Sanity in Research and Evaluation of Environmental Health

How to achieve a realistic evaluation (in seven commandments).

H. E. Stokinger

Early in 1969, before the methyl mercury story broke into headlines, I presented a Cummings Memorial Lecture titled, "The Spectre of Today's Environmental Pollution—U.S.A. Brand —New Perspectives from on Old Scout" (*1*). I attempted a sane and realistic, comprehensive toxicologic evaluation of the potential hazards to human health from man-made and natural environmental pollutants (except radiation) in air, water, and food, based on their occurrence in the continental United States then and in the foreseeable future. The evaluation was made on a "before and after" consideration of all those substances about which health-oriented groups had expressed concern. After a considered appraisal of the available facts, I judged the validity of the concern for each individual pollutant.

Of 18 major pollutants or groups of pollutants from all sources (air, water, and food) combined, only eight were reevaluated as potentially hazardous, and not all of these with the same degree of certainty. There was no question, for example, of the deleterious effects of environmental nitrates (and nitrites) on infants and on genetically hypersusceptible Alaskan Eskimos and Indians, but the hazards to public health of "hard" water constituents, while suggestive, were far from proven. Respiratory irritants (particularly oxidants) and carcinogens from all three environmental sources, either alone or in combination with respiratory irritants, headed the list as pollutants of primary concern; yet pesticides of all types, as well as teratogens and mutagens, as found in the three environmental sources, were conspicuously absent from the list. Asthmagens were not absent.

What has the record shown since? The pesticide DDT [1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane] and the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) were, on first action, banned from further use, as were all uses of organic mercurials as pesticides. Swordfish has been removed from sale, although people may still eat fish, just as they have since before the time of Christ (*2*). Cyclamates have gone, and monosodium glutamate is on its way out. Nitrilotriacetic acid (NTA), the soap industry's dream substitute for the polyphosphates that the industry itself banned from laundry detergents, was summarily prohibited on fragile and provocative evidence (*3*). Detergent enzymes appear to be on their way out. Potato chips may be next because of their increased solanin content, caused by dehydration of hot fat.

What next? If man is prohibited from consuming foodstuffs because of their content of natural toxins, where will it end? Honey contains the potent grayanotoxins (given intraperitoneally, a dose lethal to 50 percent of the animals tested is approximately 1 milligram per kilogram) (*4*). German raisins have been found to be teratogenic (*5*), while caffeine (*6*) and tannin are tumorigenic (*7*); nutmeg, parsley, and dill are highly toxic because of their myristicin and apiole contents (*8*). Vitamin C has produced tumors in mice (*9*).

The author is chairman of the Threshold Limits Committee of the American Conference of Governmental Industrial Hygienists, chairman of the Subcommittee on Toxicology of the Public Health Service Drinking Water Standards, and chairman of the National Research Council's Committee on Toxicology. He is also chief of the Laboratory of Toxicology and Pathology in the National Institute for Occupational Safety and Health, U.S. Department of Health, Education, and Welfare, Cincinnati, Ohio 45202.

The following rules, if followed, should go far in improving the criteria and standards for judging environmental pollution, as well as making them less worrisome to those who are being protected and more acceptable to those who must comply.

Commandment 1

Standards must be based on scientific facts, realistically derived, and not on political feasibility, expedience, emotion of the moment, or unsupported information. If necessary data are not available, studies should be made to supply them. Meanwhile, provisional, tentative, or best judgment standards, clearly marked and recognized as such, should be proposed, but only upon definite need. If the need is not there, it is better to withhold until such time as the facts are in.

This commandment poses relatively few difficulties for drinking water standards. Based on the accepted average daily intake of 2 liters per person (in the United States), and primarily on human health or esthetic considerations, standards have been and can be determined reasonably well. For toxic food contaminants, the problems are more numerous but not unresolvable. In this case, because of widely varied eating habits, realistic evaluation of the facts (generally derived from animals) requires more erring on the side of common sense than on the side of the overprotection complex that seems to have captivated the thinking of those committed to setting tolerances. In the case of air pollutants, scientific facts for each of the multiple criteria (for example, human health, nuisance, crop and vegetation damage, surface erosion, and soiling) must be carefully developed and painstakingly assessed before air quality standards are proposed and decisions are made about which of the multiple criteria the standards rest on.

In selecting criteria on which to base standards for the prevention of diseases caused by more than one factor, the temptation to ascribe an effect of questionable significance and doubtful connection to a pollutant, merely because that pollutant was selected for investigation, must not be yielded to. All too often in the past this commandment has not been followed, particularly in those cases in which a disease entity was not sharply defined or when there was a paucity of data on it.

