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CHAPTER

38

Pesticide Residues in Food and Cancer Risk: A Critical Analysis

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38.1 INTRODUCTION

Possible cancer hazards from pesticide residues in food have been much discussed and hotly debated in the scientific literature, the popular press, the political arena, and the courts. Consumer opinion surveys indicate that much of the U.S. public believes that pesticide residues in food are a serious cancer hazard (Opinion Research Corporation, 1990). In contrast, epidemiologic studies indicate that the major preventable risk factors for cancer are smoking, dietary imbalances, endogenous hormones, and inflammation (e.g., from chronic infections). Other important factors include intense sun exposure, lack of physical activity, and excess alcohol consumption (Ames *et al.*, 1995). The types of cancer deaths that have decreased since 1950 are primarily stomach, cervical, uterine, and colorectal. Overall cancer death rates in the United States (excluding lung cancer) have declined 19% since 1950 (Ries *et al.*, 2000). The types that have increased are primarily lung cancer [87% is due to smoking, as are 31% of all cancer deaths in the United States (American Cancer Society, 2000)], melanoma (probably due to sunburns), and non-Hodgkin's lymphoma. If lung cancer is included, mortality rates have increased over time, but recently have declined (Ries *et al.*, 2000).

Thus, epidemiological studies do not support the idea that synthetic pesticide residues are important for human cancer. Although some epidemiologic studies find an association between cancer and low levels of some industrial pollutants, the studies often have weak or inconsistent results, rely on ecological correlations or indirect exposure assessments, use small sample sizes, and do not control for confounding factors such as composition of the diet, which is a potentially important confounding factor. Outside the workplace, the levels of exposure to synthetic pollutants or pesticide residues are low and rarely seem toxicologically plausible as a causal factor when compared to the wide variety of naturally occurring chemicals to which all people are exposed (Ames *et al.*, 1987, 1990a; Gold *et al.*, 1992). Whereas public perceptions tend to identify chemicals as being only synthetic and only synthetic chemicals as being toxic, every natural chemical is also toxic at some dose, and the vast proportion of chemicals to which humans are exposed are naturally occurring (see Section 38.2).

There is, however, a paradox in the public concern about possible cancer hazards from pesticide residues in food and the lack of public understanding of the substantial evidence indicating that high consumption of the foods that contain pesticide residues—fruits and vegetables—has a protective effect against many types of cancer. A review of about 200 epidemiological studies reported a consistent association between low consumption of fruits and vegetables and cancer incidence at many target sites (Block *et al.*, 1992; Hill *et al.*, 1994; Steinmetz and Potter, 1991). The quarter of the population with the lowest dietary intake of fruits and vegetables has roughly twice the cancer rate for many types of cancer (lung, larynx, oral cavity, esophagus, stomach, colon and rectum, bladder, pancreas, cervix, and ovary) compared to the quarter with the highest consumption of those foods. The protective effect of consuming fruits and vegetables is weaker and less consistent for hormonally related cancers, such as breast and prostate. Studies suggest that inadequate intake of many micronutrients in these foods may be radiation mimics and are important in the carcinogenic effect (Ames, 2001). Despite the substantial evidence of the importance of fruits and vegetables in prevention, half the American

public did not identify fruit and vegetable consumption as a protective factor against cancer (U.S. National Cancer Institute, 1996). Consumption surveys, moreover, indicate that 80% of children and adolescents in the United States (Krebs-Smith *et al.*, 1996) and 68% of adults (Krebs-Smith *et al.*, 1995) did not consume the intake of fruits and vegetables recommended by the National Cancer Institute (NCI) and the National Research Council: five servings per day. One important consequence of inadequate consumption of fruits and vegetables is low intake of some micronutrients. For example, folic acid is one of the most common vitamin deficiencies in people who consume few dietary fruits and vegetables; folate deficiency causes chromosome breaks in humans by a mechanism that mimics radiation (Ames, 2001; Blount *et al.*, 1997). Approximately 10% of the U.S. population (Senti and Pilch, 1985) had a lower folate level than that at which chromosome breaks occur (Blount *et al.*, 1997). Folate supplementation above the recommended daily allowance (RDA) minimized chromosome breakage (Fenech *et al.*, 1998).

Given the lack of epidemiological evidence to link dietary synthetic pesticide residues to human cancer, and taking into account public concerns about pesticide residues as possible cancer hazards, public policy with respect to pesticides has relied on the results of high-dose, rodent cancer tests as the major source of information for assessing potential cancer risks to humans. This chapter examines critically the assumptions, methodology, results, and implications of cancer risk assessments of pesticide residues in the diet. Our analyses are based on results in our Carcinogenic Potency Database (CPDB) (Gold *et al.*, 1997b, 1999; http://potency.berkeley.edu), which provide the necessary data to examine the published literature of chronic animal cancer tests; the CPDB includes results of 5620 experiments on 1372 chemicals. Specifically, the following are addressed in the section indicated:

Section 38.2. Human exposure to synthetic pesticide residues it the diet compared to the broader and greater exposure to natural chemicals in the diet

Section 38.3. Cancer risk assessment methodology, including the use of animal data from high-dose bioassays in which half the chemicals tested are carcinogenic

Section 38.4. Increased cell division as an important hypothesis for the high positivity rate in rodent bioassays and implications for risk assessment

Section 38.5. Providing a broad perspective on possible cancer hazards from a variety of exposures to rodent carcinogens, including pesticide residues, by ranking on the HERP (human exposure/rodent potency) index

Section 38.6. Analysis of possible reasons for the wide disparities in published risk estimates for pesticide residues in the diet

Section 38.7. Identification and ranking of exposures in the U.S. diet to naturally occurring chemicals that have not been tested for carcinogenicity, using an index that takes into account the acutely toxic dose of a chemical (LD_{50}) and average consumption in the U.S. diet

Section 38.8. Summary of carcinogenicity results on 193 active ingredients in commercial pesticides.

38.2 HUMAN EXPOSURES TO NATURAL AND SYNTHETIC CHEMICALS

Current regulatory policy to reduce human cancer risks is based on the idea that chemicals that induce tumors in rodent cancer bioassays are potential human carcinogens. The chemicals selected for testing in rodents, however, are primarily synthetic (Gold *et al.*, 1997a, b, c, 1998, 1999). The enormous background of human exposures to natural chemicals has not been systematically examined. This has led to an imbalance in both data and perception about possible carcinogenic hazards to humans from chemical exposures. The regulatory process does not take into account (1) that natural chemicals make up the vast bulk of chemicals to which humans are exposed; (2) that the toxicology of synthetic and natural toxins is not fundamentally different; (3) that about half of the chemicals tested, whether natural or synthetic, are carcinogens when tested using current experimental protocols; (4) that testing for carcinogenicity at near-toxic doses in rodents does not provide enough information to predict the excess number of human cancers that might occur at low-dose exposures; and (5) that testing at the maximum tolerated dose (MTD) frequently can cause chronic cell killing and consequent cell replacement (a risk factor for cancer that can be limited to high doses) and that ignoring this effect in risk assessment can greatly exaggerate risks.

We estimate that about 99.9% of the chemicals that humans ingest are naturally occurring. The amounts of synthetic pesticide residues in plant foods are low in comparison to the amount of natural pesticides produced by plants themselves (Ames *et al.*, 1990a, b; Gold *et al.*, 1997a). Of all dietary pesticides that Americans eat, 99.99% are natural: They are the chemicals produced by plants to defend themselves against fungi, insects, and other animal predators. Each plant produces a different array of such chemicals (Ames *et al.*, 1990a, b).

We estimate that the daily average U.S. exposure to natural pesticides in the diet is about 1500 mg and to burnt material from cooking is about 2000 mg (Ames *et al.*, 1990b). In comparison, the total daily exposure to all synthetic pesticide residues combined is about 0.09 mg based on the sum of residues reported by the U.S. Food and Drug Administration (FDA) in its study of the 200 synthetic pesticide residues thought to be of greatest concern (Gunderson, 1988; U.S. Food and Drug Administration, 1993a). Humans ingest roughly 5000–10,000 different natural pesticides and their breakdown products (Ames *et al.*, 1990a). Despite this enormously greater exposure to natural chemicals, among the chemicals tested in long-term bioassays in the CPDB, 77% (1050/1372) are synthetic (i.e., do not occur naturally) (Gold and Zeiger, 1997; Gold *et al.*, 1999).

Concentrations of natural pesticides in plants are usually found at parts per thousand or million rather than parts per billion, which is the usual concentration of synthetic pesticide

Table 38.1
Carcinogenicity Status of Natural Pesticides Tested in Rodents[a]

Carcinogens[b]: $N = 37$	Acetaldehyde methylformylhydrazone, allyl isothiocyanate, arecoline·HCl, benzaldehyde, benzyl acetate, caffeic acid, capsaicin, catechol, clivorine, coumarin, crotonaldehyde, 3,4-dihydrocoumarin, estragole, ethyl acrylate, *N*2-γ-glutamyl-*p*-hydrazinobenzoic acid, hexanal methylformylhydrazine, *p*-hydrazinobenzoic acid·HCl, hydroquinone, 1-hydroxyanthraquinone, lasiocarpine, *d*-limonene, 3-methoxycatechol, 8-methoxypsoralen, *N*-methyl-*N*-formylhydrazine, α-methylbenzyl alcohol, 3-methylbutanal methylformylhydrazone, 4-methylcatechol, methylhydrazine, monocrotaline, pentanal methylformylhydrazone, petasitenine, quercetin, reserpine, safrole, senkirkine, sesamol, symphytine
Noncarcinogens: $N = 34$	Atropine, benzyl alcohol, benzyl isothiocyanate, benzyl thiocyanate, biphenyl, *d*-carvone, codeine, deserpidine, disodium glycyrrhizinate, ephedrine sulfate, epigallocatechin, eucalyptol, eugenol, gallic acid, geranyl acetate, β-*N*-[γ-*l*(+)-glutamyl]-4-hydroxymethylphenylhydrazine, glycyrrhetinic acid, *p*-hydrazinobenzoic acid, isosafrole, kaempferol, *dl*-menthol, nicotine, norharman, phenethyl isothiocyanate, pilocarpine, piperidine, protocatechuic acid, rotenone, rutin sulfate, sodium benzoate, tannic acid, 1-*trans*-δ^9-tetrahydrocannabinol, turmeric oleoresin, vinblastine

[a]Fungal toxins are not included.
[b]These rodent carcinogens occur in absinthe, allspice, anise, apple, apricot, banana, basil, beet, black pepper, broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, cardamom, carrot, cauliflower, celery, cherries, chili pepper, chocolate, cinnamon, cloves, coffee, collard greens, comfrey herb tea, coriander, corn, currants, dill, eggplant, endive, fennel, garlic, grapefruit, grapes, guava, honey, honeydew melon, horseradish, kale, lemon, lentils, lettuce, licorice, lime, mace, mango, marjoram, mint, mushrooms, mustard, nutmeg, onion, orange, paprika, parsley, parsnip, peach, pear, peas, pineapple, plum, potato, radish, raspberries, rhubarb, rosemary, rutabaga, sage, savory, sesame seeds, soybean, star anise, tarragon, tea, thyme, tomato, turmeric, and turnip.

residues. Therefore, because humans are exposed to so many more natural than synthetic chemicals (by weight and by number), human exposure to natural rodent carcinogens, as defined by high-dose rodent tests, is ubiquitous (Ames *et al.*, 1990b). It is probable that almost every fruit and vegetable in the supermarket contains natural pesticides that are rodent carcinogens. Even though only a tiny proportion of natural pesticides have been tested for carcinogenicity, 37 of 71 that have been tested are rodent carcinogens that are present in the common foods listed in Table 38.1.

Humans also ingest numerous natural chemicals that are produced as by-products of cooking food. For example, more than 1000 chemicals have been identified in roasted coffee, many of which are produced by roasting (Clarke and Macrae, 1988; Nijssen *et al.*, 1996). Only 30 have been tested for carcinogenicity according to the most recent results in our CPDB, and 21 of these are positive in at least one test (Table 38.2), totaling at least 10 mg of rodent carcinogens per cup of coffee (Clarke and Macrae, 1988; Fujita *et al.*, 1985; Kikugawa *et al.*, 1989; Nijssen *et al.*, 1996). Among the rodent carcinogens in coffee are the plant pesticides caffeic acid (present at 1800 ppm; Clarke and Macrae, 1988) and catechol (present at 100 ppm; Rahn and König, 1978; Tressl *et al.*, 1978). Two other plant pesticides in coffee, chlorogenic acid and neochlorogenic acid (present at 21,600 and 11,600 ppm, respectively; Clarke and Macrae, 1988) are metabolized to caffeic acid and catechol but have not been tested for carcinogenicity. Chlorogenic acid and caffeic acid are mutagenic (Ariza et al., 1988; Fung *et al.*, 1988; Hanham *et al.*, 1983) and clastogenic (Ishidate *et al.*, 1988; Stich *et al.*, 1981). Another plant pesticide in coffee, *d*-limonene, is carcinogenic but the only tumors induced were in male rat kidney, by a mechanism involving accumulation of α_{2u}-globulin and increased cell division in the kidney, which would not be predictive of a carcinogenic hazard to humans (Dietrich and Swenberg, 1991; Rice *et al.*, 1999). Some other rodent carcinogens in coffee are products of cooking, for example, furfural and benzo(*a*)pyrene. The point here is not to indicate that rodent data necessarily implicate coffee as a risk factor for human cancer, but rather to illustrate that there is an enormous background of chemicals in the diet that are natural and that have not been a focus of carcinogenicity testing. A diet free of naturally occurring chemicals that are carcinogens in high-dose rodent tests is impossible.

It is often assumed that because natural chemicals are part of human evolutionary history, whereas synthetic chemicals are recent, the mechanisms that have evolved in animals to cope

Table 38.2
Carcinogenicity Status of Natural Chemicals in Roasted Coffee

Positive: $N = 21$	Acetaldehyde, benzaldehyde, benzene, benzofuran, benzo(*a*)pyrene, caffeic acid, catechol, 1,2,5,6-dibenzanthracene, ethanol, ethylbenzene, formaldehyde, furan, furfural, hydrogen peroxide, hydroquinone, isoprene, limonene, 4-methylcatechol, styrene, toluene, xylene
Not positive: $N = 8$	Acrolein, biphenyl, choline, eugenol, nicotinamide, nicotinic acid, phenol, piperidine
Uncertain:	Caffeine
Yet to test:	~1000 chemicals

with the toxicity of natural chemicals will fail to protect against synthetic chemicals, including synthetic pesticides (Ames *et al.*, 1987). This assumption is flawed for several reasons (Ames *et al.*, 1990b, 1996; Gold *et al.*, 1997a, b, c):

1. Humans have many natural defenses that buffer against normal exposures to toxins (Ames *et al.*, 1990b) and these are usually general, rather than tailored for each specific chemical. Thus, they work against both natural and synthetic chemicals. Examples of general defenses include the continuous shedding of cells exposed to toxins—the surface layers of the mouth, esophagus, stomach, intestine, colon, skin, and lungs are discarded every few days; deoxyribonucleic acid (DNA) repair enzymes, which repair DNA that was damaged from many different sources; and detoxification enzymes of the liver and other organs, which generally target classes of chemicals rather than individual chemicals. That human defenses are usually general, rather than specific for each chemical, makes good evolutionary sense. The reason that predators of plants evolved general defenses is presumably to be prepared to counter a diverse and ever-changing array of plant toxins in an evolving world; if a herbivore had defenses against only a specific set of toxins, it would be at great disadvantage in obtaining new food when favored foods became scarce or evolved new chemical defenses.

2. Various natural toxins, which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates (Ames *et al.*, 1990b; Gold *et al.*, 1997b, 1999; Vainio *et al.*, 1995). Mold toxins, such as aflatoxin, have been shown to cause cancer in rodents, monkeys, humans, and other species. Many of the common elements, despite their presence throughout evolution, are carcinogenic to humans at high doses (e.g., the salts of cadmium, beryllium, nickel, chromium, and arsenic). Furthermore, epidemiological studies from various parts of the world indicate that certain natural chemicals in food may be carcinogenic risks to humans; for example, the chewing of betel nut with tobacco is associated with oral cancer. Among the agents identified as human carcinogens by the International Agency for Research in Cancer (IARC) 62% (37/60) occur naturally: 16 are natural chemicals, 11 are mixtures of natural chemicals, and 10 are infectious agents (IARC, 1971–1999; Vainio *et al.*, 1995). Thus, the idea that a chemical is "safe" because it is natural, is not correct.

3. Humans have not had time to evolve a "toxic harmony" with all of their dietary plants. The human diet has changed markedly in the last few thousand years. Indeed, very few of the plants that humans eat today (e.g., coffee, cocoa, tea, potatoes, tomatoes, corn, avocados, mangos, olives and kiwi fruit) would have been present in a hunter-gatherer's diet. Natural selection works far too slowly for humans to have evolved specific resistance to the food toxins in these newly introduced plants.

4. Some early synthetic pesticides were lipophilic organochlorines that persist in nature and bioaccumulate in adipose tissue, for example, dichlorophenyltrichloroethane (DDT), aldrin, and dieldrin (DDT is discussed in Section 38.5). This ability to bioaccumulate is often seen as a hazardous property of synthetic pesticides; however, such bioconcentration and persistence are properties of relatively few synthetic pesticides. Moreover, many thousands of chlorinated chemicals are produced in nature (Gribble, 1996). Natural pesticides also can bioconcentrate if they are fat soluble. Potatoes, for example, were introduced into the worldwide food supply a few hundred years ago; potatoes contain solanine and chaconine, which are fat-soluble, neurotoxic, natural pesticides that can be detected in the blood of all potato-eaters. High levels of these potato glycoalkaloids have been shown to cause reproductive abnormalities in rodents (Ames *et al.*, 1990b; Morris and Lee, 1984).

5. Because no plot of land is free from attack by insects, plants need chemical defenses—either natural or synthetic—to survive pest attack. Thus, there is a trade-off between naturally-occurring pesticides and synthetic pesticides. One consequence of efforts to reduce pesticide use is that some plant breeders develop plants to be more insect resistant by making them higher in natural pesticides. A recent case illustrates the potential hazards of this approach to pest control: When a major grower introduced a new variety of highly insect-resistant celery into commerce, people who handled the celery developed rashes when they were subsequently exposed to sunlight. Some detective work found that the pest-resistant celery contained 6200 parts per billion (ppb) of carcinogenic (and mutagenic) psoralens instead of the 800 ppb present in common celery (Beier and Nigg, 1994; Berkley *et al.*, 1986; Seligman *et al.*, 1987).

38.3 THE HIGH CARCINOGENICITY RATE AMONG CHEMICALS TESTED IN CHRONIC ANIMAL CANCER TESTS

Because the toxicology of natural and synthetic chemicals is similar, one expects, and finds, a similar positivity rate for carcinogenicity among synthetic and natural chemicals that have been tested in rodent bioassays. Among chemicals tested in rats and mice in the CPDB, about half the natural chemicals are positive, and about half of all chemicals tested are positive. This high positivity rate in rodent carcinogenesis bioassays is consistent for many data sets (Table 38.3): Among chemicals tested in rats and mice, 59% (350/590) are positive in at least one experiment, 60% of synthetic chemicals (271/451), and 57% of naturally occurring chemicals (79/139). Among chemicals tested in at least one species, 52% of natural pesticides (37/71) are positive, 61% of fungal toxins (14/23), and 70% of the naturally occurring chemicals in roasted coffee (21/30) (Table 38.2). Among commercial pesticides reviewed by the EPA (U.S. Environmental Protection Agency, 1998), the positivity rate is 41% (79/193); this rate is similar among commercial pesticides that also occur naturally and those that are only synthetic, as well as between commercial pesticides that have been canceled and those still in use. (See Section 38.8 for detailed summary results

Table 38.3
Proportion of Chemicals Evaluated as Carcinogenic

Chemicals tested in both rats and mice[a]	
Chemicals in the CPDB	350/590 (59%)
Naturally occurring chemicals in the CPDB	79/139 (57%)
Synthetic chemicals in the CPDB	271/451 (60%)
Chemicals tested in rats and/or mice[a]	
Chemicals in the CPDB	702/1348 (52%)
Natural pesticides in the CPDB	37/71 (52%)
Mold toxins in the CPDB	14/23 (61%)
Chemicals in roasted coffee in the CPDB	21/30 (70%)
Commercial pesticides in the CPDB	79/193 (41%)
Physicians' Desk Reference (PDR):	
Drugs with reported cancer tests[b]	117/241 (49%)
FDA database of drug submissions[c]	125/282 (44%)

[a]From the Carcinogenic Potency Database (Gold *et al.*, 1997c, 1999).
[b]Davies and Monro (1995).
[c]Contrera *et al.* (1997). 140 drugs are in both the FDA and the PDR databases.

of carcinogenicity tests on the 193 commercial pesticides in the CPDB, including results on the positivity of each chemical, its carcinogenic potency, and target organs of carcinogenesis.)

Because the results of high-dose rodent tests are routinely used to identify a chemical as a possible cancer hazard to humans, it is important to try to understand how representative the 50% positivity rate might be of all untested chemicals. If half of all chemicals (both natural and synthetic) to which humans are exposed were positive if tested, then the utility of a test to identify a chemical as a "potential human carcinogen" because it increases tumor incidence in a rodent bioassay would be questionable. To determine the true proportion of rodent carcinogens among chemicals would require a comparison of a random group of synthetic chemicals to a random group of natural chemicals. Such an analysis has not been done.

