Pollen chambers: interests and pitfalls

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Environmental Exposure Chamber (EEC)

- generate controlled exposures to inhaled substances in an enclosed environment
  - ✓ allergens
  - ✓ endotoxins
  - ✓ chemicals
  - ✓ dry/humid air
  - ✓ thermal shifts
  - ✓ air pollutants

Allergen Exposure Chamber (AEC)

Allergen Exposure Chamber (AEC)

Used exclusively for controlled exposure of environmental allergens to subjects with allergic rhinitis, conjunctivitis or asthma

Limited number worldwide due to technological complexity, and intricacies of the experimental protocols necessary to perform a valid study

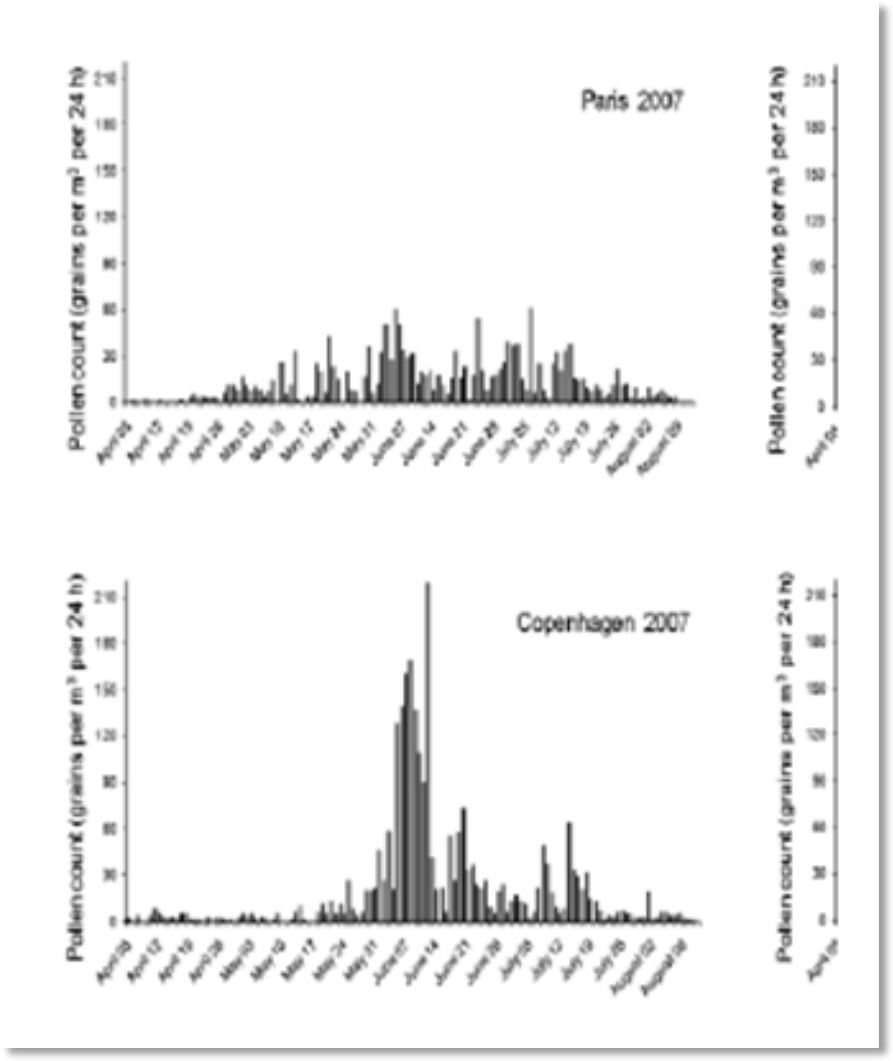
Allergen exposure chambers (AECs)

- Characterize the pathological features of respiratory diseases
- Clinical development of pharmacological treatments and allergen in allergic rhinitis, conjunctivitis and allergic asthma

In-field trial challenges

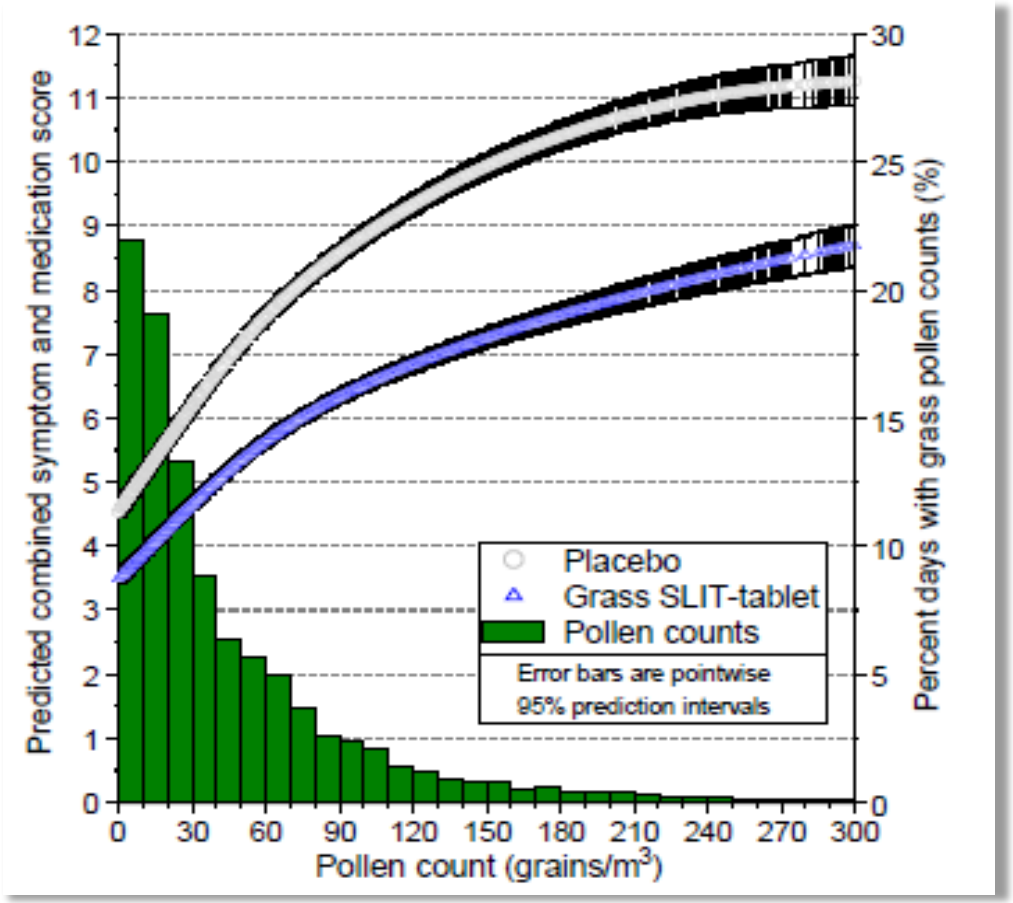
- Variability of allergen exposure
  - during season
  - over large areas and different countries
- Patient exposure not ensured (indoor activities)
- Multi-center designs difficult due to variability in exposure
- Memory bias – lack of patient compliance

Centre to centre variability in pollen counts



Devillier Allergy 2011

Magnitude of efficacy measurements in grass allergy immunotherapy trials is highly dependent on pollen exposure



Greater magnitude of treatment effect based on TCS with higher pollen exposure ($P < 0.001$)

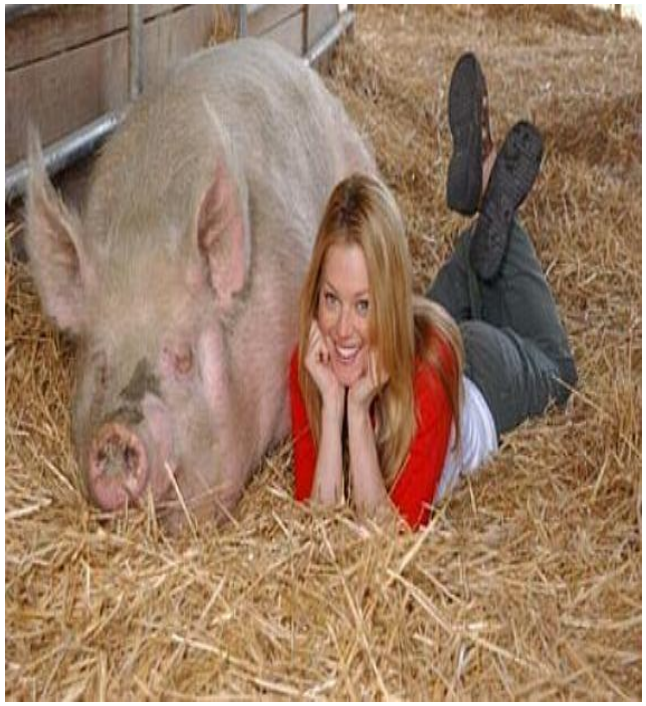
Durham Allergy 2014 69(5):617-23

Advantages of Allergen Exposure Chamber (AEC)

- Standardisation of allergen exposure (number of particles, allergen source)
- Standardisation of environmental conditions (temperature, humidity ..
- Clinically relevant allergen levels
- Consistent allergen exposure
- Dose and condition adjustment
- No other allergens in the chamber
- Avoidance of medication effect

Advantages of Allergen Exposure Chamber (AEC)

- Direct symptom assessment
- Improved data quality
- Shorter time to establish data
- Rapid biomarker assessment
- Investigation of pathophysiology of allergic diseases and pharmacological properties of new therapies



Phase II studies - primary endpoint

European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 20 November 2008
Doc. Ref. CHMP/EWP/18504/2006

GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES

4.3.2 Dose-finding studies

After establishing a tolerated dose range, studies should be performed to establish a dose-response relationship for clinical efficacy. Such studies may comprise a short term treatment (e.g. 2-4 month) with different doses in several study-arms. Provocation tests (e.g. conjunctival, nasal or bronchial provocation or allergen exposure in allergen challenge chambers) and/or clinical endpoints may be used as primary endpoints. As long as laboratory parameters such as allergen specific antibodies, T-cell reactivity or cytokines are not validated and not correlated to the clinical outcome, they can only provide supportive information but are not feasible for determining a suitable therapeutic dose.

