HEALTH BASED STANDARDS: EPIDEMIOLOGY

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Contents

Summary

It is important to understand epidemiology—the part of health studies of populations which is related to environmental exposure—because it reveals two essential aspects of guideline establishment:

a) the exposure-response relationship of the pollutant in question;
b) the determination of quantitative values of a concentration and an average time so that health effects either do not occur or do not exceed those specified as acceptable.

To this end epidemiology uses a number of research strategies. Among them cross-sectional and descriptive retrospective studies are the most important. Descriptive

retrospective studies relate health situations in a population to past exposure. This type of study contributed to establishment of guidelines for tropospheric ozone and particulate matter. Cross-sectional studies compare a cohort of people exposed to a particular pollutant with a non-exposed control group. These studies are particularly relevant in calculating risk figures for carcinogens and also contributed to guidelines for particulates.

To determine exposure-response relationships, epidemiological studies alone are insufficient. Controlled human exposure studies and methods to determine concentrations of pollutants both in the environment and in the human body (biomonitoring) are also necessary. Studies of accidental environmental poisoning episodes describe diseases and symptoms which need to be avoided by health standards and provide in this way an independent control system.

Epidemiological studies are always at risk of identifying spurious correlations. These risks can be minimized by setting criteria: the absence of identifiable bias and the analysis of positive confounding factors are part of these criteria.

As there is no standard methodology to determine an acceptable daily exposure value for epidemiological data, a set of examples in which the results contributed to guideline establishment is discussed. The global picture which emerges shows that for pollutants which have thresholds, standards can be set avoiding health effects also in sensitive populations. This applies, for example, to SO_2 and CO. If, however, ambient environmental concentrations of pollutants are so high that health effects occur (as for tropospheric ozone), it becomes important to define the effects which are acceptable. This socio-economic trade-off is also necessary for pollutants such as carcinogens and particulates which most likely do not have a threshold dose.

1. Introduction

The process of setting standards to protect human health against excessive pollution entails three steps:

(a) understand the exposure-response relationships of the pollutant under study.
(b) decide on acceptable levels of effects.
(c) set standards so that effects do not exceed those specified as acceptable (Maynard, 1994).

As health standards are primarily targeted to humans, it is important to base the values of these three steps on data describing the toxicology in humans. To this end epidemiological data are crucial. They explicitly contribute to the understanding and the quantification of the exposure-response relationship.

On the other hand, ethical reasons prevent humans from being used in controlled experiments. Therefore, epidemiology mainly provides an analytical and descriptive approach to the effects of pollution on human health. It presents important problems in identification of the causes of these relationships. Since causes and mechanisms are vary important in understanding biological phenomena, epidemiological data need to be

complemented by experimental data which are mainly derived from toxicology. Epidemiological and toxicological data are intimately related in standard establishment. The toxicological basis for setting health standards is discussed in *Health-Based Standards: Toxicology* and is therefore outside the scope of this contribution.

This article reviews the basic principles of the epidemiological types of investigation. Particular attention is given to set-ups which are more informative for standard setting. The type of information which can be derived from accidents is also reviewed. Due to the spurious correlation risk, interpretation of epidemiological data is subject to strict criteria, which are detailed in the article. Finally the contribution of epidemiological data to determine an "acceptable daily intake" (ADI)-value is addressed.

2. Definitions: epidemiology and environmental epidemiology

Epidemiology is derived from the Greek word "epidèmos" which means "dispersed among the people". Therefore epidemiology can be defined as the part of science which addresses the frequency and distribution of disease or health problems in a population. Phrased slightly differently, epidemiology is the study of patterns of disease and health states in populations. Next to the quantitative aspects, epidemiology also studies the responsible factors for the detected distribution patterns. The study of disease is the main focus of epidemiology.