It has been argued that the high positivity rate is due to selecting more suspicious chemicals to test for carcinogenicity. For example, chemicals may be selected that are structurally similar to known carcinogens or genotoxins. That is a likely bias because cancer testing is both expensive and time consuming, making it prudent to test suspicious compounds. On the other hand, chemicals are selected for testing for many reasons, including the extent of human exposure, level of production, and scientific questions about carcinogenesis. Among chemicals tested in both rats and mice, chemicals that are mutagenic in *Salmonella* are carcinogenic in rodent bioassays more frequently than nonmutagens: 80% of mutagens are positive (176/219) compared to 50% (135/271) of nonmutagens. Thus, if testing is based on suspicion of carcinogenicity, then more mutagens should be selected than nonmutagens; however, of the chemicals tested in both species, 55% (271/490) are not mutagenic. This suggests that prediction of positivity is often not the basis for selecting a chemical to test. Another argument against selection bias is the high positivity rate for drugs (Table 38.3), because drug development tends to favor chemicals that are not mutagens or suspected carcinogens. In the *Physicians' Desk Reference* (PDR), however, 49% (117/241) of the drugs that report results of animal cancer tests are carcinogenic (Davies and Monro, 1995) (Table 38.3).

Moreover, while some chemical classes are more often carcinogenic in rodent bioassays than others (e.g., nitroso compounds, aromatic amines, nitroaromatics, and chlorinated compounds), prediction is still imperfect. For example, a prospective prediction exercise was conducted by several experts in 1990 in advance of the 2-year National Toxicology Program bioassays. There was wide disagreement among the experts on which chemicals would be carcinogenic when tested, and the level of accuracy varied by expert, thus indicating that predictive knowledge is uncertain (Omenn *et al.*, 1995).

One large series of mouse experiments by Innes *et al.* (1969) has frequently been cited (U.S. National Cancer Institute, 1984) as evidence that the true proportion of rodent carcinogens is actually low among tested substances (Table 38.4). In the Innes study, 119 synthetic pesticides and industrial chemicals were tested, and only 11 (9%) were evaluated as carcinogenic. Our analysis indicates that those early experiments lacked power to detect an effect because they were conducted only in mice (not in rats), they included only 18 animals in a group (compared with the standard protocol of 50), the animals were tested for only 18 months (compared with the standard 24 months), and the Innes dose was usually lower than the highest dose in subsequent mouse tests if the same chemical was tested again (Gold and Zeiger, 1997; Gold *et al.*, 1999; Innes *et al.*, 1969).

To assess whether the low positivity rate in the Innes study was due to the lack of power in the design of the experiments, we used results in our CPDB to examine subsequent bioassays on the Innes chemicals that had not been evaluated as positive (results and chemical names are reported in Table 38.4). Among the 34 chemicals that were not positive in the Innes study and were subsequently retested with more standard protocols, 17 had a subsequent positive evaluation of carcinogenicity (50%), which is similar to the proportion among all chemicals in the CPDB (Table 38.4). Of the 17 new positives, 7 were carcinogenic in mice and 14 in rats. Innes *et al.* had recommended further evaluation of some chemicals that had inconclusive results in their study. If those were the chemicals subsequently retested, then one might argue that they would be the most likely to be positive. Our analysis does not support that view, however. We found that the positivity rate among the chemicals that the Innes study said needed further evaluation was 7 of 16 (44%) when retested, compared to 10 of 18 (56%) among the chemicals that Innes evaluated as negative. Our analysis thus supports the idea that the low positivity rate in the Innes study resulted from lack of power.

Because many of the chemicals tested by Innes *et al.* were synthetic pesticides, we reexamined the question of what proportion of synthetic pesticides are carcinogenic (as shown in Table 38.3) by excluding the pesticides tested only in the Innes series. The Innes studies had little effect on the positivity rate: Table 38.3 indicates that of all commercial pesticides in the

Table 38.4
Results of Subsequent Tests on Chemicals (Primarily Pesticides) not Found Carcinogenic by Innes *et al.* (1969)

Retested chemicals	Percentage carcinogenic when retested		
	Mice	Rats	Either mice or rats
All retested	7/26 (27%)	14/34 (41%)	17/34 (50%)
Innes: not carcinogenic	3/10 (30%)	9/18 (50%)	10/18 (56%)
Innes: needs further evaluation	4/16 (25%)	5/16 (31%)	7/16 (44%)

Of 119 chemicals tested by Innes *et al.*, 11 (9%) were evaluated as positive by Innes *et al.*
Carcinogenic when retested: atrazine (R), azobenzene* (R), captan (M, R), carbaryl (R), 3-(*p*-chlorophenyl)-1,1-dimethylurea* (R), *p*,*p*′-DDD* (M), folpet (M), manganese ethylenebisthiocarbamate (R), 2-mercaptobenzothiazole (R), *N*-nitrosodiphenylamine* (R), 2,3,4,5,6-pentachlorophenol (M, R), *o*-phenylphenol (R), piperonyl butoxide* (M, R), piperonyl sulfoxide* (M), 2,4,6-trichlorophenol* (M, R), zinc dimethyldithiocarbamate (R), zinc ethylenebisthiocarbamate (R).
Not carcinogenic when retested: (2-chloroethyl)trimethylammonium chloride*, calcium cyanamide*, diphenyl-*p*-phenylenediamine, endosulfan, *p*,*p*′-ethyl-DDD*, ethyl tellurac*, isopropyl-*N*-(3-chlorophenyl) carbamate, lead dimethyldithiocarbamate*, maleic hydrazide, mexacarbate*, monochloroacetic acid, phenyl-β-naphthylamine*, rotenone, sodium diethyldithiocarbamate trihydrate*, tetraethylthiuram disulfide*, tetramethylthiuram disulfide, 2,4,5-trichlorophenoxyacetic acid.
(M), positive in mice when retested; (R), positive in rats when retested; *, Innes *et al.* stated that further testing was needed.

CPDB, 41% 79/193 are rodent carcinogens; when the analysis is repeated by excluding those Innes tests, 47% (77/165) are carcinogens.

38.4 THE IMPORTANCE OF CELL DIVISION IN MUTAGENESIS AND CARCINOGENESIS

What might explain the high proportion of chemicals that are carcinogenic when tested in rodent cancer bioassays (Table 38.3)? In standard cancer tests, rodents are given a chronic, near-toxic dose: the maximum tolerated dose (MTD). Evidence is accumulating that cell division caused by the high dose itself, rather than the chemical *per se*, contributes to cancer in such tests (Ames and Gold, 1990; Ames *et al.*, 1993a; Butterworth and Bogdanffy, 1999; Cohen, 1998; Cunningham, 1996; Cunningham and Matthews, 1991; Cunningham *et al.*, 1991; Heddle, 1998). High doses can cause chronic wounding of tissues, cell death, and consequent chronic cell division of neighboring cells, which is a risk factor for cancer (Ames and Gold, 1990; Gold *et al.*, 1998). Each time a cell divides, there is some probability that a mutation will occur, and thus increased cell division increases the risk of cancer. At the low levels of pesticide residues to which humans are usually exposed, such increased cell division does not occur. The process of mutagenesis and carcinogenesis is complicated because many factors are involved, for example, DNA lesions, DNA repair, cell division, clonal instability, apoptosis, and p53 (a cell cycle gene that is mutated in half of human tumors) (Christensen *et al.*, 1999; Hill *et al.*, 1999). The normal endogenous level of oxidative DNA lesions in somatic cells is appreciable (Helbock *et al.*, 1998). In addition, tissues injured by high doses of chemicals have an inflammatory immune response involving activation of white cells in response to cell death (Adachi *et al.*, 1995; Czaja *et al.*, 1994; Gunawardhana *et al.*, 1993; Laskin and Pendino, 1995; Roberts and Kimber, 1999). Activated white cells release mutagenic oxidants (including peroxynitrite, hypochlorite, and H_2O_2). Therefore, the very low levels of synthetic pesticide residues to which humans are exposed may pose no or only minimal cancer risks.

It seems likely that a high proportion of all chemicals, whether synthetic or natural, might be "carcinogens" if administered in the standard rodent bioassay at the MTD, primarily due to the effects of high doses on cell division and DNA damage (Ames and Gold, 1990; Ames *et al.*, 1993a; Butterworth *et al.*, 1995; Cunningham, 1996; Cunningham and Matthews, 1991; Cunningham *et al.*, 1991). For nonmutagens, cell division at the MTD can increase carcinogenicity; for mutagens, there can be a synergistic effect between DNA damage and cell division at high doses. *Ad libitum* feeding in the standard bioassay can also contribute to the high positivity rate (Hart *et al.*, 1995). In calorie-restricted mice, cell division rates are markedly lower in several tissues than in *ad libitum*–fed mice (Lok *et al.*, 1990). In dosed animals, food restriction decreased tumor incidence at all three sites that were evaluated as target sites (pancreas and bladder in male rats, liver in male mice), and none of those sites was evaluated as target sites after 2 or 3 years (U.S. National Toxicology Program, 1997). In standard National Cancer Institute (NCI)/National Toxicology Program (NTP) bioassays, for both control and dosed animals, food restriction improves survival and at the same time decreases tumor incidence at many sites compared to *ad libitum*–feeding.

Without additional data on how a chemical causes cancer, the interpretation of a positive result in a rodent bioassay is highly uncertain. Although cell division is not measured in routine cancer tests, many studies on rodent carcinogenicity show a correlation between cell division at the MTD and cancer (Cunningham *et al.*, 1995; Gold *et al.*, 1998; Hayward *et al.*, 1995). Extensive reviews of bioassay results document that chronic cell division can induce cancer (Ames and Gold, 1990; Ames *et al.*, 1993b; Cohen, 1995b; Cohen and Ellwein, 1991; Cohen and Lawson, 1995; Counts and Goodman, 1995; Gold *et al.*, 1997b). A large epidemiological literature reviewed by Preston-Martin *et al.* (1990, 1995) indicates that increased cell division by hormones and other agents can increase human cancer.

Several of our findings in large-scale analyses of the results of animal cancer tests (Gold *et al.*, 1993) are consistent with the idea that cell division increases the carcinogenic effect in high-dose bioassays, including the high proportion of chemicals that are positive; the high proportion of rodent carcinogens that are not mutagenic; and the fact that mutagens, which can both damage DNA and increase cell division at high doses, are more likely than nonmutagens to be positive, to induce tumors in both rats and mice, and to induce tumors at multiple sites (Gold *et al.*, 1993, 1998). Analyses of the limited data on dose response in bioassays are consistent with the idea that cell division from cell killing and cell replacement is important. Among rodent bioassays with two doses and a control group, about half the sites evaluated as target sites are statistically significant at the MTD but not at half the MTD ($p < 0.05$). The proportions are similar for mutagens (44%, 148/334) and nonmutagens (47%, 76/163) (Gold and Zeiger, 1997; Gold *et al.*, 1999), suggesting that cell division at the MTD may be important for the carcinogenic response of mutagens as well as nonmutagens that are rodent carcinogens.

To the extent that increases in tumor incidence in rodent studies are due to the secondary effects of inducing cell division at the MTD, then any chemical is a likely rodent carcinogen, and carcinogenic effects can be limited to high doses. Linearity of the dose–response relationship also seems less likely than has been assumed because of the inducibility of numerous defense enzymes that deal with exogenous chemicals as groups (e.g., oxidants, electrophiles) and thus protect humans against natural and synthetic chemicals, including potentially mutagenic reactive chemicals (Ames *et al.*, 1990b; Luckey, 1999; Munday and Munday, 1999; Trosko, 1998). Thus, true risks at the low doses of most exposures to the general population are likely to be much lower than what would be predicted by the linear model that has been the default in U.S. regulatory risk assessment. The true risk might often be 0.

Agencies that evaluate potential cancer risks to humans are moving to take mechanism and nonlinearity into account. The U.S. Environmental Protection Agency (EPA) recently proposed new cancer risk assessment guidelines (U.S. Environmental Protection Agency, 1996a) that emphasize a more flexible approach to risk assessment and call for the use of more biological information in the weight-of-evidence evaluation of carcinogenicity for a given chemical and in the dose–response assessment. The proposed changes take into account the issues that were discussed previously. The new EPA guidelines recognize the dose dependence of many toxicokinetic and metabolic processes and the importance of understanding cancer mechanisms for a chemical. The guidelines use nonlinear approaches to low-dose extrapolation if warranted by mechanistic data and a possible threshold of dose below which effects will not occur (National Research Council, 1994; U.S. Environmental Protection Agency, 1996a). In addition, toxicological results for cancer and noncancer endpoints could be incorporated together in the risk assessment process.

Also consistent with the results discussed previously, are the recent IARC consensus criteria for evaluations of carcinogenicity in rodent studies, which take into account that an agent can cause cancer in laboratory animals through a mechanism that does not operate in humans (Rice *et al.*, 1999). The tumors in such cases involve persistent hyperplasia in cell types from which the tumors arise. These include urinary bladder carcinomas associated with certain urinary precipitates, thyroid follicular-cell tumors associated with altered thyroid-stimulating hormone (TSH), and cortical tumors of the kidney that arise only in male rats in association with nephropathy that is due to α_{2u} urinary globulin.

Historically, in U.S. regulatory policy, the "virtually safe dose," corresponding to a maximum, hypothetical risk of one cancer in a million, has routinely been estimated from results of carcinogenesis bioassays using a linear model, which assumes that there are no unique effects of high doses. To the extent that carcinogenicity in rodent bioassays is due to the effects of high doses for the nonmutagens, and a synergistic effect of cell division at high doses with DNA damage for the mutagens, this model overestimates risk (Butterworth and Bogdanffy, 1999; Gaylor and Gold, 1998).

We have discussed validity problems associated with the use of the limited data from animal cancer tests for human risk assessment (Bernstein *et al.*, 1985; Gold *et al.*, 1998). Standard practice in regulatory risk assessment for a given rodent carcinogen has been to extrapolate from the high doses of rodent bioassays to the low doses of most human exposures by multiplying carcinogenic potency in rodents by human exposure. Strikingly, however, due to the relatively narrow range of doses in 2-year rodent bioassays and the limited range of statistically significant tumor incidence rates, the various measures of potency obtained from 2-year bioassays, such as the EPA q_1^* value, the TD_{50}, and the lower confidence limit on the TD_{10} (LTD_{10}), are constrained to a relatively narrow range of values about the MTD, in the absence of 100% tumor incidence at the target site, which rarely occurs (Bernstein *et al.*, 1985; Freedman *et al.*, 1993; Gaylor and Gold, 1995, 1998; Gold *et al.*, 1997b). For example, the dose usually estimated by regulatory agencies to give one cancer in a million can be approximated simply by using the MTD as a surrogate for carcinogenic potency. The "virtually safe dose" (VSD) can be approximated from the MTD. Gaylor and Gold (1995) used the ratio MTD/TD_{50} and the relationship between q_1^* and TD_{50} found by Krewski *et al.* (1993) to estimate the VSD. The VSD was approximated by the MTD/740,000 for rodent carcinogens tested in the bioassay program of the NCI/NTP. The MTD/740,000 was within a factor of 10 of the VSD for 96% of carcinogens. This is similar to the finding that in near-replicate experiments of the same chemical, potency estimates vary by a factor of 4 around a median value (Gold *et al.*, 1987a; Gold *et al.*, 1989; Gaylor *et al.*, 1993).

Using the benchmark dose approach proposed in the EPA carcinogen guidelines, risk estimation is similarly constrained by bioassay design. A simple, quick, and relatively precise determination of the LTD_{10} can be obtained by the MTD divided by 7 (Gaylor and Gold, 1998). Both linear extrapolation and the use of safety or uncertainty factors proportionately reduce

a tumor dose in a similar manner. The difference in the regulatory "safe dose," if any, for the two approaches depends on the magnitude of uncertainty factors selected. Using the benchmark dose approach of the proposed carcinogen risk assessment guidelines, the dose estimated from the LTD_{10} divided, for example, by a 1000-fold uncertainty factor, is similar to the dose of an estimated risk of less than 10^{-4} using a linear model. This dose is 100 times higher than the VSD corresponding to an estimated risk of less than 10^{-6}. Thus, whether the procedure involves a benchmark dose or a linearized model, cancer risk estimation is constrained by the bioassay design.

38.5 THE HERP RANKING OF POSSIBLE CARCINOGENIC HAZARDS

Given the lack of epidemiological data to link pesticide residues to human cancer, as well as the limitations of cancer bioassays for estimating risks to humans at low exposure levels, the high positivity rate in bioassays, and the ubiquitous human exposures to naturally occurring chemicals in the normal diet that are rodent carcinogens (Tables 38.1–38.3), how can bioassay data best be used if our goal is to evaluate potential carcinogenic hazards to humans from pesticide residues in the diet? In several papers, 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 can be helpful in efforts to communicate to the public what might be important factors in cancer prevention and when selecting chemicals for chronic bioassay, mechanistic, or epidemiologic studies (Ames *et al.*, 1987, 1990b; Gold and Zeiger, 1997; Gold *et al.*, 1992). There is a need to identify what might be the important cancer hazards among the ubiquitous exposures to rodent carcinogens in everyday life.

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 to rodent carcinogens at levels that humans receive, and then to focus on those that rank highest in possible hazard (Ames *et al.*, 1987; Gold *et al.*, 1992, 1994a). 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, using the same methodology to identify a hazard, there are numerous common human exposures with much greater possible hazards. Our analyses are based on the HERP (human exposure/rodent potency) index, which indicates what percentage of the rodent carcinogenic dose (TD_{50} in mg/kg/day) a human receives from a given average daily exposure for a lifetime (mg/kg/day). 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.

The rank order of possible hazards for the given exposure estimates will be similar for the HERP ranking, for a ranking of regulatory "risk estimates" based on a linear model, or for a ranking based on TD_{10}, since all 3 methods are proportional to the dose. Overall, our analyses have shown that synthetic pesticide residues rank low in possible carcinogenic hazards 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 typical portions or average consumption of common foods. This result casts doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides (Ames *et al.*, 1987; Gold *et al.*, 1992, 1994a). A committee of the National Research Council recently reached similar conclusions about natural versus synthetic chemicals in the diet and called for further research on natural chemicals (National Research Council, 1996). (See Section 38.7 for further work on natural chemicals.)

The HERP ranking in Table 38.5 is for average U.S. exposures to all rodent carcinogens in the CPDB for which concentration data and average exposure or consumption data were both available, and for which known exposure could be chronic for a lifetime. For pharmaceuticals the doses are recommended doses; for the workplace, they are past industry or occupation averages. The 87 exposures in the ranking (Table 38.5) are ordered by possible carcinogenic hazard (HERP), and natural chemicals in the diet are reported in boldface. Our early HERP rankings were for typical dietary exposures (Ames *et al.*, 1987; Gold *et al.*, 1992), and results are similar.

Several HERP values make convenient reference points for interpreting Table 38.5. The median HERP value is 0.0025%, and the background HERP for the average chloroform level in a liter of U.S. tap water is 0.0003%. A HERP of 0.00001% is approximately equal to a regulatory VSD risk of 10^{-6} based on the linearized multi-stage model (Gold *et al.*, 1992). Using the benchmark dose approach recommended in the new EPA guidelines with the LTD_{10} as the point of departure (POD), linear extrapolation would produce a similar estimate of risk at 10^{-6} and hence a similar HERP value (Gaylor and Gold, 1998), if information on the carcinogenic mode of action for a chemical supports a nonlinear dose–response curve. The EPA guidelines call for a margin-of-exposure approach with the LTD_{10} as the POD. Based on that approach, the reference dose using a safety or uncertainty factor of 1000 (i.e., $LD_{10}/1000$) would be equivalent to a HERP value of 0.001%, which is similar to a risk of 10^{-4} based on a linear model. If the dose–response relationship is judged to be nonlinear, then the cancer risk estimate will depend on the number and magnitude of safety factors used in the assessment.

