



IRRITANT-INDUCED ASTHMA (I-IA)

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Occupational asthma or work-related asthma

- 1. Sensitization: allergic or immunologic with latency: IgE or non-IgE**
- 2. Acute exposure to high concentration of irritant (RADS) without latency**
- 3. Exacerbation or aggravation of preexisting asthma**
- 4. The gray zone: low-dose RADS?**



Occupational asthma

- 1. 469 accepted compensation claims, Ontario:1984-88**
- 2. Non-irrtant exposure: 380 (81%)**
- 3. Accidental high exposure: 89 (19%)**
 - 1. RADS: 12 (13%) or 12/489 (2%)**
 - 2. Exacerbation: 68 (76%)**
 - 3. Irritant-induced??: 9 (10%)**

Chatkin JM et al. Chest 1999;116:1780-5



Work-exacerbated asthma

- 1) 18% of all adults with asthma**
- 2) 25% of working adults with asthma**
- 3) 45% of all work-related asthma**

Henneberger PK. 2007; Curr Opinion Allergy Clin Immunology;7:146-51





RADS (reactive airways dysfunction syndrome) criteria:

- **No previous asthma complaints**
- **Onset of asthma after a single exposure/accident**
- **High irritant concentrations**
- **Asthma onset within 24 hours**
- **Definite asthma diagnosis: e.g. positive methacholine, mannitol, exercise test**
- **Exclude other respiratory diagnoses**



Irritant exposure: consequences

<u>SINGLE HIGH- LEVEL EXPOSURE</u>	<u>REPEATED MODERATE EXPOSURE</u>
Upper airway edema and obstruction	Upper airway irritation symptoms, Vocal cord dysfunction (VCD)
RADS	Irritant-induced asthma (IIA)
Adult respiratory distress syndrome	Bronchiolitis obliterans (popcorn lung)
Bronchiolitis obliterans	Increased airway hyperresponse Enhanced cough reflex Potentiated allergen effect Increased eNO, sputum neutrophil

Brooks S. Immunol Allergy Clin N Am 2011:747-68



Inhalation accident prognosis

- 1) SWORD surveillance 1989-94:
England in GPs**
- 2) 383 inhalation accidents**
- 3) 70% recovered within 1 week**
- 4) 10% persistent respiratory symptoms**
- 5) 3% persistent asthma (RADS)**

Sallie B. Ann Occup Hyg 1996;40:211-21



RADS outcome

- 1) **Median symptom duration 51 work-related:
13 months (interquartile range 6.5-43.5)**
- 2) **35 RADS cases after 13.6 years:**
 - all symptoms
 - 68% ICS
 - 17/23 positive metacholine
 - 12 depression

Shakeri MS. Occup Med (London) 2008;58:205-11
Malo JL. Am J Respir Crit Care Med 2009;179:923-8



Pathology of RAD S: non-immunologic

- 1) **Epithelial cell injury**
- 2) **Bronchial wall inflammation**
- 3) **Lymphocytes and plasma cells, no eosinophils**
- 4) **Rapid denudation of mucosa**
- 5) **Fibrohemorrhagic exudates**
- 6) **Regeneration: basal and parabasal cell proliferation over months**



Possible RADS mechanism

- 1) **Special airway nociceptors: detect noxious stimuli**
- 2) **Transient receptor potential vanilloid-1 (TRPV₁). Transient receptor potential cation channel, subfamily A, member 1 (TRPA₁)**
- 3) **Activated by capsaicin, associated with chronic cough**
- 4) **Heightened TRPV₁, TRVA₁ sensitivity**



Common causes of irritation

Exposure	Agent or process
Acids	Sulfuric, hydrochloric, hydrofluoric, glacial acetic
Alkali	Bleach, sodium hydroxide, calcium oxide, WTC dust
Gases	Chlorine, ammonia, sulfur dioxide, phosgene, mustard
Sprays	Paints, coatings
Explosion	Irritant gases, vapors, fumes released under pressure
Fire or pyrolysis	Combustion products, PVC pyrolysis, burning paint fumes
Confined spaces	Acrolein, biocides, fumigating aerosol, drain-cleaning agents
Workplace	Popcorn flavoring, Al smelting (potroom), shoe manufacture (solvents), tunnel construction, food industry cleaners



