Rodent Carcinogens: Setting Priorities
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The human diet contains an enormous background of natural chemicals, such as plant pesticides and the products of cooking, that have not been a focus of carcinogenicity testing. A broadened perspective that includes these natural chemicals is necessary. A comparison of possible hazards for 65 daily exposures to rodent carcinogens from a variety of sources is presented, using an index (HERP) that relates human exposure to carcinogenic potency in rodents. A similar ordering would be expected with the use of standard risk assessment methodology for the same human exposure values. Results indicate that, when viewed against the large background of naturally occurring carcinogens in typical portions of common foods, the residues of synthetic pesticides or environmental pollutants rank low. A similar result is obtained in a separate comparison of 32 average daily exposures to natural pesticides and synthetic pesticide residues in the diet. Although the findings do not indicate that these natural dietary carcinogens are important in human cancer, they cast doubt on the relative importance for human cancer of low-dose exposures to synthetic chemicals.

The basis of current regulatory policy is the idea that rodent carcinogens are potential human carcinogens; however, the chemicals tested for carcinogenicity in rodents have been primarily synthetic (1, 2). The enormous background of human exposures to natural chemicals has not been systematically examined. The regulatory process does not take into account that (i) natural chemicals make up the vast bulk of chemicals humans are exposed to; (ii) the toxicology of synthetic and natural toxins is not fundamentally different; (iii) about half of the natural chemicals tested chemically in rats and mice are carcinogens; (iv) testing for carcinogenicity at near-toxic doses in rodents does not provide enough information to predict the extent of human cancer that might occur at low-dose exposures; and (v) 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 greatly exaggerates risks.

Ranking Possible Carcinogenic Hazards

We have emphasized that it is important to set priorities by gaining some perspective about the vast number of chemicals to which humans are exposed. One reasonable strategy for gauging a broadened perspective is to use a simple index to compare and rank possible carcinogenic hazards from a wide variety of natural and chemical exposures at concentrations that humans typically receive and then to focus on those that rank highest (3, 4). Ranking is a critical first step that can help to set priorities when selecting chemicals for chronic bioassay or mechanistic studies, for epidemiological research, and for regulatory policy. 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 the ranking if the same methodology indicates numerous common human exposures with much greater possible hazards.

The basis of the previous evaluation of possible hazards from known rodent carcinogens (3) was the HERP index (human exposure/rodent potency). In this article we address the relative ranking by HERP of many common human exposures to rodent carcinogens that either occur naturally in food or are present in food as residues of synthetic pesticides. We use HERP, which is an index of possible hazard rather than a direct estimate of risk, because bioassay results do not provide sufficient information to estimate human risk at low dose. In general, one would expect a similar rank order of "risk estimators" with the use of current regulatory risk assessment methodology for the same exposures because linear extrapolation from the TD50 (our measure of carcinogenic potency, defined below) generally leads to low-dose slope estimates similar to those determined on the basis of the linearized multistage model (5).

Selection of Chemicals to Be Ranked

Toxicological examination of synthetic chemicals, without similar examination of chemicals that occur naturally, has resulted in an imbalance in both the data on and the perception of chemical carcinogens. Three points that we have discussed (1, 3, 6) indicate that comparisons should be made with natural as well as synthetic chemicals. 1) The vast proportion of chemicals that humans are exposed to occur naturally. Nevertheless, the public tends to view chemicals as only synthetic and to think of synthetic chemicals as toxic despite the fact that every natural chemical is also toxic at some dose. The daily average exposure of Americans to burst materials in the diet is ~2000 mg, and exposure to natural pesticides (the chemicals that plants produce to defend themselves) is ~1500 mg (1). In comparison, the total daily exposure to all synthetic pesticide residues combined is ~0.09 mg (7). Thus, we estimate that 99.99% of the pesticides humans ingest are natural (1). Despite this enormous greater exposure to natural chemicals, 79% (378 out of 470) of the chemicals tested for carcinogenicity in both rats and mice are synthetic (that is, do not occur naturally) (2).

2) It has often been wrongly assumed that humans have evolved defenses against the natural chemicals in our diet but not against the synthetic chemicals (6). However, defenses that animals have evolved are mostly general rather than specific for particular chemicals; moreover, defenses are generally inducible and therefore protect well from low doses of both synthetic and natural chemicals (6). 3) Because the toxicology of natural and synthetic chemicals is similar, one expects (and finds) a similar positivity rate for carcinogenicity among synthetic and natural chemicals (1, 2, 6, 8, 9). The positivity rate among chemicals tested in rats and mice is ~50% (1, 2, 9). Therefore, because humans are exposed to so many more natural than synthetic chemicals (by weight and by number), humans are exposed to an enormous background of rodent carcinogens, as defined by high-dose tests on rodents. We have shown that even though only a tiny proportion of natural pesticides in plant foods have been tested, the 29 that are rodent carcinogens among the 57 tested occur in more than 30 common plant foods (1). It is probable that almost every fruit and vegetable in the supermarket contains natural pesticides that are rodent carcinogens.

