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Natural and Synthetic Chemicals in the Diet: A Critical Analysis of Possible Cancer Hazards

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Abstract

Current regulatory policy to reduce human cancer risks is based on the idea that chemicals which induce tumors in rodent cancer bioassays are potential human carcinogens. The chemicals selected for testing in rodents, however, are primarily synthetic. 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; 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.

This chapter examines critically the assumptions, methodology, results, and implications of regulatory cancer risk assessments of synthetic chemicals and compares synthetic chemicals to naturally-occurring chemicals in food. Our analyses are based on results in our Carcinogenic Potency Database (CPDB), 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:

(1) Human exposure to synthetic chemicals compared to the broader and greater exposure to natural chemicals in the diet.

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

(3) Increased cell division as an important hypothesis for the high positivity rate in rodent bioassays, and the implications for risk assessment.

(4) A broad perspective on possible cancer hazards from a variety of exposures to rodent carcinogens including natural dietary chemicals and synthetic chemicals, by ranking on the HERP index. HERP indicates what percentage of the rodent carcinogenic potency (TD_{50} in mg/kg/day) a human receives from an average daily lifetime exposure (mg/kg/day). We report 72 HERP values, ranging across 10 orders of magnitude. Results indicate that some historically high exposures in the workplace and some pharmaceuticals rank high in possible carcinogenic hazard, and that there is an enormous background of naturally-occurring rodent carcinogens in average consumption of common foods that casts doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides.

(5) Identification and ranking of possible toxic hazards from exposures in the U.S. diet to naturally-occurring chemicals that have not been tested for carcinogenicity, using the HERT index. HERT is the ratio of Human Exposure/Rodent Toxicity in mg/kg/day expressed as a percentage, and rodent LD_{50} values are the measure of toxicity. This approach to prioritizing untested chemicals makes assessment of human exposure levels critical at the outset. We report 121 HERT values, ranging across 6 orders of magnitude.

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I. INTRODUCTION

Possible cancer hazards 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. 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 [1]. Overall cancer death rates in the U.S. (excluding lung cancer due to smoking) have declined 19% since 1950 [2]. The types of cancer deaths that have decreased since 1950 are primarily stomach, cervical, uterine, and colorectal. The types that have increased are primarily lung cancer (87% is due to smoking, as are 31% of all cancer deaths in the U.S. [3]), 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 [2].

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 confounder. 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 [4]. 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.

There is 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 which 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 [5]. 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 cancer. Studies suggest that inadequate intake of many micronutrients in these foods may be radiation mimics and are important in the protective effect [6]. 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 [7]. Consumption surveys, moreover, indicate that 80% of children and adolescents in the U.S. [8] and 68% of adults [9] did not consume the intake of fruits and vegetables recommended by the National Cancer Institute 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 the population consuming few dietary fruits and vegetables; folate deficiency causes chromosome breaks in humans by a mechanism that mimics radiation [6]. Approximately 10% of the U.S.

population [10] had a lower folate level than that at which chromosome breaks occur. Folate supplementation above the RDA minimized chromosome breakage [11].

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 and compares results for synthetic pesticides to results for naturally-occurring chemicals in food. Our analyses are based on results in our Carcinogenic Potency Database (CPDB) [12, 13], 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:

(1) Human exposure to synthetic pesticide residues compared to the broader and greater exposure to natural chemicals in the diet.

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

(3) Increased cell division as an important hypothesis for the high positivity rate in rodent bioassays, and the implications for risk assessment.

(4) Providing a broad perspective on possible cancer hazards from a variety of exposures to rodent carcinogens including natural dietary chemicals and synthetic chemicals, by ranking on the HERP index: Human Exposure/Rodent Potency.

(5) 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 toxic dose of a chemical (LD_{50}) and average consumption in the U.S. diet.

II. HUMAN EXPOSURES TO NATURAL AND SYNTHETIC CHEMICALS

Current regulatory policy to reduce human cancer risks is based on the idea that chemicals which induce tumors in rodent cancer bioassays are potential human carcinogens. The chemicals selected for testing in rodents, however, are primarily synthetic [12, 13]. 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; 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 natural. The amounts of synthetic pesticide residues in plant foods are low in comparison to the amount of natural pesticides produced by plants themselves [14, 15]. 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 [14, 15]. Each plant produces a different array of such chemicals.

We estimate that the daily average American exposure to natural pesticides in the diet is about 1500 mg and to burnt material is about 2000 mg [15]. 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 [16, 17]. Humans ingest roughly 5,000 to 10,000 different natural pesticides and their breakdown products [14]. Despite this enormously greater exposure to natural chemicals, among the chemicals tested in long-term bioassays in the CPDB, 77% (1051/1373) are synthetic (i.e. do not occur naturally) [12, 13].

Concentrations of natural pesticides in plants are usually measured in parts per thousand or million rather than parts per billion, which is the usual concentration of synthetic pesticide residues. Therefore, since 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 [14]. 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 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 [4]. 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 2) totaling at least 10 mg of rodent carcinogens per cup. Among the rodent carcinogens in coffee are the plant pesticides caffeic acid (present at 1800 ppm) and catechol (present at 100 ppm). Two other plant pesticides in coffee, chlorogenic acid and neochlorogenic acid (present at 21,600 ppm and 11,600 ppm respectively) are metabolized to caffeic acid and catechol but have not been tested for carcinogenicity. Chlorogenic acid and caffeic acid are mutagenic [14], and clastogenic. For another plant pesticide in coffee, d-limonene, the only tumors induced were in male rat kidney, by a mechanism involving accumulation of _2u-globulin and increased cell division in the kidney, which would not be predictive of a carcinogenic hazard to humans □ ADDIN ENRfu □□18□. Some other rodent carcinogens in coffee are products of cooking, e.g. 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 with the toxicity of natural chemicals will fail to protect against synthetic chemicals, including synthetic pesticides. This assumption is flawed for several reasons:

1. Humans have many natural defenses that buffer against normal exposures to toxins □ ADDIN ENRfu □□15□ 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; 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. 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., 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 [18, 19]. 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, e.g. DDT, aldrin, dieldrin. (DDT is discussed in Section V.) 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 [20]. 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 neurotoxins have been shown to cause birth defects in rodents [16].

5. Since 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 6,200 parts per

billion (ppb) of carcinogenic (and mutagenic) psoralens instead of the 800 ppb present in common celery [21].

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

Since 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 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 chemicals in roasted coffee (21/30) [Table 2]. Among commercial pesticides reviewed by the U.S. EPA [22] the positivity rate is 41% (79/194); 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 cancelled and those still in use.

Since 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 would be positive if tested, then the utility of a test to identify a chemical as a "potential human carcinogen" because an increase in tumor incidence is 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 since 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, mutagens are positive 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 3), because drug development tends to favor chemicals that are not mutagens or suspected carcinogens. In the *Physician's Desk Reference* (PDR), however, 49% (117/241) of the drugs that report results of animal cancer tests are carcinogenic [23] (Table 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 two-year NTP 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 [24].

One large series of mouse experiments by Innes *et al.* [25] has been frequently cited as evidence that the true proportion of rodent carcinogens is actually low among tested substances (Table 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 [12, 13].