Irritation

- 1. Somesthesia, chemesthesia, chemical nociception**
- 2. Eye, nose and throat: trigeminal nerve (CN V)**
- 3. Pulmonary irritation: vagus nerve (CN X)**
- 4. Odor: olfactory nerve (CN I)**
- 5. Toxicity: Odor ~~≠~~ irritation**



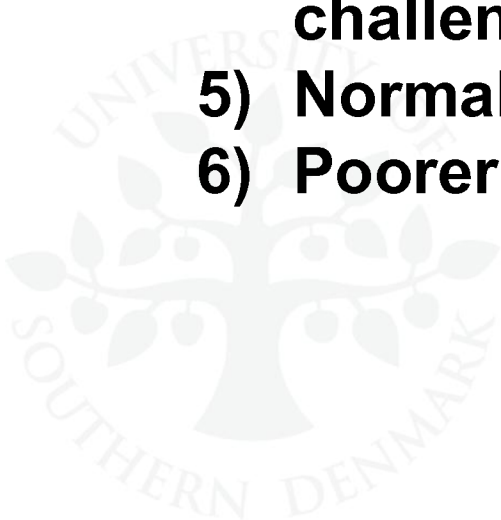
Preexposure to irritant enhances airway responsiveness to allergens

- 1. Th₂ cytokine-producing cell recruitment**
- 2. Amplifying Th₂ inflammation through thymic stromal lymphopoietin**
- 3. Allergen enzymes cause mucosal irritation enhancing immunological response**
- 4. Dust mite proteolytic allergens (Der 1 p and Der 9) dose-dependent release IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor (in-vitro)**



Asthma-like symptoms and odor

- 1) **Airway sensory hyperreactivity**
- 2) **15-30%??**
- 3) **Upper or lower airway symptoms induced by odor**
- 4) **Increased cough sensitivity to capsaicin-challenge**
- 5) **Normal methacholine**
- 6) **Poorer quality of life**





Asthma and construction work

- 1) Finnish registry linkage study
- 2) 2,548 incident cases
- 3) Increased RR
 - Welders, flamecutters: 2.34 (1.79-3.06)
 - Asphalt roofers: 2.04 (1.02-4.09)
 - Plumbers: 1.90 (1.63-2.21)
 - Brick layers: 1.83 (1.46-2.28)
- 4) New welding asthma: 7.0 (1.2-41.6)

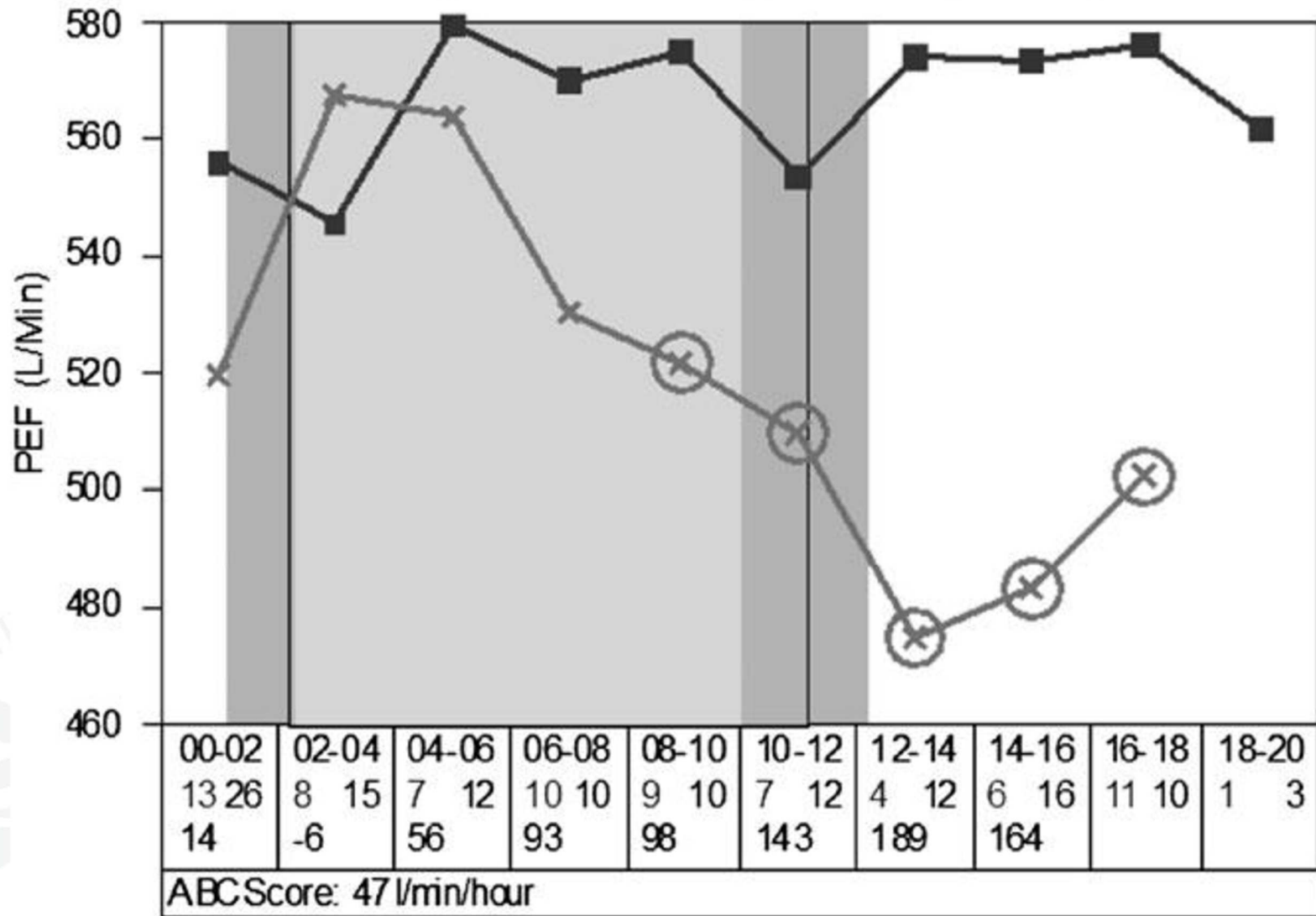
Karjallainen A. J Occup Environ Med 2002;44:752-7

