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DIETARY CARCINOGENS, ENVIRONMENTAL POLLUTION, AND CANCER: SOME MISCONCEPTIONS

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Various misconceptions about dietary carcinogens, pesticide residues, and cancer causation are discussed. The pesticides in our diet are 99.99% natural, since plants make an enormous variety of toxins against fungi, insects, and animal predators. Although only 50 of these natural pesticides have been tested in animal cancer tests, about half of them are carcinogens. About half of all chemicals tested in animal cancer tests are positive. The proportion of natural pesticides positive in animal tests of clastogenicity is also the same as for synthetic chemicals. It is argued that testing chemicals in animals at the maximum tolerated dose primarily measures chronic cell proliferation, a threshold process. Cell proliferation is mutagenic in several ways, including inducing mitotic recombination, and therefore chronic induction of cell proliferation is a risk factor for cancer.

Key words: **Pesticides, Animal cancer tests, Cancer causation.**

MISCONCEPTION No. 1: CANCER RATES ARE SOARING

Overall cancer death rates in the United States are staying steady or coming down, the major exception being smoking-related cancer. The latest update[1] from the National Cancer Institute (February 1988) indicates that 'the age adjusted mortality rate for all cancers combined except lung cancer has been declining since 1950 for all individual age groups except 85 and above.' (That represents a 13% decrease overall, 44,000 deaths below expected, and a 0.1% increase in the over-85 group.)

The types of cancer deaths that have been decreasing during this period are primarily stomach (by 75%, 37,000 deaths below expected), cervical (by 73%, 11,000 deaths below expected), uterine (by 60%, 9000 deaths below expected), and rectal (by 65%, 13,000 deaths below expected). The types of cancer deaths that are increasing are primarily lung cancer (by 247%, 91,000 deaths above expected), which is due to smoking (as is 30% of all U.S. cancer), and non-Hodgkin's lymphoma (by 100%, 8000 deaths above expected).

Clearly, changes in survival rates and incidence rates are also relevant in interpreting those changes.[1,2] Incidence rates have been increasing for some types of cancer.[1] Sir Richard Doll and Richard Peto of Oxford University, two of the world's leading epidemiologists, in their definitive study on cancer trends,[2] point out that though incidence rates are of interest, they should not be taken in isolation because of the substantial extent to which trends in the recorded incidence rates are biased by improvements in the level of registration and diagnosis, as appears to be the case, for instance, with breast cancer. Even if particular types of cancer can be shown to be increasing or decreasing, establishing a causal relation among the many changing aspects of our lives remains difficult.[3–15] There is no persuasive evidence that there is a general increase in cancer that can be attributed generally to life in the modern industrial world.[2,10,13]

Life expectancy is steadily increasing in the United States and other industrial countries. Infant mortality is decreasing. And, although the statistics are not good on birth defects, there is no evidence that they are increasing. Conclusion: Americans are the healthiest they have been in their history.

MISCONCEPTION No. 2: CHEMICALS CARCINOGENIC TO RODENTS ARE FEW IN NUMBER AND EASILY ELIMINATED

More than half of the chemicals tested to date in both rats and mice have been found to be carcinogens at the high doses administered,[3,16] the maximum tolerated dose (MTD). Synthetic industrial

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chemicals account for almost all (82%) of the chemicals (427) tested in both species. However, despite the fact that more than 99.9% of the chemicals humans eat are natural, only a small number (75) of *natural* chemicals have been tested in both rats and mice; again, about *half* (47%) are carcinogens.

The high proportion of positives is disturbing. While some synthetic or natural chemicals were selected for testing precisely because of suspect structure, many were tested because of their use: they were natural or synthetic food additives, colors, high volume industrial compounds, pesticides, or natural or synthetic drugs. Thus, the high proportion of carcinogens among synthetic test agents in rodent studies is not simply due to selection of suspicious chemical structures, and the natural world of chemicals has never been looked at systematically. We argue why clarification of the mechanism of carcinogenesis supports the idea that a high proportion of all chemicals we test in the future, both natural and synthetic, will prove to be carcinogenic at the MTD.[3] (See Misconception No. 5 below.)

High proportions of positives are also reported for teratogenicity tests, that is. tests to determine the potential for causing reproductive damage. Fully one-third of the 2800 chemicals tested in laboratory animals have been shown to cause reproductive damage in the standard high-dose protocol.[17] Thus, it seems likely that a sizable percentage of both natural and manmade chemicals will be reproductive toxins — when tested at the MTD.

The world is full of carcinogens and reproductive toxins (as defined by high-dose animal testing), and it always has been. Even table salt[18–25] and sunlight are carcinogenic to humans at high doses. Fortunately, the human exposure dose for almost all of the rodent carcinogens we are exposed to is usually tiny. The important issue is not merely to identify those chemicals that are carcinogenic or teratogenic. Rather, it is to put our efforts into discovering and eliminating the important causes of human cancer.

The major preventable risk factors for cancer, such as tobacco, dietary imbalances,[12,14,15,26–29] hormones,[11] and viruses[30,31] are discussed in other papers in this volume. Epidemiologists are constantly finding clues as to the risk factors for the different types of human cancer, and these hypotheses are then refined by animal and metabolic studies. It seems likely that this approach will lead to the elucidation of the causal factors of the major human cancers in the next decade.

MISCONCEPTION No. 3: MANMADE CHEMICAL POLLUTANTS ARE PRESENT IN SIGNIFICANT AMOUNTS

The data on the similar proportion of carcinogens among synthetic and natural chemicals imply that synthetic chemicals, except in the case of high doses such as some occupational exposures or drugs, are likely to be responsible for little, if any, human cancer. This is in agreement with the conclusion of the cancer epidemiologists.

