

Recap of the results of the second session

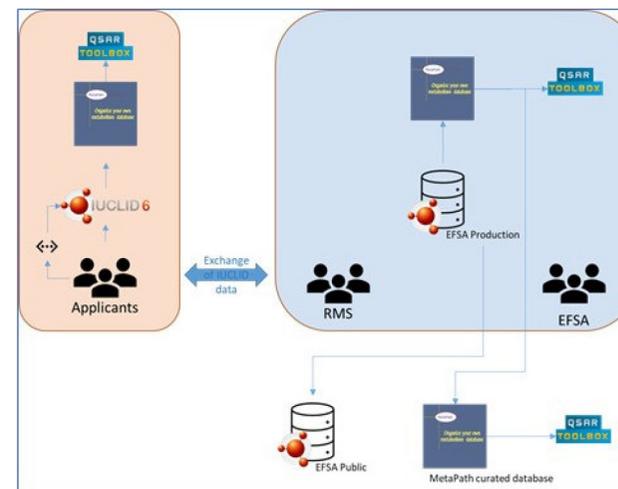
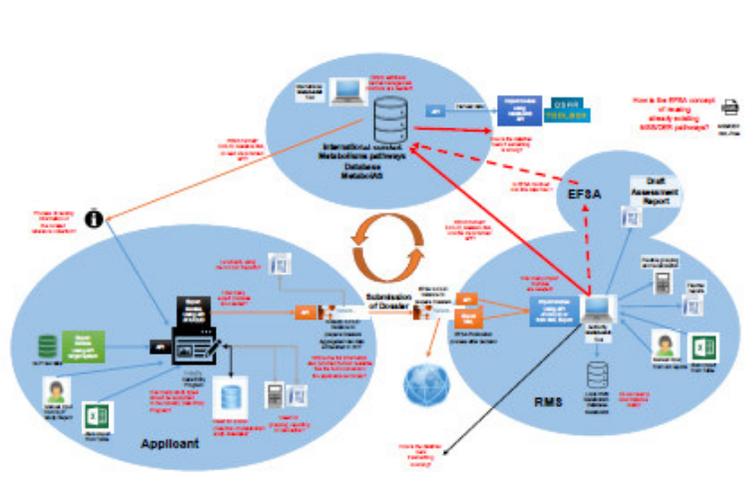
Stephan Worseck

A slogan also for today!

ECHA had given a nice short summary of the last meeting:

“There is a large agreement on the requirements, not necessarily on the solution, but that's why we are discussing today!”

BfR and ECHA had a follow up discussion to clarify the interplay of the improved MetaPath and IUCLID.



Please have a look into the [webfolder](#) to download these documents.

Summary of the second MUG sessions regarding the improvement of the information flow of metabolism studies

Presentations on the second MUG web session (18.11.2021)

7. Recap of the results of the first session

8.1. User requirements and concepts II

9.1 Improve OECD Transport Concept!

10.1 Needed framework conditions for laboratories and applicants

10.2 Needed framework conditions for evaluators

To 7. Recap of the results of the first session

BfR has presented a short summary of the first session ([download link](#))

- The recap summaries should be understood as a draft for a workshop report which will be published after the BfR final report in January.
- After the first meeting BfR had got the impression, that it was not clear expressed whether IUCLID should be improved to fulfil all user requests regarding the evaluation of metabolism studies.

Too often it was to hear: This is already implemented in IUCLID

To 7. Recap of the results of the first session

The first voting could only be a test, because not all participants had opened their voting system at the needed time point. But the result was clear. So it was not necessary to repeat the voting.

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

- 86% of the votes agreed that an improved MetaPath (MetabolAS) is needed as an evaluation tool as well as the backbone for the curated reference collection of metabolism studies.

The voting and the following discussion underlined the need of an improved MetaPath (MetabolAS).

ECHA noted, that there should be a clear separation of concern and no duplication of functionality of both systems.

