IVTIP In Vitro Testing Industrial Platform

The applicability of in vitro projects for product safety assessment

experiences of the
in vitro testing industrial platform IVTIP

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IVTIP In Vitro Testing Industrial Platform

What is IVTIP?

- IVTIP is a platform composed of companies with an active interest in *in vitro* testing
- Currently over 30 companies
  - small, medium and large enterprises
  - pharmaceutical, chemical, cosmetic, CROs or food industry
- IVTIP is an organization existing for and by the members. Members are scientists active in the area of *in vitro* and *in silico* (non-testing) methods.

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Objectives of IVTIP?

- Actively supporting and applying the 3R principle: Replacement, Reduction and Refinement.
- Promoting the fourth R: Responsibility in research promoted by industry.
- Actively promoting technology transfer between European researchers and industries.

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What are they doing to reach our goals?

- Advise EC institutions about activities and needs for alternative methods.
- Inform industry about upcoming EU activities and new regulations involving *in vitro* testing.
- Participate in EU projects, to stimulate applicability of methods for industrial use and actively supporting knowledge transfer.
- Evaluation, from an industrial point of view, of EU research projects to facilitate technology transfer to IVTIP members.

FP6/7 EU projects in which IVTIP is involved

- ReProTect: leader Workpackage 7 Technology and information scout
- Sens-it-iv: member of Workpackage 9 Dissemination of information and technology transfer

- LINTOP: Steering committee
- ESNATS: Steering committee

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What are demands of industry?

- Scientifically justified methods; results obtained with *in vitro* methods should be relevant and predictive to humans.

- Results should be reliable, reproducible,unequivocal, methods should be robust, relatively simple and cost effective.

- Preferably regulatory accepted methods. However current process of validation is slow, it is acceptable if applicability for certain compounds is demonstrated.

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When is industry using *in vitro/in silico* tests?

- Safety assessment
  - Regulatory accepted assays (few) and in-house methods (hundreds).
  - Different end points (sometimes industry specific), using different combinations of cells, tissues and compounds.

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When is industry using *in vitro/in silico* tests?

- Discovery and development of new compounds and products.
  - The *in vitro/in silico* tests are used for different purposes, e.g. to define biological activity, structural alerts, working mechanisms
  - Focusing on making go/no-go decisions regarding further development or maintenance of compounds.

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What will be the challenges for the future?

- The quality of *in vitro/in silico* data should be improved (reduce false positives)
  - using human tissue
  - target organ specific models
  - increasing the number of end-points/time-points
- Testing of new types of materials, such as those derived from the nanotechnologies and biologicals.
- Testing under long-term conditions; testing at low (physiologically relevant) doses

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Examples from industry

1. Immunotoxicity (Novozymes)

Target organ

Human cells

2. Prediction bioavailability (TNO)

Integration in vitro and in silico methods

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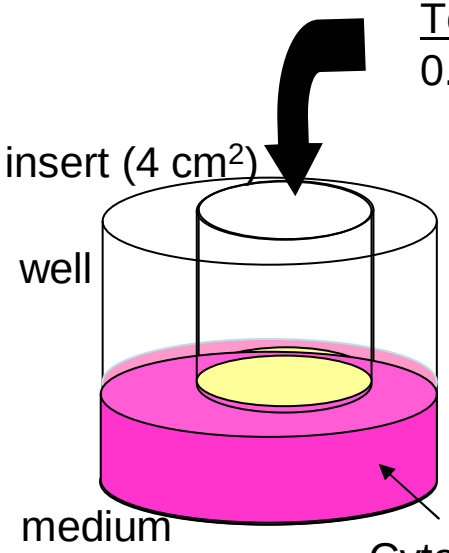
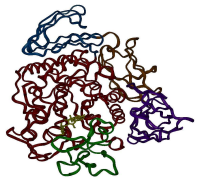
New tools for (immuno)toxicology – example from Novozymes A/S

➢ A human-cell assay

✓ **Lung (Air-Lifted Epithelial Cells)**



➢ Computer-based epitope mapping (EMT) for proteins/peptides



Search Algorithm

- *In silico* Epitope Mapping
- Epitope mutation tool

Output: 1. epitope fingerprint;
2. epitope list

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External exposure (dose)

Bioavailable fraction of compound (internal exposure)

Distribution in body via blood

Gastrointes passage of

from ntestinal tract

Excretion

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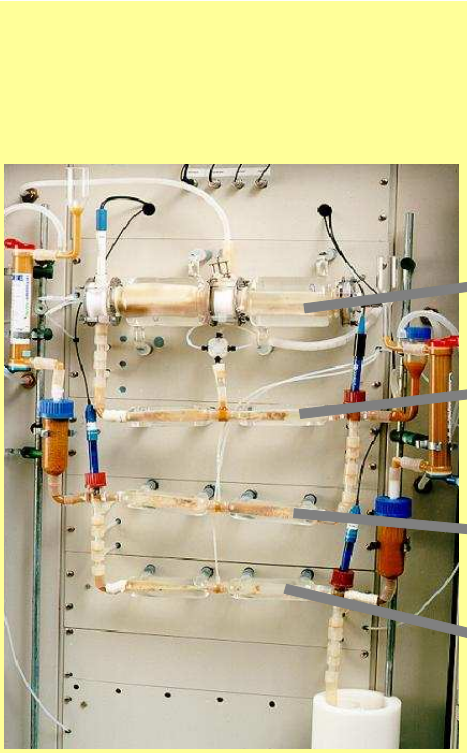
Prediction of bioavailability and plasma concentrations using kinetic modeling



Intake

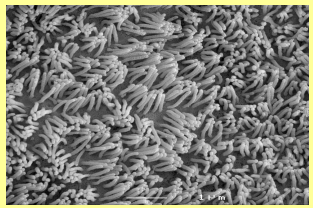
Stomach

Duodenum

Jejunum

Ileum

Efflu ent

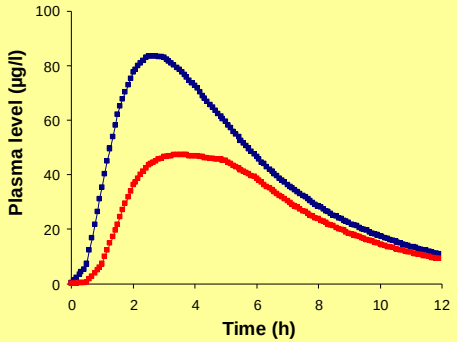


Intestinal cells

Plasma

Distribution

Elimination



Gastrointestinal Model (TIM)

Kinetic computer model

Predicted plasma concentrations

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What do we need for the future?

- Integration *in silico, in vitro, in vivo* and human data to increase the predictivity and improve extrapolation to the human situation.

- Integrated testing strategies will be challenging because of its complexity. Single replacement is usually not possible.

- Involve regulatory bodies in early development of new methods, to increase the possibilities for successful implementation and to fasten acceptability, to meet the requirements of new regulations (REACH – Cosmetic Directive).

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What should be explained in the future?

- New ways of risk evaluation are needed, including risk - communication and management and perception of general public.

- 100% safe ≠ possible

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Acknowledgement

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Executive secretary: Bart de Wever 

Board members

Novozymes, Neuropharma, L'Oreal,
Procter & Gamble, Phenion and TNO

For more information look at our (new)website
www.IVTIP.org