Methodologic Issues in Epidemiologic Risk Assessment

Markku Nurminen,' Tuula Nurminen, ' and Carlos F. Corvalan[2]

This paper reviews methodologic issues pertinent to the application *of* epidemiology in risk assessment and discusses concerns in the presentation *of* results from such an activity. Assessment *of* the health risks associated with occupational and environmental exposures involves four phases: hazard identification, ie, the detection *of* the potential for agents to cause adverse health effects in exposed populations; exposure assessment, ie, the quantification *of* exposures and the estimation *of* the characteristics and sizes of the exposed populations; dose-response assessment, ie, the modeling for risk realization; and risk characterization, ie, the evaluation of the impact *of* a change in exposure levels on public health effects.

The risk assessment process involves limitations *of* exposure data, many assumptions, and subjective choices that need to be considered when using this approach to provide guidance for health policy or action. In view *of* these uncertainties, we suggest that the provision *of* estimates *of* individual risk and disease burden in a population must be accompanied by the corresponding estimates *of* precision; risks should be presented in a sufficiently disaggregated form so that population heterogeneities are not lost in the data aggregation; and different scenarios and risk models should be applied. The methods are illustrated by an assessment on the health impacts *of* exposure to silica. (Epidemiology *1999;10:585-593)*

Keywords: epidemiologic methods, exposure estimation, health risk, silica, quantitative risk assessment.

Governing bodies at the local, national, and international levels face difficult decisions that would ideally be based on weighing the health and environmental cost of a technology against its economic and social benefits.' This requires that health effects of environmental exposures be quantified, yet data for this quantification are often limited. Quantitative risk assessment (QRA) must nevertheless be carried out for regulatory purposes. The fact that the result is often presented as a single number (for example, excess number of exposed disease cases) may imply certainty, which has obvious appeal among regulators and decision makers. Despite its apparent objectivity, QRA is dependent on a series of assumptions and subjective choices that can have critical effects on the resulting risk estimates. Thus, it is of prime importance that QRA be founded on solid scientific bases.

Health risks in human populations are increasingly being assessed by the use of empirical data from epidemiologic studies.' Although usually coupled with retrospective exposure assessments, epidemiologic studies can yield more defensible estimates of likely human health risks than those obtained from biologic models based on animal studies. Recent work that evaluated and improved the accuracy of prior estimates of exposure to benzene for a rubber worker cohort furnishes an example.3 The approach quantitatively accounted for multiple relevant factors, such as uptake of benzene due to short-term, high-level exposure to vapors; background concentrations in the manufacturing building; and con, tact with the skin. The predicted levels of exposure for the process workers, combined with morbidity and mortality data, were used to estimate the carcinogenic potency of benzene.

With nonexperimental epidemiologic methods, it is fairly easy to demonstrate that occupational groups sustain excess risks at high exposure levels. However, detecting health risks in relation to nonoccupational environmental exposures is far more difficult. The disease occurrence is often rare in the low,exposure range and, for example, in data analysis, the assumptions of the applied model cannot be tested. Thus, it is not surprising that different models may result in considerably disparate risk estimates when applied to the same data. In a review of the current methods for modeling epidemiologic studies for QRA, Stayner *et a14* suggested that a reasonable approach in choosing the appropriate model is to consider alternative (empiric and biologic) models and to present risk estimates from the models that fit the data well.

When the actual health effects are subtle, extremely large populations need to be studied to establish an exposure,disease relation, and the cost of cohort studies can be prohibitive. The use of the ecologic approach

From the 'Department of Epidemiology and Biostatistics, Finnish Institute of Occupational Health, Helsinki, Finland, and 2Department of Protection of the Human Environment, World Health Organization, Geneva, Switzerland.

Address correspondence to: Markku Nurminen, Department of Epidemiology and Biostatistics, Finnish Institute of Occupational Health, Topeliuksenkatu 41 a A, FIN-00250 Helsinki, Finland.

This paper is based on material that appeared in the unpublished document, "Linkage analysis for environmental health analysis-technical guidelines," released by the World Health Organization in 1997 (WHOIEHG/97.1 1).

The views expressed in this article are those of the authors and do not necessarily reflect the position of the World Health Organization.

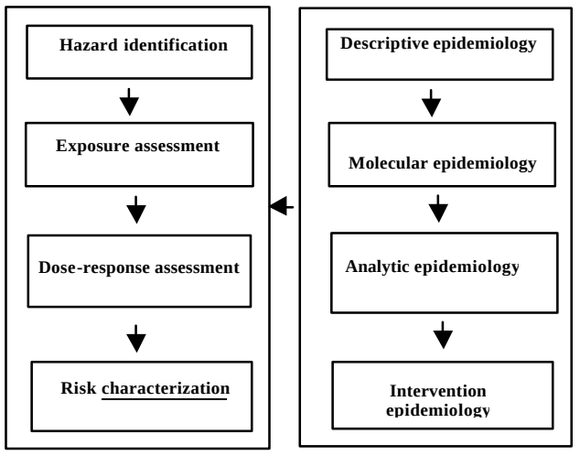

FIGURE 1. The phases of the quantitative risk assessment process (left) and the associated epidemiologic strategies (right).

permits the study of very large populations at a decidedly reduced cost, and the advances of epidemiologic study designs have brought about ways of improving the validity of such research.[5] It may be feasible to supplement aggregate data with sampled data at the individual level in a multilevel design, and the method proposed by Prentice and Sheppard[6] can be a cost-effective alternative to the study of entire cohorts.

