Environmental Health Perspectives
Vol. 52, pp. 187–191, 1983

Controlled Clinical Studies of Air Pollutant Exposure: Evaluating Scientific Information in Relation to Air Quality Standards

by Jack D. Hackney* and William S. Linn*

In controlled clinical studies, volunteers are deliberately exposed to specific air pollutants under conditions simulating ambient exposures, and health-related responses are documented. Studies of the health risks of air pollution need to be scientifically rigorous and clearly relevant to "real-world" pollution exposures. Their results should be confirmed by independent replication if they are to be used as a basis for air quality regulations. Well-designed controlled clinical studies readily meet these criteria, and complement the other methods of scientific risk assessment—animal toxicology and epidemiology. Clinical studies, toxicology, and epidemiology all have provided important information about air pollution health effects. A better understanding of the interrelationships of findings from these different fields is needed.

Introduction

This paper focuses on clinical studies of human volunteers deliberately exposed to specific air pollutants. Most such investigations are performed for the express purpose of guiding air quality regulatory decisions. They establish atmospheric conditions in a controlled laboratory setting which are considered relevant to actual ambient polluted atmospheres and attempt to document any health-related effects which result from breathing the laboratory atmospheres.

Clinical studies to some extent combine the strong point of animal toxicology—rigorous control of the experimental subject and environment—with the strong point of epidemiology—unquestioned relevance to human health. However, clinical studies are limited by ethical and practical considerations to small groups of people, short durations of exposure, and atmospheres expected to produce only mild and temporary health effects, at most. Regulatory agencies must consider large and diverse populations at risk of long-term as well as short-term effects, and must try to protect the most susceptible groups of people. Clinical studies thus often investigate a group likely to be at especially high risk from air pollution, e.g., asthmatics or people who exercise heavily outdoors, and a concentration of pollutants equal to the worst likely to occur in ambient episodes. Such "worst-case" experimental conditions are assumed to produce responses comparable to the most severe effects likely to occur in the most reactive members of relevant community populations. To the extent that this assumption is valid, prediction of responses in large populations from data on small experimental groups is not too serious a problem. Prediction of long-term effects from short-term observations clearly is a serious problem, which cannot be addressed by clinical studies alone. It may be partly resolvable, however, if appropriate links can be established between clinical-study findings and observations from animal toxicology and epidemiology. More will be said about this later.

We have reviewed past findings from human exposure studies and suggested means of applying them to regulatory decisions, in greater detail elsewhere (*1-3*). Here we wish to mention only a few recent experimental studies while presenting opinions on some more general scientific and policy questions. One important general question

*Environmental Health Service, Rancho Los Amigos Hospital Campus, University of Southern California School of Medicine, Downey, CA 90242.

concerns the proper definition of "adverse health effects" from which the law requires people to be protected. Before addressing this, we wish to discuss a related issue: maximizing the effectiveness and efficiency of the scientific air pollution risk assessment process. How can we avoid wrong conclusions from scientific studies which result either in unrealistic expectations of health benefit and socioeconomically harmful overregulation of air quality or, conversely, in failure to recognize and control genuine pollution-related health hazards? Mistakes may, of course, be made either in the choice of problems to be studied, in the scientific investigation itself, or in the subsequent policymaking process. Mistakes in the second and third categories mentioned are unlikely if both scientists and policymakers pay attention to reasonable criteria for the design, conduct, and evaluation of risk-assessment studies. Experiments should be scientifically rigorous in traditional terms: they should address a clearly formulated hypothesis using a design and measurement techniques adequate to support the hypothesis and rule out alternative possibilities. Experiments should be clearly relevant to human health and ambient air pollution problems: they should approach as closely as practical the situation of the real person at risk in the real polluted environment being evaluated. Finally, experimental results should be independently replicated before being considered fully acceptable as bases for regulatory policy decisions: we need reasonable assurance that the observations are independent of any specific observer. To restate the point more concisely: Scientific risk-assessment data should be given credence to the extent that they are scientifically rigorous, relevant to human health concerns, and redundant (independently replicated). "Unconfirmed" findings—data which fail to meet one or more of the above criteria—are not excluded from consideration, since federal air quality standards are required to incorporate a "margin of safety," i.e., to be set somewhat below the lowest exposure level known to produce an adverse effect. A decision on the magnitude of a "margin of safety" may reasonably take into account "unconfirmed" as well as "confirmed" findings.