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 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 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 of synthetic pesticides and pollutants resulted from lack of power.

Since many of the chemicals tested by Innes *et al.* were synthetic pesticides, we re-examined the question of what proportion of synthetic pesticides are carcinogenic (as shown in Table 3) by excluding the pesticides tested only in the Innes series. The Innes studies had little effect on the positivity rate: Table 3 indicates that of all commercial pesticides in the CPDB, 41% (79/194) are rodent carcinogens; when the analysis is repeated by excluding the chemicals tested only with the Innes protocol, 47% (77/165) are carcinogens.

IV. THE IMPORTANCE OF CELL DIVISION IN MUTAGENESIS AND CARCINOGENESIS

What might explain the high positivity rate among chemicals tested in rodent cancer bioassays (Table 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 [26-28]. 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 [26]. 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: e.g., DNA lesions, DNA repair, cell division, clonal instability, apoptosis, and p53 (a cell cycle control gene that is mutated in half of human tumors) [29]. The normal endogenous level of oxidative DNA lesions in somatic cells is

appreciable [30]. In addition, tissues injured by high doses of chemicals have an inflammatory immune response involving activation of white cells in response to cell death [31]. Activated white cells release mutagenic oxidants (including peroxynitrite, hypochlorite, and H_2O_2). Therefore, the very low levels of chemicals to which humans are exposed through water pollution or synthetic pesticide residues 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 [26, 28, 32]. For non-mutagens cell division at the MTD can increase carcinogenicity, and 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 [33]; in calorie-restricted mice cell division rates are markedly lowered in several tissues. 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 [26]. Extensive reviews of bioassay results document that chronic cell division can induce cancer [12, 34, 35]. A large epidemiological literature [36] 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 [12, 37], 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; the fact that mutagens, which can both damage DNA and increase cell division at high doses, are more likely than non-mutagens to be positive, to induce tumors in both rats and mice, and to induce tumors at multiple sites [12, 37]. 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 tumor incidence rates that are 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) [12, 13], 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 also seems less likely than has been assumed because of the inducibility of numerous defense enzymes which deal with exogenous chemicals as groups, e.g., oxidants, electrophiles, and thus protect humans against natural and synthetic chemicals, including potentially mutagenic reactive chemicals [15]. 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 zero.

Agencies that evaluate potential cancer risks to humans are moving to take mechanism and nonlinearity into account. The U.S. EPA recently proposed new cancer risk assessment guidelines [38] that emphasize a more flexible approach to risk assessment and call for 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 we have discussed above. 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. In addition, toxicological results for cancer and non-cancer endpoints could be incorporated together in the risk assessment process.

Also consistent with the results we discussed above, 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 [18]. 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_2 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 non-mutagens, and a synergistic effect of cell division at high doses with DNA damage for the mutagens, then this model overestimates risk [28, 39].

We have discussed validity problems associated with the use of the limited data from animal cancer tests for human risk assessment [40]. 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 [12, 35, 39-41]. 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 [41] used the ratio MTD/TD_{50} and the relationship between q_1^* and TD_{50} to estimate the VSD. The VSD was approximated by the MTD/740,000 for rodent carcinogens tested in the bioassay program of the National Cancer Institute (NCI)/National Toxicology Program (NTP). The MTD/740,000 was within a factor of 10 of the VSD for 96% of carcinogens. This variation is similar to the variation in potency when the same chemical is tested twice in the same strain and sex by the same route: in such near-replicate experiments, potency estimates vary by a factor of 4 around a median value [12].

Using the newly proposed benchmark dose of the U.S. 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 maximum tolerated dose (MTD) divided by seven [39]. 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 EPA carcinogen risk assessment guidelines, the dose estimated from the LTD_{10} divided, e.g., by a 10,000-fold uncertainty factor is similar to the dose

of an estimated risk of less than 10^{-5} using a linear model. This dose is 10 times higher than the virtually safe dose 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 bioassay design.

V. 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 1, 2, and 3), how can bioassay data best be used to evaluate potential carcinogenic hazards to humans? We have emphasized the importance of 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 cancer prevention factors, when setting research and regulatory priorities, and when selecting chemicals for chronic bioassay, mechanistic or epidemiologic studies. [4, 12]. 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 at levels that humans receive, and then to focus on those that rank highest in possible hazard [4]. 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 index (Human Exposure/Rodent Potency), which indicates what percentage of the rodent carcinogenic potency (TD_{50} in mg/kg/day) a human receives from a given average daily dose for a lifetime of exposure (mg/kg/day). TD_{50} values in our CPDB span a 10 million-fold range across chemicals [12, 13]. Human exposures to rodent carcinogens range enormously as well, from historically high workplace exposures in some occupations to very low exposures from residues of synthetic chemicals.

The rank order of possible hazards for a given exposure by the simple HERP index will be similar to a ranking of regulatory "risk estimates" using a linear model, since they are both proportional to 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 that casts doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides. A committee of the National Research Council recently reached similar conclusions about natural vs. synthetic chemicals in the diet, and called for further research on natural chemicals [42].

The HERP ranking in Table 5 is for *average* U.S. exposures to all rodent carcinogens in the Carcinogenic Potency Database for which concentration data and average exposure or consumption data were both available, and for which human exposure could be chronic for a lifetime. For pharmaceuticals the doses are recommended doses, and for workplace they are past industry or occupation averages. The 87 exposures in the ranking (Table 5) are ordered by possible carcinogenic hazard (HERP), and natural chemicals in the diet are reported in boldface.

Several HERP values make convenient reference points for interpreting Table 5. The median HERP value is 0.002%, and the background HERP for the average chloroform level in a liter of U.S. tap water is 0.0003%. Chloroform is formed as a by-product of chlorination. A HERP of 0.00001% is approximately equal to a U.S. regulatory VSD risk of 10^{-6}. 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 [39]. If information on the carcinogenic mode of action for a chemical supports a nonlinear dose-response curve, then the EPA guidelines call for a margin of exposure approach with the LTD_{10} as the POD. 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%. If the dose-response 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, and some occupational exposures. Additionally, the values for dietary pesticide residues are averages in the *total diet*, whereas for most natural chemicals the exposure amounts are for concentrations of a chemical in an individual food (i.e. foods for which data are available on concentration and average U.S. consumption).

Table 5 indicates that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. For many natural chemicals the HERP values are in the top half of the table, even though natural chemicals are markedly underrepresented because so few have been tested in rodent bioassays. We discuss several categories of exposure below 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 Exposures. 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. HERP values rank at the top of Table 5 for 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 [1].

Pharmaceuticals. Some pharmaceuticals that are used chronically are also clustered near the top of the HERP ranking, e.g. phenobarbital, clofibrate, and fluvastatin. In Table 3 we reported that half the drugs in the PDR with cancer test data are positive in rodent bioassays [23]. 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. The HERP values for less than chronic administration at typical doses would produce high HERP values, e.g., phenacetin (0.3%), metronidazole (5.6%), and isoniazid (14%).

Herbal supplements have recently developed into a large market in the U.S.; they have not been a focus of carcinogenicity testing. The FDA regulatory requirements for safety and efficacy that are applied to pharmaceuticals do not pertain to herbal supplements under the 1994 Dietary 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, like some pharmaceutical drugs, the recommended dose is high relative to the rodent carcinogenic dose.

