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Nature's chemicals and synthetic chemicals: Comparative toxicology*

(carcinogens/mutagens/teratogens/clastogens/dioxin)

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ABSTRACT **The toxicology of synthetic chemicals is compared to that of natural chemicals, which represent the vast bulk of the chemicals to which humans are exposed. It is argued that animals have a broad array of inducible general defenses to combat the changing array of toxic chemicals in plant food (nature's pesticides) and that these defenses are effective against both natural and synthetic toxins. Synthetic toxins such as dioxin are compared to natural chemicals, such as indole carbinol (in broccoli) and ethanol. Trade-offs between synthetic and natural pesticides are discussed. The finding that in high-dose tests, a high proportion of both natural and synthetic chemicals are carcinogens, mutagens, teratogens, and clastogens (30–50% for each group) undermines current regulatory efforts to protect public health from synthetic chemicals based on these tests.**

The Toxicology of Synthetic and Natural Toxins Is Similar

It is often assumed that, because plants are part of human evolutionary history whereas synthetic chemicals are recent, the mechanisms that animals have evolved to cope with the toxicity of natural chemicals will fail to protect us against synthetic chemicals (1, 64).¶ We find this assumption flawed for several reasons.

(*i*) Defenses that animals have evolved are mostly of a general type, as might be expected, since the number of natural chemicals that might have toxic effects is so large. General defenses offer protection not only against natural but also against synthetic chemicals, making humans well buffered against toxins (2–6). These defenses include the following. (*a*) 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. (*b*) The induction of a wide variety of general detoxifying mechanisms, such as antioxidant defenses (7, 8) or the glutathione transferases for detoxifying alkylating agents (9): human cells that are exposed to small doses of an oxidant, such as radiation or hydrogen peroxide, induce antioxidant defenses and become more resistant to higher doses (10–14). These defenses can be induced both by synthetic oxidants (e.g., the herbicide paraquat) and by natural oxidants and are effective against both. (*c*) The active excretion of planar hydrophobic molecules (natural or synthetic) out of liver and intestinal cells (15). (*d*) DNA repair: this is effective against DNA adducts formed from both synthetic and natural chemicals and is inducible in response to DNA damage (16). (*e*) Animals' olfactory and gustatory perception of bitter, acrid, astringent, and pungent chemicals: these defenses warn against a wide range of toxins and could possibly be more effective in warning against some natural toxins that have been important in food toxicity during evolution, than against some synthetic toxins. However, it seems likely that these stimuli are also general defenses and are monitoring particular structures correlated with toxicity; some synthetic toxic compounds are also pungent, acrid, or astringent. Even though mustard, pepper, garlic, onions, etc. have some of these attributes, humans often ignore the warnings.

That defenses are usually general, rather than specific for each chemical, makes good evolutionary sense. The reason that predators of plants evolved general defenses against toxins 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 set of specific toxins, it would be at a great disadvantage in obtaining new foods when favored foods became scarce or evolved new toxins.

(*ii*) Various natural toxins, some of which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates. Mold aflatoxins, for example, have been shown to cause cancer in trout, rats, mice, monkeys, and possibly in humans (2, 17). Eleven mold toxins have been reported to be carcinogenic (6), and 19 mold toxins have been shown to be clastogenic (18). Many of the common elements are carcinogenic (e.g., salts of lead, cadmium, beryllium, nickel, chromium, selenium, and arsenic) or clastogenic (18) at high doses, despite their presence throughout evolution. Selenium and chromium are essential trace elements in animal nutrition.

Furthermore, epidemiological studies from various parts of the world show that certain natural chemicals in food may be carcinogenic risks to humans: the chewing of betel nuts with tobacco around the world has been correlated with oral cancer (17, 19). The phorbol esters present in the Euphorbiaceae, some of which are used as folk remedies or herb teas, are potent mitogens and are thought to be a cause of nasopharyngeal cancer in China and esophageal cancer in Curacao (20, 21). Pyrrolizidine toxins are mutagens that are found in comfrey tea, various herbal medicines, and some foods; they are hepatocarcinogens in rats and may cause liver cirrhosis and other pathological states in humans (19).

