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# Soft Matter in Chemical Safety Science

13/07/2026

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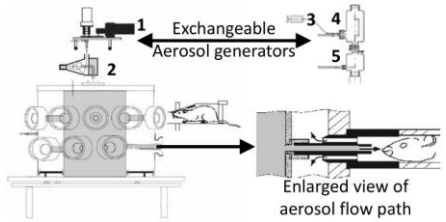
# Context :

# Assuring safety of consumer products

# Safety without animal testing

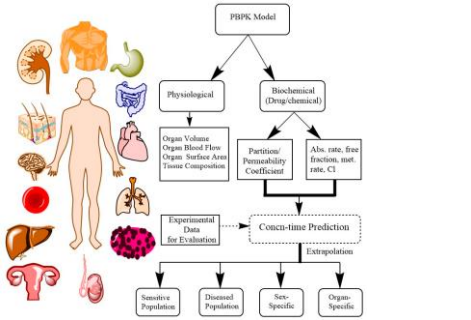
## 'Traditional' Risk Assessment → 'Next Generation' Risk Assessment

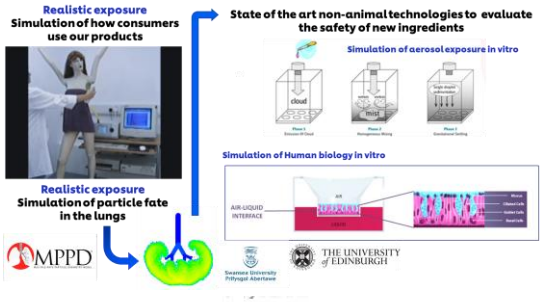
**Historically** animal testing was the typical method

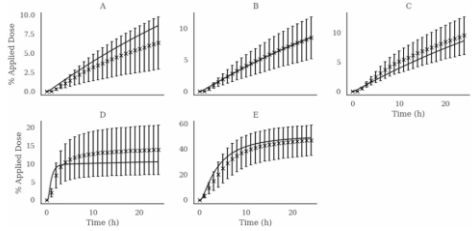


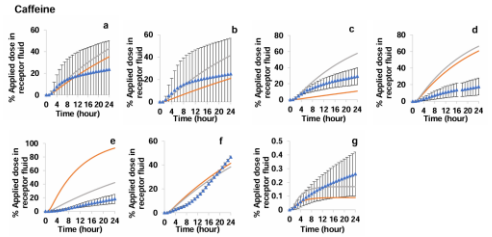

LABORATORY TEST

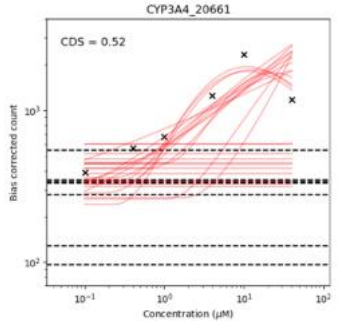
***based on advances in human biology and in vitro/computational modelling***



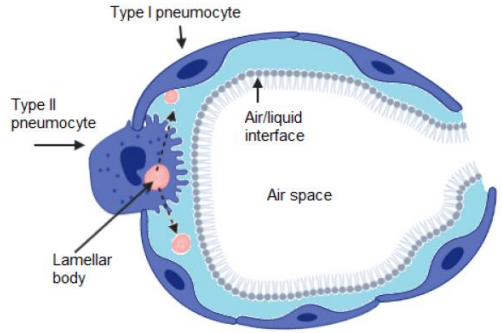

[SERS Safety Science]

Phillips et al. *JoVE* 2017 istockphoto.com

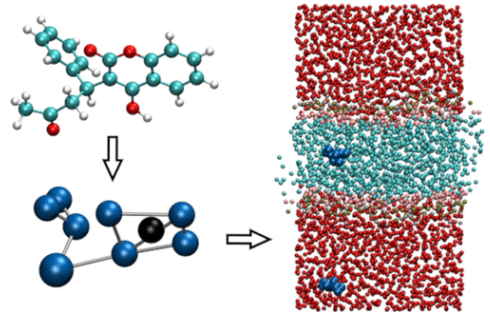
# Where does Soft Matter come in?

**Today's Showcase examples:**

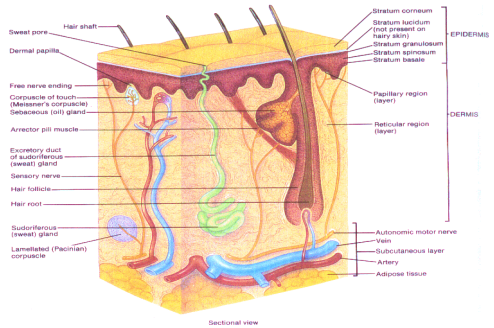
1. Lung Surfactant Disruption -> Dilational Rheology




2. Lipid Membrane modelling –> Coarse Grained Simulation



3. Skin Penetration –> Polymers and Solution theory

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# Lung Surfactant Inhibition

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FORSKNINGSCENTER FOR ARBEJDSMILJØ

NATIONAL RESEARCH CENTRE
FOR THE WORKING ENVIRONMENT

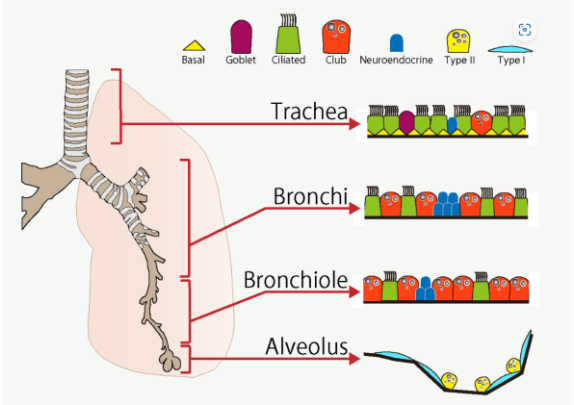
# Surfactant

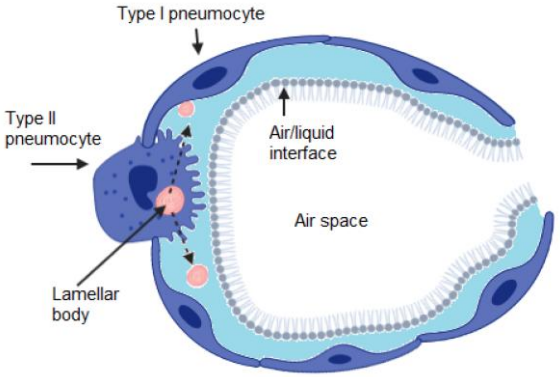
Surface Pressure $\Pi(\Gamma)$

Surface Concentration $\Gamma$

As surface expands and contracts molecules migrate between bulk and surface

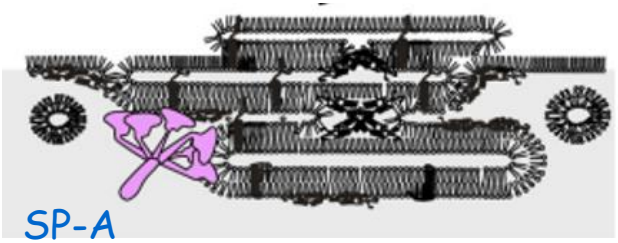
Surfactant Proteins modify the process by forming subsurface structures