The HERP ranking maximizes possible hazards to synthetic chemicals because it includes historically high exposure values that are now much lower [e.g., DDT, saccharin, butylated hydroxyanisole (BHA), and some occupational exposures]. Additionally, the values for dietary pesticide residues are averages in the total diet, whereas for most natural chemicals the ex-

Table 38.5
Ranking Possible Carcinogenic Hazards from Average U.S. Exposures to Rodent Carcinogens

Possible hazard: HERP (%)	Average daily U.S. exposure	Human dose of rodent carcinogen	Potency TD_{50} (mg/kg/day)[a] Rats	Mice	Exposure references
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)
14	Phenobarbital, 1 sleeping pill	Phenobarbital, 60 mg	(+)	6.09	AMA (1983)
6.8	1,3-Butadiene: rubber industry workers (1978–1986)	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	·	Hirono *et al.* (1978), Culvenor *et al.* (1980)
6.1	Tetrachloroethylene: dry cleaners with dry-to-dry units (1980–1990)	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)
2.4	Acrylonitrile: production workers (1960–1986)	Acrylonitrile, 405 μg	16.9	·	Blair *et al.* (1998)
2.2	Trichloroethylene: vapor degreasing (before 1977)	Trichloroethylene, 1.02 g	668	(1580)	Page and Arthur (1978)
2.1	**Beer, 257 g**	**Ethyl alcohol, 13.1 ml**	9110	(—)	Stofberg and Grundschober (1987)
1.4	Mobile home air (14 h/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	·	Hirono *et al.* (1978), Culvenor *et al.* (1980)
0.9	Methylene chloride: workers, industry average (1940s–1980s)	Methylene chloride, 471 mg	724	(1100)	CONSAD (1990)
0.5	**Wine, 28.0 g**	**Ethyl alcohol, 3.36 ml**	9110	(—)	Stofberg and Grundschober (1987)
0.5	Dehydroepiandrosterone (DHEA)	DHEA supplement, 25 mg	68.1	·	
0.4	Conventional home air (14 h/day)	Formaldehyde, 598 μg	2.19	(43.9)	McCann *et al.* (1987)
0.2	Omeprazole	Omeprazole, 20 mg	199	(—)	PDR (1998)
0.2	Fluvastatin	Fluvastatin, 20 mg	125	·	PDR (1998)
0.1	**Coffee, 13.3 g**	**Caffeic acid, 23.9 mg**	297	(4900)	Stofberg and Grundschober (1987), Clarke and Macrae (1988)
0.1	***d*-Limonene in food**	***d*-Limonene, 15.5 mg**	204	(—)	Stofberg and Grundschober (1987)
0.04	**Bread, 67.6 g**	**Ethyl Alcohol 243 mg**	9110	(—)	Stofberg and Grundschober (1987), Wolm *et al.* (1974)
0.04	**Lettuce, 14.9 g**	**Caffeic acid, 7.90 mg**	297	(4900)	TAS (1989), Herrmann (1978)
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	(—)	TAS (1989), Schreier *et al.* (1979)
0.03	**Comfrey herb tea, 1 cup (1.5 g root)** (no longer recommended)	**Symphytine, 38 μ g**	1.91	·	Culvenor *et al.* (1980)
0.03	**Tomato, 88.7 g**	**Caffeic acid, 5.46 mg**	297	(4900)	TAS (1989), Schmidtlein and Herrmann (1975a)
0.03	**Pepper, black, 446 mg**	***d*-Limonene, 3.57 mg**	204	(—)	Stofberg and Grundschober (1987), Hasselstrom *et al.* (1957)
0.02	**Coffee, 13.3 g**	**Catechol, 1.33 mg**	88.8	(244)	Stofberg and Grundschober (1987), Tressl *et al.* (1978), Rahn and König (1978)
0.02	**Furfural in food**	**Furfural, 2.72 mg**	(683)	197	Stofberg and Grundschober (1987)
0.02	**Mushroom (*Agaricus bisporus*) 2.55 g**	**Mixture of hydrazines, etc. (whole mushroom)**	—	20,300	Stofberg and Grundschober (1987), Toth and Erickson (1986), Matsumoto *et al.* (1991)

(*continues*)

Table 38.5
(*continued*)

Possible hazard: HERP (%)	Average daily U.S. exposure	Human dose of rodent carcinogen	Potency TD_{50} (mg/kg/day)[a] Rats	Mice	Exposure references
0.02	**Apple, 32.0 g**	**Caffeic acid, 3.40 mg**	297	(4900)	EPA (1989a), Mosel and Herrmann (1974)
0.02	**Coffee, 13.3 g**	**Furfural, 2.09 mg**	(683)	197	Stofberg and Grundschober (1987)
0.01	BHA: daily U.S. avg (1975)	BHA, 4.6 mg	606	(5530)	FDA (1991b)
0.01	**Beer (before 1979), 257 g**	**Dimethylnitrosamine, 726 ng**	0.0959	(0.189)	Stofberg and Grundschober (1987), Fazio *et al.* (1980), Preussmann and Eisenbrand (1984)
0.008	**Aflatoxin: daily U.S. avg (1984–1989)**	**Aflatoxin, 18 ng**	0.0032	(+)	FDA (1992b)
0.007	**Cinnamon, 21.9 mg**	**Coumarin, 65.0 μg**	13.9	(103)	Poole and Poole (1994)
0.006	**Coffee, 13.3 g**	**Hydroquinone, 333 μg**	82.8	(225)	Stofberg and Grundschober (1987), Tressl *et al.* (1978), Heinrich and Baltes (1987)
0.005	Saccharin: daily U.S. avg (1977)	Saccharin, 7 mg	2140	(—)	NRC (1979)
0.005	**Carrot, 12.1 g**	**Aniline, 624 μg**	194[b]	(—)	TAS (1989), Neurath *et al.* (1977)
0.004	**Potato, 54.9 g**	**Caffeic acid, 867 μg**	297	(4900)	TAS (1989), Schmidtlein and Herrmann (1975c)
0.004	**Celery, 7.95 g**	**Caffeic acid, 858 μg**	297	(4900)	ERS (1994), Stöhr and Herrmann (1975)
0.004	**White bread, 67.6 g**	**Furfural, 500 μg**	(683)	197	Stofberg and Grundschober (1987)
0.003	*d*-Limonene	Food additive, 475 μg	204	(—)	Clydesdale (1997)
0.003	**Nutmeg, 27.4 mg**	***d*-Limonene, 466 μg**	204	(—)	Stofberg and Grundschober (1987), Bejnarowicz and Kirch (1963)
0.003	Conventional home air (14 h/day)	Benzene, 155 μg	(169)	77.5	McCann *et al.* (1987)
0.002	**Coffee, 13.3 g**	**4-Methylcatechol, 433 μg**	248	·	Stofberg and Grundschober (1987), Heinrich and Baltes (1987), IARC (1991)
0.002	**Carrot, 12.1 g**	**Caffeic acid, 374 μg**	297	(4900)	TAS (1989), Stöhr and Herrmann (1975)
0.002	Ethylene thiourea: daily U.S. avg (1990)	Ethylene thiourea, 9.51 μg	7.9	(23.5)	EPA (1991a)
0.002	BHA: daily U.S. avg (1987)	BHA, 700 μg	606	(5530)	FDA (1991b)
0.002	DDT: daily U.S. avg (before 1972 ban)[d]	DDT, 13.8 μg	(84.7)	12.8	Duggan and Corneliussen (1972)
0.001	**Plum, 2.00 g**	**Caffeic acid, 276 μg**	297	(4900)	ERS (1995), Mosel and Herrmann (1974)
0.001	**Pear, 3.29 g**	**Caffeic acid, 240 μg**	297	(4900)	Stofberg and Grundschober (1987), Mosel and Herrmann (1974)
0.001	[UDMH: daily U.S. avg (1988)]	[UDMH, 2.82 μg (from Alar)]	(—)	3.96	EPA (1989a)
0.0009	**Brown mustard, 68.4 mg**	**Allyl isothiocyanate, 62.9 μg**	96	(—)	Stofberg and Grundschober (1987), Carlson *et al.* (1987)
0.0008	DDE: daily U.S. avg (before 1972 ban)[d]	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)	EPA (1994b)
0.0006	**Bacon, 11.5 g**	**Diethylnitrosamine, 11.5 ng**	0.0266	(+)	Stofberg and Grundschober (1987), Sen *et al.* (1979)
0.0006	**Mushroom (*Agaricus bisporus*) 2.55 g**	**Glutamyl-*p*-hydrazinobenzoate, 107 μg**	·	277	Stofberg and Grundschober (1987), Chauhan *et al.* (1985)
0.0005	**Bacon, 11.5 g**	**Dimethylnitrosamine, 34.5 ng**	0.0959	(0.189)	Stofberg and Grundschober (1987), Sen *et al.* (1979)
0.0004	**Bacon, 11.5 g**	***N*-Nitrosopyrrolidine, 196 ng**	(0.799)	0.679	Stofberg and Grundschober (1987), Tricker and Preussmann (1991)
0.0004	EDB: daily U.S. avg (before 1984 ban)[d]	EDB, 420 ng	1.52	(7.45)	EPA (1984b)
0.0004	Tap water, 1 liter (1987–1992)	Bromodichloromethane, 13 μg	(72.5)	47.7	AWWA (1993)
0.0003	**Mango, 1.22 g**	***d*-Limonene, 48.8 μg**	204	(—)	ERS (1995), Engel and Tressl (1983)

(*continues*)

Table 38.5
(*continued*)

Possible hazard: HERP (%)	Average daily U.S. exposure	Human dose of rodent carcinogen	Potency TD_{50} (mg/kg/day)[a] Rats	Mice	Exposure references
0.0003	**Beer, 257 g**	**Furfural, 39.9 μg**	(683)	197	Stofberg and Grundschober (1987)
0.0003	Tap water, 1 liter (1987–1992)	Chloroform, 17 μg	(262)	90.3	AWWA (1993)
0.0003	**Beer (1994–1995), 257 g**	**Dimethylnitrosamine, 18 ng**	0.0959	(0.189)	Glória *et al.* (1997)
0.0003	Carbaryl: daily U.S. avg (1990)	Carbaryl, 2.6 μg	14.1	(—)	FDA (1991a)
0.0002	**Celery, 7.95 g**	**8-Methoxypsoralen, 4.86 μg**	32.4	(—)	ERS (1994), Beier *et al.* (1983)
0.0002	Toxaphene: daily U.S. avg (1990)[d]	Toxaphene, 595 ng	(—)	5.57	FDA (1991a)
0.00009	**Mushroom (*Agaricus bisporus*), 2.55 g**	***p*-Hydrazinobenzoate, 28 μg**	·	454[b]	Stofberg and Grundschober (1987), Chauhan *et al.* (1985)
0.00008	PCBs: daily U.S. avg (1984–1986)	PCBs, 98 ng	1.74	(9.58)	Gunderson (1995)
0.00008	DDE/DDT: daily U.S. avg (1990)[d]	DDE, 659 ng	(—)	12.5	FDA (1991a)
0.00007	**Parsnip, 54.0 mg**	**8-Methoxypsoralen, 1.57 μg**	32.4	(—)	UFFVA (1989), Ivie *et al.* (1981)
0.00007	**Toast, 67.6 g**	**Urethane, 811 ng**	(41.3)	16.9	Stofberg and Grundschober (1987), Canas *et al.* (1989)
0.00006	**Hamburger, pan fried, 85 g**	**PhIP, 176 ng**	4.22[b]	(28.6[b])	TAS (1989), Knize *et al.* (1994)
0.00006	Furfural	Food additive, 7.77 μg	(683)	197	Clydesdale (1997)
0.00005	**Estragole in spices**	**Estragole, 1.99 μg**	·	51.8	Stofberg and Grundschober (1987)
0.00005	**Parsley, fresh, 324 mg**	**8-Methoxypsoralen, 1.17 μg**	32.4	(—)	UFFVA (1989), Chaudhary *et al.* (1986)
0.00005	Estragole	Food additive, 1.78 μg	·	51.8	Clydesdale (1997)
0.00003	**Hamburger, pan fried, 85 g**	**MeIQx, 38.1 ng**	1.66	(24.3)	TAS (1989), Knize *et al.* (1994)
0.00002	Dicofol: daily U.S. avg (1990)	Dicofol, 544 ng	(—)	32.9	FDA (1991a)
0.00001	**Beer, 257 g**	**Urethane, 115 ng**	(41.3)	16.9	Stofberg and Grundschober (1987), Canas *et al.* (1989)
0.000006	**Hamburger, pan fried, 85 g**	**IQ, 6.38 ng**	1.65[b]	(19.6)	TAS (1989), Knize *et al.* (1994)
0.000005	Hexachlorobenzene: daily U.S. avg (1990)	Hexachlorobenzene, 14 ng	3.86	(65.1)	FDA (1991a)
0.000001	Lindane: daily U.S. avg (1990)	Lindane, 32 ng	(—)	30.7	FDA (1991a)
0.0000004	PCNB: daily U.S. avg (1990)	PCNB (Quintozene), 19.2 ng	(—)	71.1	FDA (1991a)
0.0000001	Chlorobenzilate: daily U.S. avg (1989)[d]	Chlorobenzilate, 6.4 ng	(—)	93.9	FDA (1991a)
0.00000008	Captan: daily U.S. avg (1990)	Captan, 115 ng	2080	(2110)	FDA (1991a)
0.00000001	Folpet: daily U.S. avg (1990)	Folpet, 12.8 ng	(—)	1550	FDA (1991a)
<0.00000001	Chlorothalonil: daily U.S. avg (1990)	Chlorothalonil, <6.4 ng	828[c]	(—)	FDA (1991a), EPA (1987a)

Chemicals that occur naturally in foods are in bold face. *Daily human exposure:* Reasonable daily intakes are used to facilitate comparisons. The calculations assume a daily dose for a lifetime. *Possible hazard:* The human dose of rodent carcinogen is divided by 70 kg to give a mg/kg/day of human exposure, and this dose is given as the percentage of the TD_{50} in the rodent (mg/kg/day) to calculate the human exposure/rodent potency (HERP) index. TD_{50} values used in the HERP calculation are averages calculated by taking the harmonic mean (see Section 38.8) 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.

[a] ·, no data in the CPDB; a number in parentheses indicates a TD_{50} value not used in the HERP calculation because the 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}.

[b] The TD_{50} harmonic mean was estimated for the base chemical from the hydrochloride salt.

[c] Additional data from the EPA that were not in the CPDB were used to calculate this TD_{50} harmonic mean.

[d] No longer contained in any registered pesticide product (EPA, 1998).

posure amounts are for concentrations of a chemical in an individual food (i.e., foods for which data are available on concentration and average consumption).

Table 38.5 indicates that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals if the same methodology were used for both naturally occurring and synthetic chemicals. For many natural chemicals, the HERP values are in the top half of the table, even though natural chemicals are markedly underrepresented because so few have been tested in rodent bioassays. We will discuss several categories of exposure and indicate that mechanistic data are available for some chemicals, which suggest that the possible hazard may not be relevant to humans or would be low if nonlinearity or a threshold were taken into account in risk assessment.

Occupational Occupational and pharmaceutical 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 (Tomatis and Bartsch, 1990; IARC, 1971–1999). HERP values rank at the top of Table 38.5 for past chemical exposures in some occupations to ethylene dibromide, 1,3-butadiene, tetrachloroethylene, formaldehyde, acrylonitrile, trichloroethylene, and methylene chloride. When exposures are high, the margin of exposure from the carcinogenic dose in rodents is low. The issue of how much human cancer can be attributed to occupational exposure has been controversial, but a few percent seems a reasonable estimate (Ames *et al.*, 1995).

In another analysis, we have used permitted exposure limits (PELs), recommended in 1989 by the U.S. 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 (permitted exposure/rodent potency) index] (Gold *et al.*, 1987b, 1994a). We found that the PELs for 9 chemicals were greater than 10% of the rodent carcinogenic dose and for 27 they were between 1 and 10% of the rodent dose. The 1989 PELS were vacated by the Supreme Court because of a lack of risk assessment on each individual chemical. For the PELs that are currently the legal standard, PERP values for 14 chemicals are greater than 10%. For trichloroethylene, we recently conducted an analysis based on an assumed cytotoxic mechanism of action and PBPK-effective dose estimates defined as peak concentrations. Our estimates indicate that occupational respiratory exposures at the PEL for trichloroethylene would produce metabolite concentrations that exceed an acute no observed effect level (NOEL) for hepatotoxicity in mice. On this basis, the OSHA PEL is not expected to be protective. In comparison the EPA maximum concentration limit (MCL) in drinking water of 5 μg/l, based on a linearized multistage model, is more stringent than our estimate of an MCL based on a 1000-fold safety (uncertainty) factor, which is 210 μg/l (Bogen and Gold, 1997).

Pharmaceuticals Some pharmaceuticals that are used chronically are clustered near the top of the HERP ranking (e.g., phenobarbital, clofibrate, and fluvastatin). In Table 38.3, we reported that 49% of the drugs in the PDR with cancer test data are positive in rodent bioassays (Davies and Monro, 1995), as are 44% of drug submissions to the FDA (Contrera *et al.*, 1997). Most drugs, however, are used for only short periods, and the HERP values for the rodent carcinogens would not be comparable to the chronic, long-term administration used in HERP. Assuming a hypothetical lifetime exposure at therapeutic doses (i.e., not averaged over a lifetime), the HERP values would be high—for example, phenacetin (0.3%), metronidazole (5.6%), and isoniazid (14%).

Herbal supplements have recently developed into a large market in the United States; they have not, however, been a focus of carcinogenicity testing. The FDA regulatory requirements for safety and efficacy that are applied to pharmaceutical drugs do not pertain to herbal supplements under the 1994 Dietary Supplements and Health Education Act (DSHEA), and few have been tested for carcinogenicity. Those that are rodent carcinogens tend to rank high in HERP because, similar to 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 the FDA for food additives that are "generally recognized as safe" (GRAS) are also not applicable to dietary supplements (Burdock, 2000) even though supplements are used at higher doses. The NTP is currently testing several herbs or chemicals in herbs.

Comfrey is a medicinal herb whose roots and leaves have been shown to be carcinogenic in rats. The formerly recommended dose of 9 daily comfrey–pepsin tablets has a HERP value of 6.2%. Symphytine, a pyrrolizidine alkaloid plant pesticide that is present in comfrey–pepsin tablets and comfrey tea, is a rodent carcinogen; the HERP value for symphytine is 1.3% in the comfrey 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 *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). Over 200 pyrrolizidine alkaloids are present in more than 300 plant species (Prakash *et al.*, 1999). 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 (Gold *et al.*, 1997b).

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 and sold widely for a variety of purposes including the delay of aging. In rats, DHEA induces liver tumors (Rao *et al.*, 1992a; Hayashi *et al.*, 1994), and the HERP value for the recommended human dose of one daily capsule containing 25 mg DHEA is 0.5%. The mechanism of liver carcinogenesis in rats is peroxisome proliferation, similar to clofibrate (Ward *et al.*, 1998; Woodyatt *et al.*, 1999). DHEA also inhibited the development of tumors of the rat testis (Rao *et al.*, 1992b) and rat and mouse mammary gland (Schwartz *et al.*, 1981; McCormick *et al.*, 1996). 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).

Natural Pesticides Natural pesticides, because few have been tested, are markedly underrepresented in our HERP analysis. More important, for each plant food listed, there are about 50 additional untested natural pesticides. Although about

10,000 natural pesticides and their breakdown products occur in the human diet (Ames *et al.*, 1990b), only 71 have been tested adequately in rodent bioassays (Table 38.1). Average exposures to many natural-pesticide rodent carcinogens in common foods rank above or close to the median in our HERP table (Table 38.5), 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 (in mustard); *d*-limonene (in 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, as discussed in Section 38.2 (Hard and Whysner, 1994; International Agency for Research on Cancer, 1993; Rice *et al.*, 1999; U.S. Environmental Protection Agency, 1991a).

Synthetic Pesticides Synthetic pesticides currently in use that are rodent carcinogens in the CPDB and that are quantitatively detected by the FDA Total Diet Study (TDS) as residues in food are all included in Table 38.5. Many are at the very bottom of the ranking; however, HERP values are about at the median for ethylene thiourea (ETU), UDMH (from Alar) before its discontinuance, and DDT before its ban in the United States in 1972. These three synthetic pesticides rank below the HERP values for many naturally occurring chemicals that are common in the diet. The HERP values in Table 38.5 are for residue intake by females 65 and older, because 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, average 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, even though there is no convincing epidemiological evidence of a carcinogenic hazard to humans (Key and Reeves, 1994) and although natural pesticides can also bioaccumulate. 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 protocol used few animals and dosing was discontinued after 11 years, which may have reduced the sensitivity of the study (Gold *et al.*, 1999). The HERP value for DDT residues in food before the ban was 0.0008%.

Current U.S. 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 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. A 1970 National Academy of Sciences report concluded: "In little more than two decades DDT has prevented 500 million deaths due to malaria, that would otherwise have been inevitable" (National Academy of Sciences, 1970).

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.*, 1997a), 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%), which is at the median of the ranking. The HERP 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 value (U.S. Environmental Protection Agency, 1992). (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 therefore exposure levels and HERP values would be 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 (HERP = 0.0004%). This HERP value ranks low, compared to the HERP of 140% for the high exposures to EDB that some workers received in the 1970s which is at the top of the ranking (Gold *et al.*, 1992). Two other pesticides in Table 38.5, toxaphene (HERP = 0.0002%) and chlorobenzilate (HERP = 0.0000001%), have been cancelled (Ames and Gold, 1991; U.S. Environmental Protection Agency, 1998).

Most residues of synthetic pesticides have HERP values below the median. In descending order of HERP, these are carbaryl, toxaphene, dicofol, lindane, PCNB, chlorobenzilate, captan, folpet, and chlorothalonil. Some of the lowest HERP values in Table 38.5 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 the NRC to have a human cancer risk above 10^{-6} (National Research Council, 1987). The contrast between the low HERP values for synthetic pesticide residues in our ranking and the higher NRC risk estimates is examined in Section 38.6.

Cooking and Preparation of Food and Drink Cooking and preparation of food can also produce chemicals that are rodent carcinogens. Alcoholic beverages cause cancer in humans in the liver, esophagus, and oral cavity. The HERP values in Table 38.5 for alcohol in beer (2.1%) and wine (0.5%) are high in the ranking. Ethyl alcohol is one of the least potent rodent carcinogens in the CPDB, but the HERP is high because of high concentrations in alcoholic beverages and high U.S. consumption. Another fermentation product, urethane (ethyl carbamate), has a HERP value of 0.00001% for average beer consumption and 0.00007% for average bread consumption (as toast).

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 the average consumption of coffee is 0.02% and in white bread it is 0.004%. Furfural is also used as a commercial food additive, and the HERP for total average U.S. consumption as an additive is much lower (0.00006%).

