

# AOP302: Lung Surfactant Function Inhibition Leads to reduced Lung Function.

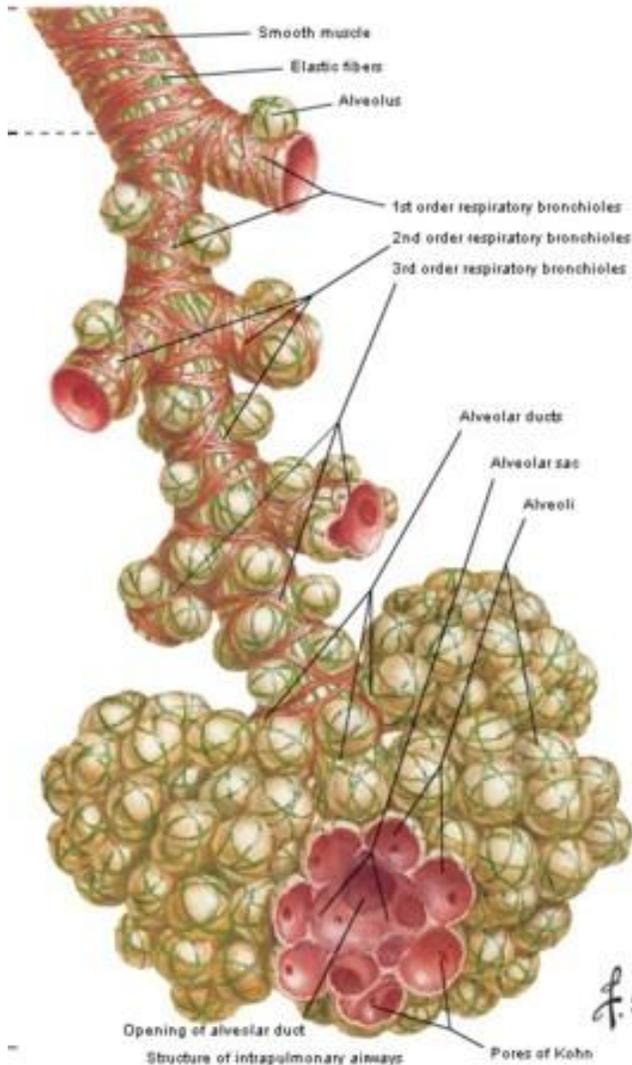
A NAM to measure the MIE and Weight of  
Evidence supporting the AOP