The Risk-Assessment Process

Focusing on epidemiology, the different phases of the QRA process vis-£1-vis the types of epidemiologic strategy may be arranged as in Figure 1. Risk assessment conventionally involves the following four steps (cf Ref 7):

1. Hazard identification aims at answering the ostensibly simple question, "Does the available evidence point to the potential for a risk agent to cause harmful health effects in exposed populations?"

2. Exposure assessment proposes to describe the exposure patterns and processes and to estimate the intensity and duration of exposure, as well as the characteristics and number of persons actually or potentially exposed.

3. Dose-response assessment is modeling for a relation between exposure to an identified hazard at different dose levels and the disease risk it induces.

4. Risk characterization seeks to provide answers to two questions: "What are the health consequences of exposure to hazards at current dose levels?" and "What would be the health benefits of risk reduction by lowering the dose levels?"

Epidemiologic approaches are used in the various phases of QRA. In cancer risk assessment, for example, techniques of "molecular" epidemiology's such as bio, logic marker? of exposure, effect, and susceptibility, and biologically based pharmacokinetic models,10 have been used to estimate doses in target organs and tissues, as well as to elucidate mechanisms of dose-response relations observed in classical epidemiologic studies. These studies bridge the gap between laboratory experimentation and population-based epidemiology.

Miettinen[11] has remarked that "descriptive relations bear on such passive matters as prognosis setting and risk assessment, whereas knowledge of causal relations is the basis for interventions, that is, for willful alterations of the outcome through perturbations of the determinant." Aggregated measurements of disease occurrence in population groups are usually associated with descriptive epidemiology, whereas measurements made at the level of the individual subject are associated with analytic epidemiology. However, to make a stark distinction would not be sensible, as it would neglect the role of the aggregate-level evidence in quantifying the relation between environment and disease.

Decision making can benefit from systematic analyses that estimate the level of exposure and the magnitude of the accompanying health effect. The upshot of a completed QRA process is risk prediction in a hypothetical scheme of change in exposure. But, in a favorable situation, an evaluation of the effectiveness of an *actual* risk reduction program can be performed by using methods of intervention epidemiology.

The usefulness of QRAs lies in the fact that they can be performed in circumstances in which only insufficient health outcome data are available. But the success of the risk assessment depends on a number of factors, such as adequacy of exposure assessment and choice of the em, ployed risk model. In the analysis of existing aggregate data, QRAs require few resources, are quick to execute, and allow rapid risk predictions. On the other hand, QRAs based on ad hoc individual-level studies can be very complex, data-intensive and time-consuming efforts. There are generally a great deal of uncertainties and a number of shortcomings associated with all of the concerned issues. A discussion of these limitations is necessarily dependent on the objective of the QRA and the practical setting in which the evaluation is conducted. Although it would be difficult to discuss in generic terms the problems that practicing risk assessors encounter in such diverse fields as cancer epidemiology or environmental pollution epidemiology, we proceed to review some major issues related to QRA using epidemiologic data and illustrate these by examples.

Hazard Identification

QRA is often based on routinely collected data. Under these circumstances, the use of either environmental data alone or health data alone may be the only means of identifying environmental hazards to the health of a population. Ideally, corroboration of either the environmental data or the health data is, required to found a relation. This involves cross-checking both environmental and health data by examining health evidence of potential problems together with relevant environmental exposure data available or, conversely, verifying whether the potential health risk implied by the exis~ tence of a hazard is substantiated by excess morbidity or

excess mortality. For hazard identification, systems for surveillance of exposures and health outcomes have been set up.

Example 1

If the aim of epidemiologic hazard surveillance is to identify and monitor exposures to carcinogenic substances in the workplace, then it would appear intuitively that the most expeditious approach would be to go directly to industry and identify the exposures. In practice, however, it is not easy to identify all exposures, not to mention quantification. This view appears to be supported by the experience in Finland, where a register of employees occupationally exposed to carcinogenic substances and processes was established (in 1979) with the aim of identifying all workplaces where there is potential exposure to known human carcinogens. It is extremely unlikely that all of the uses of carcinogens in the Finnish industry are being identified with this hazard surveillance system. The Finnish Institute of Occupational Health (FICH) showed in the 1980s that (1) small industries in particular were underreporting the use of registrable substances, (2) fewer exposures and fewer exposed workers were registered than expected from prior estimates, and (3) no exposure data existed on 50 of 138 registrable substances. [12]

Moreover, the register includes some, but not all, workers who are exposed to agents that are "probable" or "possible" human carcinogens according to the classification of the International Agency for Research on Cancer (IARC) .[12a] In 1993, for example, 80,000 Finnish workers who were exposed to quartz dust, which then was considered a probable human carcinogen, were not registered." Today, quartz dust is a "definite" human carcinogen according to the IARC, but the agent is not classified as such in the Finnish list of carcinogenic substances, and workers exposed to quartz dust are still not registered. Even if it were possible to identify every occupational exposure circumstance to every known or suspected carcinogen, this in itself would present an impossible logistical problem of trying to ensure that the risks were adequately controlled in all cases. Furthermore, much of the effort would be unproductive, because many of the uses of carcinogenic substances would involve insignificant risk, given minimal or infrequent exposure currently in Finland.

