

# **Recap of the results of the first session**

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## Recap of the results of the of the discussion

- Thank you very much for the discussion in the last webmeeting.
- EFSA asked for a clarification of the roles in this improvement process:
  - BfR's role is to make suggestions based on the in-depth analysis of the current framework conditions and the needs of the evaluation process.
  - The Metapath User Group should help to clarify open questions, to support BfR proposals or deprioritize aspects if they are not needed. The MUG is representing the adequate user forum. If a solution is later to be called a customer-oriented solution, then this forum of experts must be given an appropriate importance.
  - EFSA will have to weigh up and make decisions in 2022. This EFSA decision-making process is the topic in the second part of our third web conference.

## Recap of the results of the of the discussion

- The following summary should contain the key messages of the presentations and discussions of the last webmeeting and should be the structure for a workshop report
- Some points were added because the given answers didn't meet always the actual issue of the question. These points were marked with 
- We should not show all these slides, this is much more for a "Self-study"
  - Only one "summarizing" voting question for clarification and
  - To show an attempt for an analogy of the transport problem

## Switch to the voting system now regarding the relation of MetabolAS and IUCLID

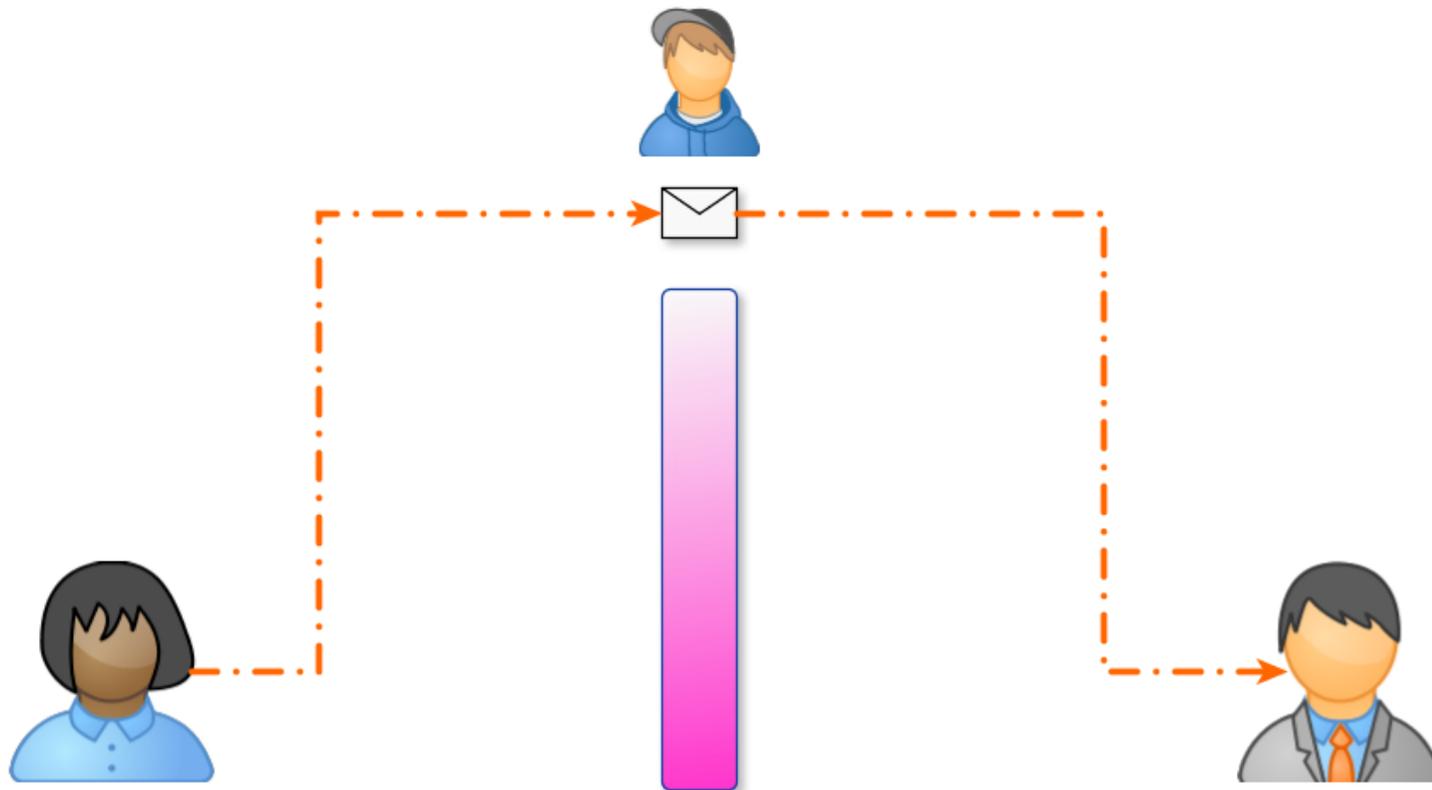
Last week the character of some technical discussions were so, that it seems that somebody wanted to ask the following question:

