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Discussion: Session 3* Policy Issues in Applying Epidemiologic Evidence

Dr. Enterline opened the discussion by asking Dr. Hunt about the interagency criteria for epidemiologic studies. The draft he had indicates that an epidemiologist should make his data available to other epidemiologists. The idea is sound because, after all, what an epidemiologist says about his data ought to be verifiable. But it is not clear whether this is a two-way street between government and nongovernment epidemiologists. Could she clarify whether government investigators will make data available to nongovernment people, as well as the reverse? Dr. Hunt replied that the "criteria" in question refer to the Interagency Regulatory Liaison Group (IRLG) Guidelines for documentation of epidemiological studies mentioned in her talk. Documentation is a key point, including exchange of data or the availability of data. The IRLG Guidelines were written in the context that when clarification of a study is needed, evaluation of the study is best made if the back-up data are available. Such data are usually not possible to obtain from published studies. When studies are germane to the regulatory process, it is reasonable for best evaluation of them for data to be shared. In terms of the availability of federal data to anybody else, as you well know we have the Freedom of Information Act under which we are operating. According to the guidelines, supporting documentation should be provided for any instruments, analytic methods used, and computer programs. If established procedures are involved, references should be given. If new or modified measures are used in the study, a description of the method, including its limitations and advantages for the study, should be stated. Data and supporting documentation underlying any study submitted should be available upon request for independent scientific analysis. Dr. Enterline pointed out that these guidelines applied to people submitting evidence for regulatory purposes.

Later the discussion on the IRLG Guidelines was reopened by Dr. Jess Kraus (University of California—Davis) and by Dr. Gary Spivey (University of California—Los Angeles). They asked for time to present a statement, which was presented by Dr. Kraus. He stated that he and Dr. Spivey, after listening to the comments on the IRLG, felt that an expression of concern should be raised on the guidelines, and particularly to this audience, whose commitment, interest and inclination is in the field of epidemiologic research. The IRLG Guidelines may very well have a profound impact on the conduct of epidemiologic research in the future, hence they felt a brief statement was in order. In the past decade or so, there have been three very important events that have shaped an important and significant amount of epidemiologic research that has been undertaken as of late. The first was the introduction of guidelines and then regulations on the conduct of human experimentation that has since extended to survey research. The second very important development has been the work toward the initiation of the American College of Epidemiology, about which there have been raised many comments. The third, he and Dr. Spivey believe, is the development of the IRLG Guidelines which could impact importantly on the future conduct of epidemiologic research. Although these views represent only two members

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Speakers: Vilma R. Hunt, Deputy Assistant Administrator for Health Research, Environmental Protection Agency, Washington, D.C.; Merle Bundy, Director of Industrial Medicine, U.S. Steel Corporation, Pittsburgh, Pennsylvania; Irwin H. Billick, Environmental Hazards Research Division, U.S. Department of Housing and Urban Development, Washington, D.C.; Lewis H. Kuller, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15261.

of the profession, they believe they express many of the concerns heard whenever the subject has been raised. For the record, it should be noted that the way in which the guidelines were developed and introduced left much to be desired. As far as the Society for Epidemiologic Research was concerned, they were approached only a short time before the guidelines were published; the Epidemiology Section of the American Public Health Association was not privy to them before they were published.

In the opinion of many of their colleagues, the guidelines show remarkable similarity to recommendations published, after several revisions, on the conduct of human studies and research involving human subjects. These recommendations today have taken on the force of regulation, and in many states, law. While there was no doubt ample need for such standards, their adoption as rule and regulation has, in their opinion, stifled much pertinent epidemiologic research. Often research of the past 10 years bears little resemblance to that of decades earlier because of newer developments, techniques or innovations in the design or execution of epidemiologic studies. The IRLG Guidelines will serve to hinder, they felt, such advances in the future. Like it or not, investigators who will want to qualify for federal funding will adopt these guidelines for expediency rather than be influenced by principles of scientific inquiry. The basis for these guidelines was the need on the part of regulators to be able to interpret epidemiologic studies, as they understood it, yet these same people may follow such guidelines blindly without increasing their level of understanding. Would it not be more profitable for those translating epidemiologic findings into policy or regulation to be educated in epidemiologic principles rather than blindfolded by rigid protocol? Dr. Hunt in her presentation mentioned on several occasions the need for creativity, ingenuity, and innovation in approaching environmentally related epidemiologic research. Yet the guidelines will result, no doubt, in suppression of methodologic approaches that will surely be needed to address these problematic areas.

