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The Science of the Total Environment 184 (1996) 97–101

the Science of the Total Environment
An International Journal for Scientific Research into the Environment and its Relationship with Man

Causal inference in environmental epidemiology: the role of implicit values

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Abstract

The current epistemologic debate in epidemiology has underlined the relevance of subjective judgment in the production and evaluation of epidemiologic evidence. The definition of criteria aimed at evaluating causal links requires the adoption of judgment, values and extra-scientific considerations, such as the inclusion of a precautionary principle. The purpose of the present analysis is to examine the influence of moral principles in the process of evaluating scientific data relevant to human health. Two case studies are discussed. The first one deals with the carcinogenic risk associated with occupational exposure to non-arsenical insecticides; the second one deals with the association between urban air pollution, mortality and asthmatic attacks.

Keywords: Environmental epidemiology; Causal inference; Human health; Moral principles; Data evaluation

1. Introduction

A central issue in environmental epidemiology is the evaluation of the causal nature of reported associations between exposure to defined environmental agents and the occurrence of disease. Besides contributing to the understanding of disease causation, etiologic studies are commonly regarded as providing the scientific basis for the adoption of preventive actions. A crucial question in this respect was formulated by Grandjean and Kilburn [1] in an editorial in the *Archives of Environmental Health*: 'In the absence of scientific certainty, how much or how little evidence is sufficient to trigger precautionary actions?'. This question was connected by these authors with the general consideration that every process of risk detection and assessment includes considerable subjectivity. The purpose of the present analysis is to investigate the particular relationship between causal inference in environmental epidemiology and decision-making in public health.

Several authors have explored the various problems associated with causal reasoning in epidemiology and environmental health, such as the multifactorial etiology of most non-transmissible diseases, difficulties in exposure assessment and the observational, non-experimental nature of epidemiologic studies [2–8].

It is proposed that the definition of sufficient scientific evidence is influenced by, among other things, how the need for preventive action is perceived; namely, whether a more or less cautious consideration of the action is intended. Hence, the

Elsevier Science B.V.
SSDI 0048-9697(95)04994-C

issue of preventive action is not only an 'a posteriori' as regards to the scientific process of risk evaluation, but also an 'a priori' intention.

In order to discuss the aforementioned hypothesis, two case-studies have been considered. The first one deals with the evaluation of carcinogenic risk associated with occupational exposure to non-arsenical insecticides. The second one deals with the health effects of air pollution at levels lower than those admitted by international standard guidelines. In both cases, causal inference can be controversial because of the complex character of the exposures under study, the difficulties inherent in designing proper epidemiologic studies, and the limited available epidemiologic evidence. An attempt to explicate what assumptions have been adopted by various authors may provide insight into the debate and help to support or refute their interpretation.

2. Case-study 1. Carcinogenic risk associated with exposures in spraying and application of non-arsenical insecticides

The International Agency for Research on Cancer (IARC) has been involved for many years in a program of periodic evaluation of the scientific evidence of carcinogenicity for humans of specific agents and/or complex mixtures. The program, which is aimed at the production of the well known IARC Monographs Series, ensures transparency of the working procedures, so that any reader may autonomously accept or reject IARC's conclusions. The adopted criteria, furthermore, are not to be viewed as rigid rules, but rather as guidelines which are expected to evolve together with the advancement of scientific knowledge. The evaluation of carcinogenic evidence and its subsequent categorization requires consideration of a number of experimental and epidemiological findings, through an inductive inferential process, taking into account the associated degree of uncertainty [9].

IARC Monograph no. 53 [10] refers, among other things, to occupational exposures in spraying and application of non-arsenical insecticides, thus dealing with a wide class of compounds with different physical, chemical and toxicologic properties. These agents are kept separate from arsenical insecticides, for which a carcinogenic effect has clearly been shown with special reference to lungs, liver and skin [11].

As discussed in the preamble to the Monograph, the epidemiologic studies selected for review had been chosen according to their relevance for evaluation. They included both descriptive and ecologic studies, and ad hoc investigations, mainly cohort or case-control studies. Altogether, 34 epidemiologic studies conducted in the U.S.A., Sweden, Germany and Italy were critically reviewed. The exposure of interest in these investigations sometimes has been defined in terms of specific insecticides, and sometimes in terms of insecticides in general. The available epidemiological evidence was considered inconclusive, but strong enough to suggest caution, and an evaluation of 'limited evidence of carcinogenicity' was formulated. Taking into account other data viewed as relevant, in terms of evaluating carcinogenicity, such as the occurrence of adverse reproductive effects and cytogenetic damage, has led to a final allocation of occupational exposures to non-arsenical insecticides to the category 'probably carcinogenic to humans' (IARC Group 2A).