Senior researcher Jorid B. Sørli

10<sup>th</sup> of April 2024

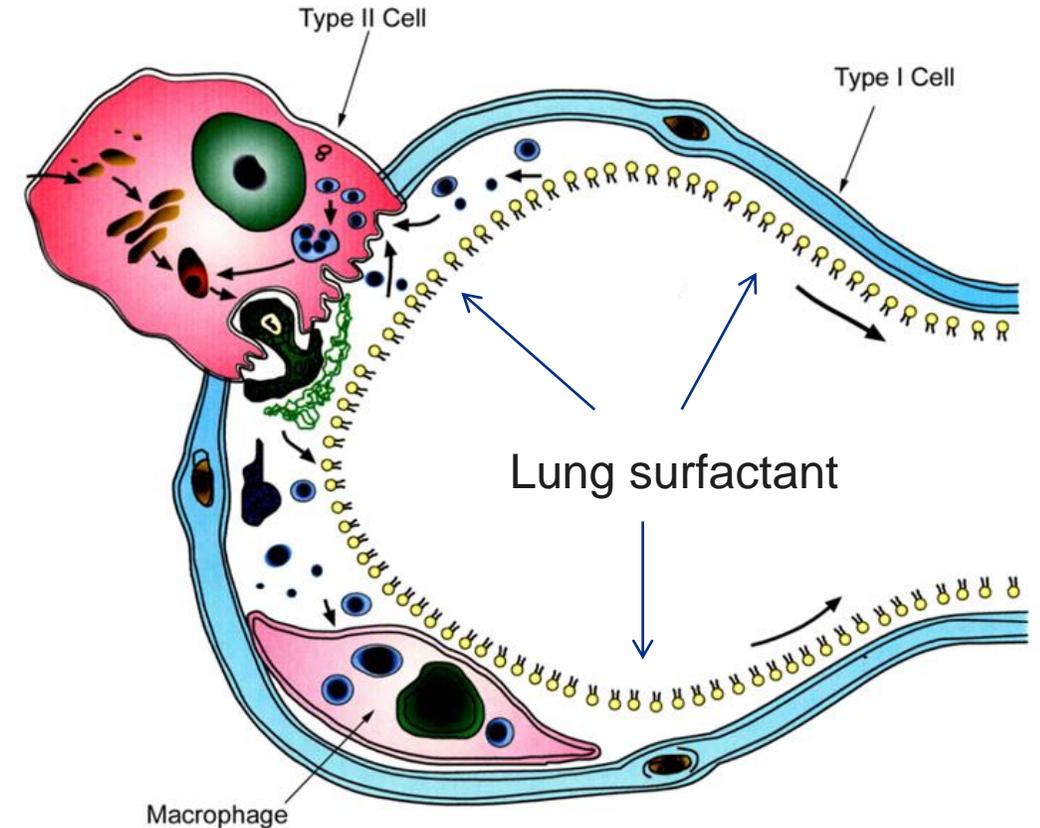


# The respiratory part of the lungs

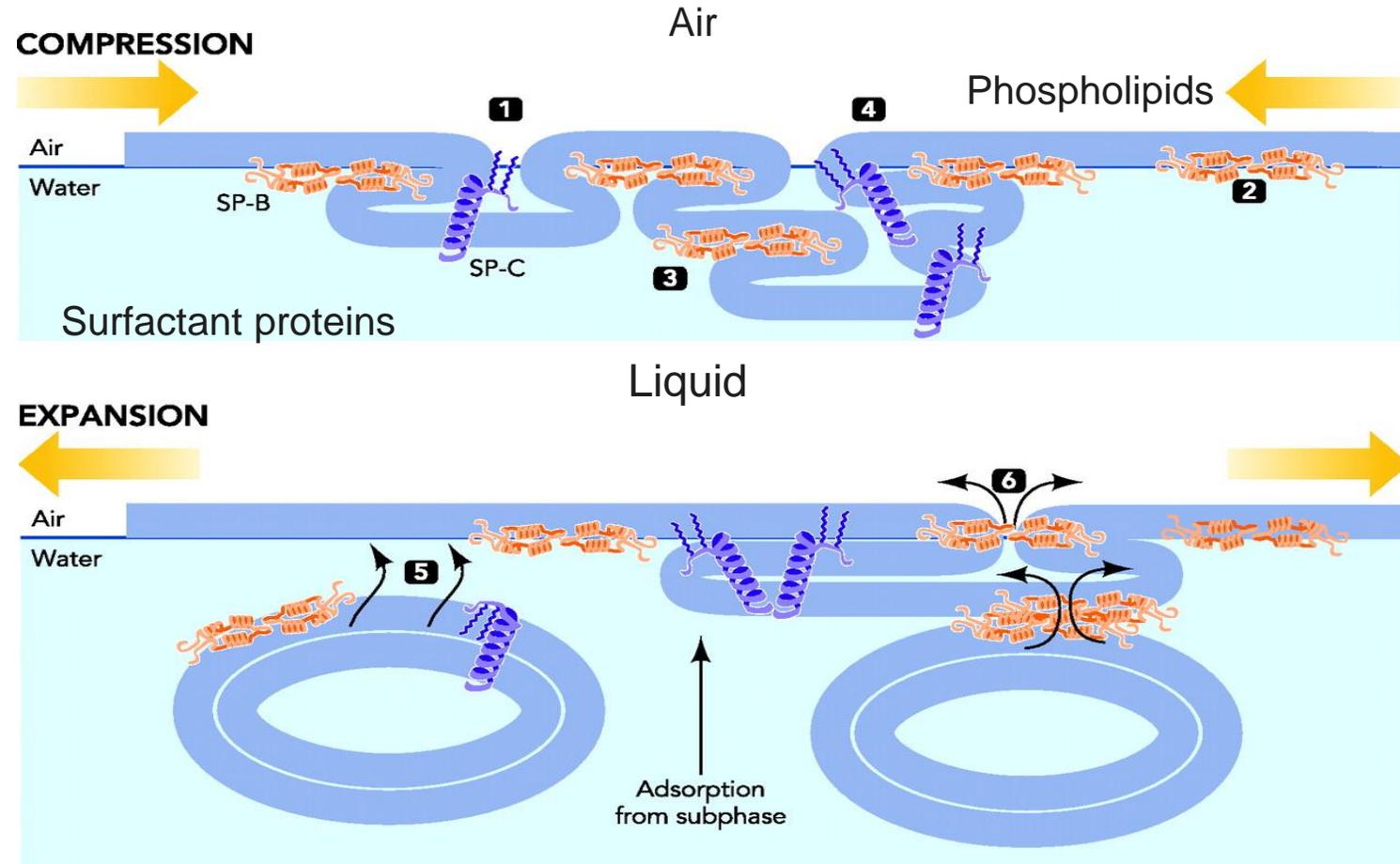