In the event that the IRLG formally adopts these guidelines and professional epidemiologists choose to reject them, will this set up a confrontation that could lead to discrimination in selection of federally funded research? For example, will investigators be required to adopt these guidelines as a condition for federal funding of environmentally related research? One approach, that seems more productive than guidelines for interpretation, would be to examine more carefully the credentials of the investigators who purport to be epidemiogists and who submit applications under this guise.

Dr. Altshuler stated that he thought there is too much emphasis on the Interagency Regulatory Liaison Group as a monolithic unit to decide things or agree on one optimum way of doing research. There is much advantage in allowing several approaches, although he agreed with the idea of coordination.

Dr. William Lloyd (Occupational Safety and Health Administration, Washington) indicated he was a member of the IRLG Epidemiology Committee. What he had heard from Dr. Kraus he could only consider as a complete misinterpretation of what the guidelines say. There is nowhere implied in that document that it is going to have any force of law or that it is going to be a standard. If there is anything missing in that document, it is the reason why these guidelines were considered to be needed. This was that in regulatory hearings many people spoke as professionals and called themselves epidemiologists, but who presented testimony that was, to put it politely, ridiculous. Even people from some of our schools of public health came in and said they were professional epidemiologists, yet presented in testimony things that they wouldn't accept from a first semester candidate for a Master's degree. Now when you have circumstances like this, people who are making regulations have to have some way to interpret what is going on. Thus it was not unreasonable at all to develop guidelines for those people, and that is exactly what they are. It is to give those responsible for regulation guidance, so that they know the appropriate kinds of questions to ask of these people when they come in to present their testimony. He believed that much of the argument against the guidelines of the IRLG committee had come from a single epidemiologist in the United States. The guidelines are not an attempt to suppress anybody or any new approaches. The committee is hoping that they will improve epidemiological investigation by having these kinds of guidelines.

Dr. Hunt added that at least 40% of the committee was in this auditorium. It included Dr. Lloyd, Dr. Williamson, Dr. Waxweiler, and herself. She thought Charles Poole of the Office of Toxic Substances was also present. In terms of the development of the guidelines, to hear an interpretation of the manner by which they were developed distorted the way it was, was beyond her. The concern of the IRLG was, as Dr. Lloyd has pointed out, the uneven quality of epidemiologic studies being presented to regulatory agencies and

the problems that people who were making the decisions had in interpreting them. One obvious misconception also was that it is epidemiologists who are making decisions about regulations.

In fact, somebody else, who is not an epidemiologist, is making such decisions based on these studies, whether we like it or not. We are not going to be able to send to schools of public health for training judges, lawyers and policy-makers who are administering the regulatory agencies. It soon became evident over the period of about three or four months the IRLG worked together that they wanted to be sure that the deliberations reached a larger audience. It happened that the Society for Epidemiologic Research was having its annual meeting and Dr. Williamson went to that annual meeting and requested an audience with the executive committee. She presented the draft as it stood at that point. They were provided with enough copies for the guidelines to be sent to the entire membership. The comment period, when it was published in the *Federal Register*, was extended at the request of the Epidemiology Section of the American Public Health Association, and that comment period closed early in March.