These conclusions have been challenged by several authors essentially because a general statement concerning exposures to hundreds of chemical agents applied in a variety of ways is supported by a limited number of epidemiologic studies conducted in a few countries [12]. Furthermore, it has been noted that the hazardous effects of non-arsenical insecticides in general have not been adequately described [13], so that the IARC designation cannot legitimate the adoption of more stringent regulations [14].

In response to this criticism, it has been noted that in many instances a causal relationship is plausible even if alternative explanations cannot be ruled out. With regard to the specific issue, it is not to be inferred that all insecticides cause cancer, but rather that some exposure circumstances in insecticide application probably cause cancer, and thus it is justifiable to take all possible precautions in order to prevent exposure [15–17].

The core issue raised by critics is that the designation of human exposures to categories of

carcinogenic evidence goes beyond the available data, and it appears to be oriented to regulatory solutions rather than to scientific judgment [18,19].

The strength of IARC's policy, in this context, rests on a clear explication of the criteria applied in making its assessments, coupled with great care for the compliance of evaluations to both epidemiologic and experimental (i.e. toxicologic) data. Qualitative evaluation of cancer risk associated with different types of exposure is a premise for the subsequent phases of risk assessment and management, including regulatory actions. The role of extra-scientific judgment in these latter steps is well established, but is not appropriate at the original evaluation stage of the process [20].

3. Case-study 2. Health effects of air pollution

During the well-known 'London smog episode' in December 1952, the concentration of airborne particulates increased to about 1200 $\mu g/m^3$ [21]. Little doubt remains that this sudden elevation in air pollution caused an increase in overall mortality resulting in thousands of excess deaths. Today, the scientific and public health interest is focused on the possible health effects of much lower pollution concentrations, based on those currently and commonly experienced in western metropolitan areas.

Several recent studies have reported associations between common levels of particulate pollution and acute health effects: small increases in daily mortality [21], increase in hospital admissions for respiratory diseases [22], and exacerbations of asthma and lung function decrements [23] have been observed. The design of such studies has overcome the limitations of previous cross-sectional investigations. Moreover, indications of chronic respiratory effects of air pollutants are available from studies investigating cause-specific mortality [24], lung function changes [25], bronchial reactivity [26], and immunological disorders [27]. From the epidemiologic literature, the evidence of a causal association can be considered sufficient if the associations under discussion have been replicated in different studies, a dose-response gradient has been demonstrated, and the criteria for specificity of the association have been fulfilled [28].

On the basis of such available evidence, urgent public health action has been required. Detels et al. [25] claimed that 'the burden of proof should now be to prove that high levels of these pollutants do not affect lung function and .....effort should be increased to improve the quality of air'. Britton [29] argued that it was time to know if the degree of morbidity caused by pollution is an acceptable price to pay and to examine the costs and benefits of restrictions on permitted pollutant concentrations. Such an attempt has been made with controversial results [30].

The possible health effects of current air pollution and the need for action have been questioned. Sceptical viewpoints have been revealed such as 'Environmental pollution: it kills trees, but does it kill people?' [31] or 'Air pollution: should we be concerned about it?'[32]. 'Too low concentrations to have an effect' seems to be the widespread view when pollution due to industrial sources is involved [33]. Others, however, argue that pollution standards that would ensure no risk to the entire population are unrealistic, since measurable effects of low levels of pollution on a defined and sensitive subgroup of the population are always to be expected [34].

The real problem in interpreting the epidemiologic evidence on the effects of air pollution is the lack of biological reasonableness of the association [35,36]. The toxicologic evidence from laboratory studies does not show pathologic effects of exposure to current levels of particulate pollution. With regard to acute effects of particulates on mortality, the assumption that pollution precipitates death in terminally ill patients whose cardiorespiratory system is already severely compromised has no support from clinical studies. In addition, the specific constituents of pollution (fine particulate matter, sulfates, acidic aerosols, or sulfur oxide) which may cause health damage are unknown [28].

4. Discussion

It has been shown in both case studies that conflicting opinions are expressed by authors who

adopt different criteria for evaluating the causal significance of an association.

One approach is characterized by the remarkable attention gained by partial findings which regards as informative a set of results affected by a margin of uncertainty; the latter is taken into account and explicitly mentioned in the evaluation. Referring to Hill's criteria for causation [37], this would mean to focus on consistency, on replication, and on the strength of the association in order to establish sufficient evidence. A peculiarity of this approach is to regard epidemiologic studies as highly sensitive tools, particularly suitable when dealing with the health effects of multiple exposures.