Moreover, under DSHEA the safety criteria that have been used for decades by FDA for food additives that are "Generally Recognized As Safe" (GRAS) are not applicable to dietary supplements even though supplements are used at higher doses. 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 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*. Poisoning epidemics by pyrrolizidine alkaloids have occurred in the developing world. In the U.S. poisonings, including deaths, have been associated with use of herbal teas containing comfrey.

Dehydroepiandrosterone (DHEA), a natural hormone manufactured as a dietary supplement, has a HERP value of 0.5% for the recommended dose of 1 daily capsule containing 25 mg DHEA. DHEA is widely taken in hope of delaying aging, and is a fastest-selling product in health food stores. The mechanism of liver carcinogenesis in rats is peroxisome proliferation, like clofibrate [10]. Recent work on the mechanism of peroxisome proliferation in rodents indicates that it is a receptor-mediated response, suggesting a threshold below which tumors are not induced. This mechanism is unlikely to be relevant to humans at any anticipated exposure level. Recent analyses of the molecular basis of peroxisome proliferation conclude that there is an apparent lack of a peroxisome proliferative response in humans [43]. 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 [44].

Natural Pesticides. Natural pesticides, because few have been tested, are markedly underrepresented in our HERP analysis. Importantly, for each plant food listed, there are about 50 additional untested natural pesticides. Although about 10,000 natural pesticides and their break-down products occur in the human diet [14], only 71 have been tested adequately in rodent bioassays (Table 1). Average exposures to many natural-pesticide rodent carcinogens in common foods rank above or close to the median in the HERP Table, ranging up to a HERP of 0.1%. These include caffeic acid (in coffee, lettuce, tomato, apple, potato, celery, carrot, plum and pear); safrole (in spices, and formerly in natural root beer before it was banned), allyl isothiocyanate (mustard), *d*-limonene (mango, orange juice, black pepper); coumarin in cinnamon; and hydroquinone, catechol, and 4-methylcatechol in coffee. Some natural pesticides in the commonly eaten mushroom, *Agaricus bisporus*, are rodent carcinogens (glutamyl-*p*-hydrazinobenzoate, *p*-hydrazinobenzoate), and the HERP based on feeding whole mushrooms to mice is 0.02%. For *d*-limonene, no human risk is anticipated because tumors are induced only in male rat kidney tubules with involvement of α_{2u}-globulin nephrotoxicity, which does not appear to be relevant for humans [18].

Cooking and Preparation of Food. Cooking and preparation of food can also produce chemicals that are rodent carcinogens. Alcoholic beverages are a human carcinogen, and the HERP values in Table 5 for alcohol in average U.S. consumption of 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 average consumption of coffee is 0.02% and in white bread 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 0.00006% (Table 5). Nitrosamines are formed from nitrite or nitrogen oxides (NO_x) and amines in food. In bacon the HERP for diethylnitrosamine is 0.0006%, and for dimethylnitrosamine it is 0.0005%.

A variety of mutagenic and carcinogenic heterocyclic amines (HA) are formed when meat, chicken or fish are cooked, particularly when charred. Compared to other rodent carcinogens, there is strong evidence of carcinogenicity for HA in terms of positivity rates and multiplicity of target sites; however, concordance in target sites between rats and mice for these HA is generally restricted to the liver [12]. Under usual cooking conditions, exposures to HA are in the low ppb range, and the HERP values are low: for HA in pan fried hamburger, the HERP value for PhIP is 0.00006%, for MeIQx 0.00003%. and for IQ 0.000006%. Carcinogenicity of the 3 HA in the HERP table, IQ, MeIQx, and PhIP, has been investigated in long-term studies in cynomolgus monkeys. IQ rapidly induced a high incidence of hepatocellular carcinoma. MeIQx, which induced tumors at multiple sites in rats and mice, did not induce tumors in monkeys. The PhIP study is in progress. Metabolism studies indicate the importance of *N*-hydroxylation in the carcinogenic effect of HA in monkeys [13]. 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 would be expected to have a carcinogenic effect [13].

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 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 U.S. in 1972. These 3 synthetic pesticides still rank below the HERP values for many naturally occurring chemicals that are common in the diet. The HERP values in Table 5 are for residue intake by U.S. females age 65 and older, since that group consumes higher amounts of fruits and vegetables than other adult groups, thus maximizing the exposure estimate to pesticide residues. We note that for pesticide residues in the TDS, the consumption estimates for children (mg/kg/day in 1986-1991) are within a factor of 3 of the adult consumption (mg/kg/day) [16].

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 [45], 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 [13] 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 [13].

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 U.S., 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. DDT was also of low toxicity to humans. 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" [46]. There is no convincing epidemiological evidence, nor is there much toxicological plausibility, that the levels of DDT normally found in the environment or in human tissues are likely to be a significant contributor to human cancer.

DDT was 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. Natural pesticides can also bioconcentrate if they are fat-soluble. Potatoes, for example, naturally contain the fat soluble neurotoxins solanine and chaconine [14], 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 [15].

For ETU the HERP value would be about 10 times lower if the potency value of the EPA were used instead of our TD_{50}; EPA combined rodent results from more than one experiment, including one in which ETU was administered *in utero*, and obtained a weaker potency [47]. (The CPDB does not include *in utero* exposures.) Additionally, EPA has recently discontinued some uses of fungicides for which ETU is a breakdown product, and exposure levels are therefore currently lower.

In 1984 the EPA banned the agricultural use of ethylene dibromide (EDB) the main fumigant in the U.S., because of the residue levels found in grain, HERP = 0.0004%. This HERP value ranks low, whereas the HERP of 140% for the high exposures to EDB that some workers received in the 1970s, is at the top of the ranking [4]. Two other pesticides in Table 5, toxaphene (HERP=0.0002%) and chlorobenzilate (HERP=0.0000001%), have been cancelled in the U.S.

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 5 are for the synthetic pesticides, captan, chlorothalonil, and folpet, which were also evaluated in 1987 by the National Research Council (NRC) and were considered by NRC to have a human cancer risk above 10^{-6} [48]. Why were the EPA risk estimates reported by NRC so high when our HERP values are so low? We have investigated this disparity in cancer risk estimation for pesticide residues in the diet by examining the two components of risk assessment: carcinogenic potency estimates from rodent bioassays and human exposure estimates [17]. We found that potency estimates based on rodent bioassay data are similar whether calculated, as in the NRC report, as the regulatory q_1^* or as the TD_{50} in the CPDB. In contrast, estimates of dietary exposure to residues of synthetic pesticides vary enormously, depending on whether they are based on the Theoretical Maximum Residue Contribution (TMRC) calculated by the EPA vs. the average dietary residues measured by the FDA TDS. The EPA's TMRC is the theoretical maximum human exposure anticipated

under the most severe field application conditions, which is often a large overestimate compared to the measured residues. For several pesticides, the NRC risk estimate was greater than one in a million whereas the FDA did not detect any residues in the TDS even though the TDS measures residues as low as 1 ppb [17].

