

Nasal air sampling used for the assessment of occupational allergen exposure and the efficacy of respiratory protection

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Summary

Background Occupational exposure to rodent allergens may cause laboratory animal allergy. Personal exposure to occupational allergens is measured by collecting airborne dust on filters using person-carried pumps. This technique cannot be used to evaluate personal protective respiratory equipment. Recently developed intranasal air samplers collect inhaled particles by impaction on adhesive strips within the samplers.

Objective The aims were to compare rodent aeroallergen exposure assessment using nasal air samplers with personal air sampling, and to evaluate the efficacy of using respiratory protection during rodent work using nasal air samplers.

Methods Aeroallergen exposure was assessed during rodent work using both nasal air samplers and personal air samplers. The efficacy of respiratory protection (P2 facemasks and fresh-air helmets) was studied in subject pairs working side by side, one person with protection, the other without. Right nostril samples were laminated with protein-binding membrane and immunostained for rat urinary allergen-containing particles. Left nostril samples and air samples were eluted in buffer and analysed in amplified ELISAs for rat (RUA) and mouse (MUA) urinary allergen content (detection limit 10 pg/mL). Allergen collection efficacy of the nasal air samplers was tested at high and low exposure levels and at different flow rates using static sampling.

Results P2 facemasks decreased the amount of inhaled allergen by about 90%, and very little allergen was inhaled using fresh-air helmets. Allergen levels in air and nasal samples correlated well (r_s was about 0.8 for both RUA and MUA). The number of RUA-positive particles and nasal allergen levels measured in ELISA also correlated significantly ($r_s = 0.8$). Collection efficacy of the nasal air sampler was better during high exposure (cleaning cages, median 73% of allergenic particles collected), than during low exposure (undisturbed room, 49% of particles).

Conclusion Nasal air sampling is a relevant and sensitive complement to personal air sampling and enables evaluation of personal respiratory protection equipment. Use of P2 facemasks and fresh-air helmets may substantially reduce occupational exposure to inhaled allergens.

Keywords airborne, allergen, mouse, occupational, rat, respiratory protection

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Background

Several methods to estimate allergen exposure have been used over the last two decades. Sampling of the allergens has been performed using vacuuming of surfaces (reservoir dust), collection of airborne allergens on filters using pumps and, occasionally, Petri dish sampling of airborne settling dust (recently evaluated by Karlsson et al. [1]). Of these methods, the collection of aeroallergens on filters using person-carried pumps may be considered as the gold standard when estimating personal allergen exposure, and is used routinely to measure personal exposure to several occupational allergens, such as

from laboratory animals [2, 3], latex [4], and flour [5]. However, personal air sampling (PAS) has limitations. Airflow using the pumps is static, and does not increase as human breathing does when workload increases. Also sampling with pumps is cumbersome: pump batteries must be reloaded, pump flow calibrated, and the heavy equipment carried around in field studies. Technical problems such as pump failures occasionally occur. Furthermore, it is not possible to evaluate the efficacy of personal respiratory equipment in reducing allergen exposure, since the sampling heads including tubes would cause leakage under, for instance, facemasks. Air sampling using pumps is thus not an option for evaluating respiratory protection.

Recently, a nasal air sampling device to collect inhaled aeroallergen was developed by the Allergen Group at the Institute of Respiratory Medicine, University of Sydney (Inhalix, Camperdown, NSW, Australia) [6]. The intranasal air sampler collects airborne particles inhaled through slits in the sampler by

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impaction on an adhesive tape within the nasal air sampler [7], see Fig. 1. Nasal air sampling (NAS) has previously been used to detect inhaled domestic allergens, such as Fel d 1 (cat) and Der p 1 (mite) [8, 9] and Bla g 1 (cockroach) [10]. Inhaled aeroallergens may be assessed after lamination of the adhesive film to protein-binding membranes. Allergens associated to particles may be visualized using staining with patient sera or monoclonal antibody, seen as 'halos', which may be counted under the microscope. Another alternative is eluting the adhesive tapes in buffer and analysing allergen content in the eluates using enhanced sensitivity sandwich ELISAs.