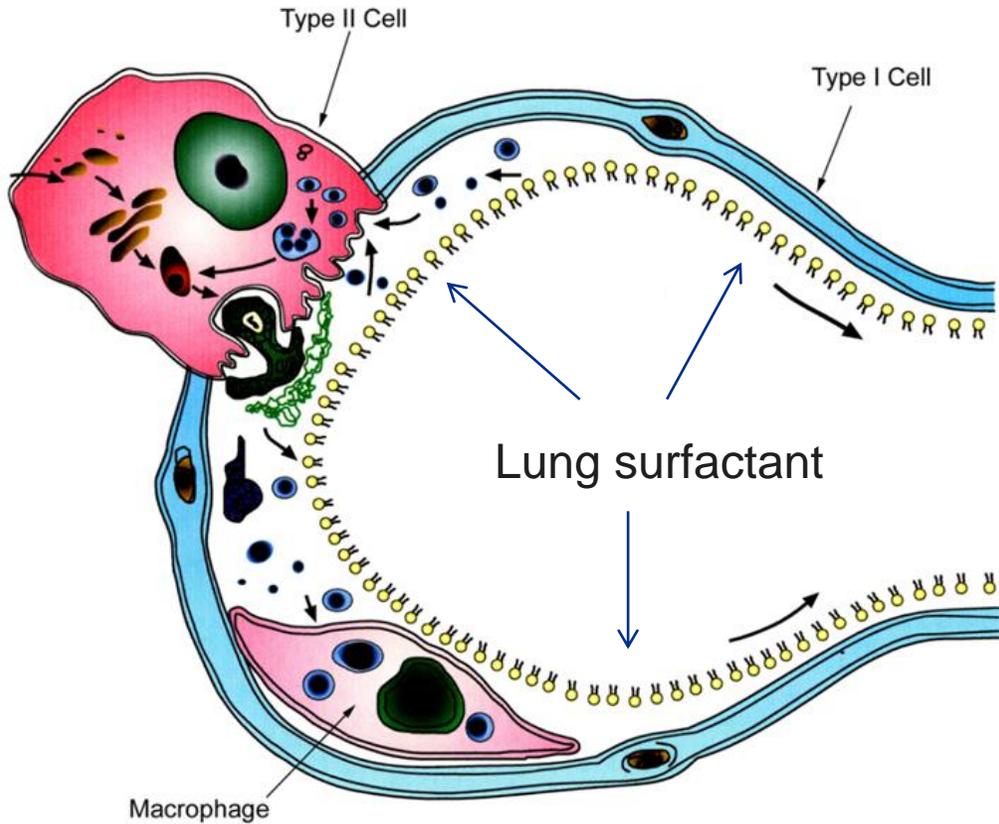


## Alveoli

- ~0.2 mm (constantly changing)
- 480 million alveoli
- Surface area ~70 m<sup>2</sup>