Technically, it is possible to link the data from the FIOH register of employees occupationally exposed to carcinogens with the Finnish Cancer Registry data on an individual basis. However, cancer risk assessments that would exploit this linkage would be handicapped by the lack of data on relevant covariates; for example, the above registers contain no information on personal smoking habits, a major risk factor for many cancers. Therefore, it is unlikely that the FIOH register data can be used, for example, f~r the estimation of the etiologic fraction of particular occupational exposures in the causation of cancers. Nevertheless, there are indications that the mere establishment of this hazard surveillance system may have reduced the use of carcinogenic materials by way of alerting industries to use substitute products. In 1993, 15,000 new notifications of individual exposed workers were made to the FIOH register. This figure is 5% less than in the previous year, which may have been caused by the register but also by the decrease of exposed workers during a recession.

Essentially, routine data on environmental conditions are most often available at the aggregate level. These tell one about the risks potentially faced by a group of people but tacitly assume that all members of the group experience the risk equally (and thus potentially experience the health consequence equally). Conversely, routine data on morbidity or mortality rates alone give only average risks expected by individuals, without data on the materialized risks (disease events experienced by individuals). Both types of data should be used with caution on their own, because ideally a linkage should be established to make accurate judgments about potential policy solutions.

Example 2

Exposure to crystalline silica (silicon dioxide) dust causes occupational disease unless it is appropriately controlled. In the past, Australian control strategies have been designed to prevent the occurrence of silicosis. At workplaces in which existing standards have been enforced by the inspectorate and modern control measures have been rigorously applied, there appears to be little evidence of adverse health outcomes, although the data may be incomplete. The various Australian standards, ranging from 0.15 to 0.2 Mg/M3 depending on the state, are historically based on the occurrence of silicosis in sandstone workers in Sydney. Worksafe Australia,14 however, has promulgated a report on crystalline silica in which lung cancer is considered one of the health effects that should be taken into account in determining exposure standards.

Australian work environmental data on the extent of silica exposure and health effects are limited. Although some industries, such as mining, have good exposure monitoring records and compensation registers on silicosis, little information is available on industries such as manufacturing and construction. Therefore, an approach to national risk assessment was needed to supplement existing records of exposure monitoring and data on health effects.

Health outcome data were derived from compensation systems and were indicative of past exposure to silica. The largest numbers of workers compensated by the New South Wales Dust Diseases Board came from the manufacturing, construction, and mining industries. Other health outcomes such as lung cancer or chronic obstructive airway disease have not been assessed for work involving exposure to silica. However, specific studies on lung cancer and airway disease in Western Australia revealed that these diseases are more prevalent among silica-exposed workers than among the general population, but it was unclear to what extent their increased frequency was due to silica exposure, cigarette smoking, or the joint operation of the two. Berry[15] has

recently reviewed the evidence that there may be an increase in the incidence of lung cancer in those exposed to silica. He concluded, "Although it has not been demonstrated that silicosis is a necessary precursor of any lung cancer that may be due to silica exposure, there is evidence that any increase in [lung cancer] risk will be greater in those with silicosis than in those without. Thus control measures effective in reducing silicosis will also be effective in reducing any excess in lung cancer."

Finally, one can question how hazard identification is conducted, particularly when numerous relevant epidemiologic study results are available. This discussion would need to pay attention to the general validity of individual studies, the criteria of causation, and meta, analysis. [16]

Exposure Assessment

EXPOSURE AND DOSE ESTIMATION

A crucial constituent in any attempt to estimate the magnitude of the health effect caused by a risk agent is the validity of the method assessing the level to which d-ie studied populations are exposed. Direct measurements are seldom available, except when routine monitoring is applied in the control of industrial exposures or environmental pollutants. Therefore, often some semi-quantitative method for estimating exposures from limited information must be used. In a complex exposure situation, exposure models may be used to describe the action of the risk agent in the environment and to provide quantitative estimates of exposure. Besides intensity, the valid representation of the actual exposure has to account for the composition and duration of exposure as well as for the time since the start of first exposure.

Example 2, Continued

For the purposes of a QRA, the members of the National Institute of Occupational Health and Safety, Australia, Expert Working Group on Crystalline Silica, used their expertise and judgment on the hygienic conditions and processes at the work sites and supplementary information from companies, where available, to evaluate the median level of exposure in the occupational subpopulations and the number of workers actually exposed to silica. Yet, owing to their crude nature, these data have to be examined with reservation. Also, because expert judgment is by its nature essentially subjective, it is important that the decisions reached and criteria used are well documented, [14] as was the case in this QRA.

Determining dose or estimating the amount of a substance actually taken in by exposed subjects can be performed by applying kinetic models. However, this is a difficult task, because the biologic phenomena in the human body are complex. For example, the uptake, distribution, and excretion of pollutants during an inhalation exposure involve dynamic processes.

