

Allergen levels causing sensitisation, bronchial hyperreactivity and asthma

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An atopic trait and exposure to allergens are pre-requisites for sensitisation. In predisposed individuals, sensitisation occurs to allergens present in the environment. Renewed exposure of sensitised individuals to allergen induces allergic reactions. Thus, when designing both primary and secondary prevention programmes it is of great importance to know how allergens are distributed in the environment of allergic children.

The distribution of allergens in the environment of children is reviewed by Munir (1) in this supplement. This review will discuss the doses inducing sensitisation and causing acute asthma as well as slight bronchial hyperreactivity, i.e. chronic asthma.

Recently, allergens have been isolated and polyclonal and/or monoclonal antibodies have been produced against these antigens using hybridisation techniques (2, 3). On this basis, several methods (4–6) have been established for determination of the amount of allergen in dust in the environment of allergic patients. Most data available refer to the allergen content of house dust. However, much more relevant would be to determine the amount of allergen actually inhaled by children or absorbed from the gut.

Doses of allergen sensitising children

Amounts of inhaled allergens

The amount of airborne allergen has been estimated in different locations by several investigators using different methods for air-dust sampling and determination of allergen content (2, 7–15). Air-sampling has been performed with high-volume air samplers and small, portable air-pumps. In homes without cats and dogs, Sakaguchi et al. (13) found pet allergens to be non-measurable using low volume samplers and a method with a total cut off of the methods employed at 16–37 pg/m³ (Fig. 1). They

also found the level in homes with these pets to be between 1 and 100 ng/m³, i.e. the sensitising dose for infants living in homes with pets would be about 3–300 ng/day or 1–100 µg during 1 year. Children exposed to dog or cat at home during the first year of life, i.e. to totally less than 100 µg of the major allergen of these pets get sensitised to that same species of animal within few years (16).

The data of Sakaguchi et al. (13) show that the concentration of pet allergens in the air is approximately at the same level as that of pollen allergen during the ragweed pollen season, i.e. 1 µg is inhaled per season (17) or some 10 to may be a maximum of 100 ng is inhaled per day.

Others, using small pumps and less sensitive methods, found airborne pet allergens at the ng level/m³ in homes without pets (12). Thus, results vary remarkably. Therefore, more data are needed before any firm conclusions can be drawn about how much allergen is actually inhaled under different conditions.

Methods for determination of the amounts of allergen inhaled by children should be based on personal sampling using pumps with much higher capacity than the present portable pumps. Furthermore, methods for determination of allergens in dust must be much more sensitive than those used in some laboratories (12, 14). Methods used must be better evaluated and data compared between centres. Then, it seems reasonable to prefer determination of the amount of allergen in the air to the concentration in dust.

Concentration of allergens in dust

A correlation probably exists between the amount of allergen in the dust and in the air (13) (Fig. 1). However, the relation between the concentration of allergen in the dust and the amount of allergen per

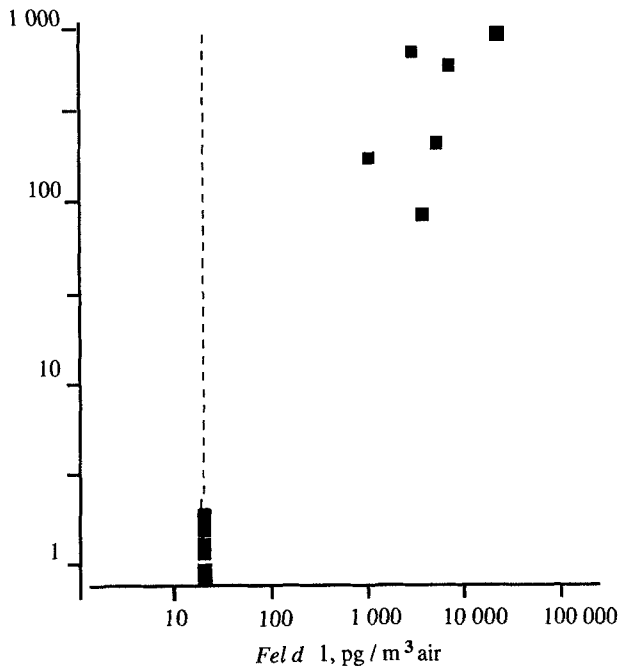


Fig. 1. The concentration of *Fel d 1* in dust and in the air in homes with and without cats. No *Fel d 1* was found in the air of homes without cats.