dataphysics-instruments.com

Increases the rate at which the surfactants re-adsorb during inhalation



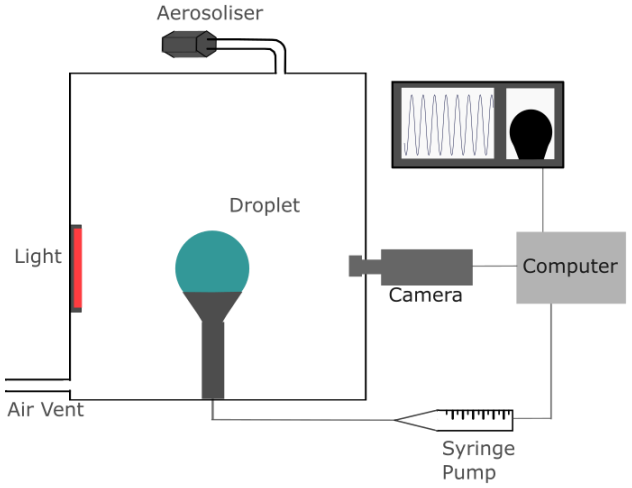


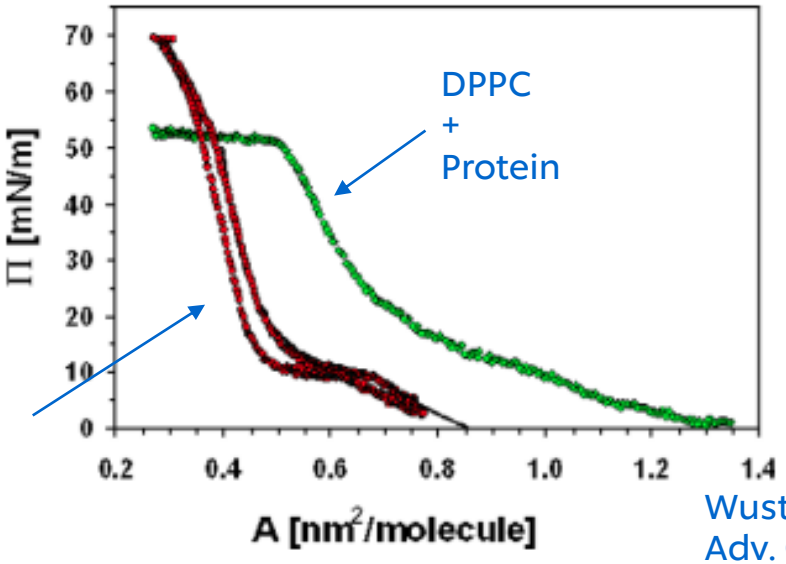
Blanco & Perez-Gil, European Journal of Pharmacology 568 (2007)

Formation of three dimensional structures increases elasticity of monolayer

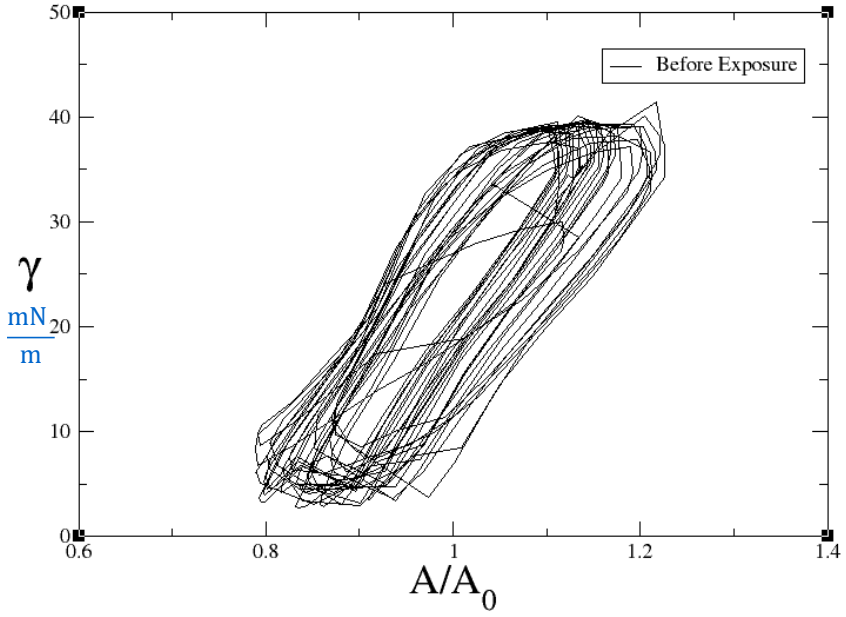
Without lung surfactant to modify the elasticity of alveoli collapse during exhalation as seen In pre-term infants

**Can the disruption of breathing due to aerosolised compounds be due to modifications of the Lung surfactant rheology?**

