



Refractory asthma phenotyping based on immunoglobulin E levels and eosinophilic counts: A real life study

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ABSTRACT

Background: Asthma is an inflammatory heterogeneous disease with variable severity. The serum IgE level and Eosinophilic count have been used as biomarkers to define treatment strategies with biological agents in severe refractory asthma.

Objective: The aim of this study is to determine the concurrence of high eosinophil count and elevated serum IgE levels in patients with severe refractory asthma.

Methods: A retrospective cross-sectional real-life study was conducted on patients attending adult refractory asthma outpatient clinic between 2015 and 2018. Serum total IgE level and blood EOS count on matched dates with spirometry and Asthma Control Test (ACT) scores were collected. All data were obtained while patients were not on biological agents.

Results: A total of 142 patients with severe refractory asthma were included. The mean age was 43 years, mean eosinophilic count 564 cells/ μ L and mean serum IgE levels of 520 IU/mL. There was a significant correlation between serum IgE level and eosinophilic count. Serum IgE and eosinophilic count were concurrently elevated in 110 patients (78%). The patients were further categorized into four subgroups. Group A: IgE 30–100 IU/mL and EOS 150–300 cells/ μ L (7.3%), Group B: IgE >100 IU/mL and EOS 150–300 cells/ μ L (19.1%), Group C: IgE 30–100 IU/mL and EOS >300 cells/ μ L (14.5%) and Group D: IgE >100 IU/mL, EOS >300 cells/ μ L (59.1%).

Conclusion: The majority of severe refractory asthma patients exhibits both elevated serum IgE level and eosinophilic counts.

1. Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation. It is defined by history of respiratory symptoms such as wheezing, cough, shortness of breath, and chest tightness that vary over time in intensity, together with variable expiratory airflow limitation [1]. The treatment intensity for asthma is determined to symptoms' severity. Inhaled corticosteroids in variable doses, short and long-acting β_2 -agonists, anticholinergic bronchodilators, leukotriene receptor antagonists, oral corticosteroids, theophylline and monoclonal antibodies are utilized to achieve control of symptoms and prevent further

exacerbations [1–3]. Moreover, severe asthma is defined as uncontrolled asthma despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased [4].

A key player in the inflammation of the lower respiratory tract in asthma is the Type 2 helper cells (T_H2) [1]. IL-4, IL-5 and IL-13, which are secreted by T_H2 cells greatly stimulate inflammation by contributing to the activation of large numbers of eosinophils (EOS) and the production of immunoglobulin E (IgE) [3]. The complexity of the role of IgE in asthma is demonstrated in its ability to influence various pathways and cells by interacting with Fc ϵ RI and Fc ϵ RII receptors [5].

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Accordingly, high levels of IgE (>400 IU/mL) have been associated with increased severity of asthma [6]. On the other hand, high EOS count in peripheral blood is detected in a significant proportion of asthmatics and has been linked to asthma severity as well [7–9].

Biological treatment in the form of monoclonal antibodies (mAb) has been introduced in the treatment algorithm of refractory asthma associated with elevated IgE and/or high EOS count [10–12]. Omalizumab, an anti-IgE humanized mAb, has been used for more than a decade ago for the treatment of moderate to severe allergic asthma phenotype characterized by elevated IgE levels [5]. More recently, several mAb targeting IL-5 and its receptor (Mepolizumab, Reslizumab, Benralizumab) and IL-4/IL-13 (Dupilumab) have been added to the armamentarium of treatment of severe refractory asthma of eosinophilic phenotype [5,13]. These biologic agents have been shown to reduce the incidence of asthma related hospitalizations and improved many of the patients' symptoms [13,14]. However, in real life it is not easy to identify these two phenotypes since some patients with severe refractory asthma exhibit both elevated IgE and EOS count; thus making the choice of mAb treatment more perplexing. The aim of this study is to determine the concurrence of high eosinophil count and elevated IgE levels in patients with severe refractory asthma.

