currently in use that are rodent carcinogens in the CPDB and that are quantitatively detected by the FDA's Total Diet Study (***TDS***) as residues in food, are all included in Table 5. Several are at the very bottom of the ranking; however, HERP values are about at the median for 3 exposures prior to discontinuance or reduction in use: ethylene thiourea (ETU), 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 HERP values in table 5 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 from 1986 to 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 (US Food and Drug Administration 1993b).

DDT and other pesticides

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 (Key & 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 & al. 1999; Thorgeirsson & al. 1994), despite doses that were toxic to both liver and central nervous system. However, the protocol used few animals and dosing was discontinued after 11 years, which may have reduced the sensitivity of the study (Gold & al. 1999).

Current exposure in the United States 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. DDT was also of low toxicity to humans. 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 & 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 & 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 & al. 1990a; Gold & 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 & 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%), 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}; the EPA combined rodent results from more than one experiment, including one in which ETU was administered in utero, and obtained a weaker potency (US Environmental Protection Agency 1992a). (The CPDB does not include in-utero exposures.) Additionally, the 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 United States, because of the residue levels found in grain. The HERP value of EDB before the ban (HERP = 0.0004%) 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 & al. 1992). Two other pesticides in table 5, toxaphene (HERP = 0.001% in 1982 and 0.0001% in 1990) and chlorobenzilate (HERP=0.0000001%), have been cancelled (Ames & Gold 1991; US Environmental Protection Agency 1998b).

HERP values for other pesticide residues are all below the median of 0.002%. In descending order of HERP values, 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 table 5 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 estimates 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 & al. 2001b; Gold & al. 1997d). We found that potency estimates based on rodent bioassay data are similar whether calculated, as in the NRC report, as the EPA's regulatory q_1^* value 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 or 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's risk estimate was

greater than one in a million whereas the FDA did not detect any residues in the TDS even though the TDS measures residues as low as 1 ppb (Gold & al. 1997d).

In the 1980s, enormous attention was given in the news media to Alar, a chemical used to regulate the growth of apples while on the tree (it is not a pesticide). UDMH, a rodent carcinogen, is the breakdown product of Alar in apples, applesauce, and apple juice (Ames & Gold 1989). The HERP value before use of Alar was discontinued, was 0.001%, just below the median of table 5. Many natural dietary chemicals that are rodent carcinogens have higher HERP values: for example, caffeic acid in lettuce, tomato, apple, and celery; safrole in spices, and catechol in coffee. Apple juice contains 353 natural volatile chemicals (Nijssen & 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

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 table 5 for alcohol are high in the ranking: HERP = 3.6% for average American consumption of all alcoholic averages combined, 1.8% in beer, and 0.6% in wine.

Cooking food is also plausible as a contributor to cancer as a wide variety of chemicals are formed during cooking. Rodent carcinogens formed during cooking 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, of white bread, is 0.004%.

Acrylamide

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; the highest concentrations are in potato chips and French fries (Tareke & al. 2002). Epidemiological studies in workers have not shown an association with cancer (Collins & al. 1989; Marsh & al. 1999). 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 American consumption; therefore, it is not included in the HERP table (table 5). The estimate for average consumption of dietary acrylamide in Sweden is 40 µg/day (Tareke & 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. Acrylamide is genotoxic and the HERP value is above the median. This suggests that further work to assess its potential hazard to humans is needed, including further study of the formation and fate of acrylamide in food during cooking and processing, absorption, metabolism, and disposition in humans of acrylamide from food, of the mode of action in the animal cancer tests, and the mechanisms of action and its dose-response characteristics.

Nitrosamines

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 & Hoffmann 1998). Most exposure to nitrosamines in the diet is for chemicals that are not carcinogenic in rodents (Hecht & Hoffmann 1998; Lijinsky 1999). The nitrosamines that are carcinogenic are potent carcinogens (table 5), and it has been estimated that in several countries humans are exposed to about 0.3–1.0 µg per day (Tricker & 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, & Scanlan 1997). By the 1990s, HERP = 0.0002% (Glória & 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 (Thorgeirsson & 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 & al. 1999; Thorgeirsson & al. 1994).