We have argued that the high positivity rate in rodent studies is due to an increase in low-dose sensitivity at high doses rather than simply to selection of suspicious chemical structures (6, 10). Most chemicals were selected for testing because of their use as industrial compounds, pesticides, drugs, or food additives (historically, there has...
been inadequate knowledge to allow predic-
tion or carcinogenicity (9).

Coffee is one example of the background of natural chemicals to which humans are chronically exposed (Table 1). A cup of coffee contains more than 1000 chemicals (11, 12). Only 16 were tested for carcino-
genicity, and 19 of these were positive at least once, totaling at least 10 mg of rodent carcinogens per cup. The average coffee consumption of Americans is about three cups per day (13). Rodent carcino-
gens in coffee include the plant pigment caffeic acid (present at 1800 ppm per mil-
ion (ppm) (11) and catechol (100 ppm) (14). Two other plant pigments, chloro-
genic acid and theochromic acid (pres-
ent at 21,600 ppm and 11,600 ppm, re-
spectively) (11), are metabolized to caffeic acid and catechol; however, these have not been tested for carcinogenicity. Chloro-
genic acid and caffeic acid are mutagenic and clastogenic (15), and caffeic acid is carcinogenic in both rats and mice (16). For d-limonene, results from rodents may not be relevant to humans: carcinogenicity in the only target organ, the male rat kidney, is associated with a urinary protein that humans do not excrete (17). Some other rodent carcinogens in roasted coffee are products of roasting (for example, fur-
fural, benz(a)pyrene, and MeQ (2-amino-
3,4-dimethylbenz(a)anthracene) (4,5,4'-sulfonated).

Ranking Natural and Synthetic Chemicals

In 1987 we compared possible hazards from several different exposures to rodent carcino-
gens by the HERP index (3). HERP indi-
cates the percentage of the rodent potencies (TD_{50} in milligrams per kilogram per day) received by a human during a given lifetime exposure (milligrams per kilogram per day). TD_{50} is the daily lifetime dose rate estimated to halve the proportion of tumor-free animals by the end of a standard lifetime (18). Values of TD_{50} in our carcinogenic potency database (CPDB) span a 10-mill-
fold range. In this paper we compare HERP indices for every rodent carcinogen in the CPDB (19) that occur naturally in coffee or tea and that is a synthetic pesticide currently in use for which reliable data are available on concentrations in food (20, 21). We double the number of HERP indices used in our previous paper (3), which discussed in detail several categories of exposure. Here we concentrate on natural chemicals in the diet and on synthetic pep-
ticide residues, which have been added to the HERP ranking.

The 10 typical daily exposures in Table 2 are ordered by possible carcinogenic hazard (HERP). Results are reported for 69 exposures to natural chemicals in the diet, 15 synthetic pesticide residues, and 16 other exposures (including drugs, workplace air, indoor air in homes, food additives, and water pollutants). Two convenient reference points are the HERP of 0.001% for the average U.S. expos-
ure to chloroform (a by-product of water chlorination) in a line of tap waters, and the upper-bound risk estimate used by regulatory agencies of one in a million (using the poten-
cy value Q_{a} derived from the linearized multi-
target model), which converts to a HERP of 0.00003% for rats and 0.00001% for mice. The medium HERP for Table 2 is 0.0003%.

Natural pesticides. Natural products produced by plants to defend themselves against fungi, insects, and other predators are an important subset of natural chemi-

cals in the diet. Although > 10,000 natural pesticides occur in the human diet, only 57 have been adequately tested in carcinogen-

icity studies. Thus, natural pesticides are markedly underrepresented in our analysis compared to synthetic pesticide residues because few natural chemicals have been tested for carcinogenicity. For each plant food listed, there are about 50 additional untested natural pesticides. In Table 2, many natural pesticide residues in common foods rank above the median, ranging up to a HERP of 0.3%. These include caffeic acid (lettuce, apple, pear, coffee, plum, cherry, and some tomatoes), trigaldehyde (baith), allyl isothiocyanate (qua-

dam), d-limonene (mango, orange juice, black pepper), 5-methoxypyrroles (pars-

nip), sulfide (in spices), and sympathrine (comfrey, herb tea). Caffeic acid is more widespread in plant species than other natural pesticides.

