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Environmental epidemiology and risk assessment

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ABSTRACT

Epidemiology is the science of public health. Environmental epidemiology specially focuses on human health risks related to exposures in the general (non-occupational) environment. Epidemiology studies may contribute to human risk assessment by identifying hazards, by assessing human exposures to toxicants, and by establishing exposure response functions that can then be used to generate risk assessments. Examples are provided for each of these. The strengths and weaknesses compared to experimental toxicology studies are discussed.

Epidemiology has a special role to play in risk assessment of environmental exposures. This is because epidemiology, unlike animal toxicology, is based on direct observations in humans. There are limitations also in that epidemiology studies cannot usually be very invasive and/or experimental in design. For these reasons, epidemiology and animal and in vitro toxicology complement each other in the risk assessment sciences.

1. What is (environmental) epidemiology?

Environmental epidemiology is a sub-specialty of epidemiology, the basic science of public health. Epidemiology is the study of the distribution of health and disease in the population, and of the determinants of this distribution. Environmental epidemiology studies the effects of *environmental* exposures on health and disease in the population. The subject matter of environmental epidemiology is *environmental health*: this, in principle, covers all factors external to the human body which may affect health. However, several other exposure-related branches have grown out of the main epidemiology tree, and environmental epidemiology does not try to cover all external factors which may conceivably influence population health. Instead, it focuses on physical, chemical and (non-infectious) biological factors in our every-day environment. A historical example portrays several aspects important to environmental epidemiology.

2. The London smog of 1952

In London, open coal fires had been used for centuries to heat homes, and public concern about air pollution has a long history there. As far back as 1661, John Evelyn, an English writer, published the booklet 'Fumifugium, or the Inconvenience of Aer and Smoake of London Dissipated'. Periodically, dense winter fogs would descend on London, and with increasing population size and energy consumption, the fogs would mix with smoke to produce 'smog' containing high concentrations of sulphur oxides, acids and soot. Almost certainly, such 'smogs' have produced temporary increases in death rates many times, but it was not until after World War II that such incidents were more systematically investigated. In early December 1952, an unusually dense fog descended again on London, and after mixing with the smoke of hundreds of thousands of coal fires, visibility was reduced so much that the city virtually came to a halt. Long-time inhabitants of London were unable to navigate their own city. Even indoors, the fog was dense enough for theatres and movie theatres to close because the audiences could not see. During the week of the smog, demand for hospital beds far exceeded supply, and death rates soared to three times the normal numbers for the time of the year, producing a short supply of coffins as well.

Fig. 1 shows the development of pollution concentrations and death rates over time during the 1952–1953 London winter. It is evident that during the 'smog' week of 5–12 December, mortality increased almost immediately after pollution levels increased. For the greater London area, the number of excess deaths was in the order of 4000. For a long period after the smog week, however, death rates did not return to normal levels. In a government report published in 1954, all deaths that occurred

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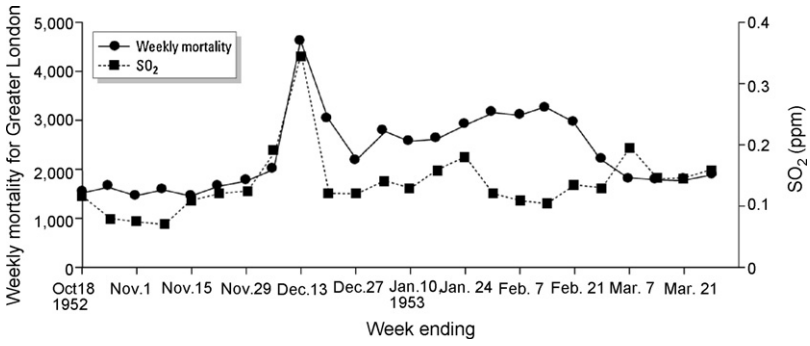

Fig. 1. Mortality and SO_2 before, during and after the London smog of December 1952 (Bell and Davis, 2001).

