EPAA PoS ADME/TK WORKSHOP #2

'Potentials and gaps for further integration of toxicokinetic *in silico* modelling into the prediction of *in vivo* dose-response curves based on non-animal tests only'

October 13th – October 14th 2011

BACKGROUND INFORMATION

INFORMATION TO BE COVERED IN FLASH PRESENTATIONS (Please fill the boxes):

- What did your company/sector try and establish so far in general in terms of alternative test methods and QSAR models to parameterise (generate parameters, provide input parameters) toxicokinetic *in silico* (PBTK[1]) models?

- What did your company/sector try and what did not work?

- For which input parameters are *in silico* QSAR models available?

- For which input parameters are *in vitro* models available?

- Which *in vitro* studies are ready to use (=reliable and useful output)?

- What are the (preliminary) applicability domains of *in silico / in vitro* models?

[1] PBTK modelling (physiologically-based toxicokinetic modelling) is regarded synonymous with PBPK modelling (physiologically-based pharmacokinetic modelling).

CHARGE QUESTIONS TO BE ANSWERED DURING BREAKOUT GROUPS:

BREAKOUT GROUP A

'Gaps in non-animal test methodology to assess A, D, M and E sufficiently'

1. What input data do we need? Which biological processes (toxicokinetic endpoints) have to be included in a PBTK model and thus have to be mimicked in *in vitro* methods? Concentrate on main stream non-pharma chemicals (i.e. highly specific organic anion transport may be something for the future).
2. What *in silico / in vitro* tools do we have, i.e. for which endpoints? At which stage of development (follow up of DG SANCO report 'State of the art cosmetics 2013')?
3. Are these tools quantitative enough for PBTK modelling? Can the model output be used directly as PBTK model input (e.g. partition coefficient)? Or does it have to be translated (e.g. P_{app} to P_{eff} for Caco-2 outcome)?
4. What data generating methodology is needed urgently? Take into account which results will have major impact (e.g. are absorption and metabolism of higher priority than renal excretion?).

Output breakout group A:
Short list of recommendations.

BREAKOUT GROUP B

'PBTK models as such'

1. For which chemical categories do we have PBTK models available that can be used for the whole group with minor modifications?
2. In other words, for which chemicals (organic chemicals, volatiles, hydrophilic chemicals or very hydrophobic chemicals, metals, inorganics etc) are they applicable?
3. What can they deliver?
4. How practical are they? How user friendly? How data hungry?
5. In which sectors are they mainly used?
6. Do you need modelling experience or is general science background sufficient?
7. How are people in the companies handling these models?
8. Is there a message for policy makers how to facilitate progress in the use of these models?

Output breakout group B:
Objective overview what various models and tools can do and what not.