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Paracelsus to parascience: the environmental cancer distraction

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Abstract

Entering a new millennium seems a good time to challenge some old ideas, which in our view are implausible, have little supportive evidence, and might best be left behind. In this essay, we summarize a decade of work, raising four issues that involve toxicology, nutrition, public health, and government regulatory policy. (a) *Paracelsus or parascience: the dose (trace) makes the poison.* Half of all chemicals, whether natural or synthetic, are positive in high-dose rodent cancer tests. These results are unlikely to be relevant at the low doses of human exposure. (b) *Even Rachel Carson was made of chemicals: natural vs. synthetic chemicals.* Human exposure to naturally occurring rodent carcinogens is ubiquitous, and dwarfs the general public's exposure to synthetic rodent carcinogens. (c) *Errors of omission: micronutrient inadequacy is genotoxic.* The major causes of cancer (other than smoking) do not involve exogenous carcinogenic chemicals: dietary imbalances, hormonal factors, infection and inflammation, and genetic factors. Insufficiency of many micronutrients, which appears to mimic radiation, is a preventable source of DNA damage. (d) *Damage by distraction: regulating low hypothetical risks.* Putting huge amounts of money into minuscule hypothetical risks damages public health by diverting resources and distracting the public from major risks.

Keywords: Cancer prevention; Micronutrients; Natural chemicals; Mutagens; Cancer mechanism; Animal cancer tests

1. Paracelsus to parascience: the dose (trace) makes the poison

About 50% of chemicals — whether natural or synthetic — that have been tested in standard, high-dose, animal cancer tests are rodent carcinogens [1–3] (Table 1). What are the explanations for this high percentage? 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, can contribute to cancer in these tests [2,4–14]. 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. 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 synthetic chemicals to which humans are usually exposed, such increased cell division does not occur. The process of mutagenesis and carcinogenesis is complicated because many fac-

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Table 1
Proportion of chemicals evaluated as carcinogenic

	Proportion	Percentage
Chemicals tested in both rats and mice[a]	350/590	(59%)
Naturally occurring chemicals	79/139	(57%)
Synthetic chemicals	271/451	(60%)
Chemicals tested in rats and/or mice[a]		
Chemicals in Carcinogenic Potency Database	702/1348	(52%)
Natural pesticides	37/71	(52%)
Mold toxins	14/23	(61%)
Chemicals in roasted coffee	21/30	(70%)
Innes negative chemicals retested[a,b]	17/34	(50%)
Physician's desk reference (PDR)		
Drugs with reported cancer tests[c]	117/241	(49%)
FDA database of drug submissions[d]	125/282	(44%)

[a] From the Carcinogenic Potency Database [1–3].

[b] The 1969 study by Innes et al. [90] is frequently cited as evidence that the proportion of carcinogens is low, as only 9% of 119 chemicals tested (primarily pesticides) were positive. However, these tests, which were only in mice with few animals per group, lacked the power of modern tests. Of the 34 Innes negative chemicals that have been retested using modern protocols, 16 were positive.

[c] Davies and Monro [91].

[d] Contrera et al. [92]. One hundred forty drugs are in both the FDA and PDR databases.

tors are involved: e.g., DNA lesions, DNA repair, cell division, clonal instability, apoptosis, and p53 [15,16]. The normal endogenous level of oxidative DNA lesions in somatic cells is appreciable [17]. In addition, tissues injured by high doses of chemicals have an inflammatory immune response involving activation of white cells in response to cell death [18–25]. Activated white cells release mutagenic oxidants (including peroxynitrite, hypochlorite, and hydrogen peroxide). Therefore, the very low levels of chemicals to which humans are exposed through water pollution or synthetic pesticide residues may pose no or minimal cancer risks.

Is the high positivity rate due to selecting more suspicious chemicals to test? This is a likely bias since cancer testing is both expensive and time-consuming, and it is prudent to test suspicious compounds. One argument against selection bias [9] is the high positivity rate for drugs (Table 1) because drug development tends to favor chemicals that are not mutagens or expected carcinogens. A second argument against selection bias is that the knowledge needed to predict carcinogenicity in rodent tests is highly imperfect, even now after decades of test results have become available on which to base predictions. For example, a prospective prediction exercise was conducted by several experts in 1990 in advance of the 2-year NTP bioassays. There was wide disagreement among them on which chemicals would be carcinogenic when tested and the level of accuracy varied by expert, thus indicating that predictive knowledge is highly uncertain [9,26]. Moreover, if the main basis for selection were suspicion rather than human exposure, then one should select mutagens (80% are positive compared to 50% of nonmutagens), yet 55% of the chemicals tested are nonmutagens [1,3,9].