Further compounding the difficulties of arriving at scientifically based standards is the modish procedure of "consensus" standards, in which individuals from all walks of life have their say through public hearings, citizens' advisory committees, and Senate investigating committees. But when all the statements have been heard and judgments and opinions sifted, the tenets of commandment 1 should prevail, with the added proviso of commandment 2.

Commandment 2

All standards, guides, limits, and so on, as well as the criteria on which they are based, must be completely documented. In such documentation it must be made emphatically clear on what basis a given standard rests. This must not only be done in a formal, written document, but in the press and other forms of news media as well, thus preventing the public from becoming unnecessarily or unduly alarmed. For example, in all the public announcements of the banning of DDT, it was never made clear that it was not for protecting human health, but for protecting such endangered species as osprey, bald eagle, and other fowl. Similarly, in the confiscation of canned tuna in 1970, no effort was made to evaluate for the public the degree of hazard or the margin of safety in eating the fish. Positive assurance should be given those with the highest fish intake (those on prescribed tuna diets for reducing) that, for a given intake, there is a given margin of safety (*10*).

Similar clear and properly phrased disclosures should be made for the bases of air quality criteria and standards. Most criteria and proposed standards that have been developed thus far tend to be misleading either (i) through juxtaposing statements [first by stating what exposure at unrealistically high levels can do to human health, directly followed by the proposed standard at an unrelated, extremely low level (*11*), when in reality it is corrosion, plant damage, or something else on which the standard rests], or (ii) through assessing the data that comprise the criteria with unwarranted bias, a practice which can lead to needlessly overprotective levels (*12*). This is not to infer that the levels are incorrect on a "consensus" basis, but that they have been erroneously depicted.

Commandment 3

Avoid the establishment of unnecessarily severe standards. This admonishment runs against the current tide of boiling popular enthusiasm for cleaning pollution up completely. But it is time that popular enthusiasm cool down, to recognize the consequences of establishing goals instead of standards. The following instances illustate and support my stand.

The townspeople of Fallon, Nevada, as well as residents on a nearby Navy base, were gravely concerned for their health when on 16 February 1969 the state's health officer informed the mayor that Fallon's water supply (which is exclusively well water) has consistently contained levels of arsenic in excess of 0.05 milligram per liter, which is considered the "mandatory" limit by the United States Public Health Service. Analyses of the well waters in the area for arsenic confirmed this statement. Depending on the season, concentrations of arsenic ranged from 0.05 to 0.22 milligram per liter, from June 1963 to June 1968. Despite a survey by the county medical society and the mayor's subsequent statement that the town's population had been drinking the water for 28 years without any known cases of arsenic poisoning; despite the fact that some of the people concerned were over 70 years of age; and despite the Attorney General's ruling, after public hearings with expert testimony, that there is no evidence that the drinking water of Fallon is harmful (a finding in consonance with that of the National Research Council's Committee on Toxicology, which conducted a study at the request of the Navy's Bureau of Medicine and Surgery), the townspeople are still worried, and the health officer is working elsewhere. All of this could have been avoided had the drinking water standard been set more appropriately at 0.2 milligram per liter (*13*).

A similar unpleasant situation could have been avoided in the Coho salmon–DDT episode had the tolerance limit of DDT in fish been set at 20 parts per million instead of 5. There is evidence that human intakes of DDT in far greater quantities than 20 parts per million were entirely safe and that the tolerance limit of 5 parts per million is unnecessary severe (*14*).

To an even greater degree, unnecessarily severe standards for air pollutants should be avoided, especially those standards not strictly related to health, for example particulates and sulfur dioxide. Here, the result of almost total elimination is either tremendous and disproportionate costs to industry (costs that are ultimately passed on to the public) or the shutting down of industries, with the resulting loss of personal and state income.

Clearly, the establishment of unnecessarily severe standards for all types of pollutants must be avoided—for a number of good and sufficient reasons; otherwise, their repercussions will be felt in a variety of undesirable ways.

Commandment 4

Determine realistic levels. What is realistic may be defined for each pollutant type (air, water, and food) as follows. For air, tested levels (dosages) should bracket the national average concentration of a particular pollutant in urban air by at least one logarithmic decrement and two logarithmic increments. Tested levels for water pollutants should similarly bracket the national average for the particular pollutant found in surface waters. In like manner for food contaminants, the focal point for bracketing in this instance being the intended level of addition; or, when naturally occurring or environmentally imposed, the span of tested dosages should embrace three logarithmic increments.