The traditional example to illustrate the importance of epidemiology refers to the 1854 study by Snow. This medical doctor studied the development of cholera during the Broad Street Epidemic in London (U.K.). By subdividing the population of the Soho neighborhood according to the origin of their drinking water, the research showed that the disease was related to the use of one particular source of drinking water. He suggested (a primitive version of) filtration using sand to avoid the spreading of the disease. All this was done decades before the *Vibrio cholera* bacteria was detected as the causing agent of this life threatening form of diarrhea. The study is not only seen as an example of epidemiological research and study design, but is cited in contemporary environmental policy literature as a noteworthy example of action based upon the precautionary principle. This sustainability anchor states that in cases of important environmental problems, scientific uncertainty should not be used as an excuse to postpone cost-effective action. Phrased more liberally: in cases of imminent environmental danger, act according to the worst case scenario. This principle is strongly advocated in a sustainable development context but only seldomly applied in environmental policy. The Snow study suggests that when it comes to the protection of human health, it might be wise to apply the precautionary principle.

Epidemiology, which is relevant for standard setting of pollutants, is often based upon data related to the study of occupationally exposed workers. Health studies following accidental exposure are also important. The general population can be studied in set-ups where a population exposed to increased concentrations of a pollutant or a polluting situation is compared to a reference group. Although the study is based upon incidences of diseases or on (presymptomatic) indicators for health, this type of research is targeted towards the determining factors of disease. To distinguish this type of investigation from disease targeted epidemiology, the term "environmental epidemiology" is used.

One major advantage of epidemiological research is that it deals with people living under prevailing environmental conditions. Moreover these conditions entail exposure to low doses, although this is more pronounced in studies involving the general population than in those involving occupational exposure. Epidemiology also allows study of the health effects resulting from combinations of substances as they occur in environmental situations (waste deposit sites, high tropospheric ozone concentrations, polluting plants, etc.). As compared to animal data, epidemiological studies avoid the uncertainties of interspecies extrapolation. Epidemiological studies also allow the evaluation of a wider range of adverse health outcomes which may be related to environmental exposures. This is particularly important for non-cancer end-points such as reproductive, neurological or immunological effects.

Epidemiological research on environmental pollution also has important limitations. Rather small changes in incidences of disease are often targeted. This necessitates the study of large groups. This limited sensitivity not only results in expensive study designs but also makes investigations sometimes impossible as the exposed group is not large enough to detect the expected frequency changes. Another limitation concerns the reference group. In industrial societies pollution is so widespread that it might be difficult to find relevant control populations which resemble the study group in all socio-economical and environmental parameters except for the pollutant under study. This difference in exposure to the pollutant must be sufficiently pronounced to expect significant health differences. Epidemiological studies seldom deal with one parameter, but involve different determinants at the same time. Therefore only rarely are clear conclusions possible. Another significant limitation concerns the fact that the potentially harmful consequences of human exposures to environmental agents cannot be discovered until after, sometimes long after, exposures have occurred. Finally, environmental epidemiological research often needs to be complemented by exposure research. This might involve studies in both external exposure (air, water, soil, food) and internal exposure (values in blood, urine, hair, semen). This complementary research might substantially increase the energy and the cost to be spent on studies in environmental epidemiology.

Notwithstanding these limitations, epidemiology remains the most powerful tool available for understanding how, and to what extent, agents in the environment affect human health.

3. Principles of epidemiological research

Epidemiological research can follow four main strategies: there are retrospective, prospective, cross-sectional and case-controlled studies. These different main approaches can be further subdivided.

3.1 Retrospective studies

Situations which happened in the past are studied to investigate their health consequences. Data are often derived from existing data bases. The results are often presented as maps showing the distribution of a disease in a particular area.

In these studies, the population is subdivided into a number of groups (sex, age, administrative area). The incidence of a particular disease is compared between these groups. More recently, these studies also use a time series design in which the data (e.g. on hospital admissions) are sequenced on a day-by-day basis. Exposure data on air or drinking water quality can be involved.

An advantage of this approach is that these studies can be done relatively quickly. Therefore they are cheaper than prospective studies. Disadvantages concern the reconstruction of the exposure situation (which can be complex) and the quality of the data. Mortality data in a country or a region are recorded by many doctors, mainly for administrative reasons, and can therefore be very different in reflecting the real causes of death. Cancer studies can be based upon diagnoses with differing accuracies (clinical, anatomo-pathological, immunological, genetic).

