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A review of epidemiological methods applied in studies on laboratory animal allergy. With a discussion of the relation between prevalence and risk of an irreversible disease in a dynamic population of constant size

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It is well-known that many persons working with laboratory animals suffer from allergic symptoms; most affected workers get rhinitis, and some of them later develop asthma [1–21]. The question of concern in occupational epidemiology is not whether there *is* in fact a risk of allergic disease in laboratory animal workers, but how large this risk is and what factors influence it.

The identification of the causal agents of occupational allergy – the sensitizing substances – is usually achieved by case studies, i.e. by comprehensive diagnosis of a few affected persons, including the assessment of the space and time patterns of the occurrence of symptoms, as well as immunological and provocation testing. By contrast, in order to *quantify* the risk of a work-related allergic disease it is necessary to conduct an epidemiological study. Risk estimation is a prerequisite of risk comparisons, a hence of the identification of high-risk groups and the assessment of the effect of protective measures.

This article summarizes the information needed and the way it has to be analyzed to provide risk estimates. Since it is common practice in epidemiological research on work-related allergic diseases to estimate prevalences, the relation between risk and prevalence in a dynamic population of constant size is described. The available epidemiological literature on laboratory animal allergy is reviewed with respect to the requirements of risk estimation.

What information is required for risk estimation?

The probability of developing an occupational allergy to a certain agent mainly depends on

1. predisposing factors (atopy being considered the most important);
2. dose of exposure, which is characterized by
   - concentration,
   - intensity (proportion of time a person is exposed at work within each day/week/month/year);
3. duration of exposure.

Ad 1. *Atopy* is considered to act as an effect modifier. In some occupations, atopic persons were found to experience sensitization and develop occupational asthma more often than non-atopics [19–21]. Hence, risk estimation should be done separately for atopics and non-atopics. Unfortunately, no standardized criterion of atopy exists [e.g., 20]; in different studies, different diagnostic schemes were applied.

Ad 2. Little is known about the relation between the *dose* of exposure and the risk of sensitization [19]. As it is difficult to quantify the dose exactly, it might be sufficient for safety considerations to analyze risk differences between groups of workers with relatively homogeneous exposure conditions.

Ad 3. The longer the *duration* of exposure to potentially sensitizing agents, the higher is the chance that a worker will actually become sensitized and develop symptoms. So that exposure duration can be taken into account, the design and analysis of a study should fulfill certain requirements.

Risk estimation in dynamic cohorts

The (time-dependent) risk of a disease is measured by a set of cumulative incidences for varying exposure times. If a *fixed cohort* of workers can be observed the cumulative incidences can be directly estimated from the relative frequencies of workers who get the disease within certain time intervals. However, this is seldom possible. In general, occupational populations are not fixed but *dynamic cohorts*; there are always workers who leave the job and are replaced by fresh personnel. Cumulative incidences cannot be estimated directly in a dynamic cohort. They can be derived from the distribution of the "failure" time spent at the exposed workplace until the onset of disease, as is well-known. This distribution is estimated from the observed (right-censored) exposure times until disease onset or until censorship by leaving the job or by the end of the study [e.g. 22].

This means that for risk estimation, information on the exposure duration of every cohort member up to the point where he or she

- gets the disease of interest, or
- leaves the job or dies, or
- the study is ended

is required. The sum of all these durations is the number of person-years at risk spent by all cohort members. If a constant hazard function can be assumed, the cumulative incidences of interest are easily computed from this sum and the number of all incident cases which ocurred during the period of observation of the dynamic cohort.
These requirements are usually not met in current epidemiological research on laboratory animal allergy (or on work-related allergic disease in other occupations). The usual type of study is cross-sectional[19,21], computing disease prevalences in certain subgroups of workers. In most studies, no observations are made on exposure duration; i.e. there is a lack of information on the distribution of these "failure" times as well as on their sum. Moreover, information on job-leavers – especially information on their disease status – is also lacking. Nevertheless, it is occasionally suggested in the discussion of study results that inferences about risk differences (e.g. between atopics and non-atopics) were drawn from observed prevalences[1,4,9,13–15,18].