Nitrosamines in food are formed by cooking from nitrite or nitrogen oxides (NO_x) and amines. Tobacco smoking and smokeless tobacco are a major source of nonoccupational 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 (Table 38.5), and it has been estimated that in several countries humans are exposed to about 0.3–1 μg/day (National Academy of Sciences, 1981; Tricker and Preussmann, 1991), primarily *N*-nitrosodimethylamine (DMN), *N*-nitrosopyrrolidine, and *N*-nitrosopiperidine. The largest exposure is 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 *et al.*, 1997). By the 1990s, the HERP was 0.0003% (Glória *et al.*, 1997). The HERP values for the average consumption of bacon are lower: DMN = 0.0005%, DEN = 0.0006%, and NPYR = 0.0004%. DEN induced liver tumors in rhesus and cynomolgus monkeys and tumors of the nasal mucosa in bush babies (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 (HAs) are formed when meat, chicken, and fish are cooked, particularly when charred. Compared to other rodent carcinogens, there is strong evidence of carcinogenicity for HAs in terms of positivity rates and multiplicity of target sites; however, concordance in target sites between rats and mice for these HAs is generally restricted to the liver (Gold *et al.*, 1994b). Under usual cooking conditions, exposures to HAs are in the low ppb range, and the HERP values for pan-fried hamburger are low. The HERP value for PhIP is 0.00006%, for MeIQx it is 0.00003%, and for IQ it is 0.000006%. Carcinogenicity of the three HAs 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). 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 in progress. Metabolism studies indicate the importance of *N*-hydroxylation in the carcinogenic effect of HAs in monkeys (Snyderwine *et al.*, 1997). IQ is activated via *N*-hydroxylation and forms DNA adducts; the *N*-hydroxylation of IQ appears to be carried out largely by hepatic CYP3A4 and/or CYP2C9/10, and not by CYP1A2; whereas the poor activation of MeIQx appears to be due to a lack of expression of CYP1A2 and an inability of other cytochromes P450, such as CYP3A4 and CYP2C9/10, to *N*-hydroxylate the quinoxalines. PhIP is activated by *N*-hydroxylation in monkeys and forms DNA adducts, suggesting that it might turn out to have a carcinogenic effect (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, and alcohol) or synthetic (e.g., BHA and saccharin; Table 38.5). The highest HERP values for average dietary exposures to synthetic rodent carcinogens in Table 38.5 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 the mechanism of carcinogenesis strongly suggest that there would be no risk to humans at the levels found in food.

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 sixfold (HERP = 0.002%) (U.S. Food and Drug Administration, 1991b); 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 *et al.*, 1990). Humans do not have a forestomach. We note that the dose–response relationship 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 the TD_{50}, the HERP values for BHA would be 25 times lower (California Environmental Protection Agency, 1994). A recent epidemiological study in the Netherlands found no association between

BHA consumption and stomach cancer in humans (Botterweck *et al.*, 2000).

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 reevaluated the potential carcinogenic risk of saccharin to humans. The NTP delisted saccharin in its *Report on Carcinogens* (U.S. National Toxicology Program, 2000a), and the IARC downgraded its evaluation to Group 3, "not classifiable as to carcinogenicity to humans" (International Agency for Research on Cancer, 1971–1999). There is convincing evidence that the induction of bladder tumors in rats by sodium saccharin requires a high dose and is related to the development of a calcium phosphate–containing precipitate in the urine (Cohen, 1995a), which is not relevant to human dietary exposures. In a recently completed 24-year study by the 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 *et al.*, 1994). The average daily dose rate of sodium saccharin (mg/kg/day) was about 100 times lower than the dose that was carcinogenic to rats (Gold *et al.*, 1997c, 1999). 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. 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, 1995a).

For three naturally occurring chemicals that are also produced commercially and used as food additives, average exposure data are available and they are included in Table 38.5. The HERP values are as follows: For furfural, the HERP value for the natural occurrence is 0.02% compared to 0.00006% for the additive; for *d*-limonene, the natural occurrence HERP is 0.1% compared to 0.003% for the additive; and for estragole, the HERP is 0.00005% for both the natural occurrence and the additive.

Safrole is the principal component (up to 90%) of oil of sassafras. 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%. In 1960, safrole and safrole-containing sassafras oils were banned from use as food additives in the United States (U.S. Food and Drug Administration, 1960). Before 1960, for a person consuming a glass of sassafras root beer per day for life, the HERP value would have been 0.2% (Ames *et al.*, 1987). Sassafras root can still be purchased in health food stores and can therefore be used to make tea (Heikes, 1994); the recipe is on the World Wide Web.

Mycotoxins Of the 23 fungal toxins tested for carcinogenicity, 14 are positive (61%) (Table 38.3). The mutagenic mold toxin, aflatoxin, which is found in moldy peanut and corn products, interacts with chronic hepatitis infection in human liver cancer development (Qian *et 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 *et al.*, 1992). The HERP value for aflatoxin of 0.008% is based on the rodent potency. If the lower human potency value calculated from epidemiological data by the FDA were used instead, the HERP would be about 10-fold lower (U.S. Food and Drug Administration, 1993b). 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 United States. Hepatitis viruses can account for half of liver cancer cases among non-Asians and even more among Asians in the United States (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 close to the median of Table 38.5 (International Life Sciences Institute, 1996; Kuiper-Goodman and Scott, 1989).

Synthetic Contaminants Polychlorinated biphenyls (PCBs) and tetrachlorodibenzo-*p*-dioxin (TCDD), 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 *et al.*, 1986; Gunderson, 1995). The HERP value for the most recent reporting of the FDA Total Diet Study (1984–1986) is 0.00008%, toward 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).

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 (U.S. Environmental Protection Agency, 2000) proposes that the source of TCDD is primarily from the atmosphere directly from emissions (e.g., incinerators) or indirectly by returning dioxin to the atmosphere (U.S. Environmental Protection Agency, 2000). 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, 2000). Dioxin emissions decreased by 80% from 1987 to 1995, which the EPA attributes to reduced emissions from incineration of medical and municipal waste (U.S. Environmental Protection Agency, 2000).

The HERP value of 0.0004% for average U.S. intake of TCDD (U.S. Environmental Protection Agency, 2000) is below the median of the values in Table 38.6. Recently, the EPA

Table 38.6
Tumor Incidence Data Used in Recalculations of Carcinogenic Potency for 19 Chemicals in the NRC Report

Pesticide[a]	Weeks on test	Sex–species[b]	Target organ	Dose groups (mg/kg/day)[c]	Tumor incidence	TD_{50} (mg/kg/day)
Acephate$^{NA(Cnq)}$	105	FM	Liver	0, 7.5, 37.5, 150	1/62, 3/61, 0/62, 15/61	499
Alachlor$^{B2(MOE)}$	110	FR	Nasal Turbinate	0, 0.5, 2.5, 15	0/44, 0/47, 0/44, 15/45	36.8
		MR			0/42, 0/42, 1/47, 14/48	
Asulam$^{NA(Cnq)}$	108	MR	Thyroid gland	0, 36, 180, 953	0/43, 9/43, 7/43, (2/40)[d]	724
Azinphosmethyl$^{D(E)}$ (Guthion)	114[e]	MR	Thyroid gland	0, 3.9, 7.8	1/9, 10/44, 12/43	31.6
Benomyl^{Cq}	104	FM	Liver	0, 75, 225, 1130	1/74, 9/70, 20/75, 15/75	4,400
Captafol^{B2}	104	FR	Liver	0, 2.8, 12.1, 54.8	4/50, 2/49, 3/50, 17/50	202
		MR	Kidney		1/50, 1/50, 0/50, 7/50	
Captan^{B2}	113	FM	Digestive tract	0, 879, 1480, 2370	3/80, 26/80, 21/80, 29/80	4,480
		MM			3/80, 19/80, 22/80, 39/80	
	95	FM		0, 15, 60, 120, 900	0/100, 1/100, 3/100, 4/100, 9/100	
		MM			0/100, 7/100, 1/100, 1/100, 7/100	
Chlordimeform^{B2}	104	FM	Hematopoietic	0, 0.3, 3, 30, 75	3/38, 1/35, 11/42, 31/39, 34/41	21.7
		MM			3/47, 1/46, 12/46, 32/47, 40/47	
Chlorothalonil$^{NA(B2)(MOE)}$	129	FR	Kidney	0, 40, 80, 175	0/59, 2/60, 7/57, 19/58	566
Cypermethrin$^{Cq(Cnq)}$	101	FM	Lung	0, 15, 60, 240	12/127, 6/64, 8/64, 14/61	954
Folpet^{B2}	113	FM	Digestive tract	0, 96, 515, 1280	0/104, 1/80, 8/80, 41/80	1,910
		MM		0, 93, 502, 1280	1/104, 2/80, 8/80, 41/80	
Fosetyl Al$^{Cq(Cnq)(Unclassified)}$ (Aliette)	104	MR	Adrenal gland	0, 100, 400, 1510	6/80, 7/78, 16/79, (18/80)[d]	1,860
Glyphosate$^{Cq(E)}$	104	MM	Kidney	0, 150, 750, 4500	1/49, 0/49, 1/50, 3/50	62,000
Linuron$^{Cq(Cnq)}$	104	MR	Testis	0, 2.5, 6.25, 31.3	4/70, 9/69, 20/70, 37/70	28.1
Metolachlor$^{Cq(Cnq)(MOE)}$	104	FR	Liver	0, 1.5, 15, 150	0/60, 1/60, 2/60, 7/60	839
Oryzalin^{Cq}	104	FR	Skin	0, 15, 45, 135	1/60, 2/60, 4/60, 9/60	394
		MR			5/60, 6/60, 6/60, 24/59	
Oxadiazon$^{B2(Cq)}$	105	FM	Liver	0, 15, 45, 150, 300	4/56, 13/61, 18/64, 27/55, 32/57	213
		MM			20/64, 40/67, 52/69, 44/65, 28/35	
Parathion$^{Cq(Cnq)}$	112	FR	Adrenal gland	0, 1.15, 2.25	1/10, 6/47, 13/42	7.95
		MR		0, 1.6, 3.15	0/9, 7/49, 11/46	
Permethrin^{Cq}	104	FM	Lung	0, 3, 375, 750	15/71, 24/68, 35/68, 44/69	717

[a] EPA weight-of-evidence evaluation reported as superscript. If more than one classification is reported, the first values are from the NRC report and values in parentheses are from the EPA's revised evaluations since 1987 (Burnam, 2000; Irene, 1995). B2: Sufficient evidence of carcinogenicity from animal studies with inadequate or no epidemiologic data—probable human carcinogen. Cq: Limited evidence of carcinogenicity from animal studies in the absence of human data—possible human carcinogen (quantifiable). Cnq: Limited evidence (not quantified by the EPA, i.e., no q_1^*). D: Human and animal data are either inadequate or absent—not classifiable as to human carcinogenicity. E: Evidence of noncarcinogenicity to humans. NA indicates that the chemical was not classified at the time of the NRC report. MOE: The Health Effects Division Carcinogenicity Peer Review Committee (HCPRC) recommended under the newly proposed EPA guidelines a margin-of-exposure approach for risk assessment for these three chemicals: alachlor, chlorothalonil, and metolachlor. For alachlor, the current Office of Pesticide Programs (OPP) classification is "Likely (high doses), Not Likely (low doses). " For chlorothalonil, the classification is "Likely" with recommendation for a nonlinear approach to risk assessment. Unclassified: For fosetyl Al, the HCPRC concluded that it "was not amenable to classification using current Agency cancer guidelines. The HCPRC concluded that pesticidal use of fosetyl-Al is unlikely to pose a carcinogenic hazard to humans" (Burnam, 2000). Captafol and chlordimeform uses have been canceled (U.S. Environmental Protection Agency, 1998).

[b] FM, female mouse; MM, male mouse; FR, female rat; MR, male rat. If more than one group is reported, the potency calculation is a geometric mean of the TD_{50} for the experiments in this table only.

[c] Unless mg/kg/day are given in the EPA memorandum, doses are converted from ppm to mg/kg body weight/day by standard EPA conversion factors: 0. 05 for rats and 0. 15 for mice. All chemicals were administered in the diet.

[d] Doses in parentheses were not used in the calculation of either the TD_{50} or the EPA q_1^*. For fosetyl Al, the adrenal gland q_1^* most closely replicated the NRC q_1^*; in later EPA documents, urinary bladder was the target site and results were not considered appropriate for quantification (Quest *et al.*, 1991).

[e] Dosing was only for 80 weeks.

has reestimated the potency of TCDD based on a change in the dose-metric to body burden in humans (rather than intake) (U.S. Environmental Protection Agency, 2000) and a reevaluation of tumor data in rodents (which determined two-thirds fewer liver tumors) (Goodman and Sauer, 1992). Using this EPA potency for HERP would put TCDD at the median of HERP values in Table 38.6, 0.002%.

TCDD 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 AhR (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 also bind to the AhR [e.g., indole-3-carbinol (I3C)]. I3C is the main breakdown compound of glucobrassicin, a glucosinolate 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). The binding affinity (greater for TCDD) and the amounts consumed (much greater for dietary compounds) both need to be considered in comparing possible harmful effects. Some studies provide evidence of enhancement of carcinogenicity by I3C (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, b; U.S. National Toxicology Program, 2000b) and is also being tested for carcinogenicity in rodents by NTP (U.S. National Toxicology Program, 2000b). 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, 2000b).

TCDD has received enormous scientific and regulatory attention, most recently in an ongoing assessment by the EPA (U.S. Environmental Protection Agency, 1994a, 1995a, 2000). Some epidemiologic studies suggest an association with cancer mortality. In 1997 the IARC evaluated the epidemiological evidence for carcinogenicity of TCDD in humans as limited (International Agency for Research on Cancer, 1997). The strongest epidemiological evidence was among highly exposed workers for overall cancer mortality. There is no sufficient evidence in humans for any particular target organ. Estimated blood levels of TCDD in studies of those highly exposed workers were similar to blood levels in rats in positive cancer bioassays (International Agency for Research on Cancer, 1997). In contrast, background levels of TCDD in humans are about 100- to 1000-fold lower than in the rat study. The similarities of worker and rodent blood levels and the mechanism of the AhR in both humans and rodents were considered by the IARC when it evaluated TCDD as a Group 1 carcinogen in spite of only limited epidemiological evidence. The IARC also 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." The NTP *Report on Carcinogens* recently evaluated TCDD in an addendum to the *Ninth Report on Carcinogens* as a known human carcinogen (U.S. National Toxicology Program, 2000a, 2001). The EPA draft final report (U.S. Environmental Protection Agency, 2000) 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). Possible limitations of data or scientific tools were given by the EPA as possible reasons for the lack of observed effects.

In summary, the HERP ranking in Table 38.5 indicates that when synthetic pesticide residues in the diet are ranked on an index of possible carcinogenic hazard and compared to the ubiquitous exposures to rodent carcinogens, they rank low. 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, and that there is an imbalance in testing of synthetic chemicals compared to natural chemicals. There is an enormous background of natural chemicals in the diet that rank high in possible hazard, even though so few have been tested in rodent bioassays. In Table 38.5, 90% of the HERP values are above the level that would approximate a regulatory virtually safe dose of 10^{-6} if a qualitative risk assessment were performed.

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. In fact, epidemiological results indicate that adequate consumption of fruits and vegetables reduces cancer risk at many sites (Block *et al.*, 1992) and that protective factors like the intake of vitamins such as folic acid are important, rather than the intake of individual rodent carcinogens.

The HERP ranking also indicates the importance of data on the mechanism of carcinogenesis for each chemical. For several chemicals, data have recently been generated that indicate that exposures would not be expected to be a cancer risk to humans at the levels consumed (e.g., saccharin, BHA, chloroform, *d*-limonene, discussed previously). Standard practice in regulatory risk assessment for chemicals that induce tumors in high-dose rodent bioassays has been to extrapolate risk to low dose in humans by multiplying potency by human exposure. Without data on the mechanism of carcinogenesis, however, the true human risk of cancer at low dose is highly uncertain and could be 0 (Ames and Gold, 1990; Clayson and Iverson, 1996; Gold *et al.*, 1992; Goodman, 1994). Adequate risk assess-

ment from animal cancer tests requires more information for a chemical about pharmacokinetics, mechanism of action, apoptosis, cell division, induction of defense and repair systems, and species differences.

38.6 PESTICIDE RESIDUES IN FOOD: INVESTIGATION OF DISPARITIES IN CANCER RISK ESTIMATES

There are large disparities in the published cancer risk estimates for synthetic pesticide residues in the U.S. diet. In our HERP ranking in Table 38.5, the possible carcinogenic hazards of such residues rank low when viewed in the broadened perspective of exposures to naturally occurring chemicals that are rodent carcinogens. This section examines the extent to which disparities in risk estimates are due to differences in potency estimation from rodent bioassay data (q_1^* vs. TD_{50}) or to differences in estimation of human dietary exposure (Theoretical Maximum Residue Contribution vs. Total Diet Study). Our analysis is based on risk estimates for 29 pesticides, herbicides, and fungicides that were published by the National Research Council (NRC) in its 1987 report, *Regulating Pesticides in Food: The Delaney Paradox* (National Research Council, 1987). The NRC used potency and exposure estimates of the EPA and concluded that dietary risks for 23 pesticides were greater than one in a million and therefore were not negligible. The methodologies to estimate both potency and exposure differed between the NRC and our HERP index, and these differences are examined here to explain the difference in evaluation of possible cancer hazards from synthetic pesticide residues. For both the EPA and the HERP, risk estimation uses a linear extrapolation and is simply potency × dose. Our analysis below indicates that the disparities in risk estimates are due to widely different exposure estimates, rather than to different estimated values of carcinogenic potency.

The NRC report used the standard regulatory default methodology of the EPA to estimate risk, that is, to evaluate the weight of evidence of carcinogenicity for a chemical from chronic rodent bioassays and extrapolate risk using an upper bound estimate of potency (q_1^*) and the linearized multistage model (LMS) (Crump, 1984). Our HERP ranking used the TD_{50} (the tumorigenic dose rate for 50% of test animals) as a measure of potency, and the HERP index is a simple proportion: exposure/potency (Section 38.4). To compare potency estimates, we first attempted to reproduce the tumor site and incidence data and the EPA q_1^* values reported by the NRC so that we could use the correct data to estimate the TD_{50} and then compare the two estimates. The NRC report did not present the tumor incidence data, and for most experiments the results did not appear in the general published literature. We obtained the results from EPA memoranda and personal communications (Table 38.6).

The NRC report and the HERP ranking used two different estimates of human exposure to pesticide residues in the diet. The NRC used the EPA Theoretical Maximum Residue Contribution (TMRC), whereas the HERP ranking used the FDA Total Diet Study (TDS). The TMRC is a theoretical maximum exposure, whereas exposure in the TDS is measured as dietary residues in table-ready food. We assess the magnitude of the differences between the two potency estimates q_1^* and TD_{50} when both use the same rodent results and then compare the differences between the two exposure estimates, TMRC and TDS, in order to determine the basis for disparate risk estimates.

Since publication of the NRC report in 1987, the EPA has made several changes in the risk estimates of some pesticides. We discuss these changes, including: reevaluations of the weight of evidence of carcinogenicity using rodent bioassay results, changes in whether risks should be quantified, changes in exposure estimation, and proposed changes in risk assessment methodology.

38.6.1 REPRODUCIBILITY OF THE q_1^* VALUES

The NRC, in *Regulating Pesticides in Food: The Delaney Paradox* (National Research Council, 1987), examined the potential human cancer risk for a group of synthetic herbicides, insecticides, and fungicides that the EPA had classified as to carcinogenicity based on rodent bioassay data. The NRC reported the following EPA data: (1) carcinogenic potency (q_1^*); (2) an upper bound estimate of hypothetical, lifetime daily human exposure, TMRC; and (3) an upper bound estimate of excess cancer risk over a lifetime, calculated as potency × exposure.

We obtained data from the EPA for 19 of the 26 chemicals discussed by the NRC (Quest *et al.*, 1993; U.S. Environmental Protection Agency, 1984a, 1985–1988, 1985a, 1985b, 1986b, 1987b, 1988b, 1989b, 1989c, 1999a). We were not able to identify the animal data used in the NRC report for cryomazine, diclofop methyl, ethalfluralin, ethylene thiourea, *o*-phenylphenol, pronamide, and terbutryn. To verify that we had identified the correct rodent results, we attempted to replicate the EPA q_1^* value for each of the 19 pesticides to define the data set for our comparison of risk estimates. The Tox-Risk program (Crump & Assoc.) was used to calculate q_1^* as the 95% upper confidence limit on the linear term in the LMS, which theoretically represents the slope of the dose–response curve in the low-dose region. If it was not clear which target site had been used by the EPA, we calculated more than one q_1^* and used in our subsequent comparison of potency estimates whichever data best reproduced the EPA q_1^* value. If the EPA memorandum for a chemical stated that the q_1^* was the geometric mean of two or more experiments, we used the same method.

The bioassay data that most accurately reproduced the EPA q_1^* for each chemical are given in Table 38.6. Superscripts indicate the EPA weight-of-evidence classification given in the NRC report, followed by subsequent reevaluations of the classification.

Using the data in Table 38.6 with the Tox-Risk program, overall there was good reproducibility in potency estimation (Table 38.7). We were able to reproduce the EPA q_1^* value for

Table 38.7
Reproducibility of the EPA q_1^* Values Reported by the NRC

Pesticide	EPA q_1^* reported by NRC $(mg/kg/day)^{-1}$	Recalculated q_1^* $(mg/kg/day)^{-1}$	Recalculated q_1^*/ EPA q_1^*
Chlorothalonil	2.4×10^{-2}	1.3×10^{-2}	0.5
Asulam	2.0×10^{-2}	1.4×10^{-2}	0.7
Oryzalin	3.4×10^{-2}	2.5×10^{-2}	0.7
Permethrin	3.0×10^{-2}	2.0×10^{-2}	0.7
Chlordimeform	9.4×10^{-1}	7.2×10^{-1}	0.8
Fosetyl Al	4.3×10^{-3}	3.7×10^{-3}	0.9
Captafol	2.5×10^{-2}	2.4×10^{-2}	1.0
Oxadiazon	1.3×10^{-1}	1.3×10^{-1}	1.0
Cypermethrin	1.9×10^{-2}	2.1×10^{-2}	1.1
Folpet	3.5×10^{-3}	3.8×10^{-3}	1.1
Linuron	3.3×10^{-1}	3.7×10^{-1}	1.1
Captan	2.3×10^{-3}	3.4×10^{-3}	1.5
Alachlor	6.0×10^{-2}	9.5×10^{-2}	1.6
Acephate	6.9×10^{-3}	1.3×10^{-2}	1.9
Benomyl	2.1×10^{-3}	4.6×10^{-3}	2.2
Metolachlor	2.1×10^{-3}	8.7×10^{-3}	4.1
Glyphosate	5.9×10^{-5}	4.8×10^{-4}	6.1
Parathion	1.8×10^{-3}	1.3×10^{0}	720
Azinphosmethyl	1.5×10^{-7}	7.3×10^{-1}	4,900,000

Recalculated q_1^* uses the bioassay data in Table 38.6 and a linearized multistage model.