Example 3

In a field study, Tossavainen *et* [a117] applied a linear one-compartment kinetic model for describing nickel (Ni) and chromium (C0 concentrations in connection with an occupational exposure to these carcinogenic substances. The measured quantities that were represented in the model were atmospheric concentration of Ni and Cr in a worker's breathing zone, concentration of Ni and Cr in plasma or urine, and recorded times of exposure measurements and biologic tests. The estimated parameters were scaling parameter, which accompanied by an assumption of individual's minute ventilation can be used to compute the accumulation or elimination rate; half-time of the concentration in plasma or urine; and baseline concentration to account for the dietary metal uptake and body burden. The model allowed a precise description to be made of a welder's and an electroplater's state of exposure at different points in time as affected by a varying concentration of the metals in the workroom air.

APPLICABILITY OF EXPOSURE ESTIMATES FOR RISK MODELING

A big concern in QRA is that the results from epidemiologic studies derived in exposed populations cannot always be applied directly to another population subjected to different exposure conditions. In the QRA for silica, for example, the exposure measures that were used to estimate the dose,related risk may accrue from work experiences of different average duration.

Example 2, Continued

Using empirical models for risk, based on the published Canadian epidemiologic experience18 with hard-rock miners, Nurminen *et al.* predicted the occurrence of silicosis in the Australian labor force currently exposed to crystalline silica dust. In the exponential model for risk of silicosis, the investigators used a cumulative index of exposure, which was a product of the median level and average duration of individual worker experiences in the particular industry or occupation or age categories. This approach, which was also used in the Canadian" and Chinese20 studies, was followed, because, in general, it is the implicitly adopted strategy for dust control measures. However, the use of such an index implies, for example, that the increase in the relative risk of silicosis caused by exposure to, say, a silica dust level of 0.1 Mg/M3 for 40 years is the same as that caused by exposure to a level of 0.4 mg/m3 for 10 years.

In QRA, one should be careful when assessing risks associated with different agents separately. In situations in which two different agents have common health endpoints, one should ensure that the estimates are adjusted for the effect of both exposures.

Example 2, Continued

In the Australian QRA,19 the investigators used the epidemiologic relation between silicosis in Ontario hard-rock miners and cumulative exposure to silica dust, which may not be directly applicable to the conditions of Australian industrial work sites. The Canadian study" cautioned about possible coexposures when risks due to silica dust in one industry or occupation are compared

with those reported in other contexts. For example, some forms of crystalline silica, such as cristobalite and tridymite, may have a greater fibrinogenic potential than silica itself. On the other hand, silica mixed with high concentrations of inert coal dust and silicates may diminish the apparent toxicity of the silica fraction. Similarly, high concentrations of clay minerals in silica dust may reduce the risk of silicosis among workers in the brick industry.

Using reassessments of South African silica exposure data," Leigh et all' revised their original estimates" of silica-related risk of lung cancer. A problem with this QRA is the assumption that the South African data" can be used as an estimate of the silica-induced risk of lung cancer when there is possible confounding with the effects of radon daughters and diesel fumes.

HETEROGENEITY OF ExposURE

In environment and health analysis, exposure data and risk statistics are usually collected and presented at a high level of aggregation. If they are averaged over many distinct classes of subjects, the results may have little relevance for any particular individual.

Example 2, Condnued

Each of the approximately 136,400 workers in the Australian labor force, who were assessed as exposed to silica dust in their work, belonged to exactly 1 of the 1,000 possible categories in a 50-times-20 industry-by-occupation cross-classification, with an accompanying average exposure intensity. There were 665 subpopulations with a nonzero exposure intensity. This classification was considered to be specific enough for monitoring the population at risk. In all industries combined, only an estimated 10% of the workers were exposed to silica at levels above 2.0 mg/m3. Such exposure matrices are generally assumed to have a normal measurement error structure of the Berkson type, in which the average of the true intensities for all subjects in an exposure assignment group is equal to the assigned value. Fortunately, if the true dose response is linear, the estimated slope of a linear regression line will be unbiased.13 In the exponential model, there is also no regression attenuation provided that the error variance is independent of the true mean value.'3 Close study of the exposure matrix led to the incontrovertible conclusion that urgent attention should be paid to the working conditions of certain occupations across all industries. For instance, in each industry with drilling plant operators, this occupation was the one associated with the highest exposures.

Dose-Response Assessment

Modeling for risk realization includes four different stag, es: (1) causal modeling for explaining the basic health consequences of exposure action, (2) statistical modeling for expressing the risk as a mathematical function of exposure, (3) demographic modeling for predicting the exposure impact on population health, and (4) model validation. Some aspects of these stages are discussed below.

The dose-response relation used in QRA is based on the premise that exposure causes disease. Causal modeling involves the specification of all of the determinants the change of which, on a conceptual level, is thought to affect the disease risk. This set of determinants includes not only the exposure variate representing the risk agent, but also variates for confounders and factors that modify the risk. Once a relation, often nonlinear, between exposure to an agent (for example, a toxic chemical) and public health risk has been found and reported, an appropriate reaction is expected from the society. Increasingly, QRA uses a "weight-of-the-evidence" approach that examines all of the relevant information: toxicology bioassay data collected from animal experiments or human exposure chamber studies; health data gathered in epidemiologic studies and disease registers; scientific knowledge about the mode and mechanism of exposure action; data on the intensity, duration, and frequency of exposure; and estimates of the sizes of exposed human populations at each anticipated dose level.