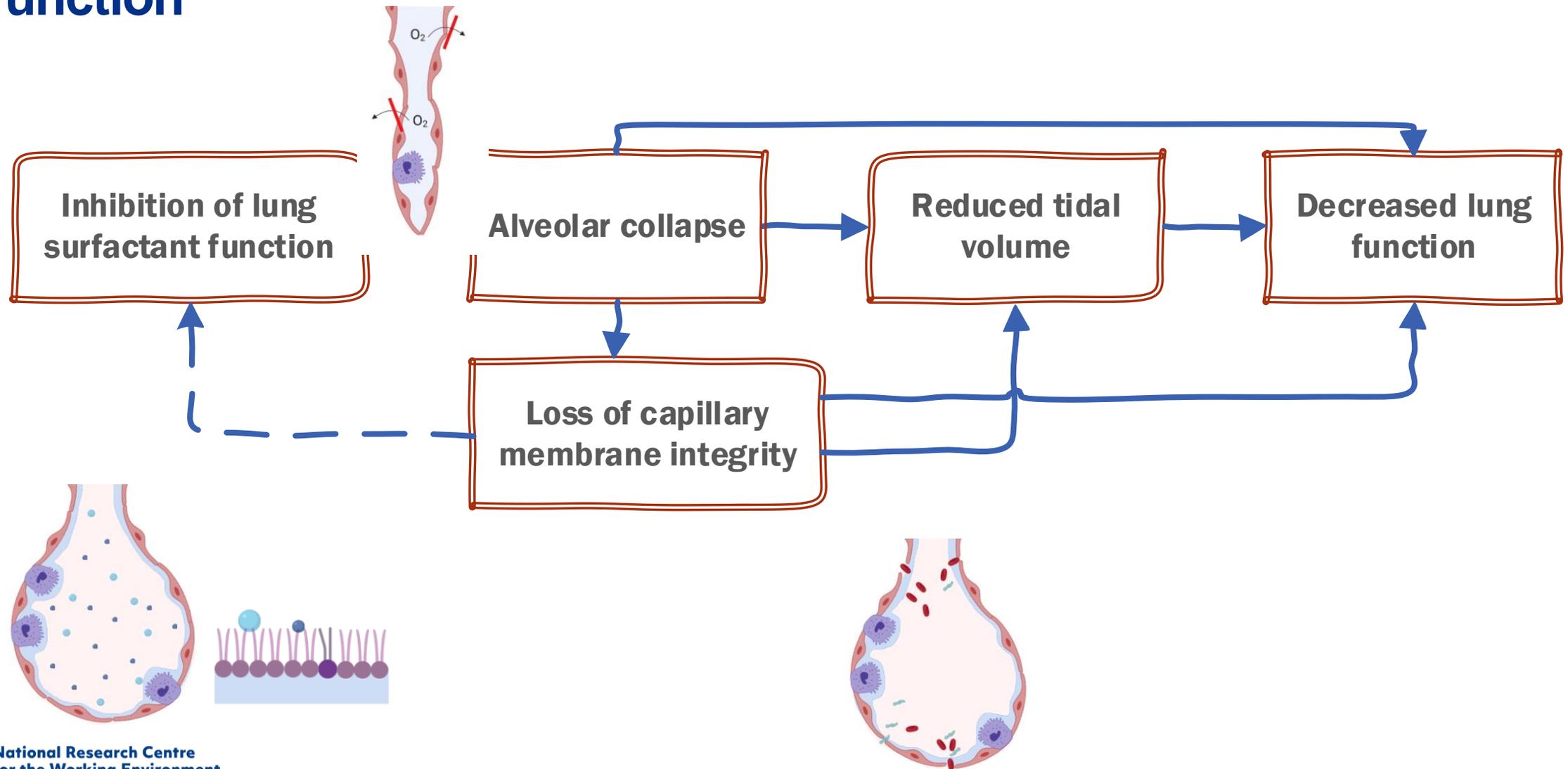
# Lung surfactant function



<http://usmle.biochemistryformedics.com/respiratory-distress-syndrome-case-discussion>

