

# **WORK-RELATED INTERSTITIAL LUNG DISEASE: BEYOND PNEUMOCONIOSIS**

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**I HAVE NOTHING TO  
DISCLOSE**

**DISCLOSURES**

**SUPPORTING  
MATERIALS**

- talk available online

[http://carlreynolds.net/work-related-  
ild-talk-sanfran-march-2017/](http://carlreynolds.net/work-related-ild-talk-sanfran-march-2017/)

- additional material available

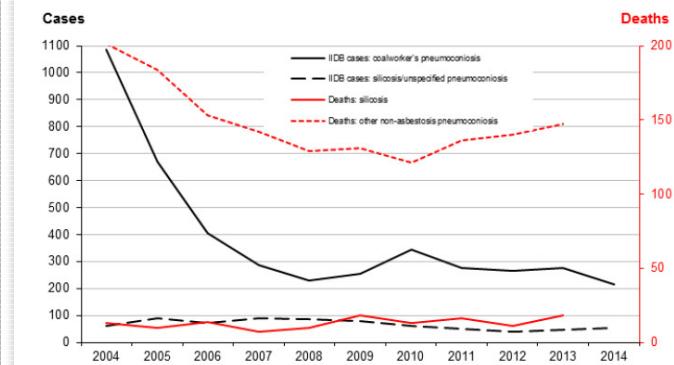
[https://github.com/drcjar/work-related-  
ild-talk-sanfran-march-2017](https://github.com/drcjar/work-related-ild-talk-sanfran-march-2017)



Kellingley colliery workers

# BEYOND PNEUMOCONIOSIS?

Figure 1: Pneumoconiosis (excluding asbestosis) in Great Britain, 2004-2014



HSE Pneumoconiosis figures

# **WHAT IS WORK-RELATED ILD?**

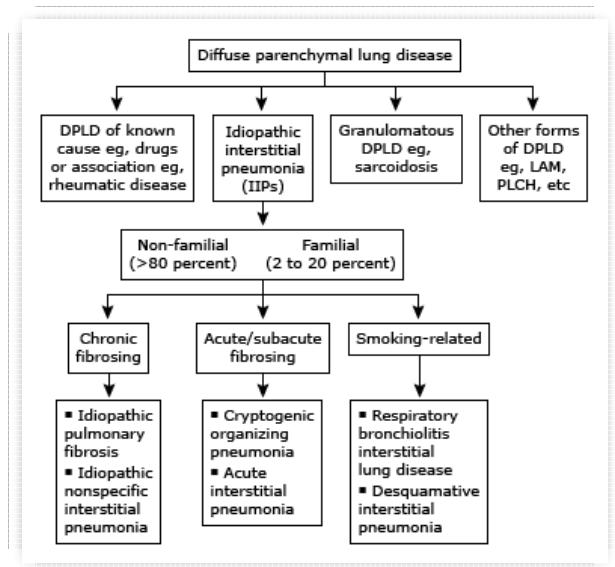
## **DEFINITIONS**

**WORK-RELATED  
DOESN'T MEAN  
OCCUPATIONAL**

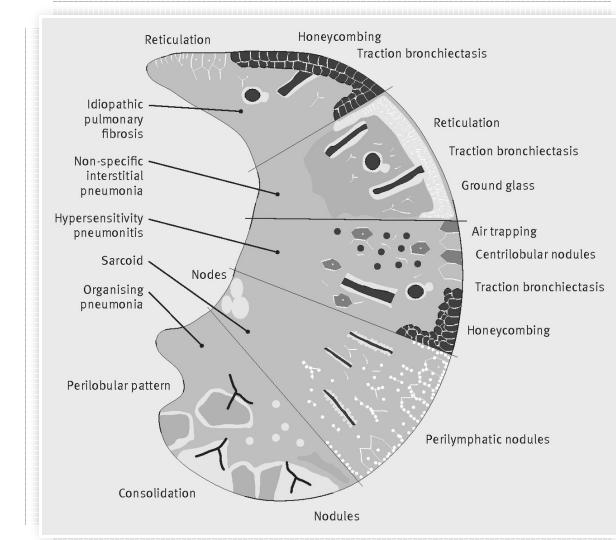
- occupational diseases are primarily caused by exposure to risk factors arising from work
- work-related diseases have multiple causes; factors in workplace may play a role (WHO 2017)