Prevalence and risk

In the following, the relation between prevalence and risk is discussed, considering the special situation of a workplace with a risk of occupational allergic disease. This situation may – with slight simplifications – be characterized by

- an irreversible disease (at least as long as exposure continues),
- a dynamic population
- a population of constant size (i.e. job-leavers are replaced immediately).

In this situation, the disease prevalence in the population at a certain point of time depends on

- the risk of disease (characterized by a set of cumulative incidences for varying time intervals, or by a hazard function),
- the distribution of exposure duration in the observed population (for instance, in a population of recently hired workers there will be a lower prevalence than in a group of long-time employees, if risk is the same),
- the rate of job-leaving among the diseased workers. (The more diseased persons stop working with the allergen, the lower will be the prevalence. As long as the population size remains constant, the rate of leaving among the non-diseased is irrelevant for this relation).

These features may be quantified by considering a simple hypothetical situation. Assume the instantaneous incidence rate, the rate of leaving the job among the diseased, and the population size to be constant. With

h = incidence per unit time
a = rate of leaving job per unit time among the diseased
(time taken in discrete units, say months or years),

the prevalence p after t time units is:

$$p(t) = h(1-a)\sum_{i=0}^{t-1}(1-h)^i(1-a)^i \qquad (1)$$

$$= h(1-a)\,\frac{1-(1-h)^t(1-a)^t}{1-(1-h)(1-a)}$$

(the finite geometric sum).

This formula is derived in the appendix.
By contrast, the risk (the cumulative incidence) at time t is given by

$$CI(t) = 1-(1-h)^t$$

(= prevalence in the case of a = 0).

The prevalence increases monotonously with time and converges (with velocity depending on h and a) to the saturation value

$$\pi = \frac{h(1-a)}{h(1-a)+a}$$

This value decreases with increasing rate of leaving the job (a), and it increases with increasing incidence (h) per unit time. It cannot be greater than 1 – a. The curves in figure 1 show the saturation value of the prevalence as a function of h for some values of a.
Table 1 gives, for some incidences and some rates of leaving the job, the length of time until the absolute change per unit time of the prevalence is lower than 1%, the corresponding prevalence after this time, and the saturation value of the prevalence.
Reading the table backwards demonstrates that a prevalence of, for example, about 0.15 could have arisen in three very different ways, involving risks from h = 0.02 up to the ten-fold higher hazard of h = 0.2. To summarize, both table and curves illustrate how sensitive the prevalence is to changes in the rate of leaving the job.
In conclusion, it should be emphasized that prevalence estimates from different studies are not comparable. Without information on or assumptions about exposure times, and about rates of leaving the job, it is not possible to draw evidence about risk from prevalences.

Review of studies on laboratory animal allergy

Six studies from the UK[1–8], four from the USA[9–12], and one each from Sweden[13], Israel[14], Switzerland[15], Germany[16,17], and Japan[18] were analyzed. To our knowledge, these are all the