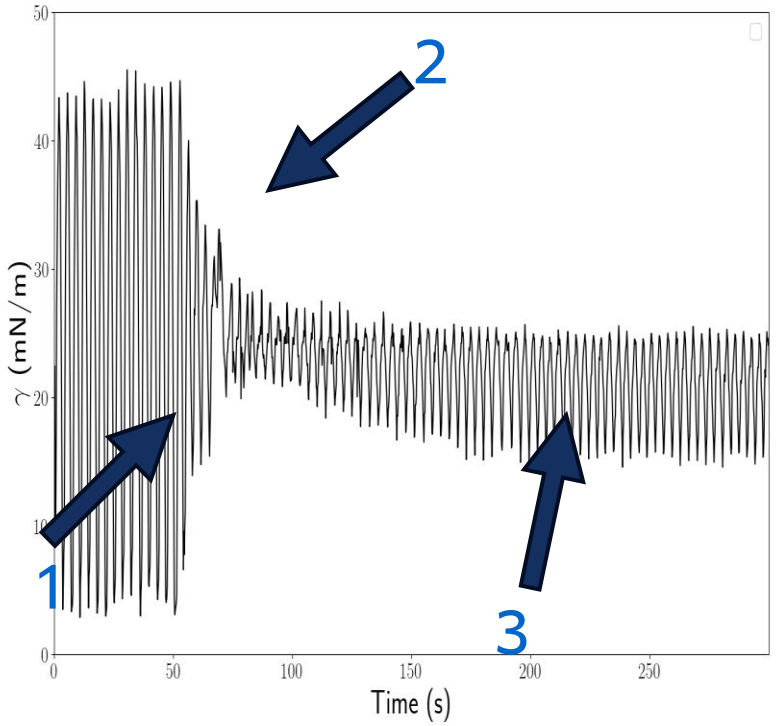



Wustneck et al.
Adv. Coll. Surf. Sci.2006

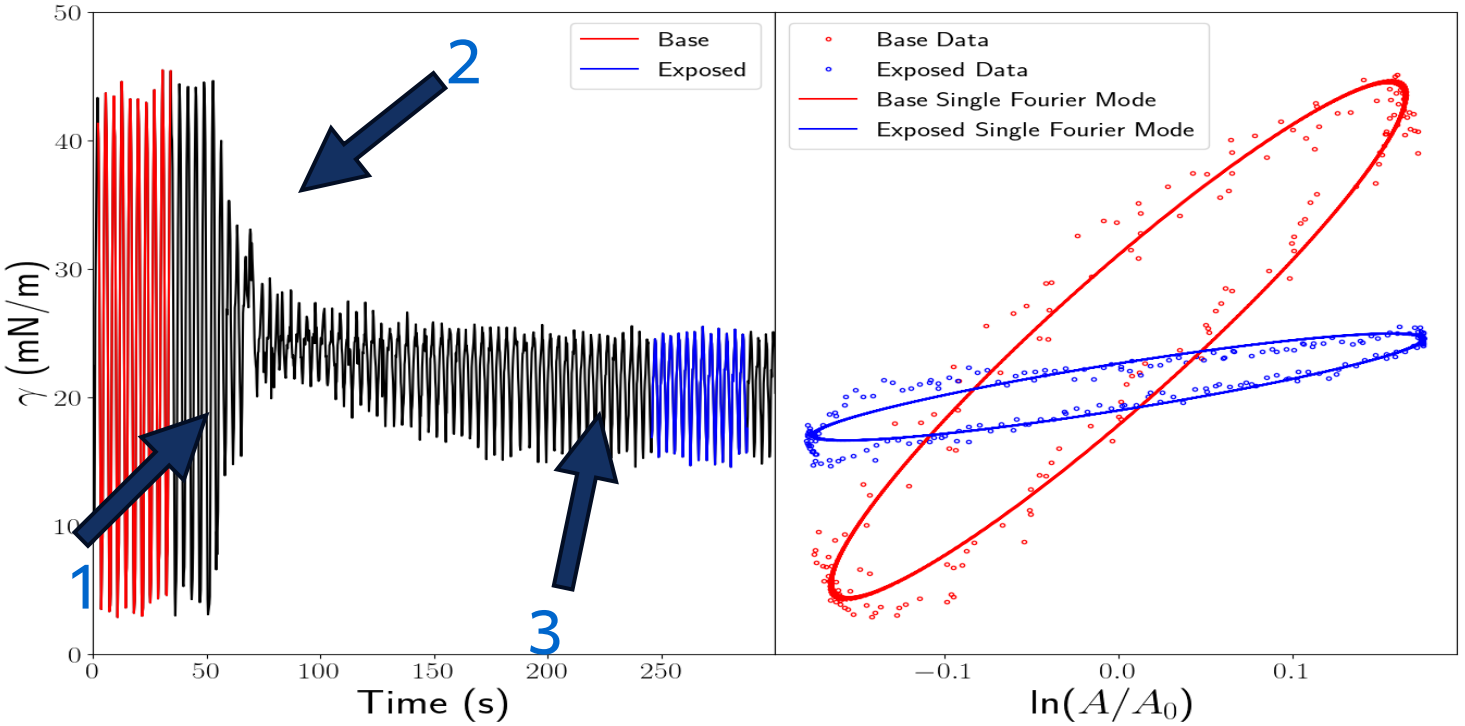


# Experiments – (Alkylsiloxane Polymer)




1. Base Response established before infusion
2. Infusion begins at 40s
3. New response appears after short time

# Experiments – (Alkylsiloxane Polymer)

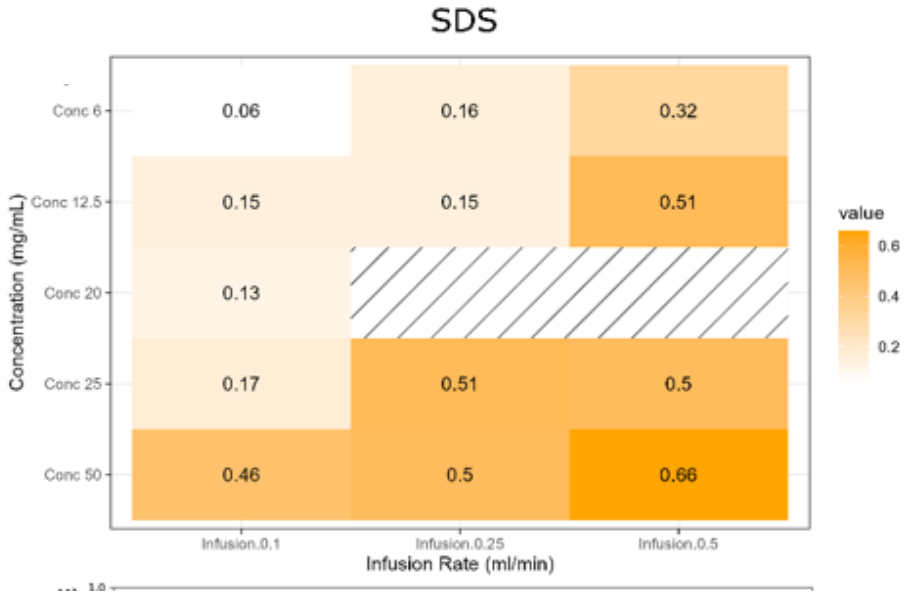



1. Base Response established before aerosol infusion
2. Infusion begins at 40s and continues
3. New **steady** response appears after short time

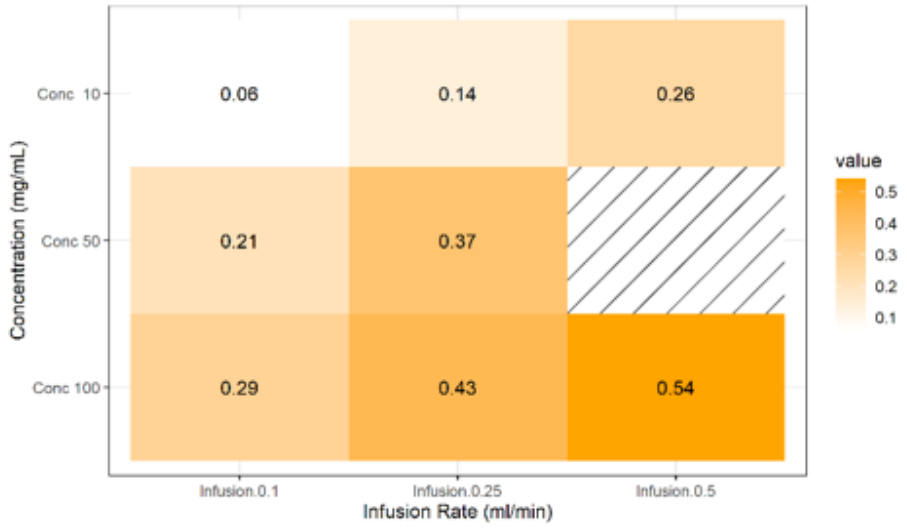
# Experiments

$$|E^*| = \sqrt{E'^2 + E''^2}$$

$$\Delta\tilde{E} = \frac{|E^*_{post}| - |E^*_{pre}|}{|E^*_{pre}|}$$




Polyhexanide



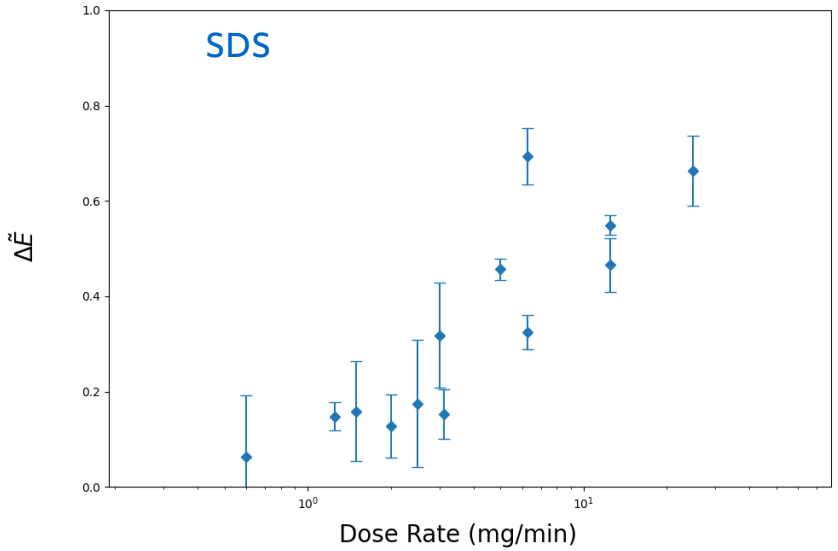
# Experiments

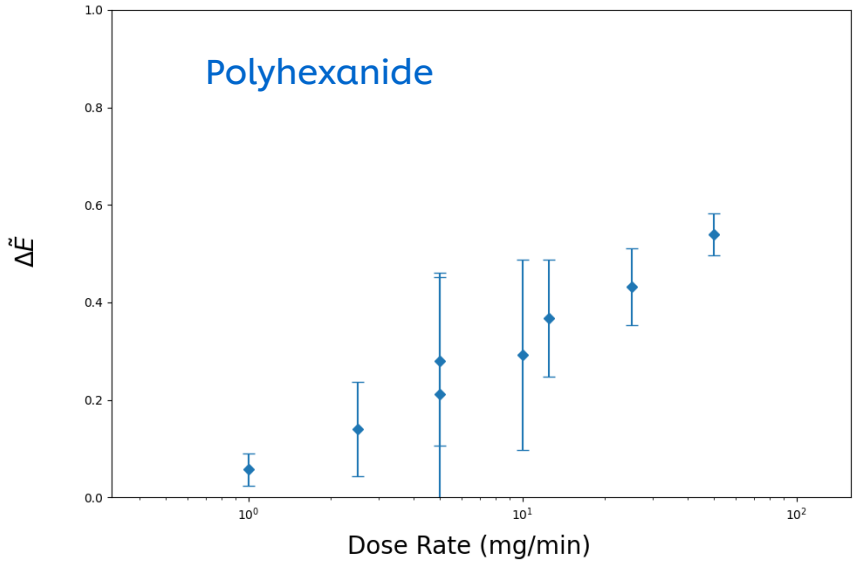
$$|E^*| = \sqrt{E'^2 + E''^2}$$

$$\Delta\tilde{E} = \frac{|E^*_{post}| - |E^*_{pre}|}{|E^*_{pre}|}$$

$$Dose\ Rate = Chemical\ Concentration \times Infusion\ Rate$$

Now can we understand what's going on based on surfactant physics?