# DIFFUSE PARENCHYMAL LUNG DISEASE IS CONFUSING

- ILD or DPLD
- heterogeneous group of disorders characterised by inflammation and fibrosis of the interstitium
- interstitium refers to tissue between the pulmonary alveoli and the bloodstream
- in practice disease can also involve airway



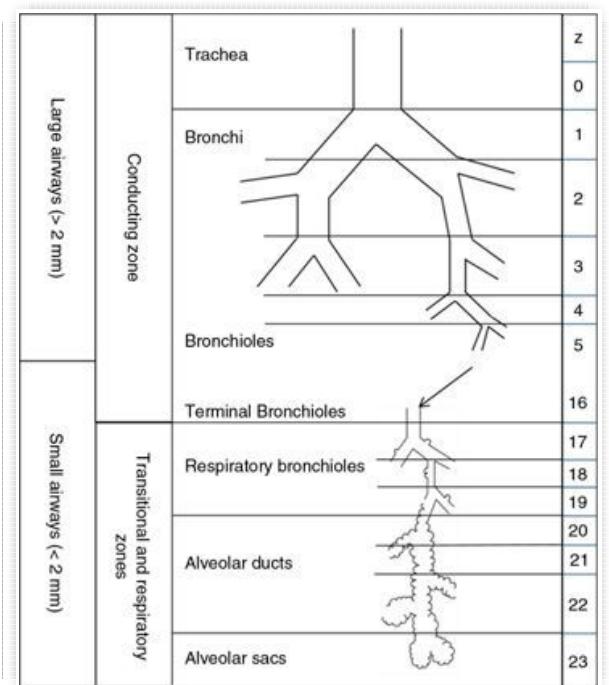
An ILD Taxonomy (7)



CT appearance ILD (5)

# LUNG PHYSIOLOGY AND INTERSTITIAL EXPOSURES

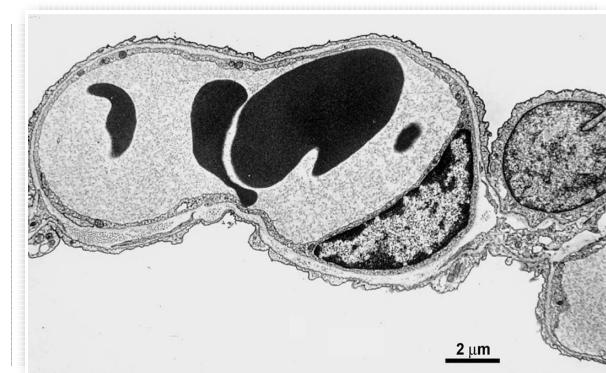
- Diffusion of gases across blood-gas barrier is passive and governed by Fick's Law.



Weibel model

$V_{gas} (\text{diffusing})$  is proportional to  
Area/Thickness \* D(diffusion constant) \*  
( $P_1 - P_2$ )

D = solubility / root of the molecular weight of the gas



Blood gas barrier

- 2 μm across (for ref sheet of paper is 50 μm, 1/20th of a mm or 0.05mm)
- 25x thinner than that. 300 million alveoli
- Each alveoli is 0.0042 mm<sup>3</sup> (a grain of sand is 0.06 mm<sup>3</sup>, so an alveoli is about 14 times smaller)
- Surface area of a tennis court

TV 500ml, dead space 150ml, RR 15/min,  
 $350\text{ml} \times 15 = \text{approx } 5\text{L/min} \rightarrow 7200\text{L/day}$