Omland O. J Allergy Clin Immunol 2011;128:761-5

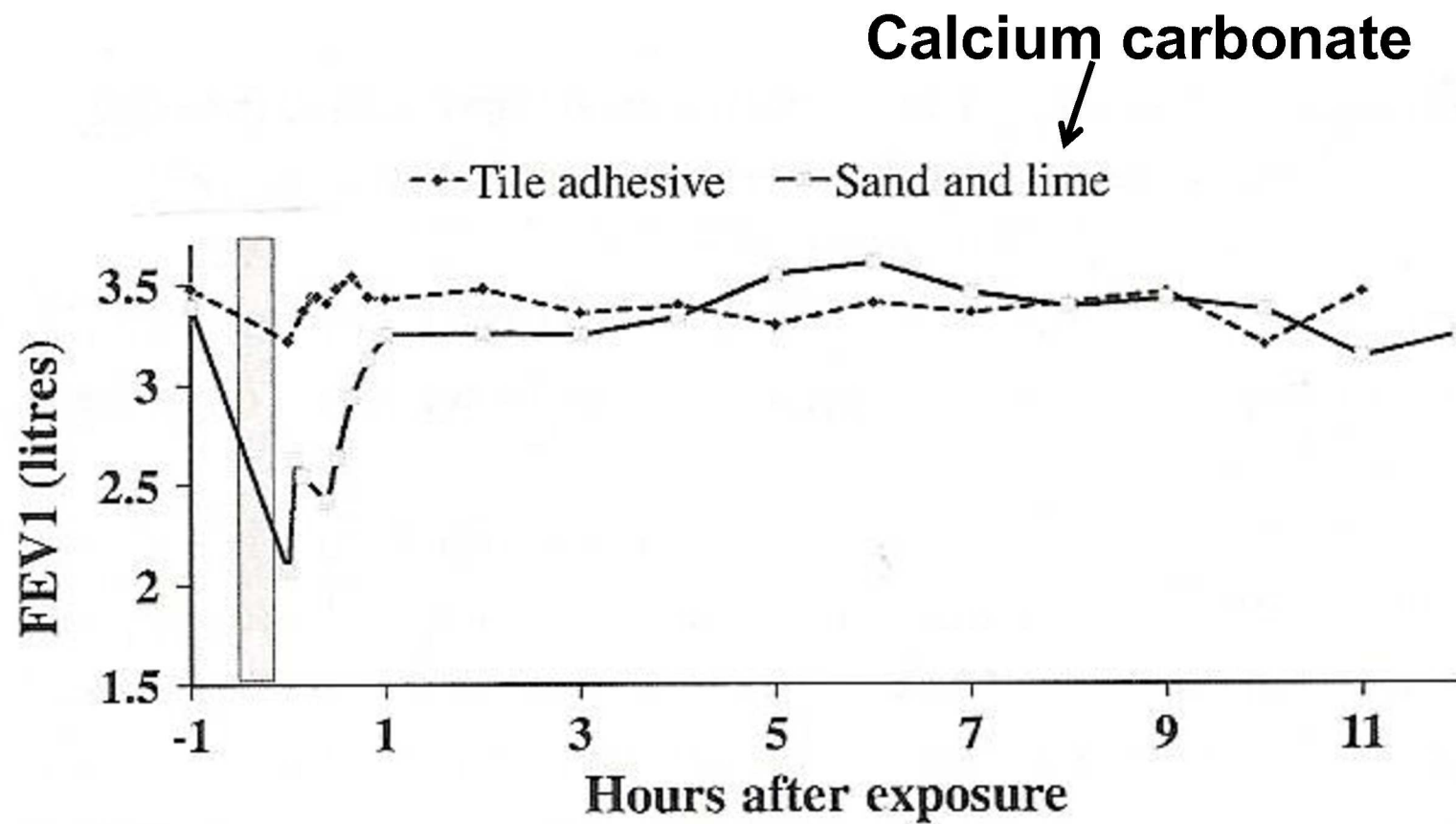


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Average Hour from Waking Rest and Day Shift days



Hours From Waking, Number of Readings And Areas (Day Shifts X) (Rest ■)



Burge PS. 2011: doi.1093/occmed/kqr211



Asthma and cleaners: a prospective study

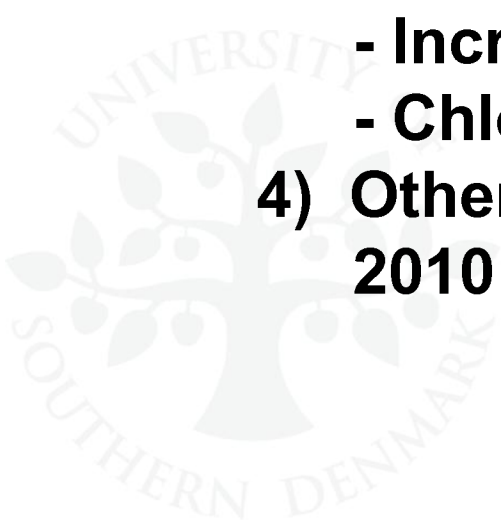
- 1) Cleaners, nurses, homemakers**
- 2) Increased risk of new-onset asthma**