after 19 December were not attributed to the 'smog', however, but to a flue epidemic that was said to have occurred at the time. Recent analyses of influenza records obtained at the time have suggested that influenza could only have been responsible for a minor part of the estimated extra 8000 deaths (Bell and Davis, 2001). Perhaps, therefore, a much larger number of deaths could be attributed to the smog of 1952. Interestingly, a paper devoted to the Meuse Valley episode which occurred in Belgium in 1930 predicted that in London, 3200 deaths would occur if conditions similar to those in the Meuse Valley in 1930 were to happen in London (Firket, 1936)—one of the early examples of a quantitative risk assessment based on very limited data, but fairly accurate nonetheless.

After the London smog episode and the introduction of the Clean Air Act later on, interest in air pollution and health effects reduced for a while but picked up again in the late 1980s to early 1990s with the introduction of the time series design and publication of the results of the Harvard Six Cities study that showed a clear relationship between levels of air pollution, specifically fine particulate matter and increased mortality in six cities in the United States (Dockery et al., 1993). Health effects were seen at much lower levels than previously expected. Air pollution remains one of the largest fields within environmental epidemiology; interest has gone beyond respiratory morbidity and mortality and includes now also cancer, cardiovascular morbidity and mortality and effects on pregnancy outcomes. In addition to 'background' pollution, traffic related air pollution has become a topic of interest as a cause of local excess health effects among subjects participating in traffic or living close to busy roads in the developed world.

3. What do we mean by 'environment'?

In principle, 'environment' is all that surrounds us. This includes the water we drink, the air we inhale, the food we eat, the soil we live on, the buildings we dwell in, the work we do, and the society we are part of. All of these environmental factors can impact health in either a positive or a negative way.

Although 'environment' is all inclusive, in this article a pragmatic choice has been made to focus on the general environment. Hence, there is no discussion of occupational exposures in detail, or nutritional issues unless the food chain serves as vehicle for potentially harmful contaminants. Another restriction is to focus on chemical, physical and mostly non-infectious biological agents, and not address the social environment as a determinant of health status. However, social factors are regularly investigated in environmental epidemiology as effect modifiers.

Clearly, such demarcations are to some extent artificial. A person who is exposed to sidestream tobacco smoke at home as well as at the office cannot be split into an 'occupational' and an 'environmental' subject. Also, for example, active smoking of cigarettes is generally not considered part of environmental epidemiology, but passive exposure to cigarette smoke from others (environmental tobacco smoke or 'ETS') is. The demarcations that have been chosen do by and large reflect the emergence of various sub-specialties in epidemiology, as is evident from textbooks, journals and learned societies catering to these sub-specialties. There is, of course, a danger in carving up public health issues in bits and pieces when the sub-specialties start to operate in isolation.

4. Studies in environmental epidemiology

It is helpful to think of studies in environmental epidemiology as measurement of associations between environment and disease. Schematically, we can discern two reasons to embark on a study: (1) concern about certain established diseases in the population that may have an environmental cause—disease looking for a cause; and (2) concern about certain environmental factors that may lead to disease in the population—cause looking for disease. In the first instance, knowledge about disease mechanisms will help to formulate which environmental exposures we may wish to examine. In the second instance, knowledge about the toxicity or harmfulness of the environmental factor of concern is helpful to formulate hypotheses on which disease endpoints may conceivably be related to the exposure of interest.

Environmental epidemiology has the capacity to provide information that can contribute to rational decision-making and allocation of resources by providing quantitative estimates of the risk reduction that could be anticipated by controlling exposures to environmental hazards. Risk estimates derived from epidemiological studies can, therefore, be used for cost-effectiveness analysis by environmental managers. Regulators often use environmental epidemiological research to inform policy decisions.