# **AMPLE OPPORTUNITY FOR SUFFICIENTLY SMALL PARTICLES TO MEET THE INTERSTITIUM**

**ILD INCIDENCE  
30/100,000 PER YEAR  
AND PREVALENCE  
70/100,000  
(APPROXIMATELY)**

## **WORK-RELATED ILD**

- precise population prevalence and incidence of ILD hard to establish (classification problems, limitations of registry and insurance claim data)
- best historic estimate of incidence 30/100,000 per year, prevalence 70/100,000 (10)
- IIP most common, IPF 1/3rd of cases, more common in men

**15-20% OF ILD DUE TO  
OCCUPATIONAL AND  
ENVIRONMENTAL  
EXPOSURES**

**AETIOLOGIES ARE  
MANY**

- common: include organic antigen, isocyanates, silica, cadmium, diacetyl, asbestos
- less common: cobalt, rare earths, plutonium

**RELATIONSHIP  
BETWEEN AETIOLOGIC  
AGENT AND  
PATHOLOGICAL  
PATTERN OFTEN NOT 1:1**

Pathology	Common Causative Exposures	Rare Causative Exposure
Granulomatous pulmonary inflammation	Hypersensitivity pneumonitis (organic antigen, isocyanates, pyrethrum, anhydrides), beryllium	Cobalt, aluminum, titanium, zirconium, talc
Usual interstitial pneumonia (UIP)	Asbestos, mixed dust, agents that cause hypersensitivity pneumonitis	
Desquamative interstitial pneumonia (DIP)	No common exposures	Cobalt, wollastonite, attapulgite, sepiolite, mica, kaolin, rare earths, aluminum
Nonspecific interstitial pneumonia (NSIP)	Hypersensitivity pneumonitis (organic antigen, isocyanates, pyrethrum, anhydrides)	Cobalt, aluminum, plutonium, asbestos, talc
Organizing pneumonia	NOx (silo-filler's lung)	Coal and silica can rarely cause a diffuse interstitial fibrosis similar to fibrotic NSIP
Acute interstitial pneumonia (AIP) (pathology = diffuse alveolar damage)	Irritant inhalational injury—NOx, SOx, cadmium, beryllium, chlorine, acid mists, etc.	Spray painting textiles—Acramin FWR.
Giant cell interstitial pneumonia (GIP)	Cobalt	
Pulmonary alveolar proteinosis	No common exposures	High level exposure to silica, titanium, or aluminum dust
Constrictive bronchiolitis	Flavoring workers (diacetyl), NOx, SOx, chlorine gas	

NOx indicates nitrogen oxide species; SOx, sulfur oxide species.

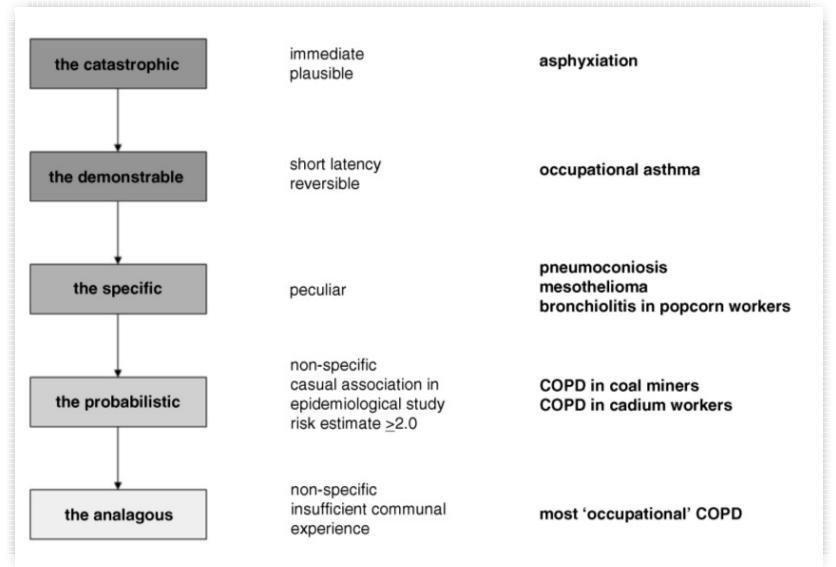
### Pathologic Patterns and Causes (4)