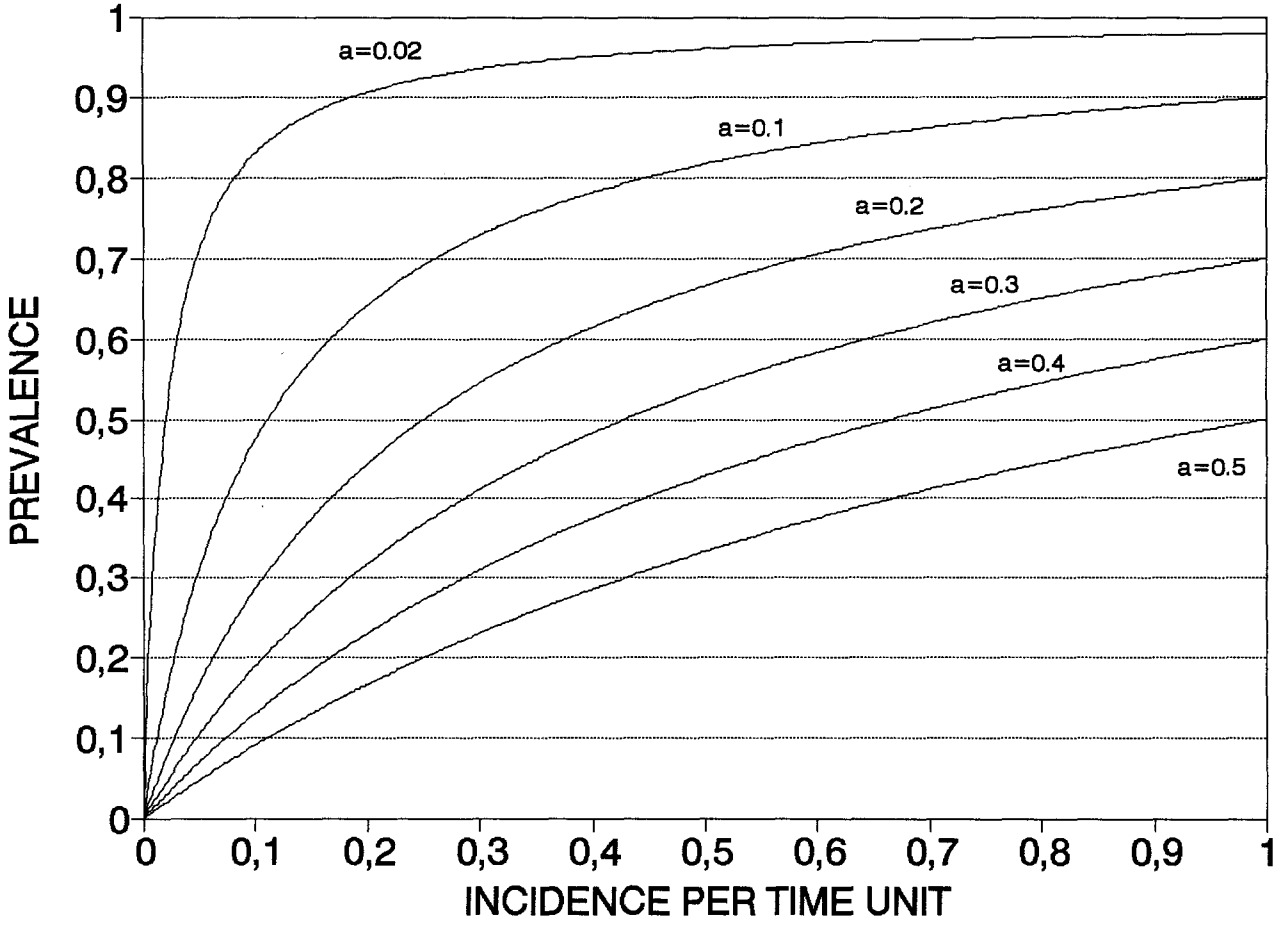

Fig. 1. Saturation value of the prevalence as a function of the incidence per unit time (h) for some value of the rate of leaving job per unit time among the diseased (a).

Tab. 1. Length of time until the absolute change in prevalence per unit time is lower than 1%, corresponding prevalences after this time, and saturation values of the prevalences, with respect to some incidences per unit time (h) and to some rates of leaving job per unit time among the diseased (a).

incidence h =	rate of leaving job a =	time units until absolute change ≤1% t =	prevalence after t time units π(t) =	saturation value of prevalence π =
0.02	0.05	9	0.14	0.28
	0.1	5	0.08	0.15
	0.2	2	0.04	0.07
	0.5	1	0.01	0.02
0.05	0.05	16	0.40	0.49
	0.1	11	0.26	0.31
	0.2	6	0.14	0.17
	0.5	2	0.04	0.05
0.1	0.05	15	0.60	0.66
	0.1	11	0.44	0.47
	0.2	7	0.27	0.29
	0.5	3	0.09	0.09
0.2	0.05	11	0.76	0.79
	0.1	9	0.62	0.64
	0.2	7	0.43	0.44
	0.5	3	0.16	0.17
0.5	0.05	6	0.90	0.91
	0.1	5	0.81	0.82
	0.2	5	0.66	0.67
	0.5	3	0.33	0.33

epidemiological studies on laboratory animal allergy which have been published since 1980.