The risk of developing a disease due to environmental or occupational exposure to agents at different levels of intensity and duration can be assessed by means of a statistical (stochastic) model for an exposure-effect relation. However, the concept of risk being a probability measure pertains to an individual. In epidemiology, risk can be estimated as a cumulative incidence rate in a population. Risk functions describe the change in risk as a function of a change in the exposure index. A simple cumulative exposure index is formed as the product of the intensity and duration of exposure. These entities can then be translated via a demographic (deterministic) model to the predicted number of disease events caused by the exposure in question.

Example 2, Continued

For silicosis, Muir et all" quantitated the risk with model relating cumulative respirable silica exposure (particle -years) to the cumulative incidence rate. The model assumed an exposure-effect relation in which the effect was proportional to the power of the exposure: $R,, = a(L . D.)P$, where $R.$ stood for the risk in the ath age category, L was the dust level or intensity of exposure (mg/m'), $D.$ was the average attained duration of expo, sure (in years) for the subjects in the *ath* age category, and " = *0.00109* and $ = 1.72 were the Weibull distribution model parameters that were estimated from the experience of hard-rock miners in Ontario.

The preceding risk model assumes, first, that silica dust is a necessary cause of silicosis. Second, it is the accumulation of silica over the years, that is, the product of level and duration, that determines the risk and not the intensity of exposure in itself. However, several additional assumptions were necessary to predict realizations of risks in terms of the numbers of people sustained (for example, stationary age distribution, constant exposure intensity, 40-year follow-up period).

The expected number of silicosis cases was computed as: S . T . I, where S = size of the industrial subpopulation, T = follow-up time in years, and I = incidence rate of silicosis (in units of cases per year). The rate I was considered a weighted average of the age-specific incidence densities, I.. The latter densities were solved from the relation between risk and incidence density, specifically: $R_a = 1 - exp(-I_a.D_a) <=> I_a = -(109(1 - RJ111)$, But, because the silicosis risks were small, an accurate approximation for I. was provided by $R_a JD_a$,

In the modeling for the risk of silicosis, a 5-year lagging of exposures was explicitly incorporated into the analysis. Thus, the time between the deposition of silica in the lungs and the clinical appearance of silicosis was taken into account when the expected numbers of cases was computed.

In addition to the statistical and demographic assumptions underlying the QRA modeling, there are also occupational hygienic and toxicologic variabilities that could make the error range even more uncertain. In general, to allow for the uncertainties associated with many of the model variables, different scenarios should be evaluated by using different inputs for the prediction formula. However, by setting the error range wide enough to swamp the uncertainty for each of the many variables separately- but not necessarily for all the variables simultaneously-risk assessments may evaluate scenarios that will rarely, if ever, come true. This problem can be overcome by modeling the key inputs as random variates having probability distributions. This method provides a quantitative way to estimate both point values and full distributions for exposures and risks."

Ideally, the predictive capability of the adopted model should be tested in a field study. Unfortunately, such model validation is seldom possible, and even if it were, the results would apply to the specific environmental conditions and they would perhaps not be applicable in a different environmental setting.

Risk Characterization

Risk characterization summarizes and interprets the information collected from previous activities and identifies the limitations and the uncertainties in risk estimates. When the results from exposure and effect estimation are at hand, the next task for the analyst is to communicate the information to the decision makers in such a form that they can readily act on it. This is especially important in the linking of environment and health data, because the decision makers often are not well versed in the specialized statistical methods. Moreover, there is a need to present the results of QRA in such terms that they can be easily transformed into inputs for a societal or individual cost-benefit analysis.

MEASURES OF RISK AND EXPOSURE IMPACT ON HEALTH

The quantitative estimate of risk is the result of main interest to the health agency or risk manager in arriving at decisions. QRA provides the link between environmental health science and environmental health policy.[25] Three basic and most commonly used quantitative measures of risk are individual risk *(ie,* the probability that an individual will develop a disease as a result of exposure in a specified time period), population risk or disease burden *(ie,* the expected number of disease cases attributable to exposure in the population under study in a specified time period), and shortened life expectancy or expected years of life lost. These measures may have different regulatory implications: the regulatory authorities may wish to evaluate either the risk incurred by individuals who are exceptionally highly exposed or highly vulnerable, or the societal risk inflicted on a large population whose members' average exposure could be much lower.

Example 2, Continued

Using the models for risk presented above, Nurminen *et a1*[19] predicted the occurrence of silicosis in the Australian labor force currently exposed to crystalline silica dust. As a result of a 0.9% (diagnostic range = 0.41.9%) average work-life risk, approximately 1,010 (range = 380-2410) silicosis cases were predicted for the next 40 years among the estimated 136,400 men exposed at current silica dust levels [0.01-0.8 (average = 0.094) Mg/M3]. Currently, 77% of the labor force at risk is exposed to silica dust levels of :f~-:0.1 Mg/M3. With this level as the limit, about 440 (range = 140-1,210) silicosis cases would appear in 40 years. Adopting this level as the national exposure standard would reduce the work-life risk of silicosis to 0.4% (range = 0.1-1.0%).

