

FAQ

11 September 2026

How important are epidemiological studies in the assessment of the health risks posed by pesticidal active substances in plant protection products and other chemicals?

Epidemiological studies investigate health-related issues within populations. This makes them a valuable tool for assessing the potential health risks posed by plant protection products (PPPs) and other chemicals. The term ‘chemical’ here refers to all substances, including both naturally occurring substances and those synthetically produced by humans. Below, we answer some questions about the possibilities and limitations of epidemiological studies in this context.

What is epidemiology and why is it important?

Epidemiology is the scientific discipline that deals with the distribution, causes and consequences of diseases and other health-related conditions and events at the population level. It plays an important role in public health because it provides data and insights to better understand the causes of disease, develop strategies to combat or prevent them (preventive measures) and promote health. It thus provides a vital basis for health-related recommendations and policy decisions.

In the risk assessment of plant protection products (PPPs) and chemicals, epidemiological studies are a method for investigating and assessing the health risks to people who are exposed to certain substances over a prolonged period. The term 'chemicals' here refers to all substances, regardless of whether they are synthetically produced by humans or occur naturally.

However, individual epidemiological studies should always be considered in the context of the overall body of evidence and in relation to other types of studies. In this way, they can provide an important impetus for further research and identify potential research needs under real-world conditions. Risk assessment of plant protection products (PPPs) and other chemicals also concerns the effects of substances on people who are unintentionally exposed to them at work or in their everyday lives as consumers. For this reason, descriptive studies and, above all, observational studies are generally included here.

How do the different types of studies differ, and what are they used for?

Broadly speaking, observational (epidemiological) studies can be distinguished from experimental ('interventional') studies. The former observe what happens without influencing the participants. In experimental studies, by contrast, an active intervention is carried out. People are deliberately exposed to a specific dose of a substance. In the medical field, for example, interventional studies, also known as clinical studies are of particular importance during the development and testing of drugs or in the assessment of new therapeutic and preventive approaches. Interventional studies involving humans do not play a role in the risk assessment for plant protection products (PPP) and other chemicals (both natural and synthetically produced substances).

Observational studies include:

Cohort study: This follows groups of people, e.g. farmers and non-farm workers in a specific region, over a prolonged period in order to answer questions such as whether exposure to a PPP increases the risk of developing a particular disease.

Case-control study: Cases (e.g. people with a particular condition) are compared with controls (e.g. people without that condition). The link between an exposure and the occurrence of the condition in the cases is investigated by comparing the exposure levels in both groups.

Cross-sectional study: This provides a snapshot of exposures, diseases and other health parameters. For example, it can show how many people are currently overweight or how high the exposure to certain plant protection product residues is in a study area, based on their excretion in urine. The latter is also referred to as human biomonitoring.

What does 'exposure' mean in the context of assessing the health risks of PPPs and other chemicals?

Exposure refers to the extent and nature of human contact with a substance, in particular the intake (dose), the duration, the frequency and the routes of entry (inhalation, skin contact, oral ingestion). Exposure may relate to individuals or groups.

Information on exposure ranges from simple classifications (e.g. exposed or not exposed) to quantitative measurements such as blood concentration, air concentration or absorbed dose (e.g. milligrams (mg) per kilogram (kg) of body weight per day).

It is ethically unacceptable to deliberately expose people to potentially harmful substances in amounts that could damage their health. For this reason, observational studies are frequently used in epidemiology. In these studies, people are observed in their natural environment in order to gain insights into the distribution and health effects of, for example, pesticidal active substances and other chemicals under conditions that are as close to real-life as possible. An epidemiological study thus provides information for risk assessment and risk management, and consequently also for health policy.