Toxicology is the science of poisons. Over the years, elaborate batteries of toxicity tests have been developed aimed at identification of adverse effects of chemical substances. Classical studies expose genetically homogenous, inbred strains of experimental animals to various but usually high amounts of the test substance in order to establish at which level animals are killed or suffer clear toxic effects. Studies can be of short duration to establish acute toxicity or be conducted over periods of months or even years to study sub-chronic or chronic toxicity. Detailed pathological studies are conducted to establish macroscopic causes of death or toxicity, and biochemical studies are being conducted to establish the kinetics of uptake and distribution, and the mechanisms of action. In addition, organ, tissue or cell cultures are being studied to establish in more detail how chemicals affect target organs or components thereof. Increasingly, animal models are being developed that mimic one or

another sort of human susceptibility, be it genetic, or related to age or disease state.

In a very limited way, the tools of toxicology are also being used to study toxic effects in humans, by experimental exposure of human subjects to chemicals of interest. Clearly, such studies are restricted to transient, mild effects; to short-term exposures and effects; and to volunteer subjects in reasonably good health. The clear advantage of toxicology (being mostly experimental) over epidemiology (being mostly observational) is that the causality of the observed effects is not usually in doubt. Epidemiology, being mostly restricted to making observations among free-living, heterogeneous populations, is more prone to producing associations between exposure and disease which may not be causal, but may be related to one or the other sort of bias that can distort observational studies. On the other hand, epidemiology is capable of studying human beings in the real world, so that results, when established to be valid, have immediate applicability to public health policy. Studies among experimental animals, on the contrary, always require extrapolation from animal to man, from high to low dose, and from single chemical exposures to exposures that occur in mixtures

5. Risk assessment

It is no wonder, then, that in *risk assessment*, epidemiology and toxicology are complimentary. Risk assessment is concerned with making quantitative assessments of the risk associated with a certain level of exposure to a substance or factor in the population. The traditional demarcations are those between *hazard assessment*, *i.e.*, establishing that a substance or factor can possibly damage health because of its intrinsic properties; *exposure response or dose–response assessment*, *i.e.*, establishing at what level of exposure (in epidemiology) or at what dose level (in toxicology) a certain adverse effect on health occurs in which frequency and/or severity; *exposure assessment*, *i.e.*, establishing the distribution of exposure within the population, and *risk characterization*, the final quantitative assessment of which proportion of an exposed population will experience an adverse effect of a certain severity. Epidemiology has a role to play in each of these.

6. Hazard identification

An example of how epidemiological studies identified a possible hazard is the two case control studies by Jaakkola et al. on the association between plastic surface materials in the home and asthma. (Jaakkola et al., 1999, 2000). In the first study, 251 children with asthma were compared to 251 children without, and 72 of the asthma cases were found to live in homes with PVC floor materials as opposed to 5 of the control children. These studies were preceded by occupational studies suggesting that materials used in plastic production may be related to asthma (Eckardt, 1976), and by some toxicological work exploring exposure pathways and mechanisms (Oie et al., 1997; Doelman et al., 1990). After the initial studies in children and in homes, further work has been done to explore this issue further (Bornehag et al., 2004; Jaakkola et al., 2004, 2006).

7. Exposure assessment

Whereas exposure assessment in itself is not epidemiology, the approaches and tools to assess population exposures for the purpose of risk assessment and for the purpose of epidemiology studies are rather similar. For the purpose of risk assessment, exposures need to be measured or estimated for the specific population of interest, that is the population for which one wishes to quantify the risk. For the purpose of epidemiology studies, exposures need to be measured or estimated for the subjects of the population which is being studied. In so far as the populations are the same, the exposure assessments can be similar. Regardless of the purpose, the tools to assess exposures in populations are the same.