2. Methods

2.1. Study design & participants

This is a retrospective cross-sectional study that was conducted in a tertiary care center, King Fahad Medical City in Riyadh, Saudi Arabia. Data was collected from electronic medical records of all patients who attended the refractory asthma clinic between 2015 and 2018. The selection of patients was based on the availability of serum total IgE level, blood EOS count, spirometry and Asthma Control Test (ACT) scores within 4 weeks of each other. Only adult patients (≥ 15 years) at the time of testing were included in the study. All data were obtained while patients were not on biological agents. Patients with missing data, concurrent hematological malignant diseases or bone marrow diseases were excluded. The data variables that were collected included: age, gender, IgE level, EOS count, body mass index (BMI), dates of usage of biologic agents, ACT score, pre-bronchodilator forced expiratory volume in 1 s (FEV₁), FEV₁/FVC ratio and reversibility study.

2.2. Statistical analysis

Cross-tabulation was made based on IgE level and EOS count to identify patients with normal IgE and EOS count (IgE ≤ 30 IU/mL and EOS ≤ 150 cells/ μ L) from patients with elevated IgE and EOS count (IgE > 30 IU/mL and EOS > 150 cells/ μ L) patients. Furthermore, patients with high IgE and EOS count were further categorized into four subgroups: Group A with IgE 30–100 IU/mL and EOS count 150–300 cells/ μ L, Group B with IgE > 100 IU/mL and EOS count 150–300 cells/ μ L, Group C with IgE 30–100 IU/mL and EOS count > 300 cells/ μ L and Group D with IgE > 100 IU/mL and EOS count > 300 cells/ μ L. The cut-off points were based on monoclonal antibodies guidelines and previous literature [15–19]. Descriptive statistics such as means and standard deviation (mean $\pm$ SD) were computed for quantitative variables: Age, BMI, ACT score, pre-FEV₁, FEV₁% predicted, FEV₁/FVC. Frequencies (n) and percentages (%) were computed to summarize categorical variables: IgE & EOS Grouping and gender. Independent *t*-test was used to find significant differences in means of age, BMI, ACT score, pre-FEV₁, FEV₁% predicted, and FEV₁/FVC. One-way ANOVA was used to find a significant difference in the means of age, BMI, ACT score, pre-FEV₁, FEV₁% predicted, FEV₁/FVC among the four subgroups. Post-Hoc (LSD) was then used to identify the groups with the significant difference. Spearman's and Pearson's correlation were used to identify a relationship between IgE levels, EOS count and ACT score. Data analysis was performed through SPSS version 23. A *p*-value of

<0.05 was defined as statistically significant.

2.3. Ethical consideration

This study was approved by the Institutional Review Board at King Fahad Medical City. All data collected were treated with extreme confidentiality.

3. Results

3.1. Study population

Of the 238 patients attending the refractory asthma clinic at King Fahad Medical City between 2015 and 2018, 142 (59.7%) had their serum total IgE and EOS counts tested on matched date (within 4 weeks) with spirometry and ACT scores. The mean age of the patients with severe refractory asthma was 43.1 ± 15.3 years, 76.8% were females, the mean serum IgE levels and EOS count were 520 ± 817 IU/mL and 564 ± 625 cells/ μ L respectively (Table 1). There was a significant correlation, although weak, between serum IgE level and EOS count ($r = 0.19$, $p = 0.024$). Only 6 patients (4.2%) had both normal serum IgE level (<30 IU/mL) and EOS count < 150 cells/ μ L, 17 patients (12%) had only IgE levels elevated (533 ± 704), 9 patients (6.3%) had Eos count elevated (664 ± 630), while 110 patients (77.5%) had both elevated IgE levels (>30 IU/mL) and EOS count (>150 cells/ μ L). The FEV₁, FEV₁% predicted and FEV₁/FVC were significantly lower in patients with both high IgE and EOS count compared to the rest ($p = 0.028$, $p = 0.008$, $p = 0.007$ respectively). On the other hand, there was no significant statistical differences in ACT between the two groups ($p = 0.173$). Among those with elevated serum IgE level and EOS count group, females had a significantly higher BMI (32.6 vs. 25.3, $p = 0.0001$) and lower ACT score (12.6 vs. 15.7, $p = 0.018$) when compared to males (Table- 2) (see Table 2).

