ETH-conference, 18th June 2025

ULTRHAS
ULtrafine particles from TRansportation - Health Assessment of Sources

Effects of direct and indirect exposure of combustion-derived particles on the human intestine tissue

Gowsinth Gunasingam

Adolphe Merkle Institute, University of Fribourg, Switzerland

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 955390

NIPH Norwegian Institute of Public Health

HelmholtzZentrum münchen German Research Center for Environmental Health

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Aim

<< We daily inhaled ~ 15 x10^{12} nanoparticles >>

<< inhaled nanoparticles can cross the air-blood barrier into the circulation and accumulate in secondary organs and tissues.>>

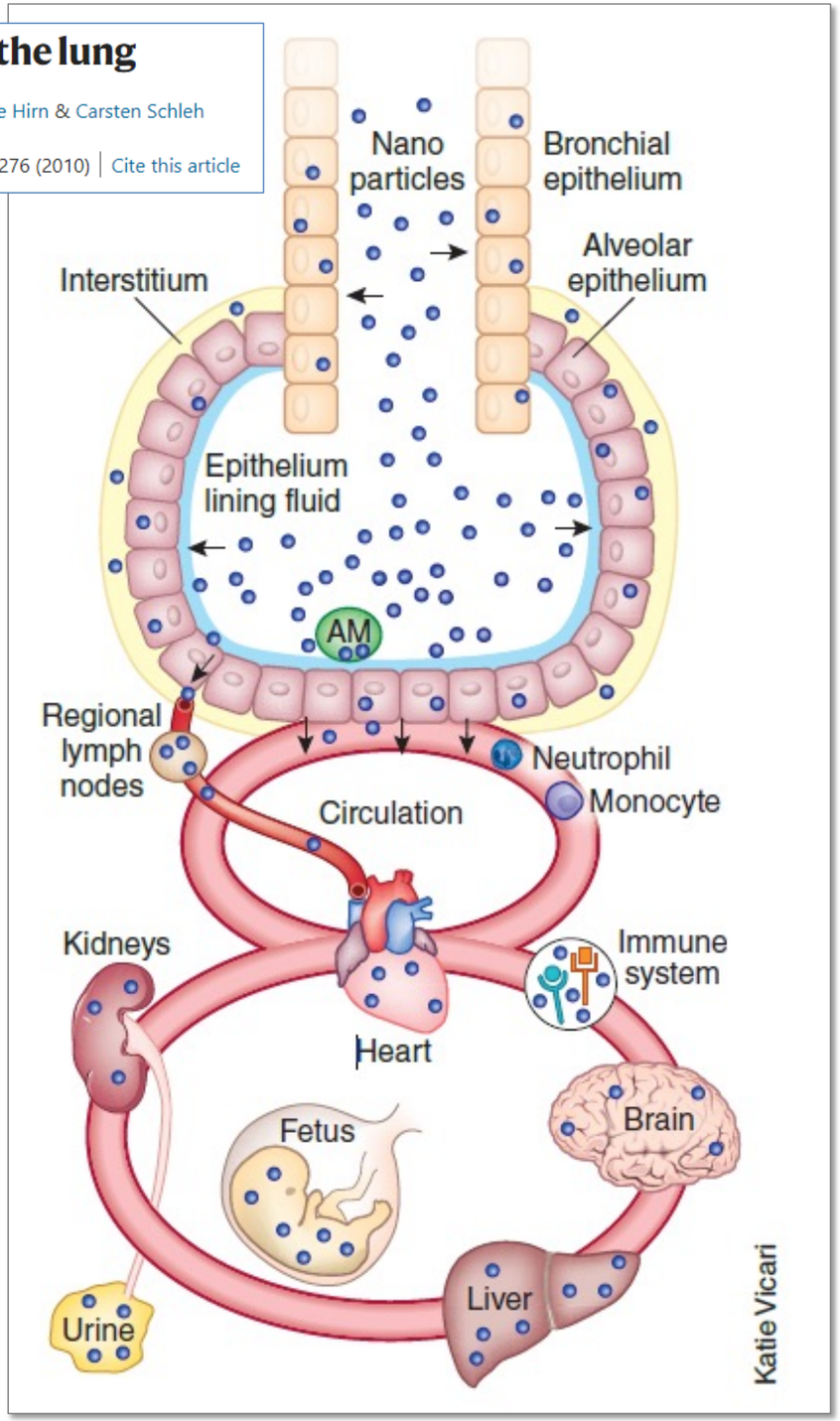
Kreyling et al., Nat Biotech (2010)

We aim to understand the toxicity of combustion-derived nanoparticles in organs beyond the lung, i.e., liver, brain, white blood cells, and intestine.