# Modelling - Volmer isotherm

Assume that lung surfactant on surface behaves as a two dimensional gas with surface concentration $\Gamma$ and migrates between bulk and surface continuously

Surface Tension $\gamma = \gamma_0 - k_B\, T\, \Pi(\Gamma)$

Surface Pressure $\Pi(\Gamma) = m \frac{\Gamma_\infty \Gamma}{\Gamma_\infty - \Gamma}$

Total Surfactant Flux $Q = \frac{d(\Gamma A)}{dt}$

Rate of change surfactant concentration $\frac{d\Gamma}{dt} = k_a \mathrm{C}(\Gamma_\infty - \Gamma) - k_d\, \Gamma e^{\frac{\xi(\Gamma)}{k_B T}} - \frac{\Gamma}{A}\frac{dA}{dt}$

Non-local Interactions $\xi(\Gamma) = k_B\, T\, \frac{m\Gamma}{\Gamma_\infty - \Gamma}$

Rate constants $k_a, k_d$

Empirical Scaling Parameter $m$

Maximum Concentration $\Gamma_\infty{}^{-1} = 50\ \text{Å}^2$

Kralchevsky et al.
Handbook of Surfactant Science
2008

# Model – Xenobiotic Effects

Assume that the aerosolised compound is introduced at fixed rate $\dot{\Gamma}_x$

Desorption rate of compound $k_{x,d}$

Non-local Interaction xenobiotic parameter $\beta_x$

$\dot{\Gamma}_x = \alpha \times$ Dose Rate

These three parameters are used to fit our model for each chemical studied

$$\gamma = \gamma_0 - k_B\, T\, \Gamma_\infty\, \Pi(\Gamma\,,\, \Gamma_x)$$

$$\Pi(\Gamma\,,\, \Gamma_x) = \mathrm{m}\frac{\Gamma+\Gamma_x}{\Gamma_\infty-\Gamma-\Gamma_x} + \frac{\beta_x}{k_B\, T}\,(\Gamma_x/\Gamma_\infty)^2$$

$$\frac{d\Gamma}{dt} = k_a \mathrm{C}(\Gamma_\infty - \Gamma - \Gamma_x) - k_d\, \Gamma e^{\frac{\xi(\Gamma,\Gamma_x)}{k_B T}} - \frac{\Gamma}{A}\frac{dA}{dt}$$

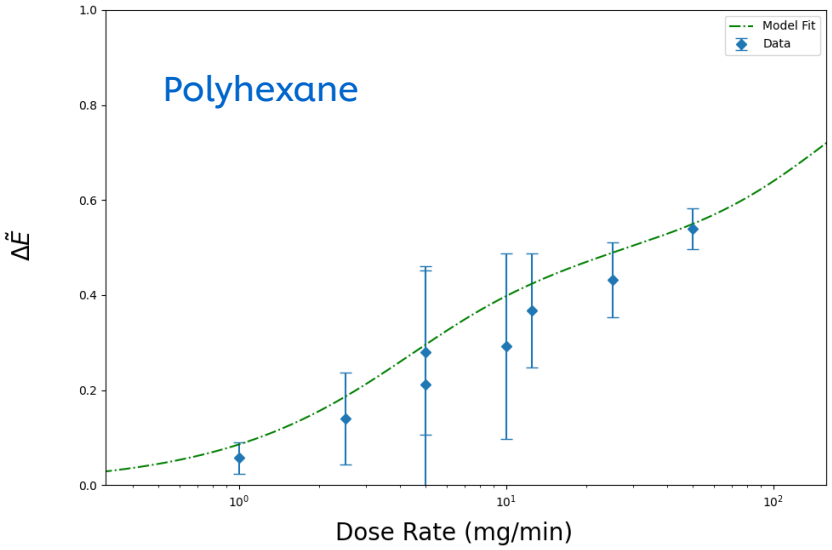
$$\frac{d\Gamma_x}{dt} = \dot{\Gamma}_x - k_{x,d}\, \Gamma_x\, e^{\frac{\xi(\Gamma,\Gamma_x)}{k_B T}} - \frac{\Gamma_x}{A}\frac{dA}{dt}$$

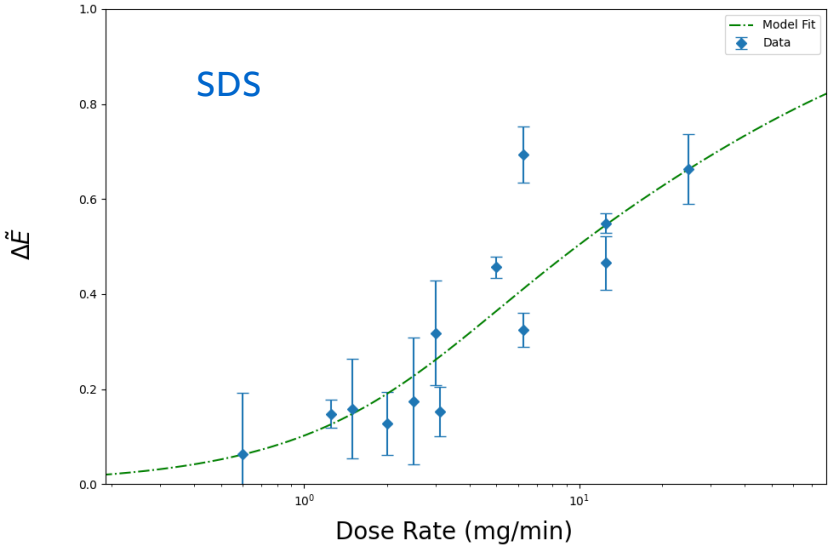
$$\xi(\Gamma\,,\Gamma_x) = k_B\, T m \frac{\Gamma+\Gamma_x}{\Gamma_\infty-\Gamma-\Gamma_x} + \beta_x \Gamma_x/\Gamma_\infty$$

# Modelling – Xenobiotic Effects

Model Accurately reproduces observed change in Lissajous curves with increasing dose rate

Model also reproduces observed change in dilational modulus for Polyhexane & SDS




## Conclusions

- Inhibition of function of lung surfactant function demonstrated to be linked to compound altering dilational rheology
- In vitro study reproduces dose rate dependence/potencies seen in literature
- Modelling successfully fits all data from experiments suggesting mechanism is generic

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# Predicting Surfactant Toxicity using Coarse Grained MD Simulations

