Identifying hazardous, inhalable surfactants: A framework for evaluating the inhalation risk of new surfactant chemicals

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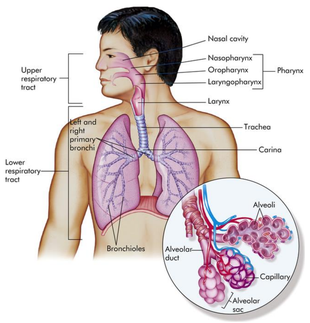
Background and purpose

- Surfactants reduce the surface tension of a liquid, or reduce interfacial tension between two liquids, a liquid and a solid, or a liquid and a gas.
- Surfactants are used in a variety of occupational settings and consumer products such as personal hygiene and household cleaning products.
- Inhaling surfactants can cause direct toxicity to the cells of the airways and/or disrupt the pulmonary surfactant, which can lead to respiratory irritation, impairment of gas exchange, pulmonary edema, and collapse of the alveoli (i.e., atelectasis).
- The surfactant chemical class has relatively little inhalation data.
- New approach methodologies (NAMs) can provide human-relevant test systems for assessing airway hazards, including the effects of surfactants.
- Due to the ubiquity of surfactants, it would be valuable to develop a NAMs-based framework that allows for the reliable identification of hazardous, inhalable surfactants, and efficient regulatory decision making that protects human health and the environment.



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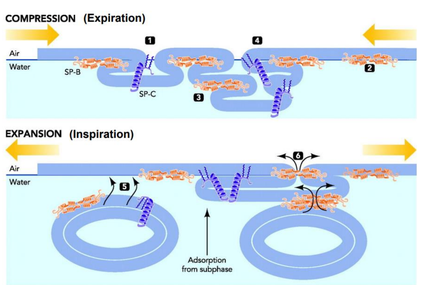