Heterocyclic amines

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 & 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 (Takahashi & al. 1998). Under usual cooking conditions, exposures to HA are in the low ppb range and the HERP values are low. The values in table 5, which rank below the median, are based on hamburger consumption because hamburger has the best available concentration estimates based on various degrees of doneness. A recent estimate of HA in the total diet was about 2-fold higher than our consumption estimates for hamburger (Bogen & Keating 2001; Keating & 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 & al. 1994) and the HERP value would be 2.5 times higher in monkeys than it would be in rats. MeIQx, which induced tumors at multiple sites in rats and mice (Gold & al. 1997c), did not induce tumors in monkeys (Ogawa & 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 & al. 1999; Snyderwine & 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] and saccharin). The highest HERP values for average dietary exposures to synthetic rodent carcinogens in table 5 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 (See **Saccharin** below).

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 table 5. The HERP value for the natural occurrence of each chemical is greater than for use as a commercial additive because the natural exposures are greater. For furfural (a product of cooking discussed above), the HERP value for the natural occurrence is 0.03% compared to 0.0003% for the additive; for *d*-limonene, the HERP value is 0.1% for the natural occurrence (e.g. in citrus and other common foods) while it is 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, the 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 & al. 2002; Tsao & al. 2002) but allyl isothiocyanate is also present in other *Brassica* vegetables such as cabbage, cauliflower, and Brussels sprouts (Nijssen & al. 1996).

Safrole is the principle component (up to 90%) of oil of sassafras. It was formerly used as the main flavoring ingredient in root beer. It is also present in the oils of basil, nutmeg, and mace (Nijssen & al. 1996). The HERP value for average consumption of naturally occurring safrole in spices is 0.03%. Safrole and safrole-containing sassafras oils have been banned from use as food additives in the United States and Canada (Canada Gazette 1995; US Food and Drug Administration 1960). For a person consuming a glass of sassafras root beer per day for life (before the 1964 ban in the US), the HERP value would have been 0.2% (Ames & 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%) (US 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 oils, in which BHA is primarily used as an antioxidant, has consistently declined in the United States. The mechanistic and carcinogenicity 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 & 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 (which is based on a linearized multistage model) 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 & 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 the NTP and the IARC re-evaluated the potential carcinogenic risk of saccharin to humans. NTP delisted saccharin in its *Report on Carcinogens* (US National Toxicology Program 2000b) and the 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 the US National Cancer Institute (NCI), 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 & al. 1994). The average daily dose-rate of sodium saccharin was about 100 times lower than the dose that was carcinogenic to rats (Gold & al. 1999; Gold & 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 & 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 & al. 1999). However, there may also be a true species difference because primate urine has a low concentration of protein and is less concentrated (lower osmolality) than rat urine (Takayama & 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%) (table 4). The mutagenic mold toxin, aflatoxin, which is found in moldy peanut and corn products, interacts with chronic hepatitis infection in the development of human liver cancer (Qian & al. 1994). 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 & al. 1992). The HERP value for aflatoxin of 0.008% is 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 (US 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 for rodents and 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 & al. 1992; Pons 1979). Liver cancer is unusual in the United States and Canada (about 2% of cancer deaths) and is more common among men than women (National Cancer Institute of Canada 2001; Ries & al. 2000). In the United States, 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 HCV), use of intravenous drugs, and sexual practices 10 to 30 years earlier (El-Serag & Mason 1999; Ince & Wands 1999). In the United States, one study estimated that hepatitis viruses can account for half of liver cancer cases among non-Asians and even more among Asians (Yu & al. 1991).

Ochratoxin A, a potent rodent carcinogen (Gold & 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 table 5 (International Life Sciences Institute February 1996; Kuiper-Goodman & 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 United States, PCBs are no longer used but some exposure persists. Consumption in food in the United States declined about 20-fold between 1978 and 1986 (Gartrell & al. 1986; Gunderson 1995). PCBs, which are

not flammable, were formerly used as coolants and lubricants in electrical equipment. The HERP value for PCB in table 5 for the most recent reporting in the FDA Total Diet Study (1984–1986) 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 United States (World Health Organization 1993). A recent epidemiological study, in which PCBs were measured in the blood of women on Long Island, found no association between PCBs and breast cancer (Gammon & al. 2002).

