

Allergo J Int (2017) 26:287–294
<https://doi.org/10.1007/s40629-017-0040-0>



Technical specifications of the Global Allergy and Asthma European Network (GA²LEN) chamber: a novel mobile allergen exposure chamber

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Received: 2 October 2017 / Accepted: 10 October 2017 / Published online: 20 November 2017
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Abstract

Background Field trials are the traditional approach for clinical trials in allergy but are under criticism for lack of standardization as they are affected by uncontrollable parameters such as environmental conditions, pollen counts, or lifestyle. Stationary allergen exposure chambers with a defined concentration of allergens under stable and standardized environmental conditions have been used to overcome these restrictions but have not allowed multicenter studies. We here describe the technical specifications and validation of a novel mobile pollen chamber specifically designed for multicenter studies—the GA²LEN chamber.

Methods Two inter-connectable standard-sized container frames were used as a structural basis for the newly developed allergen exposure chamber. One container accommodates an observation room, also used as an office, and a changing room. The other container houses the test chamber itself and the technical installations. A customized air condition system was integrated and several environmental sensors

were installed in the test chamber. Environmental tests have been performed at various outside conditions. The airflow in the test chamber was designed to prevent unspecific symptoms. To allow for an individual particle exposure at each seat, a new particle disperse and distribution system was developed, patented and validated.

Results Technical and clinical validation tests have been successfully performed with *Phleum pratense*, *Betula pendula*, and mixtures of *Dermatophagoides farinae*, and *Dermatophagoides pteronyssinus*. The newly developed particle disperse system enable individual verum and placebo exposure, an even particle distribution at every seating position. The built-in air-conditioner is able to generate a tightly controlled, standardized and comfortable environment and the airflow did not provoke clinically significant irritation to lower respiratory tract, nose, or eyes. The chamber transportation has proven to be flexible and cost-effective.

Conclusion The GA²LEN chamber provides a novel mobile exposure chamber technology for research and clinical trials allowing a fast, affordable, and standardized multicenter approach.

Keywords Allergen exposure chamber · Technical validation · Allergen immunotherapy · Allergen provocation · Allergy trial

Abbreviations

μm	Micrometer(s)
A	Ampere
AEC	Allergen Exposure Chamber
cm	Centimeter(s)
db(A)	Decibels (A)
e. g.	<i>Exempli gratia</i> (for example)

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s40629-017-0040-0>) contains supplementary material, which is available to authorized users.

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GA ² LEN	Global Allergy and Asthma European Network
GCP	Good Clinical Practice
h	Hour(s)
K	Kelvin
km	Kilometer(s)
m	Meter(s)
MARIA [®]	Multiplex Arrays for Indoor Allergens
mm	Millimeter(s)
ng	Nanogram(s)
PCT	Particle containment tape
PDU	Particle disperse units
PLU	Particle line unit
PM ₁₀	Particulate matter <10 µm
PM _{2.5}	Particulate matter <2.5 µm
ppm	Parts per million
V	Volts

Introduction

The prevalence of allergic diseases is increasing in industrial as well as in developing nations, resulting in more than 20% of the world population being affected [1]. However, they are often trivialized and undertreated leading to decreased quality of life and high avoidable medical and socioeconomic costs [2, 3]. The high diversity of symptom-eliciting allergens, individual threshold levels, and different phenotypes of the disease remain a constant challenge, both in clinical care as well as in research. Especially in inhalant allergies such as allergic rhinitis, allergic rhinoconjunctivitis or allergic asthma, changing environmental factors are difficult to overcome on the path to standardized approaches, as is requested in evidence-based medicine [4]. Clinical trials in inhalant allergies are traditionally conducted while relying on natural allergen exposure in the field trial setting. The individual aeroallergen exposure within these trials is influenced by the respective subject's lifestyle and residential situation as well as environmental factors [5–7]. Furthermore, the reproducibility and comparability of such clinical trials are affected and biased by the variability and lack of control of airborne allergens, for instance pollen counts, which are subject to local, seasonal, and diurnal variations [8–10].

Allergen exposure chambers (AECs) have been developed to overcome such difficulties in field trials by offering defined, stable, and reproducible allergen exposures under highly standardized environmental conditions. As an additional benefit they allow controlled symptom scoring and measurements as well as a minimized use of rescue medication [11–13]. AECs have been in use for decades and have undergone technical improvements in recent years. However, the chambers currently available are mainly large and immobile, and partially use technology with high airflow to ventilate the particles in the chamber [14, 15].