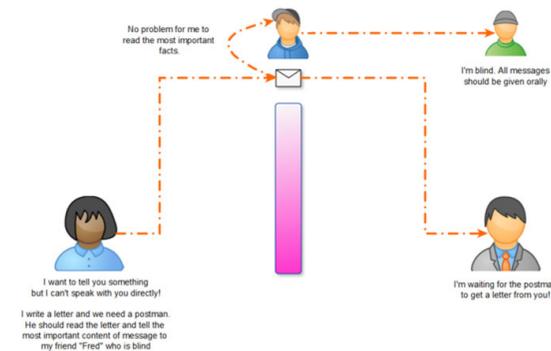
EFSA noted, that there is a real need for an improved MetaPath for the risk assessment.

To 7. Recap of the results of the first session

BfR has presented an analogy view for the transport terms “attachment” and “OHT”

BfR proposed to combine the attachment type and the need of IUCLID to harvest some data regarding the substance list and the relation between the substances via an add in into the IUCLID system.

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



Stephan Worseck, 18.11.2021, MUG Websession

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In this case a communication without any transformation could take place on attachment level and IUCLID would be able to consume the needed data.

No participant had given a comment to this proposed combined transport model. It may be that these three transportation mechanisms should be put to a vote again.

To 8.1 User requirements and concepts II

BfR has presented additional user requirements in addition to the first session ([download link](#)) regarding the

- Database
- MetabolAS Tool
- Data Management in the Reference Collection
- Management of (Q)SAR results
- Migration

To 8.1 User requirements and concepts II

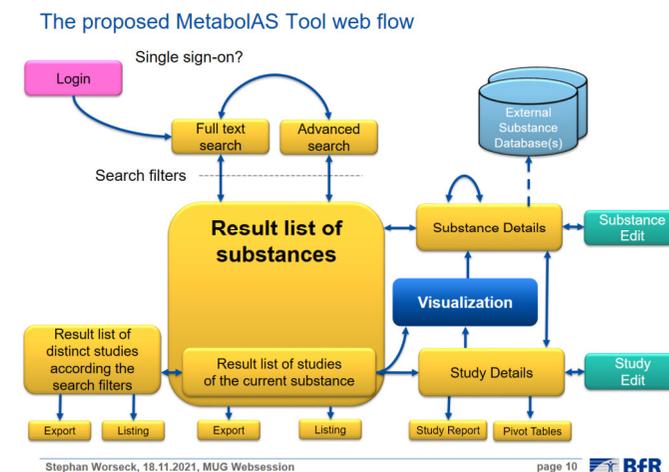
From the point of view of the BfR, it is considered that the MetaPath application and the used database implementation have serious weaknesses that a general redesign is recommended.

The XML schema of the MSS/DER composer family is appropriate to transport the raw data values to the MetaPath system. This data model would be open for a migration to an improved MetaPath (MetabolIAS) system.

The proposed MetabolIAS Tool could be the same tool on applicants and authority side because of the need of the same functions. This would be the same situation like today with MetaPath.

To 8.1 User requirements and concepts II

From ECHA's point of view, the proposed MetabolAS Tool is a repetition of functions and technology of IUCLID on basis of the data of the OHT's. IUCLID should be used as the data collecting system after the GLP report is ready.



At beginning of this session EFSA has noted, that there is a real need for an improved MetaPath for the risk assessment.

Unfortunately, there was no meeting organized since starting this project to present the ECHA concept “**integration instead of replication**” in this context.

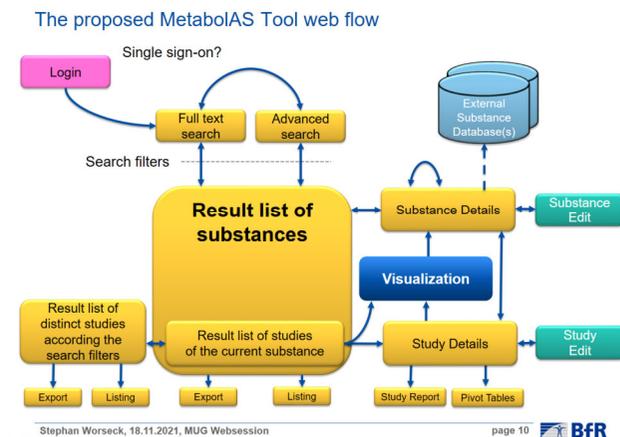
The reference that the ECHA concept is based on already published international standards is not helpful.