These 15 studies seem to be quite representative of epidemiological research on occupational respiratory allergies in general. Despite the fact that all study populations were employed in research institutions or pharmaceutical companies where statistical know-how could be expected to exist, the requirements for risk estimation are not fulfilled by the design of any of the studies. This will be demonstrated with respect to the risk determinants [1,2] and [3] discussed above. The corresponding design features of the 15 studies are given in Tables 2 and 3.

The studies are discussed here only with regard to the question of whether the epidemiological methods used were appropriate for quantitative inferences to be made on the risk of occupational allergy. Other study objectives, e.g. the development of new immunological tests, are not considered.

Different methods of characterizing *exposure* were applied and are shown in column 3 of Table 2. In six studies, no exposure assessment at all was done; in some of these studies the exposure conditions seem to have been quite homogeneous in the study

Tab. 2. Sample sizes, exposure characterization, assessment of atopy and prevalences in 15 studies on laboratory animal allergy.

Study	N	Exposure characterization	Assessment of atopy	Prevalence of respiratory symptoms: any symptom	asthma
Gross (1980)[9]	399	job titles	personal history prick-test	15%	8%
Cockcroft et al. (1981)[1]	179	job titles	prick-test	27%	12%
Klaschka, Gick (1981)[16,17]	94	–	personal history family history prick-test	data on symptoms not reported	
Beeson et al. (1983)[2]	69	hours of exposure per week	personal history family history prick-test	22%	4%
Davies et al. (1983)[3]	148	–	–	cumulative incidence (1 year): 15%	2%
Agrup et al. (1986)[13]	189	job titles	assessed only in workers with symptoms	27%	8%
Bland et al. (1986)[10]	549	job titles sum of species-specific months	personal history	24%	–
Lutsky et al. (1986)[14]	90	job titles	personal history family history prick-test	7%	4%
Botham et al. (1987)[6]	383	–	prick-test	cumulative incidence (1 year): 21%	–
Slovak, Hill (1981, 1987)[4,5]	146	–	3 different definitions applied	34%	11%
Venables et al. (1988)[7,8]	161	job titles	prick-test	45%	13%
Weissenbach et al. (1988)[15]	110	job titles	personal history prick-test	21%	13%
Kibby et al. (1989)[11]	261	measurements of allergen concentration at typical workplaces	personal history	28% 2-yr-cum. incid. in subset: 13%	– –
Aoyama et al. (1992)[18]	5641	job titles	personal history family history	23%	2%
Das et al. (1992)[12]	29	–	personal history prick-test	no incident cases in 7 months (but 24% prevalent cases at begin of study)	

population. Most studies used job titles such as "scientist" or "animal handler" for measuring exposure differences. Only one study[11] performed quantitative exposure assessment by measuring allergen concentrations at typical workplaces, but these measurements were only used to define groups of workers with high and low exposure, thus wasting most of the quantitative information. Intensity of exposure – the proportion of time of actual exposure within the total working time – was only measured in one study[2].

Atopy was assessed in most studies, and data analysis was usually stratified by atopy. However, the sources of information used in assessing atopy (see Table 2, column 4) and the criteria for considering an individual as "atopic" were different.

The information on *exposure time* and on *job-leavers* which is necessary for risk estimation was not completely provided by any of the studies.

