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Current Comments

Risk Analysis, Part 2. How We Evaluate the Health Risks of Toxic Substances in the Environment

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Almost every aspect of modern living exposes us to health risks. The air we breathe, the food we eat, the water we drink, the drugs we take, and the places where we work may be contaminated by toxic substances or additives. This is in addition to natural carcinogens, such as sunshine, and habits such as smoking, or the way our food is cooked. Their effects on our health may not be noticed until 20 or 30 years after exposure. These effects may include cancer and organ damage of one kind or another. Other unfortunate effects are suffered by future generations—genetic mutations, birth defects, inherited diseases, and so on. This tragic loss and impairment of life could be prevented or significantly reduced by identifying and regulating substances in the environment that pose risks to human health.

In the first part of this essay, I introduced the topic of risk analysis.[1] Risk analysis is a relatively new research specialty. Its objective is the estimation of potential consequences from exposure to various hazards, such as nuclear reactor accidents. This part is devoted to risk analyses of exposure to toxic substances—carcinogens, mutagens, teratogens, and so on. These include a large variety of natural and synthetic chemicals and pharmaceuticals, as well as various pollutants in the environment.

It should be noted here that many researchers feel there is a bias toward identifying cancer risks while other health risks are given a lower priority.[2,3] T. Colin Campbell, Cornell University, Ithaca, New York, says there is a "disproportionate effort given to the evaluation of chemical carcinogens" even though "a vast diversity of chemical toxicities is possible."[4] Other important health risks include black lung, brown lung, asbestosis, cardiac disease, congenital abnormalities, infertility, and so on. Ralph E. Yodaiken, National Institute for Occupational Safety and Health, Rockville, Maryland, says, "These diseases and many others should command as much attention as cancer."[3] However, cancer risks now occupy center stage[3,4] because of "the rapid rate at which we are detecting carcinogens in our environment, coupled with increased consumer awareness, indeed a fear of cancer," according to I.C. Munro and D.R. Krewski, Health and Welfare Canada, Ontario.[2] This essay will reflect the risk assessment community's focus on cancer, but you should keep in mind that other significant health risks are involved in our exposure to toxic substances.

Bruce Ames, University of California, Berkeley, says there is a critical need today for quantitative risk analyses of the large number of man-made and natural toxic substances in order to set priorities. Each year about 1,000 new chemicals are released for commercial use.[5] This is in addition to more than 70,000 man-made chemicals already being used.[6] Also, most people do not realize there is a tremendous amount and variety of toxic chemicals in our foods. These include natural defense chemicals from plants and carcinogens and mutagens made when cooking food.[5,7,8] Only a small fraction of these

substances have been screened for human health risks. Many people will already have been affected by the time certain carcinogens and mutagens are identified. Even after the significant man-made carcinogens are banned, a few of them might have already accumulated in human body fat and mother's milk—they possibly could still pose a risk to health.[5]

Over the past 60 years, the US Congress has passed many acts mandating the careful scrutiny of potentially toxic substances. The Clean Air Act; Clean Water Act; Toxic Substances Control Act; Consumer Product Safety Act; and Food, Drug, and Cosmetics Act are only a few examples. A number of federal agencies were also established to monitor the public's exposure to toxic substances and to set safety standards—Environmental Protection Agency, Food and Drug Administration, Occupational Health and Safety Administration, and Consumer Product Safety Commission are among the better known. Today, pharmaceutical companies spend over half their research budgets on tests to meet government toxicity standards. The chemical industry devotes about a fourth of its research and development costs to this end.[9]

The traditional method for analyzing human risks of cancer and genetic mutation is to expose animals to toxic chemicals and pollutants.[10] In these bioassays, rodents are exposed to various dose levels of a toxic agent. The highest dose is called the "maximum tolerated dose" (MTD). The MTD is the largest amount of the substance that can be fed or injected into rodents without causing more than ten percent weight loss, death by poisoning, or clinical side effects unrelated to cancer or genetic mutation.