Nanoparticles in the lung

Wolfgang G Kreyling ✉, Stephanie Hirn & Carsten Schleh

Nature Biotechnology **28**, 1275–1276 (2010) | Cite this article

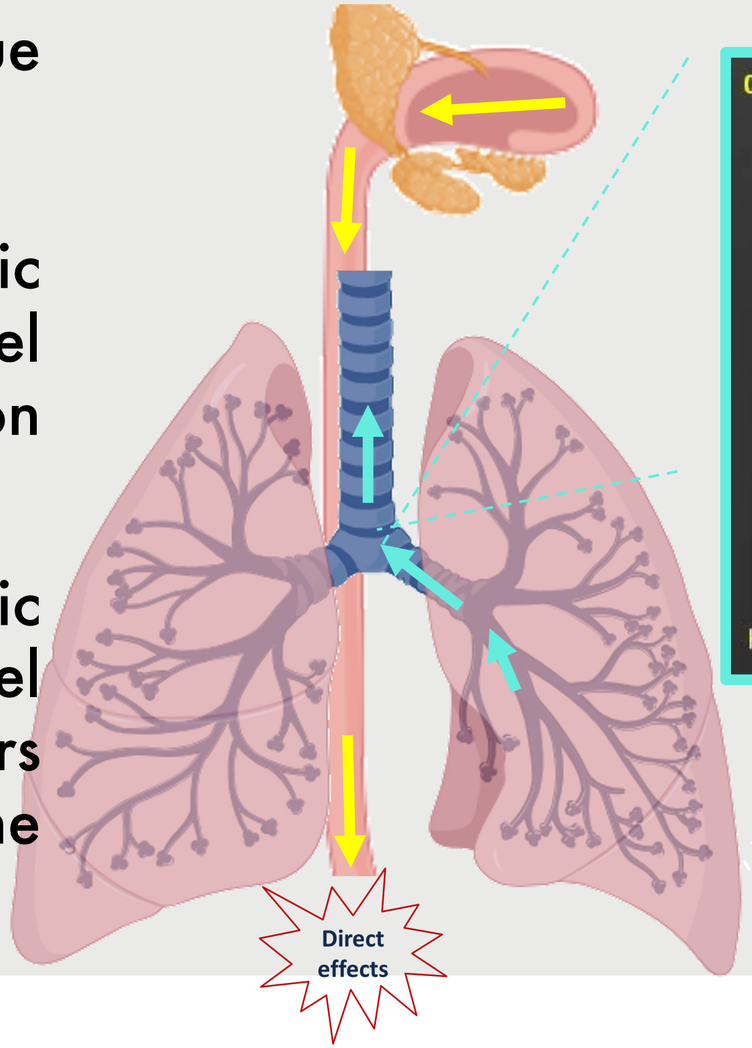


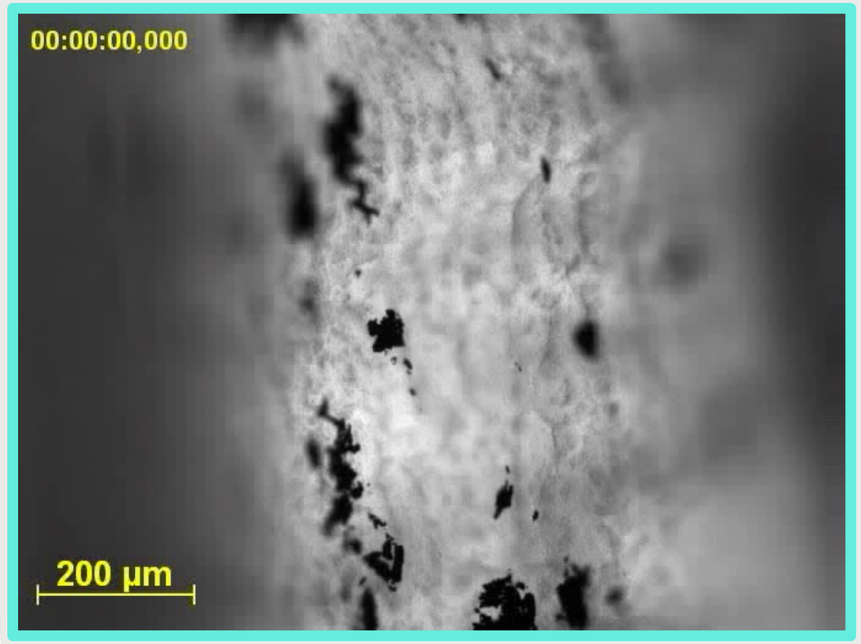
Effects of diesel exhaust particles on the human intestine

An established 3D intestinal tissue model will be used to test:

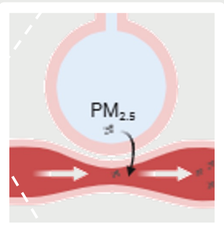
1) Direct effects, *i*.e., to mimic mucociliary clearance of diesel exhaust particles after inhalation and swallowing;

2) Indirect effects, *i*.e., to mimic exposure of the intestine via diesel exhaust particles and mediators transported from the lungs via the bloodstream.





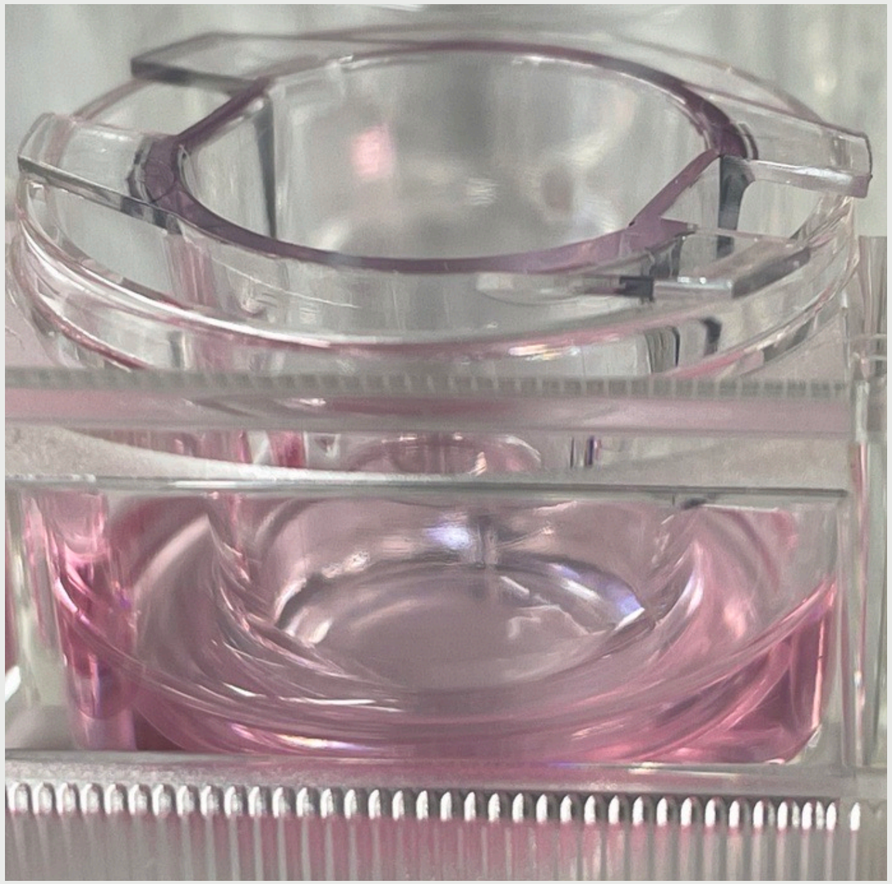
Henning *et al.*, AAPS PharmSciTech (2008)