In this study, nasal air sampling was used to assess exposure to inhaled aeroallergens when working with laboratory animal allergens. This has never been done before. Nasal air sampling was compared to the gold standard, personal air sampling using pumps. The main aim was to evaluate the efficacy of P2-filter facemasks and fresh-air helmets with P3-filters. This was studied in subject pairs simultaneously performing the same work task side by side, one in each pair wearing a mask, and both wearing nasal air samplers. A further aim was to study nasal air sampler collection efficacy at different airflows, and to assess potential leakage past the nasal air sampler.

Materials and methods

Studies

The efficacy of personal protective respiratory equipment (PPE) in reducing amount of inhaled aeroallergens. The efficacy of P2-filter disposable facemasks (9322, 3M Svenska AB, Sollentuna, Sweden) and fresh-air helmets (RACAL Breathe-Easy, RACAL Health & Safety AB, Järfälla, Sweden) was studied using nasal air samplers in 20 and 10 pairs of subjects, respectively, performing the same work task side by side, with or without personal respiratory protection. The P2-filter facemask had a frontal air-vent, and was the preferred type among three different brands available in the studied facility, according to questionnaires answered by 101 of the 118

employees (manuscript in preparation). The fresh-air helmet respirator was equipped with P3-filters. To verify that the subjects within the pairs were similarly exposed, PAS was simultaneously performed.

Personal exposure assessment using NAS and PAS Aeroallergen exposure assessment was compared using the nasal air samplers and conventional sampling of inhalable dust on filters attached to pumps at 2 L/min airflow. Both NAS and PAS samples collected in 36 subjects during animal work without personal respiratory protection were included in these analyses.

Allergen collection efficacy and allergen leakage Nasal air samplers ($n = 18$) were connected to a stationary pump run at flow rates of 2, 5 and 10 L/min, with a protein-binding membrane behind the nasal air sampler to capture allergens that escaped NAS collection.

Sampling of nasally inhaled allergens using NAS

Intranasal air samplers (Inhalix) were worn for a mean 31 min (range 11–54 min) during rat and/or mouse work, in total collecting 67 samples. Subjects were instructed not to talk and to use only nasal breathing during the sampling period. The samplers were stored at +4 °C until allergen elution, which was performed within a few days after sampling.

Right nostril adhesive tapes were laminated with 1.0 µm pore size protein-binding polyvinylidene-difluoride (PVDF) membrane and immunostained for particles containing rat urinary allergen (RUA) Rat n 1 applying the HALOgen assay (Inhalix) as described below. Left nostril adhesive tapes were eluted in 0.5 mL phosphate-buffered saline (PBS) with 0.5% Tween 20 and 0.15% Kathon CG during gentle rotation for 2 h at room temperature. After discarding the adhesive tapes, the eluates were transferred to tubes containing 5 mg bovine serum albumin (BSA, final concentration 1%). After rotation for 5 min, samples were stored at –20 °C until analysis for RUA and mouse urinary allergen (MUA) Mus m 1 content.



Fig. 1. Nasal air sampler with one of the nostril samplers assembled. The other nostril sampler shows the adhesive tape (with the yellow tabs at ends) and the silicone sleeve.

Sampling of inhalable airborne allergens using person-carried pumps (PAS)

Air samples ($n = 67$) were collected at 2.0 L/min flow on 25 mm 1.0 µm polytetrafluoroethylene (PTFE) filters (Millipore, Sundbyberg, Sweden) using SKC portable samplers (Scantec, Partille, Sweden) with Institute of Occupational Medicine (IOM) sampling heads (Scantec) for collection of inhalable dust [11]. Four samples were discarded due to pump failures. Personal samples were collected during normal animal work tasks with sampling heads fastened on the lapel.

Elution of the filters was performed on the day sampled in 1 mL PBS, 0.5% Tween 20, 0.15% Kathon CG for 2 h during rotation, after which the filter was discarded. After addition of 1% BSA, the eluates were frozen until analysis. A total of 63 air samples were analysed for RUA content, of which 45 were also analysed for MUA.

Sampling for assessment of allergen leakage through nasal air samplers

A nasal air sampler with adhesive tape was positioned in an airtight sampler holder in front of a 1-µm pore size PVDF membrane connected to a pump, to test nasal air sampler collection efficacy at different flow rates, and allergen leakage past the nasal air sampler. Ambient air (static) samples at 2, 5 and 10 L/min were collected in rat rooms at 1–1.5 m height, during low (undisturbed animal room, collection time 30 min, $n = 9$ samples) and high (cage changing, collection time 15 min, $n = 9$ samples) exposure situations. Both the nasal adhesive tapes and the PVDF membranes were cut in half. One half of each was eluted in buffer as described above and analysed for RUA content using ELISA. The other half of the nasal adhesive was laminated with PVDF membrane, and the remaining half PVDF membrane from the IOM was laminated with fresh adhesive tape. The laminated nasal and filter samples were immunostained for RUA using the HALOgen assay.