Is an improved MetaPath system (MetabolAS) needed **beside** of IUCLID in future?

1. **Yes** (IUCLID is the transport and publication system and MetabolAS the needed evaluation tool as well as the backbone for the curated reference collection of metabolism studies)
2. **No** (IUCLID has the potential to provide all the necessary assessment functionalities in this application in the future, as well as to be used as the curated reference collection of metabolism studies.)



# An analogy view for “attachment”



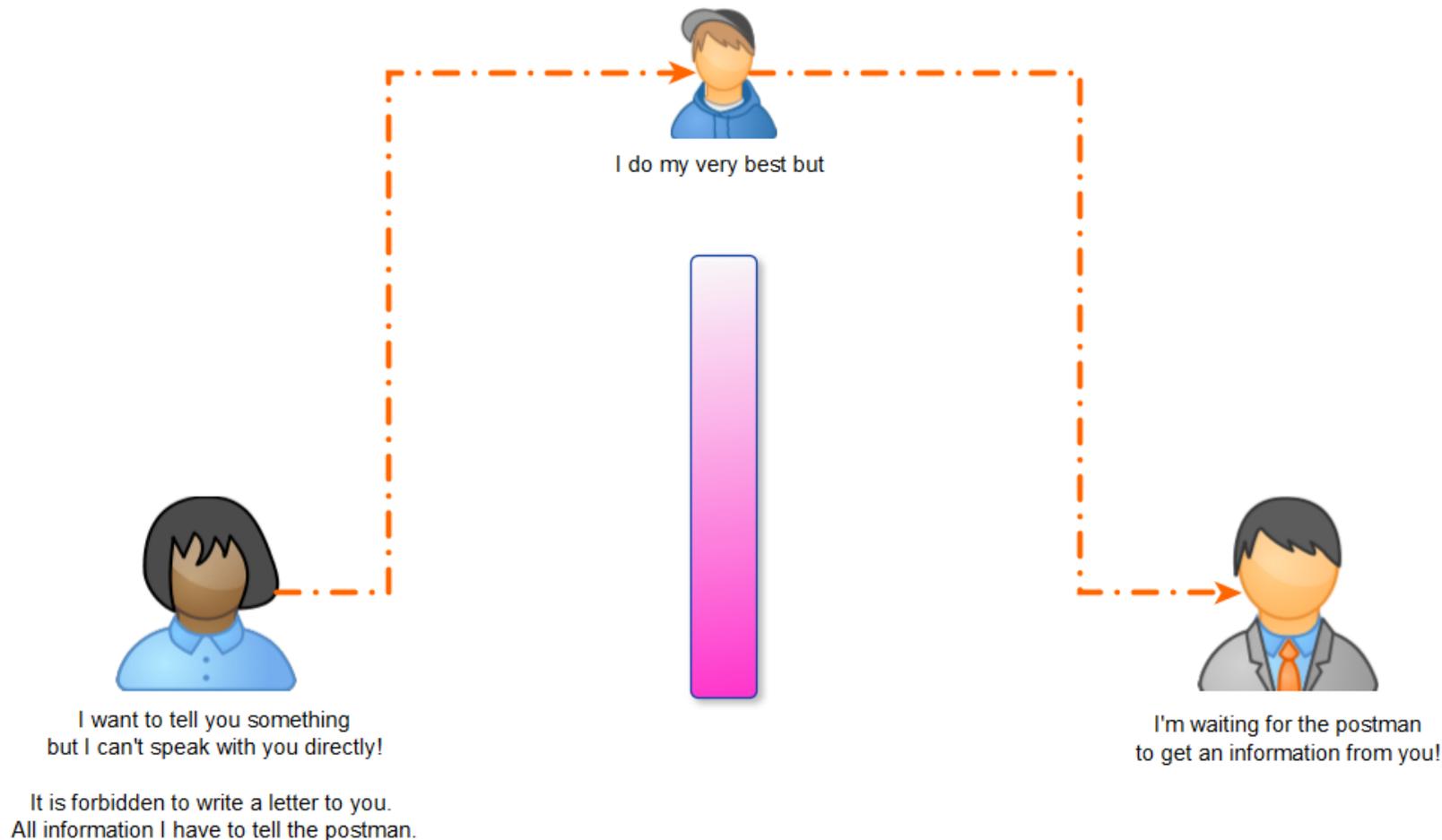
I want to tell you something  
but I can't speak with you directly!

