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When Are Studies Adequate for Regulatory Purposes? View of One Regulated

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The question of adequacy of studies for regulatory purposes has been debated for years. Nine questions need answers to determine adequacy: (1) Does the study deal with a defined problem or a defined segment of it? (2) Do the study data justify the conclusions drawn? (3) Were appropriate statistical analyses used? Is there evidence of bias versus objectivity in the collection or analysis of data? (4) Does the study support, supplement (or complement) or refute information in the literature? Is the study truly new information? (5) Does the study conform to the Interagency Regulatory Liaison Group (IRLG) guidelines for documentation of Epidemiologic Studies? (6) Does the study stand up to peer review? (7) Have other investigators been able to confirm the findings by duplicating the study? (8) Is the study acceptable or can it be made acceptable for publication in a reputable scientific journal? (9) Is the problem of such magnitude or significance that regulation is required?

Because there is no such thing as a risk-free environment or absolute safety and there is no definitive "yes" answer to each of the questions, the regulated would hope—yes, insist—that the regulators exercise judgement with great skill in promulgation of rules or regulations. The application of safety factors and the determination of acceptable levels of risk should be social decisions.

A discussion of instances where the "regulated" believes that studies have not been adequate, or others have been ignored, or misinterpreted for regulatory purposes is included. A method of settling controversial questions to eliminate the litigation route is proposed. Judgment which is so often eliminated by regulation needs to find its way back into the regulatory process. The regulated recognize the need for regulations. However, when these regulations are based on less than good scientific judgment, harm will be done to the regulatory process itself in the long run.

The subject of this paper is one that others on the side of the regulated might answer differently—all of us have our own built-in biases—and I am no different.

"The great error has been in forming theories upon observations or statements, without duly inquiring whether they have been sufficiently numerous, and have been carefully and truthfully made, upon a uniform comprehensive plan, or whether they are otherwise imperfect" (*1*). This sounds, more than just vaguely, like what we are talking about this morning. Yet this was an expression of concern by Lemmuel Shattuck in 1850, and still offers solid guidance to us in attempting to determine what epidemiologic studies are adequate and justify regulations in the conduct of the day to day operations of our business enterprise.

Let me assure you that the steel industry is well aware of at least 5700 different federal regulations; 4000 of which are promulgated and enforced by the Occupational Safety and Health Administration (OSHA) alone (*2*). An additional 26 federal agencies are looking over our shoulders enforcing the remainder. A few months ago there was some relief, but precious little to the steel industry, when OSHA revoked almost 1000 safety regulations which had very little substance to them and were, therefore, of little use in the safety field. On

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the other hand, most in industry recognize the need for some regulation because of the nature of man—not all live by the type of Judeo-Christian principles that should eliminate the need for all but the barest minimum of regulation.

Dialogue such as this symposium will contribute, I hope, to reducing some of today's hysteria to the realism of our everyday experiences.

There are a number of questions that should be asked and answered for us to decide if studies are adequate for regulatory purposes. There are some who might say they "never" can be adequate, but this is just as unreasonable a position as that taken by those who say that the slightest hint, however weak, is sufficient to require the regulatory process to be initiated. I will list nine such questions.

1. Does the study deal with a defined problem or a defined segment of it?
2. Do the study data justify the conclusions drawn?
3. Were appropriate statistical analyses used? Is there evidence of bias versus objectivity in the collection or analysis of data?
4. Does the study support, supplement (or complement) or refute information in the literature? Is the study truly new information?
5. Does the study conform to the Interagency Regulatory Liaison Group (IRLG) guidelines for documentation of Epidemiologic Studies?
6. Does the study "stand-up" to peer review?
7. Have other investigators been able to confirm the findings by duplicating the study?
8. Is the study acceptable or can it be made acceptable for publication in a reputable scientific journal?
9. Is the problem of such magnitude or significance that regulation is required?

The last question probably should be first, because it leads into a discussion of a concept that the regulated believe important. There is just no such thing as a risk-free environment or absolute safety. None of us would relish such a "cocoon". Even insects "burst out" in order to survive. In many instances, the decision-making process is and should be a sociopolitical one rather than a purely scientific evaluation. Despite their scientific character, the application of safety factors and the determination of acceptable levels of risk should be social decisions. Risk assessment, on the other hand, is a science and art which should be engaged in by those in a number of disciplines who know what they are talking about. The voice of the nonexpert has a place in sociopolitical decisions, but we wouldn't expect a beginning catechism class to establish church doctrine.