Analysis of rat and mouse allergen content with two-site ELISA assays

The analysis for airborne RUA and MUA content in the filter eluates was performed as described previously [12, 13]. Briefly, the RUA concentration was determined in a two-monoclonal sandwich ELISA assay, specific for Rat n 1 (monoclonals produced by Mabtech AB, Stockholm, Sweden [14]). The MUA concentration was determined in a rabbit polyclonal sandwich

ELISA against mainly Mus m 1 [12]. Both assays have a standard curve range between 50 and 2000 pg/mL.

Nasal air samples and filter samples near or below the detection limit were analysed in the RUA and MUA ELISA assays using AMPAK signal amplification according to the manufacturer's recommendations (Dakopatts AB, Älvsjö, Sweden) (standard curve range 5–320 pg/mL, detection limit for twofold diluted samples = 10 pg/mL). Rare samples with intra-assay CV > 10% between duplicates were re-assayed.

Analysis of rat allergen-carrying particles on adhesive tapes by immunostaining

The HALOgen assay (Inhalix) was applied for the detection of particles containing Rat n 1. Briefly, the adhesive tape from the right nostril was laminated with a PVDF protein-binding membrane (Inhalix), and after brief wetting in 80% methanol, the allergen was eluted onto the membrane overnight in borate buffer (0.2 M, pH 8.2). After elution, the borate buffer was removed and 5% skim milk (in PBS) was added and the samples incubated for 60 min. After rinsing with PBS with 0.05% Tween (PBST), monoclonal antibody RUP 6 (against Rat n 1) diluted in 2% skim milk/PBST was added and incubated for 2 h. After washing in PBST, alkaline phosphatase conjugated anti-mouse IgG (A-5781 Sigma, Stockholm, Sweden) was added and finally membranes were stained using a BCIP/NBT substrate kit according to the instructions (Bio-Rad Laboratories AB, Sundbyberg, Sweden). The number of allergen-bearing particles (particles with a stained halo) was counted under 100 × magnification.

Statistical methods

All data were analysed using Statview 5.0 software (SAS Institute Inc., Cary, NC, USA). Since values were not clearly normally or log-normally distributed, non-parametric tests were used. Correlations between methods was analysed with the Spearman Rank test (r_s). Comparisons in pairs working with and without personal respiratory protection were made using the paired Wilcoxon signed rank test. $P < 0.05$ was considered significant. For statistical calculations, samples below the detection limit were assigned a value of half of the detection limits.

The study was approved by the local ethical committee at Karolinska Institute, and all subject participation was voluntary with informed consent.

Table 1. Personal airborne RUA and MUA exposure measured using NAS and PAS during high or low exposure situations with and without PPE

Exposure situation	Inhaled RUA, ng per h Median (25–75%); n	Inhaled RUA, halos per h Median (25–75%); n	Airborne RUA, ng/m ³ Median (25–75%); n	Inhaled MUA, ng per h Median (25–75%); n	Airborne MUA, ng/m ³ Median (25–75%); n
High exposure					
No PPE	2.6 (0.6–5.0); $n = 11$	231 (131–401); $n = 11$	24.0 (8.1–185); $n = 10$	6.2 (0.7–105); $n = 6$	131 (8.5–1048); $n = 5$
P2-Mask	0.06 (< 0.04–0.7); $n = 10$	17 (10–54); $n = 10$	63.6 (4.4–167); $n = 10$	0.4 (0.2–1.0); $n = 5$	902 (6.9–2740); $n = 5$
Low exposure					
No PPE	0.1 (< 0.04–0.2); $n = 25$	11 (0–38); $n = 25$	1.1 (0.5–2.6); $n = 23$	0.06 (< 0.04–0.1); $n = 20$	1.1 (0.31–2.2); $n = 19$
P2-Mask	< 0.04 (< 0.04–< 0.04); $n = 10$	4.6 (0–10); $n = 10$	1.7 (1.3–3.2); $n = 10$	< 0.04 (< 0.04–0.2); $n = 5$	1.3 (0.4–4.5); $n = 6$
Helmet	< 0.04 (< 0.04–< 0.04); $n = 10$	0 (0–0); $n = 10$	0.25 (< 0.2–1.1); $n = 9$	< 0.04 (< 0.04–< 0.04); $n = 10$	< 0.2 (< 0.2–1.0); $n = 9$

High exposure = manual emptying of dirty cages; cleaning animal room; direct handling of animals in animal room. Low exposure = work in robotized cage cleaning area; supervision of cage cleaning or animal handling.