Recent Studies of Sulfur Dioxide

In reviewing the clinical studies of sulfur-containing pollutants in 1978 (*4*) and again in 1980 (*2*), we concluded that no physiological or clinical effects of sulfur dioxide (SO_2) had been demonstrated at exposure concentrations below 0.75 ppm—a level only infrequently reached in ambient pollution. This tended to place clinical study results at odds with a large body of epidemiologic data: many epidemiologic studies suggested associations between commonly occurring elevated levels of sulfur oxides and increased respiratory morbidity or mortality. The positive epidemiologic findings might have reflected effects of particulate pollutants coexisting with SO_2, but clinical studies of particulate pollutants generally have not shown effects at concentrations relevant to ambient exposures. The situation changed somewhat with publication of a recent study by Sheppard et al. (*5*) which indicated that young adult asthmatic volunteers developed significant increases in airway resistance while exercising during exposure to SO_2 concentrations of 0.25 and 0.50 ppm (in comparison to similar control experiments in which SO_2-free filtered air was breathed). Some subjects also developed wheezing and shortness of breath in 0.50 ppm exposures. The SO_2 was administered by mouthpiece with the nose occluded during the exercise-exposure period, which lasted 10 min.

How should this new finding be applied to air quality policy decisions? From one viewpoint, it tends to support the epidemiologic data associating ambient SO_2 with respiratory morbidity, in that the exposure concentrations examined are more or less in the same range. On the other hand, the conditions under which SO_2 was breathed in the laboratory exposure were unlike those typical of ambient SO_2 exposures, and the volunteer subject population may or may not have been comparable to epidemiologic study populations apparently affected by SO_2-containing pollution. By our previously stated criteria, independent replication of the findings of Sheppard et al. should be sought, and their degree of relevance to ambient exposures judged, before they are given the most serious consideration by air quality regulators. Some discussion of the relevance issue has already appeared in the literature. The application of Sheppard and co-workers' and similar data to air qualty standards has been challenged on the grounds that the experimental exposure procedure, involving breathing through a mouthpiece with the nose occluded, unrealistically bypasses much of the nasal and oral pollutant scrubbing capability (*6*). Thus, an unrealistically high dose to the lungs would occur at any given exposure concentration. Sheppard et al. have counter-argued that their findings have important implications for air quality standards (*7*). They contend that the quantitative reduction in SO_2 dose by upper-airway scrubbing is relatively

unimportant during exercise, particularly in people with nasal obstruction.

More than most other fields of investigation, clinical studies provide the means to resolve controversies like that described above through further experimental work. We have initiated a study which should be able to provide at least indirect confirmation of Sheppard and co-workers' findings with low-level SO_2, while at the same time testing their applicability to more realistic exposure conditions. Twenty-four young adult nonsmoking asthmatic volunteers were recruited and exposed on three separate occasions to clean air, 0.25 ppm SO_2, and 0.5 ppm SO_2, in random order. Exposures took place in a large controlled-environment chamber allowing freedom of movement and unobstructed breathing. Exposures lasted 1 hr and included intermittent exercise. Airway resistance measurements were taken before exposure, after an initial 10-min exercise period, and near the end of the hour. If significant increases occurred within 10 min and were still present at 1 hr, it would be reasonable to conclude that the responses observed by Sheppard et al. can occur in ambient exposures, and persist long enough to be of health concern. If no significant response or only a transient response (reversed by the end of the hour) were found, there might be less cause for concern. Only preliminary results, requiring verification by more extensive data analysis, are currently available from this study. They are discussed here not to suggest any definitive conclusions about effects of SO_2, but as an illustration of a (hopefully) logical and orderly means of progress in scientific risk assessment.