In 2004, the Global Allergy and Asthma European Network (GA²LEN) was founded under the sixth framework program of the European Union to initiate a joint effort to improve Europe's allergy research and clinical care capabilities and reduce the burden of allergic diseases by standardizing disease management. In 2012, the GA²LEN annual conference was dedicated to the topic of how to better standardize clinical trials in allergy, resulting in the call for the development of a novel mobile chamber solution. This mobile allergen chamber shall allow for multicenter trials utilizing exactly the same technology and overcome the present technical drawbacks, e.g. irritation of eyes and airways by strong airflow, as well as nocebo and placebo effects as all participants are provoked in the same way in one test run [16]. For the purpose of this development, GA²LEN initiated the idea to found a new company and made an open call for industrial partners to join in. As a result, the company Mobile Chamber Experts GmbH (Berlin, Germany) was founded involving the three industrial partners Allergopharma GmbH & Co. KG (Reinbek, Germany), Laboratorios LETI S.L. (Barcelona, Spain) and Stallergenes Greer (London, UK). In addition, the engineering company Bluestone Technology GmbH (Woerrstadt, Germany) was recruited to build a custom-made solution according to the required demands [7, 17]:

- A cost-effective exposure system allowing multicenter exposure chamber trials
- Standardized exposure tests at every site
- Allow for all relevant aeroallergens to be used
- Induction of comparable symptom scores in the unselected atopic population compared to natural exposure
- Enable fast turnaround times
- Avoid irritant factors (e.g. recognizable airflow)
- Enable an even particle distribution at every seating position
- Allow placebo and verum exposure simultaneously in one run
- Monitor and possibly modify PM₁₀, PM_{2.5}, O₃, or CO₂ concentrations in order to mimic inner city pollution
- Comply with all EU country-specific regulations

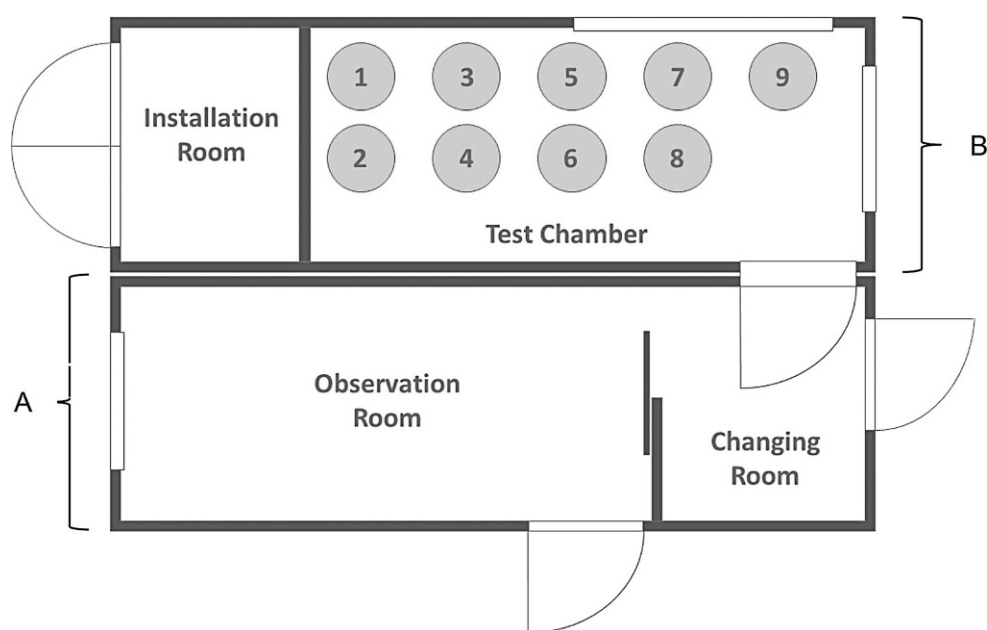
Methods

General chamber setup

The GA²LEN chamber is designed as two standard 24-foot-high cube containers forming an interconnected unit of 7.45 m × 4.90 m × 2.86 m when placed side by side (see Fig. 1).

For a chamber to be used at various trial sites, transportation and situating flexibility is crucial. Basing the chamber design on standard-sized container frames allows for standard transportation methods by

Fig. 1 Sketch of GA²LEN chamber layout. One container (A) accommodates an observation and a changing room, the second container (B) houses the test chamber itself and installations for air conditioning



truck, ship, or train without the need for special transportation permits (see Fig. 2). This also allows for loading/unloading procedures by machinery already available everywhere, such as a truck crane, reach-stacker and heavy fork lift, or, in certain situations, by way of a mobile crane.

To ensure operability of the GA²LEN chamber at a maximum number of trial sites, minimal requirements to the onsite situation were defined, whereas the system had to be as autarkic as possible. The unit requires only three 400 V 32 A connections provided by either a local installation or an external generator to be fully functional. Freshwater and wastewater can be handled by the chamber, or the chamber can be connected to local installations. All external freshwater and wastewater connections can be electrically heated to prevent freezing up to a limit of -20°C .