m^3 of air is not consistent between investigators (8, 13). The data of Sakaguchi et al. (13) indicate that the ratio, allergen in the air given as weight/m^3 allergen in dust given as weight/g of fine dust, $1/50\,000$. Based on such data, and since it is not possible to determine the amount of allergen in the air, determination of the allergen content of dusts can be used as an indicator of allergen exposure.

It has been claimed that the sensitising concentration of the major allergen of mite, *Der p 1*, is $2\text{ }\mu\text{g}$ per gram of fine dust (18). However, the studies used for estimation of the dose, were mainly cross-sectional and performed in regions with high amounts of mites in dust, investigating the mite allergen content in the dust from homes of asthmatics. Sporik et al. (19), in a retrospective study from England, found much higher levels of mite allergen in the dust of homes of children who developed asthma than the concentration found in dust from homes of controls.

In recent prospective studies one group in Berlin (20) and another one in Linköping (21), i.e. in areas with low degree of mite infestation, have found that children exposed to much lower concentrations of allergen than $2\text{ }\mu\text{g}/\text{g}$ of fine dust are sensitised. In Berlin (20) 60% of the children sensitised to inhalant allergens were sensitised, as measured by skin prick test with standardized allergens and methods or RAST, when exposed to levels of major allergens below $1\text{ }\mu\text{g}/\text{g}$ of fine dust in their homes. However, it can not be excluded that they were exposed to far higher concentrations of allergen in such other loca-

tions as day-care centres (22) or visits by pet owners or by visits to homes with pets (23). Short peaks of allergen exposure may be of great importance for the sensitising process (24). Furthermore, the higher the dust allergen level, the higher the risk for sensitisation (25, 26), i.e. at low allergen concentrations in the dust only the most susceptible individuals are sensitised, whereas when allergen exposure increases, the number of sensitised individuals increases and even only slightly atopic subjects are sensitised.

Thus, further studies should be performed, i.e. investigating the dose response relationship, allergen exposure vs. sensitisation.

Sensitisation to foods

It is well known that atopic children are sensitised before weaning, i.e. probably by doses of allergen delivered by the breast milk of their mothers. Breast milk of atopic mothers contains between 0.9 and $150\text{ }\mu\text{g}$ of β -lactoglobulin per litre (27, 28), i.e. approximately the daily intake of breast milk by older children. Thus, the oral dose causing sensitisation can be estimated to be between one μg and some milligrams. How much of the β -lactoglobulin ingested that is really absorbed or in contact with the immune system of the child can not be calculated from these data, since much of the ingested allergens are rapidly degraded (29, 30). Experimental data suggest (31) that immunologically detectable human α -lactalbumin is absorbed reaching a concentration in serum of

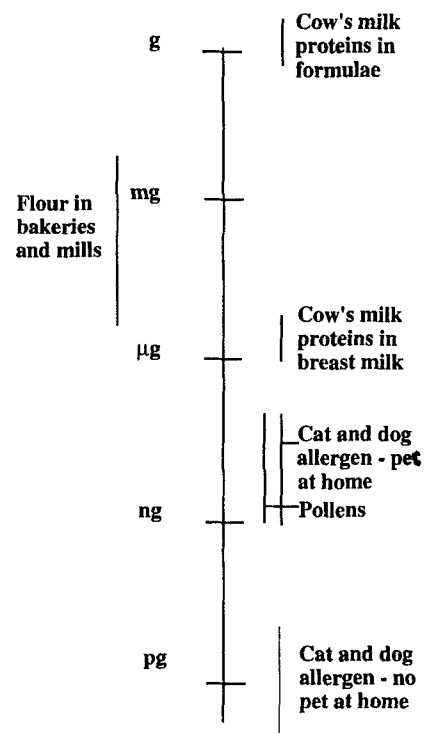


Fig. 2. Amounts of allergen ingested or inhaled per day.