Results

Efficacy of personal respiratory protection on reducing amount of inhaled aeroallergens

The amounts of inhaled RUA and MUA per hour during high and low exposure tasks, with and without personal protective equipment, is shown in Table 1. The protective effect of using a P2-filter facemask is shown in Fig. 2. In half of the subject pairs, the amount of allergen found using ELISA was reduced to below detection limit when using a facemask. The protective factor varied among pairs, but the P2 facemasks reduced in both the amount of RUA and MUA measured using ELISA by a median 88%, respectively, and number of RUA-bearing particles by a median 93%. The paired subjects had been exposed to similar amounts of airborne allergens: PAS levels correlated well within the pairs ($r_s = 0.79$ and 0.88 for RUA and MUA, respectively).

Comparison between nasal and airborne sampling

As shown in Fig. 3, PAS and NAS ELISA values correlated well: $r_s = 0.75$ for RUA, $r_s = 0.82$ for MUA. The number of inhaled RUA-positive particles (halos) and airborne RUA levels also correlated well: $r_s = 0.82$. The amount of RUA in samples measured as halos and in ELISA, respectively, also correlated significantly, $r = 0.77$.

Allergen collection efficacy at different airflows

The amount of RUA caught on and passing through the samplers, respectively, was determined both using ELISA and counting halos. For technical reasons (e.g. overloading), we were unable to count the halos on four nasal air samples and three PVDF membranes. The median capture efficacy for RUA-bearing particles was 68%, and amount of RUA analysed using ELISA was 40% (Fig. 4a). More allergen passed the nasal filter in the low exposure situation compared to the high exposure situation; the median capture efficacy for RUA-positive particles for low and high exposure was 49% and 73%, respectively. The median ng amount of captured RUA in low exposure samples was 16% vs. 57% for high the exposure situation. No clear pattern was seen for the collection efficacy at different airflows, but the collection efficacy of the nasal air sampler appeared to be greater at 5 L/min, than at 2 or 10 L/min (Fig. 4b).

Discussion

A number of methods to assess allergen exposure have been utilized during the last two decades [15], ranging from sampling dust reservoirs such as carpets in a room using a device attached to a vacuum cleaner, to sampling airborne particles on filters in the breathing zone using person-carried pumps. The relevance of different allergen sampling techniques to the amount of allergen inhaled by the individual can be questioned.

We found that it was possible to visualize and measure inhaled occupational allergens from rodents using nasal air samplers, which has not been done previously. Nasal air sampling (NAS) was compared to sampling of inhalable dust on filters with IOM cassettes attached to person-carried pumps (PAS). The amount of mouse and rat urinary allergen (Mus m 1 and