The second approach is based on sound toxicologic evidence and it (often implicitly) assumes the independent action of individual causative agents. There is insufficient evidence, in this context, until the biological plausibility [38] of the association has been demonstrated: sufficient evidence is only mentioned inasmuch as a global understanding of the whole phenomenon, including biologic mechanisms, is available. According to this approach, coherence is considered a necessary criterion for causality. Thus, one approach leads to the identification of previously unrecognized hazards, while the other aims at characterizing a given exposure in terms of mechanisms of action.

These two approaches may lead policy-makers to draw different conclusions, probably because they differ in assumptions and ultimate goals.

The adoption of an approach aimed at the prompt detection of health risks, in order to develop a reasonably rapid intervention program, implies the inclusion of a precautionary criterion in the assessment of causality. This means that the continual review of all relevant evidence should be undertaken, defining hazards in relatively crude terms, and thereby coherently promoting public health action. This attitude is subsumed by the IARC evaluation of occupational exposure to non-arsenical insecticides [10]. It also may be said to correspond to the aforementioned statement by Detels et al. [25] concerning the burden of proof, and to Landrigan's comment on the need to act on environmental pollution without waiting for major increases in mortality [39].

The second approach rests on the assumption that preventive action should be based on a detailed knowledge of the biologic mechanism of the individual agents considered, and no intervention should be implemented if an exposure-disease association has been inadequately described. It can be said that such an approach is inspired by the value of efficacy, or by a more efficacious view of prevention.

Furthermore, it can be seen that there exist conflicting views about the possibility of sacrificing a scientific approach to precautionary actions and vice versa. This point has been further explored, among others, by Weed et al. [40]. The suggestion raised by these latter authors is that a proper and ethically defensible approach may be to consider a scientifically based suspicion that a given exposure may cause damage, a basis enough for preventive action, and in the meantime to develop biological research aimed at casting light on the relevant cellular and molecular events.

Finally, it should be stressed that the aforementioned conflicts do not necessarily oppose two more or less scientific solutions, since such conflicts essentially derive from differences in approaching the highly complex problem of judgment about causality.

It thus seems reasonable to conclude that the connection between methodological choices and ultimate goals can be properly considered in the context of the epistemologic debate on the relationship between facts and values in science.

References

[1] P. Grandjean and K.H. Kilburn, Editorial: From research to preventive action. Arch. Environ. Health, 47 (1992) 166.

[2] K.J. Rothman, Modern Epidemiology. Little, Brown & Co., Boston, 1986, pp. 7–21.

[3] K.J. Rothman (Ed.), Causal Inference. Epidemiology Resources, Chestnut Hill, 1988.

[4] M. Susser, Judgment and causal inference: criteria in epidemiologic studies. Am. J. Epidemiol., 105 (1977) 1–15.

[5] M. Susser, What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am. J. Epidemiol., 133 (1991) 635–648.

[6] P. Vineis, Causality assessment in epidemiology. Theor. Med., 12 (1991) 171–181.

[7] T.L. Guidotti, Hidden assumptions in environmental research. Environ. Res., 59 (1992) 101–113.

[8] P. Comba, 'Weak' associations in cancer epidemiology: their detection, evaluation, and use in public health. J. Exp. Clin. Cancer Res., 12 (1993) 1–4.

[9] H. Vainio and I. Wilbourn, Identification of carcinogens within the IARC Monograph Program. Scand. J. Work Environ. Health, 18 (Suppl. 1) (1992) 64–73.

[10] IARC, Occupational exposures in spraying and application of insecticides, IARC Monographs on the evaluation of carcinogenic risks to humans, Vol. 53. Occupational exposures in insecticide application and some pesticides. International Agency for Research on Cancer, Lyon, France, 53 (1991) 45–92.

[11] IARC. Arsenic and arsenic compounds. In: Overall evaluations of carcinogenicity: an updating of IARC Monographs, volumes 1 to 42, IARC Monographs on the evaluation of carcinogenic risks to humans, Suppl. 7. International Agency for Research on Cancer, Lyon, France, 1987, pp. 100–106.

[12] M. Lotti, Health and the environment. Br. J. Ind. Med., 48 (1991) 433–436.

[13] Anonymous (Editorial) BIBRA Bull., 31 (1992) 55–57.

[14] C.L. Berry, Chairman, Pesticides and cancer, What are the cancer risks from insecticides? Pestic. News, 18 (1992) 14.