3.2. IgE & EOS subgroups

The 110 patients with elevated serum IgE levels (>30 IU/mL) and EOS count > 150 cells/ μ L, were further categorized into four subgroups. Group A: (n = 8) 7.3% of total sample with IgE 30–100 IU/mL and EOS 150–300 cells/ μ L, Group B: (n = 21) 19.1% with IgE >100 IU/mL and EOS 150–300 cells/ μ L, Group C: (n = 16) 14.5% with IgE 30–100 IU/mL and EOS >300 cells/ μ L and Group D: (n = 65) 59.1% with IgE >100 IU/mL and EOS >300 cells/ μ L (Fig. 1). Most of the severe refractory asthma patients with elevated serum IgE level and EOS counts were in Group D (59.1%). When Group D is compared to the other groups, there were significant differences in age ($p = 0.002$) and BMI ($p = 0.0001$) (Table 3).

Table 1

Characteristics of refractory severe asthma patients, values are presented as mean (SD).

Characteristics	Refractory Asthma Population (n = 142)
Male sex, n (%)	33 (23.2%)
Female sex, n (%)	109 (76.8%)
Age (years)	43.1 (15.3)
IgE Level (IU/mL)	520.0 (817.7)
Eosinophils Count (cells/ μ L)	564.2 (625.4)
BMI (kg/m ²)	31.1 (7.4)
ACT	13.0 (5.4)
Pre-FEV ₁ (liter)	1.95 (0.70)
FEV ₁ % predicted	73.2% (19.9)
FEV ₁ /FVC %	71.3% (10.1)

BMI: Body mass index; ACT: Asthma control test; FEV₁: Forced expiratory volume in 1 s; FVC: Forced expiratory volume.

Table 2

Sex based characteristics of refractory severe asthma patients with high serum IgE (>30 IU/mL) and EOS count (>150 cells/ μ L), values are presented as mean (SD).

Characteristics	Male (n = 27)	Female (n = 83)	P-value
Age (years)	38.4 (30.0)	43.8 (12.9)	0.191
IgE Level (IU/mL)	831.4 (1150.4)	506.7 (745.2)	0.091
Eosinophils Count (cells/ μ L)	705.6 (625.5)	639.1 (657.5)	0.645
BMI (Kg/m ²)	25.3 (5.5)	32.6 (8.1)	0.0001
ACT	15.7 (5.9)	12.6 (5.5)	0.018
FEV1 pre-drug (liter)	2.28 (0.79)	1.74 (0.62)	0.001
FEV1% predicted	69.4 (15.8)	70.8 (22.1)	0.771
FEV1/FVC %	67.2 (9.0)	70.8 (11.0)	0.127

BMI: Body mass index; ACT: Asthma control test; FEV₁: Forced expiratory volume in 1 s; FVC: Forced expiratory volume.

4. Discussion

In patients with uncontrolled severe asthma, the decision on what biological treatment to use is challenging. This real-life study specifically addressed the concurrence of elevated IgE levels and EOS counts in severe asthma cohort. We found great overlap in severe asthma phenotypes when they are primarily based on IgE levels and EOS counts. Similar findings were reported in a large cohort of patients from Europe [7]. This heterogeneity makes really difficult to define phenotypes based on these two biomarkers. For this reason, it is recommended to look for other variables for more precise classification. These variables include presence of atopy, co-morbidities such as allergic rhinitis and nasal polyposis, and exhaled of Nitric Oxide (FeNO) [2]. The constellation of these variables may aid in the determination of Th2-high asthma: eosinophilic and allergic compared to non-type 2 asthma: neutrophilic and paucigranulocytic [15]. Furthermore, there are significant variations in IgE and EOS count among individual patients. This could be due to severity of asthma symptoms, exposure to allergens, corticosteroids treatment or parasitic infections. For this reason, it is recommended to get 3 measurements at different intervals [4]. In our study, we elected to report those done in matched dates to minimize variations.