To provide some perspective, the results of QRA are often expressed as decremental risks in an envisioned situation of a lower exposure level. Thus, a risk assessor might interpret the results conditionally as follows. If an exposure level of 0.2 mg/ml were the standard adhered to, then there would be a 15% reduction in the risk of silicosis. If, however, the exposure standard were set at 0.1 mg/ml, then a reduction of about 50% would be predicted.

A new cohort study [16] of white South African gold miners assessed the silicosis risk in relation to dose up to 30 times greater than in the Canadian study [18] originally used by Nurminen *et al.* [19] When Leigh *et all'* applied the accelerated failure time model with the log-logistic distribution that was used in the South African study, the revised prediction was that, at 1 Mg/M3, more than 100 incident cases of silicosis, instead of 10, would be diagnosed annually. Multiple (physicochemical, radiographic, and epidemiologic) reasons for the marked difference between the two studies have been discussed in the literature. [17-1'] However, the fact that the South African study agrees very closely with another cohort study of white gold miners from South Dakota 30 suggests that the Canadian study underestimated the risk of silicosis.

The line between QRA and decision making is often not clear. Hence, the risk assessor must present the results in such a way that it does not preclude their direct application to policy making. Assumptions and limita-

tions have to be made explicit. Key factors modifying the risk should be explained. A good risk characterization provides the kind of information risk managers need to make informed decisions regarding the necessary magnitude of reaction and whether a range of risk reduction measures should be considered.

POPULATION HETEROGENEITY AS A SOURCE OF VARIABILITY

The many sources of variability in the QRA process include the presence of population heterogeneity. Strictly speaking, the assumption of risk homogeneity probably does not hold in most real situations, because unrecognized risk factors presumably subject different individuals to different background disease risk. As pointed out by Robins and Greenland,` the heterogeneity of background risk is almost always quite severe. This is because there are likely to be *unmeasured* constitutional (genetic, other congenital, or acquired), environmental, and behavioral factors that vary across individuals and thus strongly affect individual risk. Also, some persons (for example, children) are more susceptible to an underlying risk factor (or set of factors) than others and sufficiently so to make them contract a disease after being exposed." Under heterogeneity, one can still estimate the risk as the cumulative incidence rate (ie, the number of cases over the population size) but must recognize that the pooled statistic represents an average risk in the population. Unfortunately, the estimates of the standard error and confidence limits for the pooled population risk will be invalid when risks are markedly heterogeneous. The implication is that the practitioner of QRA should always check for heterogeneity before presenting aggregate population statistics. The question is, How should one cope with the existing heterogeneity that is not small enough to be reasonably ignored? A simple recommendation is that the populations should be split into more homogeneous subpopulations. But this sounds like begging the question, How do we choose subpopulations that are risk homogeneous enough? A possible approach is to acquire more information about the population for describing the risk as a function of exposure and covariates. The population members can then be partitioned into relatively homogeneous strata (for example, risk octiles) on the basis of their multivariate risk score.33 A limitation of the approach is that generally the risk strata lack biologic interpretation. However, an array of summary statistics can be presented to adequately reflect the variability and range of risk, rather than to give only a single pooled risk estimate.

UNCERTAINTY ANALYSIS

An adequate documentation of the source and nature of uncertainty is imperative in the characterization of risk.34 The discussion of assumptions (or lack of knowledge) and uncertainties should highlight the major limitations of the analysis and remark on the relative importance of the various sources of variation (both sampling and non sampling errors).

An analysis and display of uncertainty in public QRAs is possible by means of the Monte Carlo simulation techniques." These extended methods begin with the conventional estimation of an exposure model and continue by modeling the key inputs as random variates described by probability density functions. For example, the problems associated with the use of "reasonable maximum" and "worst-case" exposure assumptions, which result in atypically high point estimates of risk, and the need to properly account for small but highly exposed populations can be dealt with using simulation techniques. This approach imparts much more information to the risk manager concerning the distribution of the likely values of each parameter of the risk reduction model than do single-point estimates based on known or fixed parameter values. To allow for the uncertainties with the specification of the exposure and risk models and the input variables and constants for the models, different scenarios regarding the underlying assumptions can be proposed. Overall, the simulation techniques provide a simplified, quantitative way to estimate the probability distributions for exposure and health risks within the validity of the model used.14

ESTIMATION OF HEALTH BENEFITS FROM PREVENTION

Intervention epidemiology studies are important means to evaluate the effectiveness of an instituted intervention program for the reduction of excess risk or for risk prevention." They also provide support necessary to extend or alter prevention efforts. At best, an intervention study should measurably show a parallel between exposure reduction and risk reduction.

The importance of a risk factor for the incidence of a disease in a population is usually expressed as the etiologic fraction,' 1 that is, the proportion of the actual total incidence of the disease that can be attributed to that causal factor in the population. Another interpretation of this measure is that it indicates the maximal proportion of disease incidence that could be prevented by the elimination of the operation of that risk factor in the population."