As can be seen from columns 2–3 of Table 3, 10 studies (out of 15) were cross-sectional. Only one of them[13] gives the number of job-leavers; this publication also reports the frequency of allergic symptoms among them. Even in two[3,6] of the four cohort studies (observing fixed cohorts of workers from the beginning of their employment), the number of workers who had left the job cannot be derived from the published data; in one of the cohort studies that do report the number of job-leavers[16–17] there is no information given on their disease status. In one study[11] two cross-sections of a dynamical working population were observed by

Tab. 3. Overview on study design and information relevant for risk estimation in 15 studies on laboratory animal allergy.

Study	Design	Information on workers who left job	Information on duration of exposure	Information on time until disease onset
Gross (1980)[9]	cross-sectional	–	distributions in diseased and healthy workers	distribution
Cockcroft et al. (1981)[1]	cross-sectional	–	–	mean
Klaschka, Gick (1981)[16,17]	cohort (3 years)	15% no information on disease status	3 years	–
Beeson et al. (1983)[2]	cross-sectional	–	–	–
Davies et al. (1983)[3]	cohort (1 year)	–	1 year	for each case of disease
Agrup et al. (1986)[13]	cross-sectional	39% in 10 years; data on disease status collected	–	mean and range
Bland et al. (1986)[10]	cross sectional	–	computation of animal-months for each worker, but uninformative presentation of results	
Lutsky et al. (1986)[14]	cross-sectional	–	mean and range	–
Botham et al. (1987)[6]	6 cohorts (1–3 years)	uninformative presentation	1–3 years in the respective cohorts	–
Slovak, Hill (1981, 1987)[4,5]	cross-sectional	–	mean	distribution
Venables et al. (1988)[7,8]	cross-sectional	–	grouping according to exposure duration	–
Weissenbach et al. (1988)[15]	cross-sectional	–	uninformative presentation	
Kibby et al. (1989)[11]	2 cross-sections, subset of workers observed twice	uninformative presentation	mean	–
Aoyama et al. (1992)[18]	cross-sectional	–	distribution in diseased and healthy workers	distribution
Das et al. (1992)[12]	cohort (7 months) (including 24% prevalent cases)	45% no prevalent cases	7 months	(no incident cases occurred)

a time lag of two years, with a subset of workers observed on both occasions; in this study, however, the number of job-leavers is not given either.
Columns 4–5 of Table 3 show that information on exposure time is totally lacking in three cross-sectional studies, three others only report mean and range of the exposure duration. Information on exposure time until disease onset is presented in five cross-sectional studies; two of them, however, do not give information on exposure duration in non-diseased workers. On the other hand, three cross-sectional studies provide information on total exposure duration, but do not separately consider the exposure time spent by the diseased workers before getting diseased. This information is also lacking in two of the four cohort studies.
Summing up, none of the 15 studies collected and reported all information on job-leavers, exposure time, and time until disease onset which is required for risk estimation.

For sake of completeness, column 5 of Table 2 presents the observed prevalences or incidences, respectively.

Conclusion

Prevalence rates observed in cross-sectional studies do not properly reflect the risk of occupational allergic diseases. This follows from theoretical considerations which are based on two assumptions:

1. that the hazard of getting a disease is constant in time, and
2. that the disease is irreversible as long as exposure continues.

Even if the first assumption is not met – i.e. if the probability of sensitization is inhomogeneous with regard to exposure time – the risk (the cumulative

incidence) of disease will at least increase monotonously with time. Hence, the distribution of exposure time has a major influence on the prevalence of an occupational allergy.
A review of studies on workers exposed to laboratory animals shows that most studies are cross-sectional; even in the cohort studies reviewed, information which is essential for risk estimation is missing. Prospective or historical cohort studies are needed which estimate the incidence of occupational allergies, especially of asthma, in workers exposed to laboratory animals [7,19,21]; this requires that information on exposure time until disease onset or until the end of observation, as well as on job-leavers and their disease status, be collected. Quantitative or semi-quantitative exposure measurement and assessment of predisposing factors are also desirable.