I write a letter and we need a postman.

I'm waiting for the postman  
to get a letter from you!

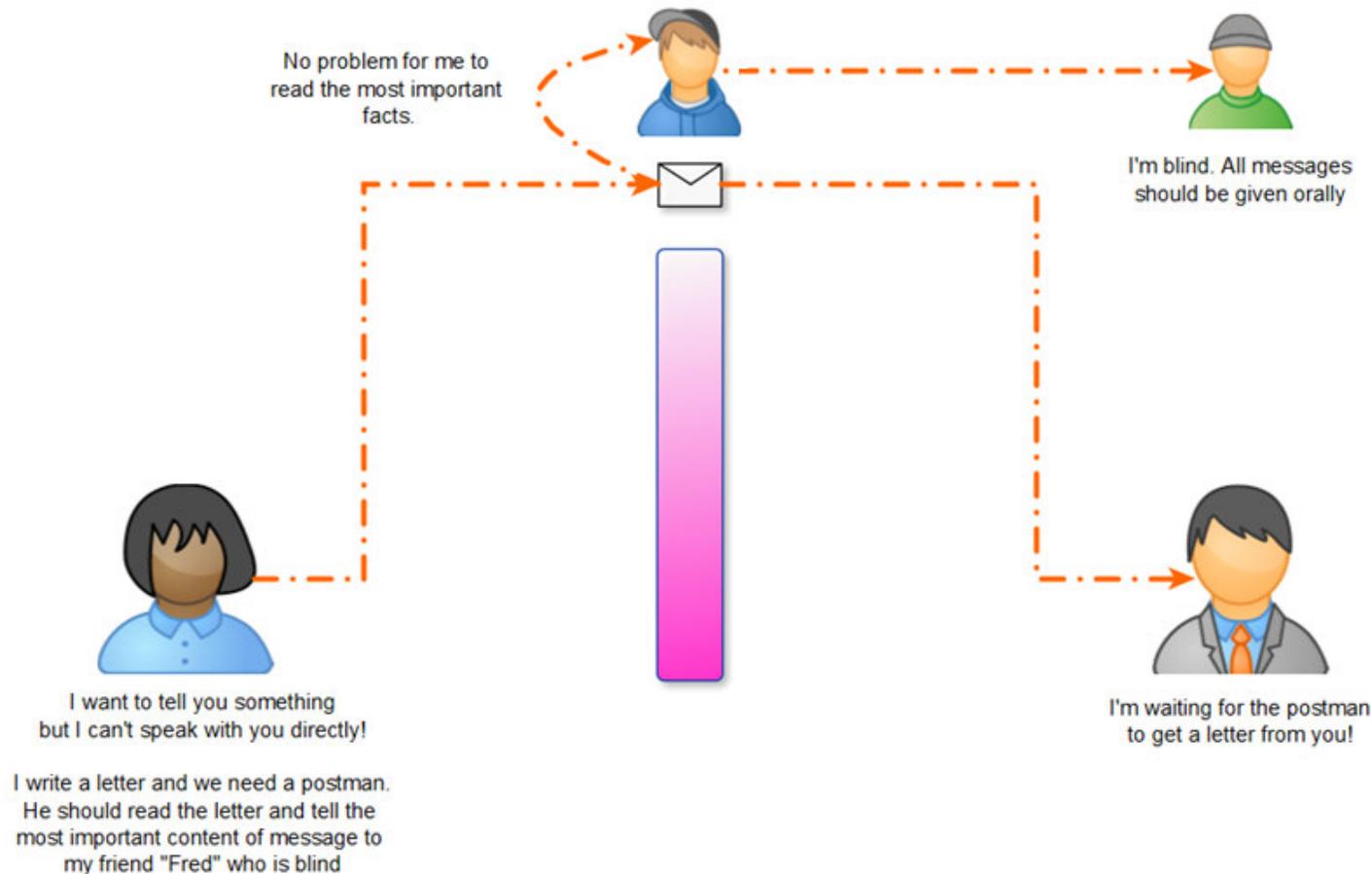
It is not the primary role of the postman to read the letter.  
The message will be transferred without any interpreter.