Data collection can be carried out using various methods, such as questionnaires, interviews, blood and urine tests (biomarkers) and medical examinations. Ideally, epidemiological studies should take into account all possible intakes (inhalation, skin contact, oral ingestion) and allow for a clear attribution to the exposure. In the case of pesticidal active substances, these would include, for example, residues in food and drinking water or direct inhalation (i.e. via breathing) and dermal (i.e. via the skin) exposure during their application to fields among field workers or other exposed groups such as local residents, etc.

Epidemiological studies can reveal associations between risk factors (e.g. exposure to a substance) and health effects; however, these results should be compared with evidence from other types of studies, such as experimental studies or further epidemiological studies. Whilst a single epidemiological study provides part of the evidence needed to reliably demonstrate a causal effect on human health, for example, by a pesticidal active substance in a plant protection product or another chemical, it is only by considering several different studies together that a complete picture emerges. Epidemiological studies are also a useful tool for identifying previously unknown associations.

Conclusion: Epidemiological studies are useful in risk assessment for identifying indications of potential hazards and assist in hazard characterisation for pesticidal active substances and other chemicals. They should be carefully planned, conducted and interpreted, and supplemented by other types of studies, such as animal experiments or studies on cell lines. Ideally, different types of study can support one another and provide a more complete picture of the available scientific evidence. This is also known as the 'weight of evidence' (WoE) approach.

What are the limitations of epidemiological studies?

The validity of an epidemiological study depends heavily on the study design, the sample size and the overall quality of the study. Observational studies are more susceptible to bias than randomised, placebo-controlled intervention studies involving humans. Randomised intervention studies are experiments in which participants are randomly assigned to groups,

intervention and control groups. One group receives a substance in a defined dose, whilst the other receives a dummy product, better known as a placebo. In the toxicology of PPPs and other chemicals, intervention studies involving humans are rarely, if ever, available. Randomisation is intended to ensure that potential confounders (factors that may influence the results and lead to incorrect conclusions) are evenly distributed across the groups.

The validity of studies with low statistical power or a high potential for bias should be regarded as low. The potential for bias refers to the possibility that the results of an epidemiological study may be distorted by systematic errors (bias).

Epidemiological studies can reveal correlations (associations), however, on their own, they usually do not prove a causal link between an exposure and, for example, a disease. The validity of epidemiological studies on a particular issue may be diminished by the diversity (heterogeneity) of the methods and/or results of the various epidemiological studies.

What are the particular challenges of epidemiological studies in risk assessment?

The question of the extent to which people are or have been exposed to a particular substance is often difficult to answer. Such estimates are frequently based on self-reported data or on information recalled from memory. Objective measurements, such as blood or urine analyses, or representative surveys along the exposure pathway, for example, repeated measurements of ambient air or reliable usage statistics, can be helpful, but are usually lacking.

Epidemiological studies, particularly prospective, longitudinal studies, can take many years to complete, which slows down the acquisition of new knowledge. In the case of pesticidal active substances in plant protection products, it must be borne in mind that such studies can only be meaningfully conducted once the relevant active substances or products have been on the market for some time and a sufficient number of people have come into contact with them. Consequently, relevant data may not be available at the time of initial authorisation.

In everyday life, people are exposed to many different factors that can affect their health. These include, for example, differences in diet, psychological factors, physical activity, chemical substances in the environment, active and passive smoking, alcohol consumption and the use of medication. An individual's genetic makeup also plays a role. All these factors can interact in a 'multicausal' manner, so that it can be difficult to determine their respective contributions to a disease or health effect and to take them into account in the overall assessment.

In the case of rare diseases, the number of cases may be small, which can weaken statistical conclusions and render them unreliable.

The validity of findings from epidemiological studies is strengthened by the reproducibility of the results in other studies. If similar results are found in different studies and these complement one another, this increases their reliability.

There are methods for systematically summarising evidence from epidemiological studies (evidence synthesis). These methods take into account the quality, design and size of the studies in order to obtain an overall picture and assess the strength of the evidence.

Can epidemiological studies alone prove that a substance causes disease?