There is significant relationship between asthma severity and IgE level and/or EOS count levels [16–19]. In our study, spirometry results were significantly lower in the high IgE and EOS group (n = 110) when compared to the low IgE and EOS group (n = 32). ACT scores were lower in low IgE and EOS (11.9) compared to high IgE and EOS (13.4);

however, it was not significant since it is less than 3, which is the cut-off point for difference in clinical status between those two groups [20]. These findings could be attributed to high degree of airway inflammation, poor control, asthma exacerbations and airway remodeling [21].

Recently, novel monoclonal antibodies have been introduced into the armamentarium of asthma treatment. These medications are recommended for eosinophilic type 2 asthma as they target specific inflammatory pathway [22–28]. Of interest is the variability in the effects of these biological agents which demonstrate the complexity and heterogeneity of asthma. In our study, group D in figure- 1 demonstrated both high IgE and EOS count. For this subgroup there are no clear guidelines or evidence of the superiority of one biological agent over another whether it is anti-IgE, anti-IL5, anti-IL5R or anti-IL4/IL13. For group B where IgE is high and EOS count is low, Omalizumab would be the drug of choice in the presence of allergic component (positive RAST

Table 3

Characteristics of subgroups of refractory severe asthma patients with high serum IgE (>30 IU/mL) and EOS count (>150 cells/ μ L), values are presented as mean (SD).

Characteristic	Group A (IgE 30–100 & EOS 150–300)	Group B (IgE >100 & EOS 150–300)	Group C (IgE 30–100 & EOS >300)	Group D (IgE >100 & EOS >300)	P- value
IgE Level (IU/ mL)	64.2 (23.1)	663.8 (1109.4)	68.2 (21.4)	753.2 (875.5)	NA
Eosinophils Count (cells/ μ L)	234.5 (52.6)	242.3 (41.8)	533.7 (256.8)	870.7 (754.3)	NA
Age (years)	58.9 (8.7)	37.9 (15.9)	45.9 (14.9)	41.1 (15.3)	0.007
BMI (kg/m ²)	40.0 (11.8)	30.2 (8.7)	32.3 (7.3)	29.5 (7.0)	0.004
ACT	12.4 (5.0)	14 (4.6)	13.6 (5.9)	13.2 (6.1)	0.924
FEV1 pre-drug (Liter)	1.41 (0.33)	2.05 (0.90)	2.03 (0.67)	1.84 (0.67)	0.183
FEV1% predicted	70.7 (14.9)	73.6 (27.4)	78.5 (23.0)	67.7 (18.6)	0.331
FEV1/FVC %	72.6 (6.7)	69.2 (8.5)	72.4 (7.7)	69.2 (12.0)	0.673

BMI: Body mass index; ACT: Asthma control test; FEV₁: Forced expiratory volume in 1 s; FVC: Forced expiratory volume.