There was now a sheaf of responses which are being closely evaluated for suggested changes, for rewording, etc. Some comments from these responses were as follows. Trade organizations and industry representatives stated that this was a good route to go because the guidelines introduce some clarity in judging studies. Within departments of universities there were sometimes diametrically opposite letters from faculty: one faculty person saying the guidelines were great; another faculty person saying they would lead to the decline of epidemiology. At this stage, the group was going through the process of presenting to the public every opportunity to comment on these guidelines and how they will be used. Those who are making decisions on epidemiology studies, very few of whom are epidemiologists, and those who are presenting epidemiology studies to a regulatory agency, are to use the guidelines to document the studies and describe them in a manner which will allow for minimum misunderstanding of the study by the regulators.

Dr. Marvin Hines (State Epidemiologist, North Carolina) emphasized the role that state epidemiologists could play in dealing with environmental problems, particularly because they are closer to the problems at issue. The need is for flexibility and quick response to emergencies, such as the case in North Carolina of PCBs being deliberately dumped along 200 miles of roads. This issue still has not been resolved, perhaps because of federal intervention. Another area where state epidemiologists can contribute is in carrying out studies of local problems, such as byssinosis in textile mills. Despite opposition from the large textile companies, he was able to carry out a study which forms the basis of the current OSHA standards for cotton dust. In another case, their staff investigated safe return times for workers after tobacco fields had been sprayed with parathion. He concluded that state epidemiologists could contribute greatly in environmental regulation, but they were too often not considered in the process of regulation nor in research potential.

Dr. Philip Landrigan (NIOSH, Cincinnati) commented on the relationship of air lead to blood lead measurements. He shared Dr. Billick's position that leaded gasoline is a public health hazard. He noted that 100,000 to 150,000 tons of lead from gasoline are emitted each year in the air in the United States, most in respirable particulate form. Thus it is a public health threat not to be taken lightly, and the Public Health Service and the Center for Disease Control support EPA in their continuing efforts to reduce the lead content of gasoline. He was, however, puzzled concerning the significance of the next relationship discussed by Dr. Billick. He did not dispute the reality of the parallel decline in air lead levels in New York City and in the blood lead levels of children living there, but he was not sure that he accepted Dr. Billick's implication of a causal relationship. First, the air lead measurements were taken at the entrance to Holland Tunnel, hardly typical of general urban air. Second, during the years 1972-76 when a decline in air lead levels was demonstrated, there was an upsurge in activity sponsored by CDC and the New York City Health Department, in which parents were being educated in the hazards of lead-based paint. As a result, thousands of children were screened for blood lead and free erythrocyte protoporphyrin, and thousands of homes were deleaded.

Thus, although lead in air constitutes a significant source, he thought Dr. Billick had overstated the case in implying that reduction air lead levels was the major cause of the reduction in children's blood levels. He considered that it was particularly important to discuss the issue because HUD is one of the major holders in the country of what might politely be called low-cost urban residential housing. It is important that HUD recognize and vigorously address the problem of lead exposure from lead paint in old housing.

Dr. Billick replied that he hoped he had not implied a causal relationship between changes in air and blood lead. In arguments about the use of

statistics to prove causal relationships, one special case of Murphy's Law is Billick's Law, which is that statistics prove causal relationships when it is your theory. Dr. Landrigan had focused on the question of the connection between air lead and blood lead rather than on the more important connection between lead from gasoline and blood lead. Dr. Billick agreed that air exposure may not be the main route by which lead consumption in gasoline is related to lead uptake. He thought that exposure comes from other routes, but ultimately from lead in gasoline. He disputed that hundreds of thousands have had homes deleaded in New York City. If you look at the New York City data, lead values in children are generally very low if one considers the population that was screened. He added that he had found the same relationship of lead in gasoline to blood lead in several cities, not just New York City.

As far as HUD being a major owner of slum properties, when one looks into the property holdings of HUD, it is not as much as one might think. HUD has very little legal authority in the area of private dwellings, and it can only influence those areas where it provides funds. As far as he was aware, HUD is the only agency that does have a preventive regulation for paint, that is, for the removal of peeling and flaking paint. Whether the regulation is adequate, well, that is a discussion that could go on forever.