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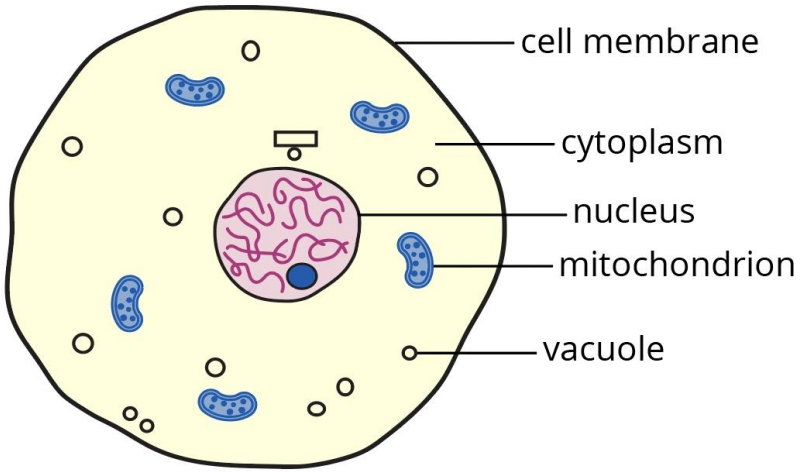
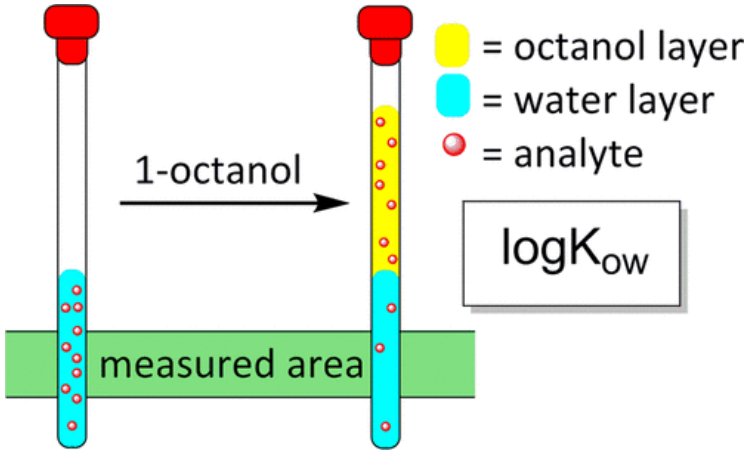
Durham University

# Log$K_{ow}$ in pharmacology

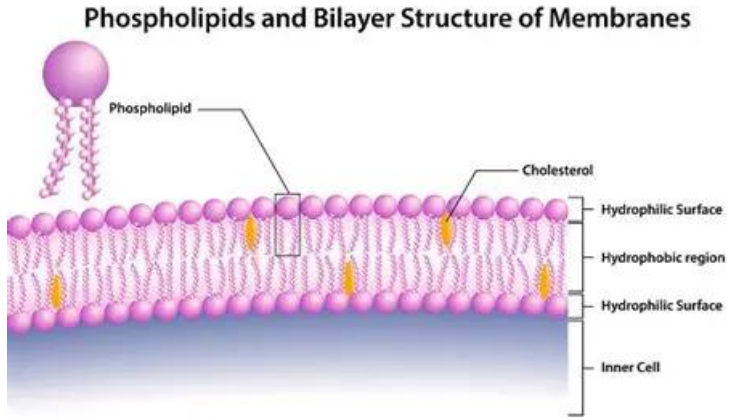
Widely used to determine the bioavailability of drugs as a measure of their lipophilicity




Lipophilicity assumed to drive bioavailability because of molecular partitioning into membranes $K_{mw}$




Cumming et al. *ACS omega* (2017)

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# $K_{ow}$ in pharmacology

$$\log K_{mw} = 0.92(\pm 0.062) \log K_{ow} + 0.37(\pm 0.20)$$

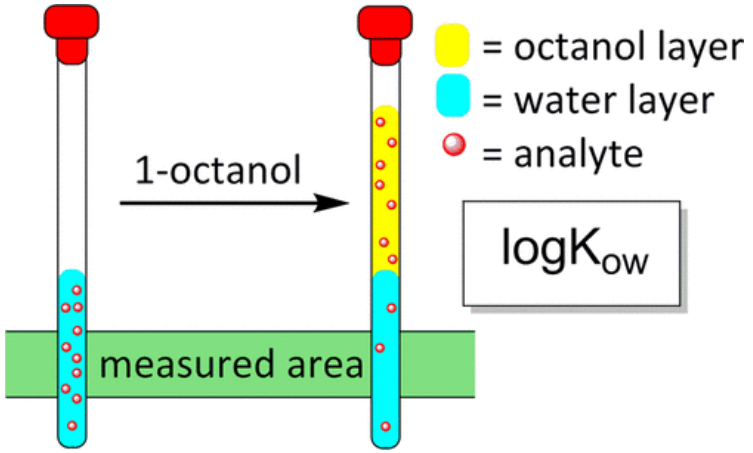
Klamt et al. J. Phys. Chem. B 2008

$$\log K_{mw} = 1.01 \log K_{ow} + 0.12$$

Bittermann et al., Chemosphere, 2016

Lucky coincidence that measuring $K_{ow}$ gets you pretty close to true quantity $logK_{mw}$

Will not work for **surfactants,** charged or large molecules

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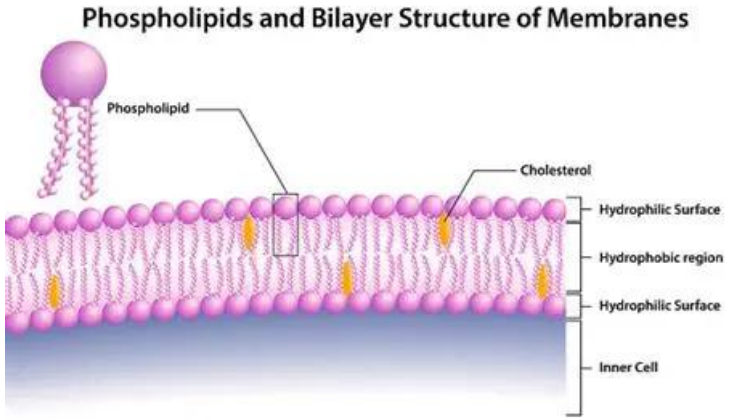


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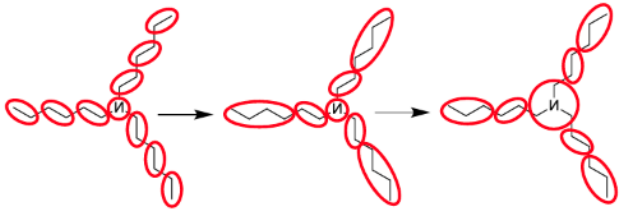
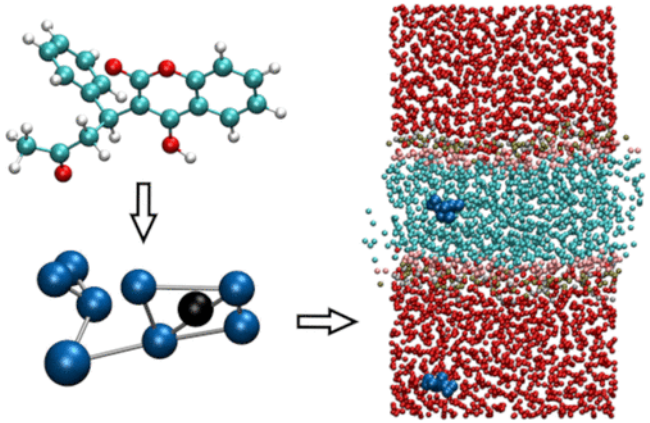
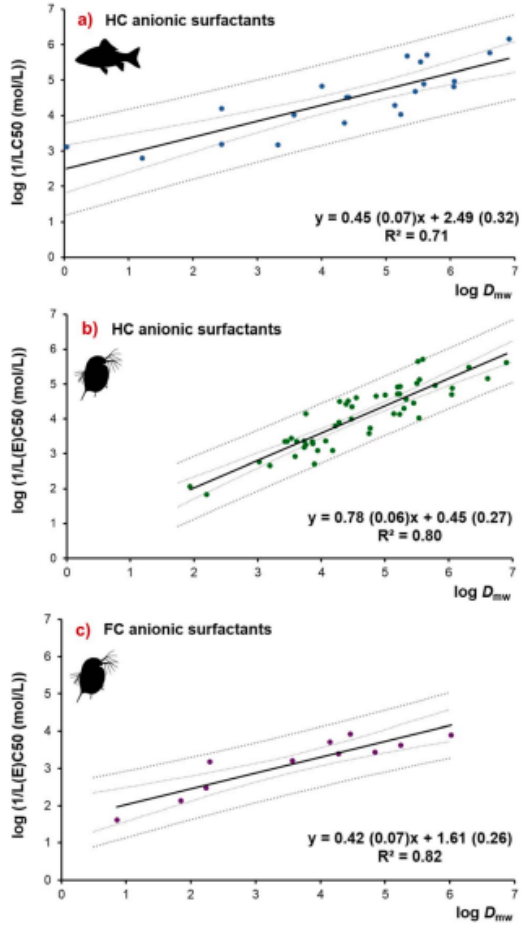
# Environmental Toxicology being doing - Simulations