[15] H. Vainio, Insecticides and human health: a closer look. BIBRA Bull., 31 (1992a) 113–114 (letter to the editor).

[16] H. Vainio, Pesticides and cancer, What are the cancer risks from insecticides? Pestic. News, 18 (1992b) 14.

[17] N. Pearce and H. Vainio, What are the cancer risks from insecticides? Pestic. News, 18 (1992) 14.

[18] R.J. Moolenaar, Overhauling carcinogen classification. Issues Sci. Technol., 8 (1992) 70–75.

[19] M. Lotti, IARC Ranking of carcinogenicity evidence: how is the message delivered and perceived? Regul. Toxicol. Pharmacol., 19 (1994) 236–241.

[20] L. Tomatis and H. Vainio, Reply to Dr. Moolenaar's article, Overhauling carcinogen classification. Issues Sci. Technol., 9 (1992) 10.

[21] J. Schwartz, Air pollution and daily mortality: a review and meta analysis. Environ. Res., 64 (1994) 36–52.

[22] J. Schwartz, D. Slater, T.V. Larson, W.E. Pierson and J.Q. Koenig, Particulate air pollution and hospital emergency visits for asthma in Seattle. Am. Rev. Respir. Dis., (1993) 1–21.

[23] W. Dockery and C. Arden Pope, Acute respiratory effect of particulate air pollution. Ann. Rev. Public Health., 15 (1994) 107–132.

[24] W. Dockery, C. Arden Pope, X. Xu, J.D. Spengler, J.H. Ware, M.E. Fay, B.G. Ferris and F.E. Speizer, An association between air pollution and mortality in six US cities. N. Engl. J. Med., 329 (1993) 1753–1759.

[25] R. Detels, D.P. Tashkin, J.W. Sayre et al., The U.C.L.A. population studies of CORD: X. A cohort study of changes in respiratory function associated with chronic exposure to SO_x, NO_x and hydrocarbons. Am. J. Public Health, 81 (1991) 350–359.

[26] F. Forastiere, G.M. Corbo, R. Pistelli, P. Michelozzi, N. Agabiti, G. Brancato, G. Ciappi and C.A. Perucci, Bronchial responsiveness in children living in areas with different air pollution levels. Arch. Environ. Health, 49 (1994) 111–118.

[27] H. Zwick, W. Popp, C. Wagner et al., Effects of ozone on the respiratory health, allergic sensitization, and cellular immune system in children. Am. Rev. Respir. Dis., 144 (1993) 1075–1079.

[28] B. Ostro, The association of air pollution and mortality: examining the case for inference. Arch. Environ. Health., 48 (1993) 336–342.

[29] J. Britton, Pollution and respiratory morbidity: how much do we accept? Thorax, 47 (1992) 391–392.

[30] A.J. Krupnick and P.R. Portney, Controlling urban air pollution: a benefit-cost assessment. Science, 252 (1991) 522–528.

[31] Anonymous, Editorial: Environmental pollution: it kills trees, but does it kill people? Lancet, 340 (1992) 821–822.

[32] R.L. Maynard, Editorial: Air pollution: should we be concerned about it? J. R. Soc. Med., 86 (1993) 63–64.

[33] J.J. Collins, J.M. Ramlow and M.J. Teta, Respiratory and irritant health effects of ambient volatile organic compounds: the Kanawha County health study, Letter to the Editor. Am. J. Epidemiol., 140 (1994) 72–73.

[34] M. Corn, Invited commentary on: Effect of urban air pollution on emergency room admissions for chronic obstructive pulmonary disease. Am. J. Epidemiol., 134 (1991) 287–289.

[35] R.E. Waller and A.V. Swan, Invited commentary on: Particulate pollution and daily mortality in Steubenville, Ohio. Am. J. Epidemiol., 135 (1992) 20–25.

[36] M. Schenker, Editorials: Air pollution and mortality. N. Engl. J. Med., 329 (1993) 1807–1808.

[37] A.B. Hill, The environment and disease: association or causation? Proc. R. Soc. Med., 58 (1965) 295–300.

[38] H. Vainio, B. Armstrong and L. Tomatis, Determining carcinogenicity. Science, 260 (1993) 815 (Letters).

[39] P.J. Landrigan, Letters to the editor, Environmental pollution and health. Lancet, 340 (1992) 1220.

[40] D.L. Weed, M. Selmon and T. Sinks, Links between categories of interaction. Am. J. Epidemiol., 127 (1988) 17–27.