Dose finding and proof of concept studies

Phase III - secondary endpoint

European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 20 November 2008
Doc. Ref. CHMP/EWP/18504/2006

GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES

(e.g. rhinomanometry) should be preferred. Provocation tests in allergen chambers deemed to be a promising tool for the evaluation of efficacy, however the results of such provocations have to be validated in comparison with clinical symptoms by natural exposure and for example the influence of measurement within or without the pollen season (influence of inflammation) has to be evaluated before such tests could be used as primary endpoints. However, the provocation in allergen chambers might be a helpful marker especially in long-term studies over several years for a pollen season in which an evaluation in regard to the natural exposure is not possible due to low pollen counts.

Phase III / Field Studies - Natural Exposure

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

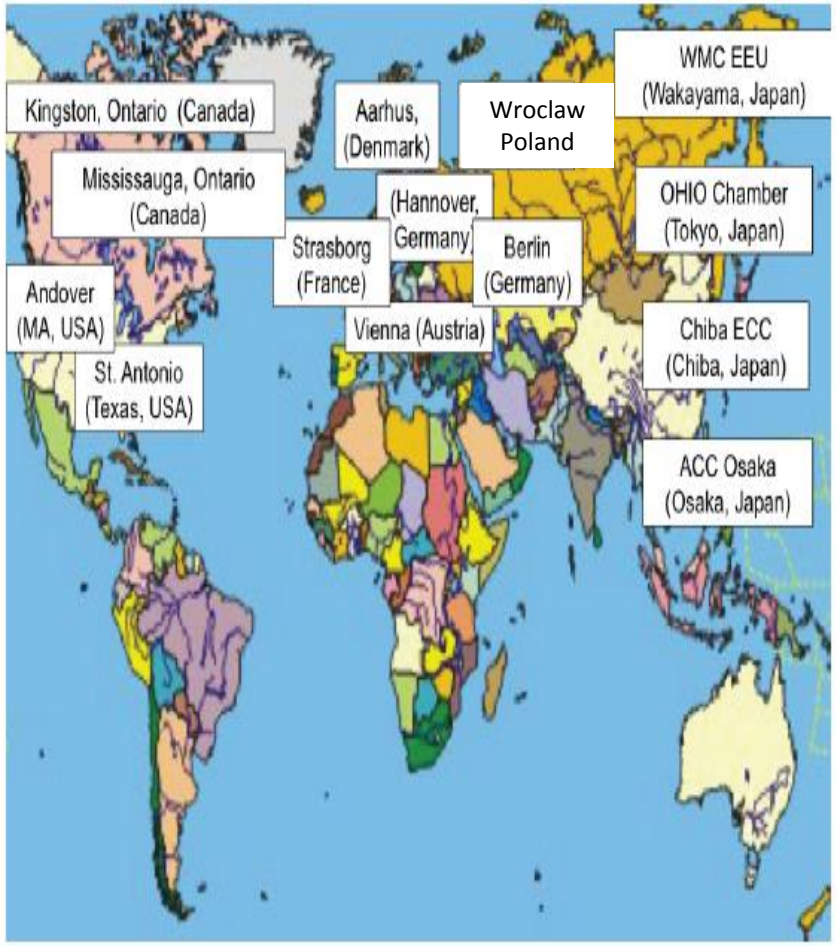
London, 20 November 2008
Doc. Ref. CHMP/EWP/18504/2006

GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES

In case of seasonal allergies it is mandatory to document the exposure to the relevant allergens and to define in the study protocol the minimum pollen count which has to be reached to define the evaluation period as well as the baseline period.

For trials in the perennial indication it is important to minimize variations in the levels of indoor allergens. Thus, if sanitation measures are planned they should be finished before the start of a clinical trial and measurement of baseline symptoms should be performed after sanitation. No further sanitation measures should be performed during the trial. In addition, it is recommended to document the exposure level for the individual patient especially for the evaluation periods to evaluate the variation of indoor allergens.

Allergen Exposure Chambers



EEU, Kingston, Canada

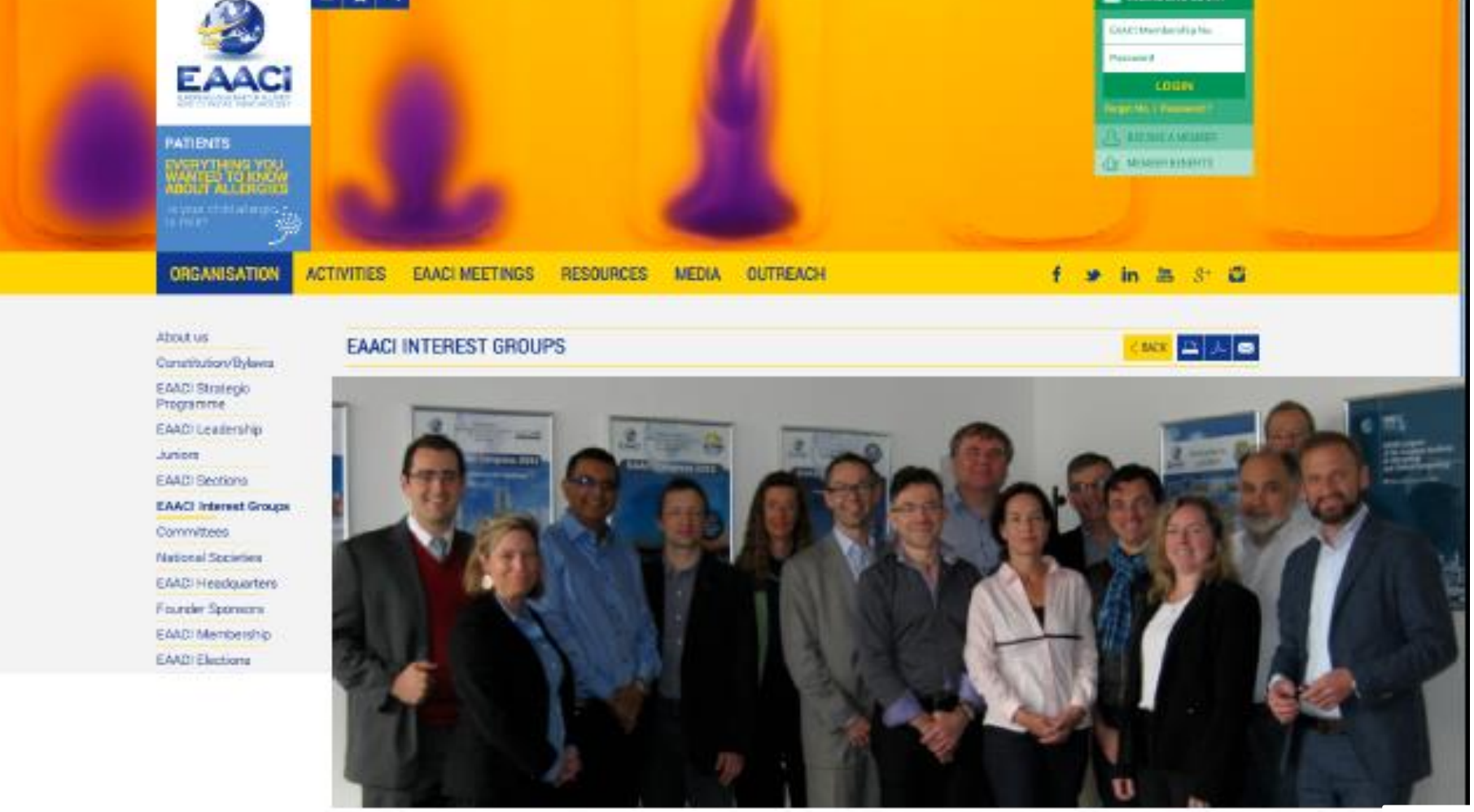
Frauenhofer ITEM, Hannover, GE

VCC, Vienna, Austria

Inflamax, Mississauga, Canada

All-Med.Wroclaw

Modified from Horak and Zieglmayer



Experts from academia and regulatory agencies discussed with chamber operators the unmet needs aiming at harmonization of current concepts in AEC

EAACI Position Paper Allergy 2017

Abbreviated AEC name used in the present report	Name and/or operator	Location
AARHUS	Aarhus University	Aarhus, Denmark
ALL-MED	ALL-MED Medical Research Institute	Wroclaw, Poland
ALYATEC	Strasbourg University Hospital	Strasbourg, France
BIOGENICS	Biogenics Research Chamber LLC	San Antonio, TX, USA
CHIBAUNIV	Chiba University	Chiba, Japan
CLIANTHA	Cliantha Research	Mississauga, Canada
FRAUNHOFER	Fraunhofer Institute for Toxicology and Experimental Medicine	Hannover, Germany
GA2LEN	Mobile Chamber Experts/Global Allergy and Asthma European Network	Berlin, Germany
KINGSTON	Queen's University and Kingston General Hospital	Kingston, Canada
RED MAPLE	Ottawa Allergen Challenge Theater, Red Maple Trials Inc.	Ottawa, Canada
VIENNA	Vienna Challenge Chamber, Power Project GmbH	Vienna, Austria

Technical standards in allergen exposure chambers worldwide – an EAACI Task Force Report in preparation

Table 4: Summary of the AECs' characteristics.

