Exposure standards for allergens: history, occurrence, exposure-response relations, risk assessment

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Outline

- Allergens
  - Definition
  - Properties
- Exposure response relations
  - Sensitization
  - Time till sensitization
  - Symptoms, asthma
- Risk assessment for allergens

High molecular weight sensitizers

- Usually proteins, molecular weight >5 kDaltons
- IgE response after sensitization period (T-helper 2 response):
- Urticaria, conjunctivitis, rhinitis, asthma
- Examples of HMWS with major public health impact:
  - **Latex** (Hevea braziliensis) Hev b1-b7
  - **Fungal α-amylase** Asp o 1 (51-54 kDa), other proteins (25-27 and 40 kDa)
  - **Rat and Mouse Urinary Proteins**: Rat n 1A (20-21 kD), Rat n 1B (16-17 kD) and Rat albumin (68 kD)
  - **House dust mite**: Der p 1

HDM allergen: >99% of Der p1 in fecal particles

Tovey et al., Nature 1981

***Der p1*: MW = 24,000**

~0.1 ng/particle (~2.5%(w/w)) → $3*10^9$ molecules/particle

Mite faeces are a major source of house dust allergens

E. R. Tovey, M. D. Chapman & T. A. E. Platts-Mills*

Division of Immunology, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ, UK

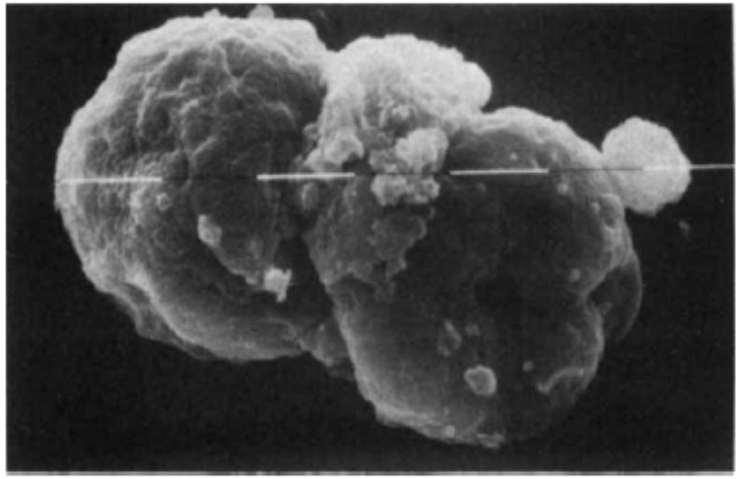


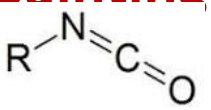
Fig. 1 Electron scanning micrograph of two mite faecal balls. Mite faeces range from 10 to 40 μm in diameter with a mean of 22 ± 6 μm s.d. For a similar species it has been reported[9] that the faeces are produced by compacting three to five foodballs covered in a peritrophic membrane. Scale bar, 10 μm.

Low molecular weight sensitizers

- Small molecules, sometimes reactive chemicals
- IgE response after sensitization period (T-helper 2 response) or other (unknown) mechanism (hapten formation and IgE response, cellular responses)
- Urticaria, conjunctivitis, rhinitis, asthma
- Examples of LMWS:
  - **Isocyanates**
  - **Acetic anhydrides**
  - **Metals: Beryllium, Chromium (Cr III), Nickel, Platinum salts**
  - **Colophony**
  - **Disinfectants: Chloramine T**

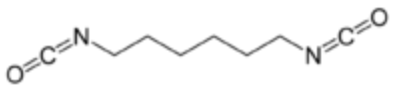
Low molecular weight sensitizers: di-isocyanates in spray painting