- 3) Incidence: 2.2/1000 person-years**
- 4) Ammonia, bleach, cleaning sprays**

Zock J-P. Am J Resp Crit Care Med 2007;176:735-41



Swimming pool asthma

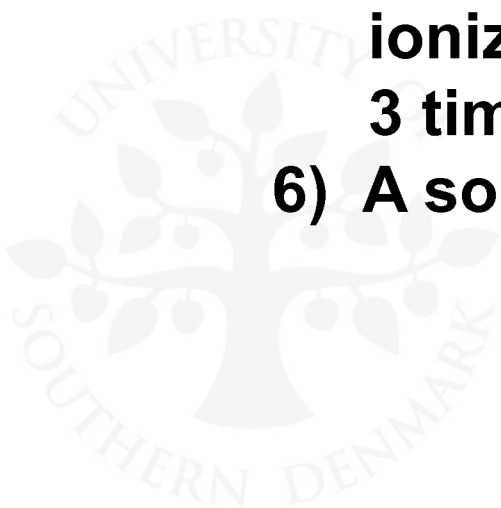
- 1) Chlorine + sweat, urine
- 2) Chlorination products: trichloramine
(nitrogen trichloride)
- 3) Children swimmers (Belgian, 2003)
 - Increased lung epithelium permeability
 - Increased asthma prevalence
 - Chlorine-atopy interaction
- 4) Other biomarker studies: 2002, 2009, 2010