Dr. Landrigan responded that he appreciated Dr. Billick's clarifying his thoughts on the relationship between air lead and blood level. Dr. Landrigan said that according to the Center for Disease Control, over 700,000 children had been tested for lead in New York City between 1973 and 1980. He added that although the number of cases of clinical lead poisoning in New York has been declining dramatically over the past decade, about a year ago, in the North Bronx, at least, there has been an upturn. Montefiore Hospital had received 39 cases of acute lead poisoning in the past 15 months, or more than they had found in the whole decade of the 1970s. The apparent reason for the increase is that black, poor, and Hispanic families are moving into houses along the Grand Concourse in the Bronx, previously very wealthy, upper-class houses, which are now for the first time being subdivided into apartments; in these homes children are for the first time coming in contact with and eating lead-based paint. For virtually every one of the 39 cases, the social staff at Montefiore Hospital has been able to trace the source of the children's exposure to paint. Meanwhile, the content of lead in the air in the Bronx continues to decline.

Dr. Robert S. Chapman, (EPA, Research Triangle Park, North Carolina) had a comment and a question. His comment was with regard to the Alsea study in Oregon. The design of that study was such that it could never adequately address the question that it purported to address. But with all the press it received, many began to think that the Alsea study exonerated the environmental challenge that it was purporting to look at. He did not think that was correct. Studies like the Alsea study neither exonerate nor incriminate the effects of environmental agents. The tendency is to interpret inconclusive studies as though they show no effect when they don't really do so.

His question was for Dr. Kuller: In light of data showing an interesting social class or income-specific effect for cancer, is there a residual effect of income on cancer rate after smoking is adjusted for? With adjustment for smoking, perhaps matching for income or some other aspect of socioeconomic status is needed. At the same time he was concerned that vigorous matching might tend unwittingly to confine cases and controls to the same geographic area, and thus to diminish the investigator's ability to detect pollution-related effects. He thought the same question would apply to race or ethnic factors as well. Dr. Kuller replied that the nature of factors contributing to cancer risk is often related to personal behavior, that is, related to diet, alcohol, cigarette smoking or perhaps even genetic factors. When one is investigating an environmental exposure to cancer in a community it is important to control for these factors very carefully. He agreed that even if you adjust for cigarette smoking, socioeconomic factors remain which can influence cancer risk. For example, for stomach cancer, which is not smoking-related, socioeconomic and ethnic variables are important, and studies of the effect of environmental agents must take them into account.

Dr. David Parkinson (University of Pittsburgh and International Steelworkers Union) stated that in the last 10 years, since the passage of the OSHA Act, a total of 23 standards have been set for the workplace, in his opinion a sorry record for the Administration. These standards were primarily single-substance standards, such as lead and asbestos, and very few of them were for substances on which we did not already have tremendous amounts of data. We have not yet gotten around to dealing with any of the exotic chemicals which have been developed over the last 20 years. His question was: How did the panel view the single toxic substance approach for standard setting? Could it ever really be a success? What about the generic standards that have been passed or are

proposed? Are they more successful or less successful than taking the single source approach? He was thinking in particular of the coke oven standard which he regarded as a generic standard, and which he thought is successful. He was also thinking about the standard for carcinogens, which again is a generic standard. What can environmental epidemiology do when dealing with a multitoxic substance world, and you are having to protect the health of workers living in that particular environment?

Dr. Bundy began by disagreeing about the 23 standards since OSHA was passed. When the law went into effect there were 400 standards that were incorporated. Perhaps they were not appropriate in all cases, but he did not view the few new standards as being way behind time. He believed that where generic standards can be applied, they may be appropriate. In this case, far too tight standards may be required in some places, and for that industry generic standards are a disservice. He did not think one could say individual standards are the best thing or generic standards are the best thing in every case. At times the combination of the two will prove better. He agreed that the coke oven standard is probably a generic standard, although citations are not issued on a generic basis. He pointed out that it is going to be several years before we will find out whether some of these standards are really correct or not. His plea to the epidemiologists in the group was to prove the standards are either right or need to be tightened.