Epidemiological studies are often a building block in establishing a causal link between exposure to a hazardous substance and an adverse health effect. In particular, when several robust epidemiological studies point in the same direction, the body of evidence from these studies can provide a decisive indication of a possible causal link. As a rule, however, further mechanistic studies are required to provide sufficient evidence of a causal link. These studies are based, for example, on cell culture experiments or animal experiments involving the substance in question, in order to elucidate the mechanism of the adverse health effect. Only when several high-quality studies deliver similar results, certain evaluation criteria are met and the findings are cross-checked against further scientific data can a well-founded assessment of the health risk be carried out.

What can lead to errors in epidemiological studies?

The rationale for sources of systematic error (bias) in epidemiological studies is primarily due to weaknesses in the study design, data collection or data analysis, and these sources differ from random errors. Three key sources of error are selection bias (also known as selection distortion), confounding (which refers to distortion caused by confounding factors) and information bias (which refers to observational or measurement errors).

What is selection bias?

Selection bias, also known as selection distortion, occurs, for example, when participation in the study is influenced by both exposure and the adverse health effect.

An example: In a (fictitious) study on the health effects of PPPs, seasonal agricultural workers are to be examined. It could be the case that, in particular, seasonal workers heavily exposed to PPPs who develop respiratory illnesses give up their jobs. They are then no longer available for the study. Consequently, the sample would consist mainly of healthy seasonal workers. As the sick and exposed individuals would then be under-represented in the study, the actual harmful health effects of the PPPs could be incorrectly underestimated in the study results.

What is meant by 'confounding'?

Confounders, or confounders, are variables that are associated with both the independent variable (e.g. a risk factor) and the dependent variable (e.g. a disease or an endpoint) in a study. They can distort the results of a study by falsely establishing a relationship between the variables under investigation or by masking the true relationship.

An example: Suppose a study aims to investigate the association between exposure to an industrial chemical (exposure) in the workplace and the risk of chronic respiratory diseases (endpoint). To this end, two groups are followed over time: exposed workers and unexposed control subjects.

A classic confounder in this scenario is smoking, which meets the three epidemiological criteria of a confounder:

Association with exposure: It is assumed that workers in production-related domains with higher chemical exposure (e.g. due to socio-economic factors or the specific workplace culture) are more likely to smoke.

Association with the endpoint: Smoking increases the risk of respiratory diseases independently of chemical exposure.

No intermediary: Smoking does not lie on the causal pathway between chemical exposure and respiratory disease, as the chemical itself is not the cause of smoking behaviour.

If smoking is not taken into account in the analysis (through statistical methods or adjustment), the study may erroneously indicate a stronger association between chemical exposure and respiratory diseases, because part of the observed disease risk is attributable to smoking.

How does information bias form?

Information bias (observational or measurement error), the third key source of error, is when information on exposure or the endpoint is systematically measured, collected or documented incorrectly.

An example: Information is biased if, in the (fictitious) study of seasonal workers, the concentration of short-lived metabolites of plant protection product residues in the blood is measured inconsistently for the purpose of assessing exposure. These metabolites have a short biological half-life, meaning they are broken down in the body within a few days. If seasonal workers with acute respiratory illnesses are examined at the medical outpatient clinic and their exposure to the PPP is measured in their blood, high levels will be recorded. If, on the other hand, blood tests for the seasonal workers who have remained healthy are carried out in batches at the end of the season, the chemical will already have been broken down in the body. This systematic disparity in the measurement of exposure would lead to the healthy workers being incorrectly classified in the 'low exposure' group. Consequently, the study would incorrectly overestimate the link between pesticide exposure and respiratory disease because the difference in blood levels is attributable to different timing of the measurements and not to the fact that the healthy workers were actually less exposed.

How can sources of error in epidemiological studies be minimised?

To minimise the impact of bias as much as possible, researchers use various methods. These include:

Randomisation: Participants are randomly assigned to the study groups.