We initially performed pilot studies, primarily to test the operation of our airway resistance measuring equipment, in which five asthmatic volunteers were exposed to clean air and to 0.5 ppm SO_2 by mouth during 10 min of moderate exercise under a protocol similar to that of Sheppard et al. All five showed increased resistance after exercise even when clean air was breathed. Four of the five showed greater increases in resistance after SO_2 than after clean air. The fifth subject did not show any excess effect at 0.5 ppm SO_2, but did when reexposed at 1.0 ppm. Only one person showed even a slight excess of respiratory symptoms with 0.5 ppm SO_2 as compared to clean air. The resistance data certainly tend to support the findings of Sheppard et al.; but they do not provide independent confirmation in the strict sense, because the number of subjects was small and the design did not control completely for time-dependent effects.

In the main study, no statistically significant variation in airway resistance attributable to SO_2 was found for the group (Table 1). A small but significant increase attributable to exercise was observed, even though the exercise level was only mild to moderate (ranging from 300 kg-m/min for the least fit subjects to 500 kg-m/min for the most fit subjects) and the relative humidity was kept high (above 90% at an exposure temperature near 75 F) to minimize bronchoconstriction due to airway cooling (8). Forced expiratory tests and symptom interviews also failed to detect a significant effect of SO_2.

The contrast between the lack of detectable SO_2 effect at 0.5 ppm with unencumbered breathing and the apparent effect with mouthpiece breathing (assuming that it stands up to further scrutiny) raises a new series of questions. Are there subgroups of asthmatics who react to 0.5 ppm or less, even with unencumbered breathing, whose responses are masked by those of the unreactive majority? Would other pollutants coexisting in ambient air increase the response? To what actual extent does the nose scrub out inhaled SO_2? What concentration of SO_2 would produce a measurable effect in people with complete nasal obstruction, or in people who breathe through tracheostomies

Table 1. Preliminary statistical results from a study of 24 asthmatic volunteers exposed to SO_2: mean specific airway resistance and results of repeated-measures analyses of variance.[a]

		Specific airway resistance[a]			
	SO_2, ppm	Exposure 0 min	Exposure ~15 min	Exposure ~55 min	Significance[b]
All subjects	0.0	5.40	7.23	7.57	p (SO_2 level) = 0.184
	0.25	4.37	5.14	4.75	p (exp. time) = 0.054
	0.50	5.42	6.68	6.51	p (interaction) = 0.179
23 subjects[c]	0.0	4.44	5.02	5.21	p (SO_2 level) = 0.164
	0.25	4.18	4.54	4.39	p (exp. time) < 0.001
	0.50	4.33	5.13	4.90	p (interaction) = 0.153

[a]Specific airway resistance = [resistance in cm H_2O/(L-sec)] × (lung volume in L).
[b]p values should be considered approximate, since adjustments for nonideal distribution of data have not been applied.
[c]Excluding one subject who had markedly greater resistance than all others on some occasions, not attributable to SO_2 exposure.

and thus are without upper-airway defense mechanisms? How would higher levels of exercise, lower air temperature, or lower humidity affect the response? Most if not all of these questions can be addressed directly in further clinical studies, the results of which might raise more questions requiring still further investigation. A particularly attractive feature of clinical studies is that each "increment" of research should require a reasonably small time and resource commitment, and should add meaningfully to the data base supporting regulatory decisions.

Proper Evaluation of "Adverse Health Effects"

The investigations just described were conducted on the premise that increases in airway resistance with pollutant exposure relate in a meaningful way to health risk from the pollutant. Is this really true? Asthmatic attacks certainly involve increased airway resistance, and certainly reflect an undesirable state of health. Increased resistance implies increased work of breathing and therefore less availability of metabolic energy for productive use. On the other hand, at least some people seem able to incur substantial increases in resistance without any obvious effect on their performance capabilities or clinical status. Some asthmatics in particular, even when symptom-free, seem to show wide variations in resistance over short periods of time in response to a variety of stimuli. How, then, should we apply experimental findings like those described to decisions on air quality policy to protect health? At one time, it was usually assumed (at least implicitly) that any detectable physiological change, under any exposure condition relatable to ambient exposures, should be considered evidence of health risk. While not unreasonable, this assumption no longer seems viable as a strict basis for policy decisions, given the increasing costs of pollution control efforts and the increasing number of recognized problems to be dealt with. Ultimately, broadly based political decisions should determine which effects are truly "adverse" and must be prevented by control efforts, and which will be tolerated in order to address other social needs. The needed scientific input to this political process is information from which to set priorities for health protection—to rate the levels of relative "adversity" of different possible effects.