TCDD, the most potent rodent carcinogen, is produced naturally by burning when chloride ion is present, for example, in forest fires or wood burning in homes. The EPA (US Environmental Protection Agency 2000) estimates that the source of TCDD is primarily from the atmosphere directly from emissions (e.g. incinerators or burning trash), or indirectly by returning dioxin that is already in the environment to the atmosphere (US 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 (US Environmental Protection Agency 2001). Dioxin emissions decreased by 75% from 1987 to 1995, which EPA primarily attributes to reduced medical and municipal incineration emissions. The decline continues (US 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 & al. 2001).

TCDD, which is not genotoxic (US 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 & 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 & al. 1990), including inhibition of estrogen-induced effects in rodents (Safe & 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 & 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 & al. 1996). Currently, I3C is in clinical trials for prevention of breast cancer (Kelloff & al. 1996a; Kelloff & al. 1996b; US National Toxicology Program 2000a) and is also being tested for carcinogenicity by the NTP (US 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 (US 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 US$3–5 billion has been spent to assess dioxin exposure and health effects to

humans and wildlife (Paustenbach 2002, in press). The US EPA has been estimating dioxin cancer risk since 1991 (US Environmental Protection Agency 1994a; US Environmental Protection Agency 1994b; US Environmental Protection Agency 1995; US Environmental Protection Agency 2000), and the EPA Science Advisory Board has recently recommended reconsideration of many issues in the EPA assessment (Paustenbach 2002, in press; Science Advisory Board 2001). A committee of the US 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: 342)

The US NTP *Ninth Report on Carcinogens* concurred with IARC in the human carcinogen evaluation (US National Toxicology Program 2000b; US 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" (US Environmental Protection Agency 2000; US 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 & al. 2003, in press).

Worldwide, dioxin has primarily been regulated by many groups on the basis of sensitive reproductive and developmental (non-cancer) effects in experimental animals, which have a threshold. In contrast, the US EPA estimates have used cancer potency factors and a standard linear risk assessment model. The level of acceptable intake for humans has been judged similarly by many groups: the World Health Organization (Van den Berg & al. 1998), the US 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 US 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 risk (one-in-a-million cancer risk). All of the agencies, including the US EPA, have based their evaluations on Toxic Equivalency (TEQ), a method that 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: for example, 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 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, in press; Science Advisory Board 2001).

In table 5, the HERP value of 0.0003%, which is for average US intake of TCDD, is below the median of the values in table 5. 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, 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 table 5 because of combining exposures to several chemicals [TEQ] and considering exposure due to bioaccumulation).

Summary of HERP analysis

In sum, the HERP analysis in table 5 demonstrates the ubiquitous exposures to rodent carcinogens in everyday life and documents that possible hazards from the background of naturally occurring rodent carcinogens are present 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 and that tumor incidence data from rodent bioassays are not adequate to assess low-

dose risk. Moreover, there is an imbalance in the testing of synthetic chemicals compared to that of 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 table 5, 90% of the HERP values are above the level that has been used for as the virtually safe dose (VSD) 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 chemical agents like those studied in rodent bioassays (**Misconception 2, p. 7**).

Table 5: Ranking possible carcinogenic hazards from average US exposures to rodent carcinogens

Description of columns

The first column, **Possible hazard HERP (%)** is calculated using the information in columns 2, 3, and 4. The second column, **Average daily US (human) exposure**, indicates a daily dose for a lifetime from drugs, the air in the workplace or home, food, water, residues, etc. The third column, **Human dose of rodent carcinogen**, 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, on the right-hand page of table 5. 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***. 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**, p. 97, for more details.)