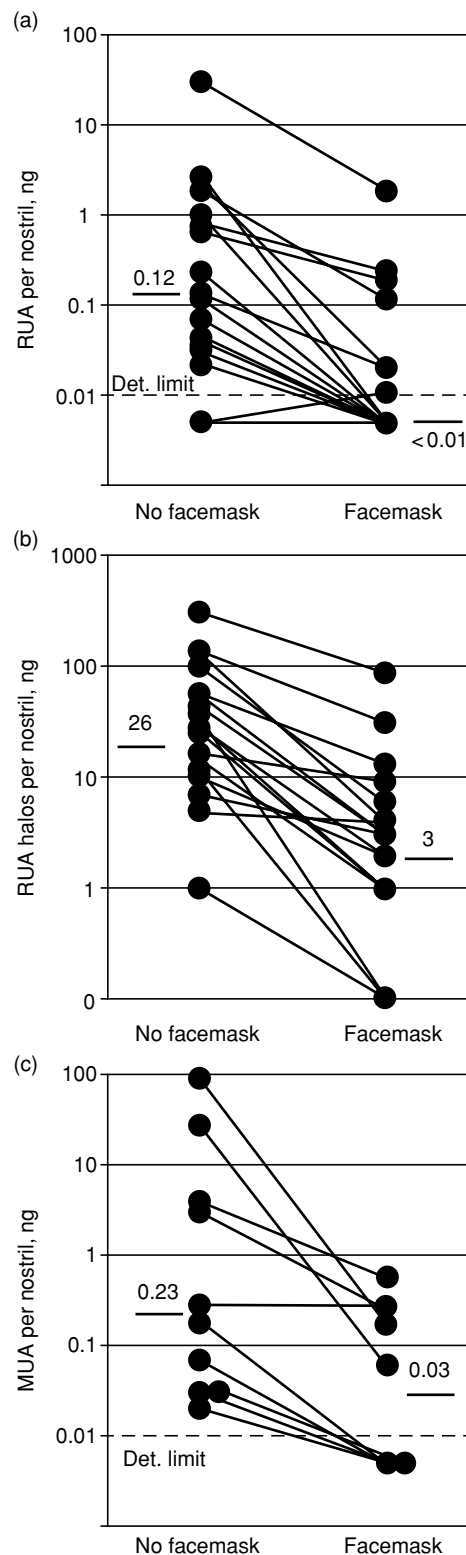


Fig. 2. Reduction of allergen exposure using P2 facemasks during laboratory animal work. Bars show median values for samples collected without or with facemasks. Values below the ELISA detection limit are illustrated given the same arbitrary value (0.005 ng) (a) Inhaled ng RUA per nostril in subject pairs without and with a P2 facemask. (b) Inhaled RUA-bearing particles per nostril in subject pairs without and with a P2 facemask. (c) Inhaled ng MUA per nostril in subject pairs without and with a P2 facemask.