Possible clinical effects of pollution can be prioritized roughly on the basis of their severity and duration. Problems which result in substantial permanent disability or decreased life expectancy clearly belong at the top of the prevention priority list. Of less concern, but still clearly within most people's definition of "adversity," are temporary disabling illnesses (e.g., viral respiratory infections) and temporary exacerbations of chronic conditions (e.g., asthma episodes). At a still lower level of concern are slight and transient clinical effects which do not prevent usual activities but do perceptibly impair performance capability and one's sense of well-being.

Physiological effects, at least those of short duration, might be prioritized according to their tendency to produce impairment of performance or clinical status, as illustrated by the following example. The effects most often reported in clinical studies are increased airway resistance, as discussed earlier, and reduced forced expiratory performance, as detected by decreases in the maximal forced expired volume in one second (FEV_1) and related measures. Resistance effects are often found in SO_2 exposures, whereas ozone exposures are more likely to produce forced expiratory effects. Which is more important to health? We would argue that reduced FEV_1 is of greater concern, since it seems more closely related to performance capability. The FEV_1 may be viewed as a very rough estimate of the maximum volume of breath a person can take during exercise, since a typical breathing pattern and typical exercise respiration rate of 30/min would allow slightly more than 1 sec for expiration. Any decrease in FEV_1 with exposure, regardless of its cause (increased resistance, coughing, pain on deep breathing, etc.) thus implies a corresponding decrease in the ability to ventilate the lungs. If impaired oxygenation were shown directly, e.g., if arterial blood oxygen content were shown to decrease with exposure, this would be cause for even greater concern, by our reasoning. (Such effects have been suggestd in a few clinical studies but not confirmed, to the best of our knowledge.) Resistance changes, if not clinically perceptible, seem of less concern since their relationship to physical performance is more tenuous.

Most likely, there will be substantial disagreement concerning the health significance of the milder physiological and clinical effects likely to result from air pollution, and the point at which they should be legally defined as "adverse." There would be much less room for disagreement if the long-term consequences of short-term, apparently fully reversible effects were understood. This would require the demonstration of links between clinical studies, which are limited to short-term effects, and animal toxicology and epi-

demiology, which can address both short- and long-term effects. Furthermore, links between observed short- and long-term effects would have to be demonstrated.

Animal toxicologists need to develop tests of short-term respiratory physiological response to pollutants which have counterparts in human studies. They could then relate physiological to pathological changes, both in the short term and in the long term, and possibly could relate this information to human health risks. Epidemiologists need to investigate exposed populations longitudinally, to better understand the ambient exposure circumstances (if any) which are associated with the development of chronic disease in the long term, and to identify any associations between long-term effects and short-term, apparently reversible effects. Of particular interest would be longitudinal studies of "panels" identified by clinical studies as having atypically high or atypically low short-term sensitivity to exposure. This would test the common (but largely unsupported) belief that people unusually sensitive to short-term effects are at increased risk to develop chronic illness in the long term.

The aforementioned links across scientific disciplines and between short- and long-term investigations now exist only very tenuously, if at all. To establish them firmly would require the solving of many difficult problems, conceptual and experimental, relating to "basic science" as well as to highly "applied" empirical investigations. A large and long-term commitment of resources would be required—not a likely prospect at present, particularly in light of other unmet needs in health care and environmental protection. We should always keep in mind, though, that the known costs of air pollution control, and the suspected costs of ill health from inadequate control, are orders of magnitude larger than research budgets. Well-planned risk assessment research is likely to be a very sound investment, paying off in greater cost effectiveness of regulatory policy.

This work was supported by Contract RP-1225 from the Electric Power Research Institute.

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