To 8.1 User requirements and concepts II

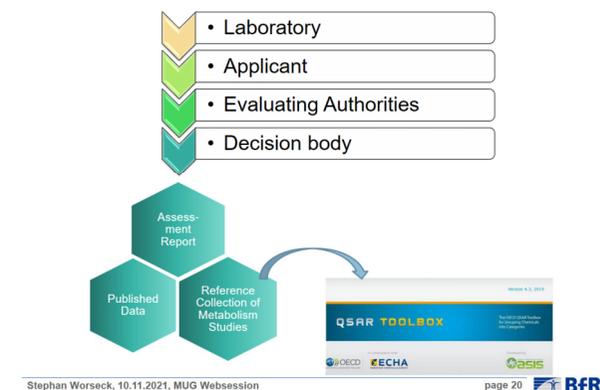
It was confirmed by BfR that of course MetaPath (MatabolIAS) will take over the content of the study summaries (including the aggregated raw data), as this is the starting point for the assessment process, besides the attached GLP study report.

It seems that BfR was not able to communicate to ECHA /EFSA what is the difference between showing the “submitted data” and

- to work / recalculate / aggregate / compare / weight ... with these data
- to create the evaluated data set as an “direct end product” of the assessment process which has to feed the curated reference collection of metabolism studies and via the reference collection (Q)SAR Tools indirectly.



The direct and the indirect “end products” of the process



To 8.1 User requirements and concepts II

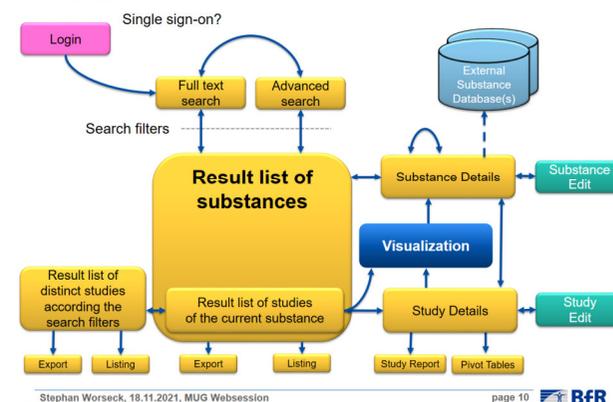
ECHA recommended that the necessary functions of MetaPath (MetabolIAS) should be aligned with the existing functions in IUCLID and preferred the motto:

"If one of the functions is already implemented, let us use this tool".

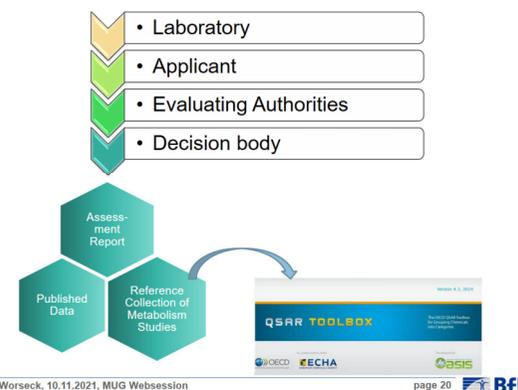
In ECHA's opinion these decisions should be taken by this user group (MUG) or even better by the OECD because they can ensure that the governance is stable longer run along the way.

EFSA emphasized that “We need interoperability to share data - not necessarily new system development.”

