National Institute of Health, ISS

# EPAA Designathon on NAM-based solutions
## Towards a future classification system for systemic toxicity in humans


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### ABSORPTION

TO predict absorption (considering that):

NO/low absorption, NO/low systemic availability

*NO/Low concern*

### Identification of the primary route of exposure key to decide the model/approach to be used

- Identification of **passive vs active transport** (*dependence on the substrate concentration/ possibility of saturation*);
- **Uncertainty** based on the model used (*the closer to the human in vivo situation, the lower the uncertainty*)

### Testing Approach

- **In silico** prediction
- Use of **intestinal** models
- In vitro **dermal** absorption studies (*OECD TG 428*);
- **Inhalation**: volatility/ particle size (*to decide the fraction reaching the alveoli*)

### DISTRIBUTION

- Evaluation/prediction of **protein binding**
- Prediction of **bioaccumulation** potential (as a first screening:
- **MW**> 1,000 Da: unlikely to be absorbed by GI tract- not to be considered, unless hydrolysed or for local effects)
- **Log K $_{O/W}$**: Prediction)
- Prediction of **alerting groups** responsible for the binding with biological macromolecules

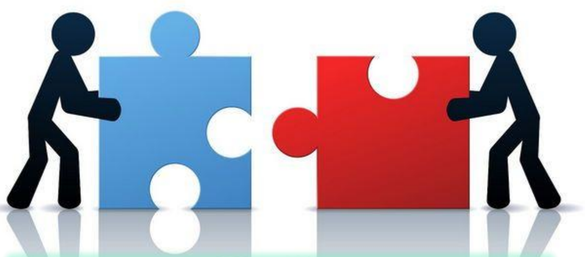
# ADME-informed NAM testing strategy

**Flow chart for systemic bioavailability**:

considering all relevant steps, mainly related to ADM (*scant info on Excretion, by using NAMS*).

- **Flexible and fit-for-purpose**
- **Aim:** reconstructing and designing **new criteria for the classification**
- To move from a **hazard- to a risk-based classification integrating TK considerations**
- **Balance** between **clearance/metabolism vs absorption and transport rates** → for defining the **3 levels of concern (LOW; MEDIUM; HIGH).**
- To be included in potential **future info requirements** in various regulations

*NAM-based solution for ADME should be integrated by sharing our idea and workload with other colleagues involved in the NAM Designathon project.*



*Connection with other EU Projects: e.g., EFSA project ADME4NGRA (WP leader-ISS, Project leader- Fraunhofer ITEM) for an in vitro/in silico testing approach in NGRA.*

### METABOLISM 1

**Fast detoxification** process (*Low* concern) *vs* **bioactivation** to **> toxic metabolites** (*High* concern)

- Fast Hydrolysis: simulator or experimental evidence (in simulated GI fluids);
- Metabolic stability: in silico data (*high uncertainty*); disappearance of the parent in metabolically competent cells or subcellular fractions (*information on similar compounds → read across*)

### METABOLISM 2

Nature of metabolites ?

- **Toxic** *vs* **detoxification metabolites** , *e.g. comparison of effects between competent and non competent cells*
- **Characterization of metabolism** (*High tier*): in vitro tiered testing strategy (i.e., recombinant enzymes/ subcellular fractions; competent cells (*e.g. intestinal cells, hepatocytes, other organs*)

### L, M and H LEVELS OF CONCERN:

*LOW* Parent Systemic bioavailability = *LOW* absorption (<10%*) and *HIGH* biotransformation

*HIGH* Parent Systemic bioavailability = *HIGH* absorption (>80%*) and *LOW* biotransformation (<10%*)

(*uncertainty: nature of metabolites, to be checked*)

**The number are merely indicative and should be checked by using real CS*

### TESTING PHASE:

*integration of TK/TD*

→ **biokinetics** evaluated throughout the testing strategy to interpret the dynamic results (GIVIMP);

→ "**validity**": characterization for human relevance of the in vitro models used (*metabolic competence, expression of specific transporters*);

→ **better quantification**: exposure-informed testing strategy, based on biokinetics→ **QIVIVE**.