# An analogy view for “OHT”



“We have a very clever postman. I give him my message to you.”  
The postman has to hear and to interpret the oral message.  
The postman has to share this message to the receiver who has to  
hear the message.

# An analogy view for “attachment” combined with an IUCLID addin



“We have a very clever postman. I asked him to read the letter and to tell the most important content to my blind friend “Fred”. And you will get the full information with my letter.

# **Summary of the first MUG sessions regarding the improvement of the information flow of metabolism studies**

## Four presentations on the first MUG web session (10.11.2021)

2. Objectives for the further development
3. Current status of the project and the aim of the workshops
- 4.1 The MetabolAS ecosystem
- 4.2 User requirements and concepts I

### **Typification of the discussion points:**

- Analysis of the **needs of the assessment process** for metabolism studies which will be the basis for the next two decades
- Discussion on **technical questions**. And the IT support should follow the needs of the end user and not vice versa.  
Selection of an optimal IT frame work.
- **Organizational questions** to initiate and move forward the project.

## 2. Objectives for the further development

EFSA has presented ([download link](#))

- the framework where this project is embedded,
- the current situation
  - of duplication of work to feed Composer XML files and IUCLID
  - the lack of data centralization of metabolic pathway information
- the objectives for the further development



Discussion:

- ECHA is not yet active working on the integration of MetaPath and IUCLID. ECHA is waiting for the outcome of this BfR analysis.

### 3. Current status of the project and the aim of the workshops

BfR has presented ([download link](#))

- the status of the project,
- An overview regarding the results of the commenting phase
  - All “important” and “very important” open questions have a technical background and are referencing the chapter 6 ”Solution approaches”
  - No open questions regarding the high level summaries or the defined terms

Discussion:

- ECHA had not took part in the commenting phase. But ECHA has the impression, that the BfR proposal for an general redesign with a new tool don't solve the problems. New tools create also new problems. **It should be clear which are the differences / reasons for this radical BfR proposal.**

## 4.1 The MetabolAS ecosystem



BfR has presented ([download link](#))

- the parts of the proposed new Ecosystem and
- the process and objects of the information flow

Discussion:

- UK regrets that the OECD no longer supported the Metapath activities. The reasons should be analyzed and OECD should revise the prioritization.  
UK want to contact the OECD directly because the current actions of EFSA (and BfR) should be noted. **It was proposed to request an additional agenda item to the Chemicals and Biotechnology Committee (CBC) for the February meeting.**
- ECHA: A restart should not duplicate already existing harmonized systems. And a restart of an OECD project will need some time.

## 4.1 The MetabolAS ecosystem



Voting results ([download link](#)):

- ~95% of the votes agreed that **OECD “should hold the role of the governance body for MetabolAS”**.
- 100% of the votes support “the implementation of an **international curated reference collection**” of metabolism studies
- The voting regarding the question “Should the international curated reference collection of metabolism study metadata be **publicly available?**” shows, that all participates agree with a publication but additional discussion is needed
  - 58% of the votes: “In principle yes”
  - 42% of the votes: “Rules for the public access should be defined”
  - 0% of the votes: “In principle no”