Establishing dosage-response relationships in this manner provides three determinants critical to the setting of realistic permissible limits or standards: a "no-effect," a borderline, and a "frank-effect" level. From these determinants, a permissible limit can be selected at some point below the no-effect level. A known safety factor, the magnitude of which would be commensurate with the seriousness of the response, can be incorporated in this limit.

To what extent have efforts to date met these minimal requirements? Examination of the criteria used for developing guides and standards in all three areas reveals that they have rarely conformed. Haste to "put a number on it" (*15*) has resulted in criteria developed by heavy-handed, opportunistic toxicologists driven by a "look what I found" attitude, and acceptance of weak, or even questionably related, information by harried standard-setters grasping at straws under legal pressure to comply with an unreasonable deadline. Current instances abound in all three areas of

pollution. For air, criteria have been accepted for some of the more common urban pollutants on evidence no stronger than a highly questionable statistical association—where adverse effects on health were "possibly related" to the pollutant investigated. [For water, see (*3*).] In the case of food, low-protein diets, or better, diets devoid of protein, resulted in the greatly increased lethality of several pesticides for rats (*16*). However, companion studies for effects under realistic environmental conditions were not performed; nor has anyone considered the question of how human beings on such a diet would be exposed to significant levels of pesticides.

Clearly, nothing short of determining complete dosage-response relationships is acceptable, if solid, unassailable criteria are to be provided. No purposeful evaluation can be made by determining such relationships from a single point.

Along the lines of appropriate data-gathering, two ancillary commandments, applying chiefly to epidemiologic studies, should be heeded: (i) study hypersusceptible populations, and (ii) make repeated samplings.

It becomes obvious upon slight reflection that, in assessing the effects that extremely low levels of pollutants have on human populations, a far greater chance of success is assured by studying the most susceptible populations. Such a procedure avoids the "diluting" effect of a random sample. For example, a study of the effects of air pollutants that irritate the respiratory system should single out asthmatics, people with a hereditary deficiency of antitrypsin serum (candidates for hereditary pulmonary emphysema) (*17*), and people with a deficiency of leukocytic enzymes (candidates for chronic granulomatous disease) (*18*). Such groups are now readily identified by simple blood tests —a deficiency of serum antitrypsin by the procedure of James *et al.* (*19*), and a deficiency of leukocytic enzymes by Schlegel and Bellanti (*20*). This is so obvious a procedure for increasing the sensitivity of epidemiologic investigations that it is surprising that greater use has not been made of it (*21*). The procedure is applicable to other types of pollutants as well. For example, hypersusceptibility to waterborne nitrate, a condition caused by hereditary methemoglobinemia (in Alaskan Eskimos and Indians), may be identified by a test for methemoglobin: nicotinamide adenine dinucelotide oxidoreductase (*22*).

One of the most serious deficiencies in the use of the epidemiologic method is the complete lack of repeated sampling of the population under study. Far-reaching conclusions on the health hazards of pollutants have invariably been based on the analysis of one sample taken at one time. Daily variations in personal habits of eating, drinking, and sleeping, as well as environmental variations in temperature and humidity, which influence not only the duration and intensity of exposure but also the metabolism of the pollutant, can result in great circadian variations in the same individual from day to day. Obviously, only repeated samplings can provide a reliable estimate of an individual's response to a particular pollutant.

Commandment 5

Interpret the "Delaney clause" with informed scientific judgment. This much-maligned clause has become an excuse for oncologists to use inappropriate and unrealistically high levels in testing for carcinogenic potential. Why this approach has been used so uniformly and without exception since the law's enactment in 1958 in difficult to understand. The Delaney clause (*23*) reads: "That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, *after tests which are appropriate for the evaluation* [italics added] . . . ." A review of the data purporting to demonstrate carcinogenicity shows complete disregard for the qualifying clause relating to appropriateness. Why?

Commandment 6

Determine trends, not pro tempore monitoring. To take official action to ban distribution and consumption of industrial commodities on the basis of newly discovered environmental levels without the perspective afforded by comparison with past levels in the environment, is to put unbridled enthusiasm for environmental control ahead of common sense. The most flagrant violations of this commandment are the previously noted recommendations that tuna and swordfish be confiscated or denied access to the family dining table. One moment's reflection would reveal that the concentration of mercury in the oceans has not changed perceptibly since the white men reached these shores, and that men have eaten these fish and lived and died without signs or symptoms of mercury poisoning. This is not to say that local, aqueous mercury or other excess pollutants should not be spotted and, when possible, controlled, but that the thoughtless and irrational extension of a local finding to global dimensions is inconceivable in persons of sound mind (*24*).

Accordingly, investigators should determine trends before summoning the news media, in order that they may present the current picture fairly in relation to the past.