The proposed MetabolIAS Tool web flow

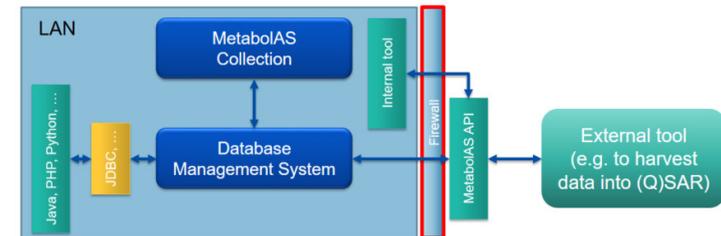


The direct and the indirect “end products” of the process



To 8.1 User requirements and concepts II

There was one open question regarding the API : “Is it realistic / purposeful to plan a data transfer from a LIMS systems into a local MetabolAS collection via APIs and / or common used access methods ?”
Only applicants should vote.



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

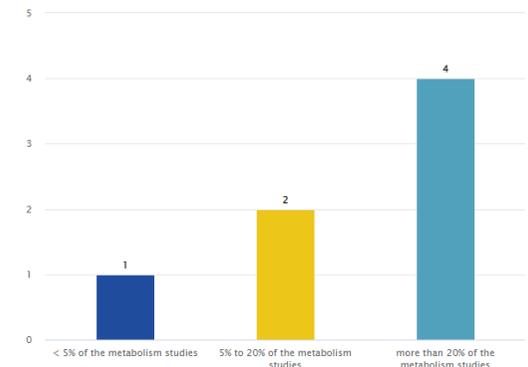
- All of the four votes agreed that these functions are needed.

The voting for the question: “How often do you have aggregated raw data in a simple electronic format (outside of LIMS)?” should help to prioritize the functions to import alternative formats.

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

- The result shows, that amount of other digital data outside of LIMS is relevant to support a flexible alternative import function.

8.1 b) How often do you have aggregated raw data in a simple electronic format (outside of LIMS)?



To 8.1 User requirements and concepts II

“Would you say a bulk import of substances / dose groups or result tables is possible most of the time?”

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

- Six of eight votes agreed.

“If a bulk import of files would be possible, is an interpretation of tables via the clipboard still necessary?”.

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

- Four of seven votes agreed.

To 8.1 User requirements and concepts II

The statement 8.1 d) was incorrect in the voting system.

We should repeat the discussion on the topic of logPow.

„The logPow (partition coefficient n-octanol/water) is often used in the risk assessment. This value could be measured or calculated from the structure.

How often do you measure this partition coefficient / do you get measured values from the applicants? “

“Is there a need to store additional phys-chem properties (beside logPow) or toxicological data as structured meta data needed in evaluation process?”.

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

- Three of five votes agreed.



We should discuss it in the Websession, which parameter are needed!

To 8.1 User requirements and concepts II

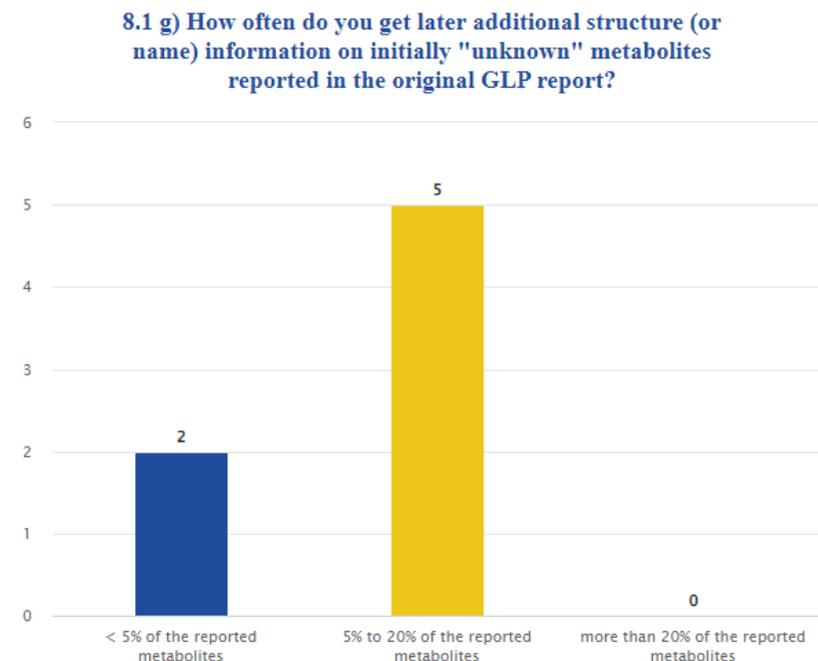
“How often do you get later additional structure (or name) information on initially "unknown" metabolites reported in the original GLP report? ”.