A second consideration of the regulated is the multiplicity of agencies who are intent on keeping their "power" base, saying "We must carry our the mandate of the law." There is some promise of reducing some of the overlapping and occasionally conflicting regulations of the past with the formation of the Interagency Regulatory Liaison Group. This will be particularly true if testing procedures and requirements are accepted by all agencies. A problem is created if some agencies require different test procedures, even if all might be equally acceptable from a standpoint of quality control. These differences cause confusion and unnecessary costs by requiring somewhat different tests having the same objectives though based on separate laws and regulations.

Returning to the task at hand, the search for a definitive answer to the question of when studies are adequate for regulatory purposes, there is, of course, no easy answer. If all above listed questions can be answered in the affirmative, then the regulated would agree that the study or studies can be considered adequate for regulation. The "rub", however, comes when we lack affirmative answers. The appeal of the regulated is that judgment be exercised with great skill in these instances.

With some trepidation, let me venture into some areas where the "regulated" believe that some studies have not been adequate, or others have been ignored, or misinterpreted, for regulatory purposes. The carcinogen debate is a good example. Schwartz (*3*) has observed that much of the emotional panic about current cancer statistics has been caused by misinterpretation of the available data. It is true that the deaths in the United States from malignancies are increasing (from 351,000 in 1973, they rose to 396,000 in 1976); however, this increase and the related rise in cancer death rates are explained in large part by the aging of the American population. Before age adjustment, there is an apparent increase in cancer death rate of more than 12% from 1968 to 1978. When the mortality data are age-adjusted, however, the cancer death rate is shown to have increased only 2.5% between 1968 and 1978. When age-adjusted figures are further corrected to eliminate the contribution of smoking-induced lung cancers, there has been no increase in the average annual mortality rate for men, and a 0.7% decrease for women (*4*).

Commenting on the alleged "cancer epidemic" in the United States in an address at the dedication in 1979 of the Northwestern University Cancer Center, Philip Handler (*5*) observed: "There is no such epidemic. The age-corrected incidences of only two forms of cancer have altered significantly

in our lifetime. Bronchiogenic carcinoma due to cigarette smoking has risen sharply, and the incidence of primary gastric carcinoma has declined dramatically for entirely unknown reasons. These two have more or less offset each other and the age-corrected incidence rate for the total of all forms of cancer has remained approximately constant for half a centurn."

Writing in the EPA Journal John Higginson, Director, International Agency for Research on Cancer, offered a similar opinion (*6*): ". . . available cancer data provide no evidence of a new cancer epidemic, apart from tobacco-related tumors."

Higginson (*7*) recently observed in an interview: "It would be so easy to be able to say 'let us regulate everything to zero exposure and we have no more cancer.' The concept is so beautiful that it will overwhelm a mass of facts to the contrary."

Unfortunately, the Environmental Protection Agency (EPA) has succumbed to this simplistic approach in the proposed air carcinogens policy and procedures. While the Agency recognizes that air pollution is just one of several "environmental factors" that contribute to the overall cancer incidence (*8*) EPA has made no attempt to estimate the relative effects of these factors. Several distinguished epidemiologists, however, have independently performed this epidemiologic exercise. Their conclusions have been remarkably similar.

Wynder and Gori (*9-11*) have estimated that diet and tobacco smoking account for almost 80% of the cancer incidence in this country. Radiation, alcohol, and occupation were judged to be minor contributors. Higginson (*12*) and Doll (*13*) have argued that the lowest reported cancer rates are baseline or "natural" rates and that "environmental influences" are responsible for any increases from these baseline figures. Higginson's (*7*) best estimates for the proportion of cancers attributable to various environmental factors are as follows: lifestyle (including diet and cultural patterns), 30% for females to 63% for males; tobacco/alcohol, 10% for females to 35% for males; sunlight, 10%; occupation, 2% for females to 6% for males; radiation, 1%; iatrogenic, 1%, congenital, 2%; and unknown etiology, 11% for females and 15% for males. Demopoulos (*14, 15*) reported that a group of independent university scientists from the comprehensive and specialized cancer centers in this country had reached the following consensus on the predominant causes of cancer: smoking, 35%; diet, 45%; occupational factors, 5%; radiation, 3%; preexisting medical disorders, 2%; iatrogenic, 1%; and unknown, 9%.

It is truly rare when the above facts are presented in their entirety or given full weight in regulatory discussions on the etiology of cancer. Instead, the frequently stated notion that 80% to 90% of all cancer is of environmental origin has been improperly linked to the view that cancer is largely a result of population exposures to industrial chemicals. EPA and other regulatory agencies must reject this suggestion. As Handler (*5*) has said: "Several hundred chemical compounds have been . . . examined in the last few years and a considerable fraction bound to be both mutagenic and carcinogenic. Nevertheless, we should lay to rest the idea that it is these man-made compounds, abroad in the land, that are responsible for the fact that 25 percent of Americans die of cancer. They are not. The possible effects of all known man-made chemicals, when totalled, could contribute only a miniscule fraction of that total of all carcinogenesis in our population. As I noted earlier, current age-corrected incidence rates are much what they were before most of these chemicals were introduced into our surroundings. They certainly cannot account for the even higher, age-corrected cancer rates in some more primitive countries which do not yet enjoy the benefits of a diverse chemical economy. . . ."