**ATTRIBUTION  
FREQUENTLY  
NON-TRIVIAL**

## CLINICAL FEATURES

- Respiratory symptoms with an appropriate occupational or environmental exposure history
- Host-factor (e.g adaptive immune response, systemic) vs exposure factor dominant presentations (local inflammatory response)
- Investigations

**NEW WORKPLACE AND  
ENVIRONMENTAL  
EXPOSURES ALL THE  
TIME**



A hierarchy of attribution in occupational lung diseases (11)

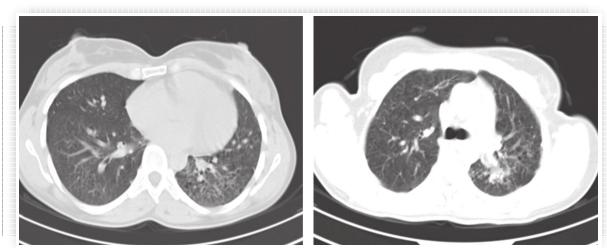
**I'LL COVER THREE  
CHEMICALS THAT  
CAUSE DISEASES  
WHERE THE HARD  
WORK OF  
ATTRIBUTION HAS**

**I CAN'T COVER IT ALL**

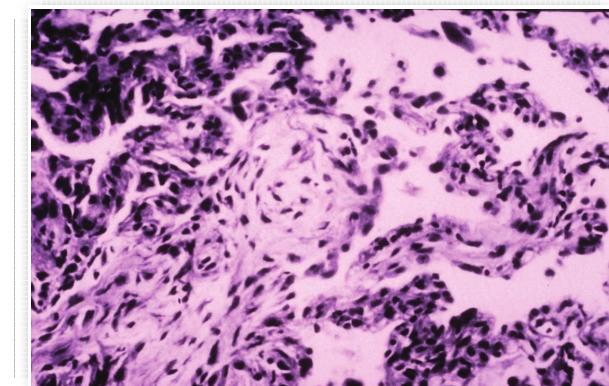
**ALREADY BEEN DONE**

1. Ardystil
2. Indium tin oxide
3. South Korean lung

# ARDYSTIL

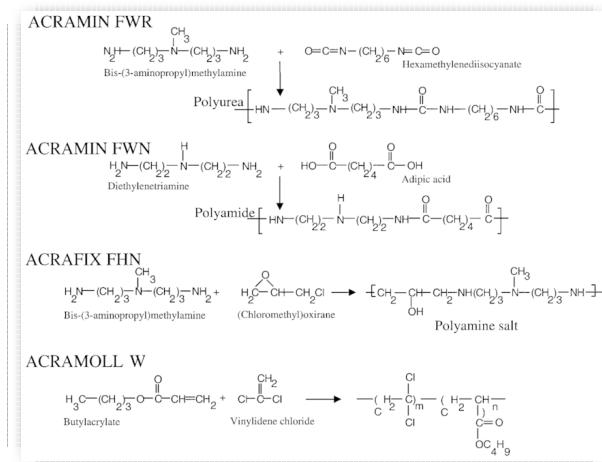


Chest computed tomography image of Acramin (Ardystil) dye-associated organising pneumonia. Two patients with dyspnoea, reduced FEV1 and FVC. 2005. (1)



Cryptogenic organising pneumonia pattern in a lung biopsy of an Acramin (Ardystil) dye-exposed worker. (1)