Appendix: Derivation of formula (1)

Formula (1) is the solution of the following recursion:
Let for $t \geq 1$ (discrete time)
$I(t)$ denote the number of incident cases between time $t-1$ and time t,
$P(t)$ the number of prevalent cases at time t, and
$R(t)$ the size of the population at risk at time t,

then we have

$R(t) = N - P(t)$ (population at risk = constant population size − prevalent cases)

$I(t+1) = h\, R(t)$ (new cases = hazard × former population at risk)

$P(t+1) = (1-a)\,(P(t) + I(t+1))$ (prevalent cases = remaining old prevalent cases + remaining new cases)

By combining the three equations we get

$$P(t+1) = (1-a)\,(P(t) + h\,(N - P(t))) = (1-a)\,(hN + (1-h)\,P(t)),$$

i.e. the prevalence follows the recursion formula

$$p(t+1) = (1-a)\,(h + (1-h)\,p(t)).$$

It can easily be seen by induction that equation (1) is a solution of this recursion.

Summary

The risk of developing an occupational allergic respiratory disease depends strongly on the duration of exposure. For estimating the instantaneous risk (hazard function) in a dynamic cohort, information is required for each cohort member on the time of exposure either until disease onset or until termination by leaving the job or the end of the study. However, most existing epidemiological studies on occupational allergies are cross-sectional, computing prevalences; no information on job-leavers and on their disease status is obtained. The functional dependency of prevalence on risk, as well as on the rate of leaving the job among the diseased and on the distribution of exposure duration, is described, with special attention to the sensitivity of the prevalence to differences of the rate of leaving the job. A literature review of 15 studies on laboratory animal allergy is given; none of the studies collected and reported all the information necessary for risk estimation.

Résumé

Allergie aux animaux de laboratoire: Une revue des méthodes épidémiologiques
Le risque d'une allergie des voies respiratoires due au lieu de travail dépend en grande partie de la durée de l'exposition. Pour déterminer le risque au moyen de l'évaluation du taux d'incidence momentané (hazard function). Dans une cohorte dynamique, on a besoin d'informations sur chaque individu en ce qui concerne la durée de l'exposition jusqu'au moment où la maladie s'est déclarée ou jusqu'à la cessation de l'exposition par la démission ou jusqu'à la fin de l'étude. La plupart des études épidémiologiques sur les allergies dues au lieu de travail sont cependant des études transversales, dans lesquelles on calcule des prévalences et dans lesquelles il manque des informations sur le nombre et sur l'état de santé des travailleurs ayant quitté le service. Il est démontré comment la prévalence dépend du risque, du taux de démission parmi les personnes atteintes par la maladie et de la durée de l'exercice de la profession, et il est démontré comment la prévalence est surtout sensible par rapport au taux de démission. Un résumé de 15 études sur les allergies causées par des animaux de laboratoire montre qu'en aucune des études les informations recueillies ne suffisent pour une évaluation du risque.

Zusammenfassung

Ein Überblick über epidemiologische Methoden in Studien zu Versuchstier-Allergien
Das Risiko einer arbeitsbedingten Atemwegsallergie hängt wesentlich von der Expositionsdauer ab.

Bei der Risikobestimmung durch Schätzung der Hazard-Funktion (momentane Inzidenzrate) in einer dynamischen Kohorte benötigt man von jedem Individuum Information über die Dauer der Exposition bis zum Beginn der Erkrankung oder bis zur Zensierung durch Ausscheiden bzw. durch das Studienende. Die meisten epidemiologischen Studien zu arbeitsbedingten Allergien sind jedoch Querschnittstudien, in denen Prävalenzen berechnet werden und Information über die Zahl und den Erkrankungsstatus ausgeschiedener Mitarbeiter fehlt. Es wird gezeigt, wie die Prävalenz vom Risiko, von der Ausscheidensrate unter den Erkrankten und von der Verteilung der Beschäftigungsdauer abhängt, und wie sensitiv sie vor allem gegenüber der Ausscheidensrate ist. Eine Übersicht über 15 Studien zu Versuchstier-Allergien zeigt, dass in keiner der Studien die gesammelte Information für eine Risikoquantifizierung ausreicht.

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