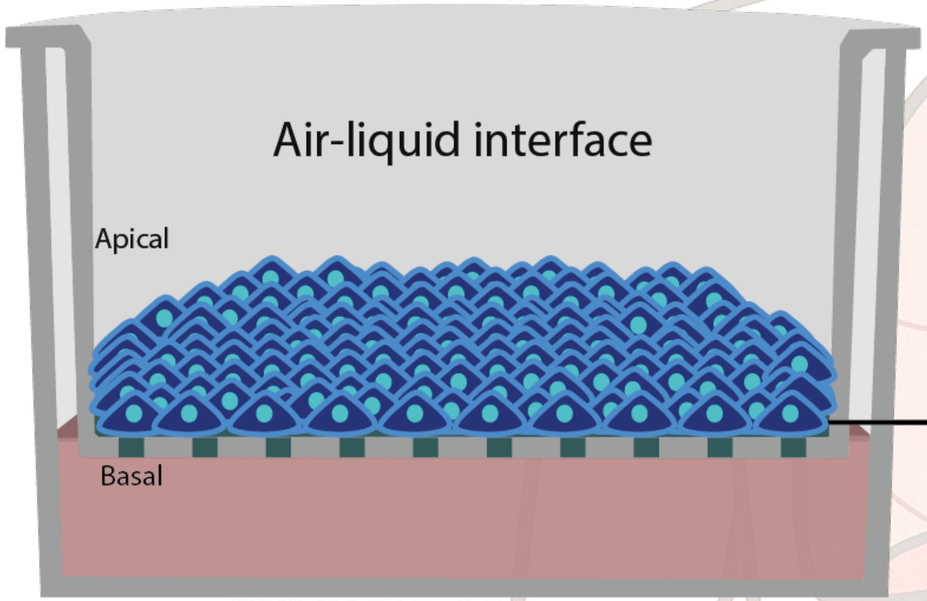


Indirect effects

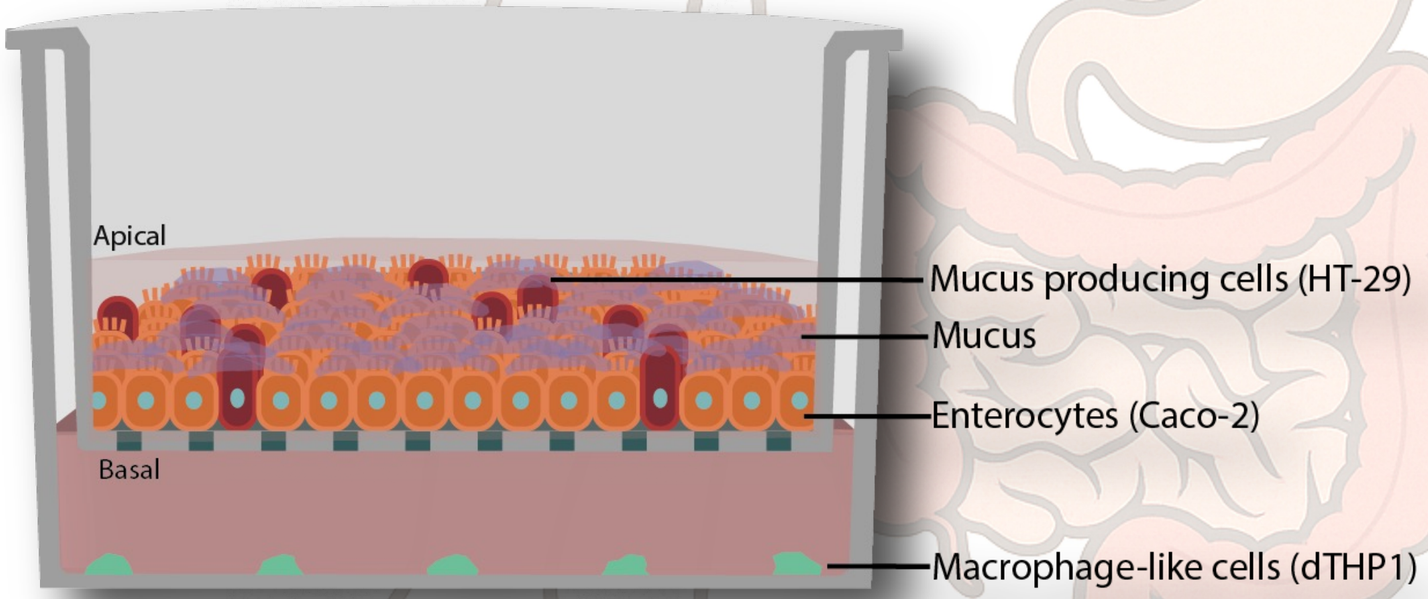
Respiratory tract
Gastrointestinal tract
Blood circulation

3D tissue models





Gunasingam et al., Particle and Fibre Toxicology (2024)