Perez-Gil & Weaver, Physiology, 2010

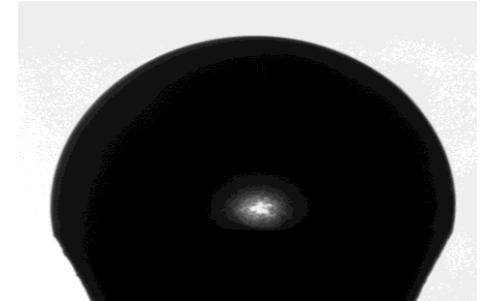
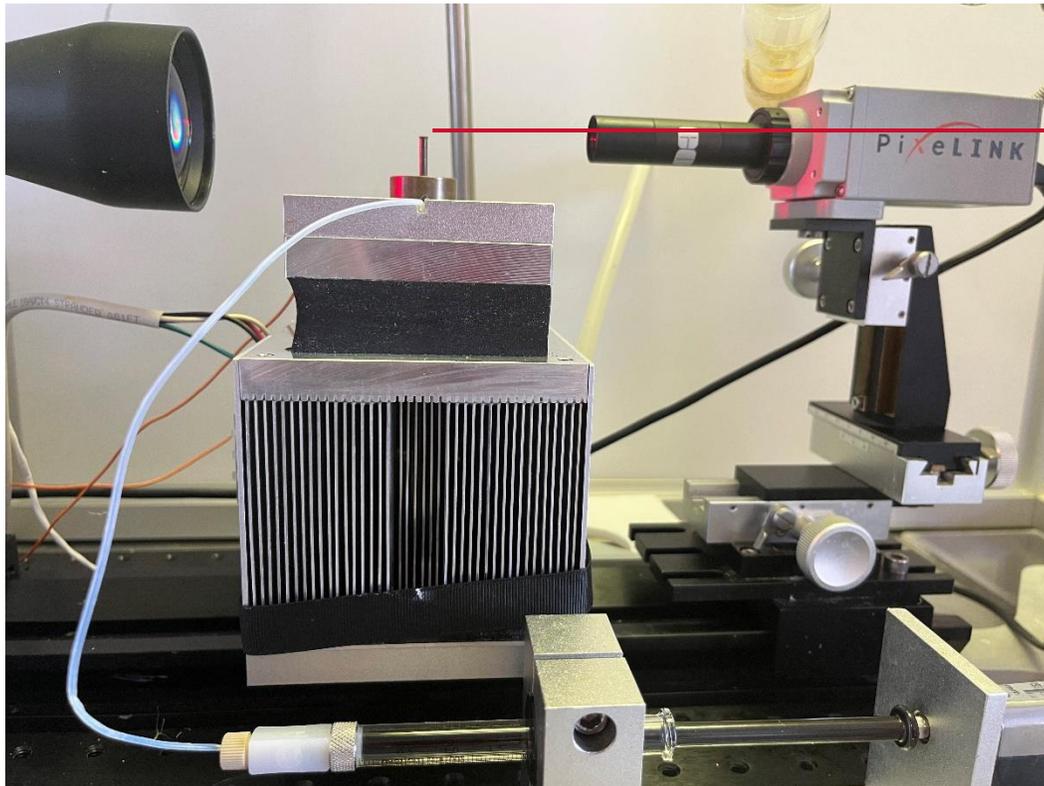
# AOP 302: Lung surfactant function inhibition leading to reduced lung function