In recent years, we have attempted to address the issue of setting priorities among possible carcinogenic hazards.[3] Since carcinogens differ enormously in potency in rodent tests, a comparison of possible hazards from various carcinogens ingested by humans must take this into account. Our analysis makes use of an exhaustive database of carcinogenic potency (currently 3976 experiments on 1053 chemicals)[32–35] that analyses animal cancer tests and calculates the TD_{50}, which is essentially the dose of the carcinogen estimated to give half of the animals tumors. The TD_{50} is close to the high doses administered and thus involves minimal extrapolation.

In our index of possible hazard, we attempted to use reasonable daily lifetime human exposure to a chemical, and express that as milligrams (of the chemical) per kilogram of body weight. That mg/kg human exposure is then expressed as a percentage of the rodent TD_{50} dose (mg/kg) for each carcinogen. We call this percentage HERP (Human Exposure dose/Rodent Potency dose). Because rodent data are all calculated on the basis of lifetime exposure at the indicated daily dose rate,[8,32] the human exposure data are similarly expressed as lifelong daily dose rates, even though the human exposure is likely to be less than daily for a lifetime.

The HERP values do not estimate human risk directly, because it is impossible to extrapolate to low doses (See Misconception No. 5.) But they do offer a way of comparing possible hazards, and thus of putting exposures into a relative context so that priorities can be more reasonably set. Carcinogens clearly do not all work in the same way, and as we learn more about mechanisms, HERP comparisons can be refined, as can risk assessments. Our results suggest that alcohol at moderate doses should be high on our priority list for epidemiological studies and cancer prevention. Further, this HERP analysis suggests that the possible carcinogenic hazard of synthetic chemicals that humans ingest from pesticide residues or water pollution appears to be trivial relative to the background of carcinogens from natural, and traditional chemicals (e.g. from the cooking of food).[3,36]

Dietary pesticides are 99.99% *all natural*

Nature's pesticides are one important group of natural chemicals that we have investigated. All plants produce toxins to protect themselves against fungi, insects, and animal predators such as man.[36–38] Tens of thousands of these natural pesticides have been discovered, and every species of plant contains its own set of different toxins, usually a few dozen. In addition, when plants are stressed or damaged, such as during a pest attack, they increase their natural pesticide levels manyfold, occasionally to levels that are acutely toxic to humans. We estimate that Americans eat about 1500 mg/day of natural pesticides, 10,000 times more than manmade pesticide residues. Their concentration is usually measured in parts per thousand or million, rather than parts per billion (ppb), which is the usual concentration of synthetic pesticide residues or of water pollutants.[3] We estimate that humans are ingesting 5000 to 10,000 natural pesticides and their breakdown products. Table 1 shows the 49 natural pesticides (and breakdown products) ingested on eating cabbage and indicates those that have been tested for carcinogenicity or clastogenicity.[39–54] Lima beans showed a different array of 23 natural toxins that, in stressed plants, range in concentration from 0.2 to 33 parts per thousand fresh weight; none appears to have been tested for carcinogenicity or teratogenicity.[55] A large literature has examined the toxicity of many of these compounds to plant predators.[38,55]

Surprisingly few plant toxins have been tested in animal cancer bioassays,[56] but among those tested, again about half (27/50) (B. N. Ames, M. Profet and L. S. Gold, manuscript in preparation) are carcinogenic. Even though only a tiny proportion of plant toxins in our diet has been tested, natural pesticide carcinogens have been shown to be present in the following foods: anise, apples, bananas, basil, broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, carrots, cauliflower, celery, cherries, cinnamon, cloves, cocoa, coffee, comfrey tea, dill, endive, fennel, grapefruit juice, honey, honeydew melon, horseradish, kale, lettuce, mangoes, mushrooms, mustard, nutmeg, orange juice, parsley, parsnips, peaches, pears, black pepper, pineapples, plums, radishes, raspberries, rosemary, tarragon and turnips. Thus, it is probable that almost every plant product in the supermarket contains natural carcinogens. The levels of the known natural carcinogens in the above plants are commonly thousands of times higher (ppm or ppt) than the ppb levels of manmade pesticides (Table 2). Table 2 shows a variety of carcinogens in the ppm range in plant foods.[57–90] We need not be alarmed by the presence of low doses of synthetic toxins and a plethora of natural toxins in our food. Humans are well protected by many layers of inducible general defenses against low doses of toxins — defenses that do not distinguish between synthetic and natural toxins. In addition, new research suggests that conventional worst-case extrapolations from very high-dose rodent cancer tests to very low-dose human exposures to chemicals markedly exaggerate the possible hazards.

Additionally, there is a fundamental trade-off between nature's pesticides and manmade pesticides. We can easily breed out many of nature's pesticides, but then we will need more manmade pesticides to protect our crops from being eaten by insects. Conversely, growers are currently breeding some plants for insect resistance and unwittingly raising the levels of natural pesticides. Caution is necessary in interpreting the implications of the occurrence in the diet of natural pesticides that are rodent carcinogens. It is not argued here that these dietary exposures are necessarily of much relevance to human cancer. Indeed, a diet rich in fruit and vegetables is, if anything, associated with low cancer rates. This may be because some anticarcinogenic vitamins and antioxidants come from plants. What is important in our analysis is that exposures to natural rodent carcinogens may cast doubt on the relevance of far lower levels of exposures to synthetic rodent carcinogens.

Residues of manmade pesticides. The intake of manmade pesticide residues from food in the United States, including the residues of industrial chemicals such as polychlorinated biphenyls (PCBs), has been estimated by the Food and Drug Administration, which assayed food for residues of the 200 compounds thought to be of greatest importance.[91] The FDA reported that human intake averages about 0.09 mg a day, which compares to 1.5 g of natural pesticides (i.e. 99.99% natural).