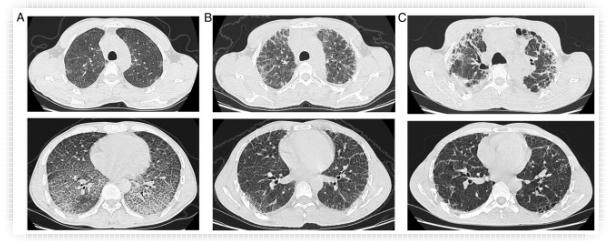
- April 1992, two young women who worked at a textile factory were treated for interstitial lung disease and severe pulmonary insufficiency in Valencia.
- Prompted investigation of all textile factories using same spraying technique in the area
- 257 employees identified. 22 cases who met radiological and biopsy criteria for organising pneumonia. Six fatal cases.
- Epidemiological analysis revealed COP-like response due to chemical Acramin (trade name Ardystyl)



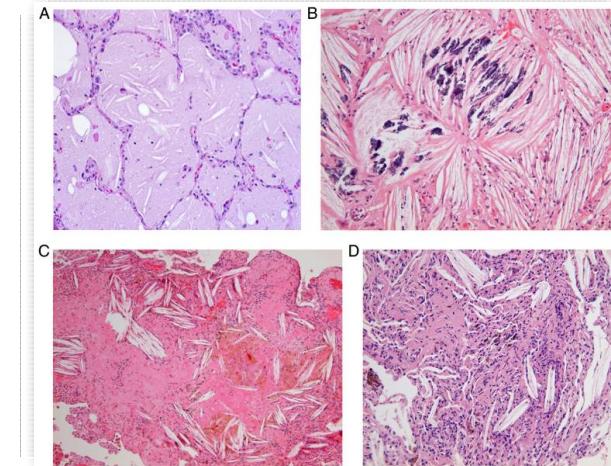
Chemical structure of Acramin FWN and Acramin FWR (12)

- Acramin FWR recently introduced as a replacement for Acramin FWN at the two factories where majority of cases had worked.
- Animal studies confirmed respiratory toxicity.
- Thought that highly negatively charged long-chain molecular structure of Acramin FWN contributes causes toxicity.

## INDIUM TIN OXIDE



CT showing progression of disease over three years in a 28 year-old Indium worker. Ground glass opacities and interlobular thickening. (13)



Range of histopathological features. A-C features of alveolar proteinosis. D multinucleated giant cells, interstitial fibrosis, and brown particles composed predominantly of indium.

(13)

- Indium tin oxide (ITO) is a sintered material used in making crystal displays for televisions and computers.
- First case of ITO-associated interstitial pneumonitis was reported in 2003 in a 27-year-old Japanese worker (1)
- Case series confirm interstitial pneumonia similar to UIP, emphysema, PAP in indium workers. Two patients have died to date. (13)
- Like ardystil outbreak notable that cases are young, have severe respiratory disease, and colleagues who are also unwell.

## SOUTH KOREAN LUNG



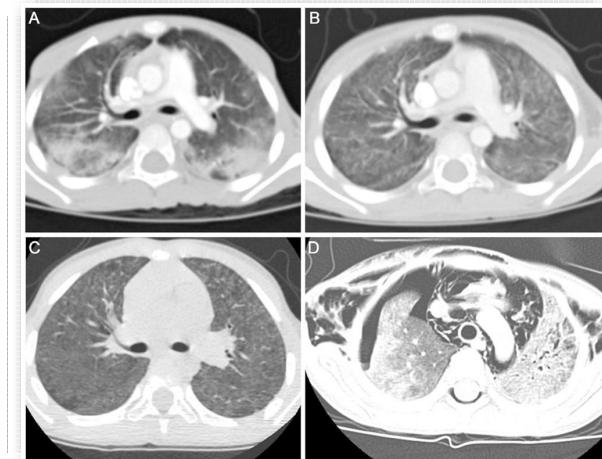
"A former South Korean executive of UK-based Reckitt Benckiser has received a seven-year prison sentence over a humidifier disinfectant linked to the death of around 100 people". BBC News website (accessed Jan 17 2017)