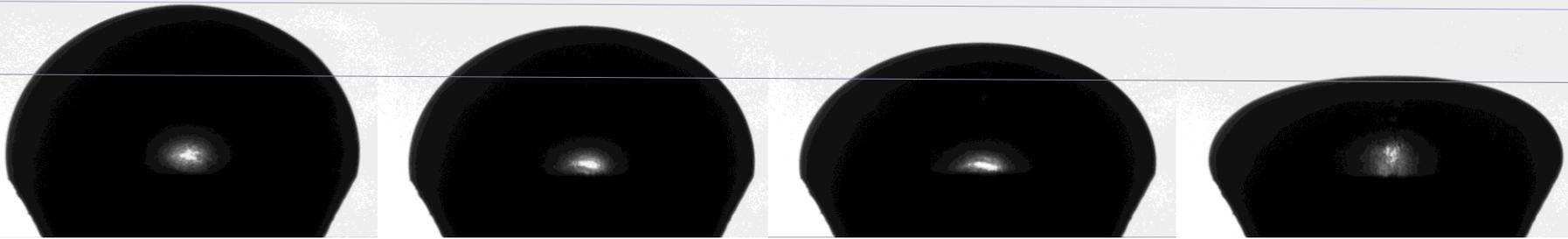
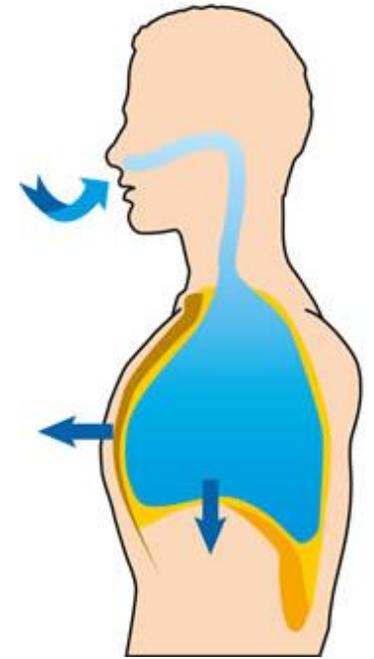
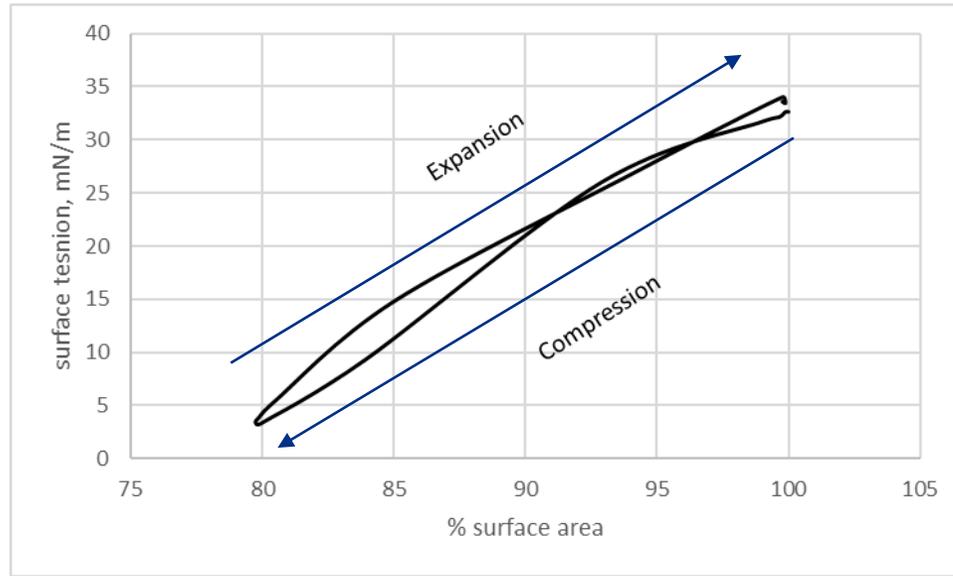
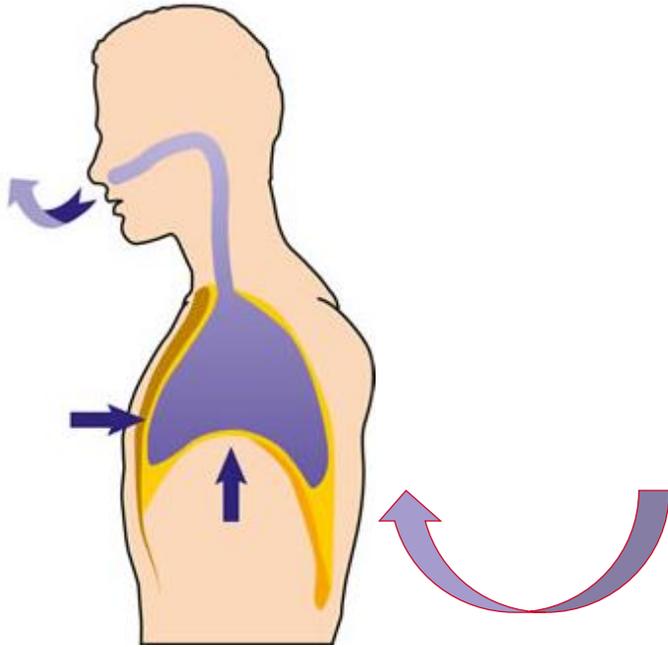