The validity of studies in the field of environmental epidemiology depends both on the assessment of exposure and of the effects on health. Each of these aspects can present difficulties and uncertainties. Thus, it is important that everyone involved in the design, conduct and interpretation of investigations has a clear understanding of the problems. Exposure assessment in environmental epidemiology therefore has a different, and more limited aim than assessment of human exposure to environmental agents in general. Other aims of exposure assessment can be the development of effective control strategies, or control of compliance to environmental quality standards. In environmental epidemiology, exposure assessment must primarily fulfill the needs of the epidemiologist. The epidemiologist, who studies the effect of exposure to environmental agents on health and disease, needs measures of exposure that are *accurate* and *precise*, so that the effect of exposure on disease can be estimated with minimal bias and maximum efficiency.

Accuracy is how close a measurement is to the truth. Each measurement method or instrument needs to be calibrated against a standard that is (often by convention!) the 'truth'. As an example, a mercury thermometer can be approximately calibrated to degrees centigrade by first immersing it in ice water to define the 0°-mark, then to immerse it in boiling water at sea level to define the 100°-mark. Now, if the tube containing the mercury would shift for some reason relative to the marks on the background, measurements with it would no longer be accurate. Other terms to describe 'accuracy' in the context of epidemiology studies are *systematic error* and *differential misclassification*. To establish the accuracy of a measurement is often *difficult*, as it is not always obvious what the 'truth' is, or how the 'truth' itself can be reliably established.

Precision is how well a measurement can be repeated, given that all measurements have some degree of inherent variability. As an example, a series of ten measurements of benzene in a parking garage will not all produce the same number, but numbers that are more or less different from each other. If the numbers follow a so-called normal, bell-shaped distribution, the variation can easily be captured by calculating the relative standard deviation, also described as the 'coefficient of variation', of the measurement. In thinking about precision, it is very important to realize that precision has several components. To begin with, any laboratory determination has a certain analytical error. Then, sampling in the field has a sampling error that needs to be taken into account. Then, if the variable to be measured is not uniform in space and/or time, there will also be an error related to temporal and/or spatial variability. To establish the precision of a measurement is often *easy*, because all it takes is to perform replicate measurements.

The combination of accuracy and precision are often defined as the *validity* of the measurement. To asses validity of exposure measurements, investigators should perform so-called *validation studies* aimed at measuring accuracy, precision or both (Table 1).

What happens when an exposure variable is used that is not completely accurate or precise? In general, the result is that the estimated relationship between exposure and disease becomes *attenuated*, or in other words, appears less strong than it actually is. A simple example illustrates this. Let's assume we are interested in a certain environmental exposure (environmental tobacco smoke, ETS) that occurs in 50% of a population of small children, and is associated with a doubling of acute respiratory infection (ARI) risk. Table 1 contains a numerical illustration. Part A shows a relative risk of 2, assuming no error in the exposure variable. In part B, we are assuming that just 20% of all subjects had their exposure misclassi-

Table 1
Hypothetical example of the effect of random misclassification of exposure on relative disease risk

	ARI	No ARI	
(A) No misclassification of exposure. Relative risk of ARI among exposed, compared to non-exposed, is (40/100)/(20/100) = 2			
ETS exposure	40	60	100
No ETS exposure	20	80	100
	60	140	200
(B) 20% misclassification of exposure. Relative risk of ARI among exposed, compared to non-exposed, is (36/100)/(24/100) = 1.5			
ETS exposure	36	64	100
No ETS exposure	24	76	100
	60	140	200

fied, in random fashion. So, of the 40 ARI cases in the ETS exposed group, 8 would erroneously be classified as non-exposed; and similarly, of the 20 ARI cases in the non-ETS exposed group, 4 would erroneously be classified as being exposed. As can be seen from part B, this modest amount of misclassification already reduces the relative risk from the 'true' value of 2 to the 'attenuated' value of 1.5. For further discussions on measurement error and optimal study designs, see (Armstrong, 1995, 1998).