About half of this intake is composed of four chemicals (ethylhexyl diphenyl phosphate, dicloran, malathion and chlorpropham), which were not carcinogenic in rodent tests.[3] Thus, the intake of carcinogens from residues (0.05 mg a day, if one assumes that all the other residues are carcinogenic, which is unlikely) is extremely tiny (about 0.06 ppm in plant food) relative to the background of natural substances (Table 2).[3,36]

We conclude that the possible hazards from these residues, even if they were all carcinogenic, are minimal compared with the background of nature's pesticides.

For comparison (Table 2), there are at least

Table 1. 49 Natural pesticides (and metabolites) in cabbage

Glucosinolates
- 2-propenyl glucosinolate (sinigrin)*
- and 13 other glucosinolates

Indoles
- indole-3-carbinol (I3C)*
- indole-3-acetonitrile (IAN)*
- 3,3′-diindolylmethane (I33′)*

Isothiocyanates and goitrin
- allyl isothiocyanate*
- 3-methyl-thio-propyl isothiocyanate
- 3-methyl-sulfinyl-propyl isothiocyanate
- 3-butenyl isothiocyanate
- 5-vinyloxazolidine-2-thione (goitrin)
- 4-methylthiobutyl isothiocyanate
- 4-methylsulfinylbutyl isothiocyanate
- 4-methylsulfonylbutyl isothiocyanate
- 4-pentenyl isothiocyanate
- benzyl isothiocyanate
- phenylethyl isothiocyanate

Cyanides
- 1-cyano-2,3-epithiopropane
- 1-cyano-3,4-epithiobutane
- 1-cyano-3,4-epithiopentane
- *threo*-1-cyano-2-hydroxy-3,4-epithiobutane
- *erythro*-1-cyano-2-hydroxy-3,4-epithiobutane
- 2-phenylpropionitrile
- allyl cyanide*
- 1-cyano-2-hydroxy-3-butene
- 1-cyano-3-methylsulfinylpropane
- 1-cyano-4-methylsulfinylbutane

Alcohols and ketones
- menthol
- neomenthol
- isomenthol
- carvone*

Phenols and tannins
- 2-methoxyphenol
- 3-caffoylquinic acid (chlorogenic acid)*
- 4-caffoylquinic acid*
- 5-caffoylquinic acid (neochlorogenic acid)*
- 4-*p*-coumaroylquinic acid
- 5-*p*-coumaroylquinic acid
- 5-feruloylquinic acid

*Discussed below; all others untested. *Clastogenicity*: Chlorogenic acid[39] and allyl isothiocyanate are positive.[40] Chlorogenic acid and its metabolite caffeic acid are also mutagens,[41–43] as is allyl isothiocyanate.[44] *Carcinogenicity*: Allyl isothiocyanate is positive in rats and negative in mice,[45,46] sinigrin (the glucosinolate, i.e. thioglycoside of allyl isothiocyanate) is co-carcinogenic for the rat pancreas,[47] and carvone is negative in mice.[48] Indole acetonitrile has been shown to form a carcinogen, nitroso indole acetonitrile, in the presence of nitrite.[49] Caffeic acid is a carcinogen[50–52] and clastogen[39] and is a metabolite of its esters 3-, 4-, and 5-caffoylquinic acid (chlorogenic and neochlorogenic acid). *Metabolites*: Sinigrin gives rise to allyl isothiocyanate on eating raw cabbage (e.g. coleslaw); in cooked cabbage it also is metabolized to allyl cyanide, which is untested. Indole carbinol forms dimers and trimers on ingestion, which mimic dioxin (TCDD) (see text). For occurrence see references 53 and 54.

9 mg of rodent carcinogens (40 ppm) in a cup of coffee (e.g. caffeic acid, hydrogen peroxide, furfural, catechol), 0.8 mg of carcinogenic estragole in a basil leaf, and typically about 2000 mg of burnt material from cooking our daily food, including the nitrosamines formed by the use of gas ovens.[3,36]

Clastogenicity/mutagenicity studies

In order to compare natural with synthetic chemicals, it may be useful to look at other types of studies as well. For example, Ishidate *et al.*[40] reviewed experiments on the clastogenicity (chromosome breakage) of 951 chemicals in mammalian cell cultures. Of these 951 chemicals, we identified 72 as natural plant pesticides. Of the 72 natural pesticides, 35 (48%) were positive for clastogenicity in some or all tests. This compares favorably with the results of the remaining 879 chemicals: 467 (53%) were positive in some or all tests.

Of particular interest are the levels at which some of these plant toxins were clastogenic:

— Allyl isothiocyanate was clastogenic at a concentration of 0.0005 ppm, which is approximately 200,000 times less than the concentration of its glucosinolate (sinigrin) in cabbage. It was among the most potent chemicals in the compendium, and it is also positive at unusually low levels in transforming[93] and mutating animal cells.[44]