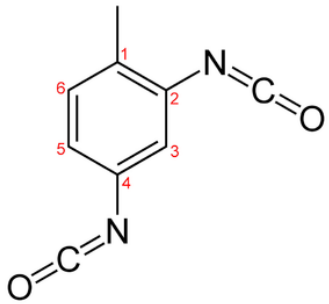
Pronk et al., Ann Occup Hyg, 2005

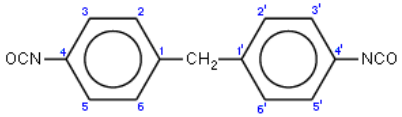


HDI factor 42.2%	TDI factor 26.8%	MDI factor 12.8%
Biuret	2,6-TAI	4,4-MDI
Diisocyanuraat	4,2-TAI	4,4-MAI
Uritidone	2,4-TAI	PIC
Unknown polyHDI	PhI*	PhI*
Isocyanurate	2,6-TDI	
1,6-HDI	MIC	
1,6-HAI	2,4-TDI	
IPDI*	IPDI*	
IPDI isomer*	IPDI isomer*	

*Present in multiple factors







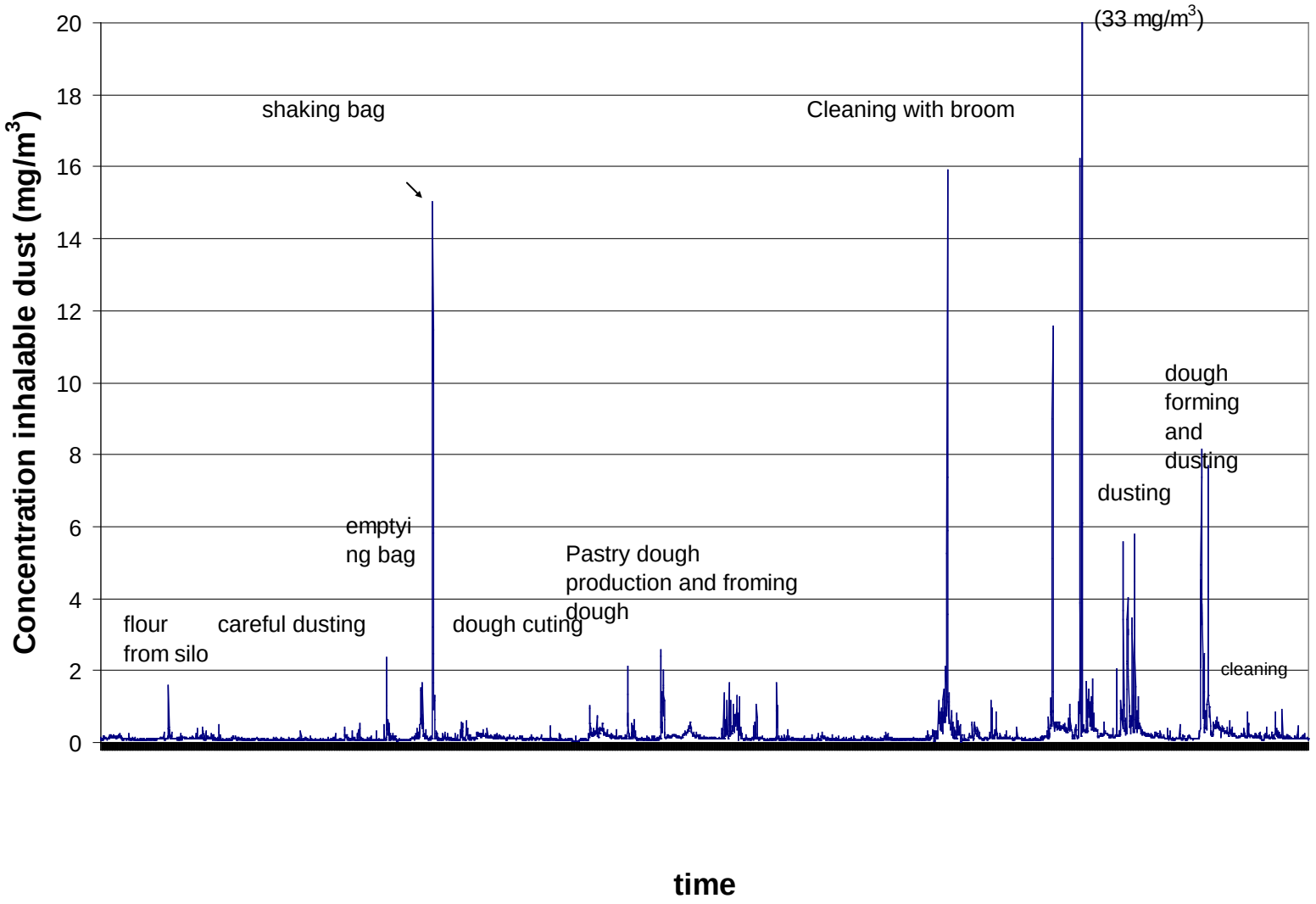
Platinum salts

Heederik et al., JACI 2015

- Low ng/m^3 exposure sufficient for sensitization
- Involves a limited number of particulates
- 5μm particle has a mass of 0.16 ng/m^3 and contains 2.5 10^{11} molecules
- 10μm particle has a mass of 1.3 ng/m^3 and contains 1.9 10^{12} molecules
- Under assumptions of MW~400, density=2.5 g/mL

Temporal patterns in exposure

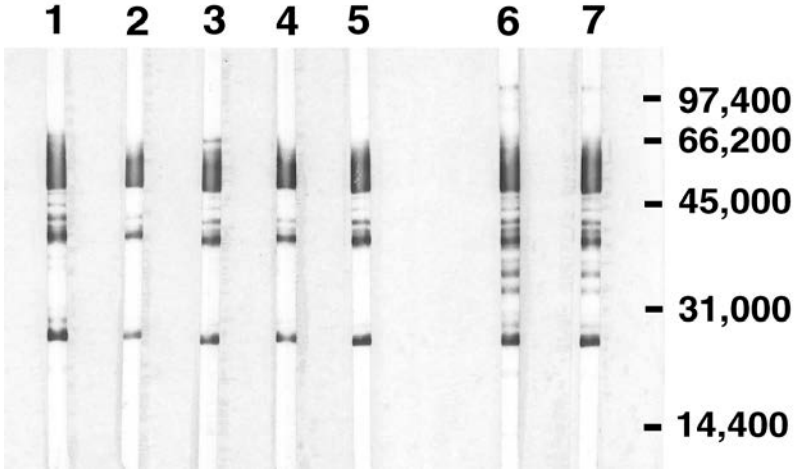