The animals are observed until they die spontaneously or are sacrificed. They then undergo extensive autopsies in which organs, tissues, and cells are scrutinized for tumors, lesions, and genetic mutations. The results are compared with those of autopsies on a "control" group of rodents that haven't been exposed to the substance. If the number of tumors in the exposed group is significantly higher than in the control group, the substance is considered a carcinogen.[10]

A common criticism of this method of risk analysis is that the doses given to test animals are many times higher than the levels at which humans are exposed to the substance in the environment.[11] Artificially high doses are necessary because the number of animals in the most thorough bioassay is small compared to the human population at risk—usually, only about 200 rodents are tested.[5] If lower doses were used on this small sample of rodents, the carcinogenic effects of a toxic substance might escape detection.

However, artificially high doses may interfere with the body's natural ability to neutralize and excrete toxic substances before cancer has a chance to start. Robert Neal, Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina, explains that the human body has a number of "normal repair mechanisms, metabolic mechanisms for inactivation, and barriers to penetration of a chemical to a target site which would not allow the compound to exert its toxic effect."[12] Thus, Richard Peto, Radcliffe Infirmary, Oxford, UK, suggests, "If we want to understand the effects of...chronic low exposure in humans, then study of the effects of acute high exposure is a really bad model."[13]

Researchers are trying to overcome this problem by developing mathematical models that predict human risk at low exposure based on results from high dose animal bioassays. Unfortunately, we still don't know enough about cancer to confidently decide which model is most appropriate. Robert Squire, Johns Hopkins University, explains: "The reason we are struggling in this area is that mechanisms of carcinogenesis remain obscure. We simply do not know what the biological events or risks are at low level exposures to carcinogens where most human exposure occurs...and we

do not know which model is best, or even if *any* come close to reflecting the actual biological process."[11]

Another area of controversy is whether a substance that causes cancers or genetic mutations in rodents will also be carcinogenic or mutagenic in humans. That is, rodent cells may be more or less sensitive to toxic substances than human cells. Squire points out: "Certain committees and individuals have...expressed the view that humans are generally more susceptible than the test animals.... Inasmuch as humans live longer, potential exposure, and thus cancer risk, is assumed to be greater than observed in test animals."[11] Peto comes to an opposite conclusion—mouse cells may be more sensitive than human cells. After correcting for differences in body mass and life span, Peto calculates that mouse cells could be a billion times more sensitive to carcinogens than human cells.[13]

There are also practical reasons why animal bioassays may be inadequate as a screening method for cancer and genetic mutation risks—time and expense. Testing one chemical costs about $300,000 and takes two or three years.[6] It would be very expensive and time-consuming to test even a fraction of the 1,000 new chemicals introduced each year, not to mention the 70,000 commercial chemicals already in use. Alternative methods that are more economical and rapid than animal bioassays have been developed over the last ten years. For example, more than 100 short-term tests for chemical carcinogens and mutagens were reviewed by Monica Hollstein and Joyce McCann, University of California, Berkeley, and colleagues in *Mutation Research*.[6]

The Ames test has become the most used short-term test for screening chemical mutagens, according to Claes Ramel and Ulf Rannug, University of Stockholm, Sweden.[14] Ames developed the test in 1973 with collaborators at the University of California, Berkeley.[15,16] The test takes only two or three days to complete, at a cost of a few hundred dollars. One person could test several compounds a day.[17] More than 5,000 chemicals already have been tested since the Ames test was introduced ten years ago.