Plants have been evolving and refining their chemical weapons for at least 500 million years and incur large fitness costs in producing these chemicals. If these chemicals were not effective in deterring predators, plants would not have been naturally selected to produce them.

(*iii*) Humans have not had time to evolve into a "toxic harmony" with all of the plants in their diet. Indeed, very few of the plants that humans eat would have been present in an African hunter–gatherer's diet. The human diet has changed

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Abbreviations: DDT, 1,1,1,-trichloro-2,2-bis(*p*-chlorophenyl)ethane ("dichlorodiphenyltrichloroethane"); TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; IC, indole-3-carbinol; Ah receptor, aromatic hydrocarbon receptor.

*This is paper no. 3 of a series. Paper no. 2 is ref. 6.

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¶"For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death." Rachel Carson (1962) *Silent Spring* (Houghton Mifflin, Boston), p. 15.

drastically in the last few thousand years, and most humans are eating many recently introduced plants that their ancestors did not—e.g., coffee, cocoa, tea, potatoes, tomatoes, corn, avocados, mangoes, olives, and kiwi fruit. In addition, cruciferous vegetables such as cabbage, broccoli, kale, cauliflower, and mustard were used in ancient times "primarily for medicinal purposes" and were spread as foods across Europe only in the Middle Ages (22, 23). Natural selection works far too slowly for humans to have evolved specific resistance to the food toxins in these newly introduced plants.

(*iv*) Poisoning from plant toxins in the milk of foraging animals was quite common in previous centuries. Cow or goat milk and other ingested dairy products were contaminated by the natural toxins from plants that were eaten by foraging animals in nonindustrial, agricultural societies, because toxins that are absorbed through the animal's gut are often secreted in the milk. Since the plants foraged by cows vary from place to place and are usually inedible for human consumption, the plant toxins that are secreted in the milk are, in general, not toxins to which humans could have easily adapted. Abraham Lincoln's mother, for example, died from drinking cow's milk that had been contaminated with toxins from the snakeroot plant (24). Foraging cows can eat bracken fern, which contains a known carcinogen; the milk from cows eating bracken fern is carcinogenic to rats (19). When cows and goats forage on lupine, their offspring may have teratogenic abnormalities, such as "crooked calf" syndrome caused by the anagyrine in lupine (25–27). Such significant amounts of these teratogens can be transferred to the animals' milk that drinking the milk during pregnancy is a teratogenic risk for humans (25–27): in one rural California family, a baby boy, a litter of puppies, and goat kids all had a "crooked" bone birth defect. Both the pregnant woman and the pregnant dog had been drinking milk obtained from the family goats, which had been foraging on lupine, the main forage in winter (25–27).

(*v*) Anticarcinogenic chemicals in the diet may help to protect humans equally well against synthetic and natural carcinogens. Although plants contain anticarcinogenic chemicals that may protect against carcinogens (28, 29, 64), these anticarcinogens (e.g., plant antioxidants) do not distinguish whether carcinogens are synthetic or natural in origin.

(*vi*) It has been argued that synergism between synthetic carcinogens could multiply hazards; however, this is also true of natural chemicals, which are by far the major source of chemicals in the diet.

(*vii*) DDT bioconcentrates in the food chain due to its unusual lipophilicity; however, natural toxins can also bioconcentrate. DDT ["dichlorodiphenyltrichloroethane," 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane] is often viewed as the typically dangerous synthetic pesticide because it persists for years; it was representative of a class of chlorinated pesticides. Natural pesticides, however, also bioconcentrate if lipophilic: the teratogens solanine (and its aglycone solanidine) and chaconine, for example, are found in the tissues of potato eaters (30–32). Although DDT was unusual with respect to bioconcentration, it was remarkably nontoxic to mammals, saved millions of lives, and has not been shown to cause harm to humans (33). To a large extent DDT, the first major synthetic insecticide, replaced lead arsenate, a major carcinogenic pesticide used before the modern era; lead arsenate is even more persistent than DDT. When the undesirable bioconcentration and persistence of DDT and its lethal effects on some birds were recognized it was prudently phased out, and less persistent chemicals were developed to replace it. Examples are the synthetic pyrethroids that disrupt the same sodium channel in insects as DDT (34), are degraded rapidly in the environment, and can often be used at a concentration as low as a few grams per acre.