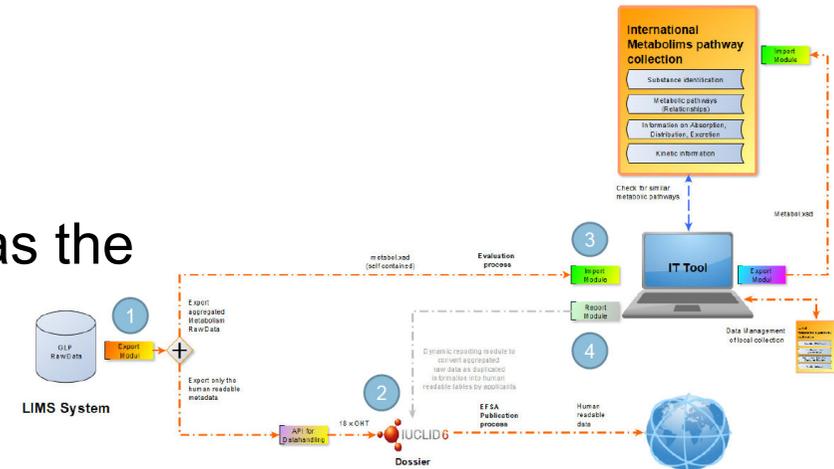
## 4.1 The MetabolAS ecosystem

BfR has presented the attachment type as the preferred option

Discussion:

- **What is the benefit to create an attachment file instead with MetaPath with another newer tool?**
  - The metabol xml schema is needed independently from IUCLID. This is the data interface between different MetabolAS instances.
  - With the attachment type the MetabolAS Tool don't need additional import data interfaces.
  - Today different composer xml schema are used; This will be simplified.
  - The generic approach opens the possibility to expand this methods on other metabolism study types;
- **IUCLID cannot analyze attachments.**

BfR: This is OK for today but a little addin could improve IUCLID to ingest the needed information from the attached file(s).



## 4.1 The MetabolAS ecosystem

BfR has presented the attachment type as the preferred option

Discussion:

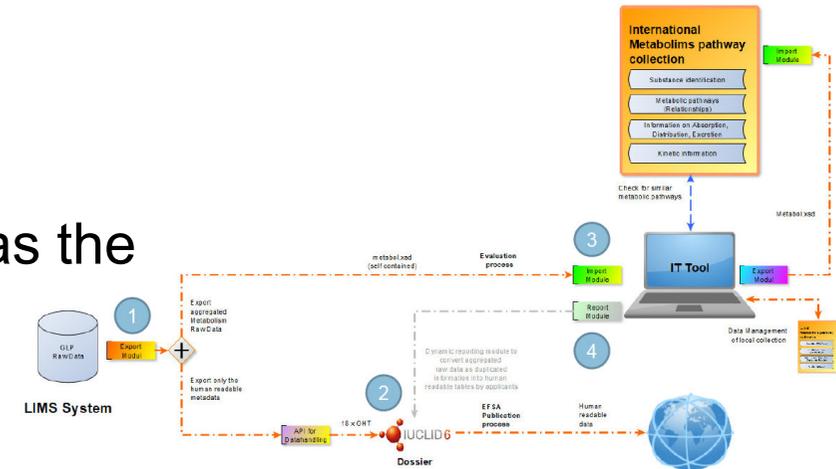
- **Which part should be published?**



BfR position: All data which a human can read with a browser application or a pdf viewer make sense for a publication. If a xml file contain only semantic duplicates of the provided information it make no sense for the public.



BfR prefer: The public should read the published data according the implemented publication rules of EFSA.  
But it is not problematic if these xml attachments would also be published after the questions of confidentiality are answered.



## 4.1 The MetabolAS ecosystem

BfR has presented the attachment type as the preferred option

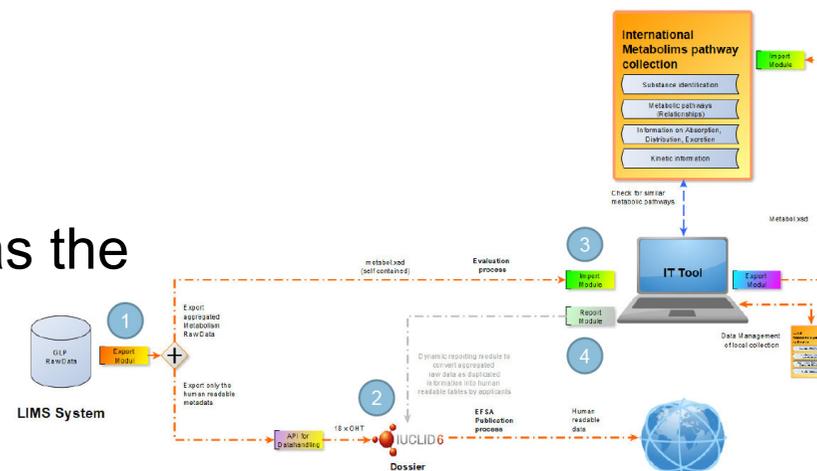
Discussion:

- **Why do we need “aggregated raw data” for metabolism studies?**

BfR: The aggregated raw level is also needed for the residue trials and perhaps also for additional OHTs in future e.g. for genotoxicity data.

