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Funded by the European Union

National Research Centre for the Working Environment

AOP302: Lung surfactant inhibition as a predictor for lung toxicity

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Text in French

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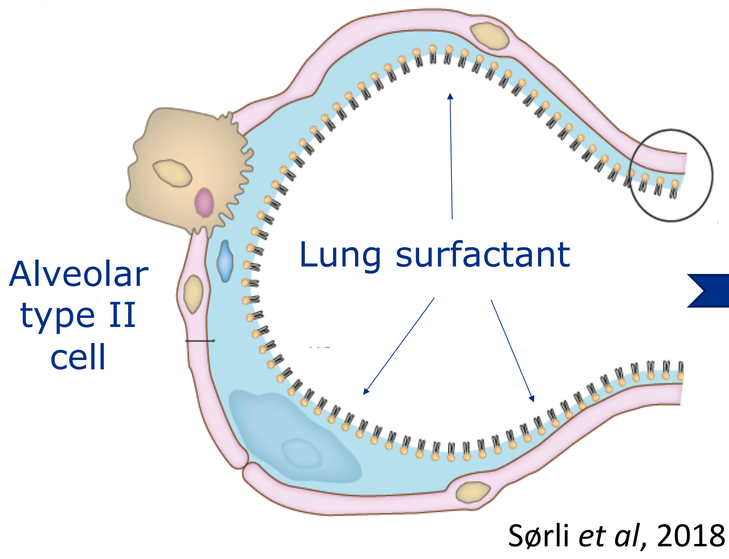
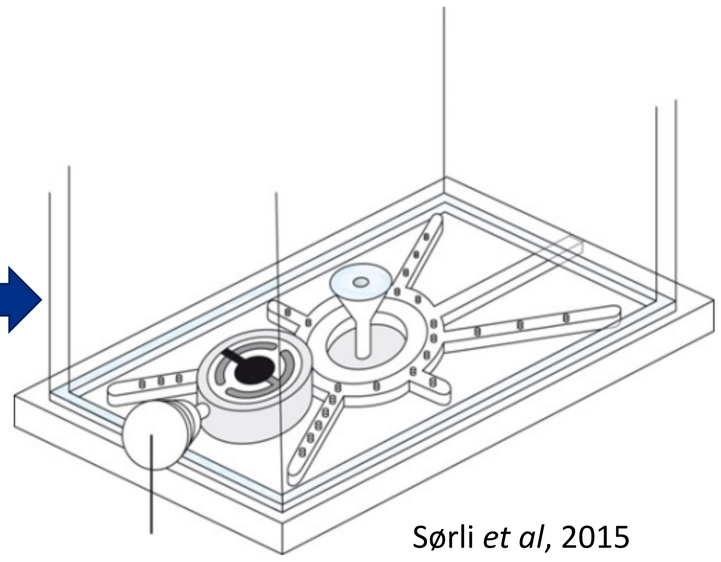
Lung surfactant

- layer of **liquid** composed of lipids (90%) and proteins (10%) produced by alveolar type II cells
- regulates **surface tension** at the air-liquid interface
- together with the epithelium and endothelium forms **physical barrier** between the outside environment and blood circulation
- first point of contact of inhaled substances



