Clinical aspects of Chemical Respiratory Allergy and Occupational Asthma

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Disclosures

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CREOD (Centre for research expertise in occupational diseeases)

Clinical practice includes assessment of patients referred from WSIB and patients referred for IMEs

The occupational contribution to asthma

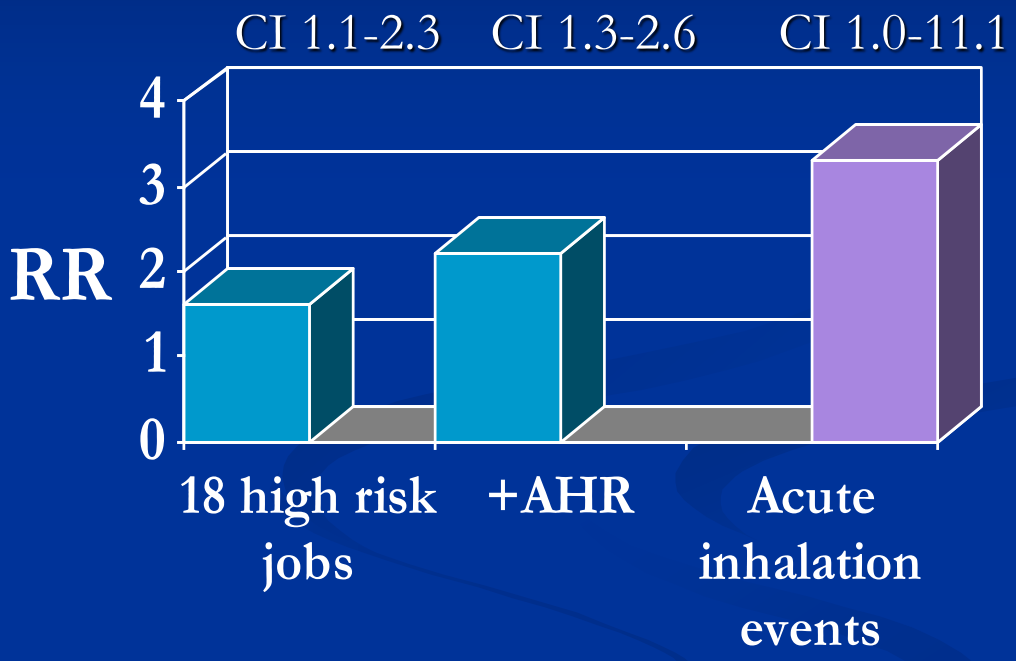
Canadian communities, population attributable risk in high risk jobs and exposures **18.2%** (Johnson et al AJRCCM 2000)

ATS statement: median **15%** population attributable risk from occupation (4%-58%) (AJRCCM 2003)

Toren K, Blanc PD. A systematic analysis ('99-'07) of estimates of the population-attributable fraction **17.6%.** BMC Pulm Med. 2009;9:7

Occupational Asthma: a significant component of new-onset asthma (~7000 subjects) Kogevinas et al Lancet 2007

- PAR for new adult asthma from occupation 10-25%, ≡ 250-300 cases/million workers/year



- Contrasts with *confirmed* clinical cases of OA ~15/million/y in Quebec (Malo and Gautrin Lancet '07), 20-30 in France, UK, USA,– reasons unclear -may reflect epi vs clinical "diagnoses" + likely missed clinical cases

Occupational Asthma: a significant component of new-onset asthma (population study, ~7000)

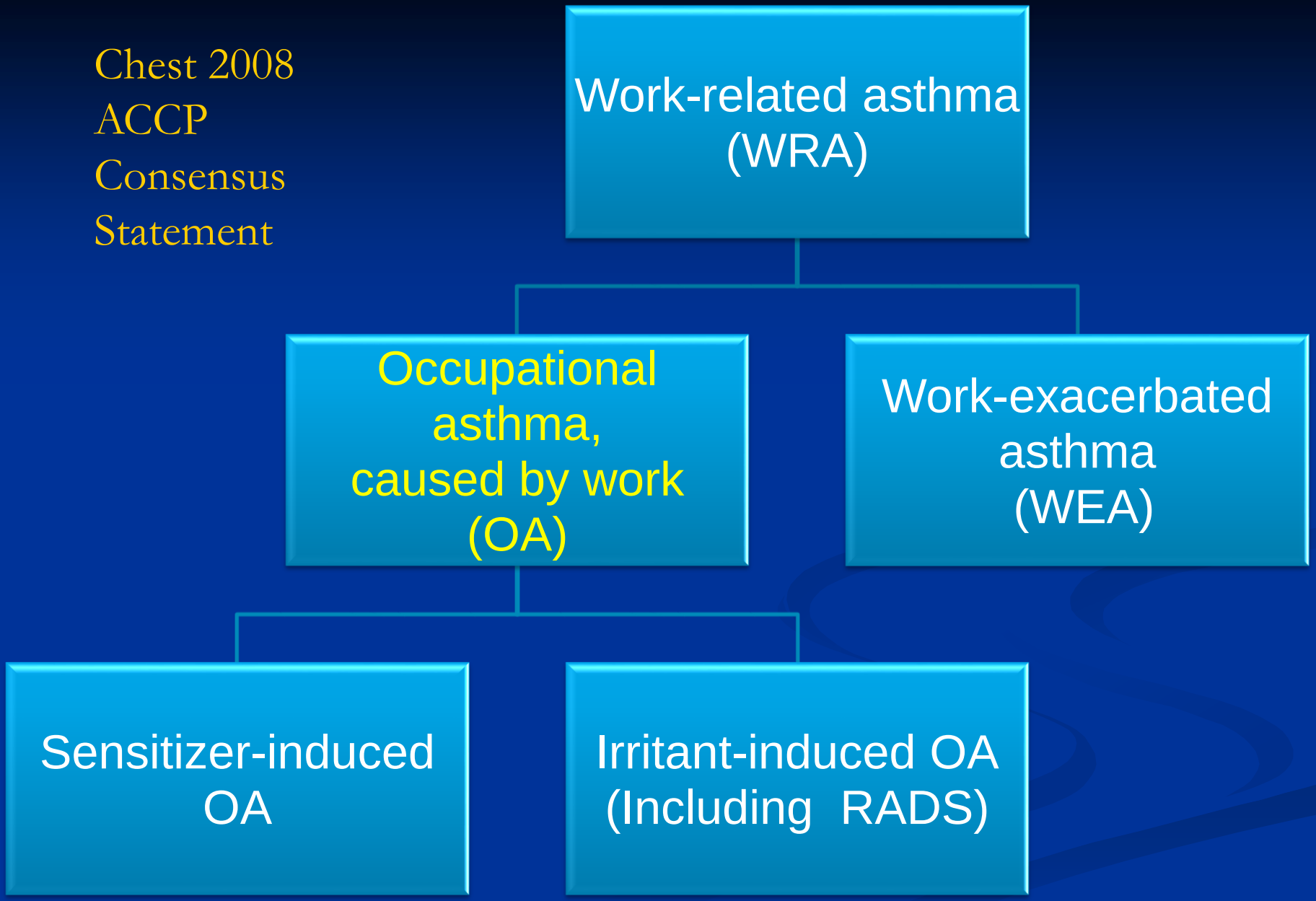
Kogevinas et al Lancet 2007

- PAR for new adult asthma from occupation 10-25%, ≡ 250-300 cases/million workers/year
- *Geographic differences*: highest PAR was in southern Europe, 23%, (95% CI 0– 43). Risk in central Europe 12%, (0–25) and northern Europe 6%, (0–22).
- Highest risks were in cleaning and nursing