The airflow in the test chamber was designed to be non-recognizable at any seating position, in order to not provoke any adverse reactions due to the airflow (e. g. irritation to respiratory tract, nose or eyes). The air conditioning system installed allows the chamber temperature to be adjustable from 15 to 38°C , and relative humidity levels can be set from 30 to 80% (non-condensing). Oxygen, carbon dioxide, carbon monoxide, and ozone levels are constantly monitored and recorded using calibrated sensors. The outside and chamber air is filtered using a multistage clean room filter system, removing almost any of PM_{10} and $\text{PM}_{2.5}$ particles. The environmental simulation capabilities of the GA²LEN chamber were tested and monitored at various outside temperatures ranging from -10 to 35°C and humidity levels from 27 to 91%, using internal redundant and calibrated humidity and temperature sensors. A camera and microphones monitor the test chamber and are accessible through the control software in the observation room. If included in

the consent form, audio and video can be recorded, e. g. to run a post analysis on sneezing occurrences. Noise level measurements have been performed with a calibrated noise level analyzer.

The test chamber can accommodate up to nine patients in addition to a study nurse and a physician, providing chairs with adjustable footrests and surfaces that can be sanitized. Each chair is equipped with a small table, which can be used for folders or tablet PCs and provides micro-USB charging cables. The chairs are at fixed positions but can be removed for full cleaning. In order to reduce the cleaning time and allow individual verum/placebo exposure for each patient, particles in the GA²LEN chamber are not dispersed using conventional disperse and distribution technology, which would result in particles sticking to every surface in the room, including the ceiling, walls, and a generally hard-to-control exposure of each individual study subject. In the GA²LEN chamber, particles are only dispersed where the subjects are seated [18], the chamber's airflow is designed in a way that other surfaces cannot be reached by the particles, except the subject chairs, tables, the floor, and the subjects themselves. The subjects wear clean-room apparel to minimize the possible amount of allergens entering and leaving the chamber. The floor is laid out as double flooring, so particles reaching the floor will fall through a metal grid, which is the upper floor. Particles falling through the grid are then sucked through 1 of the 10 existing exhaust air outlets and removed via filters, or they will just stick to the lower floor. This airflow design also prevents particles from refloating even while people are moving within the chamber.



Fig. 2 Image of GA²LEN chamber. © GA²LEN e. V.

Particle dispersal

The particle dispersion system consists of nine individual and independent particle disperse units, called PDUs [19], one at each seating position. The particle disperse rate of each individual PDU and the general control of each unit is realized through a central control software. This software also controls, monitors, and protocols the environmental settings and sensor values.

Each PDU has its own particle source, which is a dedicated containment called particle containment tape (PCT). PCTs are manufactured using a newly designed device called particle line unit (PLU). A PDU can release particles of a PCT through a nozzle that is located above the patient. The nozzle can be moved in two dimensions (e. g. an elliptic pattern), with a configurable period of 10 to 600 s. Before releasing the particles, the PDU guides the PCT through a scanning microscope. The PDU counts the number of particles or use the line width and line density to calculate the disperse amount. This data allows controlling the amount of particles to be released in nanogram per second or particles per second. Each image of the scanning microscope is stored for the possibility of a post validation analysis. The used and re-spooled PCTs are kept on file for any post validation analysis required.

Both the PLU and the PDU are designed to handle particles between 0.1 and 100 μm . The particle concentration that a PDU can generate depends on the particle density of the PCT and the speed at which the PCT is emptied. The concentration to which a subject is exposed also depends on the distance of the patient from the nozzle. Therefore, when a subject is seated, the height of the chair is adjusted so that the nostrils of the subject are at a defined level, called the calibrated exposure height. A more detailed description of PDU, PCT and PLU can be found in the online supplementary material (Annex 1 and Annex 2).

Particle distribution

The particle distribution was measured using sedimentation stripes and a calibrated laser particle