(*viii*) Natural toxins can have the same mechanisms of toxicity as synthetic toxins: the case of dioxin. Cabbage and broccoli contain a chemical whose breakdown products bind to the body's aromatic hydrocarbon (Ah) receptor, induce the defense enzymes under the control of the receptors, and possibly cause mitogenesis—just as does dioxin [2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)], one of the most feared industrial contaminants. TCDD is of great public concern because it is carcinogenic and teratogenic in rodents at extremely low doses. The doses humans ingest are, however, far lower than the lowest doses that have been shown to cause cancer and reproductive damage in rodents.

TCDD exerts many or all of its harmful effects in mammalian cells through binding to the Ah receptor (35). A wide variety of natural substances also bind to the Ah receptor [e.g., tryptophan oxidation products (36)] and insofar as they have been examined, they have similar properties to TCDD. A cooked steak, for example, contains polycyclic hydrocarbons that bind to the Ah receptor and mimic TCDD. In addition, a variety of flavones and other plant substances in the diet, such as indole carbinol (IC), also bind to the Ah receptor. IC is the main breakdown compound of glucobrassicin, a glucosinolate that is present in large amounts in vegetables of the *Brassica* genus, including broccoli (about 25 mg per 100-g portion) (62) Brussels sprouts (125 mg per 100 g) (62), and cabbage (25 mg per 100 g) (23). When tissues of these vegetables are lacerated, as occurs during chewing, they release an enzyme that breaks down the glucobrassicin. The enzyme is quite heat stable, and cooked vegetables yield most of the indole compounds that raw vegetables do (37). Therefore, we assume for the following calculation that 20% of glucobrassicin is converted to IC on eating. At the pH of the stomach, IC makes dimers and trimers that induce the same set of detoxifying enzymes as TCDD (37–39). IC, like TCDD, protects against carcinogenesis when given *before* aflatoxin or other carcinogens (39–41). However, when given *after* aflatoxin or other carcinogens, IC, like TCDD, stimulates carcinogenesis (38). This stimulation of carcinogenesis has also been shown for cabbage itself (42). These IC derivatives appear to be much more of a potential hazard than TCDD if binding to the Ah receptor is critical for toxic effects. The Environmental Protection Agency's human "reference dose" (formerly "acceptable dose limit") of TCDD is 6 fg per kg per day. This should be compared with 5 mg of IC per 100 of broccoli or cabbage (6). Although the affinity of one major indole dimer in binding to Ah receptors is less than that of TCDD by a factor of about 8000 (L. F. Bjeldanes and C. A. Bradfield, personal communication), the effective dose to the Ah receptor from a helping of broccoli would be about 1500 times higher than that of TCDD, taking into account an extra factor of 1000 for the very long lifetime of TCDD in the body (several years) and assuming that the lifetime of the hydrophobic indole dimers is as short as 1 day. Another IC dimer has recently been shown to bind to the Ah receptor with about the same affinity as TCDD (L. Bjeldanes, personal communication). However, it is not clear whether at the low doses of human exposure either is hazardous; they may even be protective. It seems likely that many more of these natural "dioxin simulators" will be discovered in the future.

If TCDD is compared with ethanol it seems of minor interest as a teratogen or carcinogen. Alcoholic beverages are the most important known human chemical teratogens (43). In contrast, there is no persuasive evidence that TCDD is either carcinogenic or teratogenic in humans, although it is both at near-toxic doses in rodents. 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 Environmental Protection Agency's reference dose of TCDD

(6 fg per kg) would be equivalent in teratogenic potential to a daily consumption of alcohol from 1/3,000,000th of a beer. That is equivalent to drinking a single beer (15 g of ethanol) over a period of 8000 years.

Alcoholic beverages in humans are a risk factor for cancer (17) as well as birth defects. A comparison of the carcinogenic potential for rodents of TCDD with that of alcohol (adjusting for the potency in rodents) (2) shows that ingesting the TCDD reference dose of 6 fg per kg per day is equivalent to ingesting one beer every 345 years. Since the average consumption of alcohol in the United States is equivalent to more than one beer per person per day, and since five drinks a day are a carcinogenic risk in humans, the experimental evidence does not of itself seem to justify the great concern over TCDD at levels in the range of the reference dose.