Work Related Asthma

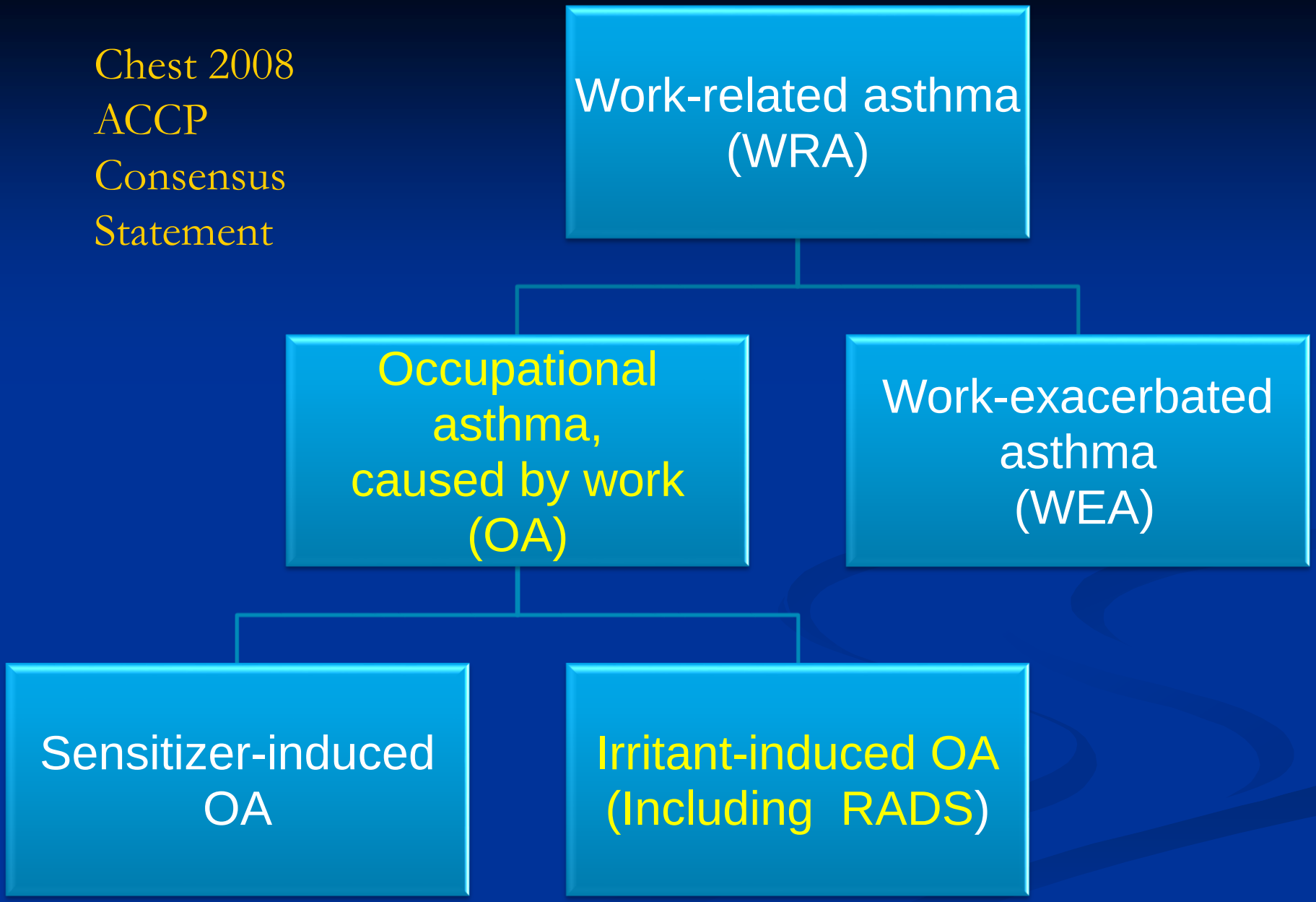
- OA – usually new-onset asthma, caused by work exposures
- WEA (also termed work-aggravated asthma)
  - Pre-existing or concurrent asthma (transiently) worsened by work exposures, e.g. dusts, fumes, sprays, cold air, or by common allergens at work such as dust mite/cats: i.e. not an expected manifestation of chemical allergy but can mimic this
  - It may range from a single short acute episode to daily symptoms at work.

Chest 2008 ACCP Consensus Statement



These groupings are not mutually exclusive; e.g. OA can be followed by WEA

Chest 2008 ACCP Consensus Statement



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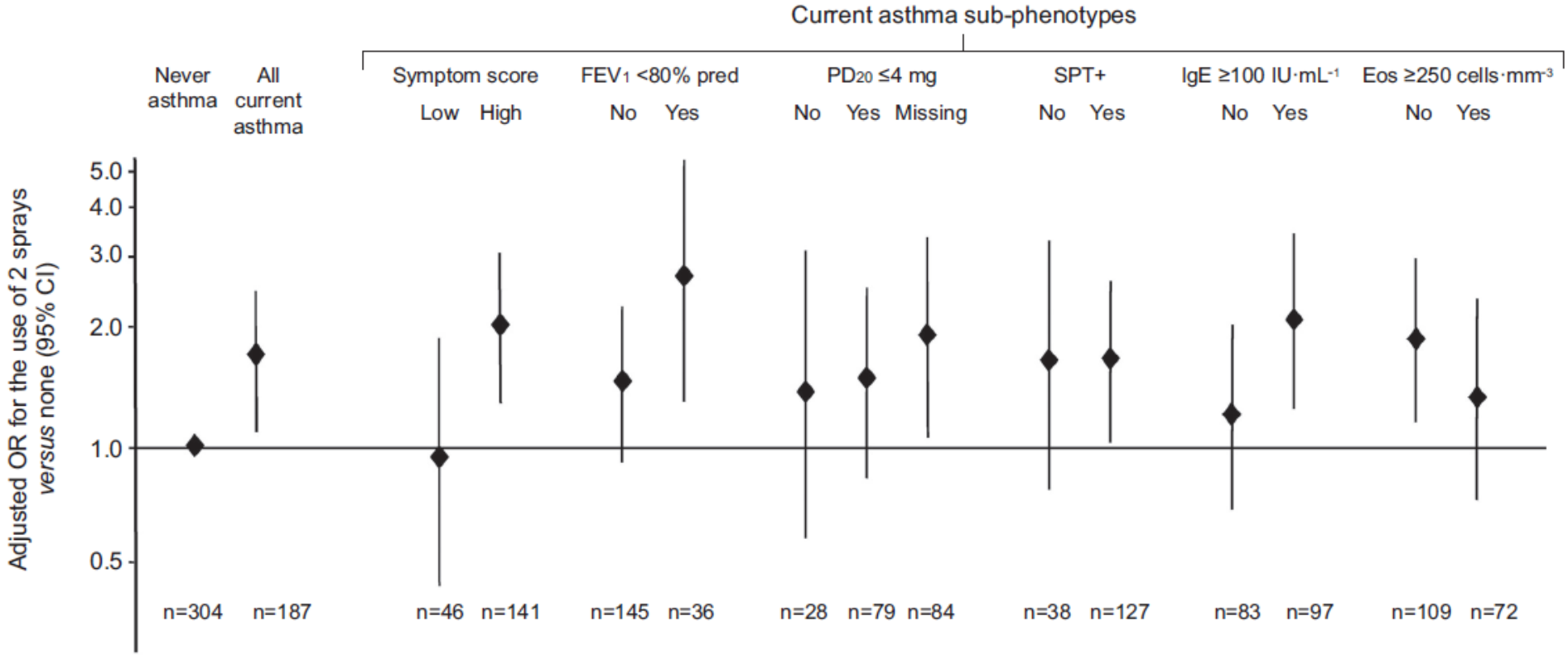
Irritant-induced Occupational Asthma

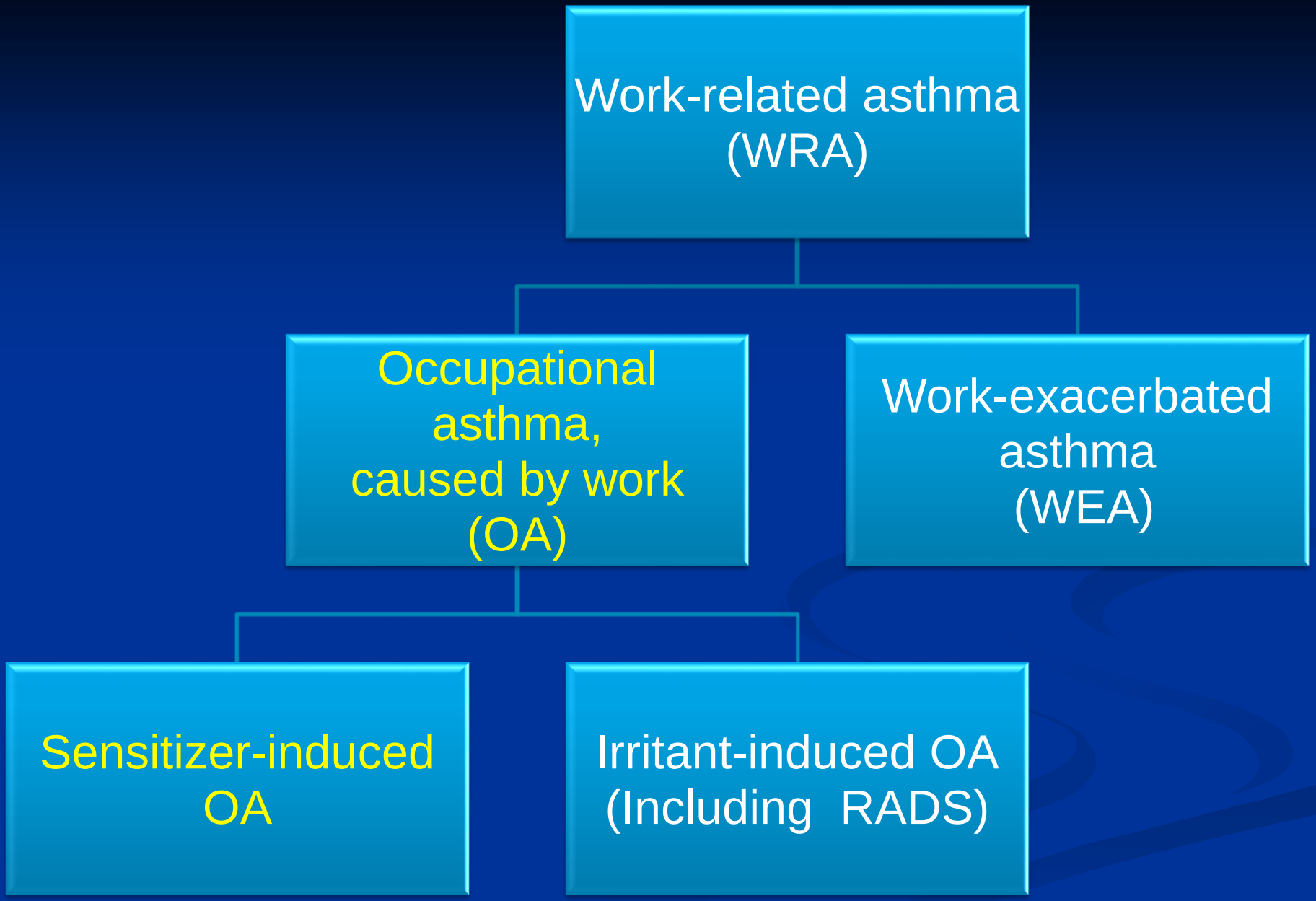
- RADS: new-onset asthma within 24 hours of a very high irritant exposure at work (similar effect can occur with exposures in home or community) - cases of IIA may not meet all RADS criteria
- Risk of new-onset asthma also seen in epi studies with chronic exposures to "lower level irritants" e.g., cleaning products, air fresheners, dusts and swimming pool chemicals.
  - True incidence/prevalence unclear.
  - Raise concerns with common exposures work and home.