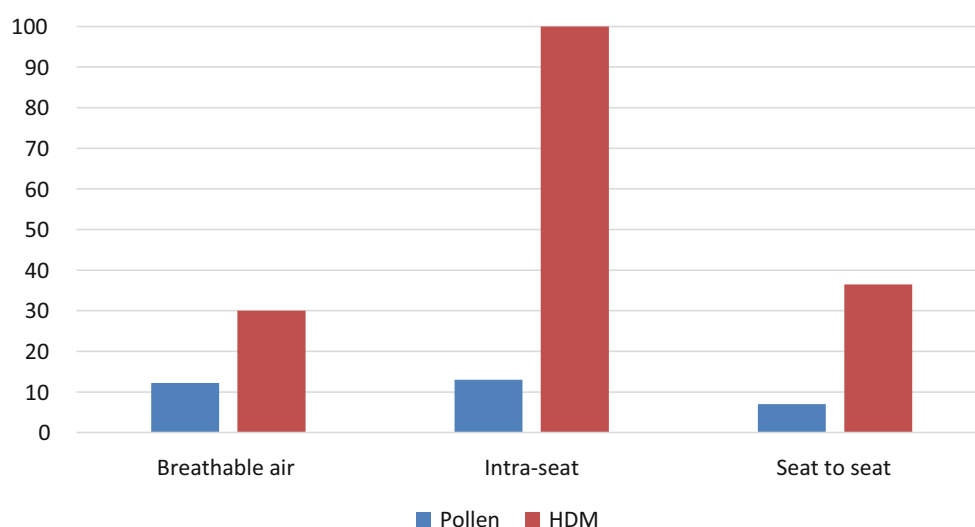
counter, with and without a patient being present. For these measurements, an average human-sized dummy was used as a substitute for a real patient. For pollen, particle distribution pattern was validated using 4000 and 8000 grains per m^3 as target concentrations and time points 0, start time plus 90 min, and start time plus 240 min. For house dust mite particles, the distribution pattern was validated at target concentration of 400 ng Der p1 per m^3 . A total of 21 sedimentation stripes (12 mm $\times$ 20 mm) were used at each measurement and each seating position while confirmatory laser particle measurements were performed at each seat. Measurement duration was 15 min for sedimentation tests and also 15 min for laser particle counter tests. Sedimentation stripes used to validate pollen distribution were analyzed by counting pollen microscopically while sedimentation stripes used for house dust mite particle distribution were analyzed using multiplex arrays for indoor allergens (MARIA®) [20]. To validate that no particle from an actively exposed seating position can access the breathable air of another seat, one patient was actively exposed with 8000 pollen grains per m^3 ; in addition, six sedimentation stripes were positioned at the nostrils of the dummy, which was seated at the neighboring, non-actively exposed position. Four more sedimentation stripes were positioned on the knees of the dummy. Another four sedimentation stripes were placed at each of the other surrounding seating surfaces. Similar tests were performed with house dust mite particles.

Clinical validation

The GA²LEN chamber has performed clinical validation runs for grass pollen (*Phleum pratense*), birch pollen (*Betula pendula*) and house dust mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*). All tests were performed in Berlin, Germany, and were approved by the ethics committee of the Charité University Hospital, Berlin. Beside an atopic population, the participation of non-atopic subjects served as a control group for unspecific symptoms.

To evaluate the ideal allergen concentration that was able to imitate the symptoms from natural exposure, the subjects have been provoked in exposures with different durations and amounts of allergens. Therefore, PCTs were produced with *Phleum pratense* (Allergon AB, Ängelholm, Sweden) for exposures with 4000 or 8000 grains/ m^3 and durations of 90 up to 240 min; *Betula pendula* (Allergon AB, Ängelholm, Sweden) for exposures with 4000, 8000 or 16,000 grains/ m^3 for durations of 90 up to 240 min, as well as *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (Laboratorios LETI S.L., Barcelona, Spain; mixture of whole bodies, body parts and fecal matter) for exposures with 250 μg mixed material per m^3 (equivalent to 400 ng Der p 1/ m^3) for durations of 60 or 90 min.

Fig. 3 Variation of target concentration ($\pm$ %) for pollen and house-dust mite (HDM) particles



Results

Chamber setup

The GA²LEN chamber was transported several times, performing over 330 validation runs with almost 200 subjects being exposed at least one time. A full clinical validation for grass pollen has been published by Zuberbier et al. [21]. Basing the chamber design on standard-sized container frames allows for standard transportation methods by truck, ship, or train without the need for special transportation permits. Even though the chamber consists of two containers, it can be transported on a single truck. The setup duration of the chamber depends on outside conditions (e.g. wind, rain) and the quality of the site preparation. However, it was always as low as 4 h, while setting up the chamber could be performed by only two operators. So far, the containers were transported over 10,000 km in total. Whereas a crane truck proved to be more efficient for short range transport (<1000 km), a megatrailer, in combination with a mobile crane, improved the efficiency for long range transport. All transportation and handling of the chamber did not affect the usability in any way, which can be underlined by the published reproducibility data [21].

The air conditioning system installed allows the chamber temperature to be adjustable from 15 to 38 °C, and relative humidity levels can be set from 30 to 80% (non-condensing). Since temperature and humidity levels can affect the patients' general well-being during the exposure, influence the severity of symptoms, and even elicit symptoms, it was decided to determine the standard test environment with 21 °C and 55% relative humidity. At all environmental tests performed, this standard test environment was reached within less than 80 min. Also, in all tested outdoor conditions, the indoor test environment was stable for more than 5 h, unbiased by the interim presence of patients. During test times, the temperature

was within +0.8 K/−0.5 K relative to the target temperature and humidity was within +5%/−3%. Lowest stable indoor temperature was 15 °C, and 35 °C was the highest. At each exposure test performed, carbon dioxide and oxygen levels were kept at physiologically compatible levels, whereas carbon monoxide and ozone levels remained unchanged during the course of the test period in all performed environmental tests so far. The airspeed at each seating position at calibrated exposure height is below 3 cm per second and was not recognizable by any of the subjects so far. In the performed clinical validation trials no clinically significant irritation to respiratory tract, nose, or eyes were observed in any of the non-atopic subjects.