Cancer atlases, which exist in most industrialized countries, are based upon retrospective studies. They invariably show, for example, a higher incidence of total cancers in urban areas for both sexes. Although these studies provide only partial clues for the interpretation of this "city effect", the phenomenon is at least partially interpreted in relation to the prevailing amounts of carcinogens in urban air pollution. Retrospective studies have also shown higher incidences of congenital malformations in populations living near waste deposit sites in Europe.

This type of study has played an important role in environmental health policy. For example early studies on the relationship between cancer mortality and drinking water quality in USA, were instrumental in the development of regulatory approaches to reduce effects of disinfection by-products.

Studies which have proved to be important for standard setting are those on irritant pollutants and particulates. Studies in which day-to-day changes in airborne pollutant loading are related to health service data such as hospital admissions, have been especially persuasive. Many important epidemiological studies have related measurements of daily average air pollution collected over a period of a year or more to a health outcome such as mortality or hospital admissions on the same day. The health data are controlled for factors such as age, season and temperature, which can have major impacts on health. When all such controls have been applied, the resulting day-to-day changes in health are related to the air pollution measurements.

3.2 Prospective studies

A selected group in the population is followed over time. This group can be an exposed group or be composed of a subset of exposed individuals and a subset of non-exposed individuals. The changes in health status are recorded. They are correlated with exposure data. Because of this study design, prospective studies are also called cohort or follow-up studies.

As compared to retrospective studies, the main advantage is that the exposure conditions can be well controlled. A time series design can also be used for these studies.

Another important characteristic is that prospective studies allow determination of a relative risk factor. This idea is based upon the difference in disease incidence among the groups studied. If a greater proportion of the exposed group develops the disease than the non-exposed group, a positive association is said to exist. The measure of association is the relative risk, defined as:

$$\text{Relative risk (RR)} = \frac{\text{The incidence in exposed}}{\text{The incidence in non-exposed}} \quad (1)$$

If the RR is greater than 1, the risk is greater in exposed persons than in non-exposed people and there is a positive association. RR figures can not only be used to provide an idea of the harmful character of a substance or a situation, but also allows ranking of substances and determination of priorities for policy action.

Prospective research happens e.g. in populations living on polluted soil. Researchers try to find out whether or to which extent soil pollution really influences health. In Belgium prospective studies have been set up for children living near a metallurgic plant in Hoboken, near Antwerp. The study showed, for example, the influence of lead on the intellectual development of the children.

In the case of lead, for instance, prospective studies have refined and corrected standards.

Also, prospective cohort studies were instrumental in the identification and quantification of environmental risks associated with chromium, asbestos and radon.

Cohort studies have been used in standard setting for particulates. In this area there are a number of long-term studies which provide indicators for the effects of chronic exposure to particulate matter over many years. In these studies a cohort of individuals is followed over time. The studies accumulated data on the morbidity and mortality in the cohort, which are initially assessed in relation to individual risk factors such as smoking, body mass index and socio-economic status. Two of the studies revealed linear relations between mortality rates and airborne concentrations of particulates measured as PM_{10} or $PM_{2.5}$ after normalizing the data for the other risk factors. These studies suggest major differences in life expectancy due to ambient exposure to fine particulates.

Occupational exposure has also been studied by this approach. These results proved to be particularly valuable in the case of chemical carcinogens, where studies of occupationally exposed workers frequently proved to be the only source of real world data. Practical examples entail:

- bladder cancer as a consequence of exposure to 2-naphtyl-amine in workers in the dye industry,
- lung cancer and mesothelioma as a consequence of exposure to asbestos in mines, shipyard and the insulation industry,

- leukemia as a consequence of benzene exposure in workers in the shoe, graphics, rubber and petrochemical industry,
- impact on kidney function as a consequence of cadmium exposure in workers in plants producing nickel-cadmium batteries,
- angiosarcoma (a rare case of liver cancer) as a consequence of exposure to monovinyl chloride (MVC) in the PVC-industry,
- lung cancer as a consequence of exposure to poly-cyclic aromatic hydrocarbons (PAH) in gases in the steel industry.