Example 4

A cohort study from Finland37 on carbon disulfide (CS2) and ischemic heart disease provides an illustration of an analytic epidemiology study leading to a risk-prevention program followed by an intervention epidemiology study. The evidence for the risk from CS2 was obtained from retrospective and prospective studies covering the years 1942-1967 and 1967-1975, respectively. Because exposure control efforts in the viscose rayon plant had been gradually improving over the years, no new action was taken until analyses of the prospective phase of the study showed persistence of the excess mortality risk. A vigorous intervention program was initiated in 1972 when the Finnish hygienic standard for CS2 was reduced from 60 to 30 mg/ml (10 ppm). Moreover, the labor safety committee of the factory drafted a detailed long-term program for lowering the CS2 concentrations in the air of the rayon fiber factory below the allowable limit.

This program was approved by the board of directors of the factory and was being enforced. Furthermore, the company management introduced a new policy of transferring to uncontaminated departments workers with a long history of exposure to CS2. An extended follow-up study that ended in 1983 demonstrated that the cardiotoxic effects of CS2 are reversible in the sense that the cessation of, or a radical decrease in, exposure reduces the risk of cardiovascular mortality to background levels.[37] The authors evaluated the impact of the intervention measures by computing the number of deaths from ischemic heart disease that would have occurred among the exposed cohort members had the same mortality risk that prevailed before 1975 continued after 1975. On the basis of the mortality rate of the reference, the results suggested that the fraction of prevented or postponed ischemic heart disease deaths among the formerly exposed workers was about 70%.

Because prevention will usually not eliminate but merely reduce the prevalence or intensity of an environmental risk factor, a measure has been developed to estimate the expected impact of a change in prevalence of a risk factor on the incidence of a disease, the potential impact fraction.36 It indicates the incidence rate that may be avoided by a planned intervention program as a proportion of the incidence rate that would be expected to occur in that population without preventive intervention. The potential impact fraction can be calculated when the prevalence of exposure to a risk factor in the population and the corresponding incidence rate ratios or risk ratios are known.

The potential impact fraction in the traditional epidemiologic literature assumes that there are no significant temporal trends in disease risk resulting from changes that are unrelated to the prevention. However, the reduction of excess risk after reduction of exposure may take many years to achieve, so that the estimates of effect will have to incorporate a time dimension. To achieve this objective, an applied epidemiologic methodology based on the preventive impact fraction31 has been developed to help apply existing epidemiologic knowledge to decision making in health policy. The computer simulation model PREVENT" can estimate the health benefits for a population of changes in risk factor prevalence. This model is a useful tool for policy makers, because it will present the results in graphic or tabular form for the intermediate output variates of etiologic fraction, trend impact fraction, and potential impact fraction, and for the following final output variates: disease-specific mortality, total mortality, disease-specific mortality difference, potential years of life gained, actual years of life gained, survival curves, and life expectancy at birth.

A preventive intervention program is often difficult to "sell" politically, because its effects take so long to become apparent. The situation can be even worse: effects will seldom become apparent as real reductions in risk because of the demographic changes in the study population over time. This does not mean that prevention will not have beneficial effects despite competing death risks, say, in an aging population. It does mean, however, that to see the actual effects it is necessary to show what happened or would happen without the preventive intervention. This demonstration may be based on the experience of a real or hypothetical reference population. The potential utility of simulation models such as PREVENT39 for policy making lies in their ability to provide more precise quantification of effect estimates by appreciating a time trend and multiple risk factors, as well as the interaction between the effects of intervention and the demographic evolution of the population.

Acknowledgments

We thank Timo Partanen and the referees for their helpful comments, and Leshe Stayner for providing relevant references.