Particle dispersal and distribution

In its current version, the PDU can generate a resulting concentration for grass or birch pollen ranging from 500 to 16,000 grains per cubic meter in the breathable air. When using house dust mite raw material, concentrations of 10 to 1000 µg/m³ can be generated. Over 400 PCTs, using *Phleum pratense*, *Betula pendula*, *Dermatophagoides farinae*, and *Dermatophagoides pteronyssinus* have been produced using a PLU and used by a PDU within the GA²LEN chamber.

The pollen concentration measured within the breathable air showed a variation of $\pm 12.2\%$ of the target concentration, while intra-seat variation was $\pm 13\%$, whereas seat-to-seat variation was less than $\pm 7\%$. For house dust mite particles, the variation was $\pm 30\%$ of the target concentration, while intra-seat variation was $+100\%$ /−50% and seat-to-seat variation $\pm 36.5\%$ (Fig. 3). No pollen particles were found on any of the sedimentation stripes placed on the dummy sitting next to an actively exposed subject and the allergen concentration for house dust mites were below recognition threshold (0.6 ng). The discrete exposure and thus the lack of particles adhering

to the walls, reduced the time needed to perform the cleaning protocol after each test, which resulted in a fast turnaround time.

Regulations

The custom built, standard-sized container frames, chosen as the structural basis for the chamber, comply with the requirements of the EU common and EU member-specific regulations with regard to transportation, housing, fire hazards, and environmental safety. Noise level measurements in the test chamber showed an average and well tolerable level of 60 db(A) $\pm$ 1 db(A) at the seating positions when all PDUs were active.

Discussion

Since the first AECs were developed in the 1980s [7], the model was continually evolved and the number of facilities increased to 15 AECs currently existing worldwide [17]. The GA²LEN chamber in its present form provides a novel technology for allergy research and clinical trials, allowing a unique, fast, and standardized multicenter approach. The general chamber setup allows for a cost-effective transportation and flexible accommodation. Even though the setup duration depends on outside conditions and appropriate site preparation, it was always as low as 4 h, when performed by two operators. Within all traditional allergen exposure systems, only the Mobile Environmental Exposure Chamber (mEECTM) from Inflamax Research Inc. (Mississauga, Ontario, Canada) was also designed for the transportability needed in multicenter trials [22]. With 9 possible seats, the maximum capacity is lower than in other AECs [6], but can be compensated by a fast turnaround time with multiple exposure runs per day. As required [7, 17] and already performed in other AECs [15, 23, 24], temperature, humidity, and volumetric air flow rate are constantly monitored and recorded throughout the exposure within the GA²LEN chamber and have been in a narrow range of the target values for the entire time. The chosen temperature of 21 °C (+0.8 K/−0.5 K) is comparable with already published data from other exposure units [15, 23, 24], whereas the relative humidity of 55% shows a smaller variation with +5%/−3% compared to the reported $\pm$ 10%. The built-in air-conditioner is able to generate a tightly controlled, standardized and comfortable environment at outside temperatures ranging from −10 up to 35 °C and the airflow was not recognizable by any of the subjects. Oxygen, carbon dioxide, carbon monoxide, and ozone levels are constantly monitored and recorded, but can currently not be systematically altered. Due to the efficacy of the used filter system and the applied maintenance interval, it is not necessary to monitor PM₁₀ and PM_{2.5}. In contrast to most of the other existing chambers, where the allergen is dispersed via fans throughout the ex-