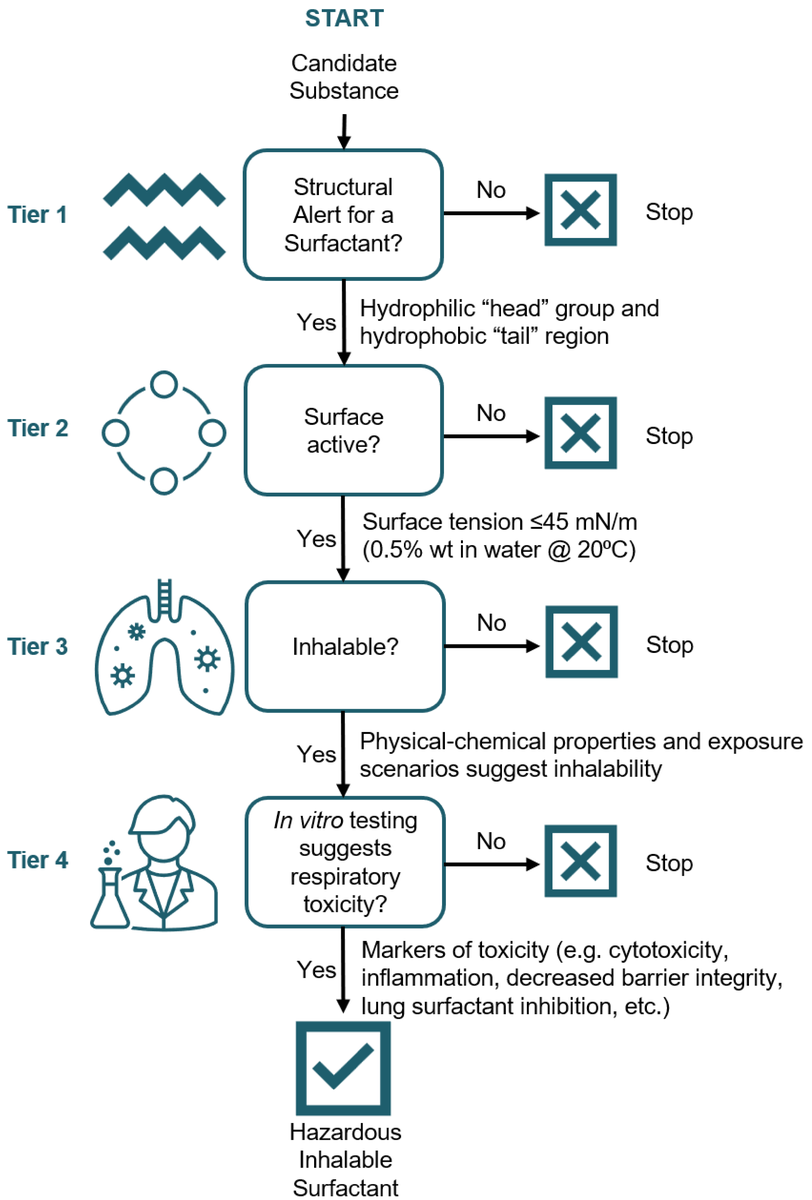
From Perez-Gil & Weaver 2010

Images courtesy of Jorid Sørli.

Criteria for hazard consideration

We propose that surfactants may be hazardous to human health via airway exposure if the following conditions are met:

1. The chemical has a hydrophilic “head” region and a hydrophobic “tail” region.
2. The chemical has a surface tension ≤45 mN/m (0.5% wt in water at 20ºC).
3. The chemical use may result in inhalation exposure.
4. The chemical demonstrates a capacity to cause airway toxicity as indicated by test data on the new chemical or an analogue.

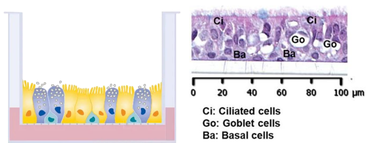


Proposed framework

The framework presented here is proposed to standardize the evaluation of new chemicals to determine if they meet the criteria of hazardous, inhalable surfactants. This framework proposes a stepwise, tiered approach for evaluating new chemicals that are candidates for categorization as hazardous, inhalable surfactants.

- Tier 1: The chemical is identified as a surfactant based on structural criteria. Move to Tier 2.
- Tier 2: The Organisation for Economic Co-operation and Development (OECD) Test Guideline 115[1] determines whether the surfactant has a surface tension ≤45 mN/m (0.5% wt in water at 20ºC). (If the substance is surface active, a critical micelle concentration may also be determined to ascertain whether the substance self-assembles into micelles.) Move to Tier 3.
- Tier 3: Physical-chemical properties and exposure scenarios are used to determine the extent to which the surfactant may be inhaled. If this potential exists, move to Tier 4.
- Tier 4: *In vitro* testing investigates endpoints of airway toxicity. A reconstructed human respiratory epithelial (RHRE) tissue model[2] can probe changes in cell viability, cytotoxicity, expression of inflammatory markers, barrier integrity, and cell morphology. In addition, a lung surfactant inhibition assay[3] can detect changes in the surface tension of a drop of lung surfactant after exposure to a test substance, which is thought to precede alveolar collapse in humans.

RHRE tissue model (bronchial) where a test substance can be exposed directly to the apical surface.



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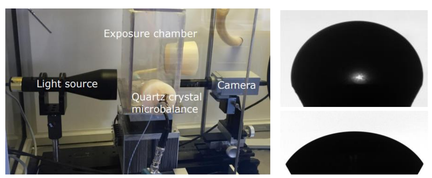
Lung surfactant inhibition assay using constrained drop surfactometer where change in surface tension can be measured after substance exposure.



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Positive findings in all four tiers would identify a chemical as a hazardous, inhalable surfactant. Implementation of this framework by the U.S. EPA would clarify agency expectations and decision-making to improve the efficiency and transparency of the new chemical evaluation process.

References

1. https://www.oecd.org/en/publications/test-no-115-surface-tension-of-aqueous-solutions_9789264069787-en.html
2. Stucki et al. *In vitro* approach for assessing respiratory toxicity of surfactants in human lung cells. Manuscript in Preparation.
3. Barlow, H., Roy Sengupta, S., Baltazar, M. T., & Sørli, J. B. (2025). Experiments and modelling of pulmonary surfactant disruption by aerosolised compounds. Colloids and Surfaces B: Biointerfaces, 248, 114482. https://doi.org/10.1016/J.COLSURFB.2024.114482