Meijster et al., Ann Occup Hyg 2008



Measuring allergens using immunoassays

- Uses antibodies (polyclonal, monoclonal)
- Measurement of single or multiple allergens in dust
- Specific and sensitive

Immunoblot for fungal α-amylase



- Absence exposure monitoring techniques for high molecular weight allergens until 1980-ies:
  - Limited insight in exposure determinants
  - No exposure-response (or exposure-effect) relationships described

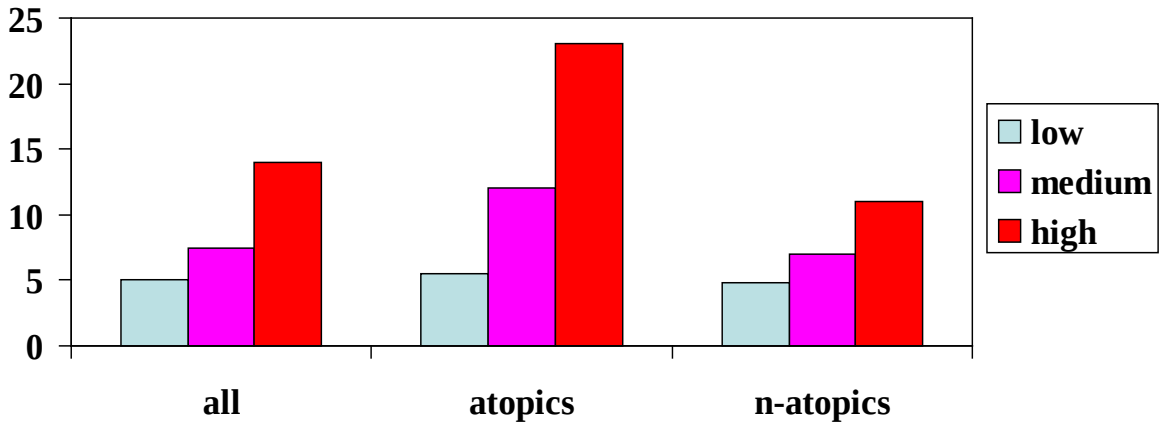
Exposure response relations

'… it seems unlikely that exposure measurements, including personal monitoring, .., would ever be sufficiently accurate, .., to permit between individual differences (-due to differences in underlying mechanisms-) in exposure response relationships to be modeled or measured in epidemiological studies …'