Abbreviation	Chamber and/or Organization Name	City, country	Number of chambers	Max participants per chamber	Total floor space (m2)	Ceiling height (m)	Allergens tested	Non-allergens tested	Temp. range (°C)	RH range (%)	Air change rate (volumes/h)	Allergen dispersion	Particle analyzers
AARHUS	Aarhus University	Aarhus, Denmark	2	*not reported*	111 (79 + 32)	*not reported*	grass (*Phleum pratense*) and birch pollen	toluene, n-decane, ozone, nitrogen oxides, house dust, cigarette smoke, diesel exhaust particles, wood smoke, candle smoke	-15°C to +40°C	0% to 100%	*not reported*	turntable-type powder dispenser	LPC and Burchard samplers
ALL-MED	ALL-MED Medical Research Institute	Wroclaw, Poland	1	20	12	*3,5*	grass (*Phleum pratense*) and birch pollen, and HDM	*not reported*	+18°C to +27°C	40% to 58%	5 to 20	computer-controlled feeder	LPC
ALYATEC	Strasbourg University Hospital	Strasbourg, Franc	1	*not reported*	65	~2.25 (calculated)	HDM, cat dander, birch	*not reported*	+18°C to +27°C	40% to 57%	4.6 to 20	nebulizer	LPC
BIOGENICS	Biogenics Research Chamber	San Antonio, TX, U	2	70 + 20	*not reported*	*not reported*	*not reported*	*not reported*	*not reported*	*not reported*	~12	computer-controlled feeder into a vortex blower	air sampling cassettes for aeroallergens and
CHIBAUNIV	Chiba University	Chiba, Japan	1	50	*71.8*	2,6	Japanese cedar and cyp	None tested	*not reported*	*not reported*	*not reported*	*not reported*	LPC
CLIANTHA	Cliantha Research	Mississaugua, Ca	2	60 + 40	94 + 49	*3,03*	grass pollen mixtures, P	*thermal shifts, dry air, ozone, and fragrance*	+20°C to +26°C	35% to 45%	3 to 30	aerosolized (within the chamber) using a proprietary device	RotorodTM impact samplers
FRAUNHOFER	Fraunhofer Institute for Toxicology and Experimental Medicine	Hannover, Germar	3	18	47 + 47 + 47	*2,8*	Grass and birch pollen,	*not reported*	-10°C to +30°C	20% to 95%	up to 20	feeder tubes or a spray-dryer	LPC
GA2LEN	Mobile Chamber Experts/Global Allergy and Asthma European Net	Berlin, Germany	1	9	*not reported*	*not reported*	*not reported*	*not reported*	*not reported*	*not reported*	*not reported*	*not reported*	LPC
KINGSTON	Kingston General Hospital	Kingston, Canada	2	35	*216* + 72	*not reported*	*not reported*	*not reported*	*not reported*	*not reported*	~5	a short-duct feeder system	Rotorod® samplers
RED MAPLE	Ottawa Allergen Challenge Theater, Red Maple Trials Inc.	Ottawa, Canada	1 (but 4 indepe	40	133	*not reported*	*Phleum pratense* and ra	*not reported*	*not reported*	*not reported*	*not reported*	*not reported*	LPC
VIENNA	Vienna Challenge Chamber, Power Project GmbH	Vienna, Austria	1	20	21,5	2,7	grass, birch and Japane	*not reported*	+20°C to +26°C	20% to 60%	*not reported*	dispensers next to the fan coils	Burchard samplers for allergens

Technical standards in allergen exposure chambers worldwide – an EAACI Task Force Report in preparation

AEC unmet needs

AEC unmet needs

- Validation process
- Standardization of the challenge procedures and assessments
- Intra-AEC reproducibility
- Inter-AEC variability and reproducibility
- Comparability with field trials
- Regulatory issues

EAACI Position Paper
Allergy 2017

Validation of the Global Allergy and Asthma European Network (GA²LEN) chamber for trials in allergy: Innovation of a mobile allergen exposure chamber

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Berlin, Mannheim, Wiesbaden, and Woerrstadt, Germany; Andover, Mass; Davos, Switzerland; Stockholm, Swede

ORIGINAL ARTICLE EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Safety, efficacy and repeatability of a novel house dust mite allergen challenge technique in the Fraunhofer allergen challenge chamber

K. Lueer[1], H. Biller[1], A. Casper[1], H. Windt[1], M. Mueller[1], P. Badorrek[1], D. Haefner[2], T. Framke[3], A. Koch[3], H. Ziehr[1], N. Krug[1,4], W. Koch[1] & J. M. Hohlfeld[1,3,4]

RESEARCH Open Access

Clinical validation of controlled exposure to birch pollen in the Environmental Exposure Unit (EEU)

Anne K. Ellis[1,2*], Mena Soliman[2], Lisa M. Steacy[2], Daniel E. Adams[2], Barnaby Hobsbawn[2] and Terry J. B. Walker[2]

Clinical validation of a house dust mite environmental challenge chamber model

J ALLERGY CLIN IMMUNOL
VOLUME 140, NUMBER 1

Petra Zieglmayer, MD[a]
Patrick Lemell, PhD[a]
Kuan Wei Chen, PhD[b]
René Schmutz, MD[a]
René Zieglmayer, DI[a]
Oliver Pfaar, MD[c,d]
Friedrich Horak, MD[a]
Susanne Vrtala, PhD[b]

Prerequisites for clinical validation

- Definition and standardization of technical parameters and of clinical SOPs
- Definition clinical and statistical parameters, and reproducible dose response
- Standardized protocol demonstrating reproducibility and consistency of results between competing chambers
- Validation of new clinical outcomes and biological markers

EAACI Position Paper; Allergy 2017

Recommendation
Validation process of AEC

- Validation of the allergenic exposure, including at least pollen grain counts and distribution
- Use of good manufacturing practice (GMP)
- Justification of single-versus-serial challenges
- Justification of low versus high dose challenges
- Disclosure of general patient selection criteria

EAACI Position Paper; Allergy 2017

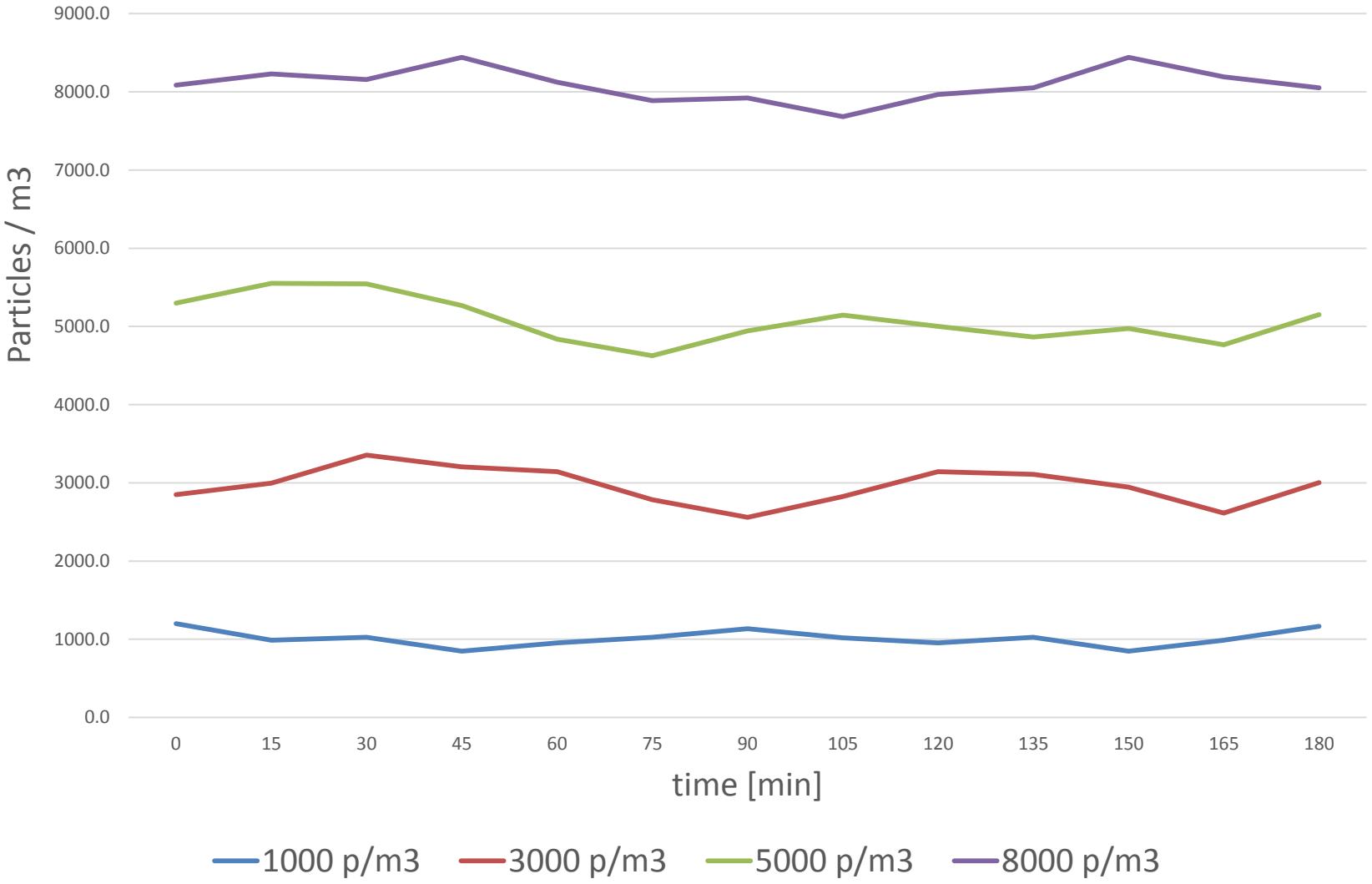
Standardization of the challenge and outcomes in allergen chambers