Allergy 2014, EAACI Task Force Statement, Vandenplas et al

Le Moual et al., ERJ 2012. Domestic use of cleaning sprays and asthma in 683 females (EGEA study)



Effects reviewed in Siracusa et al : EAACI Task Force Statement, Asthma and exposure to cleaning products. Allergy. 2013;68:1532–1545



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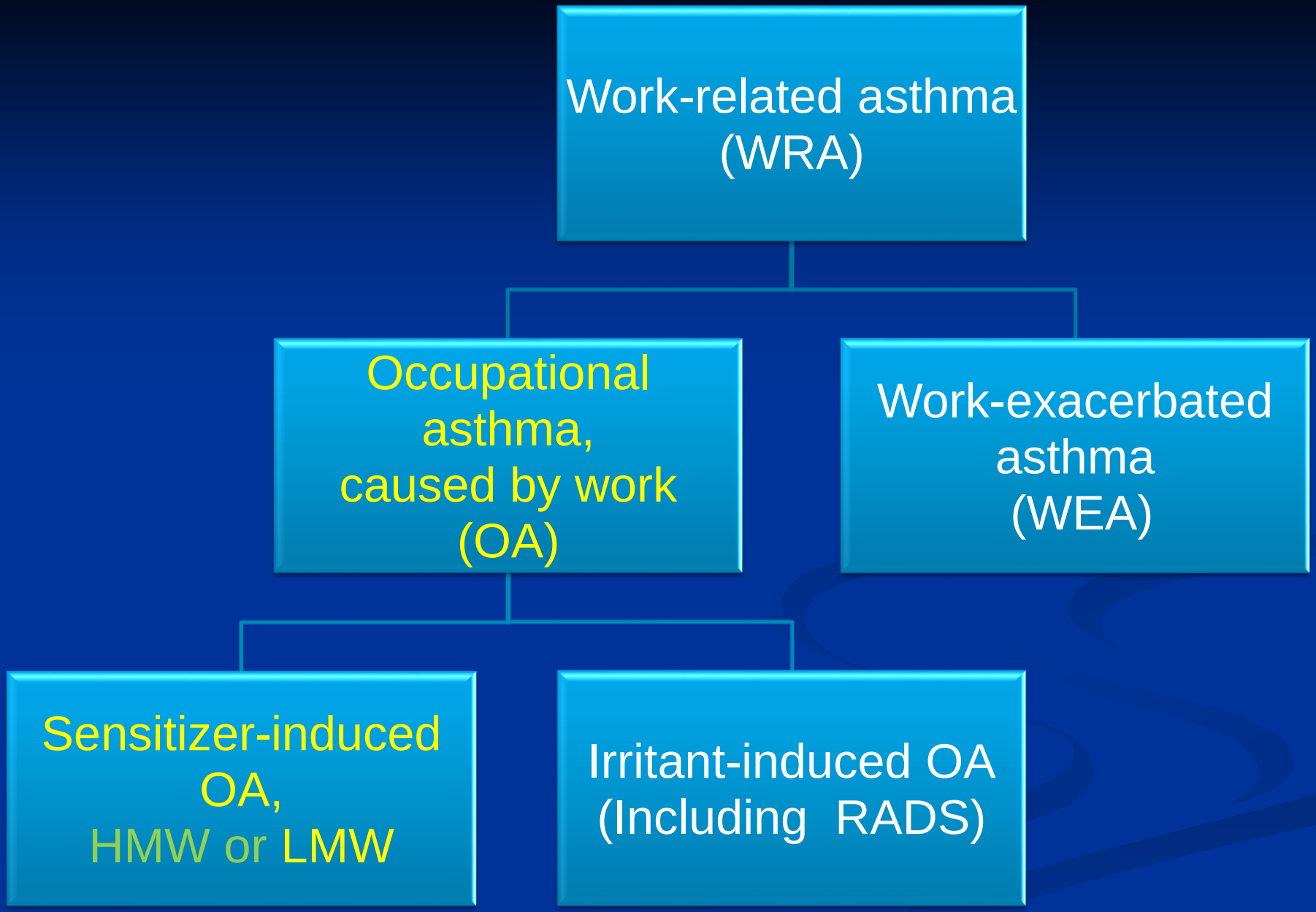

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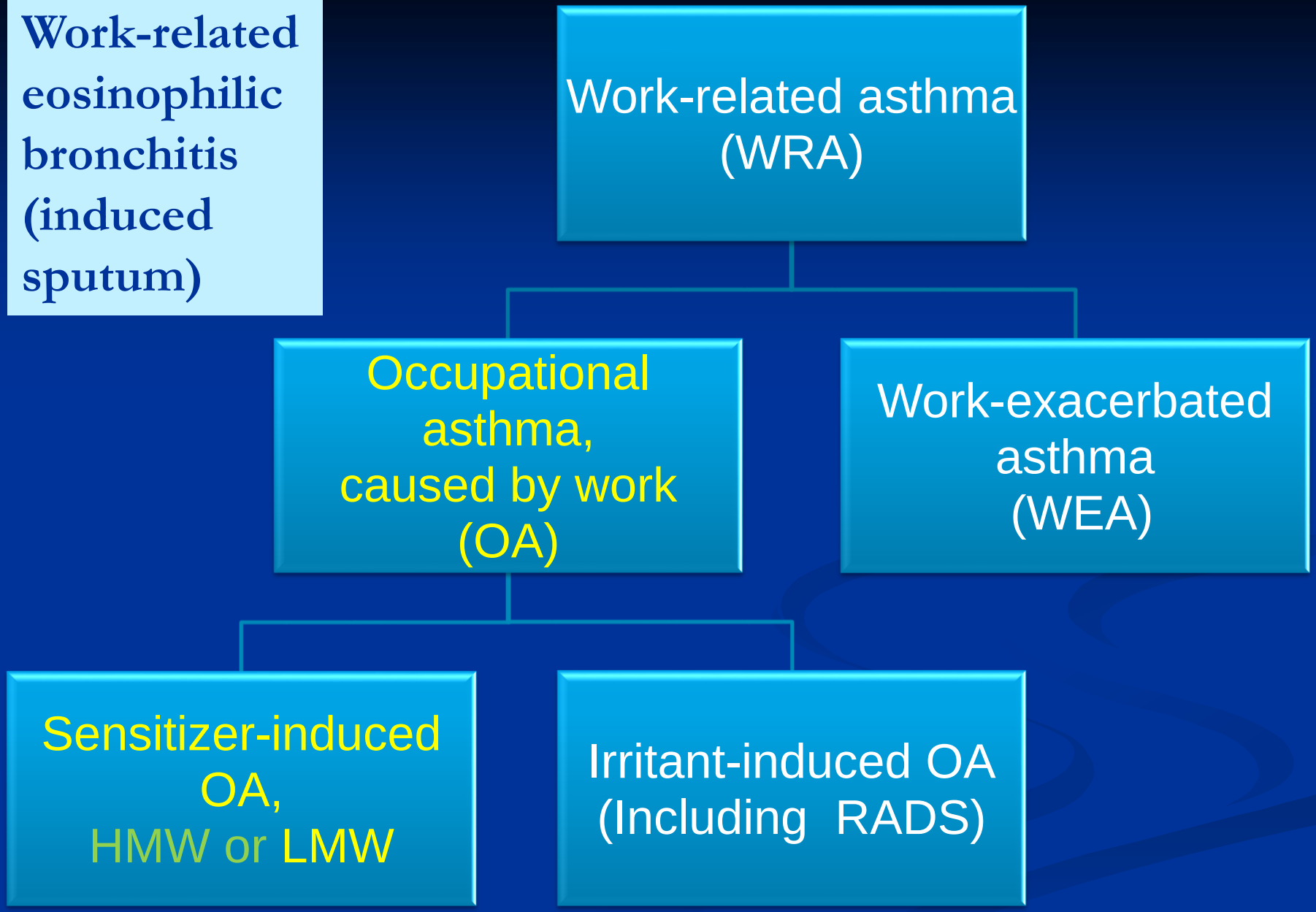
Work-related eosinophilic bronchitis (induced sputum)



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Occupational Asthma (OA)

OA= Asthma due to causes and conditions which are attributable to a particular workplace environment and not to stimuli encountered outside the workplace:

Sensitizer-induced (approx 95% in most case series)

a) High-molecular-weight
b) Low-molecular weight – chemical sensitizer

-features of a latency period

- only a minority of exposed workers affected (usually <5%, depending on exposure levels)

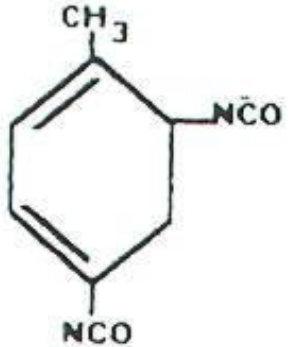
- once sensitized, small exposures exacerbate asthma

Sensitizer-induced OA

- Over 300 causes known (www.asmanet.com)
- Recent review: Baur, X. and P. Bakehe, *Allergens causing occupational asthma: an evidence-based evaluation of the literature*. Int Arch Occup Environ Health, 2013.
- LMW – reactive chemicals (usually 2 or more reactive side-chains)
- (HMW sensitizers – almost any inhaled allergen usually proteins – from animals, plants, fungi, enzymes)

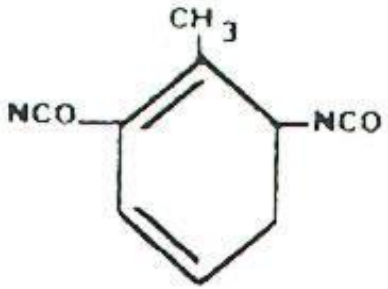
Diisocyanates?