15 chemicals within a factor of 2.2, and for 17 within a factor of 6. The median ratio of the q_1^* reported by the NRC to the recalculated q_1^* is 1.1. We could not approximate the q_1^* for parathion or azinphosmethyl. The q_1^* published in the NRC report for azinphosmethyl appears to be an error (W. Burnam, Office of Pesticide Programs, EPA, personal communication). We concluded that the data set of 15 chemicals with a q_1^* reproducibility within a factor of 2.2 would be used in the comparison of risk estimates. The four-chemicals for which we could not reproduce the q_1^* within a factor of 2.2 have all been reevaluated by the EPA since the NRC report: Azinphosmethyl and glyphosate are considered to have evidence of noncarcinogenicity to humans (i.e., superscript E in Table 38.6) (Burnam, 2000); a margin-of-exposure approach is recommended for metolachlor (MOE in Table 38.6); and parathion is classified as having limited evidence without a q_1^* value (Cnq) in Table 38.6.

38.6.2 COMPARISON OF POTENCY ESTIMATES: q_1^* AND TD_{50}

Using the incidence data identified as those used by the EPA (Table 38.6), we estimated the TD_{50}, that is, the dose rate (in mg/kg body weight/day) that is estimated to reduce by 50% the proportion of tumor-free animals at the end of a standard lifespan (Peto *et al.*, 1984; Sawyer *et al.*, 1984). The TD_{50} does not involve extrapolation to low dose. It is inversely related to the slope (Peto *et al.*, 1984; Sawyer *et al.*, 1984; see Section 38.8 for details), and a comparison with q_1^* can be made by using $\ln(2)/TD_{50}$. An adjustment for rodent-to-human extrapolation, such as a surface area or other allometric correction factor, is usually applied to the q_1^* for regulatory purposes. For comparison purposes, the TD_{50} was adjusted by the same interspecies scaling factor that was used by the EPA for q_1^*, that is, $(\text{body weight})^{2/3}$, a factor of approximately 5.5 for rats and 13.0 for mice. The two potency estimates were then compared by computing the ratio $q_1^*/(\ln(2)/TD_{50})$. The dose calculation and standardization methods used for the TD_{50} calculation in this chapter follow the EPA methods, some of which differ from the standard methodology used to estimate TD_{50} in the CPDB.

38.6.3 COMPARISON OF HUMAN EXPOSURE ESTIMATES

The risk estimates in the NRC report (National Research Council, 1987) differed from those in the HERP ranking for dietary residues of synthetic pesticides (Section 38.5). The NRC reported upper bound estimates of daily human exposure (i.e., the EPA TMRC). In contrast, the HERP values in Table 38.5 used the daily exposure estimates from the FDA Total Diet Study (TDS). Thirteen pesticides discussed in the NRC report were measured in the TDS, and we compared the exposure estimates from the two sources for these 13. We used results from the TDS for the years 1984–1986 (Gunderson, 1995; U.S. Food and Drug Administration, 1988), which are the closest to the time of the NRC report.

The EPA TMRC is a theoretical maximum estimate for potential human dietary exposure to synthetic pesticides. Pesticides registered for food crop use in the United States must first be granted tolerances under the Federal Food, Drug and Cosmetic Act (FFDCA). Tolerances are the maximum, legally allowable residues of the pesticide, or its active ingredient, on raw agricultural commodities and in processed foods. A tolerance is typically set for each pesticide for each crop use (e.g., corn, barley, wheat) based on field trials. The manufacturer conducts these trials, using varying rates of application under diverse environmental conditions, to determine both the minimum application rate needed to be effective against pest targets and the duration of time before harvest when it has to be applied (these are the rates specified on the pesticide label). Residue measurements are made on various parts of the crop at several time intervals after application to determine the rate of decline in residues of the pesticide active ingredient, its metabolites, and/or degradation products. The maximum measured residue is then used to establish the tolerance. Each crop use of a pesticide can have a different tolerance. Thus, the tolerance value is an upper bound estimate of total pesticide residue on a crop in the field, rather than in the marketplace or in table-ready foods.

To obtain the TMRC, the tolerance value is multiplied by the mean U.S. food consumption estimate for each food item on which the pesticide is legally permitted, and exposures are combined for all such foods. The EPA, in calculating the TMRC, generally assumed that (1) each pesticide is used on all (100%) acres for each crop that the pesticide is permitted to be used on and (2) residues are present at the tolerance level (the highest allowable level in the field) in every food for which the pesticide is permitted. The National Food Consumption Survey conducted by the U.S. Department of Agriculture (USDA) is used for average food consumption estimates. Thus, the TMRC represents the hypothetical maximum exposure for a given pesticide (in mg/kg body weight/day) using field trial residue data.

In contrast, the FDA Total Diet Study (TDS) measures detectable levels of pesticide residues as they are consumed, using a market basket survey of eight age-gender groups (Gartrell *et al.*, 1986; Gunderson, 1988, 1995; U.S. Food and Drug Administration, 1988, 1990, 1991a, 1992a). Market baskets of foods are collected 4 times per year, once from each of four geographic regions of the United States. Each market basket consists of 234 identical foods purchased from local supermarkets in three cities in each geographic area. The foods are selected to represent the diet of the U.S. population, prepared table-ready, homogenized together and then analyzed for pesticide residues, including some metabolites and impurities (Gartrell *et al.*, 1986; Gunderson, 1988, 1995; U.S. Food and Drug Administration, 1988, 1990, 1991a, 1992a). The levels of pesticide residues that are found are used in conjunction with the same USDA food consumption data used by the EPA in the TMRC in order to estimate the average dietary intake of pesticide residues in (mg/kg body weight/day) (Yess *et al.*, 1993). The TDS has been conducted annually by the FDA since 1961 (U.S. Food and Drug Administration, 1990), initiated primarily in response to public concern about radionuclides in foods that might result from atmospheric nuclear testing.

It is important to note that the TDS is distinct from FDA regulatory monitoring programs whose primary purpose is to ascertain that residues on crops at the "farm gate" or in the marketplace do not exceed maximum allowable levels and do not result from illegal pesticide use on crops for which the pesticide is not registered. FDA regulatory monitoring is designed only to make certain that regulations for pesticide use and application are followed, whereas the TDS is designed to provide an estimate of average daily dietary intake of pesticide residues in foods. Analytical methods for the TDS have been modified over time to permit measurement at concentrations 5 to 10 times lower than those used in FDA regulatory or incidence level monitoring. Generally, these methods can detect residues at 1 ppb (Gartrell *et al.*, 1986; Gunderson, 1988, 1995; U.S. Food and Drug Administration, 1988, 1990, 1991a, 1992a).

38.6.4 COMPARISON OF RISK ESTIMATES

Of the chemicals for which we were able to reproduce the EPA q_1^* reported by the NRC, 10 were measured in the FDA Total Diet Study, and these were used to compare risk estimates based on different exposure assessments. Our analyses of the sources of variation in cancer risk estimates for dietary synthetic pesticides are presented in Tables 38.8–38.10. A comparison of the variation in potency estimates to the variation in exposure estimates is given in Table 38.8. Table 38.9 reports hypothetical dietary exposure estimates from the NRC report, i.e., the TMRC and measured residues in the FDA TDS. In Table 38.10, risk estimates based on the TMRC are compared to risk estimates based on the TDS, using in both cases the EPA q_1^* as reported by the NRC. Because of missing data or NRC results that could not be reproduced, not all chemicals are included in every table; we have used all chemicals for which appropriate data were available.

TD_{50} values were calculated from the same dose and incidence data in Table 38.6 that were used to recalculate q_1^*, and these TD_{50} values are reported in Table 38.6. Table 38.8 compares TD_{50} values to recalculated q_1^* values for the 19 chemicals, using the ratio $q_1^*/(\ln(2)/TD_{50})$. The q_1^* and TD_{50} values are within a factor of 2 of each other for 10 chemicals, and within a factor of 3 for 18 chemicals. These small differences in potency estimates are within the range of differences in potency estimates from near-replicate tests where the same chemical is tested in the same sex, strain and species of test animal (Gold *et al.*, 1987a, 1989, 1998; Gaylor *et al.*, 1993). Differences in potency values are larger only for azinphosmethyl, by a factor of 6.1; there was no statistically significant increase in tumor incidence for azinphosmethyl.

In contrast to the similarity of potency estimation between $\ln(2)/TD_{50}$ and q_1^* ,there is enormous variation in dietary exposure estimates for synthetic pesticides between the EPA TMRC values and the FDA average dietary residues in foods prepared as consumed (Tables 38.8 and 38.9). For 5 pesticides (alachlor,

Table 38.8
Comparison of Variation in Measures of Potency and Exposure

Pesticides included in the TDS (FDA)	Ratio of potency: recalculated $q_1^*/(\ln(2)/TD_{50})$	Ratio of exposure: EPA/FDA
Permethrin^{Cq}	1.5	579
Acephate$^{NA(Cnq)}$	0.7	1,130
Parathion$^{Cq(Cnq)}$	2.6	6,300
Azinphosmethyl$^{D(E)}$	6.1	7,530
Folpet^{B2}	0.8	9,650[a]
Linuron$^{Cq(Cnq)}$	2.5	11,600
Captan^{B2}	1.7	16,900
Chlorothalonil$^{NA(B2)(MOE)}$	1.9	99,100
Alachlor$^{B2(MOE)}$	0.9	—[b]
Captafol^{B2}	1.2	—[b]
Cypermethrin$^{Cq(Cnq)}$	2.2	—[b]
Oxadiazon$^{B2(Cq)}$	3.0	—[b]
Pesticides not measured in the TDS (FDA)		
Asulam$^{NA(Cnq)}$	2.5	NA[c]
Benomyl^{Cq}	2.2	NA[c]
Chlordimeform^{B2}	1.7	NA[c]
Fosetyl Al$^{Cq(Cnq)(Unclassified)}$	1.8	NA[c]
Glyphosate$^{Cq(E)}$	2.5	NA[c]
Metolachlor$^{Cq(Cnq)(MOE)}$	1.8	NA[c]
Oryzalin^{Cq}	2.5	NA[c]

[a]Folpet was not detected by the FDA in 1984–1986. This value is for 1987.
[b]The FDA did not detect any residues; therefore, no ratio could be calculated.
[c]Not applicable because not measured by the FDA. Asulam had no food uses.

Table 38.9
Dietary Exposure Estimates in 1986 by the EPA and the FDA for Pesticides Measured in the FDA Total Diet Study[a]

Pesticide	Daily intake (μg/kg/day)	
	EPA TMRC (1986)	FDA TDS (1984–1986)
Permethrin^{Cq}	14.0	0.0242
Captan^{B2}	206	0.0122
Folpet^{B2}	92.6	0.0096
Acephate$^{NA(Cnq)}$	5.41	0.0048
Azinphosmethyl$^{D(E)}$	11.3	0.0015
Parathion$^{Cq(Cnq)}$	8.19	0.0013
Linuron$^{Cq(Cnq)}$	4.65	0.0004
Chlorothalonil$^{NA(B2)(MOE)}$	9.91	0.0001
Alachlor$^{B2(MOE)}$	0.408	ND[b]
Captafol^{B2}	23.8	ND[b]
Cypermethrin$^{Cq(Cnq)}$	0.197	ND[b]
Oxadiazon$^{B2(Cq)}$	0.0938	ND[b]
Pronamide$^{Cq(B2)}$	0.486[c]	ND[b]

[a]FDA dietary estimates are for 60–65-year-old females for 1984–1986 (Gunderson, 1995). Because of the agricultural usage of these chemicals and the prominence of fruits and vegetables in the diet of older Americans, the residues are slightly higher than for other adult age groups.
[b]Not detected at limit of quantification (∼1 ppb).
[c]Did not appear in Tables 38.1 and 38.3 because no bioassay data were available.

captafol, cypermethrin, oxadiazon and pronamide), FDA found no residues at the 1 ppb limit of quantification (Gartrell *et al.*, 1986; Gunderson, 1988, 1995; U.S. Food and Drug Administration, 1988, 1990, 1991a, 1992a; Yess *et al.*, 1993). Among chemicals detected by FDA, the TDS estimates were lower than the TMRC estimates by a factor of 99,100 for chlorothalonil, 16,900 for captan, 11,600 for linuron, and 9,650 for folpet (Table 38.8). For 4 other chemicals, the TDS estimates ranged from 579 to 7,530 times lower than TMRC. For the pesticides that EPA classified as having the strongest evidence of carcinogenicity in animal studies (B2), the differences in exposure estimates for EPA vs. FDA are particularly large (Table 38.8). Examination of FDA pesticide residue data collected over a period of 14 years (Gartrell *et al.*, 1986; Gunderson, 1988, 1995; U.S. Food and Drug Administration, 1988, 1990, 1991a, 1992a) indicates that dietary exposure to pesticide residues has not changed markedly over time. Thus, the large differences in exposure estimates between EPA and FDA cannot be explained simply by changes in pesticide use patterns.

In standard regulatory risk assessment, an estimate of the lifetime excess cancer risk is obtained by multiplying q_1^* by human exposure; the true risk, however, may be zero, as the 1986 EPA cancer risk assessment guidelines indicated (U.S. Environmental Protection Agency, 1986a). A comparison of the risk estimates obtained by multiplying the q_1^* in the NRC report by

Table 38.10
Comparison of Cancer Risk Estimates Based on Different Exposure Measures: TMRC Versus TDS[a]

Pesticide[b]	Cancer risk reported by NRC based on TMRC (EPA)	Cancer risk based on TDS (FDA)
Linuron$^{Cq(Cnq)}$	1.5×10^{-3}	1.3×10^{-7}
Captafol^{B2}	5.9×10^{-4}	0
Captan^{B2}	4.7×10^{-4}	2.8×10^{-8}
Permethrin^{Cq}	4.2×10^{-4}	7.3×10^{-7}
Folpet^{B2}	3.2×10^{-4}	3.4×10^{-8}
Chlorothalonil$^{NA(B2)(MOE)}$	2.4×10^{-4}	2.4×10^{-9}
Acephate$^{NA(Cnq)}$	3.7×10^{-5}	3.3×10^{-8}
Alachlor$^{B2(MOE)}$	2.4×10^{-5}	0
Oxadiazon$^{B2(Cq)}$	1.2×10^{-5}	0
Cypermethrin$^{Cq(Cnq)}$	3.7×10^{-6}	0
	Each risk $> 1 \times 10^{-6}$	Each risk $< 1 \times 10^{-6}$

[a]Risk estimates use q_1^* values in the NRC report for pesticides with reproducible q_1^* values (see Table 38.2, column 1). EPA risks are reported in the NRC book *Regulating Pesticides in Food* (1987).
[b]Three chemicals measured in the Total Diet Study (Table 38.4) are excluded: For parathion and azinphosmethyl, the q_1^* values could not be reproduced; for pronamide, we were unable to obtain bioassay results.

TMRC vs. TDS exposure values is presented in Table 38.10. The risks based on TMRC are also reported by NRC, and range from 10^{-3} to 10^{-6}. In contrast, risk estimates using TDS are all lower than 10^{-6}. There are no risk estimates in Table 38.10 for the chemicals that FDA did not detect, i.e., if there is no exposure, there is no risk. Even if the undetected chemicals are considered to be present in minute quantities, below the limit of quantification, risk estimates for these undetected chemicals would be negligible, i.e., less than 10^{-6}.

Thus, for synthetic pesticide residues in the diet, large discrepancies in cancer risk estimates are due to differences in exposure estimates rather than to differences in carcinogenic potency values estimated by different methods from rodent bioassay data. The high risk estimates reported by NRC in 1987 were overestimates based on EPA human exposure assessments which assumed that dietary residues were at tolerance levels. For example, the TDS did not detect any residues in table-ready foods for 4 pesticides that were evaluated in the NRC report as greater than 10^{-6} risks (Table 38.10).

38.6.5 USE OF EXPOSURE ASSESSMENTS IN RISK ASSESSMENT

The results of our analysis emphasize the importance of exposure assessment in risk estimation for synthetic pesticide residues in the diet. Both the TDS of FDA and the TMRC of EPA link estimates of food consumption patterns for groups of individuals with an estimate of pesticide concentrations in food. Since FDA and EPA use the same USDA consumption surveys to estimate dietary patterns, food consumption is not a source of variation in their exposure estimates. However, the methods of estimating the concentrations of pesticide residues in food differed markedly. The FDA measured actual residues in food items that are bought at the market and prepared as typically eaten; the EPA used a theoretical construct, based on worst case assumptions for the maximally exposed individual and maximally allowable levels, to estimate residues that could legally occur on a given food crop at the farm gate or in the marketplace.

The EPA assumption that every pesticide registered for use on a food commodity is used on every crop is another source of overestimation of exposure (Winter, 1992). In California, for example, 54 insecticides were registered for use on tomatoes in 1986; however, the maximum number of insecticides used by any tomato grower was 5, 52% of tomato growers used 2 or fewer insecticides, and 31% used none at all (Chaisson *et al.*, 1989). Similar findings are reported for herbicides and fungicides.

FDA monitoring programs have been criticized for not measuring enough pesticides or sampling enough food items, for aggregating foods under a single representative core food (e.g., apple pie to represent all types of fruit pies), and for statistical design and sampling. In several other independent studies, however, frequency of detection and residue concentrations have also been consistently low, for example, residue data from FOODCONTAM, a national database for state surveys on pesticide and other residues in foods (Minyard and Roberts, 1991). McCarthy (1991) collected residue data on 16 pesticides for 50 crops at the "farm gate"; although all crops had been treated with the label rates of pesticide application, 93% of 134 samples had concentrations below half the tolerance. Post-harvest treatment of crops, such as removing husks or outer leaves, shelling, peeling, and washing, all reduce residue levels still further (Yess *et al.*, 1993), as does processing. Eilrich (1991) measured residue levels on four produce crops "from the farm gate to the table" for a fungicide whose active ingredient is

chlorothalonil and found that dietary residues were similar to those reported by the FDA.

Analyses by Nigg *et al.* (1990) and Winter (1992) of residue data from the California Department of Food and Agriculture confirm the FDA regulatory monitoring findings. Most crops have no detectable residues; crop residues that are found are small fractions of tolerance values. Thus, tolerances are poor indicators of human exposure, a function for which they were not designed. Although it is possible that a small percentage of people who obtain food crops close to the farm gate may have higher incidental dietary exposures, these concentrations are very unlikely to persist over time and would still be substantially lower than the TMRC values.

In the TDS, approximately 264 pesticides, metabolites, and impurities are analyzed; only 51 had detectable residues, and only 3 were present in more than 10% of the sample foods (U.S. Food and Drug Administration, 1991a). These findings are similar to those obtained from the TDS during the 10 previous years (Gartrell *et al.*, 1986; Gunderson, 1988; U.S. Food and Drug Administration, 1988, 1990, 1991a, 1992a) and to those from surveys on pesticides of special interest. Even if exposure estimates based on the TDS were underestimates by an order of magnitude, the potential risks estimated using the EPA q_1^* would still be low.

The use of the TMRC as an estimate of human dietary exposure in quantitative cancer risk assessment is not justified, from either a scientific or a public policy perspective, because this measure often grossly exaggerates actual consumer exposure. The TMRC uses tolerances as surrogates for concentration in foods and therefore, by definition, the TMRC is not representative of the level likely to reach the consumer (Chaisson *et al.*, 1989). It does not take into account percentage of crop treated, actual pesticide application practices, chemical degradation from farm gate to table, and cooking or other processing. Some subsequent EPA exposure estimates have used "anticipated residues" instead of TMRC, which are calculated using tolerances and processing factors, using tolerances and percentage of crop treated, using field trial data, or using monitoring data. The anticipated residue also tends to be an overestimate because it is based on the average residue observed from maximum allowable pesticide application of a pesticide during field trials. Actual pesticide use is not always at the maximum level; hence, actual residues tend to be lower than the anticipated level (Chaisson *et al.*, 1989). For example, the EPA subsequently used anticipated residues to evaluate linuron and reported that less than 1% of the crop of barley, oats, and rye was treated. Despite this finding, for risk assessment purposes the EPA assumed that 100% of the crop was treated. The linuron comparison indicates how anticipated residues can be an overestimate: The TMRC in the NRC report was 4.65 μg/kg/day; the anticipated residue reported by EPA was 0.185 μg/kg/day (U.S. Environmental Protection Agency, 1995b); the TDS value was 0.0004 μg/kg/day (Gunderson, 1995).

Recent developments by government agencies have responded to the need for better quality information on exposure assessment of dietary residues. In response to the need identified by the National Academy of Sciences (NAS) for a standardized exposure database while developing the report *Pesticides in the Diets of Infants and Children*, the EPA has begun a National Pesticide Residue Database (NPRD) that collects data from the FDA, the USDA, and private and commercial sources (http://www.epa.gov/pesticides/nprd). A multiagency effort, the Pesticide Data Program (PDP), is providing more information on actual exposure to dietary residues, food consumption, and pesticide usage (U.S. Environmental Protection Agency, 1999a). The PDP was established by the USDA in 1991 to monitor pesticide residues in fresh and processed fruits and vegetables at terminal markets or distribution centers. Sampling procedures are designed to measure residues close to the time of consumption. Since 1994, the PDP testing protocol has included several foods in addition to fresh produce, such as canned and frozen fruits and vegetables and milk. The PDP is a critical component of the Food Quality Protection Act of 1996, and hence focuses on commodities that are consumed by infants and children (http://www.ams.usda.gov/science/pdp/what.htm). In 1998, PDP produce samples originated from 40 states and 25 foreign countries (U.S. Department of Agriculture, 2000). The PDP is currently used by the EPA to support its dietary risk assessment process [e.g., Eiden (1999)] and by the FDA to refine sampling for enforcement of tolerances. Given that exposure assessments for pesticide residues are available from the FDA TDS for about 38 years, it might be reasonable to compare those assessments to the new PDP assessments.