We evaluated the disparities in these analyses by examining the two components of risk assessment: carcinogenic potency in rodents and human exposure. Potency estimates based on rodent bioassay data are shown to be similar whether calculated, as in the NRC report, as the regulatory q_1^* or as TD_{50}. In contrast, estimates of dietary exposure to residues of synthetic pesticides vary enormously, depending on whether they are based on the Theoretical Maximum Residue Contribution (TMRC) calculated by the Environmental Protection Agency vs. the average dietary residues measured by the Food and Drug Administration in the Total Diet Study (TDS). The TMRC is the theoretical maximum human exposure anticipated under the most severe field application conditions, which are far greater than dietary residues measured in the TDS. Several independent exposure studies suggest that the FDA dietary residues are reasonable estimates of average human exposures, whereas TMRC values are large overestimates. Using standard methodology and measured dietary residues in the TDS, the estimate of excess cancer risk from average lifetime exposure to synthetic pesticide residues in the diet appears to be less than one-in-a-million for each of the 10 pesticides for which adequate data were available.

Food Additives. Food additives that are rodent carcinogens can be either naturally-occurring (e.g., allyl isothiocyanate, furfural, and alcohol) or synthetic (butylated hydroxyanisole [BHA] and saccharin, Table 5). The highest HERP values for average dietary exposures to synthetic rodent carcinogens in Table 5 are for exposures in the 1970s to BHA (0.01%) and saccharin (0.005%). Both are nongenotoxic rodent carcinogens for which data on mechanism of carcinogenesis strongly suggest that there would be no risk to humans at the levels found in food.

BHA is a phenolic antioxidant that is Generally Regarded as Safe (GRAS) by the FDA. By 1987, after BHA was shown to be a rodent carcinogen, its use declined six fold (HERP=0.002%); 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 U.S. 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 [49]. Humans do not have a forestomach. We note that the dose-response for BHA curves sharply upward, but the potency value used in HERP is based on a linear model; if the California EPA potency value (which is based on a linearized multistage model) were used in HERP instead of TD_{50}, the HERP values for BHA would be 25 times lower [50].

Saccharin, which has largely been replaced by other sweeteners, has been shown to induce tumors in rodents by a mechanism that is not relevant to humans. Recently, both NTP and IARC re-evaluated the potential carcinogenic risk of saccharin to humans. NTP delisted saccharin in its *Report on Carcinogens* [51], and IARC downgraded its evaluation to Group 3, "not classifiable as to carcinogenicity to humans" [18]. There is convincing evidence that the induction of bladder tumors in rats by sodium saccharin requires a high dose and is related to development of a calcium phosphate-containing precipitate in the urine [52], which is not relevant to human dietary exposures. In a recently completed 24-year study by 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 [13]. The average daily dose-rate of sodium saccharin was about 100 times

lower than the dose that was carcinogenic to rats [12, 13]. 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 [13]. One would not expect to find a carcinogenic effect under the conditions of the monkey study. Additionally, 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 [13]. Human urine is similar to monkey urine in this respect [27].

For three naturally-occurring chemicals that are also produced commercially and used as food additives, average exposure data were available and they are included in Table 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 principle 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 [16]. 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 U.S. [53]. Before 1960, for a person consuming a glass of sassafras root beer per day for life, the HERP value would have been 0.2%. Sassafras root can still be purchased in health food stores and can therefore be used to make tea; the recipe is on the World Wide Web.

Mycotoxins. Of the 23 fungal toxins tested for carcinogenicity, 14 are positive (61%) (Table 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 [18]. 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. The HERP value for aflatoxin of 0.008% is based on the rodent potency. If the lower human potency value calculated by FDA from epidemiological data were used instead, the HERP would be about 10-fold lower [54]. 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. Liver cancer is rare in the U.S. Hepatitis viruses can account for half of liver cancer cases among non-Asians and even more among Asians in the U.S. [55].

Ochratoxin A, a potent rodent carcinogen [12], 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 5 [10].

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 U.S. PCBs are no longer used, but some exposure persists. Consumption in food in the U.S. declined about 20-fold between 1978-1986 [56, 57]. The HERP value for the most recent reporting of the U.S. FDA Total Diet Study (1984-86) is 0.00008%, towards the bottom of the ranking, and far below many values for naturally occurring chemicals in common foods. It has been reported that some countries may have higher intakes of PCBs than the U.S. [58].

TCDD, the most potent rodent carcinogen, is produced naturally by burning when chloride ion is present, e.g. in forest fires or wood burning in homes. EPA [59] 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[59]. TCDD bioaccumulates through the food

chain because of its lipophilicity, and more than 95% of human intake is from animal fats in the diet [59]. Dioxin emissions decreased by 80% from 1987-1995, which EPA attributes to reduced medical and municipal incineration emissions [59].

The HERP value of 0.0004% for average U.S. intake of TCDD [59] is below the median of the values in Table 6. Recently, EPA has re-estimated the potency of TCDD based on a body burden dose-metric in humans (rather than intake) [59] and a re-evaluation of tumor data in rodents (which determined two-thirds fewer liver tumors). Using this EPA potency for HERP would put TCDD at the median of HERP values in Table 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 [60]. 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 [15] including inhibition of estrogen-induced effects in rodents [61]. 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 [62]. The binding affinity (greater for TCDD) and 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 of I3C. Additionally, both I3C and TCDD, when administered to pregnant rats, resulted in reproductive abnormalities in male offspring [63]. Currently, I3C is in clinical trials for prevention of breast cancer and also is being tested for carcinogenicity by NTP. I3C is marketed as a dietary supplement at recommended doses about 30 times higher than present in the average Western diet.

TCDD has received enormous scientific and regulatory attention, most recently in an ongoing assessment by the U.S. EPA [59]. Some epidemiologic studies suggest an association with cancer mortality, but the evidence is not sufficient to establish causality. IARC evaluated the epidemiological evidence for carcinogenicity of TCDD in humans as limited [18]. The strongest epidemiological evidence was among highly exposed workers for overall cancer mortality. There is a lack of evidence in humans for any specific 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 [18]. In contrast, background levels of TCDD in humans are about 100 to 1000 fold lower than in the rat study. The similarity of worker and rodent blood levels and mechanism of the AhR in both humans and rodents, were considered by IARC when they evaluated TCDD as a Group 1 carcinogen in spite of only limited epidemiological evidence. 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 as "reasonably anticipated to be a human carcinogen," i.e., rather than as a known human carcinogen [51]. The EPA draft final report [59] 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." [59] Possible limitations of data or scientific tools were given by EPA as possible reasons for the lack of observed effects.

In sum, the HERP ranking in Table 5 indicates that when synthetic pesticide residues in the diet are ranked on 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 U.S. 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 5, 90% of the HERP values are above the level that would approximate a regulatory virtually safe dose of 10^{-6}.

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, and that protective factors like intake of vitamins such as folic acid are important, rather than intake of individual rodent carcinogens.

The HERP ranking also indicates the importance of data on mechanism of carcinogenesis for each chemical. For several chemicals, data has recently been generated which indicates that exposures would not be expected to be a cancer risk to humans at the levels consumed in food (e.g. saccharin, BHA, chloroform, *d*-limonene, discussed above). 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 mechanism of carcinogenesis, however, the true human risk of cancer at low dose is highly uncertain and could be zero [4, 26, 34]. Adequate risk assessment 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. More flexible guidelines on risk assessment have recently been proposed by the U.S. EPA. The guidelines recognize the importance of more biological data and call for a more complete hazard evaluation including animal, human, and mechanistic data. In addition, the new guidelines permit the use of nonlinear approaches to low-dose extrapolation if warranted by mechanistic data [38].