Synthetic pesticides. Synthetic pesticides currently in use that are rodent carcinogens and that have been found by the Food and Drug Administration (FDA) as residues in food are all included in Table 2; exposures are reported for the most recent estimates. For pesticides that are no longer in use, dieldrin (DELD), dieldrinlphenylkhloro-

ephenyl (DEDE)-dichloro
thylchloro-
one (DDT), and non-removal - methylbromide (UVMH) from Alar, ex-
pouses in Table 2 are before discontin-
ance. All synthetic pesticides are below 0.001 medium and most are air or near the bottom of the ranking. Because few natural pesticides have been tested, the HERP values may be due to reduced usage. This is not the case, because HERPs for 3 past 10 years of FDA exposure data (7, 21) change only marginally and are still near the bottom of the ranking.

Because the exposures in Table 2 are for typical person whereas theirs for synthetic pesticides for average daily intake, we examine whether the relative rankings of these two groups of chemicals would change. Average consumption of each plant food is the basis for the HERP values of natural pesticides (Table 3) (23). Generally, if average daily intake is within a factor of 3 the typical products reported in Table 1 except for some less common foods (e.

example, mango and paprene). Table 3 reports all exposures to natural pesticidal and synthetic pesticides from Table 2 in which average consumption data are available. Strikingly, all HERP values that rank in the top third of Table 3 are for natural pesticides, even though few natural pes-
ticides have been tested.

Three synthetic pesticides, captan, carbofuran, and methomyl, were monitored by the National Research Council (NR) as a relatively high risk to humans (24). We investigated this problem in the FDA in the total diet study. Trivially few HERP values for these crops (chlorothalonil = 0.00000001 folpet = 0.00000008%, captan = 0.00000006%, carbofuran = 0.00000005%) convert with the high r estimates of the NR (which differs by a factor of 99,000 for chlorothalonil, 46,000 for fol-
pet, and 116,000 for captan) because t exposure estimates used by NR (that the EPA theoretical maximum residue content with toxicological maximum exposure estimates, whereas the FDA monitors r actual food supply to estimate dietary inta-

takes of pesticides. Hence, the use of hypothetical maxima results in much higher risk estima-

The use of measured residues.

Cooking and preparation of food. Chemi-

cal s that are rodent carcinogens can be produced by cooking and the prep-

aration of food. The HERP values in Table 4 for alcohol in wine (4.7%) and b-

(2.8%) risk high. Urethane (ethyl d-

methane sulfonate), a commercial product, is a rodent carcinogen and is present in b-

alcohol beverages (HERP, sake = 0.00% and broh (HERP, two, or white wheat toast = 0.00003). Furfur 282
Table 2. Ranking of visible carcinogenic hazards from natural (in both) and synthetic chemicals. Daily human exposure: Reasonable daily intakes are used to refer to exposure comparisons. Figures are reported in (14). The calculations assume a daily dose for a lifetime, when drugs are normally taken for a shorter period of time. The health hazard index (HRI) is derived from the risk assessment of the chemical carcinogen in man in the workplace (25). The HRI values for occupational exposure to EDI and formaldehyde are at or near the top of the ranking (1.4% and 0.4%, respectively). For EDB, the 'reasonable' exposure limit (PEL) of the U.S. Occupational Safety and Health Administration (OSHA) is still above the TDI in rodents (36); in contrast, the EPA banned the agricultural use of EDB, the main fumigant in the United States, because of the residue levels found in grain (HERP = 0.0004%)). For occupational exposure with high HERP values, little quantitative extrapolation is required from the high (MDI) does used in rodents because workers exposures. Some pharmaceuticals are also clustered near the top in the ranking; however, because most are used for short periods, the more sensitive species is used for calculating possible hazard.**

<table>
<thead>
<tr>
<th>Hazardous Substance</th>
<th>Daily human exposure</th>
<th>Human dose of rodent carcinogen</th>
<th>HRI</th>
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<tbody>
<tr>
<td>140</td>
<td>EDI workers’ daily intake</td>
<td>140 mg</td>
<td>0.2%</td>
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<tr>
<td>141</td>
<td>17 Chlorite (avg daily dose)</td>
<td>Chlorite, 2 g</td>
<td>6.6 mg/animal</td>
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<tr>
<td>142</td>
<td>Phenothalal, 1 sleeping pill</td>
<td>Phenothalal, 40 mg</td>
<td>3.3 mg</td>
</tr>
<tr>
<td>143</td>
<td>Carboxy-polyethylenes, 9 daily</td>
<td>Carboxy-polyethylenes, 0.5 mg</td>
<td>0.2 mg/animal</td>
</tr>
<tr>
<td>144</td>
<td>Insecticides (topical dose)</td>
<td>Insecticides, 0.7 mg</td>
<td>0.5 mg/animal</td>
</tr>
<tr>
<td>145</td>
<td>Methylene chloride</td>
<td>Methylene chloride, 1.2 mg</td>
<td>1.2 mg/animal</td>
</tr>
<tr>
<td>146</td>
<td>Formaldehyde workers’ avg daily intake</td>
<td>Formaldehyde, 0.1 mg</td>
<td>0.1 mg/animal</td>
</tr>
<tr>
<td>147</td>
<td>2.8</td>
<td>Aniline (2 g 354 ml)</td>
<td>Aniline, 1/10 ml</td>
</tr>
<tr>
<td>148</td>
<td>1.4</td>
<td>Formaldehyde</td>
<td>Formaldehyde, 1.25 mg</td>
</tr>
<tr>
<td>149</td>
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| 150 | 0.9 | Carbonyl 