- Use of standardized and clinically relevant outcomes
- SOPs for chamber operation including data collection/management
- SOPs for cleaning of the facilities after each exposure
- Definition of safety measures

EAACI Position Paper; Allergy 2017

Environmental Exposure Chamber (EEC) for alergen provocation „ALL-MED” MEDICAL RESEARCH INSTITUTE WROCLAW, POLAND

Stability of Timothy Grass Pollen concentration over time



Conditions inside the chamber

The chamber is ventilated and air-conditioned, the following parameters are retained:

- Temperature 21,2 ± 0,4 ^{o}C
- Relative humidity 52,4 ± 2,4 %
- CO_2 concentration 805 ± 52 ppm

Patient characteristics

	Number	Age (years)	SPT (mm) grass pollen
Patients	17	39 (19-65)	8,4 (4-14)
Women	7 (41%)	40 (19-65)	9,2 (6-14)
Men	10 (52%)	38 (26-59)	7,6 (4-10)

Inclusion criteria	• History of allergic rhinoconjunctivitisitis with or without asthma for 2 or more years • Skin prick test response of ≥ 3 mm • FEV1 of ≥70% of predicted value
Exclusion criteria	• Previous treatment with AIT • Treatment with systemic corticosteroids within the last month, • Treatment with antihistamines or other drugs with antiallergic properties within the last 3 days and • Suspicion of pregnancy

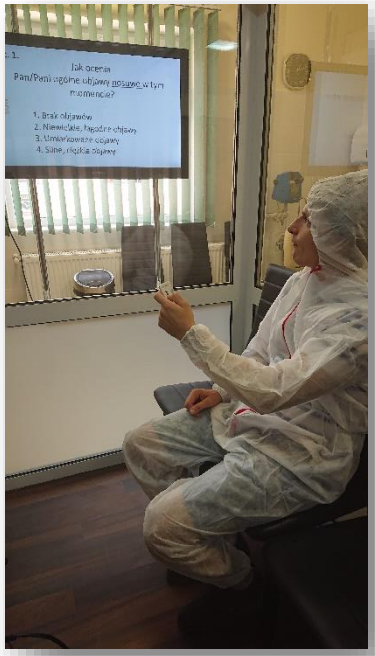
Clinical assessment

Subjective questionnaires

- TSS (total symptom score)
- TNSS (total nasal symptol score)
- TOSS (total ocular symptom score)
- TNNSS (total non-nasal symptom score)
- VAS (visual analog scale)

Objective measurement

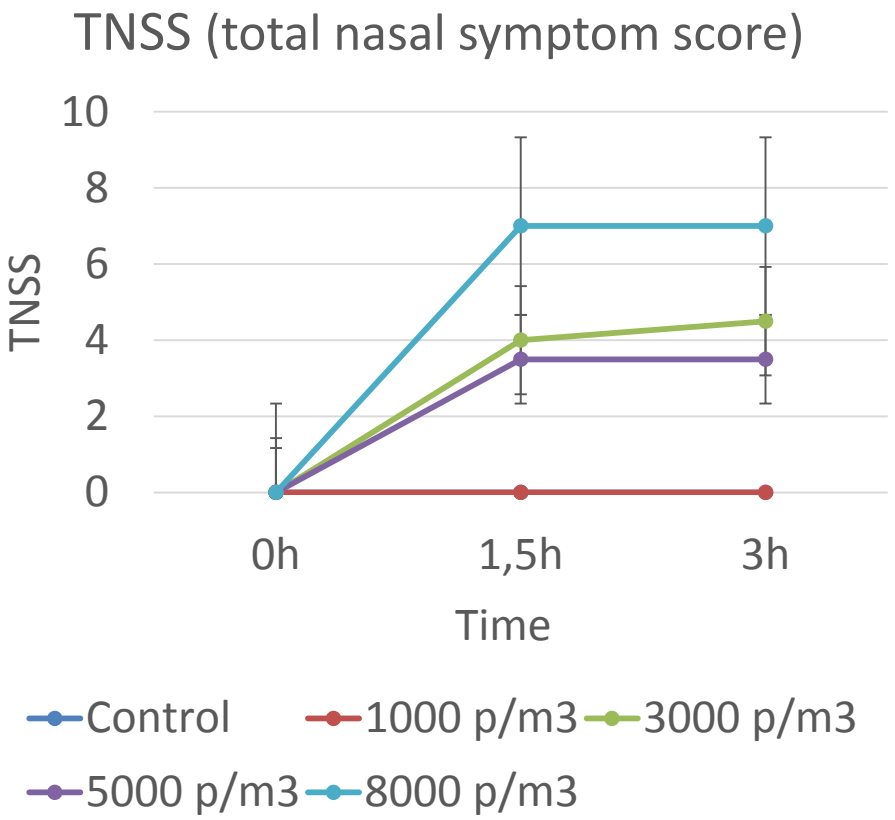
- Acoustic rhinometry
- PNIF (peak nasal inspiratory flow)
- Spirometry
- PEF (peak expiratory flow)

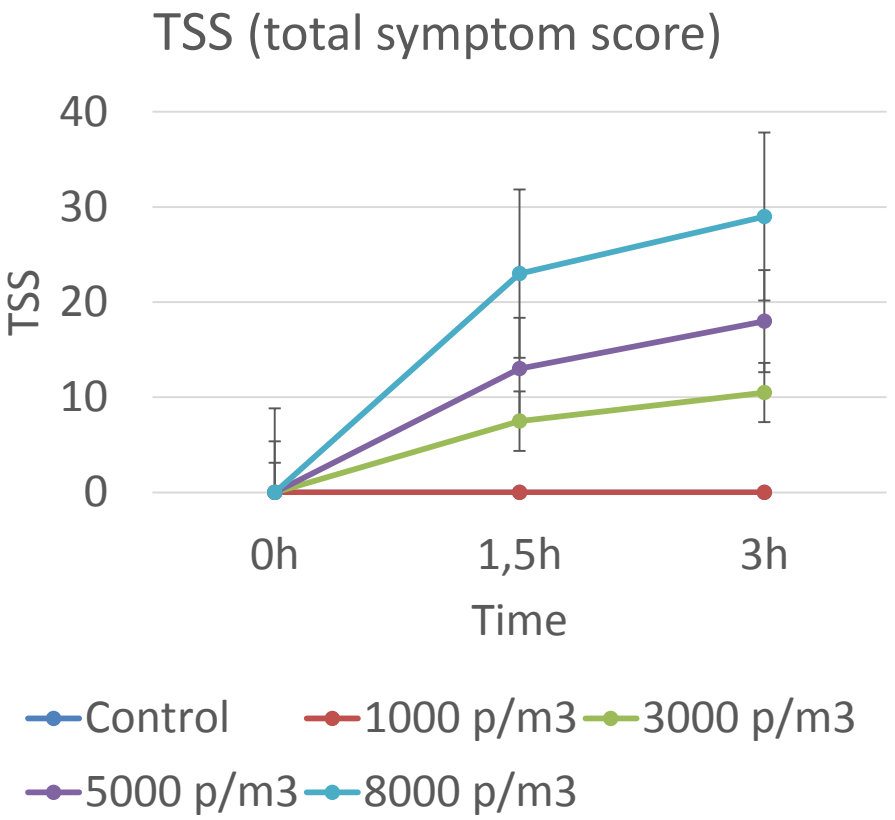


Safety parameters

- PEF (peak expiratory flow)
- TSS (total symptom score)
- Safety call 24h post-expossure