Dr. Hunt agreed that the real world is a multitoxic world, yet we have developed the strength of epidemiologic methods on the basis of studies of single effects, particularly in terms of cancer. The methodology of epidemiology currently may be quite different from what we are going to have to develop to study a multitoxic world. In terms of studying the reproductive system, one of the more sensitive biological systems to examine, all of the components, the sperm cycle, the ovarian cycle, fertility, early reproductive loss, fetal deaths, stillborns, infant mortality, development abnormalities in subsequent life, all have to be evaluated. This series of endpoints may be affected by several environmental factors, in contrast to different kinds of cancer, which often tend to be agent-specific in etiology. The creativity that she believed was present at this symposium needs to be directed toward how to deal with the multitoxic world, how to use epidemiologic methods in this complex situation.

Dr. William Morton (University of Oregon Medical School) disputed the claim of Dr. Bundy that the major cause of lung cancer is smoking. About 20 years ago Hammond and Horn showed that if you stopped smoking for a year or more the lung cancer risk goes down. For the past 15 years or so smoking prevalence in this country has plateaued in males. Based on that experience, he would have expected the lung cancer death rate would have plateaued in males with a slight lag. This roughly has happened for coronary heart disease, which is another major smoking-related disease, and which also shows an effect of stopping smoking. Since that has not happened for lung cancer, we should expect something else is going on. Clearly, smoking is a risk factor, but it is a plausible hypothesis that its relative importance has been superseded by some other factors. Several years ago in Oregon a population study of lung cancer incidence was done. A major factor found to be important and characteristic was occupation, for both sexes. A key point here was that the occupational risk seemed to be histology specific. In other words, lung cancer is not a single disease, it is a group of diseases. With regard to Dr. Kuller's illustration of a socioeconomic effect on lung cancer, if you break that down by histologic types you find that some types go just the reverse. He thought that there is plenty of reason to look for other factors contributing to lung cancer, and occupational exposures are certainly a leading possibility.

Dr. Kuller responded by pointing out that even if we might wish that if we stop smoking on Monday, on Tuesday we would not get lung cancer, unfortunately it doesn't work that way. Because of direct effects of smoke products on the coronary circulation, especially from carbon monoxide and nicotine, for coronary disease there might be acute effects which would be removed immediately by stopping smoking, but actually the British physician studies show a substantial period of time before a decline in vascular disease mortality occurs. Secondly, although we believe that we have made an impact in getting people to quit smoking, if one looks carefully at the data it turns out a large proportion of the people who have quit are those who were relatively light cigarette smokers. Heavy cigarette smokers in the population are not those likely to quit, unfortunately. In addition, for lung cancer there are significant cohort phenomena, in the sense that each succeeding cohort up until the present time have been heavier cigarette smokers than the previous cohort. We are now seeing a rise in the rates of lung cancer in women.

His experience has not been that occupational factors are critical in overall lung cancer risk. It is very hard to find noncigarette-smoking lung can-

cer cases in most communities, irrespective of the histological type considered. There clearly are occupational factors in lung cancer. For example, in the steel industry the only lung cancer excess that was clear was among coke oven workers, and that was predominantly topside coke oven workers. They had a high relative risk but in a very small segment of that industrial population. To deny that cigarette smoking is the chief element in lung cancer would be wrong. Clearly, there are other factors that are important. He thought that despite rules and regulations reducing exposures to carcinogens in the workplace in all of the industries, if the men continue to smoke the way they do now, these regulations will have a small effect on lung cancer rates. Dr. Bundy added that the fact that both males and females are starting to smoke at earlier ages may be a significant factor causing the lung cancer rate to continue to go up. A critical length of time of exposure is reached much sooner now, and this may be one of the reasons a leveling off of the lung cancer rate has not occurred in males.