Table 5(1): Ranking possible carcinogenic hazards

Possible hazard HERP (%)	Average daily US (human) exposure (Chemicals that occur naturally in foods are in bold.)	Human dose of rodent carcinogen
140	EDB: production workers (high exposure) (before 1977)	Ethylene dibromide, 150 mg
17	Clofibrate	Clofibrate, 2 g
12	Phenobarbital, 1 sleeping pill	Phenobarbital, 60 mg
6.9	Gemfibrozil	Gemfibrozil, 1.2 g
6.8	Styrene-butadiene rubber industry workers (1978-86)	1,3-Butadiene, 66.0 mg
6.2	**Comfrey-pepsin tablets, 9 daily (no longer recommended)**	**Comfrey root, 2.7 g**
6.1	Tetrachloroethylene: dry cleaners with dry-to-dry units (1980-90)	Tetrachloroethylene, 433 mg
4.0	Formaldehyde: production workers (1979)	Formaldehyde, 6.1 mg
3.6	**Alcoholic beverages, all types**	**Ethyl alcohol, 22.8 ml**
2.4	Acrylonitrile: production workers (1960-1986)	Acrylonitrile, 28.4 mg
2.2	Trichloroethylene: vapor degreasing (before 1977)	Trichloroethylene, 1.02 g
1.8	**Beer, 229 g**	**Ethyl alcohol, 11.7 ml**
1.4	Mobile home air (14 hours/day)	Formaldehyde, 2.2 mg
1.3	**Comfrey-pepsin tablets, 9 daily (no longer recommended)**	**Symphytine, 1.8 mg**
0.9	Methylene chloride: workers, industry average (1940s-80s)	Methylene chloride, 471 mg

from average US exposures to rodent carcinogens

Potency TD_{50} (mg/kg/day)[a]		Exposure references
Rats	**Mice**	
1.52	(7.45)	Ott & al. 1980; Ramsey & al. 1978
169	•	Havel & Kane 1982
(+)	7.38	American Medical Association Division of Drugs 1983
247	(–)	Arky 1998
(261)	13.9	Matanoski & al. 1993
626	•	Culvenor & al. 1980; Hirono & al. 1978
101	(126)	Andrasik & Cloutet 1990
2.19	(43.9)	Siegal & al. 1983
9110	(–)	Nephew & al. 2000
16.9	•	Blair & al. 1998
668	(1580)	Page & Arthur 1978
9110	(–)	Beer Institute 1999
2.19	(43.9)	Connor & al. 1985
1.91	•	Culvenor & al. 1980; Hirono & al. 1978
724	(1100)	CONSAD Research Corporation 1990

Table 5(2): Ranking possible carcinogenic hazards

Possible hazard HERP (%)	Average daily US (human) exposure (Chemicals that occur naturally in foods are in bold.)	Human dose of rodent carcinogen
0.6	**Wine, 20.8 g**	**Ethyl alcohol, 3.67 ml**
0.5	Dehydroepiandrosterone (DHEA)	DHEA supplement, 25 mg
0.4	Conventional home air (14 hours/day)	Formaldehyde, 598 µg
0.2	Fluvastatin	Fluvastatin, 20 mg
0.1	***d*-Limonene in food**	***d*-Limonene, 15.5 mg**
0.1	**Coffee, 11.6 g**	**Caffeic acid, 20.8 mg**
0.06	Lovastatin	Lovastatin, 20 mg
0.04	**Lettuce, 14.9 g**	**Caffeic acid, 7.90 mg**
0.03	**Safrole in spices**	**Safrole, 1.2 mg**
0.03	**Orange juice, 138 g**	***d*-Limonene, 4.28 mg**
0.03	**Comfrey herb tea, 1 cup (1.5 g root) (no longer recommended)**	**Symphytine, 38 µg**
0.03	**Tomato, 88.7 g**	**Caffeic acid, 5.46 mg**
0.03	**Furfural in food**	**Furfural, 3.64 mg**
0.02	**Coffee, 11.6 g**	**Catechol, 1.16 mg**
0.02	**Mushroom (*Agaricus bisporus* 2.55 g)**	**Mixture of hydrazines, etc. (whole mushroom)**

from average US exposures to rodent carcinogens

Potency TD_{50} (mg/kg/day)[a]		Exposure references
Rats	**Mice**	
9110	(–)	Wine Institute 2001
68.1	•	
2.19	(43.9)	McCann & al. 1987
125	•	Arky 1998
204	(–)	Stofberg & Grundschober 1987
297	(4900)	Clarke & Macrae 1988; Coffee Research Institute 2001
(–)	515	Arky 1998
297	(4900)	Herrmann 1978; Technical Assessment Systems 1989
(441)	51.3	Hall & al. 1989
204	(–)	Schreier & al. 1979; Technical Assessment Systems 1989
1.91	•	Culvenor & al. 1980
297	(4900)	Schmidtlein & Herrmann 1975a; Technical Assessment Systems 1989
(683)	197	Adams & al. 1997
84.7	(244)	Coffee Research Institute 2001; Rahn & König 1978; Tressl & al. 1978
(–)	20,300	Matsumoto & al. 1991; Stofberg & Grundschober 1987; Toth & Erickson 1986