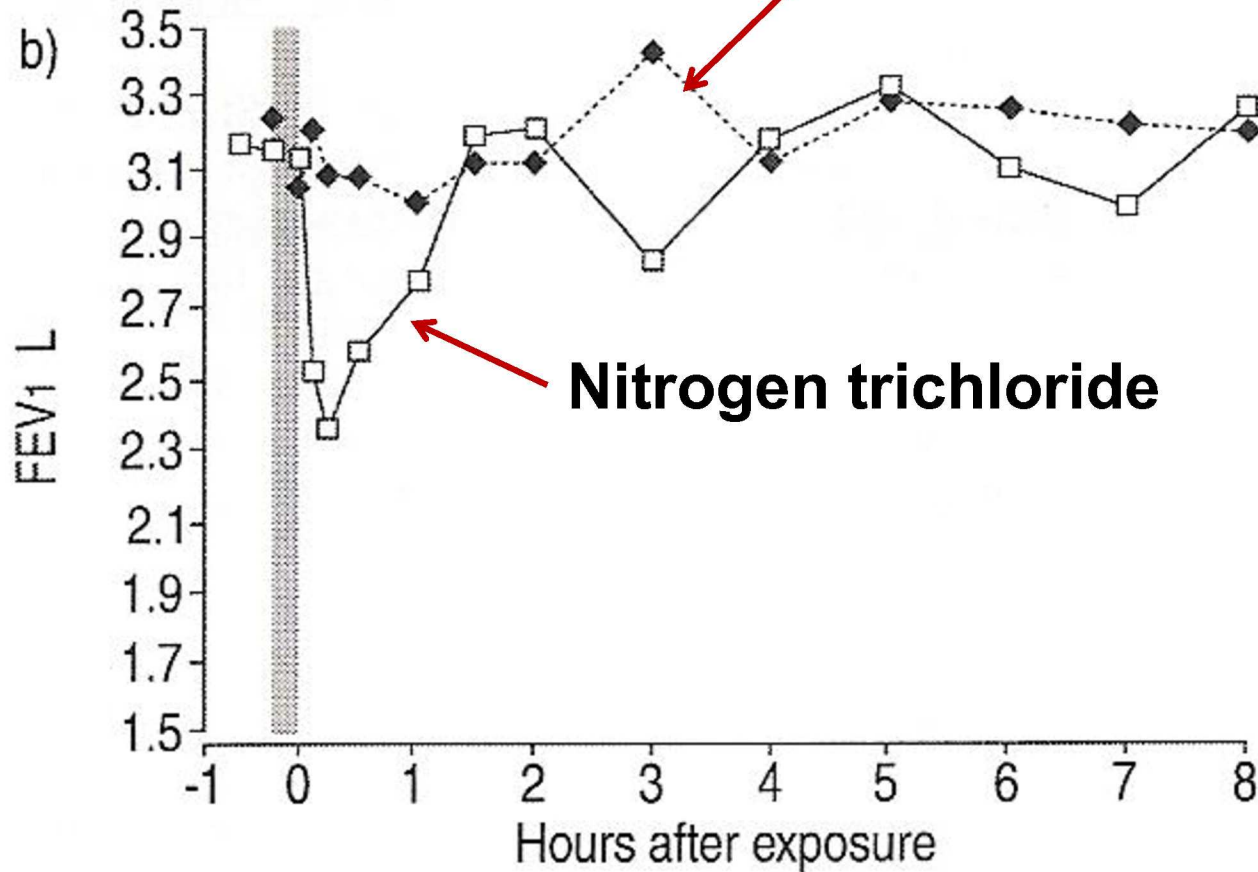
Swimming pool asthma (2)

- 4) **Elite swimmers**: increased prevalence of rhinitis and asthma. Biopsies similar to mild asthma: +/- airway hyperresponsiveness (2012)
- 5) **Chlorine-free pools** (copper-silver ionization method): asthma prevalence 2-3 times reduced (2009)
- 6) A solid hypothesis?