Trade-Offs Between Natural and Synthetic Pesticides

Since no plot of land is immune to attack by insects, plants need chemical defenses, either natural or synthetic, in order to survive pest attack. "It has been suggested that one consequence of crop plant domestication is the deliberate or inadvertent selection for reduced levels of secondary compounds that are distasteful or toxic. Insofar as many of these chemicals are involved in the defense of plants against their enemies, the reduction due to artificial selection in these defenses may account at least in part for the increased susceptibility of crop plants to herbivores and pathogens. . . ." (44). Therefore, there is a trade-off between nature's pesticides and synthetic pesticides.

Cultivated plant foods commonly contain on average fewer natural toxins than do their wild counterparts. For example, the wild potato *Solanum acaule*, the progenitor of cultivated strains of potato, has a glycoalkaloid content about 3 times that of cultivated strains and is more toxic (45, 46). The leaves of the wild cabbage *Brassica oleracea* (the progenitor of cabbage, broccoli, and cauliflower) contain about twice as many glucosinolates as cultivated cabbage (47). The wild bean *Phaseolus lunatus* contains about 3 times as many cyanogenic glucosides as does the cultivated bean (48). Similar reductions in toxicity through agriculture have been reported in lettuce, lima bean, mango, and cassava (49).

One consequence of disproportionate concern about synthetic pesticide residues is that plant breeders are developing plants that are more insect-resistant but that are also higher in natural toxins. Two recent cases illustrate the potential hazards of this approach to pest control. (*i*) When a major grower introduced a new variety of highly insect-resistant celery into commerce, a flurry of complaints were made to the Centers of Disease Control from all over the country because people who handled the celery developed rashes and burns 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 (6, 50–52). It is not known whether other natural pesticides in the celery were increased as well. The celery is still on the market. (*ii*) A new potato cultivar, developed at a cost of millions of dollars, had to be withdrawn from the market because of its acute toxicity to humans—a consequence of higher levels of two natural toxins, solanine and chaconine. Solanine and chaconine inhibit cholinesterase, thereby blocking nerve transmission, and are known rodent teratogens. They were widely introduced into the world diet about 400 years ago with the dissemination of the potato from the Andes. Total toxins are present in normal potatoes at a level of 15 mg per 200-g potato (75 ppm), which is less than a 10-fold safety margin from the measurably toxic, daily dose level for humans (45). Neither solanine nor chaconine has been tested for carcinogenicity. In contrast, the cholinesterase inhibitor malathion, the main synthetic organophosphate pesticide residue in our diet (0.006 mg per day), has been tested and is not a carcinogen in rats or mice. Common cultivars of plants differ widely in the level of particular natural toxins (6), and other factors in the plant also play a part in pest resistance. Breeding or genetic engineering can be used to increase or decrease specific chemicals or other factors.

Certain cultivated crops have become popular in developing countries because they thrive without costly synthetic pesticides. However, the trade-offs of cultivating some of these naturally pest-resistant crops are that they are highly toxic and require extensive processing to detoxify them. For example, cassava root, a major food crop in Africa and South America, is quite resistant to pests and disease; however,it contains cyanide at such high levels that only a laborious process of washing, grinding, fermenting, and heating can make it edible; ataxia due to chronic cyanide poisoning is endemic in many of the cassava-eating areas of Africa (53). In one part of India, the pest-resistant grain *Lathyrus sativus* is cultivated to make some types of dahl. Its seeds contain the neurotoxin β-*N*-oxalylaminoalanine, which causes a crippling nervous system disorder, neurolathyrism (54).

There is a tendency for nonscientists to think of *chemicals* as being only synthetic and to characterize synthetic chemicals as toxic, as if every natural chemical were not also toxic at some dose. Even a recent National Research Council report (55) states: "Advances in classical plant breeding . . . offer some promise for nonchemical pest control in the future. Nonchemical approaches will be encouraged by tolerance revocations. . . ." The report was concerned with pesticide residues but ignored natural pesticides. Tomatine, one of the natural toxins in tomatoes, is a recent chemical too, since it was introduced to the world diet from Peru 400 years ago. Neither tomatine nor its aglycone, tomatidine, an antifungal steroid-like molecule, has been tested in rodent cancer bioassays. Tomatine is present at 36 mg per 100-g tomato (360 ppm), a concentration that is much closer to the acutely toxic level in humans than are synthetic pesticide residues (45).