position room [6], the GA²LEN chamber provides an individual exposure at every seating position. The new developed particle dispersion system consists of nine individual and independent PDUs [19], and enables verum and placebo exposure simultaneously within one challenge. The PDU can release particles through a nozzle that is located above the patient. Upfront, the particles are guided through a dedicated imaging microscope, to calculate the amount of particles in nanogram per second or particles per second. This data allows to control the amount of particles to be released. The concentration to which a subject is exposed to also depends on the distance of the patient from the nozzle. Therefore, the height of the chair is adjusted when the patient is seated, so that the nostrils of the subject are at a defined level. The allergen load for pollen measured within the breathable air showed an average variation of $\pm$ 12.2% of the target concentration. These findings are comparable with already published results from Ito et al. [24] and Hamasaki et al. [25], with $\pm$ 15% and $\pm$ 12% variation during their exposure sessions. For house dust mite particles, the average variation was $\pm$ 30%. This difference might be explained by the inhomogeneous particle sizes and density of the house dust mite particles. However, no significant differences in the elicitation of symptoms were found during the clinical validation studies. Unlike in other chamber facilities, the spatial distribution cannot be measured throughout the whole test chamber, since the allergen disperse is discrete and targeted. Therefore, we measured the seat-to-seat-variation, which was less than $\pm$ 7% for pollen and $\pm$ 36.5% for house dust mite particles. In addition, we determined the distribution within one seating position, which was $\pm$ 13% for pollen and +100/−50% for house dust mite. Since up to date no other AEC is equipped with an individual, discrete pollen dispersal system, our findings cannot be compared. The unpublished data from all clinical validation studies in the GA²LEN chamber leads to the conclusion that up from a threshold dose of allergens per m³ no further increase of symptom severity is achievable. This was also reported from Zuberbier et al. [21] for the grass validation study, where concentrations of 4000 and 8000 grains/m³ elicited comparable results. To the authors' knowledge, all existing chambers that have validated house dust mite particles for their exposures did exclusively use *Dermatophagoides pteronyssinus* and monitor the Der p1 quantity in nanogram per m³. Since we used a mixture of the two most clinical relevant mite types *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, our findings are not directly comparable. In addition, our target concentration of 400 ng Der p1 per m³ is much higher than reported by other AECs [7, 26], but still no adverse events or symptoms leading to cancellation of the exposure occurred during the validation studies.

Conclusion

The GA²LEN chamber in its present form provides a novel technology for allergy research and clinical trials, allowing a unique, fast and standardized multicenter approach.

Compliance with ethical guidelines

Conflict of interest F. Goergen reports other payments from Bluestone Technology GmbH, a Mobile Chamber Experts GmbH supplier, during the conduct of the study; in addition, Mr. Goergen has a patent DE 102014116694 issued, and a patent DE102015102492 pending. T. Voegler reports personal fees and other payments from Mobile Chamber Experts GmbH, during the conduct of the study; In addition, Mr. Voegler has a patent DE 102014116694 issued, and a patent DE102015102492 pending. K.-C. Bergmann reports personal fees from Mobile Chamber Expert GmbH, during the conduct of the study; personal fees from Mobile Chamber Experts GmbH for traveling, outside the submitted work. G. Boelke reports grants from ALK-Abelló „Förderpreis Allergologie 2015“, during the conduct of the study; personal fees from Mobile Chamber Experts GmbH, outside the submitted work. T. Zuberbier has received personal fees from AstraZeneca, AbbVie, ALK, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES, HAL, Leti, Meda, Menarini, Merck, MSD, Novartis, Pfizer, Sanofi, Stallergenes, Takeda, Teva, UCB, Kryolan and L'Oreal. Dr. T. Zuberbier has received grants from Henkel and Novartis. J. Gildemeister reports personal fees as an employee from Mobile Chamber Expert GmbH, during the conduct of the study. J. Salame declares that he has no competing interests.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Annex 1

Table: Chamber technology used

	Device	Company
Air condition system	Customized Weiss Ultraclean 35.3 DXU 10.6N including the Weiss MK5-5 “Visual” humidifier	Weiss Umwelttechnik GmbH; Reiskirchen, Germany
Flow fields	Two ZQA-D-VA	Suedluft Systemtechnik GmbH; Plattling, Germany
Oxygen, carbon dioxide, carbon monoxide, and ozone sensors	Oxygen: GMF 300 Z O2 25V; Carbon dioxide: GMF 700 IR CO2 5V; Carbon monoxide: GMF 400 E CO 300 ppm; Ozone: GMF 400 E O3	UMSITEC; Denkendorf, Germany
Multistage clean room filter system	Z-Line Filter F7 and F9 MFP-F7/F9-PLA	TROX GmbH; Neukirchen-Vluyn, Germany
Humidity and temperature sensors	SHT-G	S&P Deutschland GmbH; Darmstadt, Germany
Noise level analyzer	SL300	Trotec; Heinsberg, Germany
Laser particle counter	CW-PPC300	HAL Technology; Fontana, California, U.S.A

Annex 2

Technical details about PDU, PLU and PCT

The particle dispersion system consists of nine individual and independent particle disperse units, called PDUs (see Fig. X). Each PDU has its own particle source, which is a dedicated containment called particle containment tape (PCT, see Fig. Y). PCTs are manufactured using a newly designed device called the particle line unit (PLU). In general, a PLU (see Fig. Z) consists of two source tape spools, two optional corona treatment units, the particle placer and monitoring unit, a welding unit, the destination spool, and several electronic control units. The PLU creates PCTs, which are two 12,7 mm wide tapes welded together with a line of particles in between.