It depends from the needed user actions which should be done with the data (summation, recalculation of values on another reference e.g. metabolite concentration calculated as parent substance) or if these data could be included in QSAR models.

Evaluators has to answer the question: **Do we need this level of isolated values to calculate with them?** If not, the technique is enough to read the data in the OHT in the applicants summary rich text field.



## 4.1 The MetabolAS ecosystem

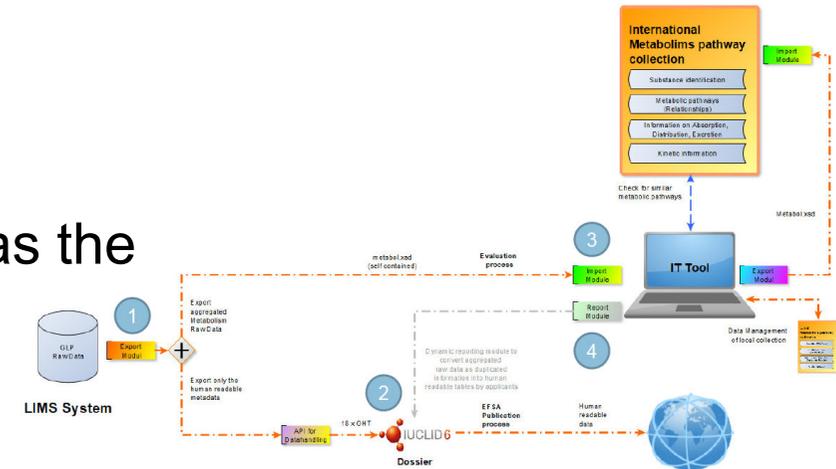
BfR has presented the attachment type as the preferred option

Discussion:

- **Why do we need “aggregated raw data” for metabolism studies?**

UK: The level of detail should support a read across and a linking to other information systems to avoid animal tests.

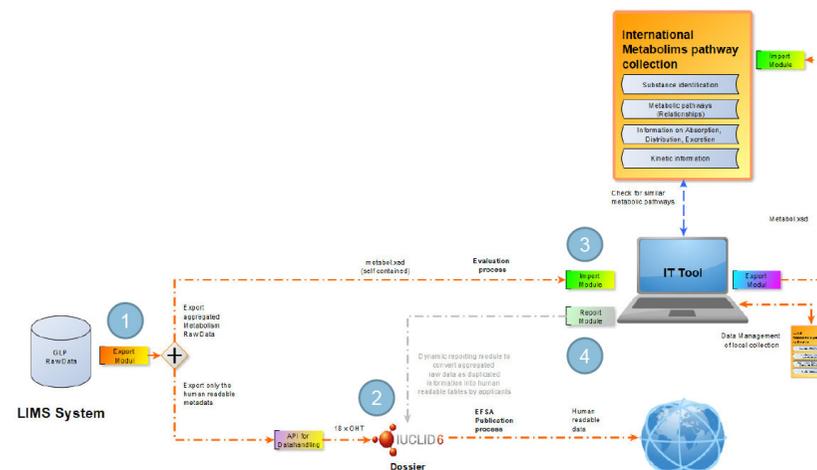
USEPA: The possibility to cover all other metabolism guideline study type would be grateful with the new system. Evaluators needs metabolic simulators.



