TNO innovation for life

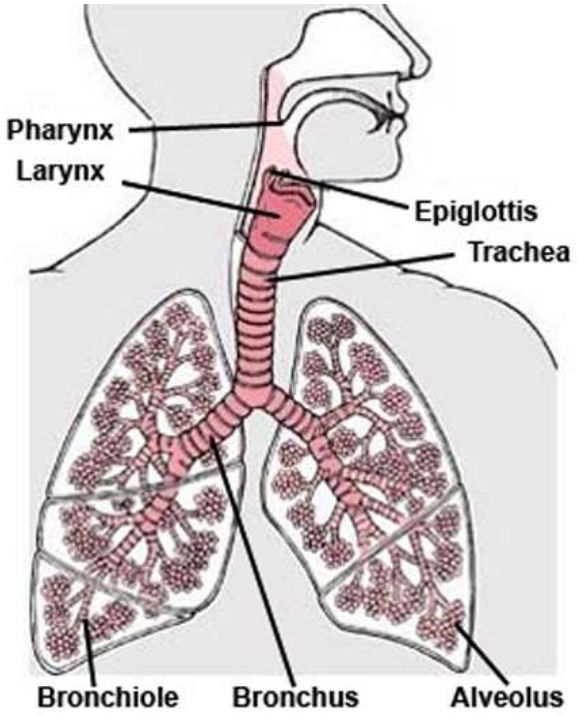
in vitro inhalation model

Why? In vitro test for inhalation exposure route

Inhalation is important route for exposure:

- intentional: drug delivery (pharmacy)
- non-intentional: risk's of chemicals (workplace, consumer products etc.)

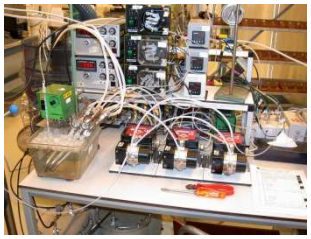
- In vivo animal models are not (always) a good representative to predict human situation



>40 year experience in inhalation studies

- Acute studies (single 4 hour exposure)
- Sub-acute studies (14-28 days)
- Sub-chronic studies (90 days)
- Chronic studies / carcinogenicity (1-2 years)
- Irritation (sensory) / Alarie test
- Respiratory allergy
- Combination with repro-studies, neuro-studies or gentox studies
- In vitro toxicity
- CxT (Concentration - time relationship in acute toxicity)

- State of the art generation and monitoring techniques for vapours, gasses and aerosols
- Custom-made designs
- Aerosols containing: - micro sized particles
  - nano structured particles
  - nano particles
- Providing well controlled test atmospheres with challenging test substances



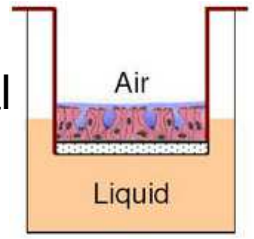
- Materials tested:
  - Chemicals (powders, liquids, vapours)
  - Agro-chemicals (pesticides)
  - Pharmaceuticals
  - Food ingredients (enzymes)

In vitro human inhalation model

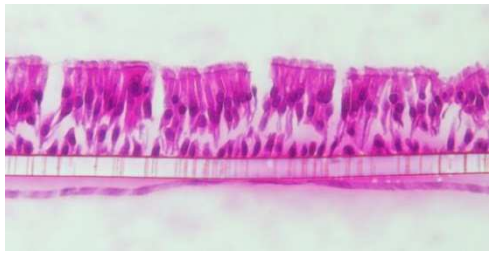
Combination of:

1.Representative primary human epithelial lung cells at a Air-Liquid Interface (ALI):

- Nasal, tracheal or bronchial
- Relevant morphology



single insert,
cross section



2. Air exposure via module:

- Testing of complex mixtures (gasses and particles)

Advantages of in vitro human inhalation model

- Relevant morphology (human origin)
  - Mucus production
  - Metabolism/ detoxification
  - Presence of tight junctions
  - Presence of ciliated cells/ ciliary beating
- Effect parameters:
  - Barrier function
  - Oxidative stress
  - Release of inflammatory mediators
  - Functional changes (ciliary beating, mucus production)
  - Cytotoxicity
  - Genotoxicity
- Potential reduction of animal use

Further development

- Assessment of various end points in the same model
  - Combined efficacy, toxicity, PK
- Dynamic air exposure (Vitrocell)
- Validation/comparison with in vivo models and other in vitro models; ideally extrapolation to clinic/human studies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Would an *in vitro* test for the inhalation route be beneficial for you?

When would this in vitro test be of value for your company?

- Screening purposes, faster
- Less material needed
- Human relevancy
- Combined efficacy/toxicity (local effects)
- Complementary to in vivo experiments
- Replacement of in vivo experiments
- Other…

Why TNO?

- **Multidisciplinarity**
  - In vitro tox, in vivo tox, systems tox, risk assessment, PK modelling and analytical equipment/expertise all under the same roof
- **Innovative toxicity tests**
  - **Track record** in development and implementation of innovative *in vitro* (toxicity & PK) assays
  - **Excellent** in inhalation (in vitro/in vivo) and skin expertise
  - Extensive (chemicals/food/pharma) industry / SME / In vitro society / authorities **network** to efficiently embed innovations
  - Option for **partnering** with governmental matching (ELIco)
  - **Quality** Standard


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- Contact information:

Ingeborg Kooter

Ingeborg.kooter@tno.nl

+31-6-10670491