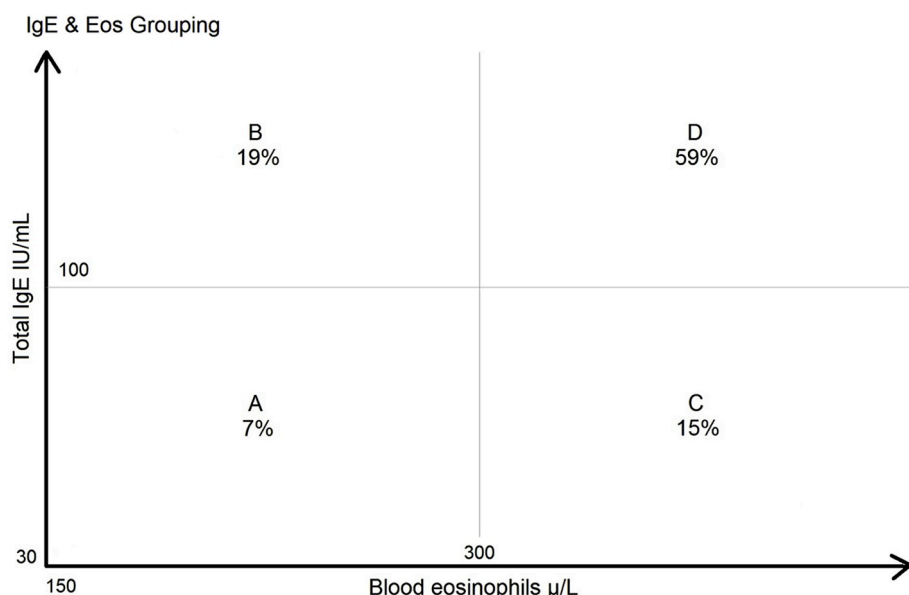


Fig. 1. Serum IgE levels and eosinophils count subgroups of patients with refractory severe asthma.

or skin prick test) [29]. For group C where IgE is low and EOS count is high, the choice would be among anti-IL5, anti-IL5R or anti-IL4/IL13. Finally, group A where IgE is low and EOS count between 150 and 300 cells/ μ L, the choice would be between two anti IL-5 (Mepolizumab or Benralizumab) [22,23] or anti-IL4/IL13 (Dupilumab) [13] since Reslizumab indication is for EOS count > 400 cells/ μ L [25]. Unfortunately, we are defining the various phenotypes according to the inclusion criteria used in various clinical trials which question the authenticity of such classification.

In our study, we observed gender differences in the high IgE and EOS group. Males had a significantly higher mean ACT (15.7 vs. 12.6) and FEV1 (2.28 vs. 1.74) than females. However, BMI was significantly higher in females than in males (32.6 vs. 25.32), this could partially explain the differences as in previous studies in which those with higher BMI had worse control and/or ran a more severe course [30,31] and more specifically in females [32].

The main limitation of our study is the fact that it was a single center retrospective study with relatively small number of patients. Another limitation was that 17.6% (n = 25/142) patients had EOS count tested on a different day than IgE but within four-weeks time.

5. Conclusion

The majority of severe refractory asthma patients exhibits both elevated serum IgE level and eosinophilic counts. Accordingly, deciding on which monoclonal antibody treatment is not an easy decision to make in such patients. More studies are needed to identify other markers that can aid in decision making.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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QUESTIONNAIRE FOR THE STUDY OF ALLERGENS IN DUTCH HOUSEHOLDS

Explanation of the questionnaire

This is the questionnaire belonging to the study 'Allergens in Dutch households' and contains questions about your home, household habits and your health.

Most questions can be answered by placing a cross next to the appropriate answer. In some cases you may find it difficult to make a choice between the answers. For the purposes of this study it is best if you do make a choice and in that case you should choose the answer that is most appropriate. In several places you will be asked to fill in an answer, in which case you should write your answer in the space provided.

Please complete this questionnaire and to return it to us in the envelope with the dust collection cloth.

To protect your privacy, your details will be entered into the computer separate from your name and address and only identifiable as a number.

If you have any questions please contact:

Ms S.A. Burt, PhD

030-253.5350

s.a.burt@uu.nl

This page will be removed on arrival and stored separately from the answers

I confirm that I wish to take part in the study about the presence of allergens in Dutch households.

PERSONAL INFORMATION

Mr / MS (delete as appropriate)

Initials: Surname (family name):

Address.

(street + house number)

(postcode + town)

Telephone: (optional)

Email: (optional)

Signature

☐ I wish to receive an email with a summary of the results of the study.

A. General questions

A.1 Are you male or female?

- ☐ Male
- ☐ Female

A.2 What is your age?

years

A.3 In which country were you born?