VI. RANKING POSSIBLE TOXIC HAZARDS FROM NATURALLY-OCCURRING CHEMICALS IN THE DIET

Since 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 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%, and the proportion positive among natural plant pesticides is also similar (Table 3).

In order to identify 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. HERT is the ratio of Human Exposure/Rodent Toxicity 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 3 analyses: First, we have found that for the exposures to rodent carcinogens for which we have calculated HERP values, the ranking 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 [41]. Since the MTD is not known for all chemicals, and 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; therefore, HERT is a reasonable surrogate index for HERP since it simply replaces TD_{50} with LD_{50}.

We have calculated HERT values using LD_{50} values as a measure of toxicity in combination with available data on concentrations of untested natural chemicals in commonly consumed foods and data on average consumption of those foods in the U.S. diet. Literature searches identified the most commonly consumed foods and concentrations of chemicals in those foods. We considered any chemical with available data on rodent LD_{50}, that had a published concentration ≥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 are marked with an asterisk. Among the set of 121 HERT values we were able to calculate (Table 6), the HERT ranged across 6 orders of magnitude. The median HERT value 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 National Toxicology Program 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; chlorogenic acid, a precursor of caffeic acid; and caffeine, for which no 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 [12, 13].

How would the synthetic pesticides that are rodent carcinogens included in the HERP ranking (Table 5) compare to the natural chemicals that have not been tested for carcinogenicity (Table 6), if they were ranked on HERT, i.e. using the same measure of a margin of exposure from the LD_{50}? We calculated HERT using LD_{50} values for the synthetic pesticide residues in the HERP table and found that they rank low in HERT compared to the naturally-occurring chemicals in Table 6; 88% (107/121) of the HERT values for the natural chemicals in Table 6 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 5). The highest HERT for the synthetic pesticides would be for DDT before the ban in 1970 (0.00004%).

Many interesting natural toxicants are ranked in common foods in the HERT table. Oxalic acid, 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. Oxalic acid is reported in many foods in Table 6; the highest contributors to the 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 [21].

Because of the high concentrations of natural pesticides in spices, we have reported the HERT values for average intake in Table 6, even though spices are not among the foods consumed in the greatest amounts by weight. The highest concentrations of chemicals in Table 6 are found in spices, which tend to have higher concentrations of fewer chemicals. (Concentrations can be derived from Table 6 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), geranial in lemon juice (14,400 ppm) and lemon oil (11,300 ppm). Natural pesticides in spices have anti-bacterial and anti-fungal activities whose potency varies by spice [64]. 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 (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 [64].

Cyanogenesis, the ability to release hydrogen cyanide, is widespread in plants, including several foods, of which the most widely eaten are cassava and lima bean. Cassava is eaten widely throughout the tropics, and is a dietary staple for over 300 million people [65]. There are few effective means of removing the cyanogenic glycosides that produce hydrogen cyanide (HCN), and cooking is generally not effective [65]. For lima beans in Table 6, HERT=0.01%. Ground flaxseed, a dietary supplement, contains about 500 ppm hydrogen cyanide glycosides. The HCN in flaxseed appear to be inactivated in the digestive tract of primates [66].

The increasing popularity of herbal supplements in the U.S. raises concerns about possible adverse effects from high doses or drug interactions [67]. Since the recommended doses of herbal supplements are close to the toxic dose, and since 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, identification, and manufacturing procedures and additionally require evidence of efficacy and safety, dietary supplements are not. We found that several dietary supplements would have ranked 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.

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Table 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 sulphate, 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, broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, cardamom, carrot, cauliflower, celery, cherries, chili pepper, chocolate, cinnamon, cloves, coffee, collard greens, comfrey herb tea, corn, coriander, 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, black pepper, pineapple, plum, potato, radish, raspberries, rhubarb, rosemary, rutabaga, sage, savory, sesame seeds, soybean, star anise, tarragon, tea, thyme, tomato, turmeric, and turnip.

Table 2. Carcinogenicity in rodents 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

Table 3. Proportion of chemicals evaluated as carcinogenic [a]

Chemicals tested in both rats and mice	
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	
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	79/194 (41%)
Innes negative chemicals retested	17/34 (50%)
Physician's Desk Reference (PDR): drugs with reported cancer tests [b]	117/241 (49%)
FDA database of drug submissions [b]	125/282 (44%)

[a] From the Carcinogenic Potency Database [12, 13].
[b] 140 drugs are in both the FDA and PDR databases.

Table 4. Results of Subsequent Tests on Chemicals (Primarily Pesticides) Not Found Carcinogenic by Innes *et al.,* 1968

	% Carcinogenic When Retested		
Retested Chemicals	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.*

(M) = positive in mice when retested; (R) = positive in rats when retested

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.

* = Innes *et al*. stated that further testing was needed

Table 5. Ranking Possible Carcinogenic Hazards from Average U.S. Exposures to Rodent Carcinogens

[Chemicals that occur naturally in foods are in bold.] *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 *H*uman *E*xposure/*R*odent *P*otency index (HERP). TD_{50} values used in the HERP calculation are averages calculated by taking the harmonic mean of the TD_{50}s of the positive tests in that species from the Carcinogenic Potency Database. Average TD_{50} values, have been calculated separately for rats and mice, and the more potent value is used for calculating possible hazard. References for average food consumption and concentration of chemicals in foods are reported in L.S. Gold, B.N. Ames, and T.H. Slone, "Misconceptions about the causes of cancer," in *Human and Environmental Risk Assessment: Theory and Practice*, ed. D. Paustenbach (New York: John Wiley & Sons, in press).