Table 5(3): Ranking possible carcinogenic hazards

Possible hazard HERP (%)	Average daily US (human) exposure	Human dose of rodent carcinogen
	(Chemicals that occur naturally in foods are in bold.)	
0.02	**Apple, 32.0 g**	**Caffeic acid, 3.40 mg**
0.01	BHA: daily US avg (1975)	BHA, 4.6 mg
0.01	**Beer (before 1979), 229 g**	**Dimethylnitrosamine, 646 ng**
0.008	**Aflatoxin: daily US avg (1984–1989)**	**Aflatoxin, 18 ng**
0.007	**Celery, 14 g**	**Caffeic acid, 1.51 mg**
0.007	*d*-Limonene	Food additive, 1.01 mg
0.007	**Cinnamon, 21.9 mg**	**Coumarin, 65.0 µg**
0.006	**Coffee, 11.6 g**	**Furfural, 783 µg**
0.005	**Coffee, 11.6 g**	**Hydroquinone, 290 µg**
0.005	Saccharin: daily US avg (1977)	Saccharin, 7 mg
0.005	**Carrot, 12.1 g**	**Aniline, 624 µg**
0.004	**Bread, 79 g**	**Furfural, 584 µg**
0.004	**Potato, 54.9 g**	**Caffeic acid, 867 µg**
0.004	**Methyl eugenol in food**	**Methyl eugenol, 46.2 µg**
0.003	Conventional home air (14 hour/day)	Benzene, 155 µg

from average US exposures to rodent carcinogens

Potency TD_{50} (mg/kg/day)[a]		Exposure references
Rats	**Mice**	
297	(4900)	Mosel & Herrmann 1974; US Evironmental Protection Agency, Office of Pesticide Programs 1989
606	(5530)	US Food and Drug Administration 1991a
0.0959	(0.189)	Beer Institute 1999; Fazio & al. 1980; Preussmann & Eisenbrand 1984
0.0032	(+)	US Food and Drug Administration 1992
297	(4900)	Smiciklas-Wright & al. 2002; Stöhr & Herrmann 1975
204	(–)	Lucas & al. 1999
13.9	(103)	Poole & Poole 1994
(683)	197	Coffee Research Institute 2001; Stofberg & Grundschober 1987
82.8	(225)	Coffee Research Institute 2001; Heinrich & Baltes 1987; Tressl & al. 1978
2140	(–)	National Research Council 1979
194[b]	(–)	Neurath & al. 1977; Technical Assessment Systems 1989
(683)	197	Smiciklas-Wright & al. 2002; Stofberg & Grundschober 1987
297	(4900)	Schmidtlein & Herrmann 1975b; Technical Assessment Systems 1989
(19.7)	18.6	Smith & al. 2002
(169)	77.5	McCann & al. 1987

Table 5(4): Ranking possible carcinogenic hazards

Possible hazard HERP (%)	Average daily US (human) exposure	Human dose of rodent carcinogen
	(Chemicals that occur naturally in foods are in bold.)	
0.002	**Coffee, 11.6 g**	**4-Methylcatechol, 378 µg**
0.002	**Nutmeg, 17.6 mg**	***d*-Limonene, 299 µg**
0.002	**Carrot, 12.1 g**	**Caffeic acid, 374 µg**
0.002	Ethylene thiourea: daily US avg (1990)	Ethylene thiourea, 9.51 µg
0.002	BHA: daily US avg (1987)	BHA, 700 µg
0.002	DDT: daily US avg (before 1972 ban)[5]	DDT, 13.8 µg
0.001	**Estragole in spices**	**Estragole, 54.0 µg**
0.001	**Pear, 3.7 g**	**Caffeic acid, 270 µg**
0.001	Toxaphene: daily US avg (before 1982 ban)[c]	Toxaphene, 6.43 µg
0.001	**Mushroom (*Agaricus bisporus* 5.34 g)**	**Glutamyl-*p*-hydrazino-benzoate, 224 µg**
0.001	**Plum, 1.7 g**	**Caffeic acid, 235 µg**
0.001	[UDMH: daily US avg (1988)]	[UDMH, 2.82 µg (from Alar)]
0.001	**Bacon, 19 g**	**Diethylnitrosamine, 19 ng**
0.0008	**Bacon, 19 g**	**Dimethylnitrosamine, 57.0 ng**