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

- There were seven votes.

Five of seven participants said, this happens for “5% to 20% of the reported metabolites”

So this is an important fact which should be reflected in the user requirements and the use cases.



To 8.1 User requirements and concepts II

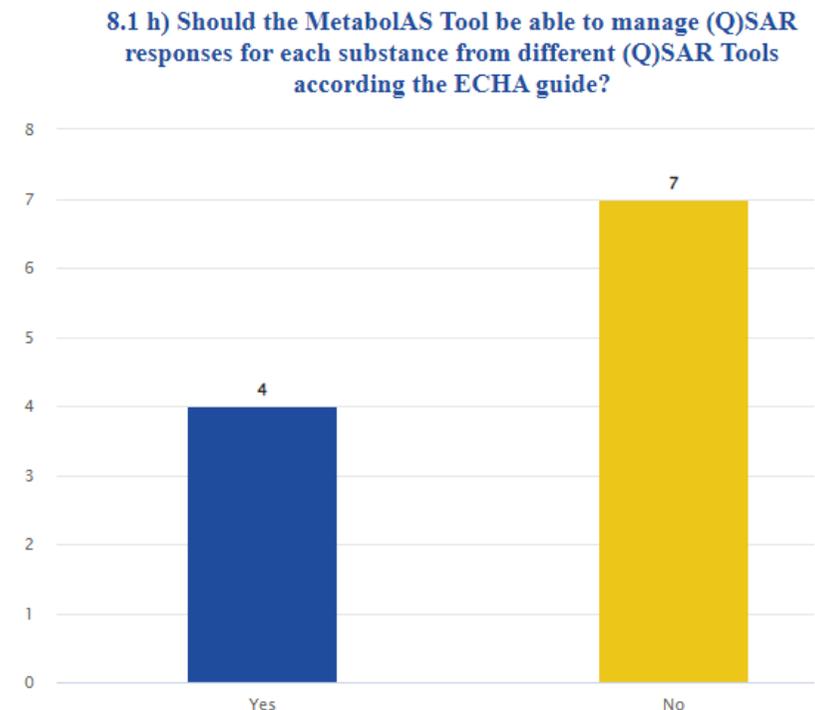
“Should the MetabolAS Tool be able to manage (Q)SAR responses for each substance from different (Q)SAR Tools according the ECHA guide?”.

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

- There were 11 votes.

1/3 of the participants
votes for such a functionality.

It seems this is undecided but have no
priority and should be discussed by
the experts.



To 8.1 User requirements and concepts II

BfR had show some important points which to be solved in the migration phase:

- Matching from strings to picklist items
- Check valid dependencies between elements (Goats and rat strain)
- Split HTML tables
- Split groups which are concatenated by comma

The effort for migration is estimated to 20% of the whole project.

“Should the migration start from the XML file?”.

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

- There were 6 votes.

2 votes said, it's better to start from MetaPath. **Only one participant had given a reason.**

To 8.1 User requirements and concepts II

- LMC makes databases mainly with the MetaPath interface. They have collected 1500 maps. LMC proposed to convert the whole database to XML files for a migration or to start the migration from the MTB database.

But LMC was the only user who has spoken about such a process. The other participant was anonymous until the end.

- So the decision to start the migration from XML is an open point.



To 9.1 Improve OECD Transport Concept!