The main problem with occupational studies is that the concentrations to which the workers are exposed far exceed those to which the general population is exposed. Workers are also healthy adults who were exposed for 40 hours a week, while the general population is made up of healthy and sick people of all ages, as well as those who might be more susceptible to disease. This general population is exposed on a chronic 24 hour a day basis. Moreover extrapolation to lower concentrations is very much an act of faith. However, for genotoxic carcinogens there are reasonable grounds to accept that the dose-response relationship is approximately linear without any threshold. This assumption is generally inherent in the standard setting process. While bodies like the USEPA base their standard setting more on quantitative risk assessment approaches than other organizations do, the use of other, more sophisticated models is routine.

3.3 Cross-sectional studies

These studies compare groups of people (cohorts) who are exposed to a particular agent or situation, with an unexposed control group. The results show the health status of both populations at a particular moment in time. This type of study has been used to compare the prevalence of disease in communities with hazardous waste sites with the prevalence of disease in communities without such sites.

Cross-sectional studies may reveal associations between risk factors and disease; however they cannot establish causal relationships. They are primarily useful in generating hypotheses for further study and for addressing questions regarding the health status of a population.

3.4 Case-control studies

Here the occurrence of disease causes are studied in a group of "cases" (usually patients) which are compared with a healthy control group. Exposure is traced back retroactively after the diagnosis of the disease has been made. The method compares the proportion of cases exposed to the risk factor of interest to the proportion of controls who were exposed. Because a case-control study does not measure disease incidence, it does not provide a direct measure of relative risk. The measure of association in a case control study is called the odds ratio, or relative odds, defined as:

$$\text{Odds ratio} = \frac{\text{The odds of exposure in the case group}}{\text{The odds of exposure in the control group}} \qquad (2)$$

If the odds ratio is greater than 1, there is a greater proportion of exposed subjects in the case group than in the controls, and a positive association is said to exist between the risk factor and the disease. The higher the odds ratio, the stronger the association.

This type of research has been successfully applied in finding out whether a medical drug has a negative impact on pregnancy. In this case a population of children with a particular malformation (e.g. cleft lip and/or palate) is compared with a group of healthy controls. The drug use of their mothers during pregnancy is reconstructed. A higher use of a particular drug by mothers of the group with the malformation is indicative of the teratological character of the drug. In this way strong evidence was provided to support the hypothesis that diethylstiboestrol (DES) caused a rare form of vaginal cancer in young adults. DES is actually one of the main models used to understand the action of xenoestrogens in the environment.

Case-control studies are based upon groups of strongly selected individuals. Therefore the question arises to what extent those groups provide information on the population as a whole. This equally explains why there are only few case-control studies in environmental epidemiology. Another difficulty with case-control studies is the challenge of reconstructing past exposure information. Often accurate information on past drug use, workplace or environmental exposure or even smoking habits, is not available.

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Biographical Sketch

Professor Luc Hens obtained his Licentiate in Biology from the Free University of Brussels (VUB) in 1974, Aggregation of Higher Secondary School Teaching from the VUB in 1975, and PhD from the Faculty of Science of the VUB in 1981.

Professor Hens is a member of several professional societies and recipient of a number of honours and awards, including the prestigious award of the Belgian Royal Academy of Sciences and Arts which he was awarded in 1984. Currently he is the Head of the Department of Human Ecology at the VUB.

He has been responsible for organising and/or participating in several international research and postgraduate teaching programmes in many countries including Bolivia, Bulgaria, Brazil, Brussels, the Czech Republic, Ghana, Hungary, Turkey, the Ukraine and Vietnam.

To date the publications of Professor Hens number about 200 including twenty-six books. He is also the co-editor of the journals *Environment, Development and Sustainability* and *Environmental Pollution.* His teaching and research interests include environmental management, sustainable development, human ecology, and related issues.