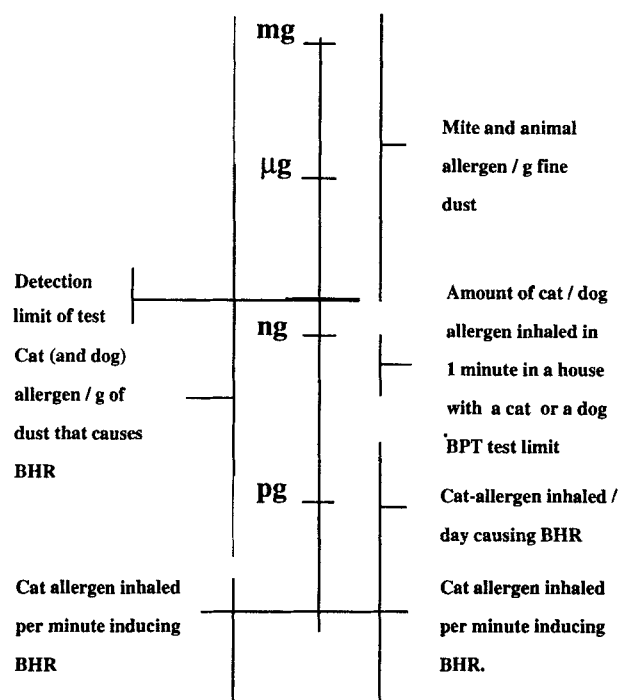


Fig. 3. Going from the top to the right, down and then up on the left side are illustrated the amounts of allergens in dust from different locations, amounts of allergen inhaled short exposure, during long-term exposure causing chronic hyperreactivity and, finally, the concentration of allergen in dust corresponding to this inhaled dose (see further text).

10–1000 µg/litre serum/litre human milk/kg body weight. Thus, an infant weighing 10 kg, would reach a total serum content of approximately 100 µg to 10 mg, i.e. a serum concentration of roughly 0.1–10 µg/mL. Both values are very high in this context, which might explain the often very early sensitisation to cow's milk.

Amounts of cow's milk protein ingested with breast milk and cow's milk formulae, to the amounts of flour protein inhaled per day in bakeries and flour mills and cat and dog allergen inhaled per day in homes with and without pets are illustrated in Fig. 2.

Prenatal doses of allergen causing sensitisation

At present under discussion is whether oral tolerance is normal or can be induced under certain circumstances (32). However, recent data from Denmark indicate that sensitisation already takes place during the fetal period, since 76% of high risk infants later developing cow's milk allergy, showed cow's milk-specific IgE-antibodies in cord blood (33, 34). The dose of allergen, or maybe anti-idiotypic antibodies, passing the placenta causing this intrauterine sensitisation is not known.

Doses inducing reactions

Doses of allergen inhaled causing acute asthma

From the data of Sakaguchi et al. (13), related earlier, it can be estimated that inhaled amounts of allergen at the ng level can cause acute asthma, since this amount is inhaled per minute in houses with cats and dogs. Using a specially designed inhalation chamber, van Metre et al. (7) found the amount of allergen inhaled causing an asthma attack in cat allergic individuals to be 60 ng.

These figures largely agree. However few homes/patients were investigated. They also agree with our data on the amount of allergen inhaled by patients during bronchial provocation tests (35) (see below).