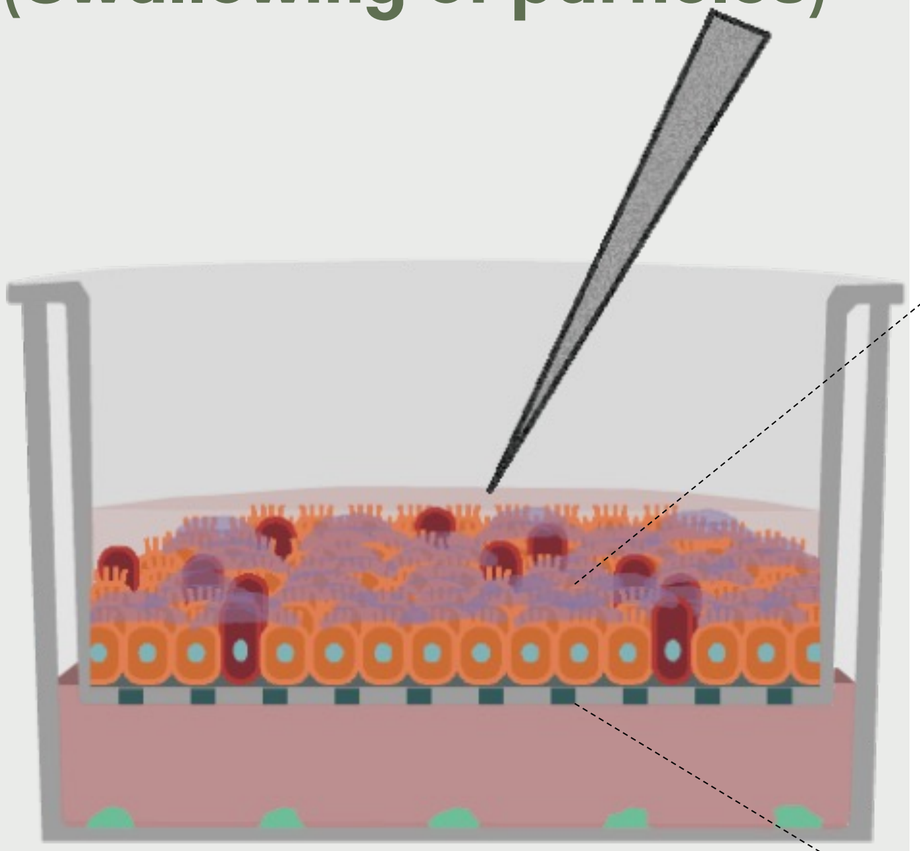


Kämpfer et al., In vitro models (2022)

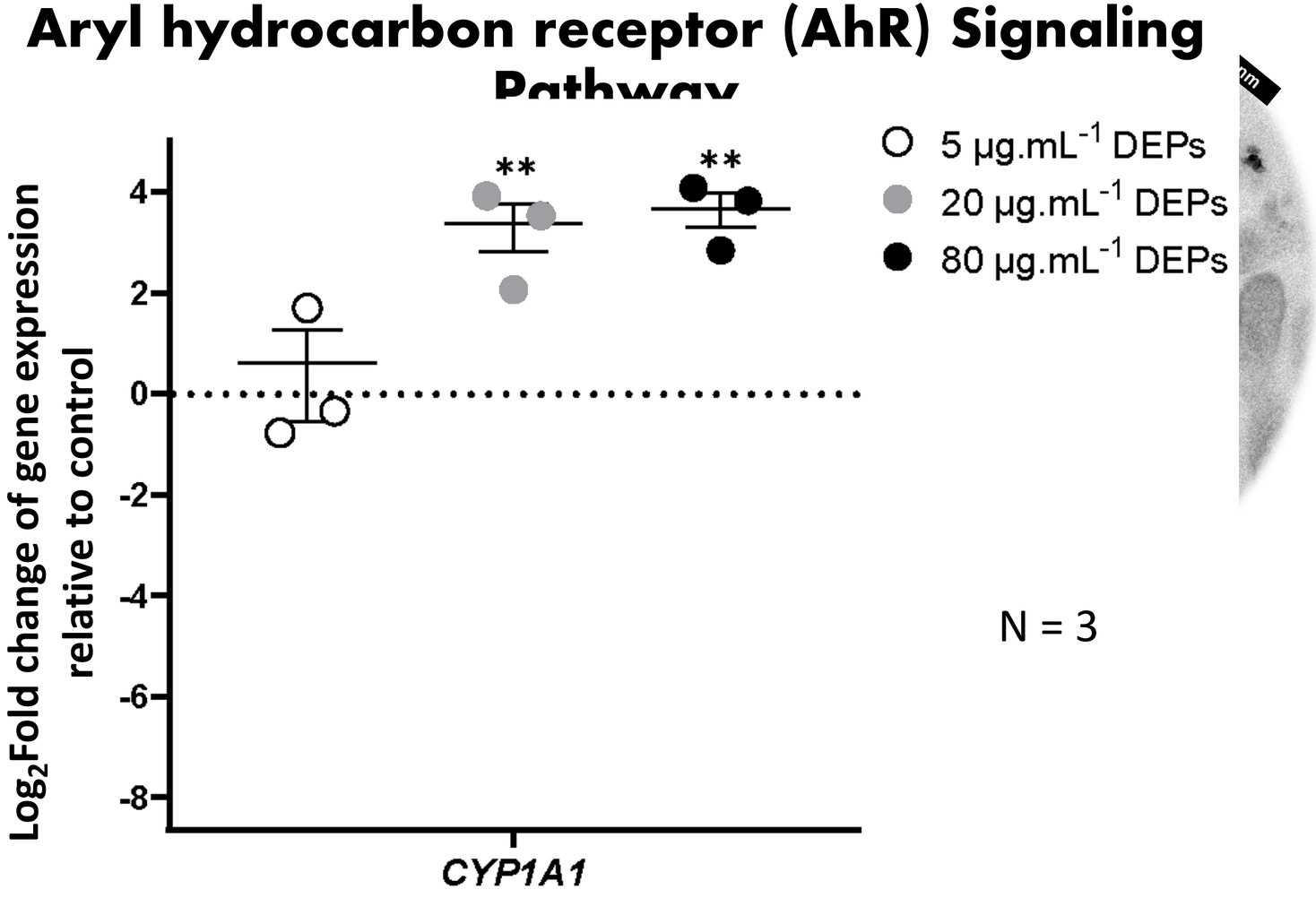
Combustion-derived particles

Direct exposure

(Swallowing of particles)