Matching: Pairing participants or groups that are similar in certain characteristics to account for these as potential confounding factors.

Statistical adjustment in the analysis: To minimise the influence of confounders such as age, gender, occupation or pre-existing medical conditions as far as possible, these are taken into account during the evaluation of the study data using various statistical methods.

Restriction: Limiting an analysis or study to a subset of the total population in order to control for confounding factors or to answer specific research questions. Examples include restricting the analysis by age, gender, exposure level or geographical area.

Can epidemiological studies be misinterpreted?

Epidemiological studies can be misinterpreted without the appropriate specialist knowledge. In other words, warnings or reassurances may be derived wrongly from epidemiological studies. Such misinterpretations can have various causes. For example, if the study design is inappropriate or the data collection is flawed, the results may be distorted. It is also possible that the sample size is insufficient for a particular question. It is not uncommon for an association between two variables (e.g. the use of a substance and the occurrence of a disease) to be confused with a causal link. This can lead to an inappropriate assessment of the study. It must therefore be clarified whether the substance can actually damage the affected organ or tissue in the manner observed. Sometimes, the results of individual epidemiological studies are overestimated or generalised without taking into account the limitations of the study, which the authors themselves specify. The way in which studies are presented in the media can also lead to misunderstandings, particularly when complex scientific information is oversimplified.

When epidemiological studies are used for health risk assessment, preference should be given, where possible, to reviews that systematically summarise several epidemiological studies. These so-called systematic reviews, some of which also include meta-analyses, provide more reliable evidence on a given topic. Summaries of such reviews, written in language accessible to the general public, are available on the BfR website at <https://www.bfr.bund.de/en/chemical-safety/plant-protection-products/exposure-estimation-for-plant-protection-products/>.

It is therefore important to examine epidemiological studies and the reporting on them carefully, and always to interpret the results within the context of the overall body of research.

How does the BfR use epidemiological studies in the assessment of active substances?

The BfR conducts an assessment of epidemiological studies alongside other scientific evidence such as that from laboratory experiments or animal experiments. In doing so, it assesses how reliable the studies are, whether there are methodological weaknesses, and to what extent potential biases might influence the results. The aim is to perform an assessment of all available data in such a way as to form the most realistic picture possible of the risk. As epidemiological data is collected from humans under real-world conditions, it has the potential to compensate for any intrinsic weaknesses in animal experiments or non-animal methods.

What significance do epidemiological studies have in the risk assessment of PPPs and other chemicals in relation to chronic diseases?

Several factors are often at play when chronic diseases form, but the exact causes are frequently unclear. There is usually no single trigger. In many cases, the onset of the disease results from the interaction of a number of factors, including, for example, genetic predisposition, environmental factors, age and individual susceptibility.

In the absence of further animal or *in vitro* models for analysing causes, it is generally difficult to draw conclusions based solely on epidemiological studies.

The relevance of epidemiological studies for the assessment of PPPs and other chemicals is therefore limited. Many studies are observational and thus prone to bias. Furthermore, individuals are often exposed to a mixture of substances, making it difficult to determine the influence of a single substance.

What is the BfR doing to improve the use of epidemiological studies?

The BfR is actively committed to further developing the use of epidemiological studies in risk assessment. In November 2023, for example, it organised an international conference entitled: *'Using Epidemiological Studies in Health Risk Assessments: Relevance, Reliability and Causality'*

Together with experts from academia and public authorities, discussions took place on how the quality, relevance and validity of such studies can be assessed and utilised even more effectively. The BfR's scientific independence is fundamental to its work.

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the German Federal Ministry of Agriculture, Food and Regional Identity (BMLEH). It protects people's health preventively in the fields of public health and veterinary public health. The BfR provides advice to the Federal Government as well as the Federal States ('Laender') on questions related to food, feed, chemical and product safety. The BfR conducts its own research on topics closely related to its assessment tasks.

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