- ☐ Netherlands
- ☐ Other country, namely

A.4 Apart from you, how many other people are there in your household?
(more than 1 answer is possible)

- ☐ I live alone
- ☐ I live with a partner
- ☐ My parents or other adult live(s) with me: (number)
- ☐ Children 18 years or older: (number)
- ☐ Children 13 - 17 years: (number)
- ☐ Children 0 - 12 years: (number)

A.5 What is the highest level of education you have achieved?

- ☐ No diploma's
- ☐ Primary school
- ☐ Lager / voorbereidend beroepsonderwijs (LTS, LEAO, LHNO, VMBO)
- ☐ Middelbaar voortgezet onderwijs (MAVO, MULO, MBO-kort, VMBO-t)
- ☐ Middelbaar beroepsonderwijs (MBO-lang, MTS, MEAO, BOL, BBS, INAS)
- ☐ Middelbaar hoger onderwijs (HAVO, VWO, Atheneum, Gymnasium, HBS, MMS)
- ☐ Hoger beroepsonderwijs (HBO, HTS, HEAO)
- ☐ University

B. Health

B.1 How would you describe your health **at the moment**?

- ☐ Bad ☐ Fair ☐ Reasonable ☐ Good ☐ Excellent

B.2 Have you ever had asthma?

- ☐ Yes ☐ No (*If no, continue from question B.8*)

If yes, ...

B.3 Has the asthma been confirmed by a doctor?

- ☐ No
☐ Yes, that was in (year)

B.4 How old were you when you had your first asthma attack?

I was then years old

B.5 Have you had an asthma attack **in the last 12 months**?

- ☐ Yes ☐ No (*If no, continue from question B.7*)

If yes, ...

B.6 How many asthma attacks have you had **in the last 12 months**?

attacks

B.7 Do you use asthma medicine at the moment?

(*for example inhalers, aerosols, tablets*)

- ☐ Yes ☐ No

B.8 Are you, or have you ever been over-sensitive or allergic to something?

- ☐ Yes ☐ No (If no, continue with Part C of the questionnaire)

If yes, ...

B.9 Please indicate with a cross which things you are over-sensitive or allergic to.
Please also indicate which symptoms you have.
(several answers possible)

If yes, symptoms of over-sensitivity or allergy:

Over-sensitive or allergic to:		Sneeze or runny nose	Wheezing	Itchy or red skin	Itchy or teary eyes
A. House dust	☐ No ☐ Yes →	☐	☐	☐	☐
B. Food	☐ No ☐ Yes →	☐	☐	☐	☐
C. Animals	☐ No ☐ Yes →	☐	☐	☐	☐
D. Plants or pollen	☐ No ☐ Yes →	☐	☐	☐	☐
☐ Other, namely		☐	☐	☐	☐

If you are over-sensitive or allergic to animals ...

B.10 Which animal(s) are you allergic to?
(more than one answer is possible)

- ☐ Cat ☐ Dog ☐ Rabbit ☐ Guinea pig or Hamster
☐ Horse ☐ Bird ☐ Mouse ☐ Rat
☐ Other, namely

C. Your home

C.1 When did you move into your present home?

		-			-					(dd – mm – yyyy)
day			month			year				

C.2 When was your home built?

- ☐ before 1920
- ☐ between 1920 and 1960
- ☐ between 1960 and 1980
- ☐ between 1980 and 2000
- ☐ after 2000
- ☐ I don't know

C.3 What type of house is your present home?

(only choose one answer: choose the answer that fits your home best)

- ☐ detached house
- ☐ semi-detached
- ☐ terraced
- ☐ flat
- ☐ maisonette
- ☐ ground floor duplex
- ☐ upper floor duplex
- ☐ other, namely.....

C.4 Do you have a garden next to your home?

- ☐ yes
- ☐ no

C.5 How far from your home do you estimate the nearest **green area (park, recreation ground)** to be?

- ☐ less than 100 metres
- ☐ between 100 - 250 metres
- ☐ between 250 - 500 metres
- ☐ between 500 - 1000 metres
- ☐ more than 1000 metres

C.6 How far from your home do you estimate the nearest water course (**canal, lake, river**) to be?