— Safrole was clastogenic at a concentration of

Table 2. Concentrations of natural pesticide carcinogens

Plant	Carcinogen	Concentration (ppm)
Parsley	5- and 8-methoxypsoralen	14
Parsnip, cooked	—	32
Celery	—	0.8
Celery, new cultivar	—	6.2
Celery, stressed	—	25
Mushroom, commercial	*p*-hydrazinobenzoate	11
Mushroom, commercial	glutamyl-*p*-hydrazinobenzoate	42
Cabbage	sinigrin* (allyl isothiocyanate)	35–590
Cauliflower	—	12–66
Brussels sprouts	—	110–1560
Mustard (black)	—	16,000–72,000
Horseradish	—	4500
Basil	estragole	3800
Fennel	—	3000
Nutmeg	safrole	3000
Mace	—	10,000
Pepper, black	—	100
Apple, Pear, Plum, Cherry, Carrot, Celery, Lettuce, Potato, Endive, Grapes, Eggplant	caffeic acid	50–200
Thyme, Basil, Anise, Sage, Dill, Caraway, Rosemary, Tarragon, Coffee (roasted beans)	caffeic acid	>1000
Apricot, Cherry, Plum, Peach	chlorogenic acid** (caffeic acid)	50–500
Coffee (roasted beans)	—	>21,600
Apple, Pear, Peach, Apricot, Plum, Cherry, Brussels sprouts, Kale, Cabbage, Broccoli,	neochlorogenic acid** (caffeic acid)	50–500
Coffee (roasted beans)		11,600

*Sinigrin is a co-carcinogen[47] and is metabolized to the carcinogen allyl isothiocyanate, although no adequate test has been done on sinigrin itself. The proportion converted to allyl isothiocyanate or to allyl cyanide depends on food preparation.[53,54] **Chlorogenic and neochlorogenic acid are metabolized to the carcinogen caffeic acid but have not been tested for carcinogenicity themselves. The clastogenicity and mutagenicity of the above compounds are referenced in Table 1. *Carcinogen refs* (refs 32–35 and the following): 5-methoxypsoralen (light activated),[57] 8-methoxypsoralen,[58] *p*-hydrazinobenzoate and glutamyl-*p*-hydrazinobenzoate,[59,60] allyl isothiocyanate,[45,46] D-limonene,[61] estragole and safrole,[56,62] ethyl acrylate,[63] benzyl acetate,[64] caffeic acid.[50–52] *Concentration refs*: 5-, 8-methoxypsoralen,[37,65–69] *p*-hydrazinobenzoates,[59,60] sinigrin,[53,54,70] D-limonene,[71–73] estragole and safrole,[74–77] ethyl acrylate,[78] benzyl acetate,[79–81] caffeic acid, chlorogenic acid, neochlorogenic acid.[82–90] D-limonene is found in citrus oil, ethyl acrylate in pineapples, and benzyl acetate in basil and jasmine tea.

about 100 ppm, which is 30 times less than the concentration in nutmeg, and roughly equal to the concentration in black pepper.

— Caffeic acid was clastogenic at a concentration of 260–500 ppm, which is less than the concentration in roasted coffee beans and many spices, and is roughly equal to the concentration in apples, lettuce, endive, and potato skin. The genotoxic activity of coffee to mammalian cells has been demonstrated.[94] Chlorogenic acid, a precursor of caffeic acid, was clastogenic at a concentration of 150 ppm, which is 100 times less than its concentration in roasted coffee beans, and is roughly within the range of its concentration in apples, pears, plums, peaches, cherries and apricots.

The carcinogenicity and genetic toxicology of plant carcinogens has been recently reviewed.[54] A number of dietary natural pesticides that have not been tested in animal cancer tests and are related to the carcinogens safrole and estragole have been shown to give DNA adducts.[95] Benzyl acetate and ethyl acrylate were also shown to mutate mouse lymphoma cells.[44] Stich and Powrie[96] have reviewed the mutagenicity, clastogenicity and carcinogenicity of plant phenolics such as caffeic acid, chlorogenic acid, and tannins (esters of gallic acid).

Breeding for resistance. An alternative to using synthetic pesticides is to raise the level of natural plant toxins by breeding. It is not clear that this approach, even where feasible, is preferable to the application of synthetic pesticides. One consequence of disproportionate concern about tiny traces of synthetic pesticide residues, such as ethylene dibromide,[3] is that plant breeders are developing highly insect-resistant plants, thus creating other hazards.

Two recent cases are instructive. A major grower introduced a new variety of highly insect-resistant celery into commerce. A flurry of complaints to the Centers for Disease Control from all over the country followed, because people who handled the celery developed a severe rash when they were subsequently exposed to sunlight. Some detective work found that the pest-resistant celery contained 6200 ppb of carcinogenic (and mutagenic) psoralens instead of the 800 ppb present in normal celery (Table 2).[37,68,69] It is unclear whether other natural pesticides in the celery were increased as well.

Solanine and chaconine (the main natural alkaloids in potatoes) are cholinesterase inhibitors (cholinesterase is an enzyme involved in nerve transmission) and known teratogens. Solanine and chaconine were widely introduced into the world diet about 400 years ago with the dissemination of the potato from the Andes. These natural alkaloids can be detected in the blood of all potato eaters. Total alkaloids are present in potatoes at a level of 15 mg per 200 g potato (75 ppm), which is less than a tenfold safety margin from the toxic level for humans.[3] Neither alkaloid has been tested for carcinogenicity. Ironically, plant breeders have produced an insect-resistant potato. However, it had to be withdrawn from the market because of its acute toxicity to humans — a consequence of higher levels of solanine and chaconine. In contrast, the pesticide malathion, the main synthetic organophosphate cholinesterase inhibitor present in our diet (0.006 mg per day), has been thoroughly tested and is not a carcinogen in rodents.

There is a tendency for non-scientists to think of *chemicals* as being only synthetic, and to characterize them as toxic, as if every natural chemical were not also toxic at some dose. Even a recent National Academy of Sciences report[92] states: 'Advances in classical plant breeding . . . offer some promise for nonchemical pest control in the future. Nonchemical approaches will be encouraged by tolerance revocations if more profitable chemical controls are not available . . .' The report was partly concerned with some pesticides used on tomatoes. Of course, tomatine, one of the natural toxins in tomatoes, is a chemical too, and was introduced from the Andes 400 years ago. Although it has not been tested in rodent cancer bioassays, it is present at 36 mg per 100 g tomato (360 ppm), a concentration that is orders of magnitude closer to the toxic level than are manmade pesticide residues.