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 [2,8,12–14,27]. Without additional data on how a chemical causes cancer, the interpretation of a positive result in a rodent bioassay is highly uncertain. The induction of cancer could be the result of the high doses tested.

In regulatory policy, the "virtually safe dose" (VSD), corresponding to a maximum, hypothetical risk of one cancer in a million, is estimated from bioassay results using a linear model, which assumes that cancer causation is directly proportional to dose and that there are no unique effects of high doses. To the extent that carcinogenicity in rodent bioassays is

due to the effects of high doses for the nonmutagens, and a synergistic effect of cell division at high doses with DNA damage for the mutagens, then this model is inappropriate [7,28]. Regulatory agencies are moving slowly to take mechanism and nonlinearity into account, e.g., US EPA.

Linearity of dose–response seems unlikely in any case due to the inducibility of the numerous defense enzymes which deal with exogenous chemicals as groups, e.g., oxidants, electrophiles, and thus protect us against the natural world of mutagens as well as the small amounts of synthetic chemicals [29–32].

2. Even Rachel Carson was made of chemicals: natural vs. synthetic chemicals

About 99.9% of the chemicals humans ingest are natural. The amounts of synthetic pesticide residues in plant foods are insignificant compared to the amount of natural pesticides produced by plants themselves [32–34]. Of all dietary pesticides that humans eat, 99.99% are natural: they are chemicals produced by plants to defend themselves against fungi, insects, and other animal predators [32–34]. Each plant produces a different array of such chemicals.

We have estimated that on average Americans ingest roughly 5000 to 10,000 different natural pesticides and their breakdown products. Americans eat about 1500 mg of natural pesticides per person per day, which is about 10,000 times more than the 0.09 mg they consume of synthetic pesticide residues [33].

Even though only a small proportion of natural pesticides have been tested for carcinogenicity, 37 of the 71 tested are rodent carcinogens. Naturally occurring pesticides that are rodent carcinogens are ubiquitous in fruits, vegetables, herbs, and spices [34] (Table 2).

Cooking foods produces about 2000 mg/person/day of burnt material that contains many rodent carcinogens and many mutagens. By contrast, the residues of 200 synthetic chemicals measured by FDA, primarily synthetic pesticides, thought to be of greatest importance, average only about 0.09 mg/person/day [33,34]. In a single cup of coffee, the natural chemicals that are *known* rodent carcinogens are about equal in weight to a year's worth of

Table 2
Carcinogenicity of natural plant pesticides tested in rodents[a]

Carcinogens: $N = 37$	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-hydroxy-methylphenylhydrazine, glycyrrhetinic acid, *p*-hydrazinobenzoic acid, isosafrole, kaempferol, *d*-menthol, nicotine, norharman, phenethyl isothiocyanate, pilocarpine, piperidine, protocatechuic acid, rotenone, rutin sulfate, sodium benzoate, tannic acid, 1-*trans*-δ^9-tetrahydrocannabinol, turmeric oleoresin, vinblastine
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.

[a] Fungal toxins are not included. From the Carcinogenic Potency Database [1,3].

synthetic pesticide residues that are rodent carcinogens, even though only 3% of the natural chemicals in roasted coffee have been adequately tested for carcinogenicity [35] (Table 3). This does not mean that coffee or natural pesticides are dangerous, rather, it makes assumptions about high- dose animal cancer tests for assessing human risk at low doses need reexamination. No diet can be free of natural chemicals that are rodent carcinogens [34].

Gaining a broad perspective about the vast number of chemicals to which humans are exposed can be helpful when setting research and regulatory priorities [32,34–36]. Rodent cancer tests by themselves provide little information about how a chemical causes cancer or about low-dose risk. The assumption that synthetic chemicals are hazardous has led to a bias in testing, such that synthetic chemicals account for 76% (451 of 590) of the chemicals tested chronically in both rats and mice (Table 1). The natural world of chemicals has never been tested systematically.

One reasonable strategy is to use a rough index to compare and rank possible carcinogenic hazards from a wide variety of chemical exposures at levels that humans typically receive, and then to focus on those that rank highest [1,3,35,37]. Ranking is a critical first step that can help to set priorities for selecting chemicals for long-term cancer tests, studies on mechanism, epidemiological research and 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 a ranking if, using the same methodology to identify hazard, there are numerous, common human exposures with much greater possible hazards. Our analyses are based on the human exposure/rodent potency (HERP) index, which indicates what percentage of the rodent carcinogenic potency (dose to give half of the animals cancer) a human receives from a given daily lifetime exposure [37]. A ranking based on standard linearized, regulatory risk assessment would be similar.