- ☐ less than 100 metres
- ☐ between 100 - 250 metres
- ☐ between 250 - 500 metres
- ☐ between 500 - 1000 metres
- ☐ more than 1000 metres

C.7 Please answer the following questions for your living room (lounge)

	Living room
On which floor is this room?	
Lower than the ground floor (1)	☐
On the ground floor (2)	☐
1st floor (3)	☐
2nd floor (4)	☐
3rd floor (5)	☐
Higher than 3rd floor (6)	☐
Is the floor insulated?	
yes (1)	☐
no (2)	☐
I don't know (3)	☐
Are the windows double glazed?	
yes (1)	☐
no (2)	☐
I don't know (3)	☐
What type of floor covering is in the living room?	
hard (vinyl/linoleum/tiles/wood/laminated) (1)	☐
wall to wall carpeting (synthetic/wool) (2)	☐
hard floor with loose rug(s) (3)	☐

D. Ventilation

D.1 How do you normally ventilate the living room?

(several answers are possible)

- ☐ by means of a ventilation grille
- ☐ by means of an open window
- ☐ by opening an external door

D.2 Does your home have a mechanical ventilation system?

(continuous extraction of air from the kitchen, toilet and bathroom)

- ☐ yes
- ☐ no
- ☐ I don't know

D.3 Have you had water damage or a leak in the house **in the last 12 months?**

- ☐ yes
- ☐ no

D.4 Have you seen patches of mould or mildew on the wall or ceiling **in the last 12 months?**

- ☐ yes
- ☐ no

D.5 Have you smelt mould or damp in the house **in the last 12 months?**

- ☐ yes
- ☐ no

D.6 Have you seen cockroaches in the house **in the last 12 months?**

- ☐ yes
- ☐ no

D.7 Have you seen mice in the house **in the last 12 months?**

- ☐ yes
- ☐ no

D.8 Have you seen rats in the house **in the last 12 months?**

- ☐ yes
- ☐ no

D.9 How often have you or others used the following cleaning agents in the last 12 months?
(Please place one cross for each cleaning agent)

	Never	Less than 1x per week	1-3x per week	4-7x per week
Bleach	☐	☐	☐	☐
Ammonia	☐	☐	☐	☐
Acids or descaler	☐	☐	☐	☐
Solvents (or stain removers)	☐	☐	☐	☐
Furniture polish	☐	☐	☐	☐
Glass cleaning spray (for windows and mirrors)	☐	☐	☐	☐
De-greasing sprays or oven cleaner	☐	☐	☐	☐
Polish or wax for the floor or furniture	☐	☐	☐	☐
General purpose cleaning liquid	☐	☐	☐	☐

D.10 How often do you or other people normally clean the living room?
(Please place one cross per method of cleaning)

	Never	Less than 1x per week	1-3x per week	4-7x per week
General cleaning	☐	☐	☐	☐
Vacuuming	☐	☐	☐	☐
Sweeping	☐	☐	☐	☐
Dusting	☐	☐	☐	☐
Wet cleaning of the floor (e.g. with mop)	☐	☐	☐	☐

D.11 Do people smoke **inside** your home?

☐ Seldom or never ☐ Sometimes ☐ Regularly ☐ (Almost) daily

E. Pets

E.1 Have you kept pets in the house **in the past 12 months?**

☐ yes ☐ no

If yes, ...

E.2 Which sort of pets have you kept in the house **in the last 12 months?**
(Please indicate what is relevant for each type of pet below)

Type of pet ...	No	Yes
1. Cat	☐	☐
2. Dog	☐	☐
3. Bird	☐	☐
4. Rabbit	☐	☐
5. Guinea pig	☐	☐
6. Hamster	☐	☐
7. Mouse	☐	☐
8. Rat	☐	☐
9. Fish	☐	☐
10. Tortoise/turtle	☐	☐

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