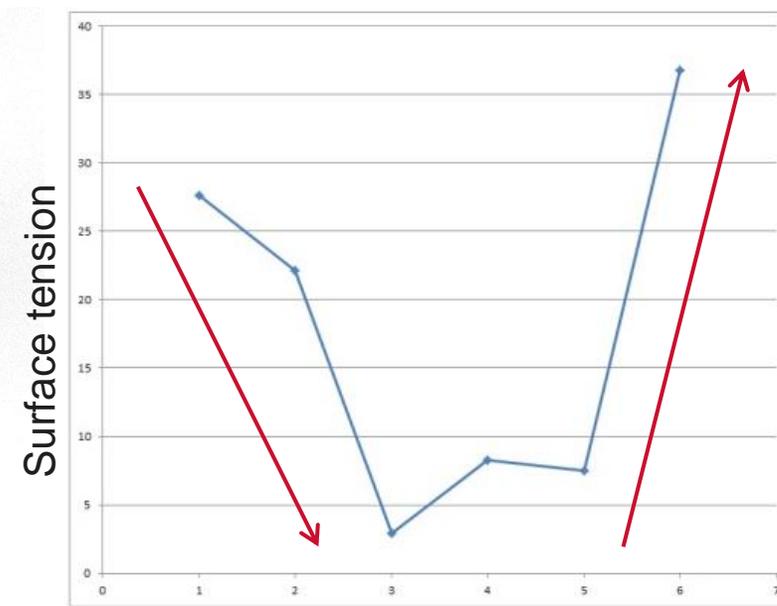
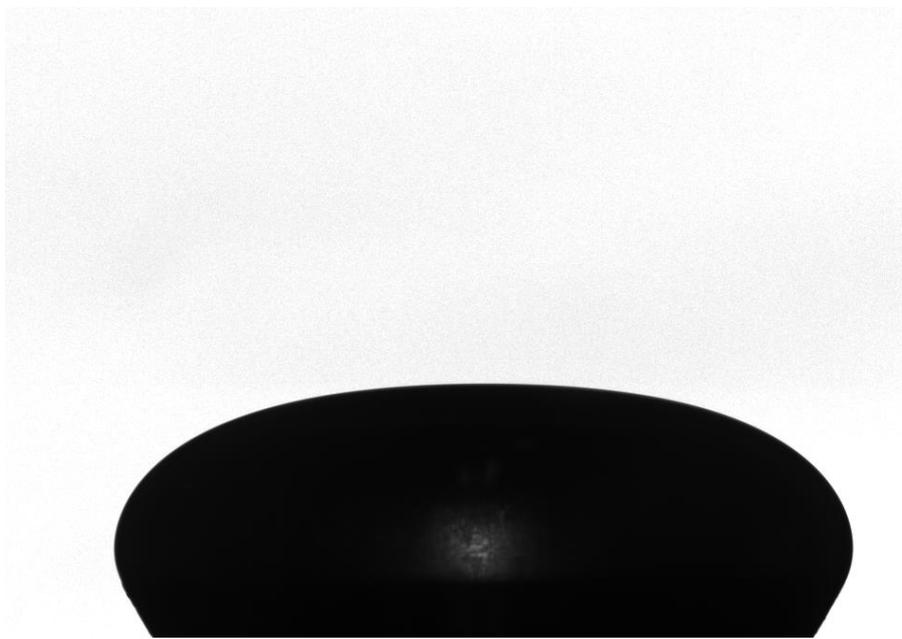
# MIE: lung surfactant function inhibition

- NAM for measuring lung surfactant inhibition in vitro needs:
  - to mimic the **surface area change** of the lungs and the **frequency** of breathing
  - **model** lung surfactant that reduces surface tension at these physiological conditions
  - **exposure** that simulates breathing air
  - **dose** measurement for comparison to in vivo data
  - positive **controls** to check that the assay is working

# In the lab







Minimum surface tension!

Aerosol exposure of test substance

# Effect of substances on lung surfactant function

- Case: impregnation products
- Predictiveness of the in vitro method
- Combining the in vitro method with exposure modeling

# Impregnation products as an example

- Make surfaces dirt and water repellent
- Used both by consumers and workers



# Human poisoning cases

- People frequently experience respiratory problems after using impregnation sprays, even if the instructions for use are followed
- Often sold in pressurized cans -> creates aerosol droplets that are small -> penetrate deep into the lungs
- Symptoms (shortness of breath, coughing, tightness in the chest, difficulty breathing) occur shortly after application
- Most recover with supportive care



# Case



- Used 2 spray cans on her new sofa
- Windows and doors open
- Sprayed 30 min
- Coughing, tightness in the chest, difficulty breathing, headache, nausea, fever

# Predictiveness of measuring lung surfactant function inhibition

Chemical or product	Lung surfactant function measure	In vivo comparison	Type of data	n	Predictiveness
Impregnation products	CDS	Breathing pattern changes in mice	Whole body plethysmographs	22	Sensitivity: 100% Specificity: 63%
		Human data	Accidental exposure	7	

Da Silva, 2021, DOI: 10.1016/j.crttox.2021.05.002.