from average US exposures to rodent carcinogens

Potency TD_{50} (mg/kg/day)[a]		Exposure references
Rats	**Mice**	
248	•	Coffee Research Institute 2001; Heinrich & Baltes 1987; International Agency for Research on Cancer 1991
204	(–)	Bejnarowicz & Kirch 1963; US Department of Agriculture 2000
297	(4900)	Stöhr & Herrmann 1975; Technical Assessment Systems 1989
7.9	(23.5)	US Environmental Protection Agency 1991a
606	(5530)	US Food and Drug Administration 1991a
(84.7)	12.8	Duggan & Corneliussen 1972
•	51.8	Smith & al. 2002
297	(4900)	Mosel & Herrmann 1974; US Environmental Protection Agency 1997
(–)	7.51	Podrebarac 1984
•	277	Chauhan & al. 1985; US Food and Drug Administration 2002
297	(4900)	Mosel & Herrmann 1974; US Environmental Protection Agency 1997
(–)	3.96	US Environmental Protection Agency, Office of Pesticide Programs 1989
0.0266	(+)	Sen & al. 1979; Smiciklas-Wright & al. 2002
0.0959	(0.189)	Smiciklas-Wright & al. 2002; Tricker & Preussmann 1991

Table 5(5): Ranking possible carcinogenic hazards

Possible hazard HERP (%)	Average daily US (human) exposure (Chemicals that occur naturally in foods are in bold.)	Human dose of rodent carcinogen
0.0008	Tap water, 1 liter (1987-92)	Chloroform, 51 µg
0.0008	DDE: daily US avg (before 1972 ban)[c]	DDE, 6.91 µg
0.0007	**Bacon, 19 g**	***N*-Nitrosopyrrolidine, 324 ng**
0.0006	Methyl eugenol	Food additive, 7.7 µg
0.0004	EDB: Daily US avg (before 1984 ban)[c]	EDB, 420 ng
0.0004	Tap water, 1 liter (1987-92)	Bromodichloromethane, 13 µg
0.0004	**Celery, 14 g**	**8-Methoxypsoralen, 8.56 µg**
0.0003	**Mango, 1.0 g**	***d*-Limonene, 40.0 µg**
0.0003	TCDD: daily US avg (1994)	TCDD, 5.4 pg
0.0003	Furfural	Food additive, 36.4 µg
0.0003	Carbaryl: daily US avg (1990)	Carbaryl, 2.6 µg
0.0003	**Mustard, 18.9 mg**	**Allyl isothiocyanate, 17.4 µg**
0.0002	**Beer (1994-95), 229 g**	**Dimethylnitrosamine, 16 ng**
0.0002	**Mushroom (*Agaricus bisporus*, 5.34 g)**	***p*-Hydrazinobenzoate, 58.6 µg**
0.0002	Estragole	Food additive, 5.79 µg

from average US exposures to rodent carcinogens

Potency TD_{50} (mg/kg/day)[a]		Exposure references
Rats	**Mice**	
(262)	90.3	American Water Works Association, Government Affairs Office 1993; McKone 1987; McKone 1993
(–)	12.5	Duggan & Corneliussen 1972
(0.799)	0.679	Stofberg & Grundschober 1987; Tricker & Preussmann 1991
(19.7)	18.6	Smith & al. 2002
1.52	(7.45)	US Environmental Protection Agency, Office of Pesticide Programs February 8, 1984
(72.5)	47.7	American Water Works Association. Government Affairs Office 1993
32.4	(–)	Beier & al. 1983; Smiciklas-Wright & al. 2002
204	(–)	Engel & Tressl 1983; US Environmental Protection Agency 1997
0.0000235	(0.000156)	US Environmental Protection Agency 2000
(683)	197	Lucas & al. 1999
14.1	(–)	US Food and Drug Administration 1991b
96	(–)	Krul & al. 2002; Lucas & al. 1999; Tsao & al. 2002
0.0959	(0.189)	Beer Institute 1999; Glória & al. 1997
•	454[b]	Chauhan & al. 1985; US Food and Drug Administration 2002
•	51.8	Lucas & al. 1999