What I want to emphasize here is the fact that improvement of accuracy and precision of exposure assessment in epidemiology has very important benefits. Working with poor surrogates reduces the statistical power to detect a relationship between exposure and disease even when it exists; all too often, it is being assumed then that there *is* no relationship, and this may endanger public health. Also, even when a relationship is established using poor surrogates, the inevitable underestimation of relative risks leads to underestimation of the public health burden associated with exposure.

The two major classes of methods for exposure assessment are: (1) *measurement* and (2) *modeling* of exposure. Exposure measurement implies the use of some instrument to measure the value of an exposure variable. Exposure modeling is the use of mathematical models to predict the value of an exposure variable. The models are based on knowledge of factors which determine or influence the exposure variable, and of the quantitative relationship between these factors and exposure.

Exposure to environmental agents has been defined as any contact between a potentially harmful agent present in an environmental medium and a surface of the human body. Interpreted in this narrow sense, exposure can only be properly assessed by measuring or modeling actual contact between the agent and the body surface. It is rarely feasible, however, to obtain this information for a sufficient number of free-living individuals in epidemiologic studies. Exposure variables used in practice in environmental epidemiology usually have to be regarded as *approximations* to the 'true' exposure of the subjects who are being studied. The accuracy and precision with which 'true' exposure is being approximated may vary widely from one 'surrogate' exposure variable to the next. A common hierarchy of exposure data can be given in tabular form as shown in Table 2.

Table 2
Hierarchy of exposure variables in environmental epidemiology

General hierarchy of exposure variables in environmental epidemiology	Conceivable hierarchy of exposure variables for carbon monoxide
Biomarker	Carboxyhemoglobin in blood
Personal sampling	Personal sampler for CO
Micro-environmental approach	Microenvironmental measurements of CO + time activity diary
Source-based approach	Source inventory for CO indoors and outdoors + habitual time activity pattern
Outdoor measurements only	Outdoor measurement of CO at background locations
Location of home or work address	Location of home or work address in relation to road pattern and use

'Hierarchy' is not suggested to mean that it is always preferable to measure the 'highest' variable in the hierarchy. The choice of exposure variable in environmental epidemiology depends on a number of factors, and its rank in the hierarchy shown in the table is just one of them. In the every-day practice of environmental epidemiology, exposure assessment is a process that makes use of 'surrogate' variables that are related to the 'true' exposure in one way or another. Obviously, investigating the validity of the 'surrogates' is an important tool to address the effects of measurement error.

7.1. Exposure response investigations

Exposure response relationships are being produced in many epidemiological studies. They can take the simplest form of a 'relative risk' describing how much larger a risk is among exposed subjects relative to unexposed subjects. They can also take complex, non-linear continuous forms, providing detailed insight in the frequency of health responses at various exposure levels. An example of a simple relative risk estimate is taken from the first paper on lung cancer risk among non-smoking wives of smokers in Japan (Hirayama, 1981). Table 3 shows the results. Such relative risks can be used to make a quantitative risk assessment in the population when we know: (a) the incidence of lung cancer deaths among non-smoking women of non-smoking husbands; (b) the number of non-smoking women exposed to tobacco smoke from their husband's smoking habits in each of the two categories of exposure.

An example of an exposure response relationship which is continuous is taken from (Fig. 2). It shows how daily deaths increase more or less monotonically with increasing concentrations of fine particles (PM2.5) as measured in six cities in the United States. Such exposure response functions can be translated into risk assessments when we know: (a) the baseline number of daily deaths in an area, and (b) the distribution of daily PM2.5 concentrations. To what extent the deaths, observed in such time series studies are brought forward by merely a few days or weeks cannot be easily decided from the studies themselves (McMichael et al., 1998) but recent evidence has suggested that the deaths are advanced by at least a few months (Schwartz, 2000).