The question of the right balance between the transmission of information in several individual fields and in aggregated texts is very old and goes back to the founding days of the OECD Harmonised Templates

- The final Report of the Expert Group Meeting to Explore Harmonizing Templates ENV/JM/RD(2004)9 had given principles to find such a good balance. The first principle was: “**be based on the needs of the reviewer and not the electronic technology requirements**”. This principle was forgotten more and more.
- The current OHT 85-5, the first Harmonized templates where aggregated raw data are included had shown:
 - Human is not able to create complex test data for programming the import tool manually
 - Human is not able to understand the content and to check for errors
 - Human would need “Ruedis” or an adequate internal IUCLID report which not exists

To 9.1 Improve OECD Transport Concept!

The need to submit aggregated raw data exists for residue data, as well as for metabolism studies which is in focus of this report. BfR sees also a need to transport “Aggregated Raw Data” for other endpoints, e.g. “Genetic toxicity in vitro” (OHT 70)

Because the generic “OECD Domain Type” for metabolism raw data could be used in many harmonized templates (~18 OHTs), **there is the realistic risk to destroy the IUCLID user interfaces for all of these harmonized templates.**

The human readable IUCLID user interface is destroyed with aggregated raw data by the number of nested repeating block. Human will not able to understand the content and to check for errors. Human would need an adequate internal IUCLID report to translate the “Aggregated Raw Data” back for the human.

To 9.1 Improve OECD Transport Concept!

- EFSA noted that, the manual data input of aggregated raw data is possible in the MSS-Composers. This is very work intensive two days per study are needed. If this will be done by IUCLID the granularity is the same. And there would be the chance to collect these data from the beginning of the process. And EFSA prefer to use this chance in the European PPP processes.

The question is, why it is more difficult to expand the OHT in IUCLID than in the composers?

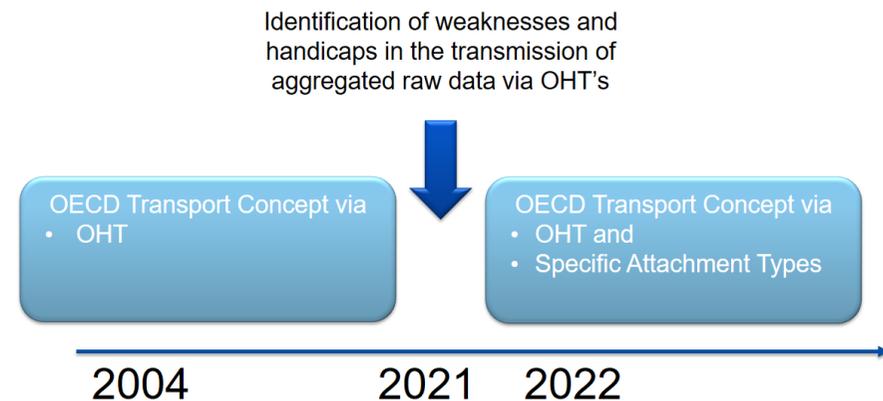
- BfR: The granularity of aggregated raw data is not the same. The MSS composer using only HTML tables where the values are included in table cells. This format is NOT adequate if you want to calculate / recalculate / group values. So you have to input isolated values and for each value all the references to the object of investigation, to the dose group, to the sample group, to the method etc. So you will expand the data input on the factor of 3 to 5 times. Nobody need the level of detail in the human user interface of IUCLID.



To 9.1 Improve OECD Transport Concept!

- EFSA noted that the information should be included in IUCLID according the transparency regulation.
- BfR: That would be realized because a semantic identical information will be submitted on attachment level (for machines) AND in the human readable format in the applicants summary.
- This is the reason, why BfR proposed the improvement of the OECD transport concept. The international processes need much more aggregated raw data, so the OECD transport should be enhanced.

It's time for an improvement of the OECD Transport Concept



- The OECD should be open for improvements according the PDCA Cycle of ISO 9001 "Quality management systems" (Plan / Do / Check / Act)
- OECD Attachment types would be an extension of the existing transport concept
- There wouldn't be an impact on the IUCLID user interface and on the internal logic

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To 9.1 Improve OECD Transport Concept!