Before coming into contact with any particles, one surface of each source tape, the one which later comes into direct contact with particles, is treated with a high voltage corona beam to ensure proper surface physics. The lower source tape is guided between the particle placer and a glass plate, initially receiving the particle line. After the particle placer and monitoring unit, the formed particle line is covered with the second tape. The welding unit then welds the two stripes together using a welding pattern that is strong enough to avoid accidental damage, but yet still allows the stripes to be torn apart when used in the PDU without the risk of ripping. The welding unit is designed to generate a maximum temperature up to and not above 45°C at the particle line in order to avoid denaturalization of organic particles. The destination spool receives the resulting tape, thus the PCT. The PCT is labeled and can then be used as the source particle provider in a PDU. The particle placer and monitoring unit consists of the particle placer, the particle provider (optional), a so-called three-dimensional vibrator, a gate slide, and two microscope cameras, one to observe the particle placer operation and the other to finally validate the quality and the particle density of the particle line formed. The particle placer is a dedicated brass or aluminum block (depending on the type of particles used) that takes particles from the source particle reservoir forming a single particle line with a dedicated width and a controllable height on the lower source stripe. A standard line width is 0.5 mm.

The reservoir is situated within the particle placer. A specified amount of particles can be placed directly inside, or particles can be fed from a particle provider, which is an external particle reservoir with the possibility to convey particles in a homogeneous way into the reservoir through vibration-based particle movement. The latter particle feeding method is used for particles that are more likely to agglutinate. To further prevent clumping in the reservoir, a three-dimensional vibrator is used to constantly move the particles with a defined frequency or upon operator's intervention by using an 80-µm wire movable in all dimensions and applying a certain moving pattern. When leaving the particle placer, the formed particle line is controlled through a dedicated imaging microscope. If countable particles are used (e.g. pollen), the images from the microscope camera are used to count the actual number of particles. If particles are used that are not homogeneous in their physical appearance, like house dust mite body and feces particles, the amount is determined by line width and average density. In both methods, a plausibility check is performed by controlling the amount of source material finally used.

The PDU can release particles of a PCT through a nozzle that is located above the patient. Before releasing the particles, the PDU guides the PCT through a scanning microscope. As with the PLU, the PDU will count the number of particles or use the line width and line density to calculate the disperse amount. After scanning, the PCT is unsealed in a low-pressure atmosphere so that no particles can contaminate the PDU in general. The low pressure is also used to suck the particles from both tapes

and release them through the attached and above-described nozzle. The strength of the low pressure applied is configurable and depends on the type of particles used. The remaining, now separated tapes are then reeled onto separate spools.

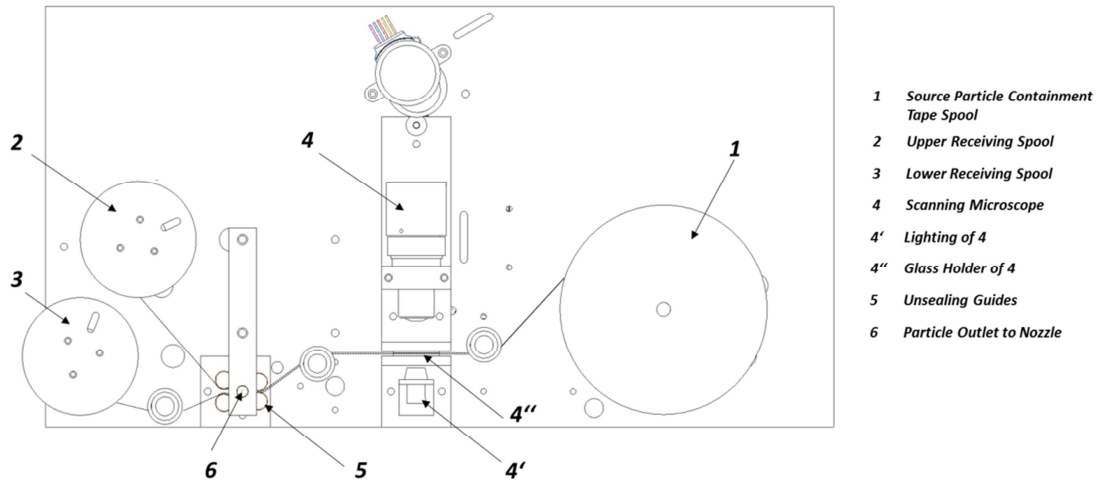


Figure X: Technical drawing of independent particle disperse unit (PDU)