Possible hazard: HERP (%)	Average daily US exposure	Human dose of rodent carcinogen	Potency TD_{50} (mg/kg/day) [a] Rats	Mice
140	EDB: production workers (high exposure) (before 1977)	Ethylene dibromide, 150 mg	1.52	(7.45)
17	Clofibrate	Clofibrate, 2 g	169	.
14	Phenobarbital, 1 sleeping pill	Phenobarbital, 60 mg	(+)	6.09
6.8	1,3-Butadiene: rubber industry workers (1978-86)	1,3-Butadiene, 66.0 mg	(261)	13.9
6.2	**Comfrey-pepsin tablets, 9 daily (no longer recommended)**	**Comfrey root, 2.7 g**	626	.
6.1	Tetrachloroethylene: dry cleaners with dry-to-dry units (1980-90)	Tetrachloroethylene, 433 mg	101	(126)
4.0	Formaldehyde: production workers (1979)	Formaldehyde, 6.1 mg	2.19	(43.9)
2.4	Acrylonitrile: production workers (1960-1986)	Acrylonitrile, 28.4 mg	16.9	.
2.2	Trichloroethylene: vapor degreasing (before 1977)	Trichloroethylene, 1.02 g	668	(1580)
2.1	**Beer, 257 g**	**Ethyl alcohol, 13.1 ml**	9110	(–)
1.4	Mobile home air (14 hours/day)	Formaldehyde, 2.2 mg	2.19	(43.9)
1.3	**Comfrey-pepsin tablets, 9 daily (no longer recommended)**	**Symphytine, 1.8 mg**	1.91	.
0.9	Methylene chloride: workers, industry average (1940s-80s)	Methylene chloride, 471 mg	724	(1100)
0.5	**Wine, 28.0 g**	**Ethyl alcohol, 3.36 ml**	9110	(–)
0.5	Dehydroepiandrosterone (DHEA)	DHEA supplement, 25 mg	68.1	.
0.4	Conventional home air (14 hours/day)	Formaldehyde, 598 μg	2.19	(43.9)
0.2	Fluvastatin	Fluvastatin, 20 mg	125	.
0.1	**Coffee, 13.3 g**	**Caffeic acid, 23.9 mg**	297	(4900)
0.1	***d*-Limonene in food**	***d*-Limonene, 15.5 mg**	204	(–)
0.04	**Lettuce, 14.9 g**	**Caffeic acid, 7.90 mg**	297	(4900)
0.03	**Safrole in spices**	**Safrole, 1.2 mg**	(441)	51.3
0.03	**Orange juice, 138 g**	***d*-Limonene, 4.28 mg**	204	(–)
0.03	**Comfrey herb tea, 1 cup (1.5 g root) (no longer recommended)**	**Symphytine, 38 μg**	1.91	.
0.03	**Tomato, 88.7 g**	**Caffeic acid, 5.46 mg**	297	(4900)
0.03	**Pepper, black, 446 mg**	***d*-Limonene, 3.57 mg**	204	(–)
0.02	**Coffee, 13.3 g**	**Catechol, 1.33 mg**	88.8	(244)
0.02	**Furfural in food**	**Furfural, 2.72 mg**	(683)	197
0.02	**Mushroom (*Agaricus bisporus* 2.55 g)**	**Mixture of hydrazines, etc. (whole mushroom)**	-	20,300
0.02	**Apple, 32.0 g**	**Caffeic acid, 3.40 mg**	297	(4900)

0.02	**Coffee, 13.3 g**	**Furfural, 2.09 mg**	(683)	197
0.01	BHA: daily US avg (1975)	BHA, 4.6 mg	606	(5530)
0.01	**Beer (before 1979), 257 g**	**Dimethylnitrosamine, 726 ng**	0.0959	(0.189)
0.008	**Aflatoxin: daily US avg (1984-89)**	**Aflatoxin, 18 ng**	0.0032	(+)
0.007	**Cinnamon, 21.9 mg**	**Coumarin, 65.0 μg**	13.9	(103)
0.006	**Coffee, 13.3 g**	**Hydroquinone, 333 μg**	82.8	(225)
0.005	Saccharin: daily US avg (1977)	Saccharin, 7 mg	2140	(–)
0.005	**Carrot, 12.1 g**	**Aniline, 624 μg**	194 [b]	(–)
0.004	**Potato, 54.9 g**	**Caffeic acid, 867 μg**	297	(4900)
0.004	**Celery, 7.95 g**	**Caffeic acid, 858 μg**	297	(4900)
0.004	**White bread, 67.6 g**	**Furfural, 500 μg**	(683)	197
0.003	*d*-Limonene	Food additive, 475 μg	204	(–)
0.003	**Nutmeg, 27.4 mg**	***d*-Limonene, 466 μg**	204	(–)
0.003	Conventional home air (14 hour/day)	Benzene, 155 μg	(169)	77.5
0.002	**Coffee, 13.3 g**	**4-Methylcatechol, 433 μg**	248	.
0.002	**Carrot, 12.1 g**	**Caffeic acid, 374 μg**	297	(4900)
0.002	Ethylene thiourea: daily US avg (1990)	Ethylene thiourea, 9.51 μg	7.9	(23.5)
0.002	BHA: daily US avg (1987)	BHA, 700 μg	606	(5530)
0.002	DDT: daily US avg (before 1972 ban) [c]	DDT, 13.8 μg	(84.7)	12.8
0.001	**Plum, 2.00 g**	**Caffeic acid, 276 μg**	297	(4900)
0.001	**Pear, 3.29 g**	**Caffeic acid, 240 μg**	297	(4900)
0.001	[UDMH: daily US avg (1988)]	[UDMH, 2.82 μg (from Alar)]	(–)	3.96
0.0009	**Brown mustard, 68.4 mg**	**Allyl isothiocyanate, 62.9 μg**	96	(–)
0.0008	DDE: daily US avg (before 1972 ban) [d]	DDE, 6.91 μg	(–)	12.5
0.0006	**Bacon, 11.5 g**	**Diethylnitrosamine, 11.5 ng**	0.0266	(+)
0.0006	**Mushroom (*Agaricus bisporus* 2.55 g)**	**Glutamyl-*p*-hydrazinobenzoate, 107 μg**	.	277
0.0005	**Bacon, 11.5 g**	**Dimethylnitrosamine, 34.5 ng**	0.0959	(0.189)
0.0004	**Bacon, 11.5 g**	***N*-Nitrosopyrrolidine, 196 ng**	(0.799)	0.679
0.0004	EDB: Daily US avg (before 1984 ban) [d]	EDB, 420 ng	1.52	(7.45)
0.0004	Tap water, 1 liter (1987-92)	Bromodichloromethane, 13 μg	(72.5)	47.7
0.0004	TCDD: daily US avg (1994)	TCDD, 6.0 pg	0.0000235	(0.000156)
0.0003	**Mango, 1.22 g**	***d*-Limonene, 48.8 μg**	204	(–)
0.0003	**Beer, 257 g**	**Furfural, 39.9 μg**	(683)	197
0.0003	Tap water, 1 liter (1987-92)	Chloroform, 17 μg	(262)	90.3
0.0003	Carbaryl: daily US avg (1990)	Carbaryl, 2.6 μg	14.1	(–)
0.0002	**Celery, 7.95 g**	**8-Methoxypsoralen, 4.86 μg**	32.4	(–)
0.0002	Toxaphene: daily US avg (1990) [c]	Toxaphene, 595 ng	(–)	5.57
0.00009	**Mushroom (Agaricus bisporus, 2.55 g)**	***p*-Hydrazinobenzoate, 28 μg**	.	454 [b]
0.00008	PCBs: daily US avg (1984-86)	PCBs, 98 ng	1.74	(9.58)
0.00008	DDE/DDT: daily US avg (1990) [c]	DDE, 659 ng	(–)	12.5
0.00007	**Parsnip, 54.0 mg**	**8-Methoxypsoralen, 1.57 μg**	32.4	(–)
0.00007	**Toast, 67.6 g**	**Urethane, 811 ng**	(41.3)	16.9
0.00006	**Hamburger, pan fried, 85 g**	**PhIP, 176 ng**	4.22 [b]	(28.6 [b])
0.00006	Furfural	Food additive, 7.77 μg	(683)	197
0.00005	**Estragole in spices**	**Estragole, 1.99 μg**	.	51.8
0.00005	**Parsley, fresh, 324 mg**	**8-Methoxypsoralen, 1.17 μg**	32.4	(–)
0.00005	Estragole	Food additive, 1.78 μg	.	51.8
0.00003	**Hamburger, pan fried, 85 g**	**MeIQx, 38.1 ng**	1.66	(24.3)
0.00002	Dicofol: daily US avg (1990)	Dicofol, 544 ng	(–)	32.9
0.00001	**Beer, 257 g**	**Urethane, 115 ng**	(41.3)	16.9
0.000006	**Hamburger, pan fried, 85 g**	**IQ, 6.38 ng**	1.65 [b]	(19.6)
0.000005	Hexachlorobenzene: daily US avg (1990)	Hexachlorobenzene, 14 ng	3.86	(65.1)
0.000001	Lindane: daily US avg (1990)	Lindane, 32 ng	(–)	30.7