TNSS and TSS

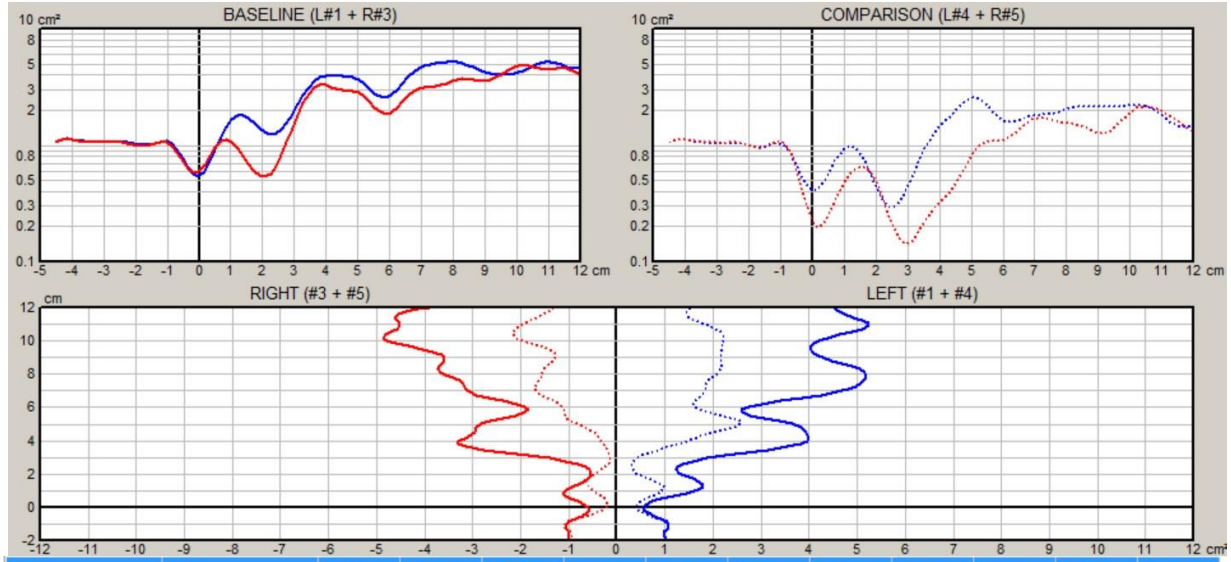




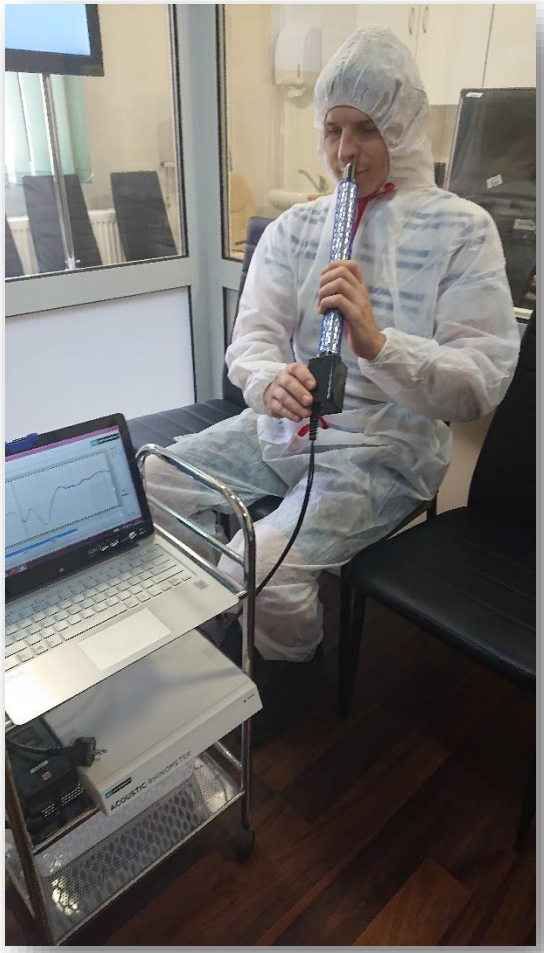
	TNSS (p)	
	1,5 h	3 h
5000 p/m3	**0,08**	0,15
8000 p/m3	**0,014**	**0,017**

	TSS (p)	
	1,5 h	3 h
5000 p/m3	**0,07**	**0,06**
8000 p/m3	**0,02**	**0,07**

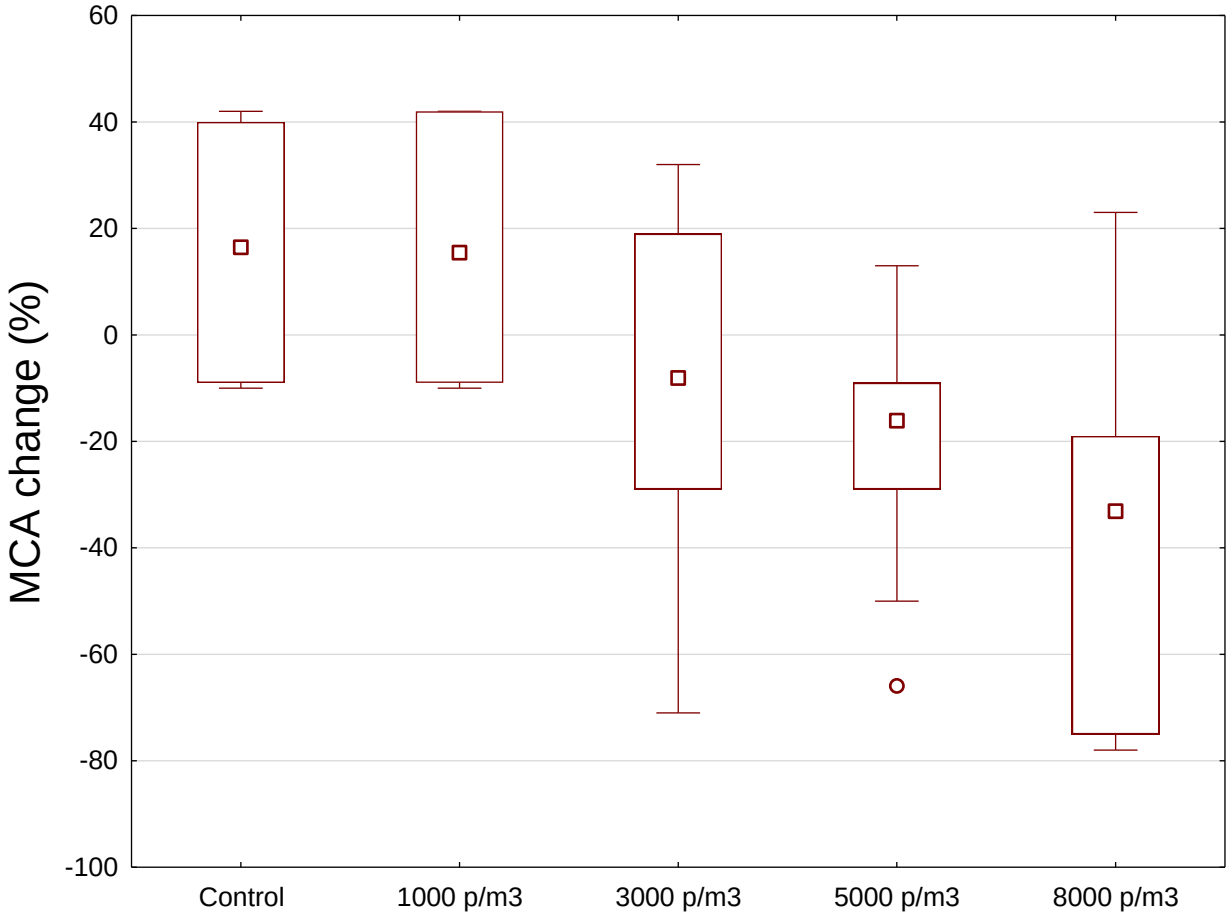
Acoustic rhinometry



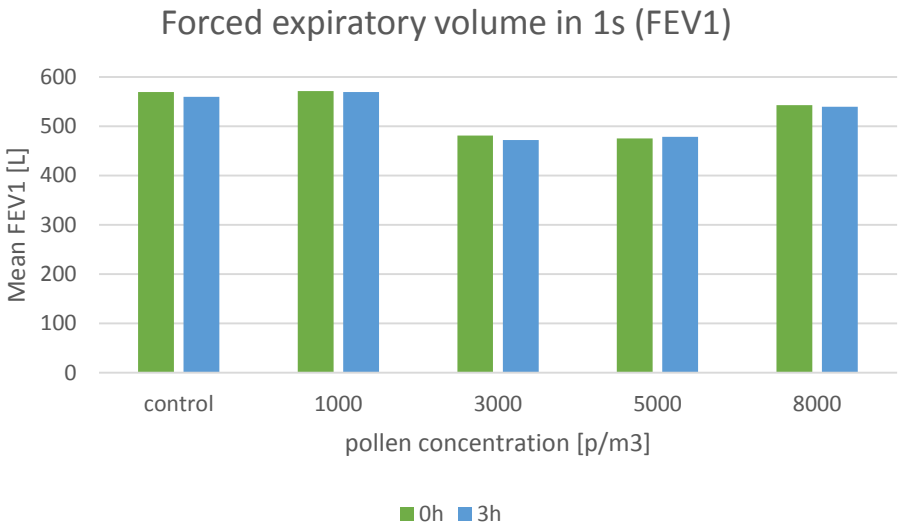
Group	Side	Vol 0-5	Vol 2-5	Vol 0-3	Area 3	Area 5	MCA	Dist.	Min. 1	Dist. 1	Min. 2	Dist. 2
BASELINE	#4 LEFT	8.28	5.68	3.89	1.30	2.52	1.12	2.77	1.12	2.77	N/A	N/A
	#5 RIGHT	6.45	4.83	2.30	1.09	2.39	0.53	2.07	0.53	2.07	N/A	N/A
	L+R	14.73	10.50	6.19	2.38	4.91	1.66	-	1.66	-	N/A	-
	R/L	0.78	0.85	0.59	0.84	0.95	0.48	-	0.48	-	N/A	-
COMPARISON	#6 LEFT	5.39	3.31	3.08	0.70	1.84	0.69	3.11	0.90	1.21	0.69	3.11
	#7 RIGHT	3.16	1.84	1.82	0.38	1.68	0.38	3.29	0.53	1.56	0.38	3.29
	L+R	8.54	5.15	4.90	1.08	3.52	1.07	-	1.43	-	1.07	-
	R/L	0.59	0.55	0.59	0.54	0.92	0.54	-	0.59	-	0.54	-
LEFT	Change %	-35	-42	-21	-46	-27	-38	-	-20	-	N/A	-
RIGHT	Change %	-51	-62	-21	-65	-30	-29	-	-1	-	N/A	-
TOTAL	Change %	-42	-51	-21	-55	-28	-35	-	-14	-	N/A	-