Alveolus



Constrained drop surfactometer

Test substances

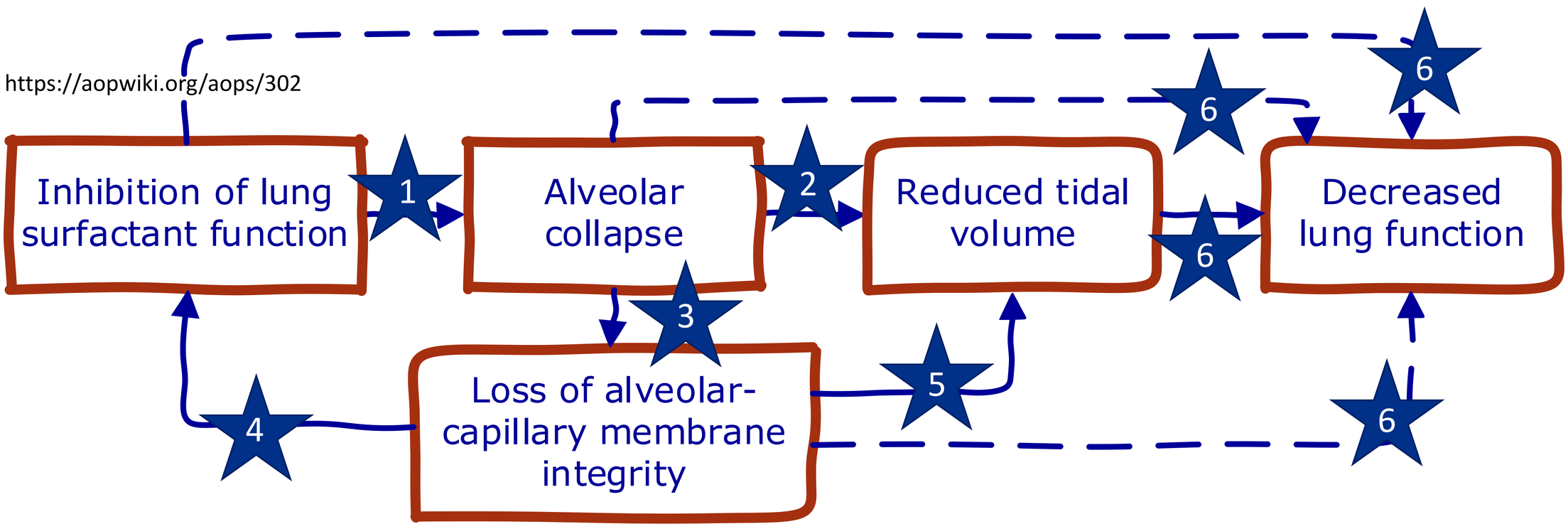
- Impregnation products [a]
- PFAS [b]
- Inhaled pharmaceuticals and enhancers [c]
- Industrial chemicals [d]
- Nanomaterials [e]
- Plant protection products and biocides [f]
- Cleaning products [g]
- Surfactants and polymers [h]

Measurement of lung surfactant function

- assessed in a **lung surfactant bioassay**, e.g. the Constrained Drop Surfactometer (CDS)
- lung surfactant is cycled in the same extent and frequency as the breathing lungs, **the change in surface area** results in **change in surface tension**
- to simulate substance exposure by breathing, the test substance is **aerosolized** in the **exposure chamber**
- The adverse outcome was defined as the **inhibition** of the ability to regulate surface tension, specifically **increase in minimum surface tension**

Adverse outcome pathway #302

- inhibition of lung surfactant function -> **high minimum surface tension**
- high surface tension -> **alveolar collapse**
- reopening of collapsed alveoli -> damage to the alveolar-capillary membrane
- **decreased lung function** -> shortness of breath, coughing, trouble breathing



Conclusion

The **biological plausibility** of the AOP is **high**, however the **empirical evidence** for the relationships are **high to low**. Much of the supporting evidence is **indirect**. The **essentially** of the events still need more work as dose-response relationships are difficult to establish both in vitro and in human data. Several chemical groups have been tested for inhibition of lung surfactant function.

Key event relationship	Plausibility	Empirical evidence
1	high	moderate
2	high	low
3	high	moderate
4	high	moderate
5	high	low
6 (several)	high	low to high

References
Sørli et al 2015, DOI: 10.1165/rcmb.2015-0294MA
Sørli et al 2018, DOI: 10.1016/j.ijpharm.2018.08.031
[a] 10.1093/toxsci/kft225, 10.14573/altex.1705181, 10.3390/jox14020039
[b] 10.1016/j.tiv.2019.104656 [c] 10.1165/rcmb.2015-0294MA, 10.1016/j.ijpharm.2018.08.031 [d] 10.1016/j.bbamem.2020.183499 [e] 10.1177/1091581820933146 [f] 10.1016/j.tox.2023.153546 [g] 10.1016/j.fct.2022.112999, 10.1016/j.colsurfb.2024.114482 and 10.14573/altex.2410221