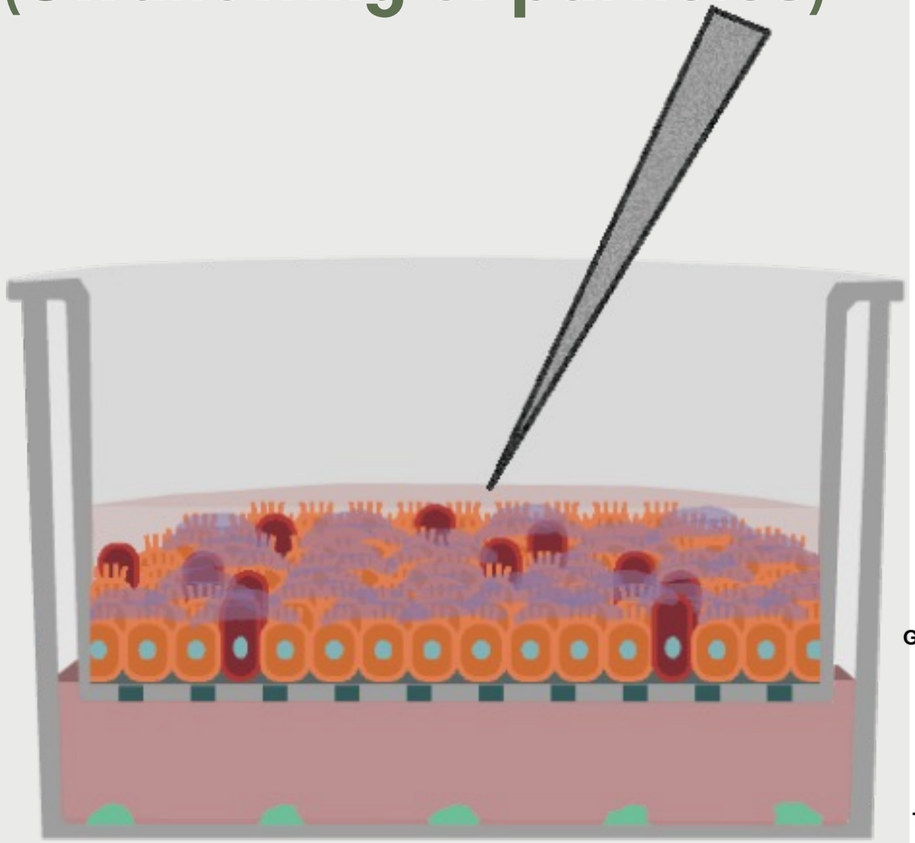
Exposure for 24 hours, at 37°C



- Significant upregulation of *CYP1A1* gene expression 24 hours after swallowing particles.

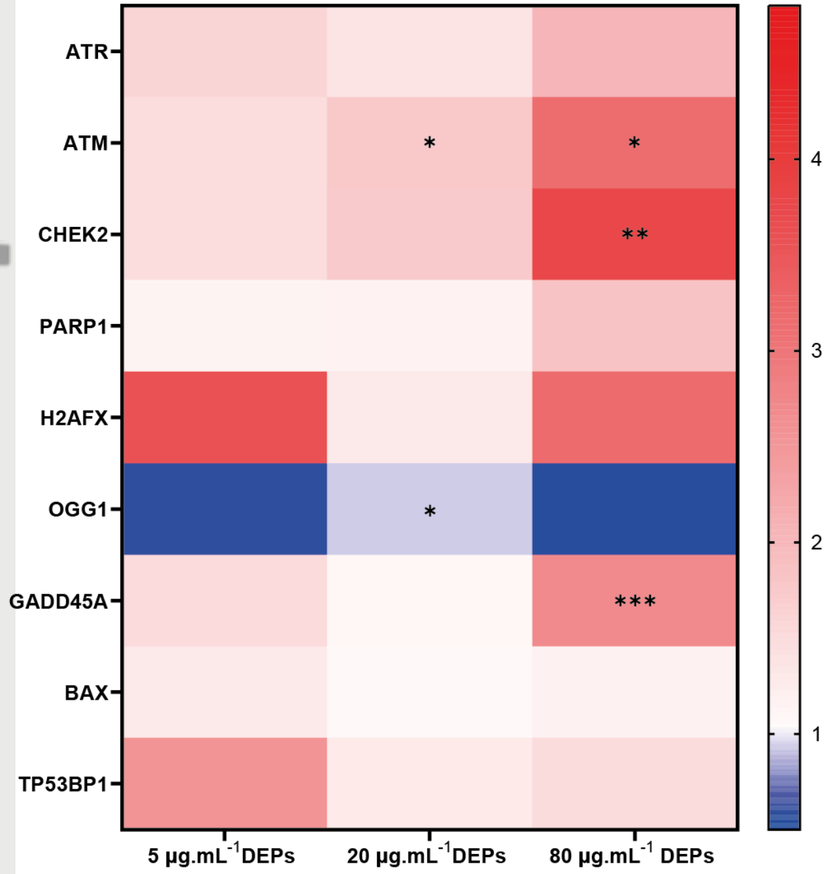
Direct exposure

(Swallowing of particles)



Exposure for 24 hours, at 37°C

Genotoxicity: DNA damage & Repair mechanism



	5 µg.mL^{-1}	20 µg.mL^{-1}	80 µg.mL^{-1}
ATR	1.6	1.4	2.1
ATM	1.5	1.8*	3.1*
CHEK2	1.5	1.8	3.8**
PARP1	1.1	1.2	1.8
H2AFX	3.6	1.3	3.2
OGG1	0.6	0.9*	0.6
GADD45A	1.5	1.1	2.7***
BAX	1.3	1.1	1.2
TP53BP1	2.6	1.3	1.5