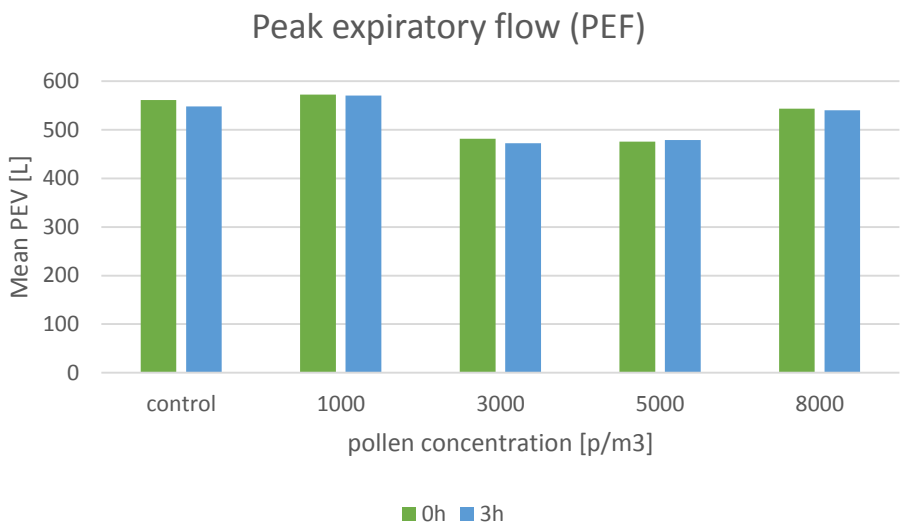


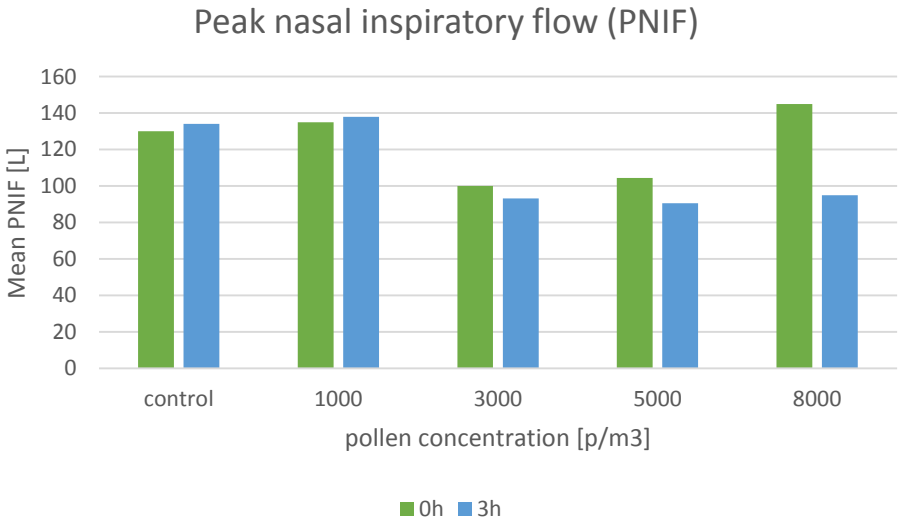
Acoustic rhinometry

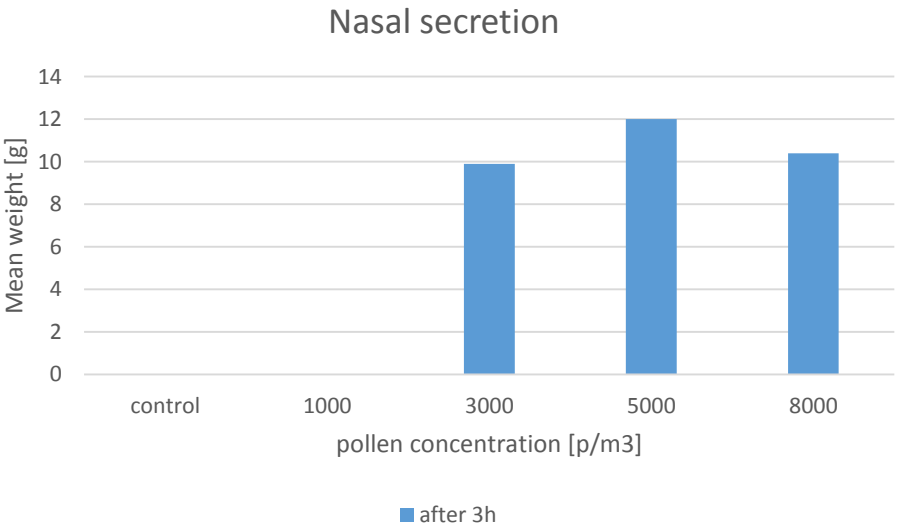


	MCA change (p)
	3h
5000 p/m3	**0,009**
8000 p/m3	**0,05**

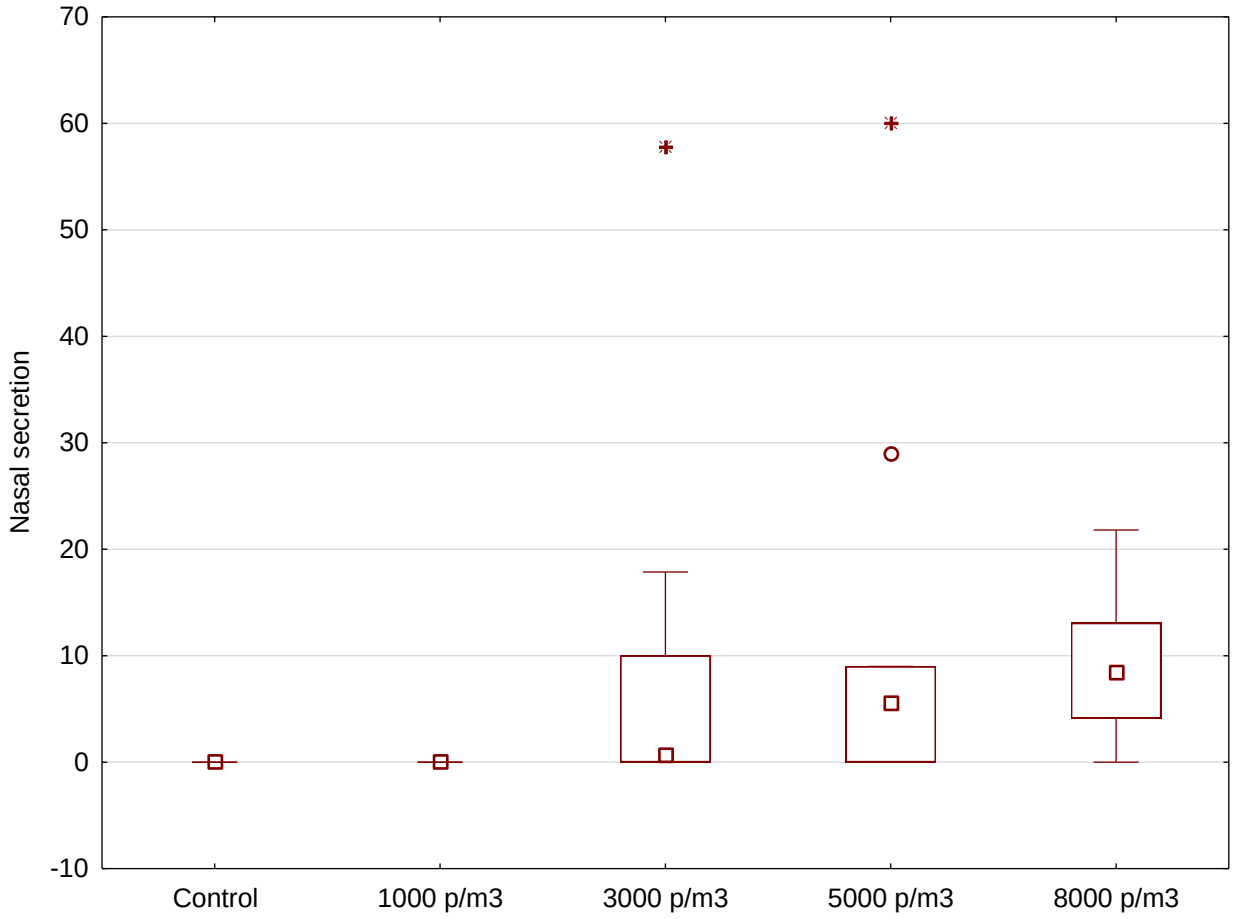

Forced expiratory volume in 1s (FEV1)
Mean FEV1 [L]
600
500
400
300
200
100
0
control
1000
3000
5000
8000
pollen concentration [p/m3]
0h
3h


Peak expiratory flow (PEF)
Mean PEV [L]
600
500
400
300
200
100
0
control
1000
3000
5000
8000
pollen concentration [p/m3]
0h
3h


Peak nasal inspiratory flow (PNIF)
Mean PNIF [L]
160
140
120
100
80
60
40
20
0
control
1000
3000
5000
8000
pollen concentration [p/m3]
0h
3h

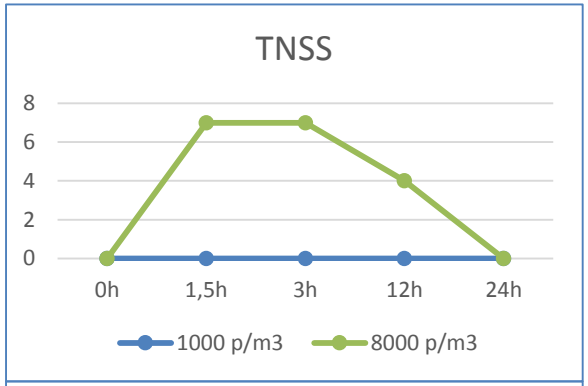

Nasal secretion
Mean weight [g]
14
12
10
8
6
4
2
0
control
1000
3000
5000
8000
pollen concentration [p/m3]
after 3h