TCDD (dioxin) compared with alcohol and broccoli. Common sense suggests that a chemical pollutant should not be treated as a significant hazard if its possible hazard level is far below that of common food items. TCDD is a substance of great public concern, because it is a carcinogen and teratogen in rodents at low doses. And yet, the doses humans ingest are very low relative to the levels that cause cancer and reproductive damage in rodents.

TCDD might be compared with alcohol, for example. Although alcohol is an extremely weak carcinogen and teratogen, the doses humans are exposed to are very high relative to the dose known to cause cancer or birth defects in rodents. Indeed, alcoholic beverages are the most important known human teratogen. In contrast, there is no persuasive evidence that TCDD is carcinogenic or teratogenic in man, although it has such effects in rodents.

The Environmental Protection Agency's human 'reference dose' (formerly 'acceptable dose limit') of TCDD is 6 femtograms (fg) per kilogram per day. If one compares the teratogenic potential of TCDD to that of alcohol for causing birth defects (after adjusting for their respective potency as determined in rodent tests), then a daily consumption of the reference dose of TCDD is equivalent in teratogenic potential to the amount of alcohol ingested daily from 1/3,000,000 of a beer. That is the equivalent of drinking one beer (15 g ethyl alcohol) over a period of 8000 years. A daily slice of bread, or a daily glass of orange juice, contains much more natural alcohol than that.

Alcoholic beverages in man are clearly carcinogenic as well as teratogenic. A comparison of the carcinogenic potential of TCDD with that of alcohol, adjusting for the potency in rodents, shows that the TCDD reference dose of 6 fg per kilogram per day is equivalent to the alcohol in ingesting one beer every 345 years. Since the average consumption of alcohol in the United States is equivalent to more than one beer per day per capita, the great concern over TCDD at levels in the range of the reference dose seems unreasonable.

TCDD binds to the Ah receptor in mammalian cells: evidence strongly suggests that all of the harmful effects of TCDD are through this binding.[97]

A wide variety of natural substances also bind to the Ah receptor, and insofar as they have been examined, they have similar properties to TCDD. A cooked steak, for instance, contains polycyclic hydrocarbons, which bind to the Ah receptor and mimic TCDD. In addition, our diet contains a variety of flavones and other substances from plants, which bind to the Ah receptor. The most interesting of the flavones is indole carbinol (IC), which is present in large amounts in broccoli (500 mg per kg), cabbage, cauliflower, and other members of the *Brassica* family.[98] IC makes dimers and trimers at the pH of the stomach, and these induce the same set of enzymes as TCDD.[99] When given before aflatoxin or other carcinogens, IC protects against carcinogenesis, as does TCDD.[100] However, when given *after* aflatoxin or other carcinogens, IC is a strong promoter of carcinogens, as is TCDD.[101] This stimulation of carcinogenesis has also been shown for cabbage itself.[102]

The 6 fg per kg of TCDD per day EPA 'reference dose' should be compared with 50 billion fg of IC per 100 g of broccoli (one portion). Although the affinity of the indole derivatives in binding to Ah receptors is less than TCDD by a factor of about 8000, the effective dose to the Ah receptor from a helping of broccoli appears to be roughly 20 million times higher than the TCDD reference dose. The very long lifetime of TCDD in the body (several years) should be taken into account in comparisons, but the lifetime of the hydrophobic indole dimers is not known. Although these IC derivatives appear to be much more of a possible hazard than TCDD, it is not clear whether at these low doses *either* is a hazard. Another study[103] also shows that when sunlight oxidizes tryptophan, a normal amino acid, it converts it to a variety of indoles, which bind to the Ah receptor and mimic the action of TCDD. It seems likely that many more of these 'natural dioxins simulators' will be discovered in the future.

Water pollution. The possible hazards from carcinogens in contaminated well water in places such as California's Santa Clara ('Silicon') Valley or in Woburn, Massachusetts,[104–109] should be compared with the possible hazards of ordinary tap water.[3] Of the 35 wells that were shut down in Santa Clara Valley because of a supposed carcinogenic hazard (low traces of trichloroethylene), only two were of a possible hazard greater than ordinary tap water. Well water is not usually chlorinated and therefore lacks the 83 ppb chloroform present in average chlorinated tap water.[3] Water from the most polluted well in the Santa Clara Valley had a relative hazard that was orders of magnitude less than for the carcinogens in an equal volume of beer or wine.[3] The consumption of tap water is only about one or two liters per day, and animal evidence[3] provides no good reason to expect that chloroform in water or current levels of manmade pollutants in water would pose a significant carcinogenic hazard.[3]

Similarly, the trace amounts of chemicals found in polluted wells should be a negligible cause of birth defects, when compared with the background level of known teratogens such as alcohol. The important risk factors for birth and reproductive defects in humans are the age of the mother, her consumption of alcohol, her smoking habits, and whether or not she has been exposed to the rubella virus.

Cooking food. The cooking of food generates a variety of mutagens and carcinogens. The total amount of browned and burnt material eaten in a typical day is at least several hundred times more than that inhaled from severe outdoor air pollution.[36] Nine heterocyclic amines, isolated on the basis of their mutagenicity from proteins or amino acids that were heated in ways that reproduce cooking methods, have now been tested. All have been shown to be carcinogens in rodents.[110,111] Many others are still being isolated and characterized.[110,111]

Three mutagenic nitropyrenes present in diesel exhaust have now been shown to be carcinogens,[112] but the intake of these carcinogenic nitropyrenes has been estimated to be much higher from grilled chicken than from air pollution.[110,111,113] Gas flames generate NO_2, which can form both carcinogenic nitropyrenes[3] and the potently carcinogenic nitrosamines when food, such as fish, is cooked in gas ovens. Food cooked in gas ovens may be a major source of dietary nitrosamines and nitropyrenes.