Occupational asthma and exposure response studies (Becklake M, in Bernstein et al. Asthma in the Workplace, 1999)

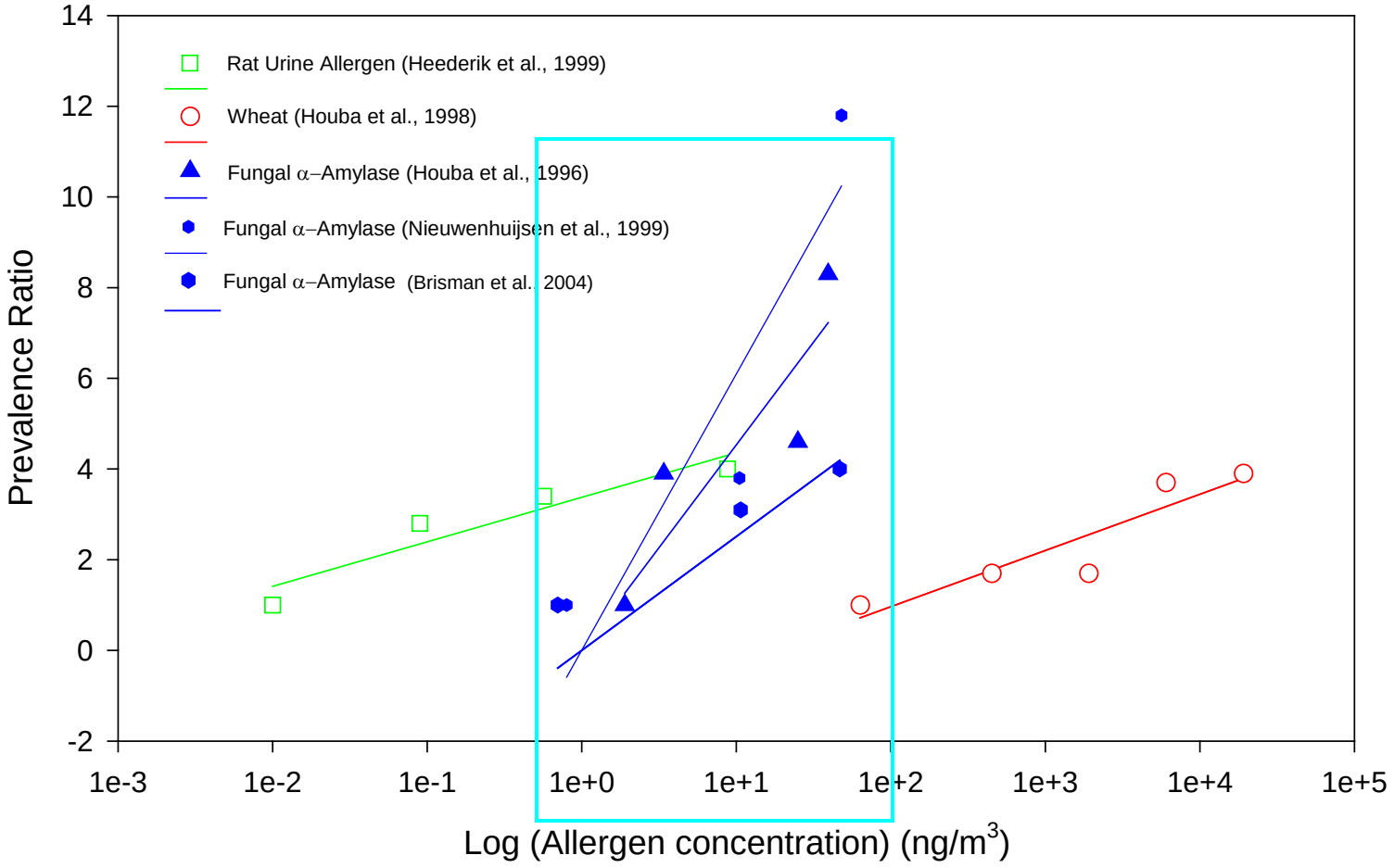
Exposure response relationships: wheat allergen exposure in bakers