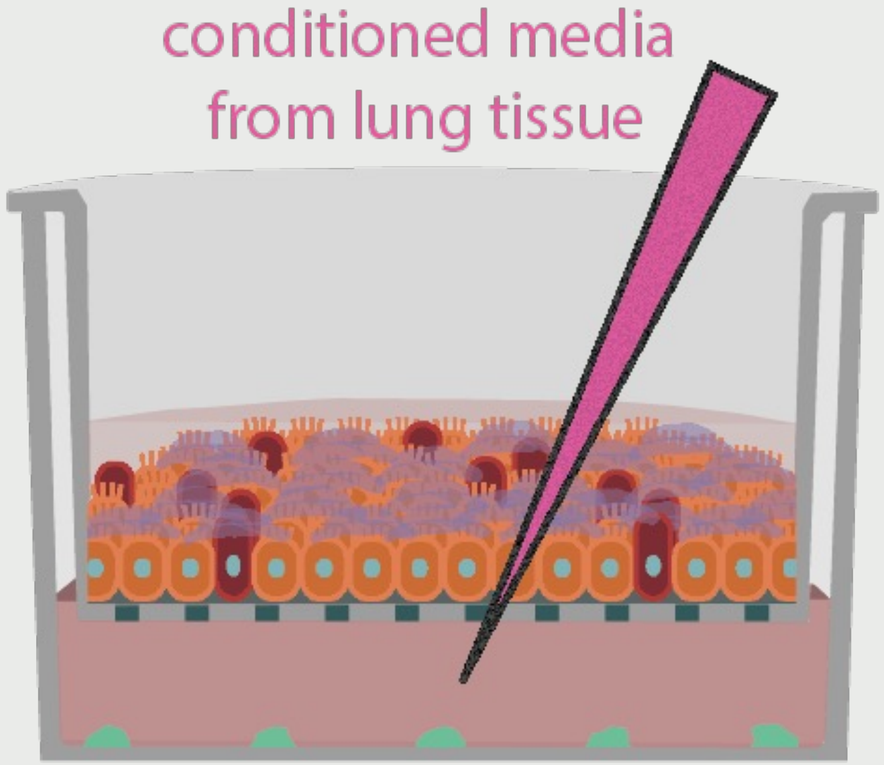
N = 3

- Significant upregulation of genes associated with DNA damage and repair 24 hours after swallowing particles.

Indirect exposure

(Systemic effects)

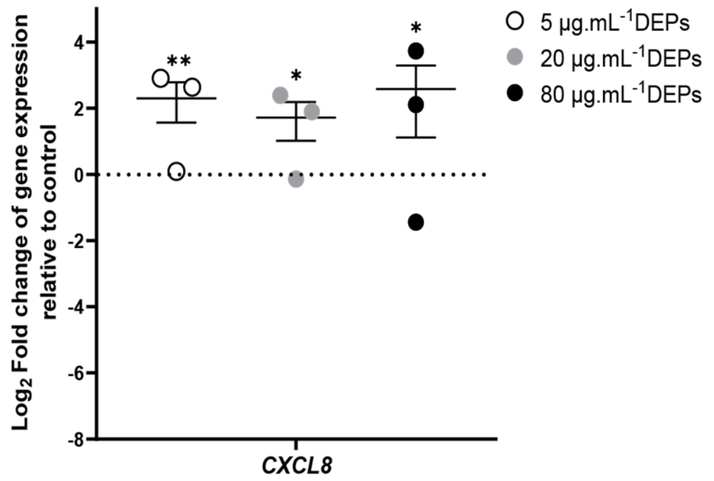
Condi **i**



Exposure for 24 hours, at 37°C

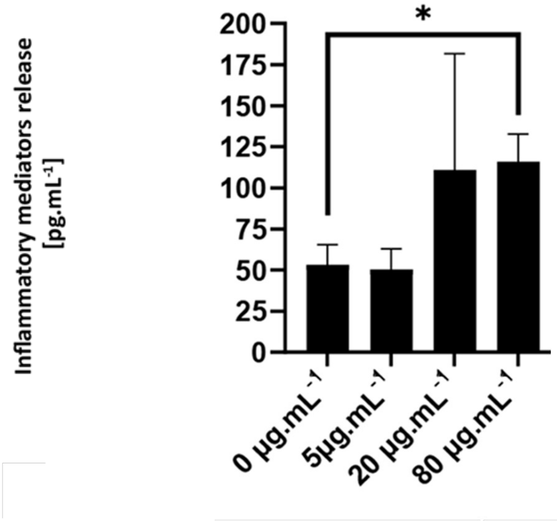
Inflammatory reactions: Gene & Inflammatory mediators

***CXCL8* gene expression associated with inflammation from indirect basal exposure of the intestine tissue to DEPs**



Inflammatory mediators release from indirect basal exposure of the intestine tissue to DEPs

Tumor Necrosis Factor alpha (TNFα)