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<td>Carbonyl, 0.12 mg</td>
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**The value refers to that reported in our earlier HERP paper (12), owing to more recent experimental results in the CPDR. *Estimate based on average dietary intake for 60- to 70-year-old females. Its only adult group reported for 1990. Because of the agricultural usage of these chemicals and the prominence of fruits and vegetables in the diet of older Americans, these results are generally highly relevant to other adult groups.
and because HERP is an index for lifetime exposure, the possible carcinogenic hazards would usually be markedly lower than indicated in Table 2.

Discussion and Conclusions

Caution is necessary in drawing conclusions from the occurrence in the diet of natural chemicals that are rodent carcinogens. It is not assumed here that these dietary exposures are necessarily of much relevance to human cancer. What is important in our analysis is that widespread exposure to naturally occurring rodent carcinogens may cause doubt on the relevance to human cancer of far lower exposures to synthetic rodent carcinogens. In view of the finding that a high percentage of all chemicals appear to be rodent carcinogens, these results call for a reevaluation of the utility of animal cancer tests done at the MTD for providing information that is useful in protecting humans against low doses of rodent carcinogens.

To the extent that increases in tumor incidence in rodent studies are due to the secondary effects of inducing cell division by the MTD, any chemical is a likely carcinogen at the MTD, and carcinogenic effects at low doses are likely to be much less linear than a linear model would predict (and may often be zero). With intacture there is some theoretical justification for thinking that carcinogenic effects may occur at low doses even though no cell division is induced, although the complexities of inducible protection systems may produce a dose-response threshold or even protective effects at all doses, such as with radiation (26).

It is also possible that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. However, these results do not necessarily indicate that coffee consumption, for example, is a significant risk factor for human cancer even though it is thousands of times the HERP equivalent to the one-in-a-million worst-case risk used by EPA. Epidemiological evidence may help to clarify this risk (27). Adequate risk assessment from animal cancer tests requires more information about many aspects of toxicology, such as effects on cell division, induction of defense and repair systems, and other hazards (28).

With respect to natural pesticides in plant foods, stronger epidemiological evidence indicates this low intake of fruits and vegetables doubles the risk of most types of cancer compared to high intake (29, 30). This can probably be attributed to the presence of anticarcinogenic antioxidants and vitamins in fruits and vegetables (10-12). However, only 9% of adult Americans (29) eat the recommended five servings of fruits and vegetables per day (30), we should be eating more of these foods, not less. Particular natural pesticides can be bred out of plants, and cooking methods can be modified, provided that further studies on mechanism or epidemiology indicate that it is important to do so.

The HERP rankings presented indicate that there is an enormous background of human exposure to rodent carcinogens in the diet and that perspective is clearly needed in setting priorities for regulatory policy and research. Although our ranking does not assign the risks to humans, it can be regarded as anatonal for setting priorities for concern. The number of people exposed is also relevant. By this index, synthetic pesticide residues and flytnt pollution seem to be a minor concern for human cancer. A similar result is expected if one ranking were to use the usual EPA linearized risk assessment methodology for the same exposure values. This is because the upper bound risk estimator is obtained by multiplying exposure by potency, and because potency estimates from rodent tests are restricted to a narrow range about the high dose tested (33). The usual "one-in-a-million risk" can be approximated merely by dividing the high dose in a positive experiment by 300,000 (34).

It is by no means clear that many significant risk factors for human cancer are single chemicals that will be discovered by screening assays (27). The major preventable risk factors for cancer identified thus far are tobacco (35), dietary imbalance (29-32), hormones (46, and chronic in-fections (36, 37). High-dose exposure, or toxicological minima, in an occupational setting (4, 38) may also contribute to few percent of human cancers (56, 37). High-dose animal cancer tests are clear relevant for some occupational or medical exposure that can be at doses close to the MTD, as discussed. Epidemiologic studies do not implicate low-dose exposure to synthetic polychlorinated or pesticidal residues as important risk factors for human cancer (56, 36, 17). High calorie (49) intake may be the more striking rodent carcinogen because reductive markedly lowers cancer rates and increases longevity (40).

The arguments presented in this article thus underestimate many assumptions of current regulatory policy and necessitate rethinking of policy designed to reduce human cancer. Economic analyses indicate that, even if current risk assessment metodology is assumed to be correct, the enor-