DIISOCYANATES



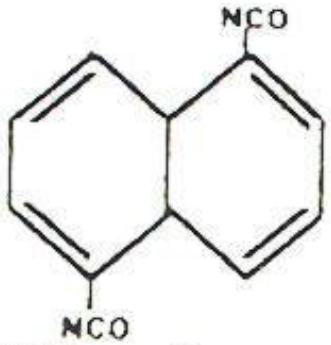
2,4 toluene diisocyanate

TDI



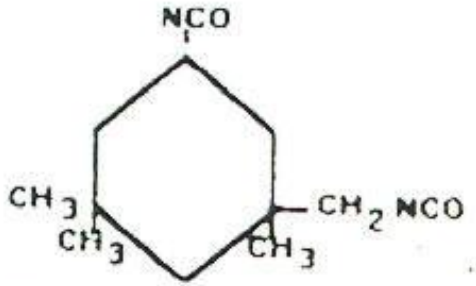
2,6 toluene diisocyanate

TDI



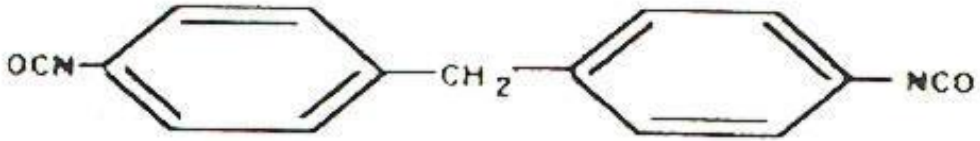
naphthalene diisocyanate

NDI



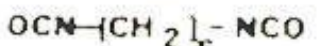
isophorone diisocyanate

IPDI



methylene diphenyldilsocyanate

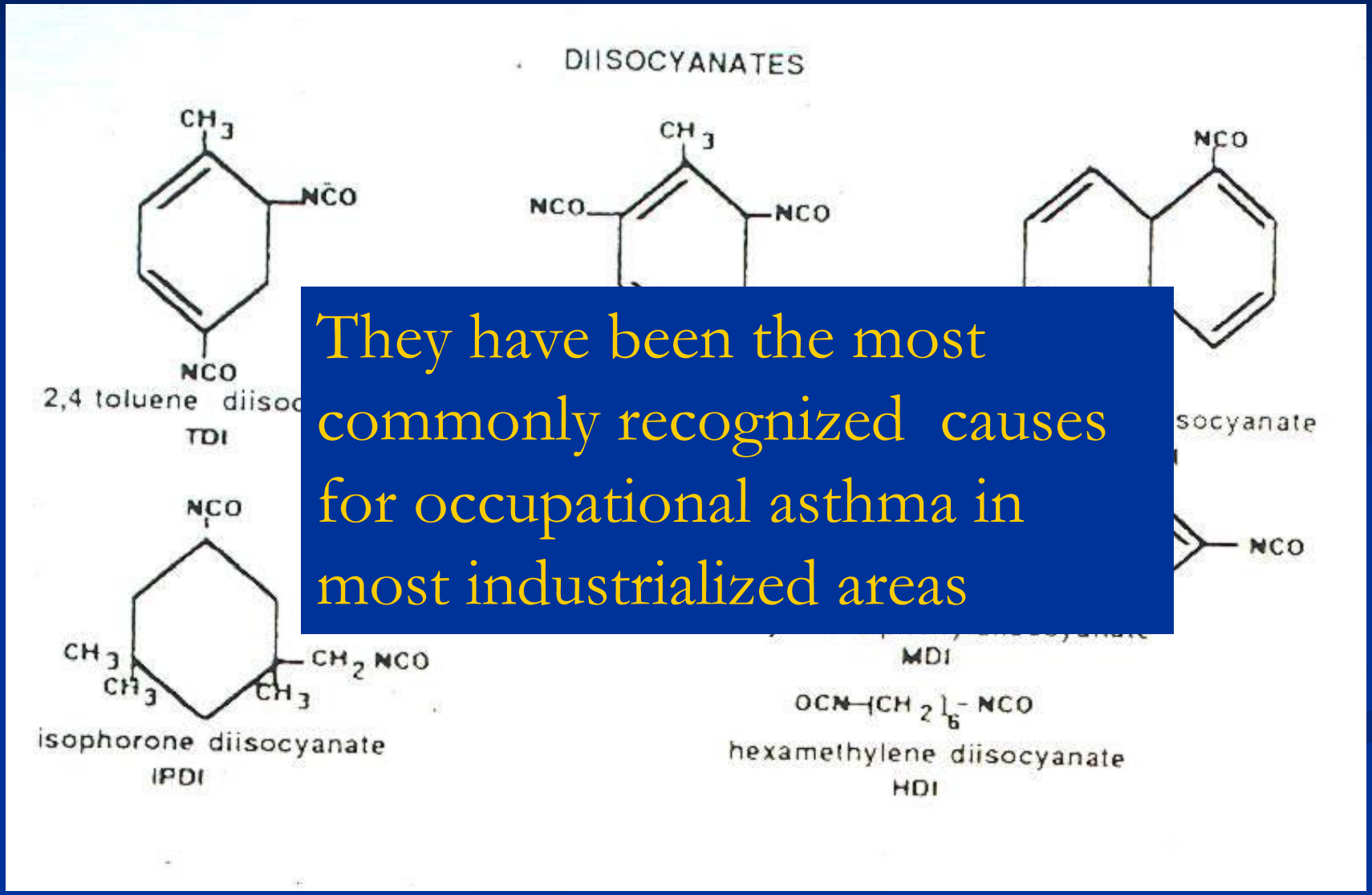
MDI



hexamethylene diisocyanate

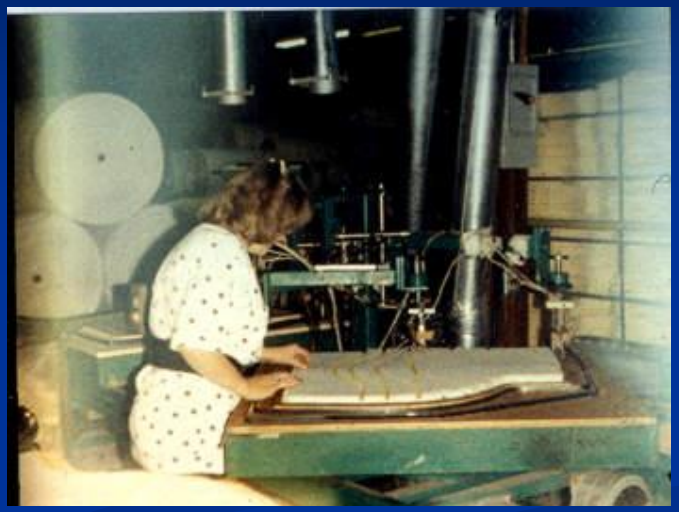
HDI

Diisocyanates?



They have been the most commonly recognized causes for occupational asthma in most industrialized areas

Diisocyanates are widely used in industrial areas – traditional uses



Also, glues, spray foam, foundry molds etc etc

Newer uses

- Spray foam insulation – MDI
  Assistants often wear no respiratory protection

- MDI use in production of oriented strand board (with softwood and phenolformaldehyde resin)
- Use in floor sealants (MDI)
- Potential also for bi-stander or consumer exposures

Sensitizer-induced OA – some other common LMWt causes/exposures (several could also be relevant for consumers)

- Common causes
  - Colophony
  - Plicatic acid
  - Amines
  - Acid anhydrides
  - Aldehydes
  - Quaternary ammonium compounds
  - Pharmaceutical products
  - Metal salts, e.g., complex Pl salts
- Exposures
  - Soldering
  - Red cedar workers
  - Reactive chemicals
  - Plastics, coatings
  - Hospital workers, e.g., cleaning endoscopes
  - Cleaners
  - Manufacturers, health care workers

….new causes each year

- eugenol, - hairdresser
- Rhodium salts – electroplating
- Limonium tataricum – farmer
- potassium tetrachloroplatinate - production of cytotoxic drugs
- EDTA - cleaners