Overall, our analyses have shown that HERP values for some historically high exposures in the workplace (e.g., butadiene and tetrachloroethylene) and some pharmaceuticals (e.g., clofibrate) rank high, and that there is an enormous background of naturally occurring rodent carcinogens in typical portions of common foods that cast doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides [1,3,35,37,38]. A committee of the National Research Council of the National Academy of Sciences recently reached similar conclusions about natural vs. synthetic chemicals in the diet, and called for further research on natural chemicals [39].

The possible carcinogenic hazards from synthetic pesticides are minimal compared to the background of nature's pesticides, though neither may be a hazard at the low doses consumed. Analysis also indicates that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. 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. Data call for a reevaluation of the utility of animal cancer tests in protecting the public against minor hypothetical risks.

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. This assumption is flawed for several reasons [32,40].

(1) Humans have many natural defenses that buffer against normal exposures to toxins [32] and these are

Table 3
Carcinogenicity in rodents of natural chemicals in roasted coffee[a]

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

[a]From the Carcinogenic Potency Database [1,3].

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. It makes good evolutionary sense to conclude that human defenses are usually general, rather than specific for each chemical. 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 [32,37]. Mold toxins, such as aflatoxin, have been shown to cause cancer in rodents and other species including humans (Table 1). Many of the common elements are carcinogenic to humans at high doses, e.g., salts of cadmium, beryllium, nickel, chromium and arsenic, despite their presence throughout evolution. Furthermore, epidemiological studies from various parts of the world show that certain natural chemicals in food may be carcinogenic risks to humans; for example, the chewing of betel nut with tobacco causes oral cancer. Drink up Socrates, it's natural.

(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, mangoes, 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) DDT is often viewed as the typically dangerous synthetic pesticide because it concentrates in adipose tissues and persists for years. DDT, the first synthetic pesticide, eradicated malaria from many parts of the world, including the US. It 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 food, making fresh, nutritious foods more accessible to poor 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 [41]." 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 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 [42]. Natural pesticides also can bioconcentrate if they are fat-soluble. Potatoes, for example, 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 [32], though they have not been tested for carcinogenicity.

(5) Since no plot of land is immune to attack by insects, plants need chemical defenses — either natural or synthetic — to survive pest attack. Thus, there is a trade-off between natural-occurring pesticides and synthetic pesticides. One consequence of disproportionate concern about synthetic pesticide residues is that some plant breeders develop plants to be more insect-resistant by making them higher in natural pesticides. A recent case illustrates the potential hazards of this approach to pest control. When a major grower introduced a new variety of highly insect-resistant celery into commerce, people who handled the celery developed rashes when they were subsequently exposed to sunlight. Some detective work found that the pest-resistant celery contained 6200 parts per billion (ppb) of carcinogenic (and mutagenic) psoralens instead of the 800 ppb present in common celery [32].

3. Errors of omission: micronutrient inadequacy is genotoxic

Endogenous hormones [43,44], dietary imbalances [45,46], inflammation due to infection [47] and genetic factors, none of which involve an exogenous carcinogenic chemical, are major contributors to human cancer [46].

High consumption of fruits and vegetables is associated with a lowered risk of degenerative diseases including cancer, cardiovascular disease, cataracts and brain dysfunction [46,48]. More than 200 studies in the epidemiological literature show, with great consistency, an association between low consumption of fruits and vegetables and high cancer incidence [49–51] (Table 4). The quarter of the population with the lowest dietary intake of fruits and vegetables has roughly twice the cancer rate of the quarter with the highest intake for most types of cancer (lung, larynx, oral cavity, esophagus, stomach, colorectal, bladder, pancreas, cervix and ovary).

Table 4
Review of epidemiological studies on cancer showing protection by consumption of fruits and vegetables[a]

Cancer site	Fraction of studies showing significant cancer protection	Median relative risk of low quarter vs. high quarter of consumption
Epithelial		
Lung	24/25	2.2
Oral	9/9	2.0
Larynx	4/4	2.3
Esophagus	15/16	2.0
Stomach	17/19	2.5
Pancreas	9/11	2.8
Cervix	7/8	2.0
Bladder	3/5	2.1
Colorectal	20/35	1.9
Miscellaneous	6/8	–
Hormone-dependent		
Breast	8/14	1.3
Ovary/endometrim	3/4	1.8
Prostate	4/14	1.3
Total	129/172	

[a]From Ref. [49].