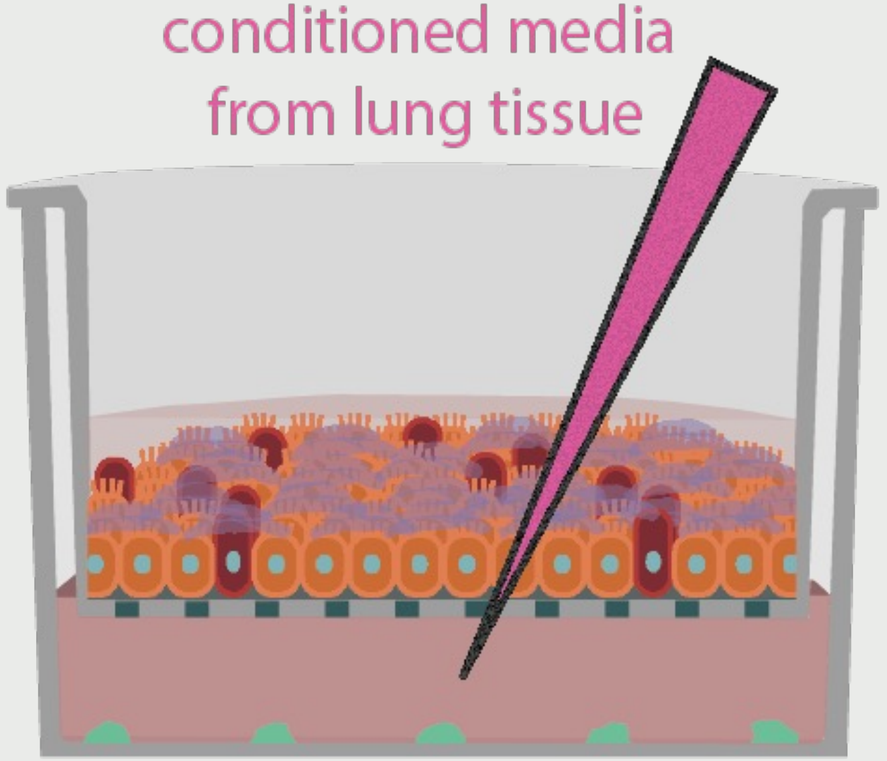


N = 3

- Significant systemic effects of conditioned media from lung tissue on the intestine.

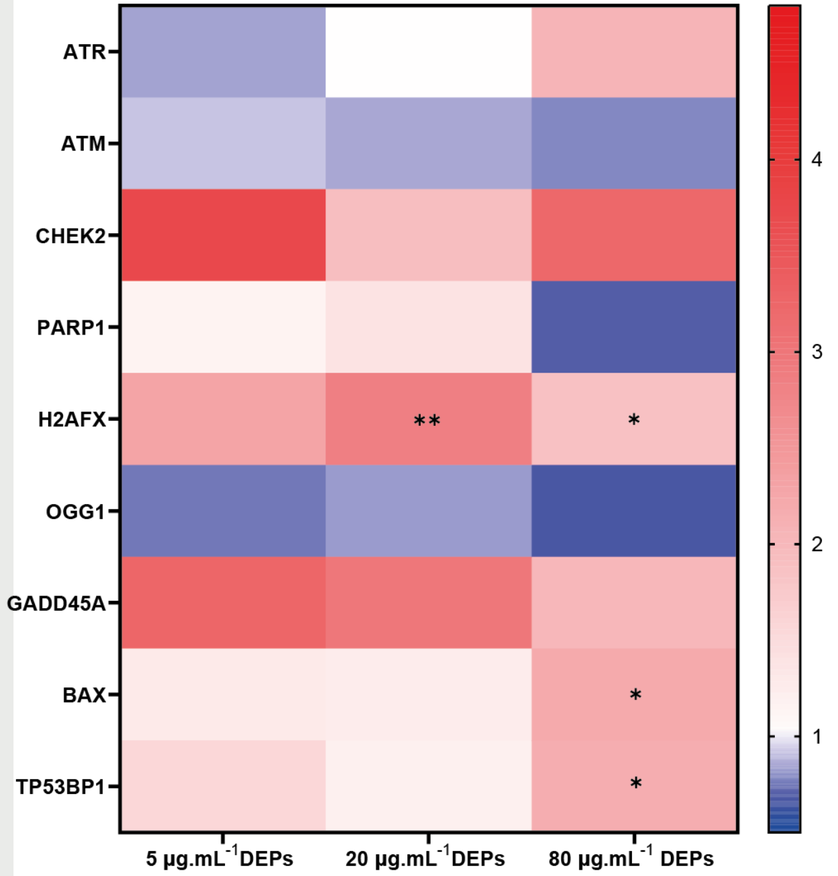
Indirect exposure

(Systemic effects)



Exposure for 24 hours, at 37°C

Genotoxicity: DNA damage & Repair mechanism



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BAX	1.3	1.3	2.2*
TP53BP1	1.6	1.2	2.2*

N = 3

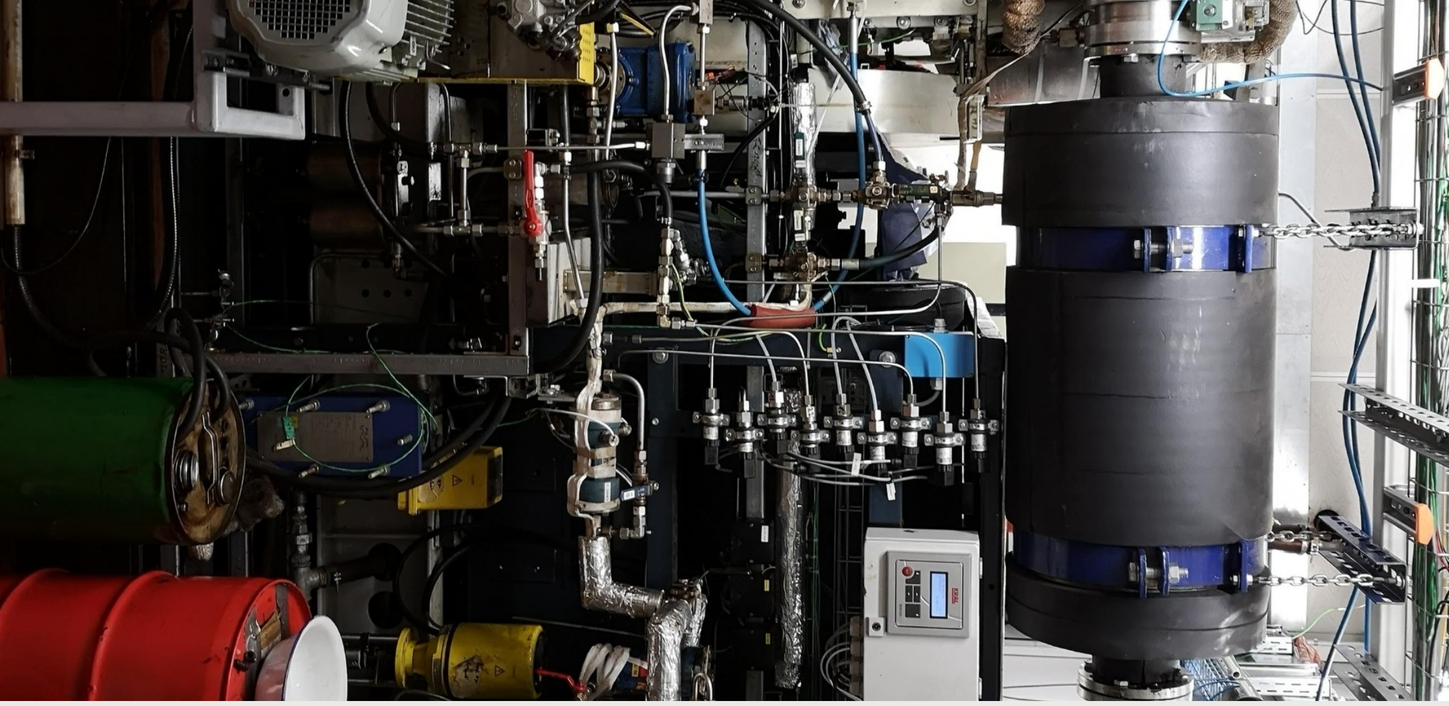
- Significant upregulation of genes associated with DNA damage and repair 24 hours after systemic effects.