MISCONCEPTION No. 4: THE TOXICOLOGY OF MANMADE CHEMICALS IS DIFFERENT FROM THAT OF NATURAL CHEMICALS

In the debate over the effects of natural versus synthetic chemicals, it has been proposed that nature is relatively benign and that the process of natural selection has equipped us to cope with the toxic chemicals in the natural world.[114] In contrast, goes the argument, we are ill-prepared to cope with synthetic toxins. That argument is not compelling[7] for several reasons.

(1) There is no reason to think that the process of natural selection in human beings should have eliminated the hazard of carcinogenicity of a plant toxin, since cancer generally occurs past the reproductive age; however, selection may have occurred protecting humans against acute effects, since these occur early in life as well. Thus, one would expect, and in fact finds, that the proportion of mutagens, clastogens, and rodent carcinogens should not differ between synthetic and natural pesticides.

Aflatoxin, a potent mold toxin that presumably arose early in evolution, causes cancer in trout, rats, mice, monkeys, and humans, although the species vary in sensitivity.[5,115] Many of the common metal salts are carcinogens (such as lead, cadmium, beryllium, nickel, chromium, selenium, and arsenic), despite their presence during all of evolution.

(2) Some argue that humans (as opposed to rats or mice) may have developed resistance to each of the tens of thousands of plant toxins or chemicals in cooked food,[114] whereas resistance to synthetic toxins is lacking. This is unlikely, because, as discussed,[3,9,36] both rodents and humans have developed many types of *general* defenses against the large amounts and enormous variety of nature's pesticides in plants. These defenses include the constant shedding of the surface layer of cells of the digestive system, the glutathione transferases for detoxifying alkylating agents, the active excretion of hydrophobic toxins out of liver and intestinal cells, numerous defenses against oxygen radicals, and DNA excision repair. These defense systems are almost all inducible in response to the particular stress, so we are well buffered against toxins.

The fact that defenses are usually general, rather than specific for each chemical, makes good evolutionary sense, and it is supported by various studies. Experimental evidence indicates that these general defenses are effective against both natural and synthetic compounds,[116] since the basic mechanisms of carcinogenesis are not unique to either.

(3) The human diet has changed drastically in the last few thousand years, and most of us are eating recently introduced plants (such as coffee, potatoes, tomatoes, and even kiwi fruit) that our ancestors did not. It follows that the process of natural selection, which works very slowly, could not have led to the development of specific resistance to the toxins in foods that are comparatively new to our diet.

(4) Some have suggested that plants contain anticarcinogens that protect us against plant carcinogens. While true, that argument also is irrelevant to the debate. Plant antioxidants, the major known type of ingested anticarcinogens, do not distinguish whether oxidant carcinogens *are synthetic or natural in origin*. Thus, they help to protect us against both.

(5) It has been argued that synthetic carcinogens can be synergistic with each other. However, this is also true of natural chemicals. Thus, the argument is irrelevant in evaluating the assertion that synthetic pesticide residues in food or synthetic pollutants in water appear to be a trivial increment over the background of natural carcinogens.

MISCONCEPTION No. 5: WE CAN PREDICT HUMAN CANCER RISKS AT LOW EXPOSURES TO RODENT CARCINOGENS WITHOUT UNDERSTANDING THE MECHANISMS OF CARCINOGENS

It is prudent to assume that if a chemical is a carcinogen in rats and mice at the maximum tolerated dose, it may well be a carcinogen in humans *at doses close to the MTD*. However, until we understand more about the mechanisms of carcinogenesis, we cannot reliably predict risk to humans at low doses that are often hundreds of thousands of times below the dose where an effect is observed in rodents. *Thus, quantitative risk assessment is currently not scientifically possible.*[3,4,7]

Mechanisms of carcinogenesis

The study of mechanisms of carcinogenesis is a rapidly developing field and is essential for evaluating both the role of mutagenicity tests and the

methods for risk assessment in regulatory policy. Both DNA damage and cell proliferation (i.e. promotion) are important aspects of carcinogenesis, and agents that increase either are carcinogens.[3,117,118] Endogenous rates of DNA damage are enormous: 10^4 hits/cell/day from just oxidative damage in man and 10× higher rates in rodents.[119] The classical chemical promoters such as phenobarbital and tetradecanoyl phorbol acetate would be expected to be, and are in fact, carcinogens in animals when tested thoroughly.[120] In non-dividing tissues, such as the liver (the major target site for carcinogens in rodents[16]), mutation is not sufficient for carcinogenesis: cells are communicating and inhibiting growth of neighboring cells.[121–123] Unless there is a cluster of proliferating cells, an essential step for carcinogenesis may be lacking. It is of interest that even in dividing tissues, agents causing cell proliferation are carcinogens, e.g. a variety of hormones in human cancer[11] or salt in human stomach cancer.[18–25]

Cell proliferation is itself mutagenic in numerous ways:

(1) It triggers mitotic recombination, the conversion of adducts to gaps, gene conversion, and nondisjunction, which together are orders of magnitude more effective than an independent second mutation[124–128] in converting a heterozygous recessive oncogene mutation to homozygosity.[129,130,131]

(2) It leads to gene duplication, which can cause expression of oncogenes that are otherwise not expressed.

(3) It allows adducts to convert to mutations.

(4) It makes more sensitive single-stranded DNA available as a target.