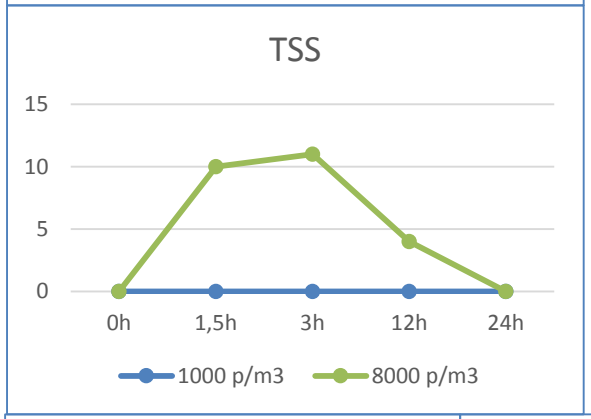
Nasal secretion

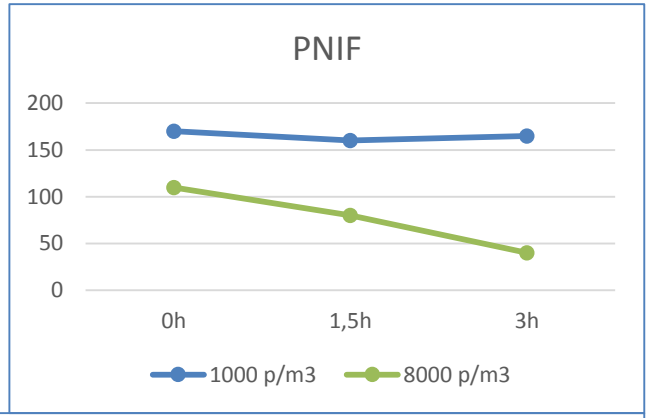


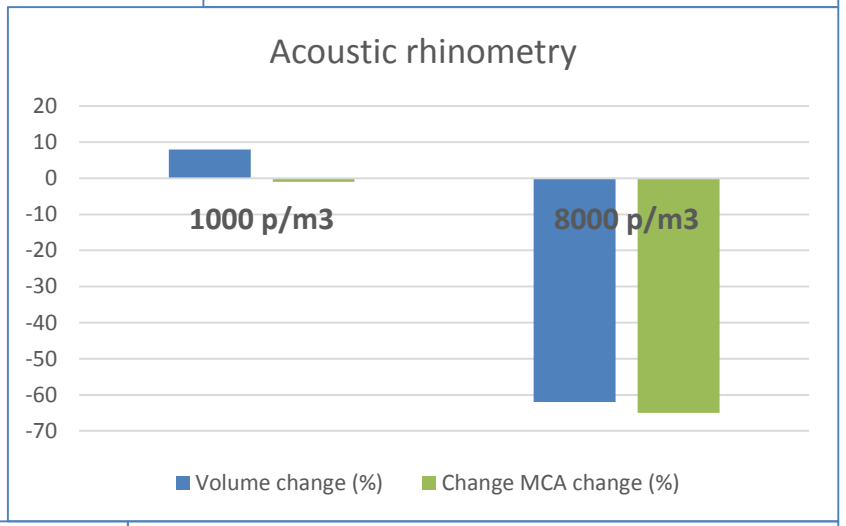
	Nasal secretion (p)
	3h
3000 p/m3	**0,045**
5000 p/m3	**0,024**
8000 p/m3	**0,012**

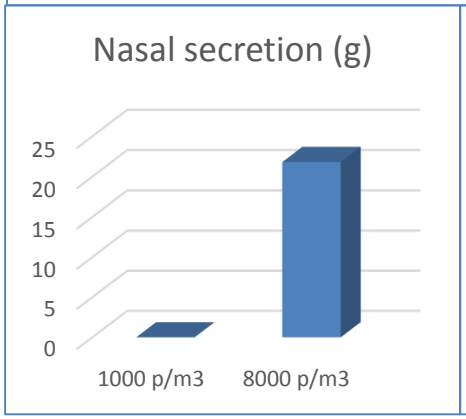
Patient: 14 MK, 37 years old, female

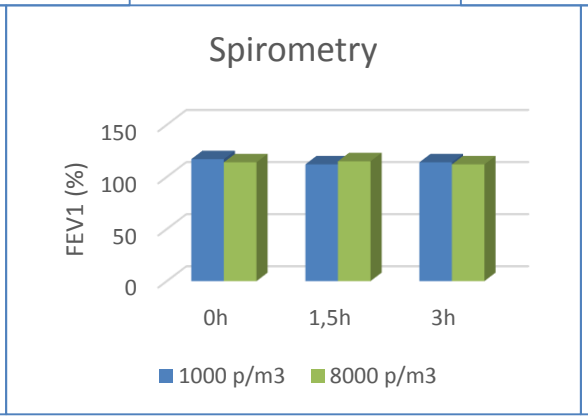


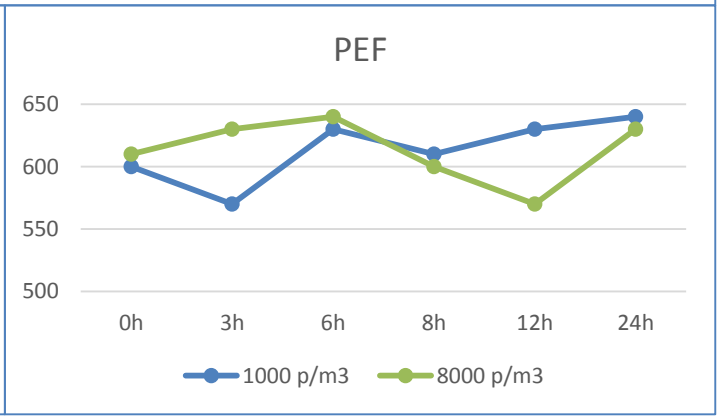












Nose and eye symptoms show a similar pattern during exposure

Strong positive correlation between the TSS and nasal or eye symptoms at all time points (p<0,0014)

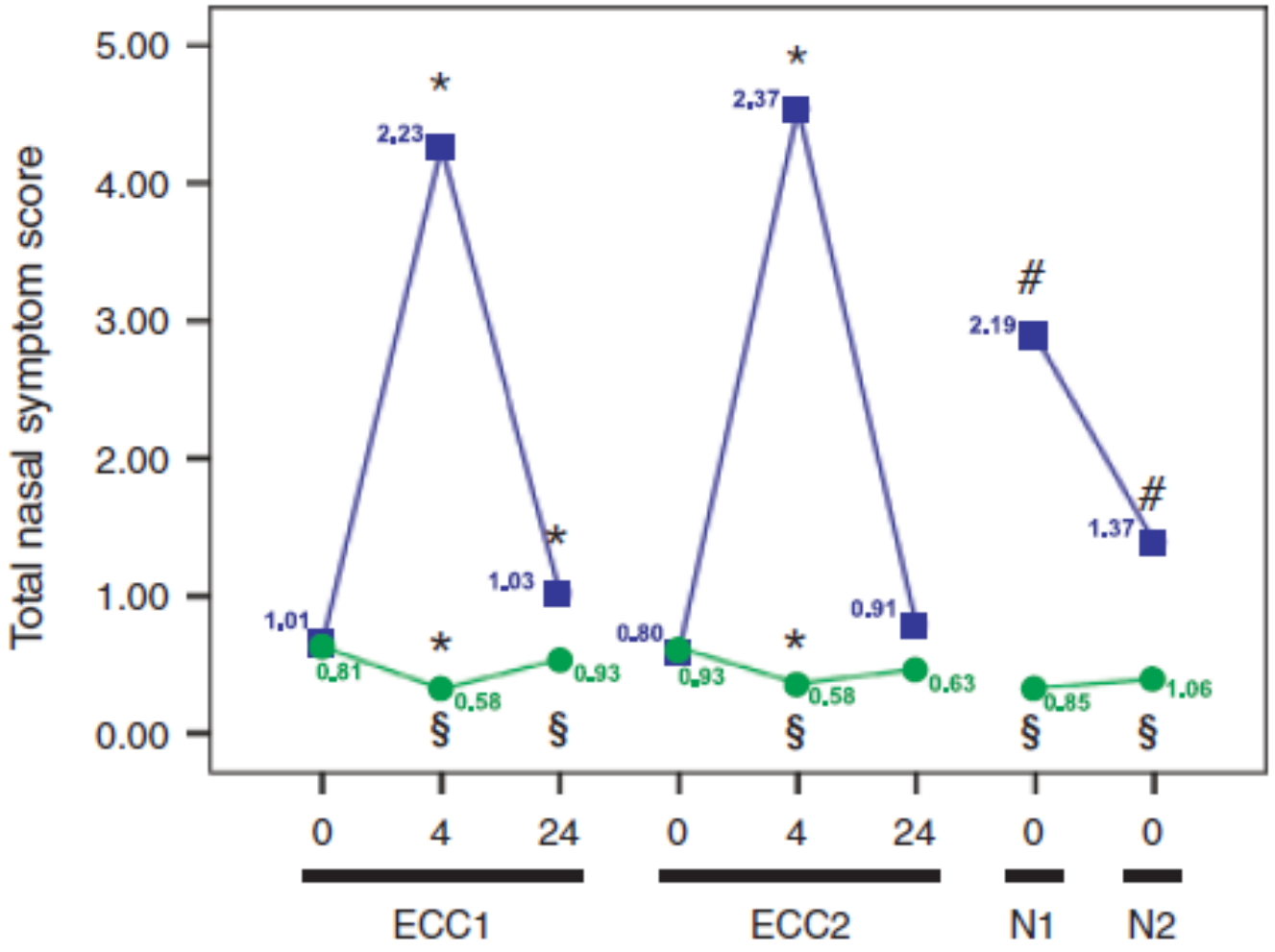
No statistically significant correlation with the symptoms assessed after 24 hours