Eighty percent of US children and adolescents [52] and 68% of adults [53] did not meet the intake recommended by the National Cancer Institute and the National Research Council: five servings of fruits and vegetables per day.

Publicity about hundreds of minor hypothetical risks, such as pesticide residues, can result in loss of perspective on what is important: half the US public does not know that fruit and vegetable consumption is a protection against cancer [54]. Fruits and vegetables are of major importance for reducing cancer; if they become more expensive because of reduced use of synthetic pesticides then consumption is likely to decline and cancer to increase. People with low incomes eat fewer fruits and vegetables and spend a higher percentage of their income on food.

Folic acid deficiency, one of the most common vitamin deficiencies in the population consuming few dietary fruits and vegetables, causes chromosome breaks in humans [55]. The mechanism of chromosome breaks has been shown to be deficient methylation of uracil to thymine, and subsequent incorporation of uracil into human DNA (4 million/cell) [55]. Uracil in DNA is excised by a repair glycosylase with the formation of a transient single-strand break in the DNA; two opposing single-strand breaks cause a double-strand chromosome break, which is difficult to repair. Thus, folate deficiency appears to be a radiation mimic. Both high DNA uracil levels and chromosome breaks in humans are reversed by folate administration [55]. Folate supplementation above the RDA minimized chromosome breakage [56]. Folate deficiency has been associated with increased risk of colon cancer [57,58], and the 15-year use of a multivitamin supplement containing folate lowered colon cancer risk by about 75% [59]. Folate deficiency also damages human sperm [60], causes neural tube defects in the fetus and an estimated 10% of US heart disease [61]. Diets low in fruits and vegetables are commonly low in folate, antioxidants (e.g., vitamin C) and many other micronutrients [46,49,62].

Approximately 10% of the US population [63] had a lower folate level than that at which chromosome breaks occur [55]. In two small studies of low income (mainly African–American) elderly [64] and adolescents [65] done nearly 20 years ago nearly half had folate levels that low; the issue should be reex-

amined. Recently, in the US, flour, rice, pasta, and cornmeal have been supplemented with folate [66].

Since radiation causes oxidative damage, insufficiency of dietary antioxidants is likely to be a radiation mimic. Antioxidants such as vitamin C (whose dietary source is fruits and vegetables), vitamin E, and selenium protect against oxidative damage caused by normal metabolism [17], smoking [45], and inflammation [48].

Low intake of any one of nine dietary micronutrients — folic acid, niacin, iron, zinc, selenium, and vitamins B6, B12, C, and E — appears to mimic radiation by breaking DNA and chromosomes, or causing oxidative damage to DNA, or both [45]. Some of these micronutrients come from fruits and vegetables and could account for much of their protective effect against cancer.

Many other micronutrients whose main dietary sources are not fruits and vegetables are also likely to play a significant role in the prevention and repair of DNA damage, and thus are important to the maintenance of long-term health.

Deficiency of vitamin B12 whose main dietary source is meat is common. About 4% of the US population consume less than half of the RDA of vitamin B12 [67]. About 14% of elderly Americans and about 24% of elderly Dutch have mild B12 deficiency, in part accountable by the Americans taking more vitamin supplements [68]. Vitamin B12 would be expected to cause chromosome breaks by the same mechanism as folate deficiency. Both B12 and methyl-THF are required for the methylation of homocysteine to methionine. If either folate or B12 is deficient, then homocysteine, a major risk factor for heart disease [61,69], accumulates. When B12 is deficient, then tetrahydrofolate is trapped as methyl-THF; the methylene-THF pool, which is required for methylation of dUMP to dTMP, is consequently diminished. Therefore, B12 deficiency, like folate deficiency, should cause uracil to accumulate in DNA, and there is accumulating evidence for this (Ingersoll et al., unpublished; Ref. [70]). The two deficiencies may act synergistically. In a study of healthy elderly men [71], or young adults [56], increased chromosome breakage was associated with either a deficiency in folate, or B12, or with elevated levels of homocysteine. B12 supplementation above the RDA was necessary to minimize chromosome breakage [56]. B12 deficiency is known to cause neuropathy due to demyelination and loss of peripheral neurons (reviewed in Ref. [55]).

Niacin, whose main dietary sources are grain and meat, contributes to the repair of DNA breaks [72,73]. As a result, dietary insufficiencies of niacin (2% of the US population ingests $< 50\%$ of the RDA [67]), folate and antioxidants may act together to increase DNA damage.