Commandment 7

Delimit banning. With the reexamination of the list of foods generally regarded as safe (*25*) by the National Research Council's Food Protection Committee has come a succession of bannings of long-used food additives, coumarin (vanilla flavor), safrole (root-beer flavor), red and yellow food colorings derived from coal tar products, and cyclamates. These compulsory actions on food additives are now setting a pattern for banning industrial chemicals, but for entirely different reasons. The banned food additives were either unnecessary or could be readily substituted with less harmful substances. Not so the totally banned DDT and alkyl mercury compounds. First, DDT does not present an "imminent hazard" to public health, despite misstatements to the contrary; second, its use for controlling the spread of malaria and African trypanosomiasis is unexcelled, and equivalent substitutes are not available at this time (*26*). Nevertheless, the banning of DDT "for all uses" was made official by court order (*27*), in spite of remonstrances and admonitions from the World Health Organization. Similarly, evidence is being gathered to ban organic mercurials, although in some uses (treating seeds for example) the mercurials are agents par excellence.

Instead of wholesale banning in situations of this sort, limited use should be permitted by a procedure of "licensing" and provisions for "restricted use." Such procedures have been used in the U.S.S.R. for about a decade (*28*) and are working well. Monsanto, the sole producer of the polychlorbiphenyls, highly persistent but relatively nontoxic chemicals for mammalian species, has voluntarily adopted a form of this "restricted use" by confining its sales and distribution only to those uses and processes known to be controllable. Such

procedures offer a saner approach to environmental control than do the present ventures of complete removal from commerce.

Consequences of Dereliction

When the pollution-oriented health administrators and the public alike begin to focus clearly on the enormity of the bill that would be required to reduce pollution to meet unnecessarily severe standards (versus commandment 3) precipitously prepared from undigested, dubiously related facts (versus commandments 1 and 4) on which the public has been ill-advised or misled (versus commandment 2), then will come the day of reckoning and rude awakening to the folly of past antipollution actions. Already industry has felt the bite; shortly, the public will. Hardest hit are the mineral and chemical industries. On top of multimillion-dollar outlays for air pollution control, and sums of similar magnitude for water, are multibillion-dollar legal suits that stagger the imagination, cripple large industry, and eliminate small industries. Two consequences of profound economic importance are the increased price of basic chemicals and the loss of employment. Already a number of small manufacturing plants have been forced to close, unable to bear the burden of meeting pollution standards. Heavy industry, unable to survive on repeated annual financial losses or to continue on less than a 4 to 6 percent profit margin, will ultimately pass the needless charge on to the consumer.

It thus should be evident that such actions, with their unbearable consequences, should only be taken when it is clear beyond a shadow of scientific doubt that human health is in imminent danger, as was the case in the localized pollution of water by mercury. In all other situations, the consequences of eliminating pollution must determine the character of antipollution actions. Does the public really want to spend billions to reduce particulates in the vicinity of heavy industry to levels of an air-conditioned, air-filtered home? Or does the public want to ban DDT, thereby eliminating the questionable harm to the osprey and bald eagle while certainly reducing food production and possibly allowing malaria to return to the United States?

The ruinous concept of "zero tolerance" for pollutants must go! Man has never, before he was a man or ever after, survived in an unpolluted void. One has only, on a sultry day, to cast his eyes unto the terpene-laden haze of the hills, or, on a humid day, to bring into view the fog born of condensation nuclei of many chemicals from the oceans to realize that this is true. Physiologically, man needs continual toxicologic nudging to maintain the homeostatic mechanisms that keep him physically and mentally alert. On the practical side, zero tolerance can only be attained by compete elimination of the source of pollutants, a situation that may not be desirable, or, in fact, possible if the pollutant is ubiquitous.

Finally, it may be too much to hope that antipollutionists will not direct a blind eye and turn a deaf ear to the precepts I have put forth as necessary for proceeding rationally against problems with which we are all deeply concerned and involved. No matter what the immediate reception may be, antipollution efforts must ultimately take the direction indicated in these commandments, or we will be faced with an economic upheaval approaching disaster.