The possibility that air pollution might be a significant factor in the development of human cancer was first considered nearly 50 years ago (*16, 17*). Numerous studies in the intervening years, however, have failed to support this hypothesis.

It is clear that an urban-rural gradient in mortality statistics exists for certain specific cancers. There is no convincing evidence, however, that this "urban factor" is related to air pollution. Waller (*16*) has suggested that the differences in smoking habits between city and country account for the observed trend in mortality statistics: ". . . the present situation may be a legacy of lower levels of cigarette smoking in rural areas thirty or more years ago, even though current habits are similar in town and country."

Other investigators have reached similar conclusions. In a recent report, Doll (*18*) notes that the "urban factor" probably accounts for less than 5 deaths per 100,000 in the absence of cigarette smoking. Goldsmith (*19*) has recently presented evidence that most of the so-called "urban factor" in cancer rates can be accounted for by differences between urban and rural residents in smoking habits and occupation. Goldsmith's analysis revealed the following facts, which, he said, led him to conclude that air pollution plays little, if any, role in causing cancer:

- If air pollution were responsible, the excess

cancer incidence should be greatest in those states and countries where there is the heaviest urban pollution, but it is not.

- The largest, most polluted cities should have the highest lung cancer rates, but they do not.
- Lung cancer rates should be higher among those who have lived their entire lives in cities, but it is not. Rather, migrants to urban areas have higher rates than lifetime residents.
- The effect on lung cancer rates should be the same for both men and women, but it is not.

Demopoulos (*14*, *15*) has also presented evidence that air pollution is not an important cause of cancer in urban areas. In a study of seven industrial American cities with vastly different levels of air pollution, he found that lung cancer incidence was no more common in cities characterized as "dirty" (Detroit, Pittsburgh and Birmingham) than in the "clean" cities of Atlanta, San Francisco, Dallas and Minneapolis.

Hammond (*20*) has analyzed the American Cancer Society's prospective data on males living 10 or more years in their present area. No significant difference was found in lung cancer mortality in relation to either residence or population size of residential area. Furthermore, when data were standardized by age and tobacco consumption, and occupational exposures were excluded, urban pollution was not found to be an etiologic factor in lung cancer risk.

Lawther (*21*) has considered the possible magnitude of effects of exposure to the normal concentrations of benzo(a)pyrene in urban air. He concluded that public exposure to this carcinogen in urban air pollution has no clearly discernible effect on lung cancer mortality: "Thus it seems even more unlikely that this factor has any important bearing on lung cancer mortality in the general population today, and there is little doubt that variations in smoking habits are of paramount importance in determining variations in lung cancer mortality between subgroups of the population. . . ."

Higginson (*7*) has aptly summarized the nonrelationship between pollution and cancer: "The dangers of point-source pollution are well recognized, but you cannot explain much of existing cancer patterns only in terms of simple general pollution by industrial chemicals in low doses. You can't explain why Geneva, a non-industrial city, has more cancer than Birmingham in the polluted central valleys of England. In the United States, reports are coming out that there are few differences in cancer patterns between the so-called dirty and clean cities. In fact, the only thing you can say is that air pollution may, and I emphasize, MAY, increase lung cancer in cigarette smokers. These and other epidemiologic discrepancies simply cannot be explained by variations in general pollution. Some can, however, be explained by differences in life-style. . . . (This simplistic approach) has prevented possible acceptance of the idea that there may be doses of carcinogens which, for practical purposes, are unimportant. . . ."

In summary, therefore, despite attempts by several eminent epidemiologists to correlate cancer incidence/mortality and general air pollution, a consistent relationship between these variables has never been established. Instead, the overwhelming body of scientific evidence supports the conclusion that dietary factors and cigarette smoking are, by far, the major contributors to overall cancer incidence. If this fact is recognized and accepted, the resources of federal regulatory and research bodies can be best utilized in the public interest.

As Frank Rauscher, Vice President, American Cancer Society, observed, "I don't see how people can point to the smoke stacks and blame industry when they ignore what they have between their fingers. We know what causes 70 percent of all cancers, and we have known that for about 10 years."(*22*).