A more complete characterization of exposures has been undertaken for some chemicals using biomarkers of exposure or distributions of exposure factors. Monte Carlo methods and other variance propagation techniques have been used to characterize the interindividual variability in exposures within a population and the uncertainty in exposure estimates (McKone, 1997).

38.6.6 USE OF TOXICOLOGICAL DATA IN RISK ASSESSMENT

Throughout this chapter, we have presented data indicating the limitations of tumor incidence results from rodent cancer tests in efforts to estimate human risk at low exposures. Our analysis of differences in risk estimates for dietary pesticide residues indicated that carcinogenic potency values were similar for $\ln(2)/TD_{50}$ and q_1^* and therefore did not contribute substantially to the disparities in risk estimation. Similarity in potency estimates is expected: Bernstein *et al.* (1985) showed that carcinogenic potency values from standard bioassays are restricted to an approximately 32-fold range surrounding the maximum dose tested, in the absence of 100% tumor incidence. Estimates of carcinogenic potency derived from statistical models are highly correlated with one another because they are all highly correlated with the MTD, regardless of whether the estimate is based on the one-stage, multistage, or Weibull model (Krewski *et al.*, 1990). This constraint on potency estimation

contrasts with the enormous extrapolation that is required from the MTD in bioassays to the usual human exposure levels of pesticide residues, often hundreds of thousands of times lower than the MTD.

One implication of the boundedness of potency estimation based on tumor incidence data is that for a given exposure estimate, the risk estimate can be approximated from the MTD in the bioassay without conducting an experiment. We have shown that the VSD at 10^{-6} (Gaylor and Gold, 1995) and the risk estimate based on the LTD_{10}, whether using safety factors for a nonlinear dose–response relationship or a linear model, can all be approximated from the MTD within a factor of 10 of the estimate that would be obtained from tumor incidence data in standard bioassays (Gaylor and Gold, 1998) (see Section 38.4).

Adequate qualitative evaluation of the weight of evidence for carcinogenicity of a chemical and quantitative extrapolation from high to low dose requires more information for a chemical, about pharmacokinetics, mechanism of action, cell division, induction of defense and repair systems, and species differences. The new EPA guidelines and recent evaluations of several chemicals by the EPA, recognize the importance of such additional information (U.S. Environmental Protection Agency, 1996a). The proposed EPA guidelines permit the use of nonlinear approaches to low-dose extrapolation if warranted by mechanistic data. In recent years, the EPA has reevaluated several of the weight-of-evidence classifications for pesticides in the NRC report. This is consistent with the recommendation in the proposed EPA cancer risk assessment guidelines, which calls for use of available toxicological data in a characterization of the weight of evidence. Several pesticides are no longer considered appropriate for quantitative risk estimation (see the superscripts in parentheses in Table 38.6). Of the 19 pesticides from the NRC report for which we obtained bioassay data from EPA, only 11 are currently considered by the EPA as appropriate for quantitative risk estimation (Table 38.6 superscripts). This contrasts with the NRC report evaluation that the risks for 16 of the 19 were greater than 10^{-6}. For example, linuron had the highest risk estimate of all pesticides in the NRC analysis. It was subsequently reclassified by the EPA as inappropriate for quantitative risk assessment based on biological considerations: The testicular tumors in rats were late forming and benign and were a relatively common tumor type; the hepatocellular tumors in mice were benign and only in the highest dose group; and there was no evidence of mutagenic activity (U.S. Environmental Protection Agency, 1988a, 1999b).

For evaluation of the mode of action of a given chemical using the new EPA risk assessment guidelines, information other than bioassay data can be developed and included in the assessment of weight of evidence and whether the dose-response relationship is likely to be nonlinear; for example, pharmacokinetic data on absorption, distribution, and metabolism can be used to predict target organ concentrations and then compared in different species. Other relevant results can be obtained from studies of cell division at and below the carcinogenic dose or from receptor-binding assays. New animal models with genetic alterations that are designed to make an animal resemble the human more closely or to make the animal more sensitive to a given response can complement or take the place of long-term cancer tests, for example, transgenic mouse models that use unique phenotypic properties such as the p53 gene–deficient model or receptor-binding assays (Blaauboer *et al.*, 1998). Critical evaluation and validation of these new methodologies and increasing use of fundamental toxicological research will improve the regulatory evaluation of potential human risk. Although the proposed guidelines offer some incentive to generate mechanistic data on a chemical, for most chemicals no such data will be available, and the default procedure will continue to be used. If bioassay data are to be used in risk assessment, it is desirable to facilitate generation of mechanistic data on the chemicals of interest (Clayson and Iverson, 1996), including chemicals for which past risk assessments have resulted in regulation.

38.7 RANKING POSSIBLE TOXIC HAZARDS FROM NATURALLY OCCURRING CHEMICALS IN THE DIET

Because naturally occurring chemicals in the diet have not been a focus of cancer research, it seems reasonable to investigate some of them further as possible hazards because they often occur at high concentrations in common foods. Only a small proportion of the many chemicals to which humans are exposed will ever be investigated, and there is at least some toxicological plausibility that high-dose exposures may be important. Moreover, the proportion positive in rodent cancer tests is similar for natural and synthetic chemicals, about 50% (see Section 38.3), and the proportion positive among natural plant pesticides is also similar (Table 38.3). Therefore, one would expect many of the untested natural chemicals to be rodent carcinogens.

In order to identify and prioritize untested dietary chemicals that might be a hazard to humans if they were to be identified as rodent carcinogens, we have used an index, HERT, which is analogous to HERP (see Section 38.5). HERT is the ratio of human exposure/rodent toxicity (LD_{50}) in mg/kg/day expressed as a percentage, whereas HERP is the ratio of human exposure/rodent carcinogenic potency (in mg/kg/day) expressed as a percentage. HERT uses readily available LD_{50} values rather than the TD_{50} values from animal cancer tests that are used in HERP. This approach to prioritizing untested chemicals makes assessment of human exposure levels critical at the outset.

The validity of the HERT approach is supported by three analyses: First, we have found that for the exposures to rodent carcinogens for which we have calculated HERP values (Gold *et al.*, 1992), the rankings by HERP and HERT are highly correlated (Spearman rank order correlation = 0.89). Second, we have shown that without conducting a 2-year bioassay the regulatory VSD can be approximated by dividing the MTD by 740,000 (Gaylor and Gold, 1995; and Section 38.4). Because the MTD is not known for all chemicals and the MTD and LD_{50} are both measures of toxicity, acute toxicity (LD_{50}) can reasonably be used as a surrogate for chronic toxicity (MTD).

Third, LD_{50} and carcinogenic potency are correlated (Travis *et al.*, 1990; Zeise *et al.*, 1984); therefore, HERT is a reasonable surrogate index for HERP because it simply replaces TD_{50} with LD_{50}.

We have calculated HERT values using LD_{50} values as a measure of toxicity and human exposure estimates based on the available data on concentrations of untested natural chemicals in commonly consumed foods and average consumption of those foods in the U.S. diet. Literature searches identified the most commonly consumed foods (Stofberg and Grundschober, 1987; Technical Assessment Systems 1989; United Fresh Fruit and Vegetable Association, 1989) and concentrations of chemicals in those foods (Nijssen *et al.*, 1996; U.S. National Institute for Occupational Safety and Health, 1999). We considered any chemical with available data on rodent LD_{50} that had a published concentration of $\geq$10 ppm in a common food and for which estimates of average U.S. consumption of that food were available. The natural pesticides among the chemicals in the HERT table (Table 38.11) are marked with an asterisk. Among the set of 121 HERT values (Table 38.11), the HERT ranged across 6 orders of magnitude. The median HERT value for average dietary exposures is 0.007%.

It might be reasonable to investigate further the chemicals in the diet that rank highest on the HERT index and that have not been adequately tested in chronic carcinogenicity bioassays in rats and mice. We have nominated to the NTP the chemicals with the highest HERT values as candidates for carcinogenicity testing. These include solanine and chaconine, the main alkaloids in potatoes, which are cholinesterase inhibitors that can be detected in the blood of almost all people (Ames, 1983, 1984; Harvey *et al.*, 1985); chlorogenic acid, a precursor of caffeic acid; and caffeine, for which no adequate standard lifetime study has been conducted in mice. In rats, cancer tests of caffeine have been negative, but one study that was inadequate because of early mortality, showed an increase in pituitary adenomas (Yamagami *et al.*, 1983).

How would the synthetic pesticides that are rodent carcinogens and that are included in the HERP ranking (Table 38.5) compare to the natural chemicals that have not been tested for carcinogenicity (Table 38.11) if they too were ranked on HERT? We calculated HERT using LD_{50} values for the synthetic pesticide residues that are rodent carcinogens in the HERP table and found that they rank low in HERT compared to the naturally occurring chemicals in Table 38.11; 88% (107/121) of the HERT values for the natural chemicals in Table 38.11 rank higher in possible toxic hazard HERT than any HERT value for any synthetic pesticide that is a rodent carcinogen in the HERP table (Table 38.5). The highest HERT for the synthetic pesticides would be for DDT in 1970 before the ban (0.00004%), which is more than 100-fold lower than the median HERT for the natural chemicals in the HERT table.

Many interesting natural toxicants are ranked in common foods in the HERT table. Oxalic acid, a plant pesticide, which is one of the most frequent chemicals in the table, occurs widely in nature. It is usually present as the potassium or calcium salt and also occurs as the free acid (Hodgkinson, 1977). Oxalic acid is reported in many foods in Table 38.11; the highest contributors to the average U.S. diet are coffee (HERT = 0.09%), carrot (0.08%), tea (0.02%), chocolate (0.01%), and tomato (0.01%). Excessive consumption of oxalate has been associated with urinary tract calculi and reduced absorption of calcium in humans (Beier and Nigg, 1994; Hodgkinson, 1977).

Because of the high concentrations of natural pesticides in spices, we have reported the HERT values for average intake in Table 38.11, even though spices are not among the foods consumed in the greatest amounts by weight. The highest concentrations of chemicals in Table 38.11 are found in spices, which tend to have higher concentrations of fewer chemicals (Nijssen *et al.*, 1996). (Concentrations can be derived from Table 38.11 by the ratio of the average consumption of the chemical and the average consumption of the food.) High concentrations of natural pesticides in spices include those for menthone in peppermint oil (243,000 ppm), γ-terpinene in lemon oil (85,100 ppm), citral in lemon oil (75,000 ppm) piperine in black pepper (47,100 ppm), and geranial in lemon juice (14,400 ppm) and lemon oil (11,300 ppm). Natural pesticides in spices have antibacterial and antifungal activities (Billing and Sherman, 1998) whose potency varies by spice. A recent study of recipes in 36 countries examined the hypothesis that spices are used to inhibit or kill food spoilage microorganisms. Results indicate that as mean annual temperature increases in a geographical area (and therefore so does spoilage potential), there is an increase in number of spices used and use of the spices that have greatest antimicrobial effectiveness. The authors argue that spices are used to enhance food flavor, but, ultimately, are continued in use because they help to eliminate pathogens and therefore contribute to health, reproductive success, and longevity (Billing and Sherman, 1998).

Cyanogenesis, the ability to release hydrogen cyanide, is widespread in plants, including several foods, of which the most widely eaten globally are cassava and lima bean (Poulton, 1983). Cassava is consumed widely throughout the tropics and is a dietary staple for over 300 million people (Bokanga *et al.*, 1994). There are few effective means of removing the cyanogenic glycosides that produce hydrogen cyanide (HCN), and cooking is generally not effective (Bokanga *et al.*, 1994; Poulton, 1983). For lima beans in Table 38.6, the HERT is 0.01%. Ground flaxseed, a dietary supplement (http://www.heintzmanfarms.com/; Gruenwald *et al.*, 1998), contains about 500 ppm hydrogen cyanide glycosides. The HCN in flaxseed appear to be inactivated in the digestive tract of primates (Mazza and Oomah, 1995).

The increasing popularity of herbal supplements in the United States raises concerns about possible adverse effects from high doses or drug interactions (Saxe, 1987). Because the recommended doses of herbal supplements are close to the toxic dose and because about half of natural chemicals are rodent carcinogens in standard animal cancer tests, it is likely that many dietary supplements from plants will be rodent carcinogens that would rank high in possible carcinogenic hazard (HERP) if they were tested for carcinogenicity. Whereas pharmaceuticals are federally regulated for purity, identifica-

Table 38.11
Ranking Possible Toxic Hazards to Naturally Occurring Chemicals in Food on the HERT (Human Exposure/Rodent Toxicity) Index

Possible hazard: HERT (%)	Average daily consumption of food	Average human consumption of chemical	LD_{50} (mg/kg) Rats	LD_{50} (mg/kg) Mice	Exposure references
4.3	Coffee, 500 ml (13.3 g)	*Caffeine, 381 mg	(192)	127	Stofberg and Grundschober (1987), Macaulay *et al.* (1984), IARC (1991)
0.3	Tea, 60.2 ml (903 mg)	*Caffeine, 29.4 mg	(192)	127	Stofberg and Grundschober (1987), Martinek and Wolman (1955), Wolman (1955), Lee (1973), Groisser (1978), Bunker and McWilliams (1979), Galasko *et al.* (1989), IARC (1991)
0.3	Potato, 54.9 g	*α-Chaconine, 4.10 mg	(84P)	19P	TAS (1989), Bushway and Ponnampalam (1981), Takagi *et al.* (1990)
0.2	Cola, 174 ml	*Caffeine, 20.8 mg	(192)	127	EPA (1996b), Bunker and McWilliams (1979), Galasko *et al.* (1989)
0.1	Coffee, 500 ml	*Chlorogenic acid, 274 mg	4000P		Stofberg and Grundschober (1987), Baltes (1977), IARC (1991)
0.09	Coffee, 500 ml	*Oxalic acid, 25.2 mg	382		Stofberg and Grundschober (1987), Kasidas and Rose (1980), IARC (1991), Vernot *et al.* (1977)
0.09	Black pepper, 446 mg	*Piperine, 21.0 mg	(514)	330	Stofberg and Grundschober (1987)
0.08	Carrot, boiled, 12.1 g	*Oxalic acid, 22.7 mg	382		TAS (1989), Zarembski and Hodgkinson (1962), Vernot *et al.* (1977)
0.08	Chocolate (cocoa solids) 3.34 g	*Theobromine, 48.8 mg	(1265)	837	Stofberg and Grundschober (1987), IARC (1991)
0.05	Lemon juice, 1.33 ml	*Geranial, 19.2 mg	500		EPA (1996b), Mussinan *et al.* (1981)
0.05	Coffee, 500 ml	*Trigonelline, 176 mg	5000		Stofberg and Grundschober (1987), Clinton (1986), IARC (1991)
0.03	Chocolate (cocoa solids) 3.34 g	*Caffeine, 2.30 mg	(192)	127	Stofberg and Grundschober (1987), Zoumas *et al.* (1980)
0.02	Tea, 60.2 ml	*Oxalic acid, 6.67 mg	382		Stofberg and Grundschober (1987), Zarembski and Hodgkinson (1962), Kasidas and Rose (1980), IARC (1991), Vernot *et al.* (1977)
0.02	Isoamyl alcohol: U.S. avg (mostly beer, alcoholic beverages)	Isoamyl alcohol, 18.4 mg	1300		Stofberg and Grundschober (1987)
0.01	Beer, 257 ml	Isoamyl alcohol, 13.6 mg	1300		Stofberg and Grundschober (1987), Arkima (1968)
0.01	Chocolate (cocoa solids) 3.34 g	*Oxalic acid, 3.91 mg	382		Stofberg and Grundschober (1987), Kasidas and Rose (1980), Vernot *et al.* (1977)
0.01	Tomato, 88.7 g	*Oxalic acid, 3.24 mg	382		Stofberg and Grundschober (1987), Zarembski and Hodgkinson (1962), Kasidas and Rose (1980), Vernot *et al.* (1977)
0.01	Coffee, 500 ml	2-Furancarboxylic acid, 821 μg		100P	Stofberg and Grundschober (1987), Tressl *et al.* (1978), IARC (1991), Kitamura *et al.* (1978)
0.01	Lima beans, 559 mg	Hydrogen cyanide, 28.5 μg		3.7	EPA (1996b), Viehoever (1940), Montgomery (1964)
0.01	Potato chips, 5.2 g	*α-Chaconine, 136 μg[a]	(84P)	19P	Stofberg and Grundschober (1987), Friedman and Dao (1990)
0.01	Sweet potato, 7.67 g	*Ipomeamarone, 336 μg		50	Stofberg and Grundschober (1987), Coxon *et al.* (1975)
0.009	Potato, 54.9 g	*α-Solanine, 3.68 mg	590		TAS (1989), Bushway and Ponnampalam (1981), Takagi *et al.* (1990)
0.008	Isobutyl alcohol: U.S. avg	Isobutyl alcohol, 14.1 mg	2460		Stofberg and Grundschober (1987)
0.008	Hexanoic acid: U.S. avg (beer, grapes, wine)	Hexanoic acid, 15.8 mg	3000	(5000)	Stofberg and Grundschober (1987)
0.007	Phenethyl alcohol: U.S. avg	Phenethyl alcohol, 8.28 mg	1790		Stofberg and Grundschober (1987)
0.007	Carrot, 12.1 g	*Carotatoxin, 460 μg		100J	Crosby and Aharonson (1967), Wulf *et al.* (1978)
0.006	Ethyl acetate: U.S. avg (mostly alcoholic beverages)	Ethyl acetate, 16.5 mg	(5620)	4100	Stofberg and Grundschober (1987)

(*continues*)

Table 38.11
(*continued*)

Possible hazard: HERT (%)	Average daily consumption of food	Average human consumption of chemical	LD_{50} (mg/kg) Rats	Mice	Exposure references
0.005	Celery, 7.95 g	*Oxalic acid, 1.39 mg	382		ERS (1994), Zarembski and Hodgkinson (1962), Vernot *et al.* (1977)
0.005	Coffee, 500 ml	*3-Methylcatechol, 203 μg		56V	Stofberg and Grundschober (1987), Heinrich and Baltes (1987), IARC (1991)
0.005	Potato, 54.9 g	*Oxalic acid, 1.26 mg	382		TAS (1989), Zarembski and Hodgkinson (1962), Vernot *et al.* (1977)
0.004	Beer, 257 ml	Phenethyl alcohol, 5.46 mg	1790		Stofberg and Grundschober (1987), Arkima (1968)
0.004	Corn, 33.8 g	*Oxalic acid, 1.12 mg	382		Stofberg and Grundschober (1987), Kohman (1939), Vernot *et al.* (1977)
0.004	Corn, 33.8 g	Methylamine, 906 μg		317	Stofberg and Grundschober (1987), Neurath *et al.* (1977)
0.004	Peppermint oil, 5.48 mg	*Menthone, 1.33 mg	500		Stofberg and Grundschober (1987)
0.004	White bread, 67.6 g	Propionaldehyde, 2.09 mg	(1410)	800	Stofberg and Grundschober (1987), Lorenz and Maga (1972)
0.004	Beer, 257 ml	Isobutyl alcohol, 6.40 mg	2460		Stofberg and Grundschober (1987), Arkima (1968)
0.003	Tomato, 88.7 g	Methyl alcohol, 13.4 mg	5628	(7300)	TAS (1989), Nelson and Hoff (1969), Kazeniac and Hall (1970)
0.003	Wine, 28.0 ml	Isoamyl alcohol, 3.00 mg	1300		Stofberg and Grundschober (1987), Postel *et al.* (1972)
0.003	Coffee, 500 ml	Pyrogallol, 555 μg		300	Stofberg and Grundschober (1987), Tressl *et al.* (1978), IARC (1991)
0.003	Apple, 32.0 g	*Oxalic acid, 704 μg	382		EPA (1989a), Zarembski and Hodgkinson (1962), Kasidas and Rose (1980), Vernot *et al.* (1977)
0.003	Butyl alcohol: U.S. avg (mostly apple, beer)	Butyl alcohol, 1.45 mg	790		Stofberg and Grundschober (1987)
0.003	Lettuce, 14.9 g	Methylamine, 567 μg		317	TAS (1989), Neurath *et al.* (1977)
0.003	Beer, 257 ml	Propyl alcohol, 3.29 mg	1870	(6800)	Stofberg and Grundschober (1987), Arkima (1968)
0.002	Banana, 15.7 g	*trans*-2-Hexenal, 1.19 mg	(780)	685	TAS (1989), Hultin and Proctor (1961)
0.002	Orange, 10.5 g	*Oxalic acid, 651 μg	382		TAS (1989), Zarembski and Hodgkinson (1962), Vernot *et al.* (1977)
0.002	Wine, 28.0 ml	Ethyl lactate, 4.16 mg	(>5000)	2500	Stofberg and Grundschober (1987), Postel *et al.* (1972), Shinohara *et al.* (1979)
0.002	Tomato, 88.7 g	**p*-Coumaric acid, 1.02 mg		657P	TAS (1989), Schmidtlein and Herrmann (1975a)
0.002	White bread, 67.6 g	Butanal, 3.44 mg	2490		Stofberg and Grundschober (1987), Lorenz and Maga (1972), Smyth *et al.* (1951)
0.002	Tea, 60.2 ml	*Theobromine, 1.11 mg	(1265)	837	Stofberg and Grundschober (1987), Blauch and Tarka (1983), Nagata and Sakai (1985), IARC (1991)
0.002	Apple, 32.0 g	*Epicatechin, 1.28 mg		1000P	EPA (1989a), Risch and Herrmann (1988)
0.002	Tomato, 88.7 g	*Tomatine, 621 μg		500	TAS (1989), Eltayeb and Roddick (1984)
0.002	Beer, 257 ml	Ethyl acetate, 4.42 mg	(5620)	4100	Stofberg and Grundschober (1987), Rosculet and Rickard (1968)
0.002	Lettuce, 14.9 g	*Oxalic acid, 447 μg	382		TAS (1989), Kasidas and Rose (1980), Vernot *et al.* (1977)
0.001	Apple, 32.0 g	**p*-Coumaric acid, 573 μg		657P	EPA (1989a), Mosel and Herrmann (1974)
0.001	Apple, 32.0 g	*Chlorogenic acid, 3.39 mg	4000P		EPA (1989a), Jurics (1967), Pérez-Ilzarbe *et al.* (1991)
0.001	Coffee, 500 ml	Maltol, 462 μg	(1410)	550	Stofberg and Grundschober (1987), Tressl *et al.* (1978), IARC (1991)
0.001	Coffee, 500 ml	Nonanoic acid, 188 μg		224V	Stofberg and Grundschober (1987), Kung *et al.* (1967), IARC (1991)