References and Notes

1. H. Stokinger, *Amer. Ind. Hyg. Ass. J.* **30**, 195 (1969).
2. Matthew 14:17; Mark 6:38; Luke 9:13; John 6:9. Measurements of ocean waters in the 20th century indicated that they contain an average of 127 kilograms of mercury per cubic mile (4.1 cubic kilometers), or 2 parts per billion, probably only slightly more than at the time of Christ [*Encycl. Chem. Technol.* **8**, 562 (1952)].
3. For the record, first, it should be noted that polyphosphates were removed from laundry detergents not for reasons of human health, but solely to reduce the growth of algae in stagnant surface waters. Second, I call the evidence "fragile and provocative" because the questionably determined teratogenic effects were not for NTA (nitrilotriacetic acid), but for cadmium-NTA chelate and an NTA-methyl mercury combination at 6 milligrams per kilogram of a rat's body weight. However, we do not know when levels of this magnitude may be encountered in the environment. Critical experiments not done: extension of dosage-response curves to realistic environmental levels and parallel experiments with related NTA chelates, citric acid, humic acids, salicylates, and others.
4. P. Scott, B. Coldwell, C. Wiberg, *Food Cosmet. Toxicol.* **9**, 179 (1971); N. Medveditskova, *Vop. Pitan.* **28**, 76 (1969).
5. S. Peters and M. Strassburg, *Arzneimittel-Forschung* **19**, 1106 (1969).
6. T. Fujii, H. Sasaki, H. Nishimura, *Jap. J. Pharmacol.* **19**, 134 (1969).
7. *Survey of Compounds Which Have Been Tested for Carcinogenic Activity* (Suppl. 1, Public Health Service Publication No. 149, Government Printing Office, Washington, D.C., 1957.
8. W. von Oettingen, *Phenol and Its Derivatives: The Relation between Their Chemical Constitution and Their Effect on the Organism* (National Institutes of Health Bulletin No. 190, Government Printing Office, Washington, D.C., 1949.
9. N. Dobrovolskaia-Zavadskaia, *C. R. Seances Soc. Biol.* **119**, 83 (1935).
10. Data from the Food and Drug Administration indicate that, for man, levels of less than 50 micrograms of methyl mercury per 100 grams of blood are symptom-free. From the knowledge that the average content of methyl mercury in ocean fish is somewhat below 1 part per million of body weight, it is possible to stipulate the safe daily intake of ocean fish, making due allowance for mercury intake from other sources.
11. *Air Pollution Control Rules Concerning Air Quality Standards* (public hearing proposals, New York State Department of Environmental Conservation, New York, 1970).
12. *Air Quality Criteria for Sulfur Oxides* (National Air Pollution Control Administration, Washington, D.C., 1969).
13. Consideration is now being given to this suggestion by the Drinking Water Standard Committee on Toxicology of the Division of Water Hygiene.
14. The finding of a concentration of 19 parts of DDT per million of body weight (the highest concentration found) in the edible part of Coho salmon resulted in the ban on Coho salmon fishing. Assuming the highly unlikely daily consumption of 1 kilogram of fish containing 20 parts per million of DDT, that 20 milligrams of DDT per day is still about one-half of the daily dose found entirely safe [See W. Hayes, Jr., W. Dale, C. Pirkle, *Arch. Environ. Health* **22**, 119 (1971)].
15. A. Wolman, *Chem. Eng. News* (30 November 1970), p. 5.
16. E. Boyd, I. Dobos, C. Krijnen, *Arch. Environ. Health* **21**, 15 (1970).
17. S. Makino, L. Chosy, E. Valdivia, C. Reed, *J. Allergy* **45**, 40 (1970).
18. T. Washburn, D. Medearis, B. Childs, *Pediatrics* **35**, 57 (1965).
19. K. James, M. Collins, H. Fudenberg, *J. Lab. Clin. Med.* **67**, 528 (1966).
20. R. Schlegel and J. Bellanti, *Lancet* **1969-II** 826 (1969).
21. The closest approaches have made use of records of hospital visits by asthmatics, and a study of school children and respiratory "cripples."
22. E. Scott and D. Hoskins, *Blood* **13**, 793 (1958).
23. Federal Food, Drug, and Cosmetic Act, Section 409(c)(3)(A).
24. The tuna caught off Nova Scotia originate off Africa's northwest coast, swim to Bimini, and thence northward along the Atlantic coast in pursuit of herring. These tuna scarcely ever enter the mercury-rich St. Clair estuary. (Could control officials have overlooked frowning upon kippered herring?)
25. Reference to a list prepared in 1958 by the Food and Drug Administration, which defines a GRAS substance as one "generally recognized as safe."
26. *The Place of DDT in Operations against Malaria and Other Vector-Borne Diseases* World Health Organization Report No. EB 47/WP/14, World Health Organization, Geneva, 1971).
27. The court order was issued on 15 January 1971. On 18 March, the Environmental Protection Agency announced that "DDT and Aldrin, Dieldrin, and Mirex may stay on the market."
28. H. Magnuson, D. Fassett, H. Gerarde, V. Rowe, H. Smyth, H. Stokinger, *Amer. Ind. Hyg. Ass. J.* **25**, 185 (1964).