## 4.1 The MetabolAS ecosystem

Voting results ([download link](#)):

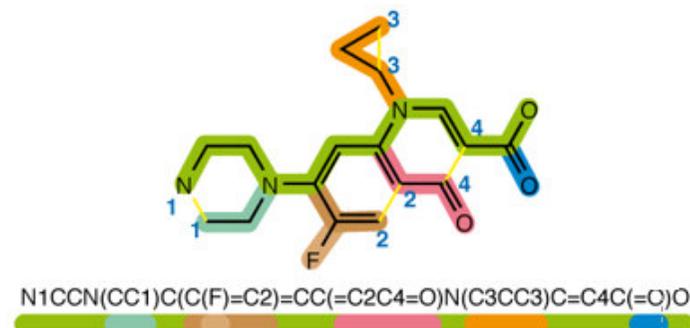
- The voting regarding the question “Which transport concept would you recommend regardless of the political hurdles / necessary decisions?” shows, that all participants wishes an OECD solution. An additional discussion is needed:
  - 53% of the votes: “Create an OECD Domain Type”
  - 47% of the votes: “Create an OECD Attachment Type”
  - 0% of the votes: “Use of 3rd Party Attachment Types”



## 4.2 User requirements and concepts I

BfR has presented ([download link](#))

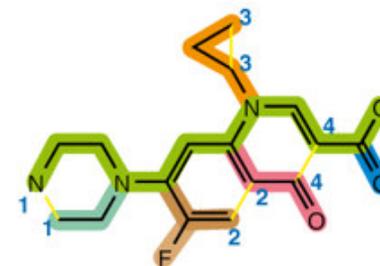
- **different chemical structure notations,**
- **the need of generic Markush notations**



Discussion:

- Which chemical notation would be better than SMILES?  
The Metapath and the (Q)SAR toolbox are using the SMILES notation.
- Possibility of conversion of SIMILES into InChI and vice versa?
- Is it possible to migrate MetaPath SMILES codes in the MetabolAS InChI code?
- Regarding the generic Markush notation LMC noted that LMC had provided in a customer version of MetaPath an own concept of generic notation based on SMILES. This function could be provided next year in a MetaPath update.

## 4.2 User requirements and concepts I



N1CCN(CC1)C(C(F)=C2)=CC(=C2C4=O)N(C3CC3)C=C4C(=O)O

Voting results ([download link](#)):

- 40% of the votes agreed that generic Markush notation is needed in a relevant extent in metabolism studies.

**This means that coding of generic structures is a “show stopper” for this project.**

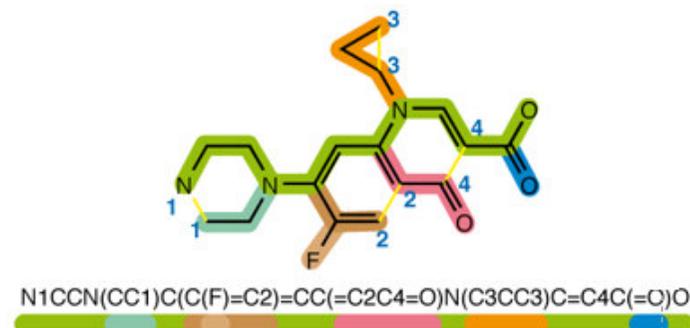
## 4.2 User requirements and concepts I

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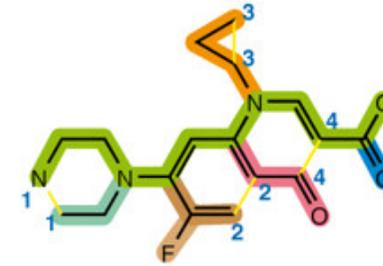
- different chemical structure notations,
- the need of generic Markush notations
- **the need of grouping and calculations**
- methods for visualizations

Discussion:

- EFSA: Why do we need grouping and calculations also in MetabolAS where it is already implemented in Ruedis?  
BfR: Ruedis manage residue data, not the metadata of metabolism studies. The reference to Ruedis was not only to show, which user functions could be usable for evaluators and give a benefit in the assessment process.
- EFSA: All the existing good functions of MetaPath should be implemented with priority.



## 4.2 User requirements and concepts I



N1CCN(CC1)C(C(F)=C2)=CC(=C2C4=O)N(C3CC3)C=C4C(=O)O

Voting results ([download link](#)):

- 75% of the votes agreed that evaluators need user functions for grouping and calculation in the assessment process.

**To provide such functionality, the MetabolAS has to manage the isolated reported measured values instead of reporting them in HTML tables.**

- 2 participants had noted, that they have additional for visualization. Please send these ideas to BfR to include them into the report.

# **Thank you for your attention**

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