Doses of allergen in dust causing acute asthma

In a number of studies, data have been accumulated showing that patients with acute asthma and sensitisation to environmental allergens are exposed in their homes to 2–10 µg or more of the major allergen of cat or mite per gram of fine dust (18).

Doses of allergen inhaled causing slight asthma or increased bronchial hyperreactivity in asthmatics

The doses causing slight asthma are probably substantially lower than those causing acute asthma. There are several factors which must be considered.

Of importance is the fact that the sensitivity of the skin (36), conjunctiva (37) and bronchi (35) varies million-fold between patients sensitive to the same allergen, i.e. the dose inducing symptoms may vary considerably between individuals.

A second factor to be considered is that the lowest dose inducing immediate bronchial constriction in sensitive asthmatics is about 0.1 Nordic BU (35) or 0.1 ng of major allergen (38). This dose is inhaled during one or a few minutes via a nebulizer. This amount is similar to the amount inhaled per minute (13) in homes with cats or dogs. Only a few very sensitive individuals react within one or a few minutes when entering a home with a pet to which he/she is sensitised (unpublished results).

A third factor is that, according to recent results, 1‰* of the dose causing an immediate reaction, inhaled once a day for one week, induces an increase

* In the study by Ihre & Zetterström (12) the dose inhaled was 1 Nordic BU. They claimed this was 1/100 of the dose "normally" causing bronchoconstriction. The dose causing immediate bronchoconstriction was never investigated in their patients. However, I found (35) that the mode of the distribution of threshold concentrations causing asthma was between 1000 and 10000 BU, i.e. the dose chosen by them was less than 1/1000 of the dose causing bronchoconstriction in the median sensitive patient.

of the bronchial hyperreactivity of asthmatic patients (39). Thus, the daily dose causing bronchial hyperreactivity in the most sensitive patient would be about 0.1 pg, and the dose inducing chronic hyperreactivity in such a patient would be about 0.0001 pg of major allergen inhaled per minute. Recently, it has been reported (13) (Fig. 1) that the dose of dog or cat allergen inhaled in homes without animals at home is $< 16 \text{ pg/m}^3$, or $< 0.02 \text{ pg inhaled/minute}$ by a child. This fits roughly with the figures given above (Fig. 3).

The levels of dog and cat allergen in dust found in schools (40), day-care centres (22) and other public places (41, 42) are intermediate between those found in homes of allergic and asthmatic children (23, 26, 43) and in homes with dogs and cats (6, 26, 43).

Doses of allergen in dust causing slight asthma or increased bronchial hyperreactivity in asthmatics

Going from the data given above, the dose of allergen/g fine dust causing slight asthma in sensitive individuals would be 50 000 "times" higher than the concentration in the air causing such symptoms i.e. $50\,000 \times < 16 \text{ pg/m}^3$, i.e. $< 50 \text{ ng/g}$ of fine dust (13, 44).

These data fit very well with each other and with the fact that many individuals sensitised to dog and cat have increased bronchial reactivity when visiting areas that seem to be free of pets and increased symptoms when school starts after the Summer vacations, i.e. they are exposed to ngs to μgs of allergen/g of fine dust.

This generates the hypothesis that lower levels of allergens than previously thought to be of pathogenic importance for induction of chronic bronchial hyperreactivity, i.e. asthma, cause slight symptoms in susceptible individuals (44). Investigations are under way estimating the amount of allergen actually inhaled by chronic asthmatic children with monosensitisation.

Conclusions

Levels of allergens in dust can be determined, but these levels are only indirect measures of allergen exposure. Methods for determination of allergens in the air are presently under development, but accurate determination of the amount of allergen actually inhaled by patients as measured by portable devices are not available as yet.

There are no hard data on the doses actually inhaled causing sensitisation of atopic children or inducing symptoms in sensitised patients.

Concentrations of allergens in dust can probably be used as a substitute for determination of amounts

of inhaled allergen. Lower concentrations of allergens in dust than those previously thought to be harmful are probably both sensitising and causing increased bronchial hyperreactivity.

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