The Ames test uses bacteria instead of animals as subjects for exposure to toxic chemicals. It tests for mutagenicity—that is, the ability to mutate bacterial genes. Of course, carcinogenic effects—tumors or lesions—can't be observed in bacteria. But Ramel and Rannug cite "a wealth of data" and "experimental evidence" showing that both carcinogens and mutagens alter DNA. They conclude, "Most and possibly all carcinogens also act as mutagens."[14] Thus, the Ames test appears to be an inexpensive, rapid, sensitive indicator of a toxic substance's cancer and genetic mutation risks.[5,16,18]

In the Ames test, four strains of *Salmonella* bacteria are used. All have been genetically engineered to be unable to grow unless a particular amino acid, histidine, is in their diets, or "growth medium." The bacteria are mixed with the chemical and poured onto a petri dish. If necessary, a liver homogenate is also added. The liver homogenate provides important enzymes which, in mammals, "biotransform" chemicals into carcinogens. Many environmental chemicals are not carcinogenic *per se* until they are "activated" in the liver. After incubation, the number of "revertant colonies" growing on the dish are counted and compared to a control plate without the toxic substance. The revertant bacteria thrive without histidine in their diet—that is, they are *re*mutated into normal bacteria by the toxic substance. The substance is rated as a strong or weak mutagen according to the dose required to mutate the bacteria.[6,14-16]

One of the major uses of the Ames test has been to isolate and characterize mutagens from complex mixtures. A number of chemicals isolated as mutagens from cooked proteins were later shown to be carcinogens, for example.[7] Another major use of the Ames test, and

other short-term tests, has been as an early screen for chemicals under development, and almost all of the chemical and drug companies were quick to adopt them.[5,18]

The basis of the Ames test is that DNA is made of the same components in all living things.[14] Thus, mutagens, or substances damaging DNA, can be detected in any organism. A possible shortcoming of the Ames test, and some other short-term tests, is that bacteria are not identical to mammals in the organization of the genetic material. Bacteria are procaryotes—cells without a nucleus containing the genetic material. Mammalian cells are eucaryotes—their genetic material is doubly protected by the nuclear membrane. Ramel and Rannug add, "The genetic material is organized as distinct chromosomes, which contain proteins and have far more complicated structures than the...bacterial genetic material."[14] Thus, short-term tests using bacteria could miss chemicals that affect higher genetic structures, such as chromosomes.

Ames acknowledges that the *Salmonella* test misses some important classes of carcinogens.[18] Ames suggests using a combination of short-term tests that, as a group, would detect carcinogens and mutagens that single tests might miss: "Positive results from a battery of these short-term test systems are meaningful; these systems, as well as complementing animal cancer tests, provide useful toxicological information...."[5]

Short-term mutagenicity tests, like the Ames test, are also criticized for "optimizing all the factors leading to mutagenicity."[14] For example, the bacteria's ability to repair their DNA is modified by genetic engineering in the Ames test.[6] Another feature of the test makes it easier for molecules of a toxic substance to penetrate the barrier protecting the bacteria's DNA.[6] Thus, short-term mutagenicity tests may be "overpessimistic"[14] in their estimation of a chemical's risk to humans. Nevertheless, the Ames test is a reliable indicator of toxicity. It showed positive results on about 83 percent of chemicals that cause cancer in humans and animals.[18] Just as important, it showed negative results on chemicals that *don't* cause cancer.[6]

The Ames test is an economical and rapid method for ranking thousands of chemicals according to their potential risk to humans. Ames recommends that "chemicals to which humans are exposed which are clearly positive in the test should be considered potential human health hazards, and should be thoroughly tested in animal systems, and where extensive human exposure has occurred, appropriate epidemiologic studies should be done."[17]

Of course, epidemiologic surveys are the surest way to assess the human risk from toxic substances. Epidemiologists analyze the incidence of death and disease in humans, not rodents or bacteria. And they can directly relate this to actual levels of exposure in humans. Thus, risk assessments based on epidemiologic studies avoid the uncertainty of extrapolating from one species to another, or from an extremely high to a low level of exposure.[19]