Table 5(6): Ranking possible carcinogenic hazards

Possible hazard HERP (%)	Average daily US (human) exposure (Chemicals that occur naturally in foods are in bold.)	Human dose of rodent carcinogen
0.0002	Allyl isothiocyanate	Food additive, 10.5 µg
0.0002	**Hamburger, pan fried, 85 g**	**PhIP, 176 ng**
0.0001	Toxaphene: daily US avg (1990)[c]	Toxaphene, 595 ng
0.00008	PCBs: daily US avg (1984-86)	PCBs, 98 ng
0.00008	**Toast, 79 g**	**Urethane, 948 ng**
0.00008	DDE/DDT: daily US avg (1990)[c]	DDE, 659 ng
0.00007	**Beer, 229 g**	**Furfural, 9.50 µg**
0.00006	**Parsnip, 48.8 mg**	**8-Methoxypsoralen, 1.42 µg**
0.00004	**Parsley, fresh, 257 mg**	**8-Methoxypsoralen, 928 ng**
0.00003	**Hamburger, pan fried, 85 g**	**MeIQx, 38.1 ng**
0.00002	Dicofol: daily US avg (1990)	Dicofol, 544 ng
0.00001	**Hamburger, pan fried, 85 g**	**IQ, 6.38 ng**
0.000009	**Beer, 229 g**	**Urethane, 102 ng**
0.000005	Hexachlorobenzene: daily US avg (1990)	Hexachlorobenzene, 14 ng
0.000001	Lindane: daily US avg (1990)	Lindane, 32 ng

from average US exposures to rodent carcinogens

Potency TD_{50} (mg/kg/day)[a]		Exposure references
Rats	**Mice**	
96	(–)	Lucas & al. 1999
1.64[b]	(28.6)[b]	Knize & al. 1994; Technical Assessment Systems 1989
(–)	7.51	US Food and Drug Administration 1991b
1.74	(9.58)	Gunderson 1995
(41.3)	16.9	Canas & al. 1989; Smiciklas-Wright & al. 2002
(–)	12.5	US Food and Drug Administration 1991b
(683)	197	Beer Institute 1999; Lau & Lindsay 1972; Tressl 1976; Wheeler & al. 1971
32.4	(–)	Ivie & al. 1981; US Environmental Protection Agency 1997
32.4	(–)	Chaudhary & al. 1986; US Environmental Protection Agency 1997
1.66	(24.3)	Knize & al. 1994; Technical Assessment Systems 1989
(–)	32.9	US Food and Drug Administration 1991b
0.921[b]	(19.6)	Knize & al. 1994; Technical Assessment Systems 1989
(41.3)	16.9	Beer Institute 1999; Canas & al. 1989
3.86	(65.1)	US Food and Drug Administration 1991b
(–)	30.7	US Food and Drug Administration 1991b

Table 5(7): Ranking possible carcinogenic hazards

Possible hazard HERP (%)	Average daily US (human) exposure	Human dose of rodent carcinogen
	(Chemicals that occur naturally in foods are in bold.)	
0.0000004	PCNB: daily US avg (1990)	PCNB (Quintozene), 19.2 ng
0.0000001	Chlorobenzilate: daily US avg (1989)[c]	Chlorobenzilate, 6.4 ng
0.00000008	Captan: daily US avg (1990)	Captan, 115 ng
0.00000001	Folpet: daily US avg (1990)	Folpet, 12.8 ng
<0.00000001	Chlorothalonil: daily US avg (1990)	Chlorothalonil, <6.4 ng

Note a: • = no data in Carcinogenic Potency Database; 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 test(s); (+) = positive cancer test(s) not suitable for calculating a TD_{50}.

Note b: TD_{50} harmonic mean was estimated for the base chemical from the hydrochloride salt.

from average US exposures to rodent carcinogens

Potency TD_{50} (mg/kg/day)[a]		Exposure references
Rats	**Mice**	
(–)	71.1	US Food and Drug Administration 1991b
(–)	93.9	US Food and Drug Administration 1991b
2080	(2110)	US Food and Drug Administration 1991b
(–)	1550	US Food and Drug Administration 1991b
828[d]	(–)	US Environmental Protection Agency 1987; US Food and Drug Administration 1991b

Note c: No longer contained in any registered pesticide product (USEPA, 1998).

Note d: Additional data from the EPA that is not in the CPDB were used to calculate this TD_{50} harmonic mean.