Houba et al., Am J Resp Crit Care Med 1998



Exposure sensitization relationships for three different allergens

Heederik et al., Occup Environ Med 1999 with Brisman et al., 2004 added



WR-symptom prevalence by sensitization and wheat exposure

Houba et al., Am Rev Respir Crit Care Med 1998

	WORK RELATED SYMPTOMS	PREVALENCE
SENSITISED WF (36)		
LOW	1/7	14.3%
INTERMEDIATE	4/10	40.0%
HIGH	10/19	52.6%
NON-SENSITISED WF (310)		
LOW	17/110	15.5%
INTERMEDIATE	21/97	21.6%
HIGH	25/103	24.3%

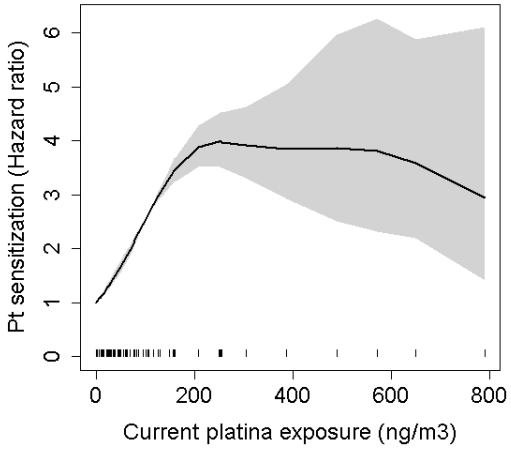
Time till development of symptoms in a retrospective cohort study among 99 LA Workers

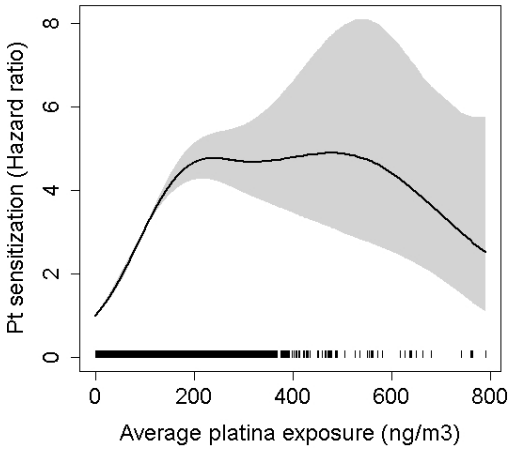
Kruize et al., Occup Environ Med 1997

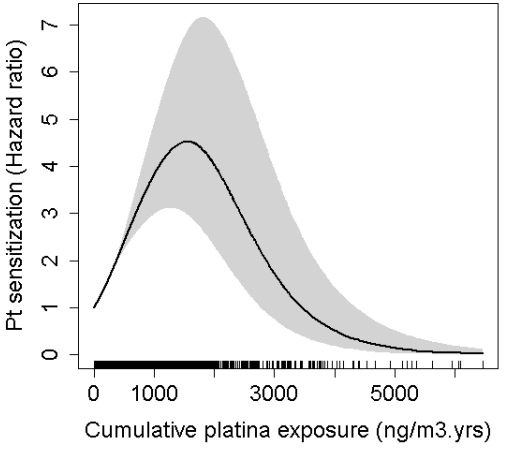
	LAA cases	*Median time till LAA (months)*	*Range*
Non atopics	9	98	7-270
Atopics	10	27	<1-117
Exp <2 hrs/wk	2	83	30-36
2≤Exp<15	6	113	83-270
15≤Exp<38	7	56	1-192
Exp≥38	4	14	<1-36