0.0000004	PCNB: daily US avg (1990)	PCNB (Quintozene), 19.2 ng	(–)	71.1
0.0000001	Chlorobenzilate: daily US avg (1989) [c]	Chlorobenzilate, 6.4 ng	(–)	93.9
0.00000008	Captan: daily US avg (1990)	Captan, 115 ng	2080	(2110)
0.00000001	Folpet: daily US avg (1990)	Folpet, 12.8 ng	(–)	1550
<0.00000001	Chlorothalonil: daily US avg (1990)	Chlorothalonil, <6.4 ng	828 [d]	(–)

[a] "." = no data in CPDB; a number in parentheses indicates a TD_{50} value not used in the HERP calculation because TD_{50} is less potent than in the other species. (–) = negative in cancer tests; (+) = positive cancer test(s) not suitable for calculating a TD_{50}.
[b] TD_{50} harmonic mean was estimated for the base chemical from the hydrochloride salt.
[c] No longer contained in any registered pesticide product (USEPA, 1998).
[d] Additional data from the EPA that is not in the CPDB were used to calculate this TD_{50} harmonic mean.

Table 6. Ranking possible toxic hazards to naturally-occurring chemicals in food on the HERT index (Human Exposure/Rodent Toxicity)

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 U.S.; when a chemical is listed rather than a food item, the value is the per person average in the total diet. For drugs, the usual or therapeutic dose; for drugs normally taken only a short period, HERT is in brackets. 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). A "*" preceding a chemical name indicates that the chemical is a natural pesticide. References for average food consumption and concentration of chemicals in foods are reported in L.S. Gold, T.H. Slone, and B.N. Ames, "Pesticide residues in food and cancer risk: A critical analysis," in *Handbook of Pesticide Toxicology*, ed. R.I. Krieger (New York: Academic Press, in press).

Possible hazard: HERT (%)	Average daily consumption of food	Average human consumption of chemical	LD_{50} (mg/kg) Rats	Mice
4.3	Coffee, 500 ml (13.3 g)	*Caffeine, 381 mg	(192)	127
0.3	Tea, 60.2 ml (903 mg)	*Caffeine, 29.4 mg	(192)	127
0.3	Potato, 54.9 g	*α-Chaconine, 4.10 mg	(84P)	19P
0.2	Cola, 174 ml	*Caffeine, 20.8 mg	(192)	127
0.1	Coffee, 500 ml	*Chlorogenic acid, 274 mg	4000P	
0.09	Coffee, 500 ml	*Oxalic acid, 25.2 mg	382	
0.09	Black pepper, 446 mg	*Piperine, 21.0 mg	(514)	330
0.08	Carrot, boiled, 12.1 g	*Oxalic acid, 22.7 mg	382	
0.08	Chocolate, 3.34 g	*Theobromine, 48.8 mg	(1265)	837
0.05	Lemon juice, 1.33 ml	*Geranial, 19.2 mg	500	
0.05	Coffee, 500 ml	*Trigonelline, 176 mg	5000	
0.03	Chocolate, 3.34 g	*Caffeine, 2.30 mg	(192)	127
0.02	Tea, 60.2 ml	*Oxalic acid, 6.67 mg	382	
0.02	Isoamyl alcohol: US avg (mostly beer, alcoholic beverages)	Isoamyl alcohol, 18.4 mg	1300	
0.01	Beer, 257 ml	Isoamyl alcohol, 13.6 mg	1300	
0.01	Chocolate, 3.34 g	*Oxalic acid, 3.91 mg	382	
0.01	Tomato, 88.7 g	*Oxalic acid, 3.24 mg	382	
0.01	Coffee, 500 ml	2-Furancarboxylic acid, 821 μg		100P
0.01	Lima beans, 559 mg	Hydrogen cyanide, 28.5 μg		3.7
0.01	Potato chips, 5.2 g	*α-Chaconine, 136 μg [a]	(84P)	19P
0.01	Sweet potato, 7.67 g	*Ipomeamarone, 336 μg		50
0.009	Potato, 54.9 g	*α-Solanine, 3.68 mg	590	
0.008	Isobutyl alcohol: US avg	Isobutyl alcohol, 14.1 mg	2460	
0.008	Hexanoic acid: US avg (beer, grapes, wine)	Hexanoic acid, 15.8 mg	3000	(5000)
0.007	Phenethyl alcohol: US avg	Phenethyl alcohol, 8.28 mg	1790	
0.007	Carrot, 12.1 g	*Carotatoxin, 460 μg		100J
0.006	Ethyl acetate: US avg (mostly alcoholic beverages)	Ethyl acetate, 16.5 mg	(5620)	4100
0.005	Celery, 7.95 g	*Oxalic acid, 1.39 mg	382	
0.005	Coffee, 500 ml	*3-Methylcatechol, 203 μg		56V
0.005	Potato, 54.9 g	*Oxalic acid, 1.26 mg	382	
0.004	Beer, 257 ml	Phenethyl alcohol, 5.46 mg	1790	
0.004	Corn, 33.8 g	*Oxalic acid, 1.12 mg	382	
0.004	Corn, 33.8 g	Methylamine, 906 μg		317
0.004	Peppermint oil, 5.48 mg	*Menthone, 1.33 mg	500	
0.004	White bread, 67.6 g	Propionaldehyde, 2.09 mg	(1410)	800
0.004	Beer, 257 ml	Isobutyl alcohol, 6.40 mg	2460	