Automated Coarse grained mapping
Algorithm developed by Durham





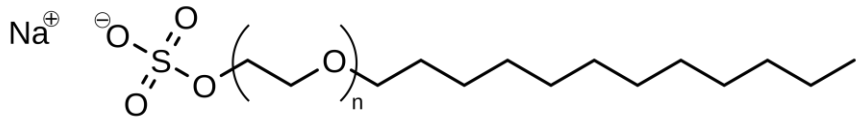
Membrane-Water Partitioning applied successfully for environmental impacts

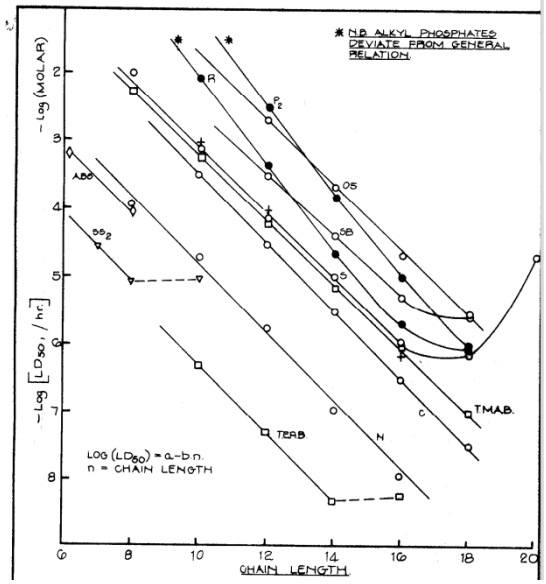



Potter et al. JCTC 2021

Gredelj et al. Envion. Sci.: Processes Impacts 2025

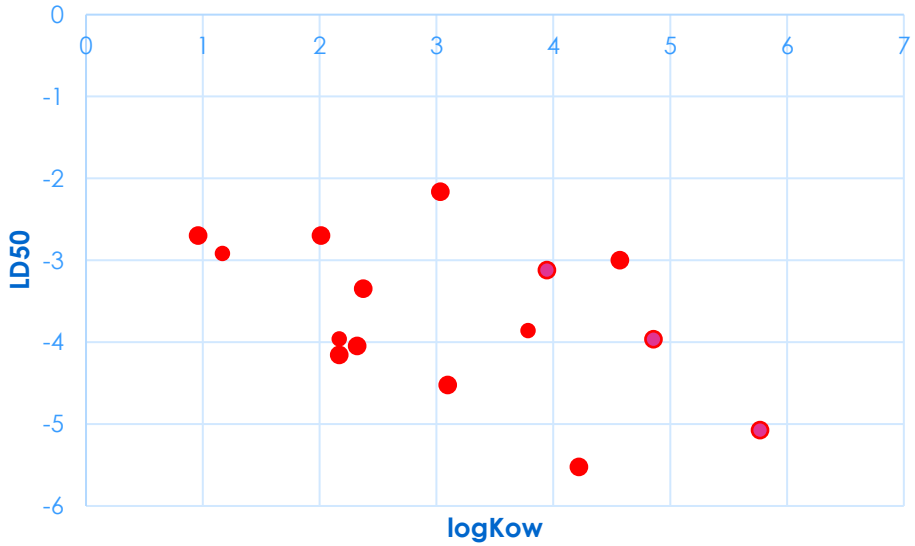
# Literature Experimental Studies




Experiments looking a HeLa cells show increasing toxicity with increasing chain length for several different headgroups

Traditional logKow method fails to yield an overall Trend for fixed chain-length (12 Carbons)



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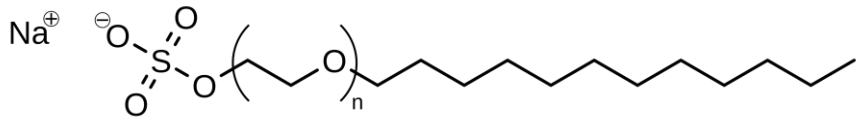
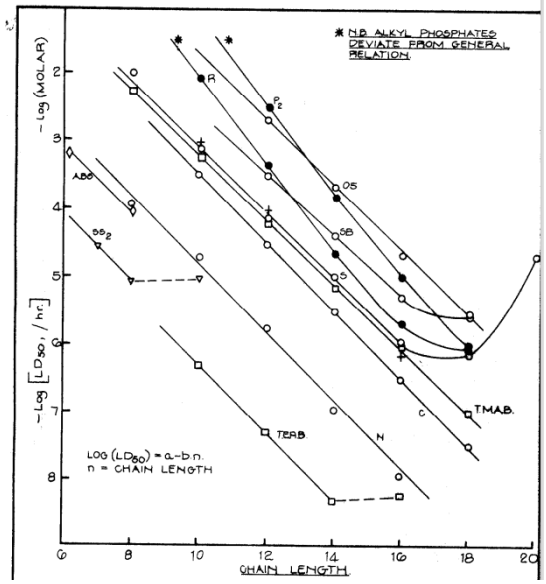
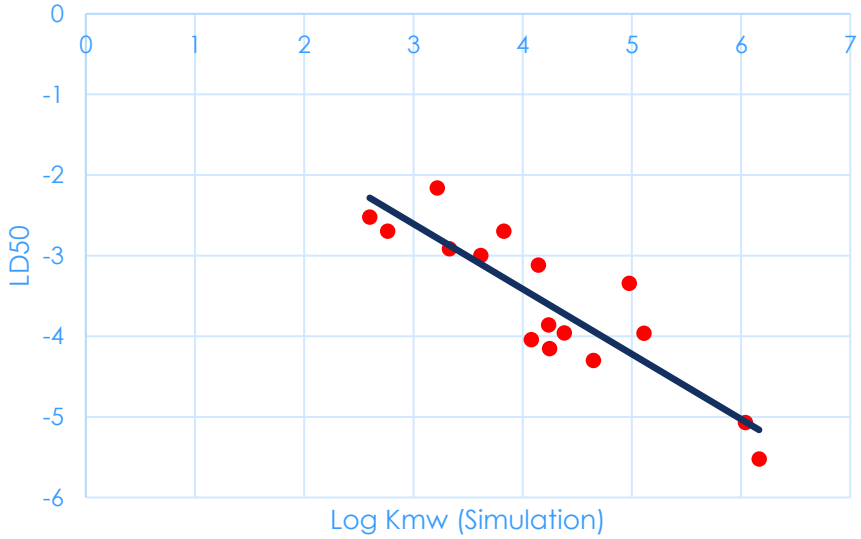



Experiments looking a HeLa cells show increasing toxicity with increasing chain length for several different headgroups

Traditional log$K_{ow}$ method fails to yield an overall Trend for fixed chain-length (12 Carbons)