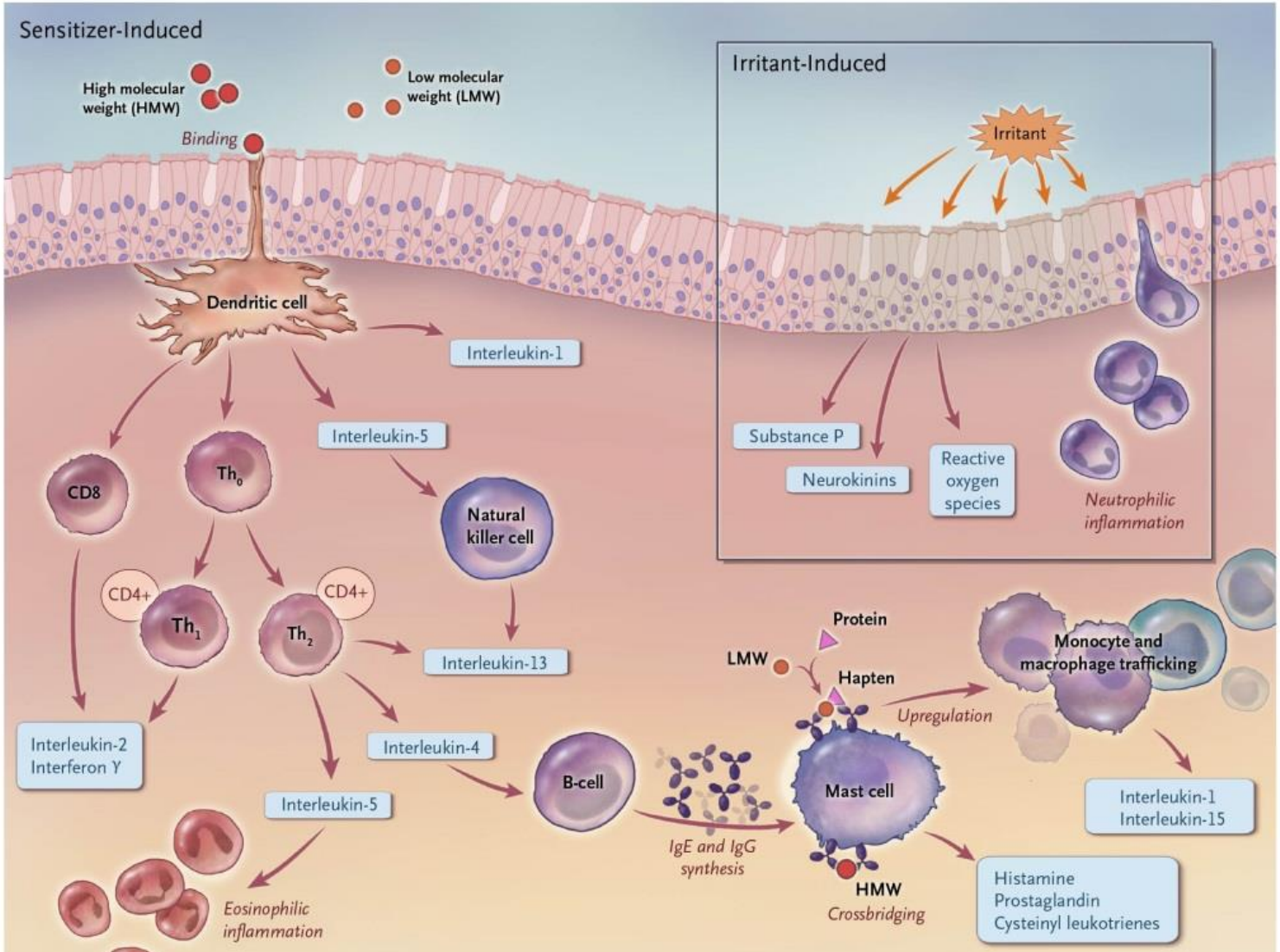
Mechanisms of sensitizer-induced OA

- IgE antibody associated mechanisms
  - Most clearly demonstrated for HMW agents (allergens, usually proteins)
  - A few LMW sensitizers are associated with specific IgE, eg complex Pl salts, acid anhydrides, diisocyanates

- Non-IgE –associated mechanisms
  - Most LMW sensitizers – mechanisms unknown
  - More likely associated with isolated late or dual asthmatic responses
  - May have eosinophilic or neutrophilic inflammatory changes

1. Mechanisms of OA

(from Occupational Asthma– medical progress. Tarlo SM, Lemiere C. Occupational Asthma. N Engl J Med 2014; 370:640-649.)



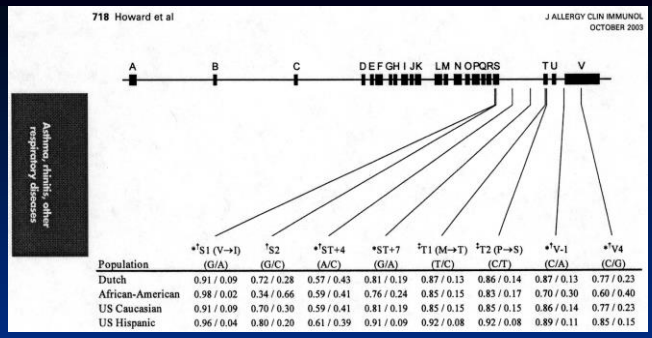
Risk factors

- Exposure features – airborne exposures
  - higher inhaled exposures have higher risk
  - - skin exposures might sensitize
- Host factors – genetic

  - smoking

  - atopy

Genetic



Difficulties

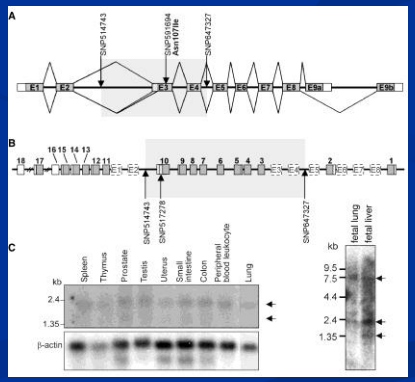
- May vary with specific sensitizer
- Can be more than one mechanism per sensitizer
- Small numbers
- Need proven phenotype
- Need control group with similar exposures, and asthma control group
- Likely polygenic

Diisocyanate genetic associations

- Variants in antioxidant genes and associated with genes that control catenins (involved in cell-cell adhesions) and genes related to TH2 responses.

(Bernstein et al Annals of Allergy, 2006

Bernstein et al JACI 2011)



Clinical presentation

- **Development of asthma symptoms in a worker: episodic dry cough, wheeze, retrosternal chest tightness, shortness of breath**
- **Symptoms are associated with work exposure: timing with work exposures may be immediate, late or dual (i.e. at work or after work)**
- **Typically improve on weekends off work and/or on holidays away from work and worsen when back at work**
- **± Exposure to a known sensitizer at work**

Other conditions can mimic asthma, and ~50% of specific challenges in those with suspected OA are negative emphasizing need for objective tests.

Diagnostic pathway

(from ACCP Consensus 2008)

- In patients with a hx of possible OA:
- Confirm a diagnosis of asthma objectively
- Review MSDS and any other exposure information
- Skin test where feasible
- PEFR and Methacholine responses work and off work, considering possible confounding factors
- Add induced sputum if available
- Consider specific challenges if available, especially if the diagnosis is in doubt

Similar suggestions from European consensus documents

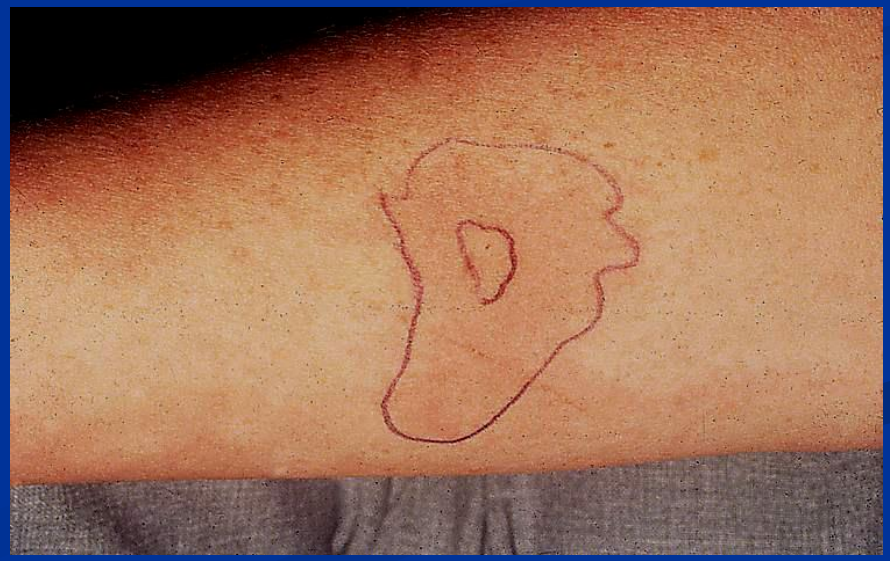
Objective diagnosis of asthma

- FEV1 pre/post bronchodilator
- Methacholine/histamine challenge
  - sensitive for diagnosis of asthma if patient is still working and symptomatic
  - positive findings do not confirm that asthma is work related
  - negative findings do not exclude OA if patient not had recent exposer to the sensitizer
  - occasional reports of normal responsiveness in diisocyanate-OA

Skin tests/ immunologic tests

- Limited skin test extracts commercially available for occupational allergens, especially LMW sensitizers
  - Few are standardized
  - Immunologic sensitization is more common than OA in exposed workers
  - Useful e.g.,for complex