Take home messages

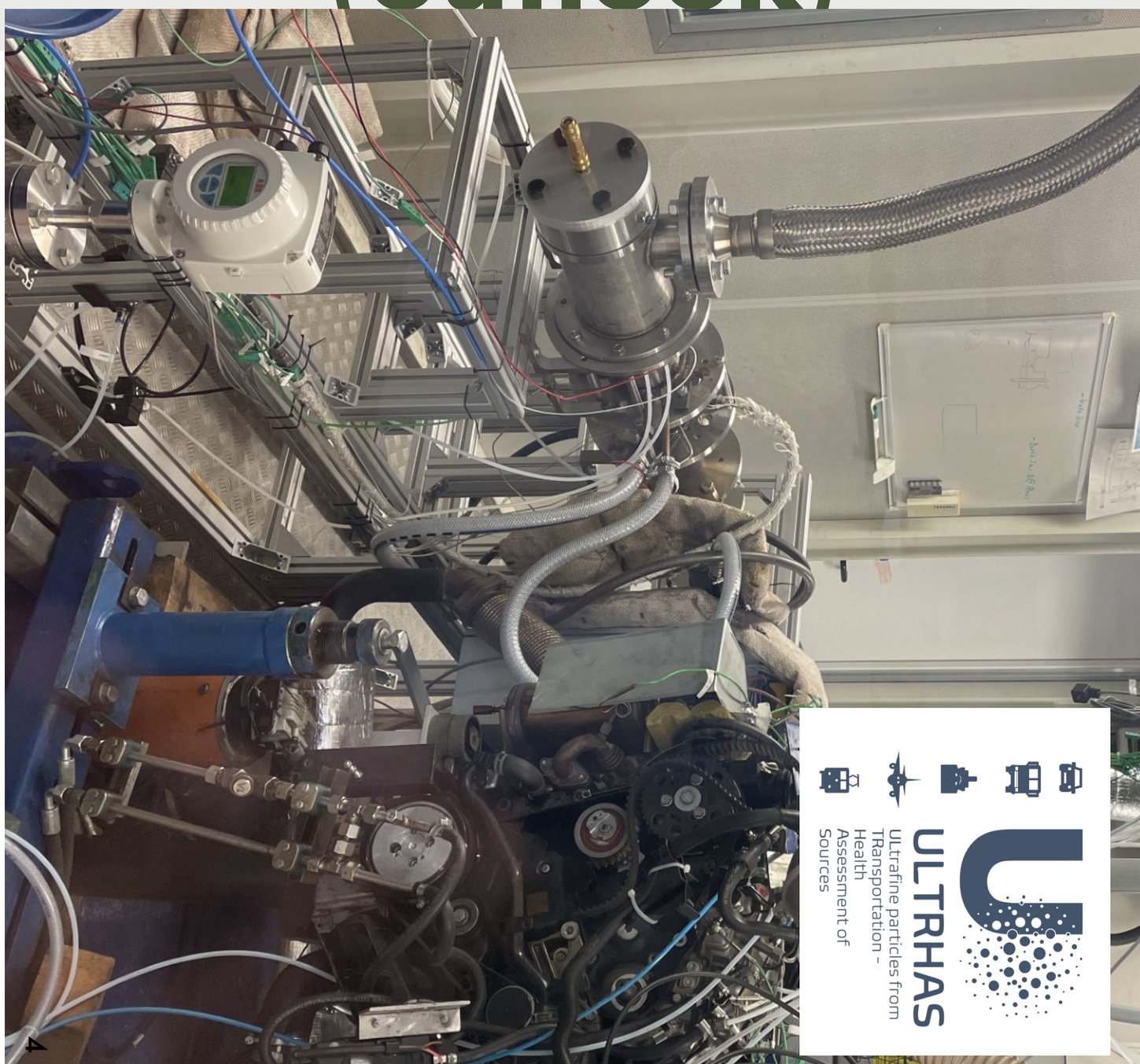
- The human intestinal 3D co-culture model can be used to mimic direct and systemic effects;

<u>Direct exposure:</u>
No inflammatory reactions were observed, potentially due to particles trapped in the mucus; However, increased expression of the CYP1A1 and stronger genotoxic responses were observed, potentially due to, e.g., PAH/metals detachment from the particles that interacted with the intestinal cells.

<u>Conditioned medium exposure:</u>
Inflammatory reactions were observed in the intestinal tissue, potentially due to the inflammatory mediators in the conditioned cell culture medium from lung-exposed tissue.



Combustion-derived particles (outlook)



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Prof. Dr. Barbara Rothen - Rutishauser

Prof. Dr. Alke Petri - Fink

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