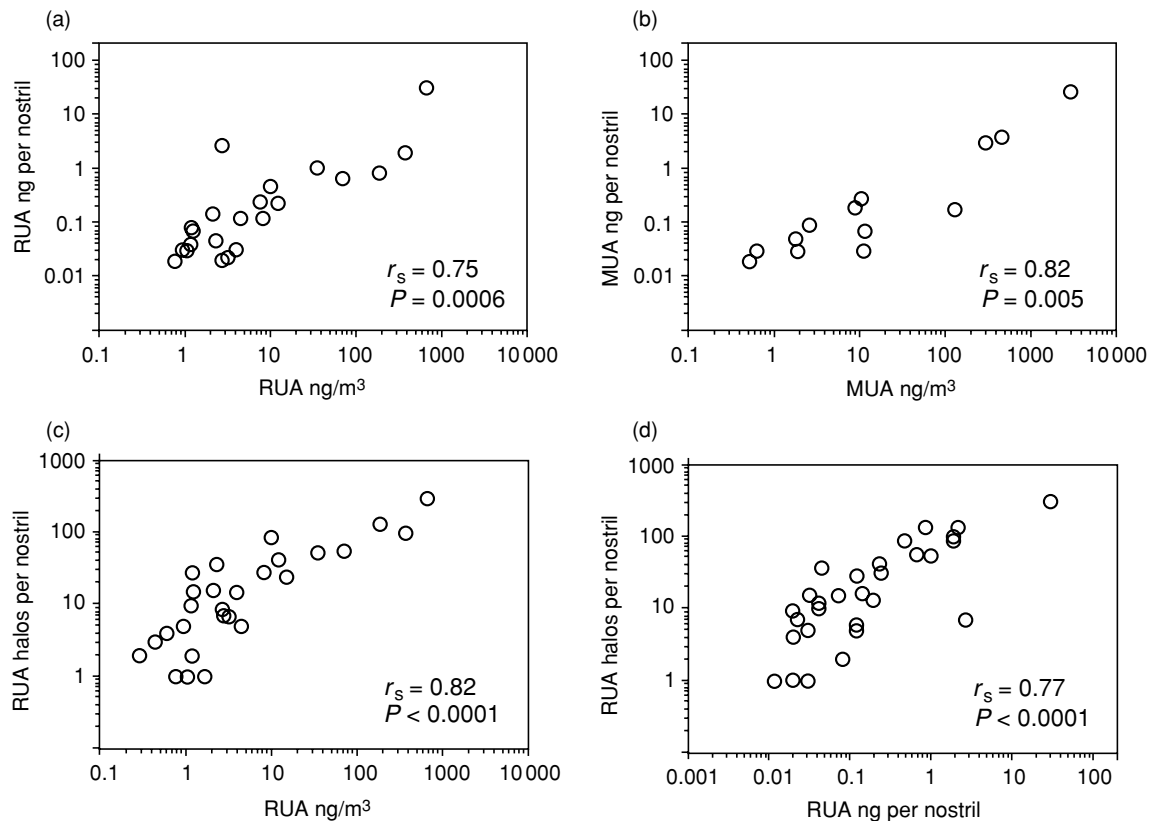


Fig. 3. Correlations between different sampling or detection methods. Samples above detection limit included in the analyses (Spearman rank test). (a) Correlation between PAS (ng/m³) and NAS RUA (ng/nostril) measured using ELISA. (b) Correlation between PAS (ng/m³) and NAS MUA (ng/nostril) measured using ELISA. (c) Correlation between PAS (ng/m³) RUA measured using ELISA and NAS RUA-positive particles (halos). (d) Correlation between NAS RUA (ng/nostril) measured using ELISA and NAS RUA-positive particles (halos).

Rat n 1, respectively) captured on the adhesive surfaces was determined in eluates of the adhesive film, measured using sensitive ELISAs. The number of inhaled Rat n 1-bearing particles on the adhesive film was counted after immunostaining. We found that the two detection methods for RUA correlated very well (r_s about 0.8). PAS and simultaneous NAS, detected using ELISA or immunostaining also correlated well for both MUA and RUA, with r_s about 0.8. Part of the present variability may be due to variations in airflow between the left and right nostrils: in pilot studies, the correlation (r_s) between nostrils is about 0.9 (data not shown). The assessment of personal allergen exposure using nasal air samplers can be regarded as being as relevant as using the gold standard, sampling with person-carried pumps to collect inhalable dust.

There are differences in applicability however: the nasal air sampler design allowed evaluation of personal respiratory protection equipment. When subject pairs worked in parallel (confirmed to be exposed to similar allergen amounts), we found that wearing P2-filter facemasks reduced inhaled allergen by about 90%. During sampling wearing a P3-filter fresh-air helmet, levels of allergen were below or very near the detection limit in the ELISA, and no stained particles were found. Incidentally, we have found that our microscopy photos of allergen staining with and without personal respiratory protection are a powerful educational tool, illustrating the need to use PPE for staff exposed to laboratory animals.

Since peak exposures have been proposed as the most important for sensitization and symptom expression [16], using

respiratory protection appears most important in high-exposure work situations, when hundreds of allergen-bearing particles otherwise might be inhaled per hour. It has been hypothesized that a 10-fold reduction of allergen exposure might be clinically meaningful for laboratory animal workers [17], a task that P2-filter masks accomplish. In high-exposure situations, more powerful protection such as fresh-air helmets is required. However, the primary aim should be to minimize occupational exposure through suitable technical solutions, such as cage wash robots, which reduce cage work allergen exposure by more than 99% [13].

The NAS technique [6] is to date the method probably closest to true assessment of short-time personal allergen exposure. The sampler has been shown to effectively collect most spherical latex particles above 10 μm and about 50% of particles $> 5 \mu\text{m}$ in aerodynamic diameter at normal breathing flow rates [7]. Sizes of particles to which laboratory animal aeroallergens are associated have been measured using for instance Andersen samplers in a number of studies [18–21]. A vast majority of rat allergens are found on particles above 5 μm aerodynamic diameter, whereas mouse urinary particles are more often found on smaller particles. In disturbed circumstances, a greater proportion of airborne particles are associated to larger particles, whereas they are smaller in undisturbed situations [21]. Consistent with this, we found that more particles escaped collection by the nasal air sampler during low disturbance, when usually a greater proportion of smaller particles are airborne. The lower collection efficacy of the nasal air sampler at low exposure