  Pl salts

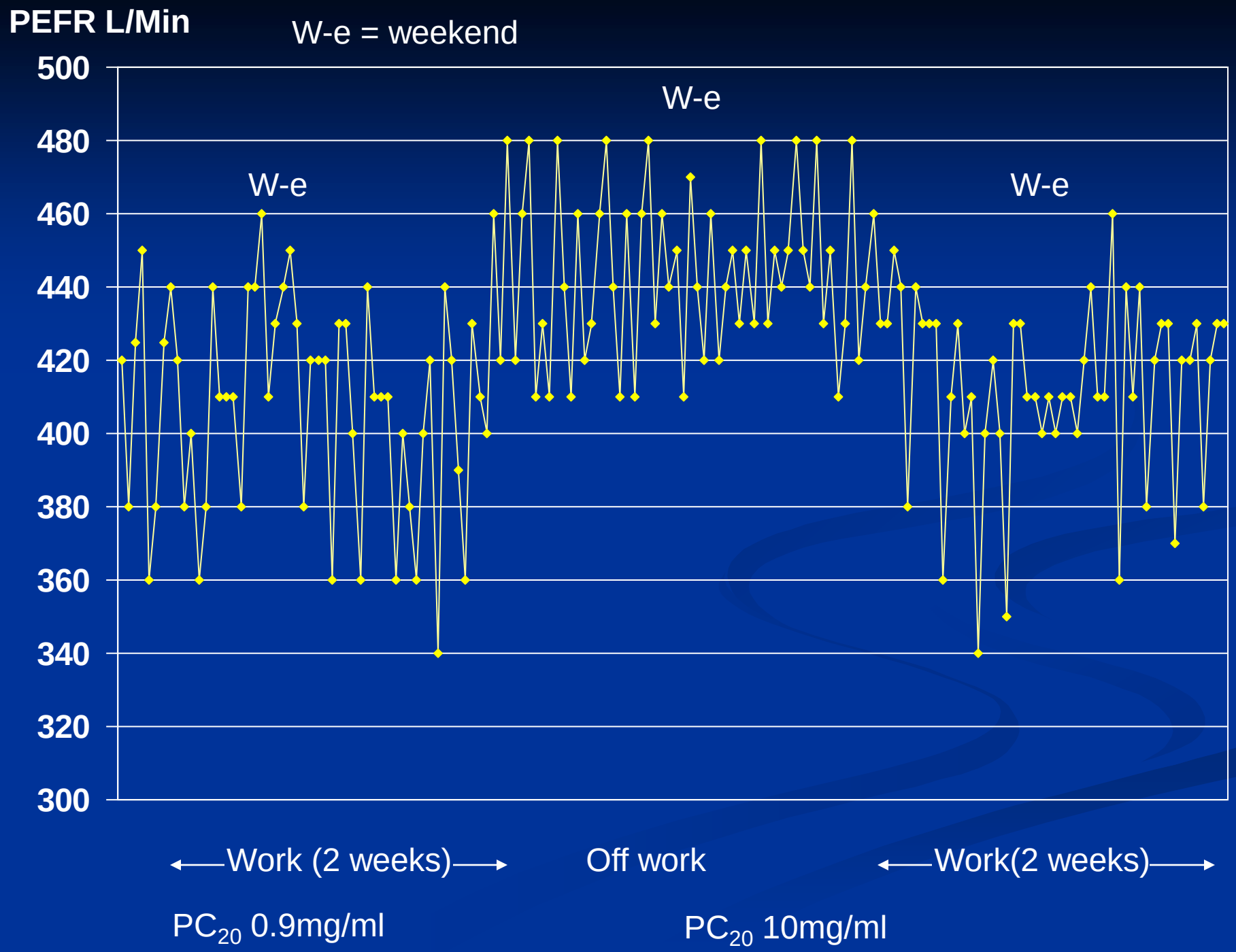


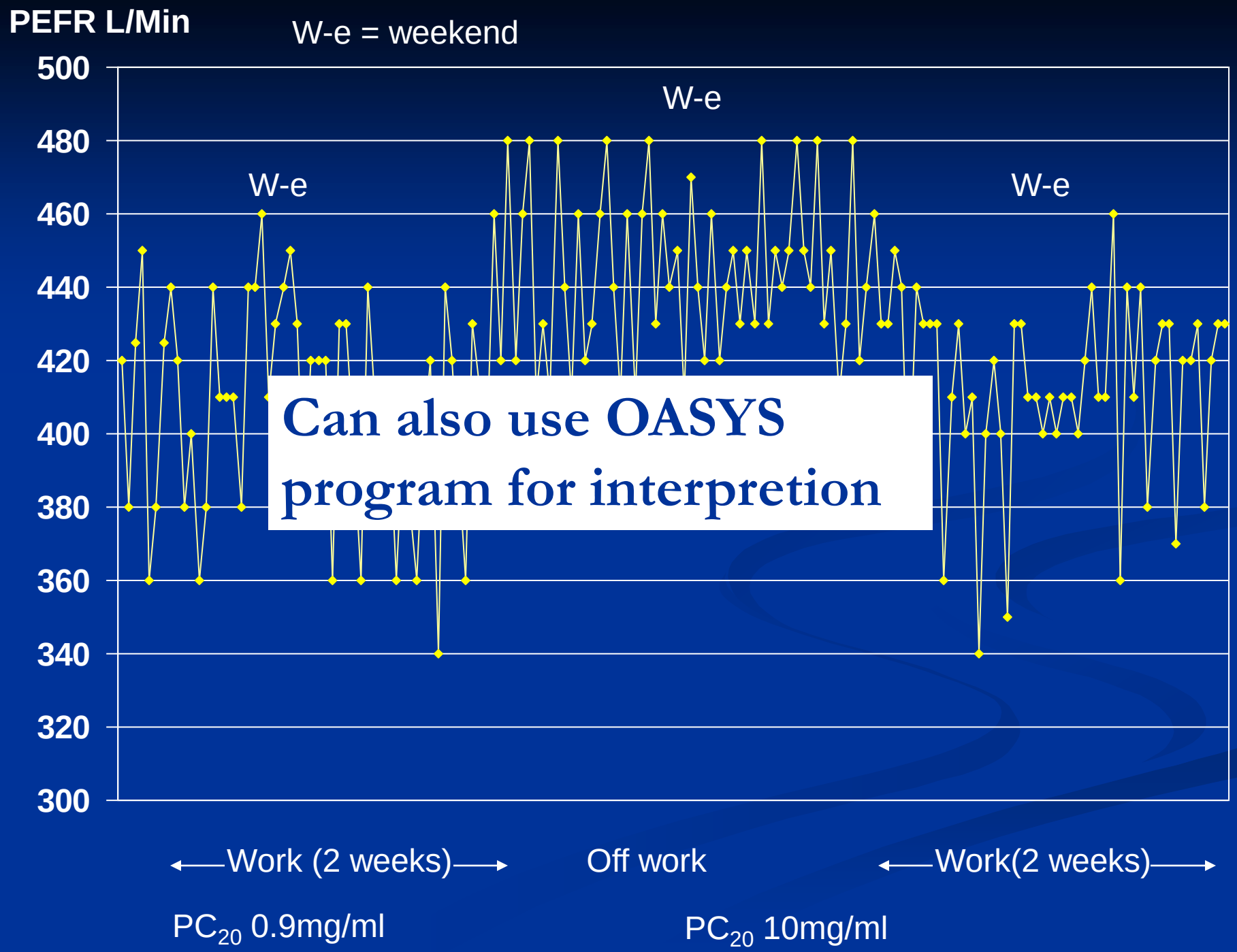
In-vitro immunologic tests

- In-vitro immunologic tests only reliable in a few centres and for a few LMW agents.
  - Limited sensitivity or specificity for low molecular-weight sensitizers at present, e.g. diisocyanate (low sensitivity but good specificity), acid anhydrides in research labs.

Objective documentation of work-related changes in asthma

- Serial peak expiratory peak flow monitoring (PEFR) with sx and med diary
  - **at least 4x per day, several weeks at work and off work**
  - **requires careful patient instruction and compliance**
  - **effort-dependent**
  - **no generally accepted objective criteria for interpretation**
  - **by themselves, positive results do not distinguish OA from work-aggravation of asthma**


PEFR L/Min
W-e = weekend
500
480
460
440
420
400
380
360
340
320
300
W-e
W-e
W-e
Work (2 weeks)
Off work
Work(2 weeks)
PC20 0.9mg/ml
PC20 10mg/ml


PEFR L/Min
W-e = weekend
500
480
460
440
420
400
380
360
340
320
300
W-e
W-e
W-e
Can also use OASYS program for interpretion
Work (2 weeks)
Off work
Work(2 weeks)
PC20 0.9mg/ml
PC20 10mg/ml

Peak flow interpretation confounders

- Inadequate technique
- Poor compliance with recordings
- Fabrication of results
- Intercurrent cold or non-occupational exposure to asthma triggers
- Work exposures not representative of those causing symptoms
- Changes masked by medications