As an alternative to synthetic pesticides, it is legal for "organic farmers" to use the natural pesticides from one plant species against pests that attack a different plant species, e.g., rotenone (which Indians used to poison fish) or the pyrethrins from chrysanthemum plants. These naturally derived pesticides have not been tested as extensively for carcinogenicity (rotenone is negative, however), mutagenicity, or teratogenicity as have synthetic pesticides; therefore, their safety compared to synthetically derived pesticides should not be prematurely assumed.

Synthetic pesticides have markedly lowered the cost of plant food, thus increasing consumption. Eating more fruits and vegetables and less fat may be the best way to lower risks of cancer and heart disease, other than giving up smoking (35, 56, 57).

"Toxic Chemicals" and Human Risk

Positive results are remarkably common in high-dose screening tests for carcinogens, clastogens (agents that break chromosomes), teratogens, and mutagens. About half of the chemicals tested, whether natural or synthetic, are carcinogens in chronic, high-dose rodent tests (5, 6) and about half are clastogens in tissue culture tests (18). A high proportion of positives is also reported for rodent teratogenicity tests: 38% of the 2800 chemicals tested in laboratory animals "have been teratogenic" in the standard, high-dose protocol (58). It is therefore reasonable to assume that a sizeable percentage of both synthetic and natural chemicals will be reproductive toxins at high doses. Mutagens may also be common: of the 340 chemicals tested for carcinogenicity in both rats and mice and for mutagenicity in *Salmonella* (ref. 59; L.S.G., unpub-

lished work), 46% were mutagens, and mutagens were nearly twice as likely to be carcinogenic than were nonmutagens. Of these 340 chemicals, 70% were either mutagens or carcinogens or both. How much this high frequency of positive results is due to bias in selecting chemicals is not known (5). Even if selection bias doubled the percentage of positives, which we think is unlikely (5), the high proportion of positives would still mean that almost everything natural we eat contains carcinogens, mutagens, teratogens, and clastogens (6). Thus, testing a random group of natural pesticides and pyrolysis products from cooking should be a high priority for these various tests so that an adequate comparison can be made to synthetic toxins.

Dozens of mammalian metabolites are commonly produced from any reasonably complex molecule. Therefore, even nonmutagenic, nonclastogenic, noncarcinogenic, and nonteratogenic chemicals, whether synthetic or natural, are likely to produce some carcinogenic, clastogenic, teratogenic, and mutagenic mammalian metabolites.

Several chemicals that have been shown to be carcinogens at high doses in rodents have also been shown to be anticarcinogens in other animal models at lower doses—e.g., limonene, caffeic acid, TCDD, and IC (28, 29). Therefore, the dose and context of a chemical exposure may be critical.

The first rule of toxicology is that all chemicals are "toxic chemicals;" it is the dose that makes the poison. High-dose tests are relevant for some occupational or medicinal exposures that can be at high doses (2, 60). With mutagens there is some theoretical justification for thinking that low doses may have an effect, although the complexities of inducible protection systems may well produce a dose–response threshold, or even protective effects at very low doses. The high endogenous DNA damage rate is also relevant (5). In any case, there should be a threshold of attention for hypothetical risks that are low compared to background risks, otherwise resources are diverted from more important risks. The arguments in this and the preceding papers (5, 6) undermine many assumptions of current regulatory policy and necessitate a rethinking of policy designed to reduce human cancer. Minimizing pollution is a separate issue and is clearly desirable for reasons other than effects on public health.

It is by no means clear that many significant risk factors for human cancer will be single chemicals that will be discovered by screening assays. Dietary imbalances are likely to be a major contributor to human cancer (43, 56, 57) and understanding these should be, but is not, a major priority of research. Understanding why caloric restriction dramatically lowers cancer and mitogenesis rates and extends life-span in experimental animals (61, 62) should also be a major research priority. More studies on mechanisms of carcinogenesis are also a high priority.

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