- EFSA noted that this group has developed a good MetaPath application which is helpful in the evaluation process. If we are creating new tools, we need time to validate those tools to get them in accepted and adopted. So we should just think about how we can improve that MetaPath and the MSS composers, particularly on the key areas that people would like to see improvement one.
- BfR added note: The EFSA opinion shows that EFSA is not yet prepared to recognize the general need for a reform of MetaPath and the MSS composers. In the lifecycle of a software application, one regularly comes to the point where technological jumps are necessary that are comparable in scope to a new development of the software. In some cases, maintaining backwards compatibility is even a real cost factor. If these technological “jumps” were not allowed, we would still be working with Word97 under MSDOS today.



To 9.1 Improve OECD Transport Concept!

- ECHA noted that the OECD transport mechanisms in this area have been under continuous development since 2004 and that the OECD is open to discussion.
- BfR noted, that a request to the OECD makes only sense if this is supported by the MetaPath User Group, by Germany or better by Europe.
- USEPA had added additional aspects:
 - There not only bugs in the current systems. User want to have also additional functions for the risk assessors which makes the job easier to do.
 - The current concept of MSS composer is not able to capture the other guidelines with radio isotopes.
 - Who as to host the new service?
 - Don't look only to the cost resources in term of money. Look also to the needed time. Are we locking at 5 or 10 years?

To 9.2 Preferred transport option for the needed information flow

ECHA hadn't prepared a separate presentation to this topic.

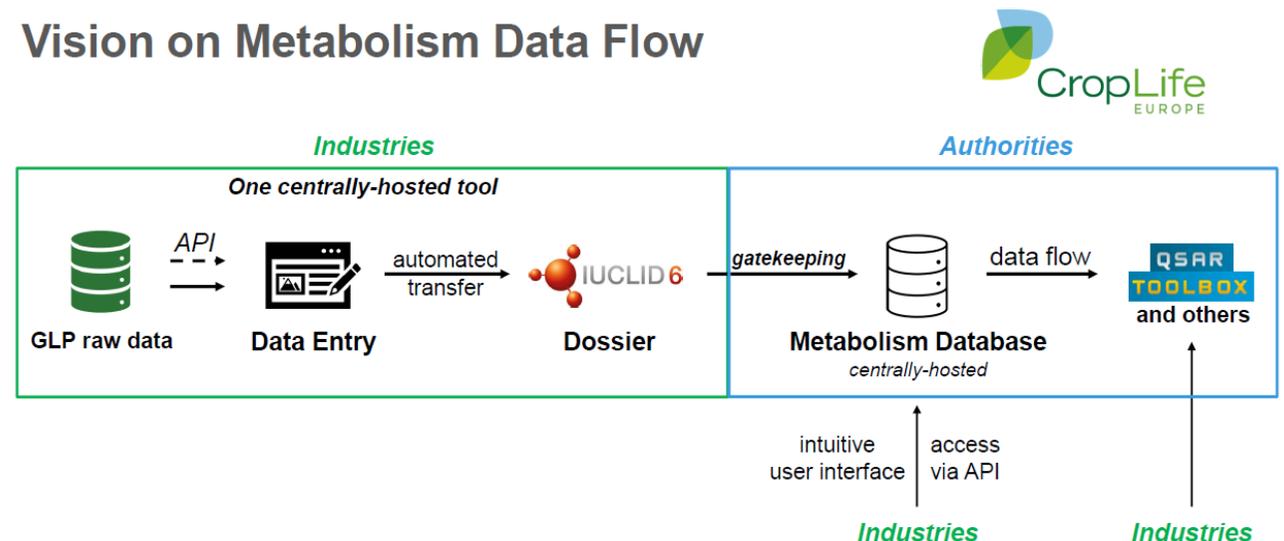
The ECHA position was already explained quite clear. Our proposal is to reuse systems and not to create new tools.