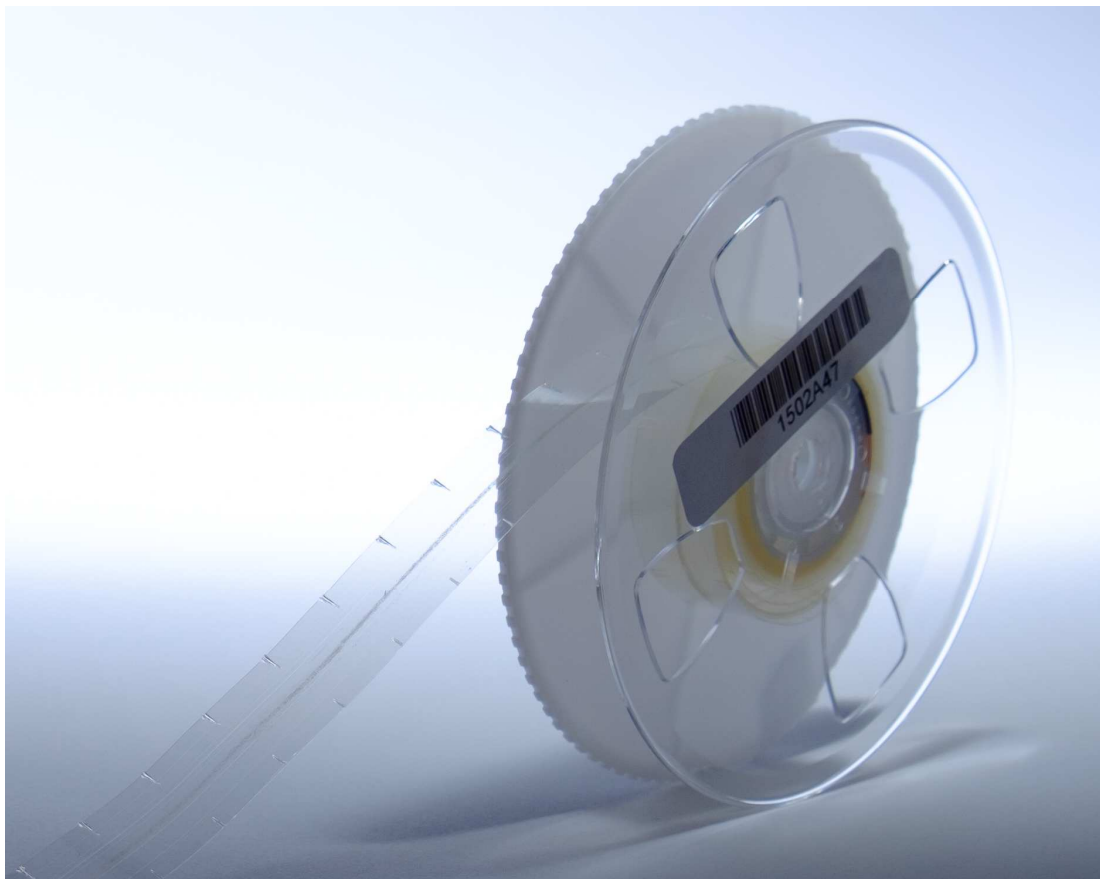


Figure Y : Image of particle containment tape (PCT)

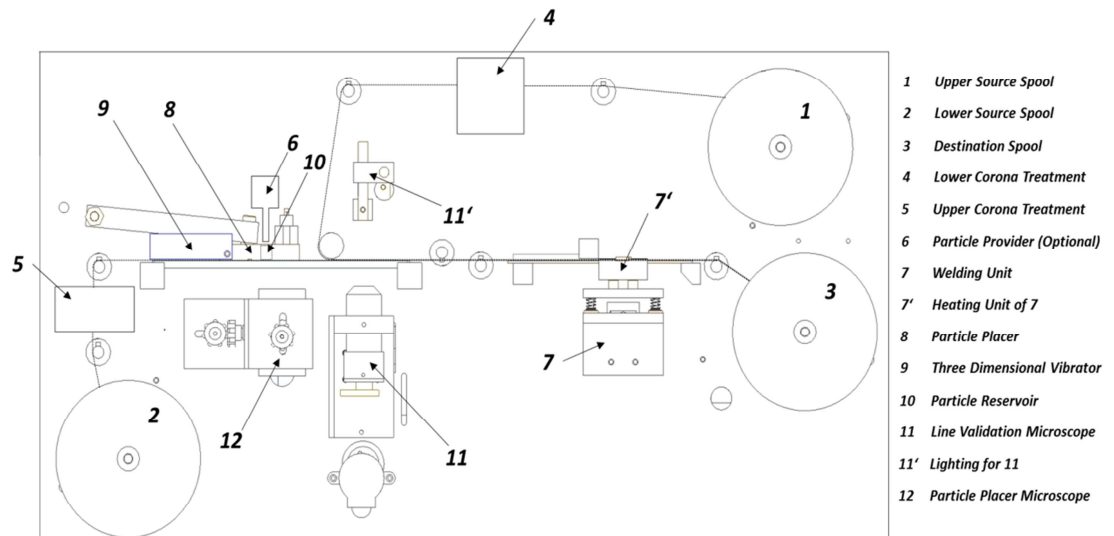


Figure Z: Technical drawing of particle line unit (PLU)