Sodium hypochlorite



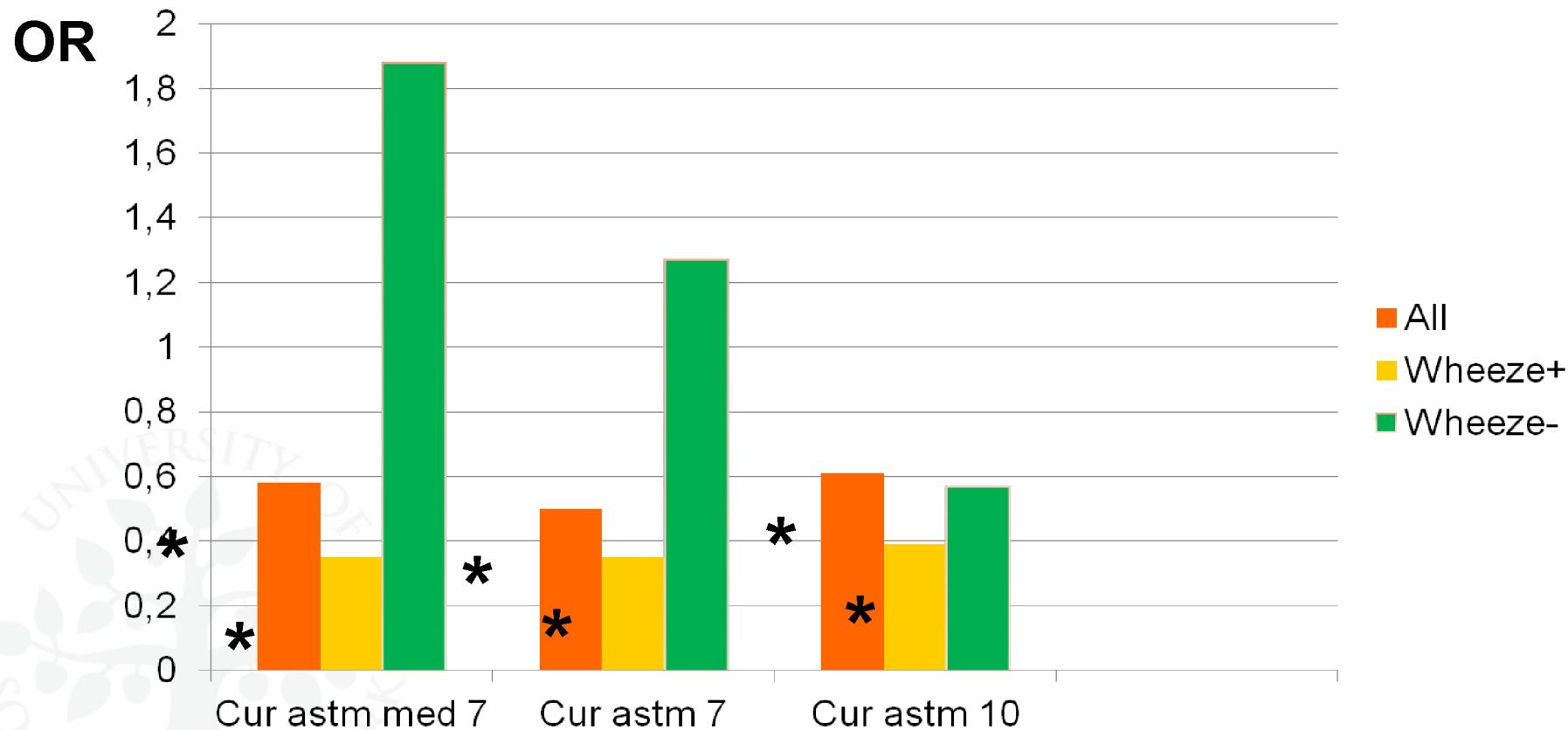
Nitrogen trichloride

Thickett KM. Europ Resp J 2002;19:827-32



Asthma: highest vs lowest swimming

5738 kids 10y follow-up



Font-Ribera L. Am J Respir Crit Care Med 2011;183:582-8



New irritants

- 1) **Alcohol hand gels: denatonium (a quaternary ammonium, quat)**
- 2) **Robertsen A. ERS 2011 Poster 4948, Birmingham Chest Clinic**
- 3) **Controlled provocation**
 - **A midwife: OASYS score 3.43 (<2.5), dual asthmatic reaction**
 - **A nurse: OASYS score 3.93, prolonged immediate reaction**



Quirce S. Immunol Allergy Clin N Am 2011;31:677-98

<http://www.occupationalasthma.com>



Summary

- 1) Work-exacerbation is very common
- 2) Demonstrate work relation
- 3) Peak flow (OASYS:
<http://www.occupationalasthma.com/oasys.aspx>)
- 4) Evaluate atopy and specific allergens
- 5) Consider irritant-induced asthma
- 6) Consider irritant-allergen interaction
- 7) Causation: non-specific chronic irritation or a specific non-IgE reaction