0.003	Tomato, 88.7 g	Methyl alcohol, 13.4 mg	5628	(7300)
0.003	Wine, 28.0 ml	Isoamyl alcohol, 3.00 mg	1300	
0.003	Coffee, 500 ml	Pyrogallol, 555 μg		300
0.003	Apple, 32.0 g	*Oxalic acid, 704 μg	382	
0.003	Butyl alcohol: US avg (mostly apple, beer)	Butyl alcohol, 1.45 mg	790	
0.003	Lettuce, 14.9 g	Methylamine, 567 μg		317
0.003	Beer, 257 ml	Propyl alcohol, 3.29 mg	1870	(6800)
0.002	Banana, 15.7 g	trans-2-Hexenal, 1.19 mg	(780)	685
0.002	Orange, 10.5 g	*Oxalic acid, 651 μg	382	
0.002	Wine, 28.0 ml	Ethyl lactate, 4.16 mg	(>5000)	2500
0.002	Tomato, 88.7 g	**p*-Coumaric acid, 1.02 mg		657P
0.002	White bread, 67.6 g	Butanal, 3.44 mg	2490	
0.002	Tea, 60.2 ml	*Theobromine, 1.11 mg	(1265)	837
0.002	Apple, 32.0 g	*Epicatechin, 1.28 mg		1000P
0.002	Tomato, 88.7 g	*Tomatine, 621 μg		500
0.002	Beer, 257 ml	Ethyl acetate, 4.42 mg	(5620)	4100
0.002	Lettuce, 14.9 g	*Oxalic acid, 447 μg	382	
0.001	Apple, 32.0 g	**p*-Coumaric acid, 573 μg		657P
0.001	Apple, 32.0 g	*Chlorogenic acid, 3.39 mg	4000P	
0.001	Coffee, 500 ml	Maltol, 462 μg	(1410)	550
0.001	Coffee, 500 ml	Nonanoic acid, 188 μg		224V
0.001	5-Methylfurfural: US avg (mostly coffee)	5-Methylfurfural, 1.71 mg	2200	
0.001	β-Pinene: US avg (mostly pepper, lemon oil, nutmeg)	*β-Pinene, 3.28 mg	4700	
0.001	Broccoli, 6.71 g	*Oxalic acid, 268 μg	382	
0.001	Strawberry, 4.38 g	*Oxalic acid, 261 μg	382	
0.0009	Orange juice, 138 ml	Methyl alcohol, 3.48 mg	5628	(7300)
0.0009	α-Pinene: US avg (mostly pepper, nutmeg, lemon oil)	*α-Pinene, 2.25 mg	3700	
0.0009	White bread, 67.6 g	2-Butanone, 1.65 mg	2737	(4050)
0.0008	Coffee, 500 ml	Pyridine, 519 μg	891	(1500)
0.0008	Acetone: US avg (mostly tomato, bread, beer)	Acetone, 1.74 mg	(5800)	3000
0.0008	Cucumber, pickled, 11.8 g	Dimethylamine, 182 μg	(698)	316
0.0008	Cabbage, raw, 12.9 g	Methylamine, 169 μg		317
0.0007	Tomato, 88.7 g	*Chlorogenic acid, 2.06 mg	4000P	
0.0007	Wine, 28.0 ml	Methyl alcohol, 2.84 ml	5628	(7300)
0.0007	Coffee, 500 ml	2-Methylpyrazine, 894 μg	1800	
0.0007	Coffee, 500 ml	2,6-Dimethylpyrazine, 432 μg	880	
0.0007	Cabbage, raw, green, 12.9 g	**p*-Coumaric acid, 303 μg		657P
0.0006	Peach, 9.58 g	*Chlorogenic acid, 1.78 mg	4000P	
0.0006	Black pepper, 446 mg	*3-Carene, 2.00 mg	4800	
0.0006	Cabbage, boiled, 12.9 g	*Oxalic acid, 155 μg	382	
0.0006	Coffee, 500 ml	Butyric acid, 785 μg	2000	
0.0006	Coffee, 500 ml	2,5-Dimethylpyrazine, 399 μg	1020	
0.0005	Coffee, 500 ml	5-Methylfurfural, 798 μg	2200	
0.0005	Grapes, 11 g	*Oxalic acid, 138 μg	382	
0.0005	Grapes, 11 g	*Chlorogenic acid, 1.38 mg	4000P	
0.0005	Black pepper, 446 mg	*β-Pinene, 1.50 mg	4700	
0.0004	Cucumber (raw flesh), 11.8 g	*Oxalic acid, 118 μg	382	
0.0004	Potato chips, 5.2 g	*α-Solanine, 179 μg	590	
0.0004	Coffee, 500 ml	Propanoic acid, 785 μg	2600	
0.0004	Peach, canned, 9.58 g	*Oxalic acid, 115 μg	382	
0.0004	Lettuce, 14.9 g	Benzylamine, 172 μg		600P
0.0004	Lemon juice, 1.33 ml	Octanal, 1.60 mg	5630	
0.0004	α-Phellandrene: US avg (mostly pepper)	*α-Phellandrene, 1.59 mg	5700	

0.0004	White bread, 67.6 g	Hexanal, 1.35 mg	4890	(8292)
0.0004	Black pepper, 446 mg	*α-Pinene, 1.02 mg	3700	
0.0004	Banana, 15.7 g	2-Pentanone, 424 μg	1600	1600
0.0003	Grapes, 11 g	*Epicatechin, 243 μg		1000P
0.0003	Onion, raw, 14.2 g	Dipropyl trisulfide, 189 μg		800
0.0003	Coffee, 500 ml	2-Ethyl-3-methylpyrazine, 186 μg	880	
0.0003	Pear, 3.29 g	*Chlorogenic acid, 823 μg	4000P	
0.0003	Carrot, 12.1 g	*Chlorogenic acid, 780 μg	4000P	
0.0003	Lemon oil, 8 mg	*γ-Terpinene, 681 μg	3650	
0.0003	Lemon oil, 8 mg	*Geranial, 90.4 μg	500	
0.0003	Lemon oil, 8 mg	*β-Pinene, 832 μg	4700	
0.0002	Broccoli (raw), 6.71 g	**p*-Coumaric acid, 90.6 μg		657P
0.0002	Lemon oil, 8 mg	*Citral, 600 μg	4960	(6000)
0.0001	Isoamyl acetate: US avg (mostly beer, banana)	Isoamyl acetate, 1.70 mg	16,600	
0.0001	Corn, canned, 33.8 g	Dimethyl sulfide, 324 μg	3300	(3700)
0.0001	Onions, green, cooked, 137 mg	*Oxalic acid, 31.5 μg	382	
0.0001	Coffee, 500 ml	Hexanoic acid, 245 μg	3000	(5000)
0.0001	Pear, 3.29 g	*Epicatechin, 80.9 μg		1000P
0.00007	Nutmeg, 27.4 mg	*Myristicin, 207 μg	4260	
0.00006	Banana, 15.7 g	Methyl alcohol, 236 μg	5628	(7300)
0.00005	Lemon oil, 8 mg	*α-Pinene, 139 μg	3700	
0.00005	Banana, 15.7 g	Isoamyl acetate, 584 μg	16,600	
0.00005	Strawberry, 4.38 g	*Chlorogenic acid, 136 μg	4000P	
0.00004	Black pepper, 446 mg	*α-Phellandrene, 162 μg	5700	
0.00002	Grapefruit juice, 3.29 ml	Methyl alcohol, 95.4 μg	5628	(7300)
0.00002	Lemon oil, 8 mg	*α-Terpinene, 23.2 μg	1680	
0.00001	Lemon oil, 8 mg	*α-Terpineol, 29.6 μg		2830
0.00001	Black pepper, 446 mg	*α-Terpineol, 25.0 μg		2830
0.00001	Garlic, blanched, 53.3 mg	Diallyl disulfide, 2.05 μg	260	
0.00001	Lemon oil, 8 mg	*Terpinolene, 29.6 μg	4390	
0.000008	Garlic, blanched, 53.3 mg	Diallyl trisulfide, 592 ng		100
0.000001	Garlic, blanched, 53.3 mg	Diallyl sulfide, 2.28 μg	2980	

Abbreviations for LD_{50}values: LO = LD_{LO}, P = intraperitoneal injection, V = intravenous injection, J = injection (route not specified).

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