(*continues*)

Table 38.11
(*continued*)

Possible hazard: HERT (%)	Average daily consumption of food	Average human consumption of chemical	LD_{50} (mg/kg) Rats	Mice	Exposure references
0.001	5-Methylfurfural: U.S. avg (mostly coffee)	5-Methylfurfural, 1.71 mg	2200		Stofberg and Grundschober (1987)
0.001	β-Pinene: U.S. avg (mostly pepper, lemon oil, nutmeg)	*β-Pinene, 3.28 mg	4700		Stofberg and Grundschober (1987)
0.001	Broccoli, 6.71 g	*Oxalic acid, 268 μg	382		ERS (1994), Kohman (1939), Vernot *et al.* (1977)
0.001	Strawberry, 4.38 g	*Oxalic acid, 261 μg	382		Stofberg and Grundschober (1987), Zarembski and Hodgkinson (1962), Kasidas and Rose (1980), Vernot *et al.* (1977)
0.0009	Orange juice, 138 ml	Methyl alcohol, 3.48 mg	5628	(7300)	TAS (1989), Kirchner and Miller (1957), Tanner and Limacher (1984), Nisperos-Carriedo and Shaw (1990)
0.0009	α-Pinene: U.S. avg (mostly pepper, nutmeg, lemon oil)	*α-Pinene, 2.25 mg	3700		Stofberg and Grundschober (1987)
0.0009	White bread, 67.6 g	2-Butanone, 1.65 mg	2737	(4050)	Stofberg and Grundschober (1987), Lorenz and Maga (1972)
0.0008	Coffee, 500 ml	Pyridine, 519 μg	891	(1500)	Stofberg and Grundschober (1987), Silwar *et al.* (1987), IARC (1991)
0.0008	Acetone: U.S. avg (mostly tomato, bread, beer)	Acetone, 1.74 mg	(5800)	3000	Stofberg and Grundschober (1987)
0.0008	Cucumber, pickled, 11.8 g	Dimethylamine, 182 μg	(698)	316	Stofberg and Grundschober (1987), Neurath *et al.* (1977)
0.0008	Cabbage, raw, 12.9 g	Methylamine, 169 μg		317	Stofberg and Grundschober (1987), Neurath *et al.* (1977)
0.0007	Tomato, 88.7 g	*Chlorogenic acid, 2.06 mg	4000P		TAS (1989), Winter and Herrmann (1986)
0.0007	Wine, 28.0 ml	Methyl alcohol, 2.84 ml	5628	(7300)	Stofberg and Grundschober (1987), Postel *et al.* (1972)
0.0007	Coffee, 500 ml	2-Methylpyrazine, 894 μg	1800		Stofberg and Grundschober (1987), Silwar *et al.* (1987), IARC (1991)
0.0007	Coffee, 500 ml	2,6-Dimethylpyrazine, 432 μg	880		Stofberg and Grundschober (1987), Silwar *et al.* (1987), IARC (1991)
0.0007	Cabbage, raw, green, 12.9 g	*p-Coumaric acid, 303 μg		657P	Stofberg and Grundschober (1987), Schmidtlein and Herrmann (1975b)
0.0006	Peach, 9.58 g	*Chlorogenic acid, 1.78 mg	4000P		Stofberg and Grundschober (1987), Jurics (1967), Möller and Herrmann (1983), Senter *et al.* (1989)
0.0006	Black pepper, 446 mg	*3-Carene, 2.00 mg	4800		Stofberg and Grundschober (1987), Pino *et al.* (1990)
0.0006	Cabbage, boiled, 12.9 g	*Oxalic acid, 155 μg	382		Stofberg and Grundschober (1987), Zarembski and Hodgkinson (1962), Vernot *et al.* (1977)
0.0006	Coffee, 500 ml	Butyric acid, 785 μg	2000		Stofberg and Grundschober (1987), Kung *et al.* (1967), IARC (1991)
0.0006	Coffee, 500 ml	2,5-Dimethylpyrazine, 399 μg	1020		Stofberg and Grundschober (1987), Silwar *et al.* (1987), IARC (1991)
0.0005	Coffee, 500 ml	5-Methylfurfural, 798 μg	2200		Stofberg and Grundschober (1987), Silwar *et al.* (1987), IARC (1991)
0.0005	Grapes, 11 g	*Oxalic acid, 138 μg	382		Stofberg and Grundschober (1987), Kohman (1939), Vernot *et al.* (1977)
0.0005	Grapes, 11 g	*Chlorogenic acid, 1.38 mg	4000P		Stofberg and Grundschober (1987), Jurics (1967)
0.0005	Black pepper, 446 mg	*β-Pinene, 1.50 mg	4700		Stofberg and Grundschober (1987), Pino *et al.* (1990)
0.0004	Cucumber (raw flesh), 11.8 g	*Oxalic acid, 118 μg	382		Stofberg and Grundschober (1987), Kasidas and Rose (1980), Vernot *et al.* (1977)
0.0004	Potato chips, 5.2 g	*α-Solanine, 179 μg	590		Stofberg and Grundschober (1987), Ahmed and Müller (1978)
0.0004	Coffee, 500 ml	Propanoic acid, 785 μg	2600		Stofberg and Grundschober (1987), Kung *et al.* (1967), IARC (1991)

(*continues*)

Table 38.11
(*continued*)

Possible hazard: HERT (%)	Average daily consumption of food	Average human consumption of chemical	LD_{50} (mg/kg) Rats	Mice	Exposure references
0.0004	Peach, canned, 9.58 g	*Oxalic acid, 115 μg	382		Stofberg and Grundschober (1987), Zarembski and Hodgkinson (1962), Vernot *et al.* (1977)
0.0004	Lettuce, 14.9 g	Benzylamine, 172 μg		600P	TAS (1989), Neurath *et al.* (1977)
0.0004	Lemon juice, 1.33 ml	Octanal, 1.60 mg	5630		EPA (1996b), Mussinan *et al.* (1981)
0.0004	α-Phellandrene: U.S. avg (mostly pepper)	*α-Phellandrene, 1.59 mg	5700		Stofberg and Grundschober (1987)
0.0004	White bread, 67.6 g	Hexanal, 1.35 mg	4890	(8292)	Stofberg and Grundschober (1987), Lorenz and Maga (1972)
0.0004	Black pepper, 446 mg	*α-Pinene, 1.02 mg	3700		Stofberg and Grundschober (1987), Pino *et al.* (1990)
0.0004	Banana, 15.7 g	2-Pentanone, 424 μg	1600	1600	TAS (1989), Hultin and Proctor (1961)
0.0003	Grapes, 11 g	*Epicatechin, 243 μg		1000P	Stofberg and Grundschober (1987), Jurics (1967), Lee and Jaworski (1987)
0.0003	Onion, raw, 14.2 g	Dipropyl trisulfide, 189 μg		800	Stofberg and Grundschober (1987)
0.0003	Coffee, 500 ml	2-Ethyl-3-methylpyrazine, 186 μg	880		Stofberg and Grundschober (1987), IARC (1991)
0.0003	Pear, 3.29 g	*Chlorogenic acid, 823 μg	4000P		Stofberg and Grundschober (1987), Jurics (1967)
0.0003	Carrot, 12.1 g	*Chlorogenic acid, 780 μg	4000P		TAS (1989), Winter *et al.* (1987)
0.0003	Lemon oil, 8 mg	*γ-Terpinene, 681 μg	3650		Stofberg and Grundschober (1987), Ikeda *et al.* (1962), Staroscik and Wilson (1982a, 1982b)
0.0003	Lemon oil, 8 mg	*Geranial, 90.4 μg	500		Stofberg and Grundschober (1987), Bernhard (1960), Staroscik and Wilson (1982a, 1982b)
0.0003	Lemon oil, 8 mg	*β-Pinene, 832 μg	4700		Stofberg and Grundschober (1987), Ikeda *et al.* (1962), Staroscik and Wilson (1982a, 1982b)
0.0002	Broccoli (raw), 6.71 g	*p-Coumaric acid, 90.6 μg		657P	ERS (1994), Schmidtlein and Herrmann (1975b)
0.0002	Lemon oil, 8 mg	*Citral, 600 μg	4960	(6000)	Stofberg and Grundschober (1987), Günther (1968)
0.0001	Isoamyl acetate: U.S. avg (mostly beer, banana)	Isoamyl acetate, 1.70 mg	16,600		Stofberg and Grundschober (1987)
0.0001	Corn, canned, 33.8 g	Dimethyl sulfide, 324 μg	3300	(3700)	Stofberg and Grundschober (1987), Williams *et al.* (1972), Buttery *et al.* (1994)
0.0001	Onions, green, cooked, 137 mg	*Oxalic acid, 31.5 μg	382		EPA (1996b), Kohman (1939), Vernot *et al.* (1977)
0.0001	Coffee, 500 ml	Hexanoic acid, 245 μg	3000	(5000)	Stofberg and Grundschober (1987), Kung *et al.* (1967), IARC (1991)
0.0001	Pear, 3.29 g	*Epicatechin, 80.9 μg		1000P	Stofberg and Grundschober (1987), Mosel and Herrmann (1974), Risch and Herrmann (1988)
0.00007	Nutmeg, 27.4 mg	*Myristicin, 207 μg	4260		Ehlers *et al.* (1998)
0.00006	Banana, 15.7 g	Methyl alcohol, 236 μg	5628	(7300)	TAS (1989), Hultin and Proctor (1961)
0.00005	Lemon oil, 8 mg	*α-Pinene, 139 μg	3700		Stofberg and Grundschober (1987), Ikeda *et al.* (1962), Staroscik and Wilson (1982a, 1982b)
0.00005	Banana, 15.7 g	Isoamyl acetate, 584 μg	16,600		TAS (1989), Tressl *et al.* (1970)
0.00005	Strawberry, 4.38 g	*Chlorogenic acid, 136 μg	4000P		Stofberg and Grundschober (1987), Jurics (1967)
0.00004	Black pepper, 446 mg	*α-Phellandrene, 162 μg	5700		Stofberg and Grundschober (1987), Pino *et al.* (1990)
0.00002	Grapefruit juice, 3.29 ml	Methyl alcohol, 95.4 μg	5628	(7300)	Stofberg and Grundschober (1987), Kirchner *et al.* (1953), Lund *et al.* (1981), Tanner and Limacher (1984), Pino *et al.* (1986)
0.00002	Lemon oil, 8 mg	*α-Terpinene, 23.2 μg	1680		Stofberg and Grundschober (1987), Staroscik and Wilson (1982a, 1982b)
0.00001	Lemon oil, 8 mg	*α-Terpineol, 29.6 μg		2830	Stofberg and Grundschober (1987), Staroscik and Wilson (1982a, 1982b)

(*continues*)

Table 38.11
(*continued*)

Possible hazard: HERT (%)	Average daily consumption of food	Average human consumption of chemical	LD_{50} (mg/kg) Rats	Mice	Exposure references
0.00001	Black pepper, 446 mg	*α-Terpineol, 25.0 μg		2830	Stofberg and Grundschober (1987), Pino *et al.* (1990)
0.00001	Garlic, blanched, 53.3 mg	Diallyl disulfide, 2.05 μg	260		EPA (1996b), Yu *et al.* (1989)
0.00001	Lemon oil, 8 mg	*Terpinolene, 29.6 μg	4390		Stofberg and Grundschober (1987), Staroscik and Wilson (1982a, 1982b)
0.000008	Garlic, blanched, 53.3 mg	Diallyl trisulfide, 592 ng		100	EPA (1996b), Yu *et al.* (1989)
0.000001	Garlic, blanched, 53.3 mg	Diallyl sulfide, 2.28 μg	2980		EPA (1996b), Yu *et al.* (1989)

LD_{50}: Values are from the Registry of Toxic Effects of Chemical Substances (RTECS). Parentheses indicate the species with the higher (weaker) LD_{50}, which is not used in the HERT calculation. *Daily human exposure*: The average amount of the food consumed daily per person in the United States; when a chemical is listed rather than a food item, the value is the per person average in the total diet. All other calculations assume a daily dose for a lifetime. *Possible hazard:* The amount of chemical reported under "Human dose of chemical" is divided by 70 kg to give a mg/kg of human exposure. The HERT is this human dose (mg/kg/day) as a percentage of the rodent LD_{50} (mg/kg). An * preceding a chemical name indicates that the chemical is a natural pesticide.
Abbreviations for LD_{50} values: LO, LD_{LO}; P, intraperitoneal injection; V, intravenous injection; J, injection (route not specified).

tion, and manufacturing procedures and additionally require evidence of efficacy and safety, dietary supplements are not. We found that several dietary supplements would rank high in the HERT table if we had included them by using the recommended dose and the LD_{50} value for the extract: ginger extract (HERT = 0.8%), ginkgo leaf extract (HERT = 0.7%), ginseng extract (HERT = 0.7%), garlic extract (HERT = 0.1%), and valerian extract (HERT = 0.01%). These results argue for greater toxicological testing requirements and regulatory scrutiny of dietary supplements on the grounds that they may be carcinogens in rodents and that, if so, they are likely to rank high in possible carcinogenic hazard. Because these products lack requirements for toxicological testing, the NTP has established a research program on medicinal herbs and ingredients.

38.8 SUMMARY OF CARCINOGENICITY RESULTS IN THE CPDB ON ACTIVE INGREDIENTS OF COMMERCIAL PESTICIDES THAT HAVE BEEN EVALUATED BY THE U.S. EPA

This section presents summary results on each of 193 commercial pesticide ingredients that are listed by the EPA in "Status of Pesticides in Registration, Reregistration, and Special Review," its Rainbow Report (U.S. Environmental Protection Agency, 1998) and that are also included in the CPDB. Results for pesticides that are negative for carcinogenicity in the CPDB are included. Approximately 1900 pesticides are listed in the Rainbow Report, but only 193 have published results of carcinogenicity experiments that meet the inclusion criteria of the CPDB (Gold and Zeiger, 1997). Table 38.12 provides a quick overview of the CPDB results on each pesticide, including the following information: the sex–species groups that have been tested, the strongest level of evidence of carcinogenicity based on the opinion of the published author, carcinogenic potency (TD_{50}), target organs in each species, and mutagenicity in *Salmonella typhimurium*. Carcinogenicity results for rats and mice are reported in Table 38.12, and in Table 38.13 for hamsters, monkeys, and dogs. For each pesticide, the details on each experiment are reported in the CPDB, published in the *CRC Handbook of Carcinogenic Potency and Genotoxicity Databases* (Gold *et al.*, 1997c) and in *Environmental Health Perspectives* (Gold *et al.*, 1999) as well as reported in http://potency.berkeley.edu.

The following describe the data reported in Tables 38.12 and 38.13.

Pesticides A chemical is considered a pesticide if it appears in the EPA "Status of Pesticides in Registration, Reregistration, and Special Review" (U.S. Environmental Protection Agency, 1998), the Rainbow Report. Included in the Rainbow Report is the status of pesticides that are undergoing pesticide reregistration, that have completed pesticide reregistration, that are under special review, or that are "new" (i.e., that have been registered since 1984). For 79 of the 193 commercial pesticides in the table, the active ingredient is no longer contained in any registered pesticide product; for these cases of voluntary or regulated cancellation, we indicate this fact by an asterisk next to the chemical name. If a commercial pesticide is also a chemical that occurs naturally, the chemical name is in boldface.

Mutagenicity in *Salmonella* A chemical is classified as mutagenic in the *Salmonella* assay "+" if it was evaluated as either "mutagenic" or "weakly mutagenic" by Zeiger (1997) or as "positive" by the Gene-Tox Program (Auletta, personal communication; Kier *et al.*, 1986). All other chemicals evaluated for mutagenicity by these two sources are reported as "—." The symbol "•" indicates that these sources did not provide an

Table 38.12
Summary of Carcinogenicity Results in Rats and Mice in the Carcinogenic Potency Database on 193 Active Ingredients Commercial Pesticides that Have Been Evaluated by the U.S. Environmental Protection Agency

Pesticide	CAS	Sal-monella	Harmonic mean of TD_{50} (mg/kg/day)		Rat target sites		Mouse target sites	
			Rat	Mouse	Male	Female	Male	Female
Acrolein	107-02-8	+	—	—	—	—	—	—
Acrylonitrile*	107-13-1	+	16.9[m,v]	·	ezy nrv orc smi sto	ezy mgl nas nrv orc smi sto	·	·
Aldicarb	116-06-3	—	—	—	—	—	—	—
Aldrin*	309-00-2	—	—	1.27[m]	—	—	liv	liv(B)
Allantoin*	97-59-6	·	—	·	—	—	·	·
Allyl isothiocyanate	57-06-7	+	96	—	ubl	—	—	—
3-Aminotriazole[s]	61-82-5	—	9.94[m]	25.3[m]	thy	pit thy	liv	liv
Anethole*	104-46-1	—	·	—	·	·	·	—
Anilazine*	101-05-3	—	—	—	—	—	—	—
Antimony potassium tartrate*	28300-74-5	—	·	·	·	·	B—	B—
Arsenate, sodium[s]	7631-89-2	·	·	·	B—	B—	·	·
Arsenious oxide	1327-53-3	·	·	—	·	·	—	—
Arsenite, sodium*	7784-46-5	·	·	·	B—	B—	B—	B—
Aspirin	50-78-2	—	—	—	—	B—	—	—
Atrazine	1912-24-9	—	31. 7[m]	—	mgl	hmo ute	—	—
Azinphosmethyl	86-50-0	+	—	—	—	—	—	—
Benzaldehyde*	100-52-7	—	—	1490[m]	—	—	sto	sto
Benzene*	71-43-2	—	169[m]	77.5[m,v]	ezy nas orc ski sto vsc	ezy nas orc sto vsc	ezy hag hmo lun pre	ezy hmo lun mgl ova
Benzoate, sodium*	532-32-1	·	—	—	—	—	—	—
Benzoic acid*	65-85-0	—	—	·	—	·	·	·
Benzyl alcohol*	100-51-6	—	—	—	—	—	—	—
o-Benzyl-*p*-chlorophenol	120-32-1	—	—	1350	—	—	kid	—
Biphenyl*	92-52-4	—	·	—	·	·	—	—
Bis(tri-*n*-butyltin)oxide, technical grade	56-35-9	—	—	·	—	—	·	·
Boric acid	10043-35-3	—	·	—	·	·	—	—
tert*-Butyl alcohol	75-65-0	—	64.6	21900	kid	—	—	thy
Butyl *p*-hydroxybenzoate*	94-26-8	·	·	—	·	·	—	—
p-tert-Butylphenol*	98-54-4	·	—	·	—	·	·	·
Cadmium chloride[s]*	10108-64-2	—	0.0114[m,v]	—	hmo lun pro tes	lun	·	—
Calcium chloride*	10043-52-4	—	—	·	—	·	·	·
Capsaicin	404-86-4	·	·	167[m,n]	·	·	lgi	lgi
Captan	133-06-2	+	2080[m]	2110[m]	kid	ute	smi	smi
Carbaryl	63-25-2	+	14.1	—	tba(B)	tba(B)	—	—
Carbon tetrachloride	56-23-5	—	2.29[m,n]	150[m]	liv	liv mgl	adr liv	adr liv
Chloramben*	133-90-4	+	—	5230	—	—	—	liv
Chloranil*	118-75-2	·	·	—	·	·	—	—
Chlordane, technical grade*	57-74-9	—	—	1.37[m,v]	—	—	liv	liv
Chlorinated trisodium phosphate	56802-99-4	+	·	—	·	·	—	—
Chlorine	7782-50-5	—	·	·	B—	B—	·	·
3-Chloro-*p*-toluidine	95-74-9	—	—	—	—	—	—	—
Chlorobenzilate*	510-15-6	—	—	93.9[m,v]	—	—	liv	liv
(2-Chloroethyl) trimethyl-ammonium chloride	999-81-5	—	—	—	—	—	—	—

(*continues*)

Table 38.12
(*continued*)