- Household clustering was observed in a series of patients admitted to ICU with severe respiratory distress in the spring of 2011. (15)
- Case series consisted of 17 patients with median age 35. Six were pregnant at presentation.
- All presented with cough and dyspnoea. CT showed patchy consolidation followed by ground glass opacity and bronchiolocentric fibrotic changes. Ten patients
- Ten patients required mechanical ventilation. Four had lung transplants. Five of the six who did not have a lung transplant died.

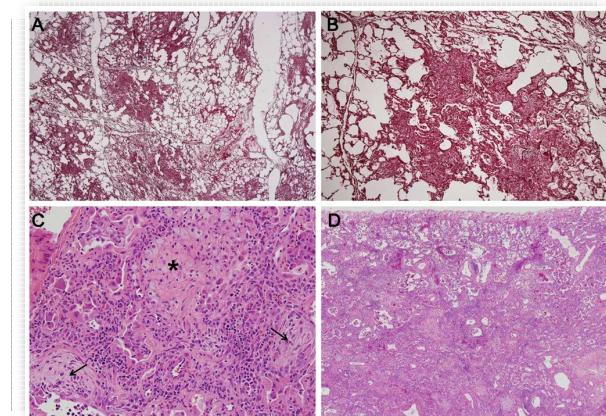
- Epidemiological investigation (a hospital based case-control study) revealed that all patients had used humidifier disinfectant in their homes.
- It transpired that children had also been affected.
- From 2006 epidemics of fatal lung injury in children were observed in Korea every spring (14).
- Clinical characteristics of suspected cases between 2006-2011 were reviewed and association with humidifier disinfectant use made.
- 138 cases, average age 30.4 months. 80 children died.
- No new cases following humidifier disinfectant ban in 2011.

- Mechanism by which polyhexamethylene guanidine phosphate, poly(oxyalkylene guanidine) hydrochloride, chloromethylisothiazolinone/methylisothiazolinone (toxic materials within humidifier disinfectant) not yet known.

emphysema. (14)



Representative CT findings for cases. A: 3/52 from onset, patchy consolidation. B: 1/12, diffuse centrilobular ground-glass attenuation. C: 1 year, diffuse centrilobular fibrosis. D: 5 year old girl, severe disease, ~~pneumomediastinum pneumothorax subcutaneous~~



Representative pathological findings. A: centrilobular interstitial thickening and fibrosis. B: Bronchiolocentric destruction. C: Inflammatory infiltration and fibroblastic proliferation within alveolar septa and bronchioles. D: Loss of airspaces because of extensive interstitial thickening and

# MCQS

**WHICH OF THE THREE  
CHEMICAL EXPOSURES  
CAUSING ILD WAS NOT  
WORK-RELATED?**

1. Ardytstil
2. Indium tin oxide
3. South Korean lung
4. 1 + 3

# **WHAT WAS RECENTLY IMPLICATED IN THE DEATHS OF ABOUT 100 SOUTH KOREANS (MOSTLY WOMEN AND CHILDREN)?**

1. Ardystil
2. Indium tin oxide
3. Humidifier disinfectant
4. Carbon monoxide poisoning

# **INDIUM TIN OXIDE (ITO) IS USED IN THE MANUFACTURE OF?**

1. Crystal displays for computers and televisions
2. Car windshields
3. Jewellery
4. Car doors

# **SUMMARY**

1. Occupational and environmental exposures change over time giving risk to new disease outbreaks
2. Interstitial lung disease examples include Ardystil, Indium tin oxide, and South Korean lung
3. Stay vigilant

# **QUESTIONS?**

# **QUESTIONS AND CONTACT**

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- [www.carlreynolds.net](http://www.carlreynolds.net)

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