The earliest study that identified an occupational cancer risk was done by Percival Pott in 1775. He examined British chimney sweeps and was able to establish a correlation between chimney soot and scrotum cancer. Pott's report is reproduced in *Some Classics of Experimental Oncology*,[20] papers in cancer research selected by my old friend Michael Shimkin, University of California, San Diego. This book is a useful companion to Shimkin's comprehensive study on the development of cancer research from 500 BC to the present.[21]

Unfortunately, epidemiology identifies health risks *after* humans have been exposed to toxic agents. Remember that tumors and birth defects occur 20 or 30 years after exposure to a carcinogen or mutagen. Richard Doll, Imperial Cancer Research Fund, UK, and Peto explain, "By the time effects are clearly evident to the epidemiologist, irreversible damage may have been done to large numbers of people, so that even

after exposure is recognized and stopped cancers may continue to occur for many years."[19] Epidemiology is not a useful method in risk analyses of toxic agents—the point is to identify health risks *before* the public is exposed.

But epidemiology is a valuable tool for pinpointing cancers that have avoidable causes. In a monumental study, Doll and Peto classified environmental and life-style factors that contribute to cancer in 12 general categories—industrial products, pollution, food additives, tobacco, alcohol, diet, and so on.[19] They examined the incidence in men and women of about 40 types of cancers that could be attributed to factors within the 12 categories. They then estimated the proportion of US cancer deaths in 1978 that could have been avoided if the environmental or life-style factors were avoided.

For example, Doll and Peto state that 155,000 deaths from respiratory, upper digestive, bladder, and pancreatic cancers were recorded in the US in 1978. Epidemiologic evidence suggests that smoking is a major cause of these four types of cancer. By examining the incidence of these cancers among nonsmokers, they estimated that only about 40,000 deaths are "attributable to these four types of cancer in 1978 if no American had ever smoked."[19] The difference—115,000—was considered as cancer deaths caused by smoking. Thus, smoking was responsible for about 30 percent of the 402,000 cancer deaths in the US in 1978.

This study presents an interesting perspective on human risks from various chemical pollutants and additives. The combined effects of food additives, occupational exposure to toxic agents, air and water pollution, and industrial products accounted for only seven percent of 1978 US cancer deaths. Even if we were successful in removing all pollutants and additives in the air, water, food, and workplace, the resulting decrease in cancer mortality would be small. Of course, even this small percentage represents a significant number of human lives. But the combined effects of alcohol, diet, and smoking are related to *70 percent* of US cancer deaths. These are patterns of exposure over which we have considerable personal control, yet we choose not to avoid them.

Government regulatory agencies should give a high priority to informing the public about what they can do to break their fatal habits. They should give even higher priority to educating children about dietary, alcohol, and smoking risks *before* they acquire the bad habits of their parents. There is no question that we should continue to screen new chemicals and pharmaceuticals for potential cancer risks before they are released on the market or in the workplace. But it becomes absurd to invest billions of dollars in tests that identify toxic agents in the environment that cause only a small proportion of annual fatalities. A much smaller expenditure on education and public awareness programs could have a significant impact on cancer fatality rates. Of course, this also depends on the public's compliance with the medical profession's recommendations. I'll discuss patient compliance in an upcoming essay.

An important part of risk analysis is concerned with determining how the public perceives risks to human health. In the first part of this essay,[1] I discussed several studies by Baruch Fischhoff and colleagues, Decision Research, Eugene, Oregon. They studied people's subjective ratings of various risky activities and technologies.[22,23] They found that laypeople don't tend to rate risks in terms of the number of annual fatalities they cause. Instead, laypeople regard as risky any activity or technology that is new, imposed on them, beyond their control, or unfamiliar. Thus, activities such as diet, smoking, and alcohol consumption, which are voluntary and familiar, may be *perceived* as being less risky than involuntary exposure to unfamiliar pollutants and additives in food, air, water, and the workplace. People may simply not be impressed that these "less risky" activities actually account for

Table 1: 1981 *ISI/BIOMED*™ research fronts relevant to cancer risk analysis of toxic substances. Numbers in parentheses refer to core/citing papers in each research front.

