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Risk estimation for carcinogens based on epidemiological data: A structured approach, illustrated by an example on chromium

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Abstract

It is generally recognized that human, epidemiological data, if available, are preferred as the starting point for quantitative risk analysis above the use of data from animal studies. Although methods to obtain proper risk estimates from epidemiological data are available, several impediments prevent their widespread application. These impediments include unfamiliarity with epidemiological methods and the lack of a structured and transparent approach. We described a framework to conduct quantitative cancer risk assessment based on epidemiological studies in a structured, transparent, and reproducible manner. Important features of the process include a weight-of-the-evidence approach, estimation of the optimal exposure-risk function by fitting a regression model to the epidemiological data, estimation of uncertainty introduced by potential biases and missing information in the epidemiological studies, and calculation of excess lifetime risk through a life table to take into account competing risks. Sensitivity analyses are a useful tool to obtain insight into the impact of assumptions made and the variability of the underlying data. The framework is sufficiently flexible to allow many types of data, ranging from published, sometimes incomplete data to detailed individual data, while maintaining an optimal result, i.e., a state-of-the-art risk estimate with confidence intervals, based on all available evidence of sufficient quality.

Keywords: Risk assessment; Epidemiology; Uncertainty; Variability; Sensitivity analysis; Probabilistic; Potency; Excess lifetime risk; Chromium; Lung cancer

1. Introduction

Quantitative analysis of cancer risks associated with (occupational) exposure to carcinogens and the establishment of a risk estimate play an important role for risk characterization of carcinogenic chemicals (Sanner et al., 2001; U.S. Environmental Protection Agency, 2005). It is generally recognized that human data from epidemiological studies, if available, are preferred as the starting point for quantitative risk analysis of carcinogens above the use of data from experimental animal studies. This is, because effects observed in animal species have to be translated into effects expected in humans, i.e., an extrapolation step is needed that not only is substantially uncertain, but also, from a precautionary principle approach, has to be conservative in nature (Vermeire et al., 1999). Besides the advantage that epidemiological data relate to the same species (i.e., man), the most important other advantages of epidemiological data over animal data are that exposure conditions and other circumstances that may modify the risk are usually much more comparable to those in the target population than those simulated in an animal experiment. Quantitative risk assessment based on epidemiological studies entails therefore substantially less uncertainty than if based on animal models, irrespective of some inherent uncertainties introduced by the epidemiological design itself.

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Despite the availability of epidemiological data, emphasis used to be on calculating cancer risks from experimental animal data. One of the reasons is that a clear, transparent, and generally accepted protocol for calculating cancer risk from epidemiological data is not available, despite substantial and important contributions to the development of epidemiological risk-assessment methods from distinguished scientists, e.g., Hertz-Picciotto and Hu, 1994; Hertz-Picciotto, 1995; Moolgavkar et al., 1999; Samet et al., 1998; Shore, 1995; Stayner et al., 1995, 1999a,b, 2000; Steenland and Deddens, 2004; van Wijngaarden and Hertz-Picciotto, 2004. The relative complexity of issues involved in epidemiological data analysis also hampers acceptation by non-epidemiologists.

This situation is illustrated by the case of hexavalent chromium. In several reports, quantitative risk assessments are based on epidemiological data on exposure to chromium and lung cancer (Canadian Environmental Protection Act, 1994; Dutch Expert Committee on Occupational Standards, 1998; European Union Risk Assessment Report, 2002; Scientific Committee on Occupational Exposure Limits, 2003; Sorahan et al., 1998b; U.S. Environmental Protection Agency, 1998; WHO, 2000a). These reports differ with respect to the epidemiological data sets used and the methods applied. As a result, the risk estimates differ as well, sometimes substantially. Such different risk estimates do not pose a problem as such, as they are by nature derived with substantial uncertainty. More troubling, however, is that the multitude of choices, assumptions, and extrapolations, which are inherent in risk assessment, were often not motivated or made explicit. For this reason, it is difficult—not only for toxicologists and regulators, but also for most epidemiologists—to follow, interpret, compare and evaluate these risk assessments.

The objective of the present paper is to describe and discuss a systematic approach to quantitative risk assessment based on epidemiological data, focusing on the purpose and the essential features of the consecutive steps in the process. The steps include selection and evaluation of epidemiological data, derivation of a relative risk as function of exposure from the selected epidemiological data and calculation of excess lifetime risk for an exposed target population of interest. The approach is illustrated by the derivation of an excess lifetime risk estimate of lung cancer for exposure to hexavalent chromium, using different data sets and options. The approach is compared with some of the available quantitative risk assessments for hexavalent chromium. For a better comprehension of the risk estimation approach based on epidemiological data, some critical aspects, such as epidemiological study design, frequently used risk parameters, and exposure assessment in epidemiological studies are discussed first.

As hazard characterization is the main focus of this paper, hazard identification from epidemiological studies will not be discussed. The focus is on derivation of excess lifetime risks for the worker population, but the principles can equally be applied to other populations.

We hope that this systematic approach stimulates the use of existing epidemiological data and the conduct of new studies for the purpose of risk assessment for carcinogens and also enhances confidence in their use.

2. Basic epidemiological concepts

2.1. Epidemiological study design

In animal experiments efforts are made to generate genetically and environmentally homogeneous conditions except for the factor under study. Such conditions are usually not found in epidemiological studies. Human populations are heterogeneous in behavior and genetic susceptibility. Epidemiological, observational studies take this real life situation into account and conclude from it with respect to disease risk. Observational studies, where persons have not been randomly assigned to exposed versus unexposed groups, may be affected by confounding, which distorts the exposure-disease association. Confounding can occur because study participants also differ in many other aspects relating to exposure. In experimental studies, random allocation of subjects to different treatments will minimize the effect of this variation. In observational studies, random allocation to exposure is not possible. Instead, epidemiologists make use of many methods—in the design and in the statistical analysis of an observational study—to minimize most sources of bias and confounding.[1] High quality studies are usually those in which such methods are appropriately applied and biases are quantified. For the purpose of epidemiological risk assessment, two different types of observational studies are the most relevant: cohort or follow-up studies and case-control studies (see text boxes).

2.2. Risk, rate, relative risk, and excess risk

To non-epidemiologists, the concepts of risk, rate, and the effect measures as used in epidemiology are always a source of much confusion. A basic comprehension of these concepts is necessary to understand how epidemiological studies can be used for risk assessment in a way comparable to animal studies. Without using mathematical formulas, an explanation and comparison of the key concepts and their application will be given below. A summary of these concepts is given in Table 1.

Risk refers to a person and is defined as the probability for that person to get (or die of) the disease of interest during a specific time period. This time period may be lifetime, up to a certain age (e.g., 75), or starting and ending at specified ages. Since it is impossible to measure a probability in a person, we measure risk among a larger group of people.

[1] It is outside the scope of this paper to discuss all potential biases and the possible solutions to be applied to avoid such biases. Epidemiologists are trained to discern potential methodological problems in studies and to assess the suitability of any chosen solutions.