Membrane water simulations cause overall curve collapse




**Conclusion** : Membrane partitioning predicted from simulation predicts surfactant toxicity in vitro

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# Skin Penetration

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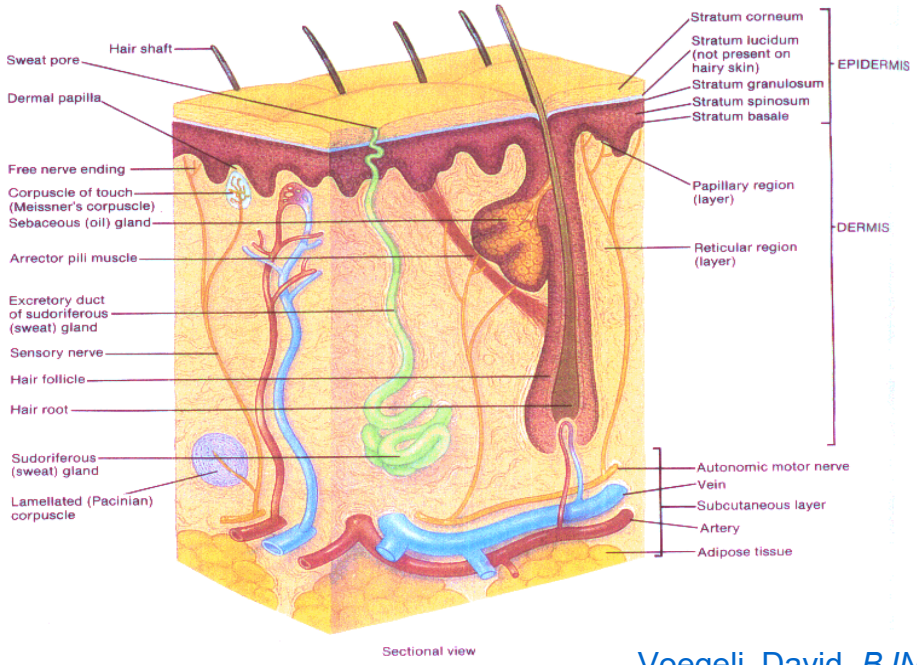
# Skin Penetration

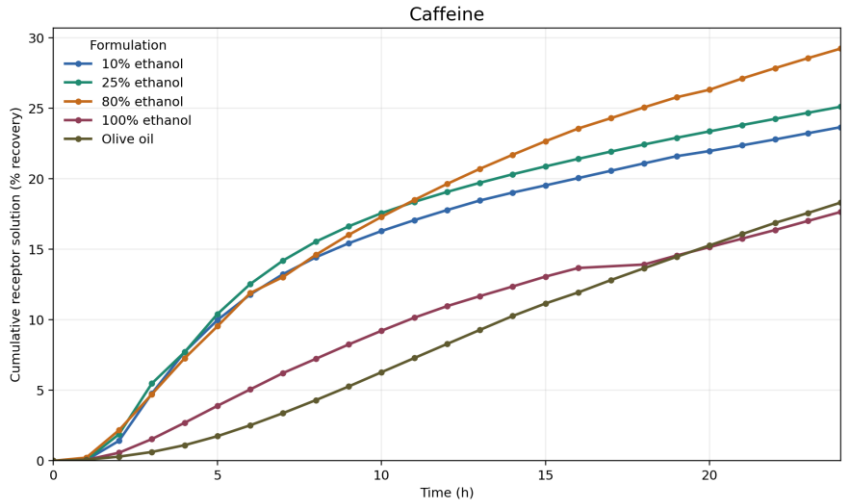
Skin is a complex structure of proteins, lipids with pores, blood vessels and other intricacies which all affect the penetration of different chemicals .

Typical method on real human skin with radiolabelled chemicals is expensive.

Both **chemical** and **formulation** properties affects skin penetration




Voegeli, David. *BJN* (2011)

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# Skin Penetration

## Surrogate membranes

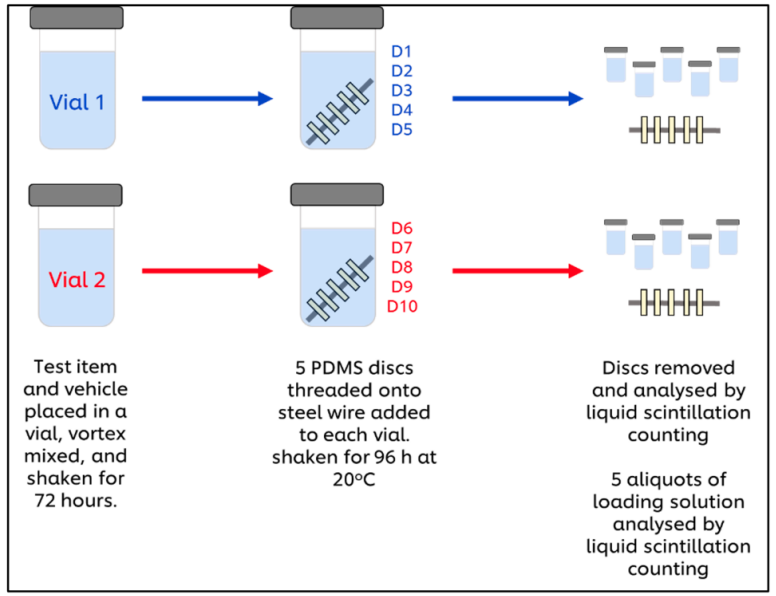
Assume that initial partitioning into skin is formulation dependent but diffusion remains constant

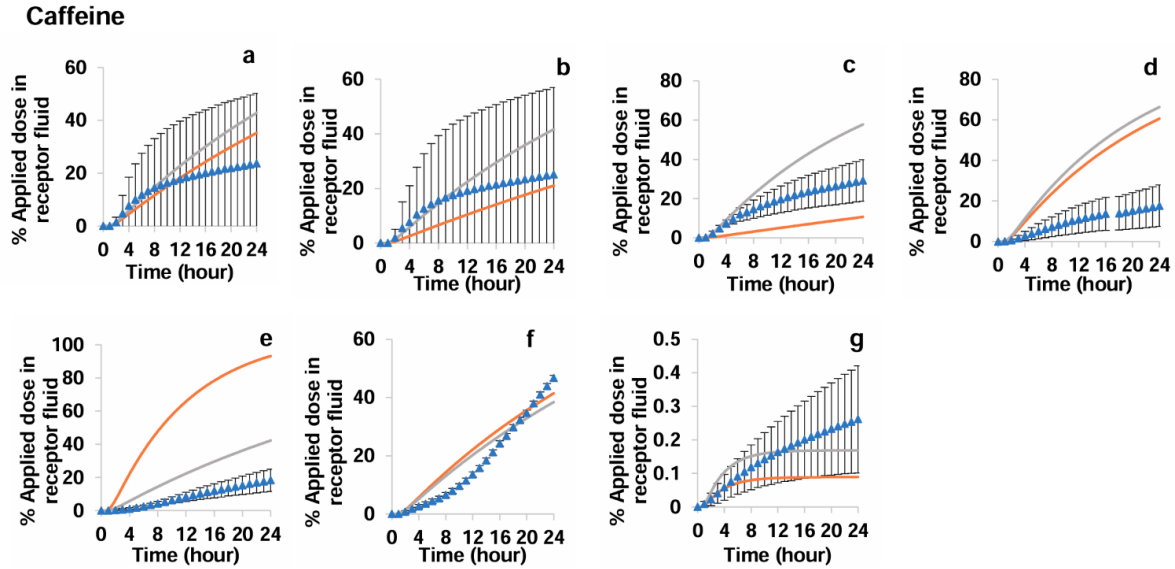
$$K_{i,j} \sim e^{\beta E_i} / e^{\beta E_j}$$