Correlations		Spearman's rank factor (r)	p
TNSS 30 min	TOSS 30 min	0,63	0,004648 ***
TNSS 60 min	TOSS 60 min	0,48	0,029176 *
TNSS 90 min	TOSS 90 min	0,51	0,021858 *
TNSS 120 min	TOSS 120 min	0,45	0,041985 *
TNSS 150 min	TOSS 150 min	0,70	0,025999 *
TNSS 12h	TOSS 12h	0,89	0,020172 *

****p<0,0014; ***p<0,005; **p<0,01; *p<0,05; . p<0,1

AEC and real life allergen exposure

No correlation of TNSS in the ECC at 4 h with the TNSS in-season
TNSS at 24 h correlated with TNSS in-season(r = 0.41)



Hohlfeld JM, Exp Allergy. 2010;40(7):998

Comparison to field studies

Box 3: Regarding comparability of allergen chamber trials with field trials, the group recommends that

1. Direct comparison is not possible (as natural allergen exposure cannot be determined and rescue medication is allowed in field trials)
2. Indirect comparison of effect sizes is possible when allergic subjects with comparable clinical characteristics are evaluated
3. Hybrid designs are feasible and may be an option

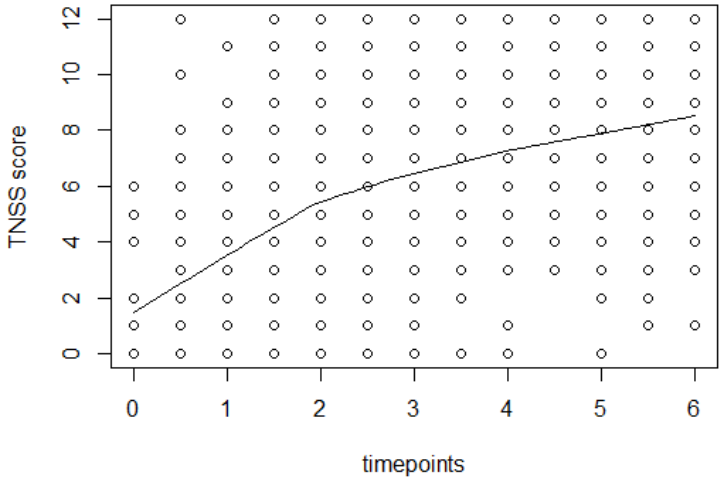
EAACI Position Paper; Allergy 2017

Benefits of AEC

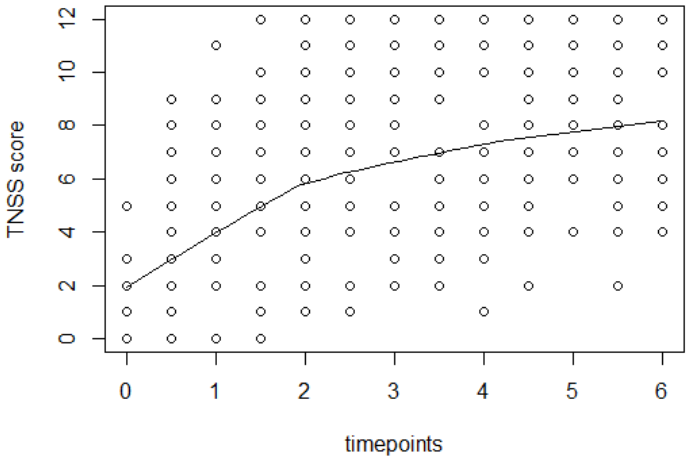
- Strong research and diagnostic tool

AEC research approaches - timepoint for assessmet

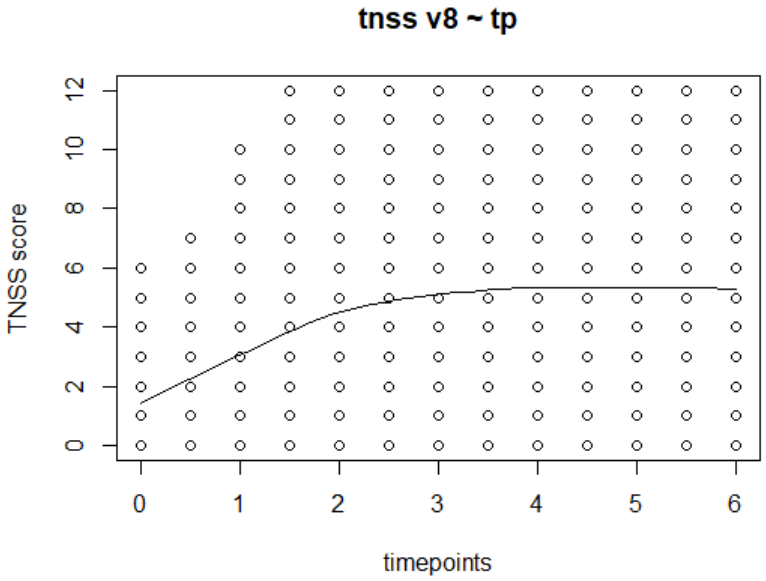
Verum

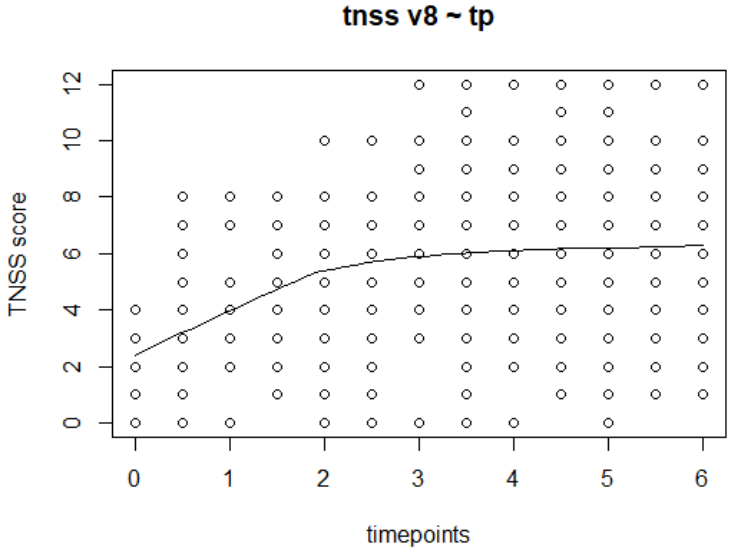


Placebo



Before AIT

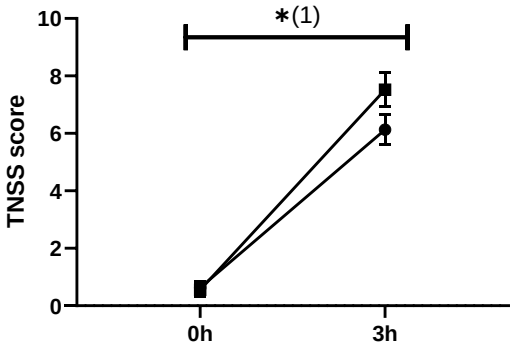




After AIT

AEC research approaches

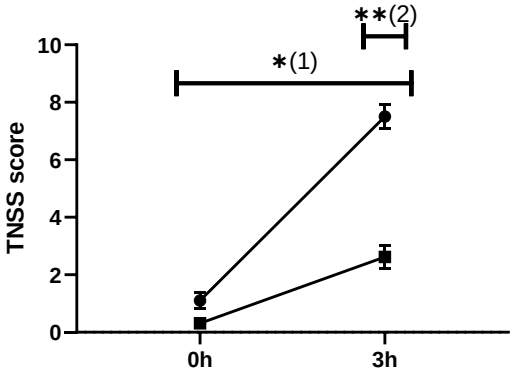
Verum before AIT (30% cutoff NR v R)



Non-Responders
Responders

(1) overall significant effect of time (total 0h versus total 3h)

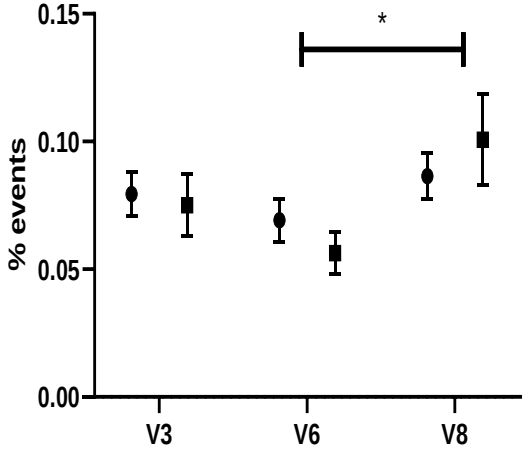
Verum after AIT (30% cutoff NR v R)



Non-Responders
Responders

(1) overall significant effect of time (total 0h versus total 3h)
(2) sign. difference between NR-R at timepoint 3

Treg in VERUM, nr vs R



Non-Responders
Responders

Benefits of AEC

- Strong research and diagnostic tool
- Better patient selection for AIT
- Better quality and " rapid" data collection
  especially in proof-of-concept and biomarker studies
- Primary end point in phase II studies
- Secondary endpoint in phase III studies
  (primary endpoint under development)
- Option for developing therapeutics for rare allergies

Regulatory authorities

- **European regulatory authorities have shown interest in the broader utility of AEC, specifically for AIT product development**
- **Defined criteria and procedures elaborated by all operators with respect to marketing authorizations**

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