Pesticide	CAS	Salmonella	Harmonic mean of TD_{50} (mg/kg/day)		Rat target sites		Mouse target sites	
			Rat	Mouse	Male	Female	Male	Female
Chloroform[s]	67-66-3	—	262[m]	90.3[m]	kid	liv	kid liv	liv
3-(*p*-Chlorophenyl)-1,1-dimethylurea*	150-68-5	—	131	—	kid liv	—	—	—
Chloropicrin	76-06-2	+	I	—	I	I	—	—
Chlorothalonil	1897-45-6	—	2270[m]	—	kid	kid	—	—
Citric acid	77-92-9	·	—	·	—	·	·	·
Clonitralid	1420-04-8	·	—	—	—	—	I	—
Copper-8-hydroxyquinoline	10380-28-6	·	·	—	·	·	—	—
Coumaphos	56-72-4	—	—	—	—	—	—	—
Cyanamide, calcium*	156-62-7	+	—	—	—	—	—	—
Cyclohexanone*	108-94-1	—	—	—	—	—	—	—
Daminozide	1596-84-5	—	2500[n]	1030[m]	—	ute	kid lun vsc	lun vsc
p,p′-DDD*	72-54-8	—	—	30.7[m]	—	—	liv lun	lun
DDT[s]*	50-29-3	—	84.7[m]	12.8[m,v]	liv	liv	hmo liv lun	hmo liv lun
Deltamethrin	52918-63-5	·	—	—	—	—	—	—
Diallate*	2303-16-4	+	·	26.7[m]	·	·	liv	—
Diazinon	333-41-5	—	—	—	—	—	—	—
1,2-Dibromo-3-chloropropane*	96-12-8	+	0.259[m]	2.72[m]	nas orc sto	adr mgl nas orc sto	lun nas sto	lun nas sto
1,2-Dibromoethane*	106-93-4	+	1.52[m]	7.45[m,v]	nas per pit sto vsc	liv lun mgl nas pit sto vsc	lun sto vsc	eso lun mgl nas sto sub vsc
3,5-Dichloro(*N*-1,1-dimethyl-2-propynyl)benzamide	23950-58-5	·	·	119	·	·	liv	·
2,3-Dichloro-1,4-naphthoquinone*	117-80-6	·	·	—	·	·	—	—
2,6-Dichloro-4-nitroaniline	99-30-9	+	·	—	·	·	—	—
1,2-Dichlorobenzene*	95-50-1	—	—	—	—	—	—	—
1,4-Dichlorobenzene	106-46-7	—	644	398[m]	kid	—	liv	liv
Dichlorodifluoromethane*	75-71-8	·	—	—	—	—	—	—
1,2-Dichloroethane*	107-06-2	+	8.04[m]	101[m]	sto sub vsc	mgl	lun	lun mgl ute
α-(2,4-Dichlorophenoxy)propionic acid	120-36-5	·	·	—	·	·	—	—
2,4-Dichlorophenoxyacetic acid	94-75-7	—	·	—	·	·	—	—
2,4-Dichlorophenoxyacetic acid, *n*-butyl ester*	94-80-4	—	·	—	·	·	—	—
2,4-Dichlorophenoxyacetic acid, isopropyl ester	94-11-1	·	·	—	·	·	—	—
3-(3,4-Dichlorophenyl)-1,1-dimethylurea	330-54-1	·	·	—	·	·	—	—
Dichlorvos	62-73-7	+	4.16	70.4[m]	hmo pan	—	sto	sto
Dicofol	115-32-2	—	—	32.9	—	—	liv	—
Dieldrin[s]*	60-57-1	—	—	0.912[m]	—	—	liv	liv
O,O-Diethyl-*o*-(3,5,6-trichloro-2-pyridyl)phosphorothioate	2921-88-2	—	—	·	—	—	·	·
Dimethoate	60-51-5	+	—	—	—	—	—	—
Dimethoxane	828-00-2	+	716	·	hmo kid liv ski sub	·	·	·

(*continues*)

Table 38.12
(*continued*)

Pesticide	CAS	Sal-monella	Harmonic mean of TD_{50} (mg/kg/day)		Rat target sites		Mouse target sites	
			Rat	Mouse	Male	Female	Male	Female
Dimethylarsinic acid	75-60-5	—	·	—	·	·	—	—
2,4-Dinitrophenol*	51-28-5	—	·	·	·	·	B—	B—
Dioxathion*	78-34-2	+	—	—	—	—	—	—
n-Dodecylguanidine acetate	2439-10-3	·	·	—	·	·	—	—
EDTA, trisodium salt trihydrate*	150-38-9	—	—	—	—	—	—	—
Endosulfan	115-29-7	—	—	—	I	—	—	—
Endrin*	72-20-8	—	—	—	—	—	—	—
Ethoxyquin	91-53-2	—	—	·	—	—	·	·
Ethyl alcohol	64-17-5	—	9110	—	adr liv pan pit	—	—	—
p, *p*′-Ethyl-DDD*	72-56-0	+	—	—	—	—	—	—
Ethylene glycol*	107-21-1	—	·	—	·	·	—	—
Ethylene oxide	75-21-8	+	21.3[m,v]	63.7[m]	hmo nrv per	nrv sto	hag lun	hag hmo lun mgl ute
Ethylenebisdithiocarbamate, disodium	142-59-6	·	·	—	·	·	—	—
di(2-Ethylhexyl)phthalate*	117-81-7	—	625[m]	894[m]	liv	liv	liv	liv
Eugenol	97-53-0	—	—	—	—	—	—	—
Fenaminosulf, formulated*	140-56-7	+	—	—	—	—	—	—
Fenthion	55-38-9	—	—	—	—	—	—	—
Fenvalerate	51630-58-1	·	—	—	—	—	—	—
Ferric dimethyldithiocarbamate	14484-64-1	·	·	—	·	·	—	—
Fluometuron	2164-17-2	—	—	—	—	—	—	—
Fluoride, sodium	7681-49-4	—	—	—	—	—	—	—
Formaldehyde[s]	50-00-0	+	2.19[m,v]	43.9	hmo nas	hmo nas	nas	—
Fosetyl Al	39148-24-8	·	3660	·	ubl	—	·	·
Furfural[s]*	98-01-1	+	683	197[m]	liv	—	liv	liv
Gibberellic acid	77-06-5	—	·	—	·	·	—	—
Glycerol α-monochlorohydrin*	96-24-2	+	—	·	—	—	·	·
Heptachlor	76-44-8	—	—	1.21[m]	—	—	liv	liv
β-1,2,3,4,5,6-Hexachlorocyclo-hexane	319-85-7	—	·	27.8[m]	·	·	liv	liv
γ-1,2,3,4,5,6-Hexachlorocyclo-hexane	58-89-9	—	—	30.7[m]	—	—	liv	liv lun
Hexachlorophene*	70-30-4	—	—	—	—	—	—	—
3-(Hexahydro-4,7-methanoin-dan-5-yl)-1,1-dimethylurea*	2163-79-3	·	·	—	·	·	—	—
Hydrochloric acid	7647-01-0	·	—	·	—	·	·	·
Hydrogen peroxide	7722-84-1	+	·	7540	·	·	—	smi
8-Hydroxyquinoline*	148-24-3	+	—	—	—	—	—	—
Isopropyl-*N*-(3-chlorophenyl) carbamate[s]	101-21-3	·	—	—	—	—	—	—
Isopropyl-*N*-phenyl carbamate[s]*	122-42-9	·	·	—	·	·	—	—
Kepone*	143-50-0	—	2.96	0.982[m]	—	liv	liv	liv
Malathion	121-75-5	—	—	—	—	—	—	—
Maleic hydrazide	123-33-1	—	—	—	—	—	—	—

(*continues*)

Table 38.12
(*continued*)

Pesticide	CAS	Salmonella	Harmonic mean of TD_{50} (mg/kg/day)		Rat target sites		Mouse target sites	
			Rat	Mouse	Male	Female	Male	Female
Manganese ethylenebisthiocarbamate	12427-38-2	·	157	—	tba(B)	tba(B)	—	—
2-Mercaptobenzothiazole*	149-30-4	—	344[m]	—	adr hmo pan pre	adr pit	—	—
2-Mercaptobenzothiazole, zinc	155-04-4	·	·	—	·	·	—	—
Mercuric chloride*	7487-94-7	—	3.12	—	sto	—	—	—
Methidathion	950-37-8	·	·	6.04	·	·	liv	—
Methoxychlor	72-43-5	—	—	—	—	—	—	—
Methyl bromide	74-83-9	+	—	—	—	—	—	—
Methyl parathion	298-00-0	+	—	—	—	—	—	—
Methylene chloride*	75-09-2	+	724[m,i]	1100[m,i]	mgl	mgl	liv lun	liv lun
Metronidazole*	443-48-1	+	542[m]	506[m]	pit tes	liv mgl	lun	hmo lun
Mexacarbate*	315-18-4	·	—	—	—	—	—	—
Mirex*	2385-85-5	—	1.77[m]	1.45[m]	adr kid liv	hmo liv	liv	liv
Naphthalene	91-20-3	—	·	163[i]	·	·	—	lun
1-Naphthalene acetamide	86-86-2	+	·	—	·	·	—	—
1-Naphthalene acetic acid	86-87-3	—	·	—	·	·	—	—
Nickel (II) sulfate hexahydrate*	10101-97-0	—	—	—	—	—	—	—
Nicotine	54-11-5	—	—	·	—	—	·	·
Nitrate, sodium	7631-99-4	·	—	·	—	—	·	·
Nitrite, sodium[s]	7632-00-0	+	167[m]	—	hmo(B) liv	hmo(B) liv	—	—
Nitrofen*	1836-75-5	+	420	115[m]	—	pan	liv vsc	liv
Oleate, sodium*	143-19-1	·	—	·	—	—	·	·
Oxamyl	23135-22-0	·	—	—	—	—	—	—
Oxytetracycline.HCl	2058-46-0	—	—	—	—	—	—	—
Parathion	56-38-2	—	—	—	—	—	—	—
Pentachloronitrobenzene	82-68-8	—	—	71.1	—	—	liv	—
2,3,4,5,6-Pentachlorophenol (Dowicide EC-7)	87-86-5	—	—	24[m]	—	—	adr liv	adr liv vsc
Phenol	108-95-2	—	—	—	—	—	—	—
Phenothiazine*	92-84-2	—	·	—	·	·	—	—
Phenylmercuric acetate*	62-38-4	—	·	—	·	·	—	—
o-Phenylphenate, sodium	132-27-4	—	545[m,v]	—	kid ubl	ubl	—	—
o-Phenylphenol	90-43-7	+	232	—	ubl	·	—	—
Phosphamidon*	13171-21-6	+	I	—	I	I	—	—
Picloram, technical grade	1918-02-1	—	—	—	—	—	—	—
Piperonyl butoxide in solvent	51-03-6	—	·	—	·	·	—	—
Piperonyl sulfoxide*	120-62-7	—	—	62.2	—	—	liv	—
Polysorbate 80*	9005-65-6	—	—	—	—	—	—	—
Potassium bicarbonate	298-14-6	·	13,000[m]	·	ubl	ubl	·	·
Propazine	139-40-2	·	·	—	·	·	—	—
Propyl *N*-ethyl-*N*-butylthiocarbamate	1114-71-2	·	·	—	·	·	—	—
n-Propyl isome*	83-59-0	·	·	—	·	·	—	—
Propylene glycol*	57-55-6	—	—	·	—	—	·	·
1,2-Propylene oxide	75-56-9	+	74.4[m,v]	912[m]	adr nas	mgl nas sto	nas	nas
FD & C red no. 3*	16423-68-0	—	—	—	—	—	—	—
Rotenone	83-79-4	—	—	—	—	—	—	—

(*continues*)

Table 38.12
(*continued*)

Pesticide	CAS	Salmonella	Harmonic mean of TD_{50} (mg/kg/day)		Rat target sites		Mouse target sites	
			Rat	Mouse	Male	Female	Male	Female
Safrole*	94-59-7	—	441[m]	51.3[m,v]	liv	liv(B)	liv	liv
Simazine	122-34-9	—	·	—	·	·	—	—
Sodium bicarbonate	144-55-8	·	—	·	—	·	·	·
Sodium chloride	7647-14-5	—	—	—	—	·	—	—
Sodium chlorite	7758-19-2	·	—	—	—	—	—	—
Sodium dichromate	10588-01-9	+	4.64[i]	·	lun	·	·	·
Sodium hypochlorite	7681-52-9	—	—	—	—	—	—	—
Strobane*	8001-50-1	·	·	0.884[m]	·	·	hmo liv	—
Sulfallate*	95-06-7	+	26.1[m]	42.2[m]	sto	mgl	lun	mgl
Telone II	542-75-6	+	94[m]	49.6	liv sto	sto	I	lun sto ubl
2,4,5,4′-Tetrachlorodiphenyl sulfone*	116-29-0	·	·	—	·	·	—	—
Tetrachloroethylene*	127-18-4	—	101[m]	126[m]	hmo kid	hmo	liv	liv
Tetrachlorvinphos	961-11-5	—	—	228	—	—	liv	—
Tetrakis(hydroxymethyl)phosphonium sulfate	55566-30-8	—	—	—	—	—	—	—
Tetramethylthiuram disulfide	137-26-8	·	—	—	—	—	—	—
Thiabendazole	148-79-8	+	—	·	—	—	·	·
Toxaphene*	8001-35-2	+	—	5.57[m]	—	—	liv	liv
Trichloroacetic acid*	76-03-9	—	—	584[m]	—	·	liv	liv
1,1,1-Trichloroethane, technical grade*	71-55-6	+	—	—	—	—	—	—
Trichlorofluoromethane*	75-69-4	—	—	—	—	—	—	—
N-(Trichloromethylthio)phthalimide	133-07-3	+	—	1550[m]	—	—	smi sto	smi
2,4,6-Trichlorophenol*	88-06-2	—	405	1070[m]	hmo	—	liv	liv
2,4,5-Trichlorophenoxyacetic acid*	93-76-5	—	—	—	—	—	—	—
Triethanolamine	102-71-6	—	—	100[m]	—	—	tba	tba
Triethylene glycol	112-27-6	·	—	·	—	·	·	·
Trifluralin, technical grade	1582-09-8	+	—	330	—	—	—	liv lun sto
Triphenyltin hydroxide	76-87-9	—	—	—	—	—	—	—
Urea*	57-13-6	—	—	—	—	—	—	—
Xylene mixture (60% *m*-xylene, 9% *o*-xylene, 14% *p*-xylene, 17% ethylbenzene)	1330-20-7	—	—	—	—	—	—	—
FD & C yellow no.5	1934-21-0	—	—	—	—	—	—	—
Zinc dimethyldithiocarbamate	137-30-4	+	40.7[m]	—	tba(B) thy	tba(B)	—	—
Zinc ethylenebisthiocarbamate*	12122-67-7	—	255	—	tba(B)	tba(B)	—	—

Abbreviations: ·, not tested; (B), data reported only for both sexes combined.
Tissue codes: adr, adrenal gland; eso, esophagus; ezy, ear/Zymbal's gland; hag, harderian gland; hmo, hematopoietic system; kid, kidney; lgi, large intestine; liv, liver; lun, lung; mgl, mammary gland; nas, nasal cavity (includes tissues of the nose, nasal turbinates, paranasal sinuses, and trachea); nrv, nervous system; orc, oral cavity (includes tissues of the mouth, oropharynx, pharynx, and larynx); ova, ovary; pan, pancreas; per, peritoneal cavity; pit, pituitary gland; pre, preputial gland; pro, prostate; ski, skin; smi, small intestine; sto, stomach; sub, subcutaneous tissue; tba, all tumor bearing animals; tes, testes; thy, thyroid gland; ubl, urinary bladder; ute, uterus; vsc, vascular system.
In a series of footnotes, we provide additional information about TD_{50} values and test results in the CPDB. These are as follows: i, carcinogenic in rodents only by the inhalation route of administration; m, more than one positive test in the species in the CPDB; n, no results that were evaluated as positive by the published author for this species in the CPDB have statistically significant TD_{50} values (two-tailed $p < 0.1$); s, species other than rats or mice are reported for this chemical in Table 38.13; v, variation is greater than 10-fold among statistically significant ($p < 0.1$) TD_{50} values from different positive experiments.
Note: The commercial pesticides in boldface also occur naturally.
*Voluntary or regulated cancellations. The Active Ingredient Is No Longer Contained in Any Registered Pesticide Product.

Table 38.13
Summary of Carcinogenicity Results in the Carcinogenic Potency Database in Other Species on 11 Commercial Pesticides Ingredients Evaluated by the U.S. Environmental Protection Agency

Pesticide	CAS	Salmonella	Harmonic mean of TD_{50} (mg/kg/day)	Target sites
Hamsters				
3-Aminotriazole	61-82-5	—	—	—
Cadmium chloride*	10108-64-2	—	—	—
DDT*	50-29-3	—	—	—
Dieldrin*	60-57-1	—	—	—
Formaldehyde	50-00-0	+	—	—
Furfural*	98-01-1	+	—	—
Isopropyl-*N*-(3-chlorophenyl)carbamate	101-21-3	·	—	—
Isopropyl-*N*-phenyl carbamate*	122-42-9	·	—	—
Nitrite, sodium	7632-00-0	+	—	—
Cynomolgus monkeys				
DDT*	50-29-3	—	—	—
Rhesus monkeys				
Arsenate, sodium	7631-89-2	·	—	—
DDT*	50-29-3	—	—	—
Dogs				
Chloroform	67-66-3	—	—	—

The Commercial Pesticides in Boldface also Occur Naturally.
*Voluntary or regulated cancellations. The Active Ingredient Is No Longer Contained in Any Registered Pesticide Product.
Abbreviations: ·, not tested.

evaluation. For a chemical of interest, results for other genotoxicity tests are reported for some chemicals in the Genotoxicity Database (Zeiger, 1997).

Carcinogenicity For each positive chemical in the CPDB, results are included on carcinogenic potency (by species) and target organ (by sex–species); if there are no positive results, then the symbol "—" appears. The classification of positivity in this summary table is based on a positive result in at least one experiment. There may be additional experiments on the same chemical that are negative in the CPDB, but this is not reflected in the table. An experiment is classified as positive or negative on the basis of the published author's opinion. A target site is classified as positive for NCI/NTP if the evaluation in technical report was "carcinogenic" or "clear" or "some" evidence of carcinogenic activity ["c" or "p" on the plot of the CPDB (Gold *et al.*, 1997c, 1999)]. In the general literature, a site is classified as a target if the author of the published paper considered tumors to be induced by compound administration ("+" on the plot). In some cases authors do not clearly state their evaluation (blank in author's opinion in plot), and in some NCI/NTP technical reports the evidence for carcinogenicity is considered "associated" or "equivocal"; these are not classified as positive. We use the author's opinion to determine positivity because it often takes into account more information than statistical significance alone, such as historical control rates for particular sites, survival and latency, and/or dose response. Generally, this designation by author's opinion corresponds well with the results of statistical tests for the significance of the dose–response effect (two-tailed $p < 0.01$). For some chemicals, the only experiments in the CPDB for a species or a sex–species group were NCI/NTP bioassays that were evaluated as inadequate, and we indicate these with an "I," in the potency and target organ fields.

Carcinogenic Potency In the CPDB, a standardized quantitative measure of carcinogenic potency, the TD_{50}, is estimated for each set of tumor incidence data. In a simplified way, the TD_{50} may be defined as follows: For a given target site(s), if there are no tumors in control animals, then the TD_{50} is that chronic dose rate (in mg/kg body weight/day) that would induce tumors in half the test animals at the end of a standard life span for the species. Because the tumor(s) of interest often does occur in control animals, the TD_{50} is more precisely defined as that dose rate (in mg/kg body weight/day) that, if administered chronically for the standard life span of the species, will halve the probability of remaining tumorless throughout that period. The TD_{50} is analogous to the LD_{50}, and a low TD_{50} value indicates a potent carcinogen, whereas a high value indicates a weak one. The TD_{50} and the statistical procedures adopted for estimating it from experimental data have been described elsewhere (Gold *et al.*, 1997c; Peto *et al.*, 1984; Sawyer *et al.*, 1984). The range of TD_{50} across chemicals in the CPDB is at least 10 million-fold for carcinogens in each sex of rat or mouse.

In Table 38.12, a carcinogenic potency value is reported for a chemical in each species with a positive evaluation of carcinogenicity in at least one test. If there is only one positive test on the chemical in the species, then the most potent TD_{50} value from that test is reported. When more than one experiment is positive, in order to use all the available data, the reported potency value is a harmonic mean of the most potent TD_{50} values from each positive experiment. We have shown that the harmonic mean is similar to the most potent TD_{50} value for chemicals with more than one positive test (Gold *et al.*, 1989, 1997b). The harmonic mean (T_H) is defined as

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

To obtain the harmonic mean from each positive experiment, we select the lowest TD_{50} value from among positively evaluated target sites with a statistically significant dose response (two-tailed $p < 0.1$). If no positive sites have a significant dose response, then we select the most potent (lowest TD_{50}) from among positively evaluated sites with $p \geq 0.1$. When some experiments have positive significant results and others have only positive nonsignificant results, we discard the nonsignificant experimental results for the calculation of the harmonic mean. In some experiments, no TD_{50} could be estimated because all dosed animals had the tumor of interest, and only summary data were available for animals with the tumor. For these cases, we use the 99% upper confidence limit of TD_{50} as a replacement for the TD_{50}.

In a series of superscripts following the TD_{50} value, we provide additional information about the carcinogenic potency and other test results in the CPDB. These are as follows:

i = carcinogenic in rodents only by the inhalation route of administration.

m = more than one positive test in the species in the CPDB.

n = no results that were evaluated as carcinogenic by the published author for this species in the CPDB have statistically significant TD_{50} values (two-tailed $p < 0.1$).

s = species other than rats or mice are reported for this chemical in Table 38.13.

v = variation is greater than 10-fold among statistically significant (two-tailed $p < 0.1$) TD_{50} values from different positive experiments.

Target Sites Target sites are reported for each sex–species group with a positive result in the CPDB. Target sites are identified on the basis of an author's positive opinion for the particular site, in any experiment in the sex–species, using all results from both the general literature and the NCI/NTP bioassays. Hence, if a chemical has two target sites listed in a sex–species, the results may represent two different experiments. Occasionally, the CPDB results are only for both sexes combined and this has been indicated with (B) next to the target site.

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