While still speaking of carcinogenesis, the importance of potency should be emphasized. Regulatory agencies tend to ignore differences in the potency of chemical carcinogens. While exposures at the lowest technically feasible level would not be identical for all chemicals, the universal application of the most drastic remedy ignores the practical reality that carcinogens differ greatly in potency, and that different levels of control, not always the lowest level feasible, are appropriate (*23*). It ignores, for example, the 10,000-fold differences between a threshold limit value for chloroform, a weak carcinogen, and bischloromethyl ether, a strong one. It is not unfair to suggest that this is roughly equivalent to arguing that because the elephant and the mouse are both mammals, the same chains are required to prevent their escape.

The public at large ought to be informed of widely different potencies. If they are going to be told that aflatoxin and saccharin are both carcinogens in animals, they ought at least to know that there appears to be a one millionfold difference in potency between the two.

Aflatoxins (*24*) are naturally occurring contaminants of such common foods as peanuts, corn and grain. In spite of their potent carcinogenicity, 15 ppb amounts of aflatoxins are tolerated in the food supply because they are not deliberately added to foods.

Switching briefly to the sulfur oxides and the controversy surrounding their regulation, Weir (*25*) states: ". . . neither the animal studies, the clinical investigations nor the industrial experiences agree with the recently reported community epidemiological studies that are currently receiving attention. It may well be that the toxicological data are correct in that there are no important long-term effects from exposure to the sulfur oxides. Certainly the laboratory studies, animal or human, do not support more stringent standards for either the occupational or the community environment."

An example where an agency, the Environmental Protection Agency (EPA), apparently has relied on a study that has not withstood the peer review process was noted when controversy exploded in the recent EPA cancellation hearings on the herbicide 2,4,5-T. Blair (*26*) has charged that 2,4,5-T is being victimized by an agency which has expended too many man-hours and tax dollars to admit now that the herbicide is safe when used properly. Furthermore, he cited EPA's denial of its own Scientific Advisory Panel's decision as an indicator of the Agency's preconceived political objective. Most uses of 2,4,5-T and a related herbicide, silvex, were suspended in February, 1979 after EPA received reports that an abnormally high number of allegedly TCDD-related miscarriages had occurred in isolated spray areas in the northwest. TCDD is a trace dioxin contaminant of these herbicides. The international scientific community has rejected the EPA's Alsea II (Oregon) study on which the suspension was largely based. The Scientific Advisory Panel in EPA concluded after extensive review of the data that no evidence of an immediate or substantial hazard to human health or to the environment associated with the use of 2,4,5-T or silvex on rangeland, rice, orchards, sugar cane and the noncrop uses specified in the decision documents was found.

So that you will not think that this type of controversy occurs just in the environmental pollution area, I need only mention the controversy concerning the University Group Diabetes Program (UGDP) (*27*) report on the use of oral hypoglycemics in the treatment and management of adult-onset diabetes.

The leukemia controversy in benzene exposure levels of around 10 ppm is an example where an agency (OSHA) has relied upon a study (*28*) that has been severely criticized by peer groups but has ignored excellent studies (*29-31*) which did not support OSHA's reliance on the critcized study conducted by Infante, et al. (*28*) of the National Institute for Occupational Safety and Health (NIOSH). In addition, another nearby plant, which should have been and could have been studied, would not have supported the contention that benzene in these low level exposures is a leukemogen. Since no new cases of leukemia are occurring in the studied plant, the likelihood of the "cluster" phenomenon unrelated to occupational exposure originally suggested by many of the peer critics is gaining more stature.

Scientists in the government should acknowledge the views of reputable peer groups. It has been proposed that a "blue-ribbon" panel of scientists, independent of those who do the regulating as well as of those who are to be regulated, be put into place preferably in the National Academy of Sciences to evaluate data in the decision making process of government regulation of carcinogens (*32*). It would seem to the regulated that this practice might assure that indeed regulation of carcinogens would not be based at times on the product of bureaucratic interpretation. If this practice proved to be a workable procedure, then the natural expansion to other areas of government regulation would be appropriate at least, where controversy rears its head. Not everyone would be totally satisfied, I'm sure, but this would be much better than the litigation route that must be resorted to today to bring reason into the process.

In closing, I would like to reemphasize the difficulty in providing a definitive answer to the question of when a study is adequate for regulatory purposes. Judgment which is so often eliminated by regulation needs to find its way back into the regulatory process. The balancing of risk and potency requires the best scientific judgment available to prevent overkill and over regulation. I suspect that some will think I have spent too much time using examples where regulations or proposed regulations are based on less than good scientific judgment—but I submit that in the long run, bad regulation will do great harm to the regulatory process itself.

Let me assure you in the strongest terms that the regulated do not wish to count bodies—as has been stated by some of our critics—but we do want to be sure that the regulations we must live with are the best that good judgment can produce based on sound scientific input.

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