Platinum salt surveillance study

Heederik et al., JACI 2015







exposure just before sensitization was strongest related to sensitization

Spline model with 3d.f. not-lagged/lagged 0.5 and 1.0 year comparable models fits (AIC 1195-1197)
Lagging > 1.5 year AICs >1208

Exposure standards for allergens

- ACGIH standard for subtilisin adopted in 1975 60 ng/m^3
- Nordic expert group 1996 (wheat flour) 1994 (industrial enzymes). ACGIH standard does not protect against development of sensitization and allergy
- Netherlands Health Council advice for an exposure standard for wheat dust 10th August 2004

Exposure standards: Nordic expert group 1996

Tikkainen et al, 1996

"… existing data on exposure-response relationships do not allow the identification of a NOAEL for flour dust. Due to the nature of allergy it is unlikely that the setting of a NOAEL for flour dust will be practicable even in the near future "

"… since sensitization is not a disease", and the relationship between sensitization and symptoms is weak and the predictive value of sensitization with respect to development of disease is unclear, it "appears unrealistic and not sufficiently founded to suggest and OEL to prevent sensitization" ().

Exposure standards: DECOS

Rijnkels et al., Allergy 2008

"… an OEL should prevent against allergic sensitization, as sensitization plays a crucial biological role and is a prerequisite for the development of allergy.

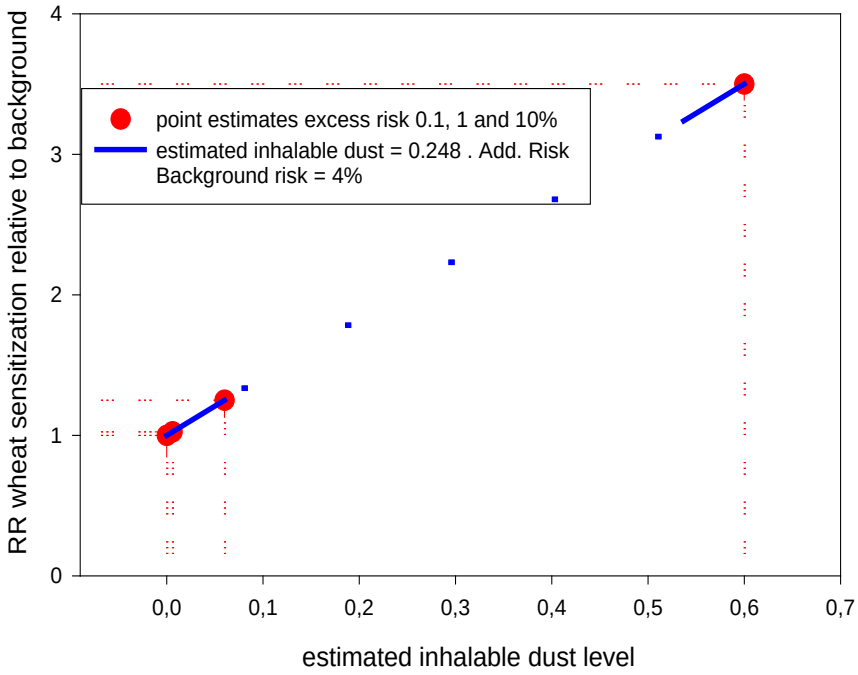
… the exposure level below which no allergic sensitization develops for most allergens is so low, that OELs are difficult to set with the current knowledge and technical feasibilities.

… An alternative approach is to accept exposure, which carries a small predefined risk in developing allergic sensitization."

RISK based approach

Health based exposure standard for wheat dust (HBROEL)

- Netherlands Health Council risk based approach
  - No exposure threshold
  - Estimation of exposure level associated with 1% excess sensitization risk
  - wheat sensitization background (Gautrin et al., 1997)
  - Exposure response (Houba et al., 1998)
  - Assessment factor for variability allergen content of 2
  - 0.5 mg/m^3 proposed at 1% additional risk point
  - Parallel with DMEL in REACH



Deriving exposure standards for allergens

- Feasible
- Transparent
- Evidence based

- Several examples:
  - DECOS wheat, soy, amylase, isocyanates
  - OSHA beryllium