To 10.1 Needed framework conditions for laboratories and applicants

CropLife Europe has presented their point of view ([download link](#)) regarding the metabolism dataflow:

- the current weaknesses of MetaPath and the 4 MSS-Composers which are centrally managed. The users will not be informed regarding new versions, ...
- the most important critical point is the friendliness, the usability and the bad performance of these tools
- the need for an API to MetaPath
- the need of a metabolism database which is centrally hosted

Vision on Metabolism Data Flow



To 10.1 Needed framework conditions for laboratories and applicants

The improvement of the metabolism dataflow will be one of the most important issues, if this is done in a harmonized and long-term approach at a global level.

We need drastic improvements and rearrangements to really meet all the requirements from applicants side at least.

EFSA asked regarding the confidentiality aspects of a centralized curated reference collection of metabolism studies.

CropLife Europe: Gatekeeping and to data protection during the evaluation process is very important to industries. It should be possible to access a global reference collection of metabolism studies as well as local instances. And the used software shell always up-to-date.

To 10.1 Needed framework conditions for laboratories and applicants

BfR asked regarding the needed functions in the assessment process on applicants side.

CropLife Europe: The development of an active substance is an ongoing process on industry side. If we do an assessment at the end we really have all data together.

EFSA noted several times that the improvement process should need in maximum of 2 years and not 5 or even 10 years. So they don't want a radical redesign.

There were different opinions regarding the need for uniqueness of metabolism studies in the database collections. The BfR prefers the uniqueness solution in order to enforce the rule “**One study - one assessment**”. ECHA prefers mechanisms for the subsequent detection of duplicates (deduplication).



To 10.2 Needed framework conditions for evaluators

EFSA has presented the risk assessor's view ([download link](#)) regarding the metabolism dataflow.

- Improvement should be in line with the upcoming assessment demands on OECD and EU level.
- Publication of the new OECD guidance will be intended in 2023. MetaPath has to be integrated with other tools (e.g. OECD Toolbox) to facilitate assessment of pesticide metabolites
- The needed functions for risk assessors are:
 - Support & facilitate actions
 - Prediction
 - Extend & connect
- Only with a tool like MetaPath it will be possible to fulfil the new OECD guidance
- Support the principal: Beyond pesticides area **'One substance – One assessment'**

To 10.2 Needed framework conditions for evaluators

- To initiate a “read across approach” in other tools would be the most important new additional needed function in MetaPath on substance level.

ANSES has presented some aspects for improving the existing functionalities of MetaPath ([download link](#)):

- ANSES had implemented the usage of MetaPath in the evaluation process.
- Grouping of metabolites and read across are important functions that ANSES has been waiting for many years.
- A central world wide database of metabolism studies and for the residue definition would helpful
- Support the colleague from EPA to need small local databases for specific projects.
- ANSES supports that we need a lot of maps more

To 10.2 Needed framework conditions for evaluators

- Do not lose any metabolic pathways of the entered in the last 10 years!
- ANSES asked to keep the name, the proposed doesn't sounds very nice in in French.
- What have to be kept:
 - Maps and metabolites visualisation
 - Comparison of maps
 - Identification of common metabolites, search tools
 - All the works already done to populate the database
- What have to be added/improved
 - Few bugs
 - Improve the possibility / the way to use data fill in the MSS Composers?
 - Edition of report
 - Extraction of data from metabolism studies to generate summary tables, list of metabolites
 - prediction
 - Kinetics



To 10.2 Needed framework conditions for evaluators

BfR has presented some aspects for improving the existing functionalities of MetaPath ([download link](#)):

- We have a lot of knowledge data bases of the qualitative and quantitative data like residue data (Ruedis), Exposure, Environmental monitoring data etc. but we have not possibility to combine these data with MetaPath
- We need a better integration to these existing information bases. This should be understand as “Interoperability” of MetaPath.
A key is to combine the quantitative data with a qualitative data

To 11 Closing the workshop

ECHA had given a nice short summary of the meeting:

**“There is a large agreement on the requirements,
not necessarily on the solution,
but that's why we are discussing today!”**

Thank you for your attention

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