Deficiency of zinc, iron, or vitamin B6, can lead to DNA damage and appear to be radiation mimics [45]. Low intake ($< 50\%$ of the RDA) in the US population is 18% for zinc, 10% for B6, and 19% of menstruating women for iron [45]. We estimate that half of the US population may be low in at least one of these nine micronutrients. Optimizing micronutrient intake (through better diets, fortification of foods or multivitamin–mineral pills) can have a major impact on public health at low cost. More research in this area and educational efforts aimed at increasing micronutrient intake and balanced diets, should be high priorities for public policy.

4. Damage by distraction: regulating low hypothetical risks

Synthetic, hormonally active agents have become an environmental issue. Hormonal factors are important in cancer [43,44]. The 1996 book, *Our Stolen Future* [74], claims that traces of synthetic chemicals, such as pesticides with weak hormonal activity, may contribute to cancer and reduce sperm counts. The book ignores the fact that our normal diet contains natural chemicals that have estrogenic activity millions of times higher than that due to the traces of synthetic estrogenic chemicals [75,76] and that lifestyle factors can markedly change the levels of endogenous hormones. The low levels of human exposure to residues of industrial chemicals are toxicologically implausible as a significant cause of cancer or reproductive abnormalities, especially when compared to the natural background [75–78]. In addition, it has not been shown convincingly that sperm counts are declining [79–81], and even if they

were, there are many more likely causes such as smoking and diet.

Because there is no risk-free world and resources are limited, society must set priorities based on cost-effectiveness in order to save the most lives [82,83]. The EPA projected in 1991 that the cost to society of US environmental regulations in 1997 would be about US$140 billion per year (about 2.6% of gross national product) [84]. Most of this cost is to the private sector. Several economic analyses by others have concluded that current expenditures are not cost-effective; that is, resources are not being utilized so as to save the most lives per dollar. One estimate is that the US could prevent 60,000 deaths per year by redirecting the same dollar resources to more cost-effective programs [85]. For example, the median toxin control program costs 146 times more per year of life saved than the median medical intervention program [85]. The true difference is likely to be greater, because cancer risk estimates for toxin-control programs are worst-case, hypothetical estimates, and there maybe no risk at low dose [35,37,46]. Rules on air and water pollution are necessary (e.g., it was a public health advance to phase lead out of gasoline) and clearly, cancer prevention is not the only reason for regulations. However, worst-case assumptions in risk assessment represent a policy decision, not a scientific one, and they confuse attempts to allocate money effectively for public health.

Regulatory efforts to reduce low-level human exposures to synthetic chemicals because they are rodent carcinogens are expensive; they aim to eliminate minuscule concentrations that now can be measured with improved techniques. These efforts are distractions from the major task of improving public health through increasing scientific understanding about how to prevent cancer (e.g., what aspects of diet are important), increasing public understanding of how lifestyle influences health, and improving our ability to help individuals alter their lifestyles.

Why has the government focused on minor hypothetical risks at huge cost? A recent article in *The Economist* [86] had a fairly harsh judgment:

"Predictions of ecological doom, including recent ones, have such a terrible track record that people should take them with pinches of salt instead of lapping them up with relish. For reasons of their own, pressure groups, journalists and fame-seekers will no doubt continue to peddle ecological catastrophes at an undiminishing speed.... Environmentalists are quick to accuse their opponents in business of having vested interests. But their own incomes, their fame and their very existence can depend on supporting the most alarming versions of every environmental scare. 'The whole aim of practical politics' said H.L. Mencken, 'is to keep the populace alarmed — and hence clamorous to be led to safety — by menacing it with a series of hobgoblins, all of them imaginary.' Mencken's forecast, at least, appears to have been correct."

Aaron Wildavsky discusses worst-case risk assessment in his book *But Is It True: A Citizen's Guide to Environmental Health and Safety Issues* [87].

"We should be guided by the probability and extent of harm, not by its mere possibility. The search for possibilities is endless and it trivializes the subject. There is bound to be great diversion of resources without reducing substantial sources of harm. Consternation is created but health is not enhanced.... Weak causes are likely to have weak effects. Our search should be for strong causes with palpable effects, like cigarette smoking. They are easier to find and their effects are much more important to control.... The past necessity of proving harm has been replaced by a reversal of causality: now the individuals and businesses must prove that they will do no harm. My objection to this... is profound: our liberties are curbed and our health is harmed."

Acknowledgements

This essay has been adapted in part from [45,88,89]; for more detailed literature, the reader is referred to these publications.

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