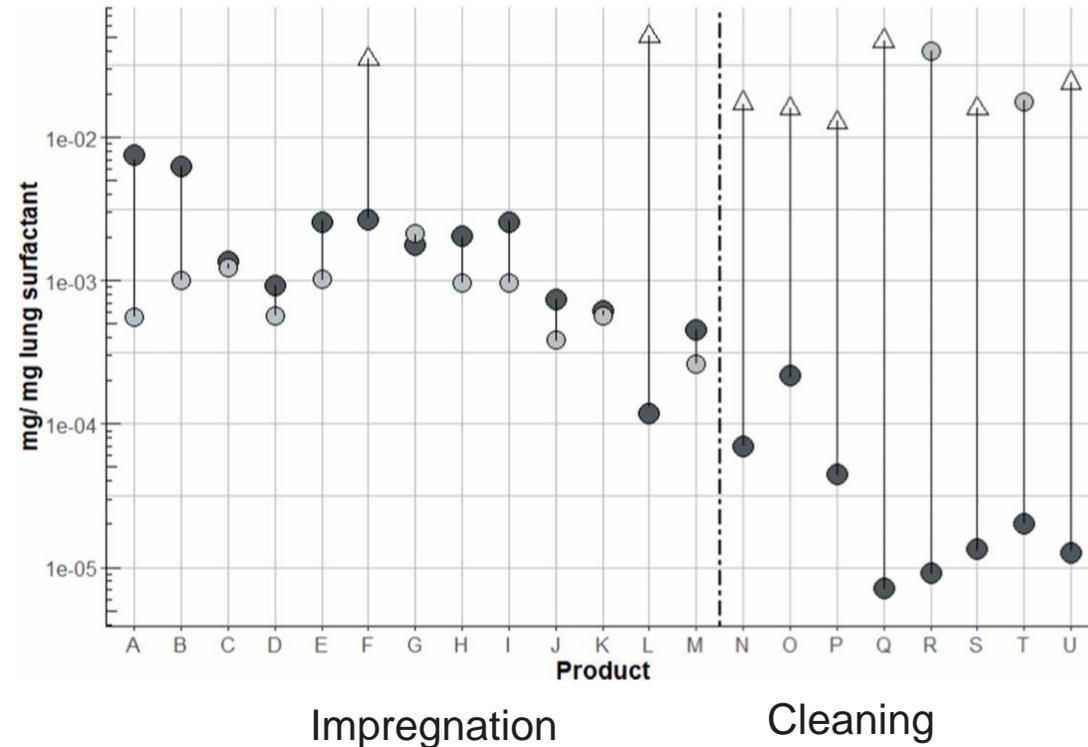
Sørli, 2018, DOI: 10.14573/altex.1705181.

Sørli, 2018, DOI: 10.1016/j.ijpharm.2018.08.031.

Sørli, 2016, DOI: 10.1165/rcmb.2015-0294MA.

# Combining *in vitro* assay and exposure modelling

- 13 products for impregnation
- 8 cleaning spray products
- Exposure assessment in chamber
- Estimating alveolar deposited dose by modelling
- Test for lung surfactant function inhibition



- Deposited alveolar dose in use scenario
- Inhibiting dose
- | Margin of safety

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Risk assessment of consumer spray products using *in vitro* lung surfactant function inhibition, exposure modelling and chemical analysis

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# Ongoing work with the AOP and NAM

- Mechanistic model of lung surfactant inhibition – collaboration with Unilever, Hugh Barlow
- Test particles from industrial cases for lung surfactant function inhibition – EU funded project nanoPASS
  - Compare with data generated in the rest of the consortium
- Exploring how mixing chemicals affect lung surfactant function – FFIKA Sreyoshee Sengupta Ph.D. student
  
- **Challenges**
  - Dose estimation is possible, but sometimes challenging. Does not always compare to in vivo estimated doses
  - Only tests one toxicological target in the lungs and needs to be combined with other in vitro methods

# Funding and acknowledgments

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- NFA – National Research Center for the Working Environment
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# Thank you for your attention