Code Number	Research Front Name
81-0273	Effect of diet on colon cancer (9/125)
81-0505	Oral contraceptives associated with liver cancer (6/63)
81-1090	Influence of dietary fat on the incidence of mammary tumors (4/44)
81-1112	Carcinogenicity of chromium, nickel, cadmium, and their salts (12/105)
81-1370	Vinyl-chloride and carcinogenesis (3/45)
81-1547	Asbestos-related tumors (4/56)
81-2081	Lung cancer, heart disease and cigarette smoking (2/32)
81-2239	Benzopyrene metabolism and other polycyclic aromatic carcinogens (2/98)
81-2361	Chemical carcinogenesis and human cells (2/35)
81-2379	Cancer and cholesterol (4/50)

Table 2: 1981 *ISI/BIOMED*™ research fronts relevant to genetic mutation risk analysis of toxic substances. Numbers in parentheses refer to core/citing papers in each research front.

Code Number	Research Front Name
81-0469	Mutagenesis in mammalian cells (3/38)
81-1296	Mutagens of cooked meat and cooked fish (3/39)
81-2381	Mutagens resulting from pyrolysis of proteins (4/53)
81-2460	DNA damage caused by mutagens (2/63)
81-2748	Teratogenicity and mutagenicity of cyclophosphamide and cytochalasin-D (2/24)
81-2849	Mutagenicity of nitrated polycyclic aromatic hydrocarbons in bacteria (5/81)

Table 3: 1981 *ISI/BIOMED*™ research fronts relevant to various health risk analyses of toxic substances. Numbers in parentheses refer to core/citing papers in each research front.

Code Number	Research Front Name
81-0515	Renal toxicity of lithium (11/107)
81-0836	Hepatotoxicity of acetaminophen (11/163)
81-1275	Effects of saccharin on urinary bladder (2/39)
81-2272	Oral contraceptives and cardiovascular disease (4/67)
81-2462	Effects of lead and cadmium on immune response (2/24)
81-2472	Cardiovascular effects of ethanol (2/28)
81-2595	Pulmonary toxicity in chemotherapy (3/38)
81-2700	Ethanol enhancement of drug toxicity (2/35)
81-2997	Biological effects of lead exposure (2/29)

about ten times the number of deaths from exposure to toxic chemicals. Chauncey Starr, Electric Power Research Institute, Palo Alto, California, believes that "the public is willing to accept 'voluntary' risks roughly 1000 times greater than 'involuntary' risks."[24]

As I noted earlier, risk analysis is a relatively new research area. We can expect its theories and methods to improve as we gain more experience with epidemiologic surveys, short-term tests, and animal bioassays. Significant advances in risk analysis will be made when we know more about the mechanisms of carcinogenesis, mutagenesis, and teratogenesis. Perhaps the most significant advances will be made when we find out how to motivate people to avoid voluntary exposure to high risk life-style activities, such as smoking, alcohol abuse, and poor diet. Much research in many fields is currently devoted to solving these problems.

ISI®'s data bases help to identify research that is relevant to the concerns of the multidisciplinary risk analysis community. Our research front specialty searches are a particularly effective way to retrieve research in a new specialty, such as risk analysis. We identified several research fronts in our *ISI/BIOMED*™ data base that deal with topics generally related to risk analysis of toxic substances. Table 1 lists some of the *ISI/BIOMED* research fronts on cancer risks from toxic substances, and Table 2 includes a few on genetic mutation risks. Table 3 shows several research fronts covering various risks, including damage

to the liver, lungs, heart, and bladder. The numbers in parentheses in these tables refer to how many core/citing papers are included in each research front. For a complete list of research fronts, readers should refer to the *Index to Research Fronts in ISI/BIOMED™ 1982*.[25]

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