Any of these may need further repeat PEFS

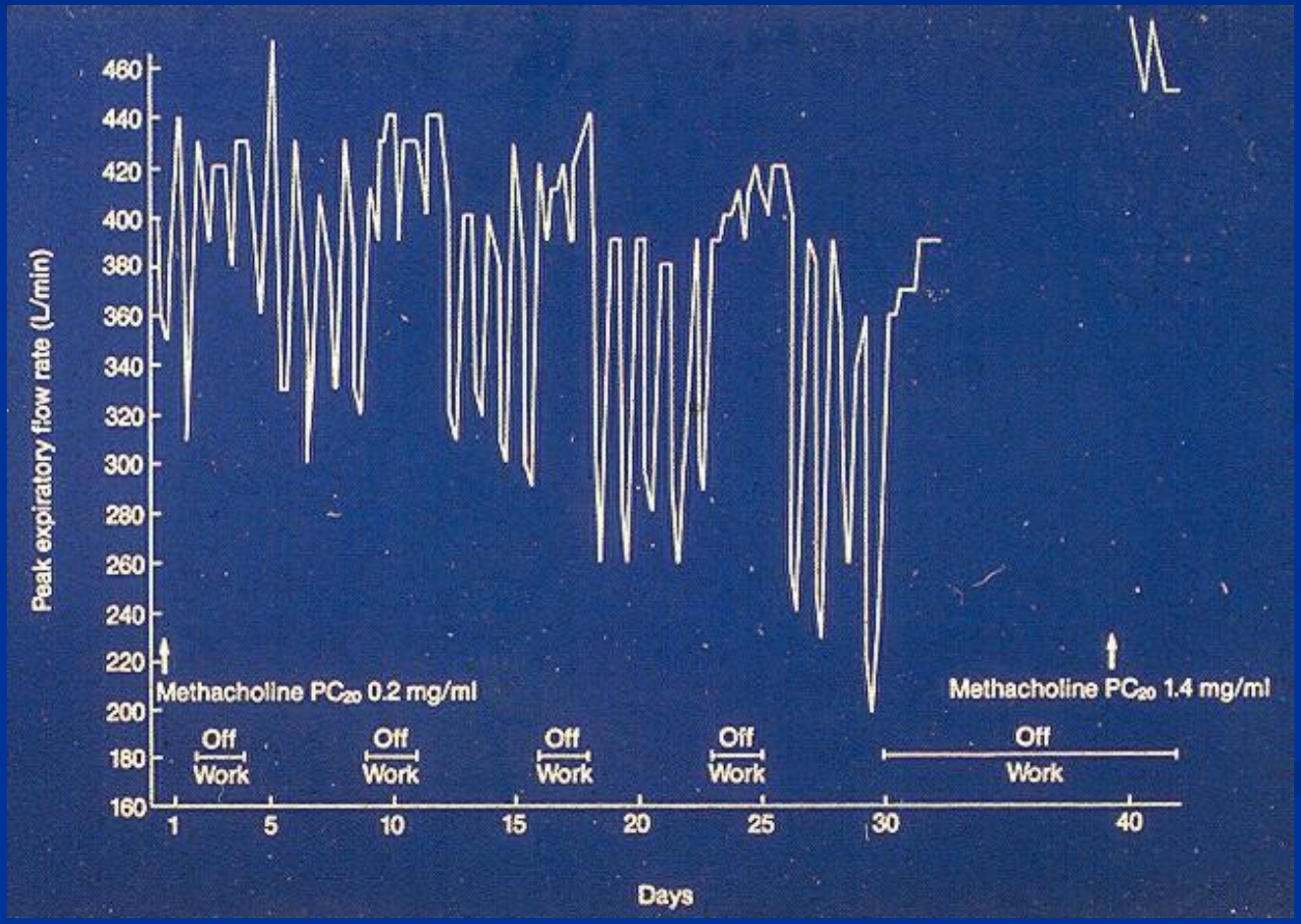
Methacholine challenges

- Serial inhalation of increasing concentrations of nebulized methacholine
- Spirometry pre- and post- each dose.
- Test is stopped with at least a 20% drop in FEV1
- PC20 calculated (lower = more hyper-responsive, cut-off 8mg/ml, borderline 4-16mg/ml)
- A 3-fold or greater worsening in PC20 at work is significant (if there are no confounding factors)

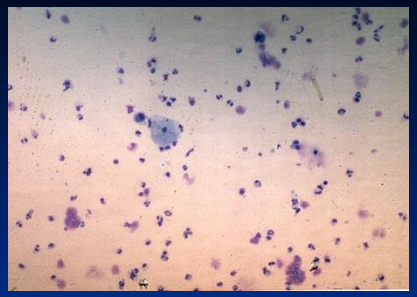
Methacholine challenge

- A single test is useful to diagnose asthma – with current asthma symptoms/exposures
- Paired tests (one at the end of a work week and one after a period off work) is useful to assess work-related changes (e.g. OA)
- Confounders: lab technique, intercurrent colds or other non-occupational exposures, insufficient time away from work exposure

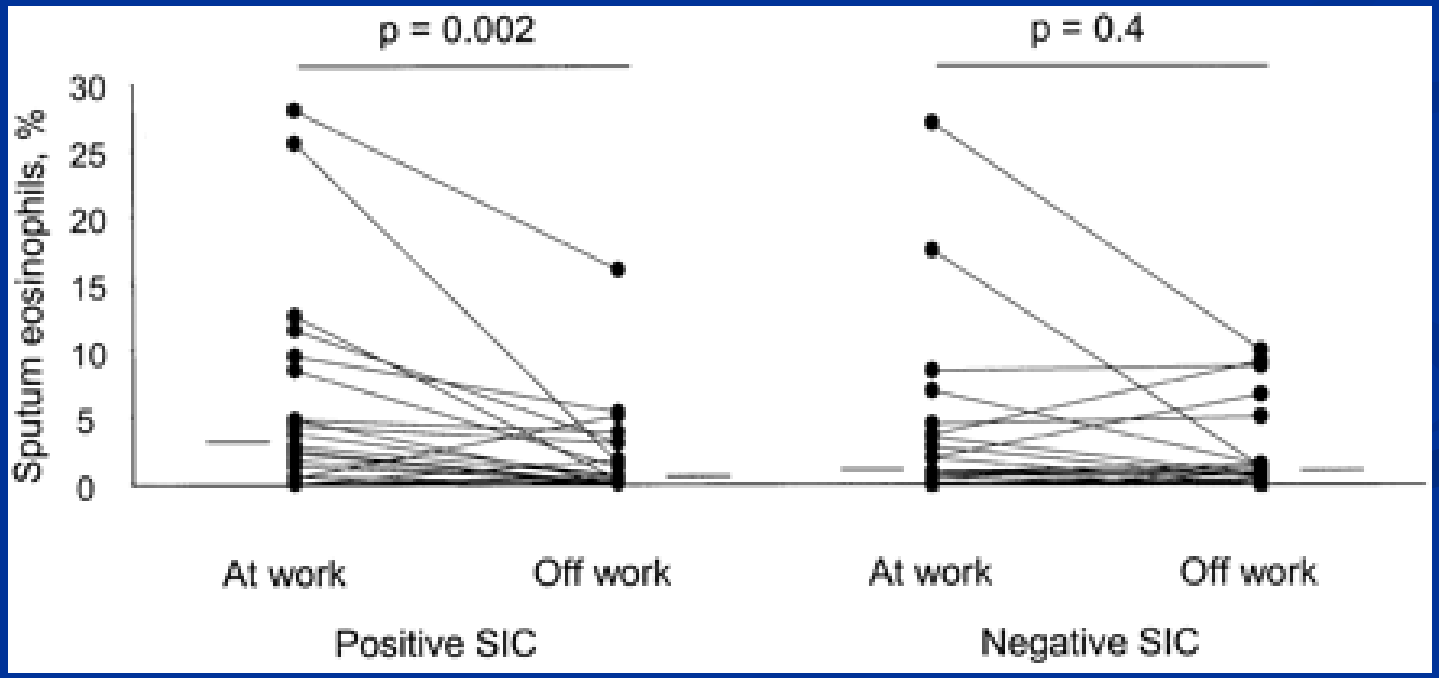
Peak flows and methacholine responses



Induced sputum eosinophilia as a diagnostic test (Girard et al AJRCCM '04)



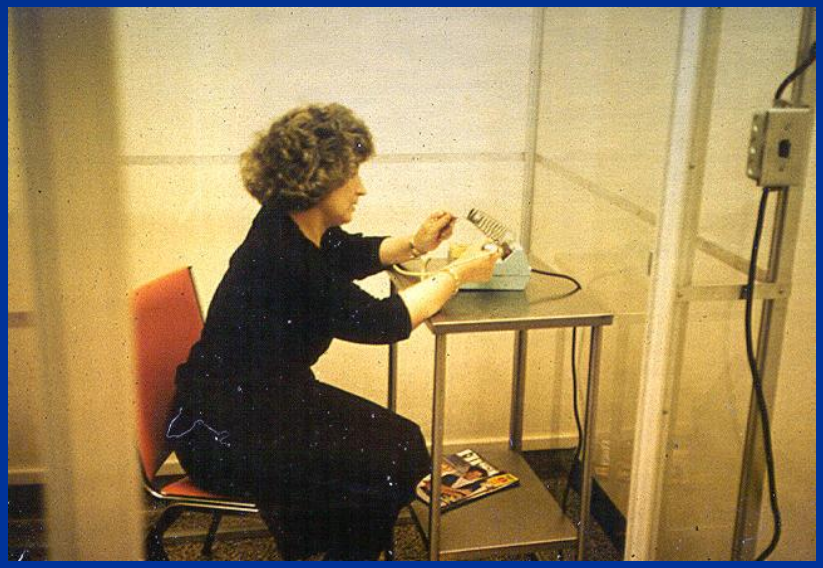
Induced sputum working and off work (Confounders include inhaled steroid use, URIs and co-incidental allergen exposures)

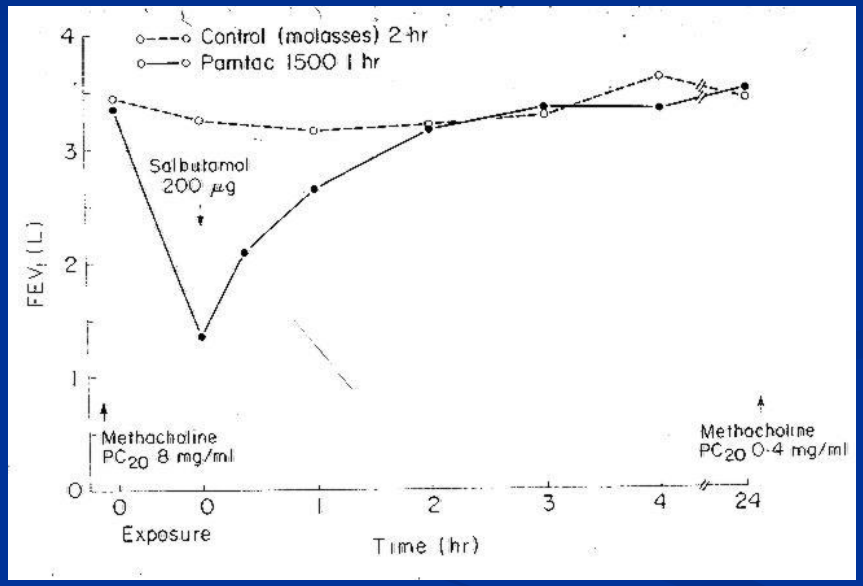


Specific laboratory challenges

- Labour-intensive and expensive
- Require specialized facilities with exposure-monitoring as well as prolonged response-monitoring
- Although they have been referred to as a "gold standard", there are potential false positive and false negative responses
- In some countries, medicolegal concerns regarding positive responses have also limited use