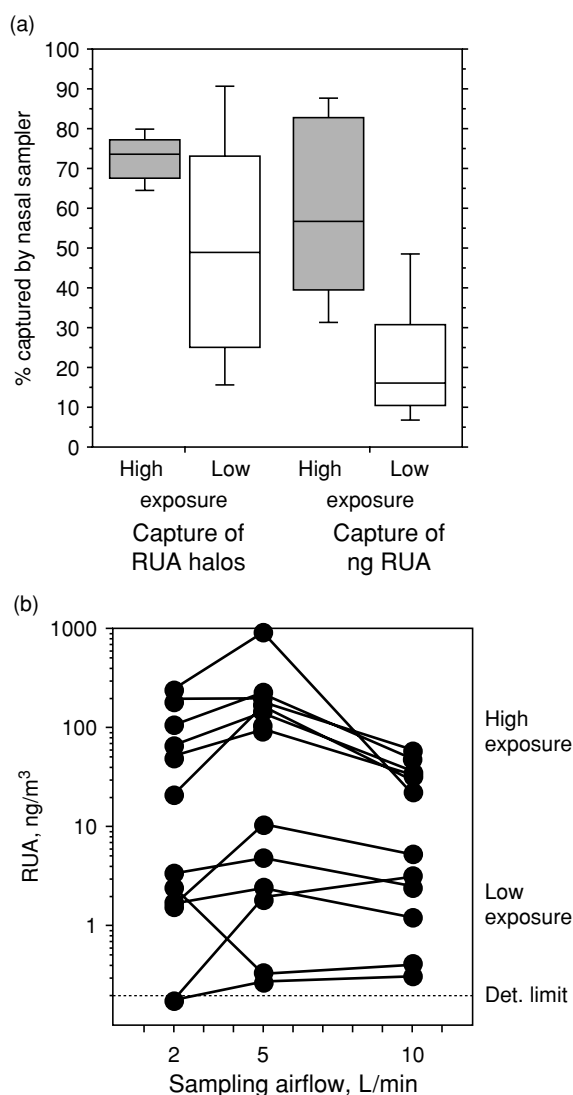


Fig. 4. Static sampling during High (rat cage changing) and Low (undisturbed rat room) exposure. (a) NAS collection efficacy of RUA in high and low exposure situations. Box plot. (b) RUA (ng/m³) collection using nasal air sampling at flow rates of 2, 5, and 10 L/min.

conditions may lead to an underestimation of exposure, especially when measuring allergen eluted from the adhesive using ELISA.

Since both rat and mouse allergens are normally mainly found on particles above 5 µm, the inhaled particles captured by the sampler may be deposited in the nose and upper airways, which makes NAS a clinically relevant allergen exposure assessment method for especially allergic rhinitis subjects. The smaller particles, although fewer, will not be as effectively captured by the sampler, and will travel further down into the airways, and might give rise to asthma symptoms in sensitized subjects.

The collection efficacy of the nasal air sampler appeared to be greater at 5 L/min, than at 2 or 10 L/min. Either there may be more particle 'bounce' at higher flows, or more particle loss as flakes may be pulled off the adhesive film with persistent flow.

Nasal air samplers are light, silent and require no power sources but the subjects' own inhalation. A clear advantage in

relevance using intranasal air sampling compared to personal air sampling using pumps, is that increased workload – resulting in increased breathing – will also increase the sampled dose inhaled. However, the nasal air samplers are not suitable during very heavy work, when subjects switch to oral breathing. As was noted at some occasions in this study, in very high exposure situations, the filters risk overloading, making immunostaining difficult, as well as counting. Possibly the collection and retention of particles is also compromised, leading to an underestimation.

The nasal air samplers are mainly suitable for short-term sampling for reasons besides the risk of overloading at high exposures. The tested samplers fit snugly into the nostrils of most adults (they may be too large for children under 10 years of age and persons with quite small nostrils). However, they grow uncomfortable after prolonged periods of time. Additionally, during sampling, the wearers are instructed not to speak to ensure that all inhaled air passes the sampler, and if they must speak, they should inhale through the nose. Compliance during sampling for up to an hour has in our experience not been any problem, but sampling for many hours would be more difficult. The samplers are thus suitable for task sampling but not for whole-day exposure assessments.

In conclusion, nasal air sampling is a relevant, sensitive (since as few as one allergen-bearing particle can be detected) and useful new device to assess allergen exposure in occupational exposure assessments. This sampling method is a complement to personal air sampling and can provide information on personal aeroallergen exposure not previously obtainable. Using the nasal air samplers, we found that when wearing P2-filter facemasks, levels of inhaled rodent allergens could be reduced significantly.

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