Exogenous factors can cause cell proliferation in several ways:

(1) Toxicity can cause injury to tissues, resulting in cell proliferation: the experimental model is to remove part of the liver surgically so that neighboring cells proliferate.[132,133] The incidence of liver cancer is low in humans (but not in many strains of rodents) *unless* some agent chronically damages the liver. Alcohol excess, for example, causes cirrhosis of the liver, which is a risk factor for cancer. Chronic toxicity also can cause an inflammatory reaction, since phagocytic cells unleash a barrage of oxidants in destroying dead cells at a wound. The oxidants produced are the same as in ionizing radiation, so chronic inflammation is the equivalent of irradiating the tissue.[134] Oxidants produced as a result of inflammation could stimulate oncogenes and cell proliferation.[135–138] Chronic inflammation is, as expected, a risk factor for cancer;[139–141] asbestos is one of many examples of this,[142] and asbestos is one of many examples of this,[142] and asbestos and the NO_x in cigarette smoke may be primarily promotional carcinogens.

(2) Viruses, particularly those causing chronic infections cause cell killing and consequent cell proliferation and are thus risk factors for cancer. Two examples are the human carcinogenic virus hepatitis B, a major cause of liver cancer in the world,[31,143] and human papilloma virus 16 (HPV 16), a major risk factor for cervical cancer, whose main effect on cells is to induce proliferation.[30]

(3) Hormones can cause cell proliferation and are major risk factors for a number of human cancers such as breast cancer.[11]

(4) Chemicals interfering with cell–cell communication are carcinogens because they cause cell proliferation, as has been emphasized by Trosko and his associates.[121,122]

Agents causing cell proliferation are proper carcinogens and may even be the most numerous and important class of human carcinogen. There is much evidence to suggest that agents causing cell proliferation exhibit thresholds.[117,118]

Carcinogenesis is a multihit and multistage process. Several mutations appear necessary for carcinogenesis; there are many layers of defense against carcinogens, and most of these defenses are inducible. These considerations suggest an upward-curving (quadratic-type) dose–response relation to carcinogenesis, which is consistent with both the animal and the human data (D. G. Hoel and C. J. Portier, 'Nonlinearity of dose–response functions for carcinogenicity,' submitted for publication).[3–7,144] Inducing both mutation and cell proliferation should generally give a multiplicative effect. Multiplicative interactions are common in human cancer causation. We have discussed some of these and other arguments for this view of promotion in detail elsewhere.[3,119]

Animal cancer tests and cell proliferation

Administering chemicals in cancer tests at the MTD commonly causes cell proliferation and inflammatory reactions.[3,145,146] It seems likely, therefore, that a high percentage of all chemicals, both manmade and natural, will cause cell proliferation at the MTD and increase tumor incidence.

Analyses of animal cancer tests to date indicate that a high proportion (~40%) of chemicals that are carcinogenic under bioassay conditions are not mutagenic,[35,147,148] although mutagens (in contrast to non-mutagens) are (a) more likely to be carcinogenic, (b) more likely to be positive in both rats and

mice, (c) toxic at lower doses, and (d) more likely to cause tumors at multiple sites.[35] Since cell proliferation is itself mutagenic, non-mutagens at the MTD are likely to be acting by this mechanism. Since the MTD approaches the level that kills the animal because of toxicity, and cytotoxicity is a threshold process, for nongenotoxic chemicals the exact dose is clearly critical for tumor induction. The evidence from our database suggests that the observed relationship between TD_{50} and MTD has a biological as well as a statistical basis.[149,150] The MTD is needed to see a carcinogenic effect.

> If some compounds were highly carcinogenic compared with their MTDs, then we would expect to observe 100% (or at least very high) incidence rates at all of the experimental dose levels. This was not seen with the compounds under study. If the saturation of a metabolic activation process was involved, the dose response might plateau. From our data base we observed that approximately 10% of the dose-response functions were . . . indicating possible saturation. For the compounds in which this was observed, it was, however, generally not replicated in other target sites in the same experiment, in the other sex of the same species, or in other species.[149]

We postulated that the MTD of a carcinogen causes cell death, which allows neighboring cells to proliferate, and also causes oxygen radical production from phagocytosis and thus chronic inflammation, both important aspects of the carcinogenic process.

Even such a well characterized mutagenic carcinogen as diethylnitrosamine may be active at the MTD primarily through inducing cell proliferation. At doses near the MTD, the induced ethylated adducts show a linear dose–response, and the induced cell proliferation shows a threshold; the induced tumors at high doses, however, show a clearly upward-curving dose–response.[144] A similar case is seen with the mutagen formaldehyde,[144] with which the primary carcinogenic action appears to be due to cell proliferation. Mutagens, because they damage DNA, are very effective at killing cells and thus are also very effective at causing cell proliferation and inflammatory reactions. If a chemical is non-mutagenic and its carcinogenicity is due to cell proliferation resulting from near-toxic doses, one might commonly expect a threshold.[3,117,118,145,146] An analysis of the shape of the dose–response curves in 344 NCI/NTP animal cancer tests indicates that even at the high doses used, a quadratic dose–response is compatible with more of the data than a linear one (D. G. Hoel and C. J. Portier, 'Non-linearity of dose–response functions for carcinogenicity,' submitted for publication).

The high percentage of chemicals carcinogenic at the MTD emphasizes the importance of understanding cancer mechanisms for a rational risk assessment. A list of carcinogens is not enough. The main rule in toxicology is that the 'dose makes the poison': at some level, every chemical becomes toxic, but there are safe levels below that. However, the precedent of radiation, which is both a mutagen and a carcinogen, gave credence to the idea that there could be effects of chemicals even at low doses. A scientific consensus evolved in the 1970s that we should treat carcinogens differently, that we should assume that even low doses might possibly cause some cancer, even though we lacked the methods for measuring effects at low levels. This idea evolved because most carcinogens appeared to be mutagens.