Laboratory challenges





Recent European Consensus: ERJ 2014, Vandenplas et al

Management and outcome of OA

- Cochrane review 2011, and a meta-analysis (Vandenplas et al ERJ 2011) both found better medical outcome with removal from exposure and trend to less benefit from reducing exposure
- Asthma improvement is best with early diagnosis when asthma is relatively mild and the worker is removed from further exposure
- Significant socio-psycho-economic impacts are common after the diagnosis, even with workers' compensation support
- Other co-workers should be considered with a "sentinel" diagnosis, to identify cases and prevent others

Prevention

Primary – avoidance

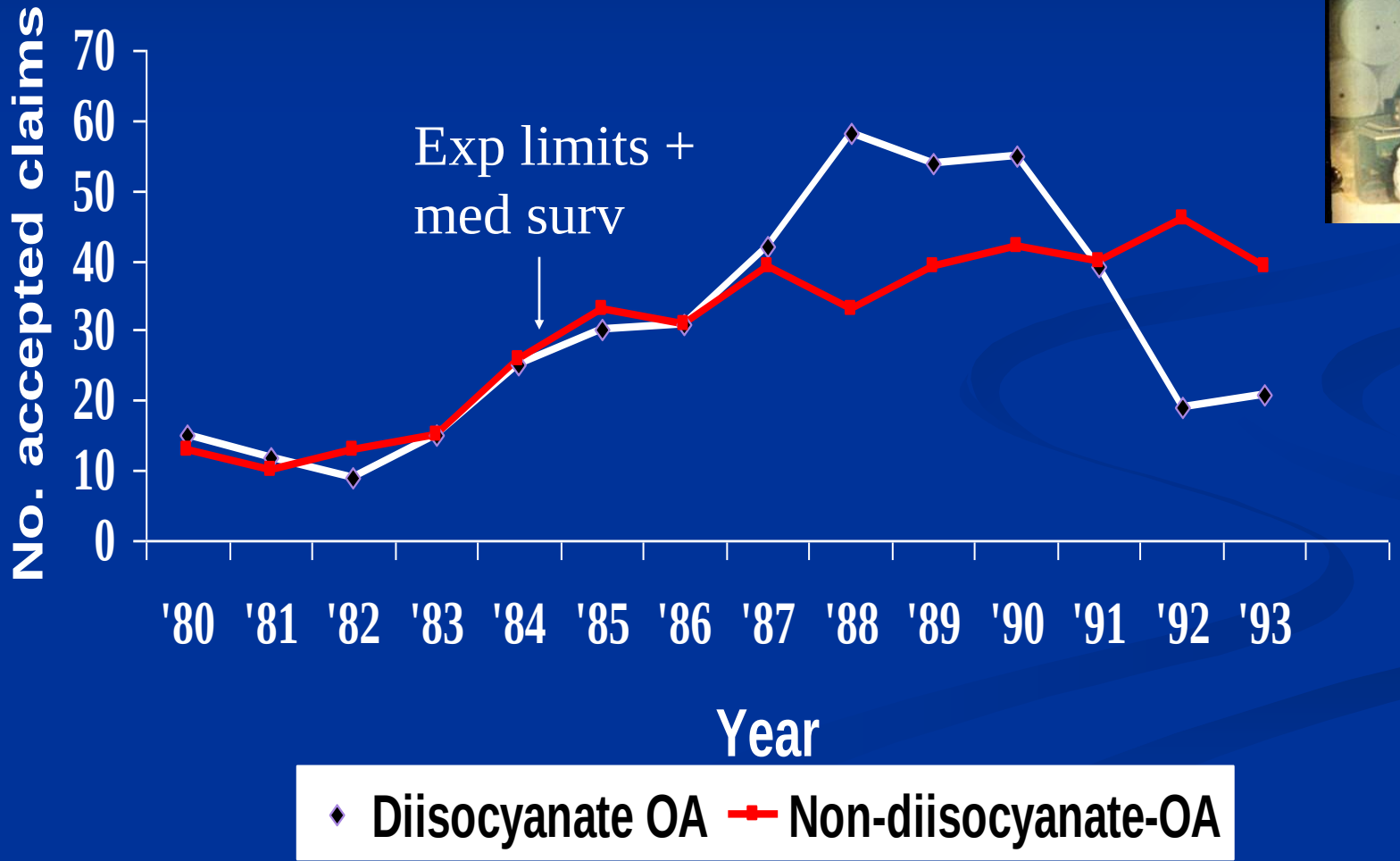
Secondary – early detection

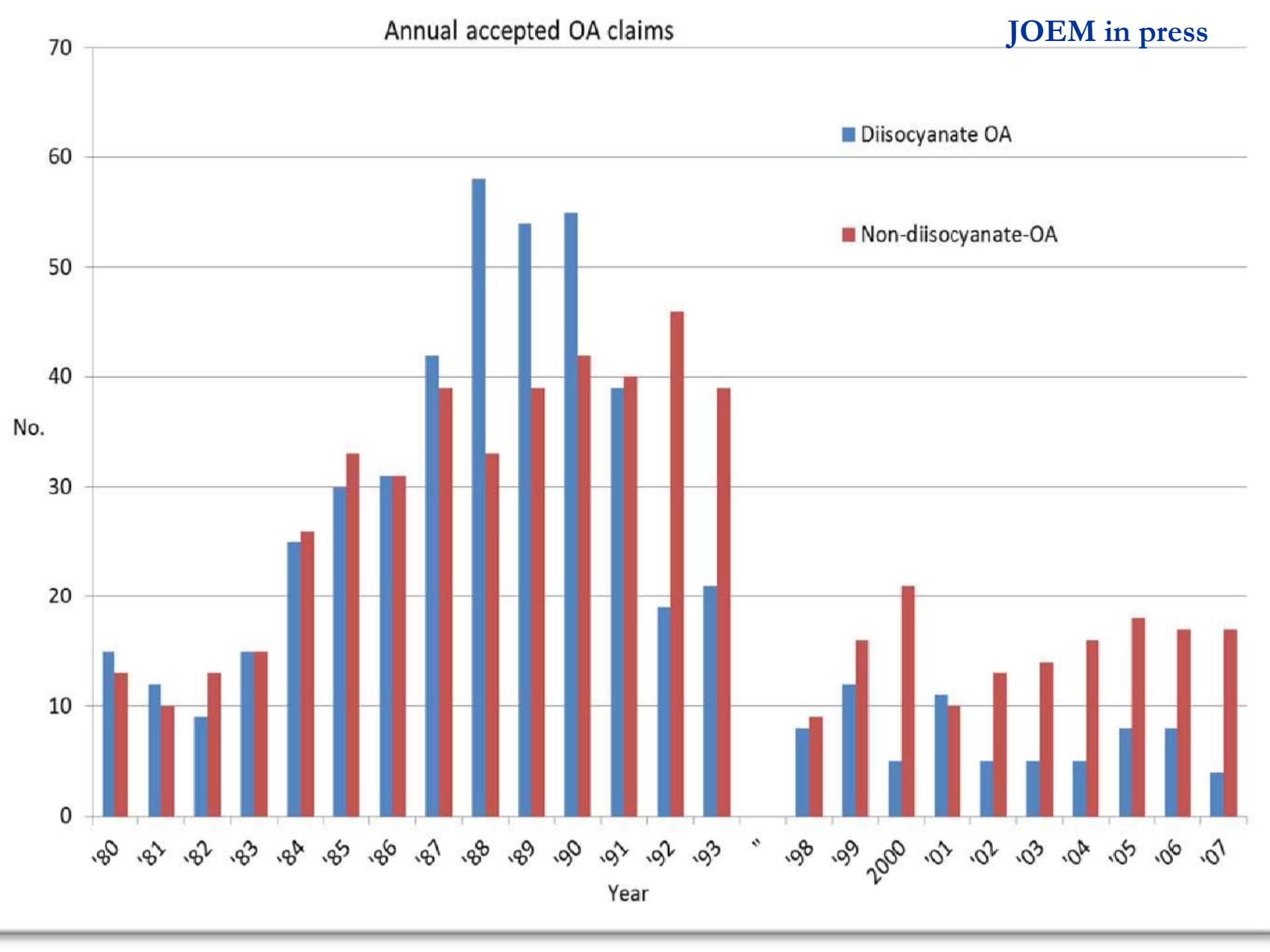
Best outcome for sensitizer-induced OA is with early diagnosis and removal from exposure when asthma is relatively mild (medical surveillance, early identification by worker/ physician)

e.g., web-based tool for Canadian workers at http://lung.ca/workrelatedasthma/

Tertiary – optimal management of cases

Ontario accepted claims for diisocyanate-induced asthma and accepted asthma claims from other causes, by year of onset (OEM 2002)




Annual accepted OA claims
JOEM in press
Diisocyanate OA
Non-diisocyanate-OA
No.
Year
70
60
50
40
30
20
10
0
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Summary/Key Points

- Suspect occupational asthma (OA) in any worker with new-onset asthma
- Investigate early and thoroughly while the patient is still working
- If a diagnosis of OA is confirmed, avoid further exposure, treat asthma, consider the co-workers