Table 3
Relative risk of lung cancer among non-smoking wives of smoking men (Hirayama, 1981)

	Husband's smoking habits		
	Husband non smoker (reference)	Husband ex-smoker or smoking 1–19 cigarettes/day	Husband smoking more than 20 cigarettes/day
Relative risk of lung cancer	1.00	1.61	2.08

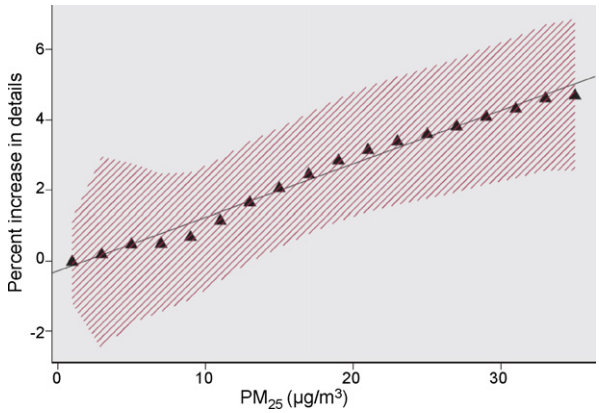

Fig. 2. Relationship between daily deaths and daily PM2.5 in six U.S. cities (Schwartz et al., 2002).

A different and conceptually strong design in epidemiology is to conduct intervention studies. This is more like an experiment; in epidemiology, the randomised controlled trials of new medications are the hallmark of experimental research, but it is clear that in environmental epidemiology, double blind placebo controlled trials are hardly if ever possible. Nevertheless, planned and unplanned environmental changes do occur, and can be utilized to the advantage of the epidemiologist. A recent example is the introduction of smoking bans in bars and restaurants in various European countries. A paper from Italy (where a ban was introduced) and Austria (where it was not) documented a large change in ETS exposure in bars and restaurants in Italy, and no change in Austria (Gorini et al., 2008). The authors used the data to conduct a risk assessment suggesting that the lifetime excess lung cancer risk was from 10–15 per 10,000 for hospitality workers using the pre-ban exposures, and that it was reduced to just 0.01 per 10,000 using the post-ban exposure levels. Another study from Italy showed that acute coronary events in the population of Rome significantly decreased after implementation of the smoking ban in all indoor public places (Cesaroni et al., 2008). The ratio of post- to pre-smoking ban hospitalisations was 0.89 (95% confidence interval 0.85–0.93) in 35–64-year olds and 0.92 (0.88–0.97) in 65–74-year olds, whereas no difference was seen in the over 75-year olds. This was attributed to the much lower attendance of bars and restaurants by the very old. Similar results were reported for New York state (Juster et al., 2007). Another example is the implementation of emergency response systems in France after the large numbers of deaths that occurred during the 2003 heat wave. An analysis of the number of deaths observed during the 2006 heat wave suggested that the number was less than half of the expected number based on long-term trends in heat wave related deaths, which was attributed by the authors to the implementation of the emergency response system (Fouillet et al., 2008).

8. Final remarks

Environmental epidemiology has many things to offer to risk assessment. The tools developed for exposure assessment in epidemiological studies are often ideally suited for use in exposure assessments for risk assessment and management. Exposure response relationships derived from epidemiology have direct relevance for risk assessment in the real world. A major drawback for epidemiology, however, is that because it studies effects of exposures in the real world, it is not suitable for predicting risks associated with exposures which have not yet occurred. So, for predictive risk assessments, we will rely primarily on toxicology studies. Another drawback is that epidemiology is largely observational, and questions about the validity of observed associations arise with some regularity. There are ways to pass judgment on the causality of associations observed in epidemiology, and ever since the seminal paper by Hill about this (Hill, 1965), epidemiologists have debated this issue with persistence. Apart from temporality (cause precedes effect), none of the hints provided by Hill provide absolute guidance, however. Nevertheless, support from animal or cell culture experimental studies usually gives us more confidence in causal interpretations of epidemiological exposure response relationships. Working in conjunction, epidemiology and toxicology both can be important pillars for risk assessment, and in the end, for risk management. Further guidance can be found in documents such as http://www.euro.who.int/document/e68940.pdf.

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