Assume Stratum Corneum similar to hydrophobic polymer PDMS

Use water as reference formulation

$$K_{sc,v} = \frac{K_{sc,w}}{K_{w,v}} = K_{sc,w} \frac{K_{v,PDMS}}{K_{w,PDMS}}$$

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# Skin Penetration

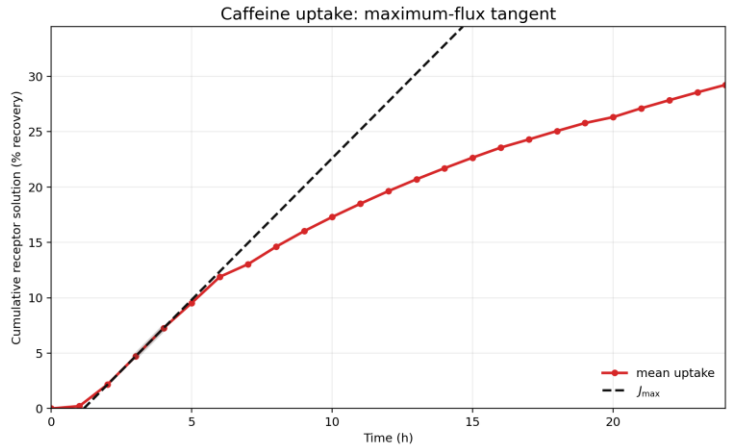
## Solubility Theory

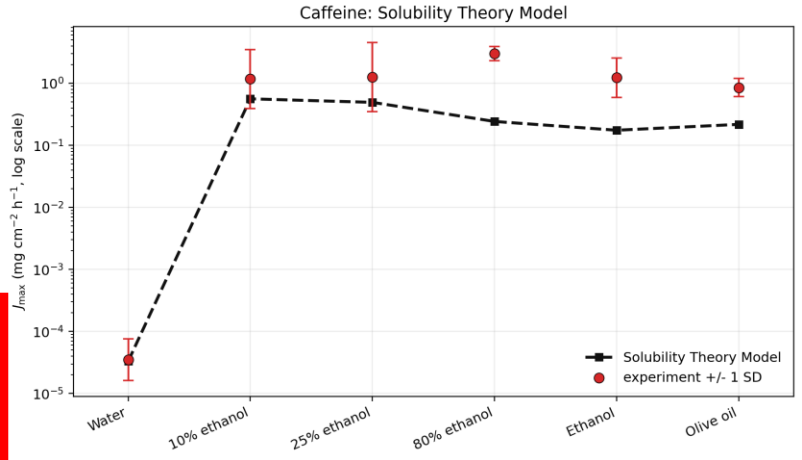
Reduce uptake curves to just early maximum flux $J_{max}$

Hansen Solubility Parameters characterise solubility of compounds in terms of δD (Dispersion), δP (Polarity) & δH (Hydrogen bonding)

Combined with solubility theory we can approximately predict the formulation effects

Conclusion : Skin partitioning physics can gain Insights from both polymer and solution theory in future




$$\mathrm{J_i} = \mathrm{J_0}\,\frac{\mathrm{a_i}}{1+\mathrm{a_i}}\exp(\lambda_v\, V_i^{2/3})$$

$$\mathrm{a_i} = \mathrm{a_0}\,\mathrm{x_i}\exp(-\mathrm{b}\,\Delta\mathrm{G_i}/\mathrm{RT})$$

$$\mathrm{x_i} = C_i/\mathrm{MW_i}$$

$$\Delta\mathrm{G}_i = \Delta\mathrm{G}_{i,sc} - \Delta\mathrm{G}_{i,v} - \Delta\tilde{\mathrm{G}}_{v,sc}$$

$$\Delta\mathrm{G}_{i,sc} = \mathrm{V_i}\,\mathrm{Ra_i}^2$$

$$\Delta G_{i,v} = \sum_{\mathrm{k}\in\mathrm{v}} \mathrm{w_k V_i}\,\mathrm{Ra_{i,k}}^2$$

$$\Delta\tilde{\mathrm{G}}_{v,sc} = \mathrm{V_v}\,\mathrm{Ra}_{v,sc}{}^2 - \langle\,\mathrm{V_v}\,\mathrm{Ra}_{v,sc}{}^2\rangle$$

$$\mathrm{Ra_{i,j}}^2 = 4(\delta\mathrm{D_i} - \delta\mathrm{D_j})^2 + (\delta\mathrm{P_i} - \delta\mathrm{P_j})^2 + (\delta\mathrm{H_i} - \delta\mathrm{H_j})^2$$

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# Skin Penetration

## Solubility Theory

Reduce uptake curves to just early maximum flux $J_{max}$

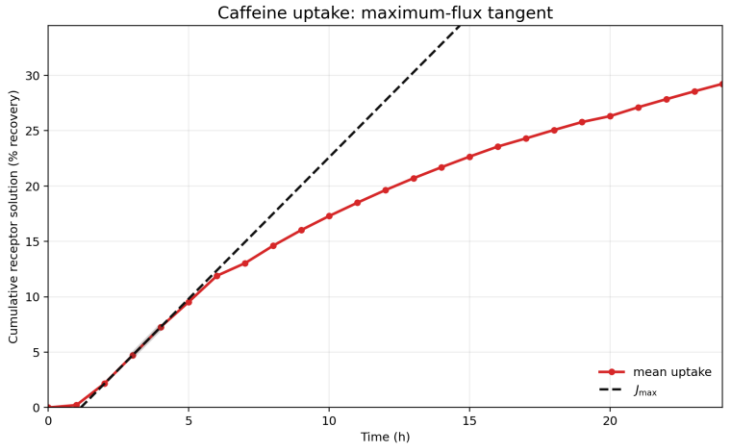
Hansen Solubility Parameters characterise solubility of compounds in terms of δD (Dispersion), δP (Polarity) & δH (Hydrogen bonding)

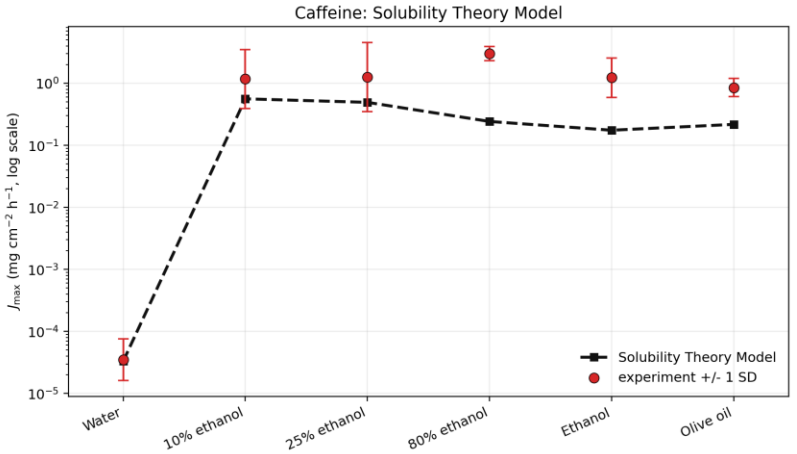
Combined with solubility theory we can approximately predict the formulation effects

$$\mathrm{J_i} = \mathrm{J_0}\ \frac{\mathrm{a_i}}{1+\mathrm{a_i}} \exp(\lambda_v\ V_i^{2/3}) \quad \mathrm{a_i} = \mathrm{a_0}\ \mathrm{x_i}\ \exp(-\mathrm{b}\ \Delta \mathrm{G_i}/\mathrm{RT})$$

$$\mathrm{x_i} = C_i/\mathrm{MW_i}$$

$$\Delta \mathrm{G}_{i,sc} = \mathrm{V_i}\ {\mathrm{Ra_i}}^2$$
$$\Delta G_{i,v} = \sum_{\mathrm{k}\in \mathrm{v}} \mathrm{w_k V_i}\ {\mathrm{Ra_{i,k}}}^2$$
$$\Delta \tilde{\mathrm{G}}_{v,sc} = \mathrm{V_v}\ {\mathrm{Ra}_{v,sc}}^2 - \langle\ \mathrm{V_v}\ {\mathrm{Ra}_{v,sc}}^2 \rangle$$




Conclusion : Skin partitioning physics can gain Insights from both polymer and solution theory in future

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$$\Delta \mathrm{G}_i = \Delta \mathrm{G}_{i,sc} - \Delta \mathrm{G}_{i,v} - \Delta \tilde{\mathrm{G}}_{v,sc} \quad {\mathrm{Ra_{i,j}}}^2 = 4(\delta \mathrm{D_i} - \delta \mathrm{D_j})^2 + (\delta \mathrm{P_i} - \delta \mathrm{P_j})^2 + (\delta \mathrm{H_i} - \delta \mathrm{H_j})^2$$

# Overall Conclusion

Unilever

Soft matter science offers many opportunities for developing alternatives to animal testing

- Lung Surfactant Inhibition
- Surfactant Toxicity
- Skin Absorption

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# Acknowledgements

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FOR THE WORKING ENVIRONMENT


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# Thank you and Questions?