Dr. Radford commented that even though we all agree that more human epidemiologic studies are needed for purposes of control of hazards, as a matter of fact the funding situation is getting worse. First, there is a cut-back generally in research budgets. Secondly, the Congress is not sympathetic to epidemiology, nor is the scientific community, such as experimental biologists, physicists and chemists, who often disbelieve epidemiologic results. An important point about human epidemiology is that you cannot actually replicate an experiment, unlike the situation in laboratory science. For this reason, it is imperative that data obtained on large human studies have to be open to review. Biases that may be present have to be very carefully dealt with, which is why the point that the IRLG guidelines raised about making data available for scrutiny by one's peers is extremely important. How we can do this professionally is uncertain. He agreed with Dr. Bundy that replication was critical in validating the results of human studies. One implication of that is that you need at least two studies that are reasonably in agreement before you can regulate. Finally, with regard to the use of the National Academy of Sciences as an "impartial" arbiter of scientific truth, he believed that the Academy has become just as politicized as any other group. The NAS can get out of its reports anything that it wants to, depending on who is selected to serve on the committees preparing them.

Dr. Marvin Schneiderman asked to show some data that relate to what Dr. Bundy said about the trend of cancer rates in relation to the significance of occupationally induced cancers. Table 1 gives cancer incidence data for white males, age-adjusted to the 1970 United States population, comparing rates for 1969-71 to 1976. Cancer incidence (as well as mortality) data all show increases over the time period 1969-76, for black males (not shown) even greater than for white males. To prepare Table 1, he had first isolated the forms of cancer that he and others have indicated were likely to be industrially related and those not likely to be industrially related. Two groups of cancers were included in the occupationally related category: those more likely to be work-related and those less likely. Then he had corrected the rates for these possible occupational cancers that could be related to cigarette smoking (and also exposure to sunshine because he had included melanomas), for the effects of these known risk factors. The subheading entitled "other" included not only the remaining cancer types, but also that portion of lung, bladder and pancreatic cancers and melanoma attributable to smoking and sunlight exposure. For those cancer types identified as more likely to

Table 1. Changes in cancer incidence, U.S. white males, 1969–71 through 1976. Rates per 100,000 age-corrected to 1970.[a]

	Rate per 100,000		Average annual change, %[b]
	1969–71	1976	
Sites "more likely" to be related to occupation[c]	55.0	69.5	+4.0
Sites "less likely" to be related to occupation[d]	70.9	75.8	+1.1
Total sites likely to be related to occupation	125.9	145.3	+2.4
Total others[e]	216.6	228.7	+0.9
Total all sites	342.5	374.0	+1.5

[a]Data sources: 1969–71: Third National Cancer Survey; 1976: SEER (NCI).
[b]Average annual percentage change calculated from slope of linear regression fitted to annual incidence data.
[c]Cancers of lung, urinary tract and liver, plus lymphomas and melanoma.
[d]Cancers of stomach, lower intestinal tract (including rectum) and of the pancreas. Note: Smoking effects removed for cancers of lung, bladder and pancreas, and effect of sunlight corrected for melanomas.
[e]Includes all other sites, plus portions of lung, bladder, pancreas and melanoma attributed to smoking and sunlight.

be occupationally related, the annual average increase for white males has been more than four times as great as for the "other" category. The less likely sites, primarily intestinal tract cancers, showed only a slight difference.

Dr. Schneiderman said that the important conclusion about these results was that in commenting about whether cancer trends are changing or not, one should use up-to-date data. Also changes in cancer incidence are more important than changes in cancer mortality. He thought it was most inappropriate for Dr. Philip Handler or other people to talk about changes in cancer mortality that have occurred in the last 40 or 50 years, and not talk about the changes in incidence that have occurred in the last seven or eight years.