Some recent work on radiation carcinogenesis suggests that cell killing is important,[151,152] as well as mutation, and that low doses of radiation may be of no harm or may even be protective.[153–156] We should bear in mind that enzyme systems for protecting cells are usually inducible, not only against radiation and other oxidants.[155,157]

MISCONCEPTION No. 6: STORKS BRING BABIES AND POLLUTION CAUSES CANCER AND BIRTH DEFECTS

The number of storks in Europe has been decreasing for decades. At the same time, the European birth rate also has been decreasing. We would be foolish to accept this high correlation[158] as evidence that storks bring babies. The science of epidemiology tries to sort out from the numerous chance correlations those that are meaningful. That is, epidemiology attempts to define those correlations that involve cause and effect. However, it is not easy to obtain persuasive cause-and-effect evidence by epidemiological methods because of inherent methodological difficulties.[10] There are many sources of bias in observational data, and chance variation is also an important factor. For example, because there are so many different types of cancer or birth defects, by chance alone one might expect some of them to occur at a high frequency in a small community here and there. Toxicology provides evidence that can help us decide whether an observed correlation might be causal or accidental.

In any event, there is no persuasive evidence from epidemiology or toxicology that pollution is a significant source of birth defects or cancer. For example, the epidemiological studies on the Love Canal community in Niagara Falls, New York, of dioxin in Agent Orange,[159,160] of pollutants produced by the refineries in Contra Costa County, California,[161,162] of the contaminants in the wells of Silicon Valley,[163]

or of Woburn, Massachusetts,[104–109] or on DDT, the now-banned pesticide, provide no persuasive evidence that in any of these well-publicized exposures was pollution the cause of human harm. At Love Canal, where people were living next to a toxic waste dump, the epidemiological evidence for an effect on public health is equivocal. Analyses of the toxicology data on many of these cases suggests that the amounts of the chemicals involved were much too low relative to the background of natural and traditional carcinogens to be credible sources of increased cancer in humans.[3] With respect to birth defects, a comparative analysis of teratogens using a HERP-type index, which would express the human exposure level as a percentage of the dose level known to cause reproductive damage in rodents, would be of interest. But such a study has not been done in a systematic way.

Environmental exposure to TCE, PCE, trichloroethane, ethylene dibromide and other pollutants is thousands of times lower than the exposure to these same agents in the workplace.[3,8] Thus, if parts per billion of these pollutants were causing cancer or birth defects, one might expect to see an effect in the work-place. However, studies on these chemicals so far do not provide any evidence for suggesting a causal association,[115] though epidemiological studies are inherently insensitive.

Historically, cases of cancer due to workplace exposure resulted mainly from exposures to chemicals at very high levels. For example, the EDB levels that workers were allowed to be exposed to were once shockingly high in California.[3] We testified in California in 1981 that our calculations showed that the workers were allowed to breathe in a dose higher than the dose that gave half of the test rats cancer. California lowered the permissible worker exposure more than a hundred-fold. Despite the fact that the epidemiology on EDB in highly exposed workers does not show any significant effect, the uncertainties of our knowledge make it important to have strict rules about workers, because they can be exposed to extremely high doses.

MISCONCEPTION No. 7: TECHNOLOGY IS DOING US IN

Modern technologies are almost always replacing older, more hazardous technologies. Billions of pounds of TCE (one of the most important industrial non-flammable solvents) and PCE (the main dry-cleaning solvent in the United States) are used because of their low toxicity, and because they are not flammable.

Eliminating a carcinogen may not always be a good idea. For example, ethylene dibromide (EDB), the main fumigant in the United States before it was banned, was present in trivial amounts (about 0.4 ppb) in our food; the average daily intake was about one-tenth of the possible carcinogenic hazard of the aflatoxin in the average peanut butter sandwich, a minimal possible hazard in itself.[3] The elimination of EDB fumigation might result in insect infestation and subsequent contamination of grain by carcinogen-producing molds. This might result in a reduction in public health, not an advance, and it might also greatly increase costs. Additionally, the alternatives to the use of EDB, none of which are very satisfactory, may be more hazardous and expensive.

Similarly, modern synthetic pesticides replaced more hazardous substances such as lead arsenate, one of the major pesticides before the modern era. Lead and arsenic are both natural, highly toxic, and carcinogenic. Pesticides have increased crop yields and brought down the price of foods, a major public health advance. Each new generation of pesticides is more environmentally and toxicologically benign.

Every living thing and every industry 'pollutes' to some extent. The fact that scientists have developed methods to measure parts per billion of carcinogens and are developing methods to measure parts per trillion makes us more aware of pollution, but does not mean that significant pollution is necessarily increasing, or that the pollution found is a cause of human harm. Minimizing pollution is a separate issue from cancer prevention and is clearly desirable aside from any effect on public health, but it involves trade-offs. How to get the most pollution reduction for the lowest economic cost is an important issue.[164]

Failure to spend efforts on important problems is counterproductive. If we divert too much of our attention to traces of pollution and away from important public health concerns such as smoking (400,000 deaths per year), alcohol (100,000 deaths per year), eating unbalanced diets (for example, too much saturated fat and cholesterol), AIDS, radioactive radon coming up from the soil into our homes, and high-dose occupational exposure, we do not improve public health — and the important hazards are lost in the confusion.

It is the inexorable progress of modern technology and scientific research that will continue to provide the knowledge that will result in steady progress in decreasing death rates from cancer, decrease the incidence of birth defects, and lengthen the human lifespan.

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