References

1 . McMichael Aj. Setting environmental exposure standards: the role *of* the epidemiologist. Int J Epidemiol 1989;18:10-16.
2. Shore RE, lyer V, Altshuler B, Pastemack BS. *Use of* human data in quantitative risk assessment *of* carcinogens: impact on epidemiologic prac, rice and the regulatory process. Regul Toxicol Pharmacol 1992;15:180-221.
3. Paustenbach DJ, Price PS, Ollison W, Blank C, jernigan JD, Bass RD, Peterson HD. Re-evaluation *of* benzene exposure for the Pliofilm workers (1939-1976). J Toxicol Environ Health 1992;36:177~231.
4. Stayner L, Smith R, Bailer A), Luebeck EG, Moolgavgar SH. Modeling epidemiologic studies of occupational cohorts for the quantitative assess. ment of carcinogenic hazards. Am J Ind Med 1995;27:155-170.
5. Morgenstem H. Ecologic studies. In: Rothman Kj, Greenland S, eds. Mod. ern Epidemiology. 2nd ed. Philadelphia: Lippincott-Raven Publishers, 1998: 459-480.
6. Prentice RL, Sheppard L. Aggregate data studies of disease risk factors. Biometrika 1995;82:113-125.
7. Covello VT. Risk assessment. In: Waldron HA, Edling C, eds. Occupational Health Practice, 4th ed. Oxford: Butterworth-Heineman, 1997.
8. Schulte PA, Perera FP, eds. Molecular Epidemiology: Principles and Practices. San Diego: Academic Press, Inc, 1993.
9. Hulka BS, Margolin BH. Methodologic issues in epiderniologic studies using biologic markers. Am J Epidemiol 1992;135:200-209.
10. Bailer Aj. An introduction to the use of physiologically based pharmacokinetic models in risk assessment. Stat Methods Med Res 1997;6:341-358.
11. Miettinen 05. Theoretical Epidemiology: Principles of Occurrence Research in Medicine. Albany, NY: Delmar Publishers Inc, 1985.
12. Rantanen J, Heikkilg P. Carcinogens in the work environment (address to Symposium on Experimental and Epidemiologic Applications to Risk Assessments of Complex Mixtures). Espoo, Finland, May 1989.
12a. Intemational Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC, Lyon, France, 1999.
13. Finnish Institute of Occupational Health (FIOH). Annual Report. Helsinki, Finland: FICH, 1995.
14. Worksafe Australia. National Occupational Health and Safety Commission Report 1991-1992. Canberra: Australian Government Publishing Service, 1993.
15. Berry G. Crystalline silica: health impacts and possible lung cancer risks. J Occup Health Safety-Aust N Z 1996;12:157-167.
16. Greenland S. Meta,analysis. In: Rothman Kj, Greenland S, eds. Modem Epidemiology. 2nd ed. Philadelphia: Lippincott-Raven Publishers, 1998: 643-673.
17. Tossavainen A, Nurminen M, Mutanen P, Tota S. Application of mathe, matical modelling for assessing the biological half-times of chromium and nickel in field studies. Br J Ind Med 1980;37:285-291.
18. Muir DCF, Julian JA, Shannon HS, Verma DK, Sebestyen A, Bernholz CD. Silica exposure and silicosis among Ontario hardrock miners. Ill. Analysis and risk estimates. Am J Ind Med 1989;16:29-43.
19. Nurminen M, CorvalAn C, Leigh J, Baker G. Prediction of silicosis and lung cancer in the Australian tabor force exposed to silica. Scand J Work Environ Health 1992;18:393-399.
20. Pang D, Fu S, Yang GC. Relation between exposure to respirable silica dust and silicosis in a tungsten mine in China. Br J Ind Med 1992;49:38-40.
21. HniAo E, Sluis-Cremer GK. Silica exposure, silicosis and lung cancer: a mortality study of South African gold miners. Br J Ind Med 1991;48:53-60.
22. Leigh J, Macaskill P, Nurminen M. Revised quantitative risk assessment for

silicosis and silica related lung cancer in Australia. Arm Occup Hyg 1997; 41(suppi l):480-484.
23. Armstrong BO. The effects of measurement errors on relative risk regressions. Am j Epidemiol 1990;132:1176-1184.
24. Thompson KM, Burmaster DE, Crouch EAC. Monte Carlo techniques for quantitative uncertainty analysis in public health risk assessments. Risk Anal 1992;12:53-63.
25. Hertz-Picciotto 1. Epidemiology and quantitative risk assessment: a bridge from science to policy. Am J Public Health 1995;85:484-491.
26. Hnizdo E, Sluis-Cremer OK. Risk of silicosis in a cohort of white South African gold miners. Am J Ind Med 1993;24:447-457.
27. Hughes JM, Weill H. Silicosis risk: Canadian and South African miners.
Am J Ind Med 1995;27:617-618.
28. Hnizdo E. Risk of silicosis: comparison of South African and Canadian miners. Am J Ind Med 1995;27:619-622.
29. Rice FL, Stayner LT. An assessment of silicosis risk for occupational exposure to crystalline silica. Scand J Work Env Health 1995;21 (suppi 2):87-90.
30. Steenland K, Brown D. Silicosis among gold-miners: exposure-response analyses and risk assessment. Am J Public Health 1995;85:1372-1377.
31. Robins J, Greenland S. Estimability and estimation of expected years of life lost due to hazardous exposure. Stat Med 1991;10:79-93.
32. Perera FP. Molecular epidemiology: insights into cancer susceptibility, risk assessment, and prevention. j Nad Cancer Inst 1996;88:496-509.
33. Strauss D. On Miettinen's multivariate confounder score. J Clin Epidemiol 1998;51:233-236.
34. Morgan MG, Henrion M. Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis. Cambridge, United Kingdom: Cambridge University Press, 1990.
35. Wegman DH. The potential of epidemiology on the prevention of occupational disease. Am J Public Health 1992;82:944-954.
36. Morgenstern H, Bursic ES. A method for using epidemiologic data to estimate the potential impact of an intervention on the health status of a target population. j Commun Health 1982;7:292-309.
37. Nurminen M, Hemberg S. Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulphide: a 15 year follow up. Br j Ind Med 1985;42:32-35.
38. Gunning-Schepers Q. The health benefits of prevention, a simulation approach. Health Policy 1989;12:1-256.
39. Gunning-Schepers Q, Barendregt JJM, van der Maas Pj. PREVENT, a model to estimate health benefits of prevention. In: World Health Organization (WHO). Tools for Health Futures Research. Geneva: WHO, 1993; 7-21.