20.04.2021

Analysis of the informational flow of pesticide related metabolism studies

Part
Results of the international survey

Table of Content

1 Background

According to the specific agreement SA1 under the framework partnership agreement No GP/EFSA/AMU/2020/02, a “pilot study with industry” should be organized under topic D 4.1.3.
During the conception phase of the pilot project with industry, it became clear that the term "metabolism study" is not only applicable to OHT's 58, 85-2 and 85-3.

In order to be able to comprehensively analyse the handling of study summaries on metabolism studies, a stakeholder survey should be organised. This survey should help EFSA and BfR to:

- analyse the current situation;
- understand user needs and perspectives;
- define a practical workflow for 2021;
- make proposals for further improvement of the informational data flow on long-term perspective.

The main topics for the survey should be:

- the understanding of terms and the framework conditions;
- usage of MSS-Composers and DER Composer as tools to collect experimental data on metabolism;
- usage of MetaPath as a tool to collect, organize and analyse experimental data on metabolism;
- usage of OECD Harmonised Templates and IUCLID as transport container for results of metabolism studies;
- usage of QSAR-Toolbox function to simulate metabolism properties of chemicals.

2 Summary

The project „Analysis of the informational flow of pesticide related metabolism studies“ was divided into different report parts. This part describes the organization and the analysis / interpretation of the results collected by a stakeholder survey.

This report will be published. The stakeholders which are involved in this information flow are invited to analyse the results of the survey according to their own points of interests, to draw conclusions for their own area of responsibility and to participate with their own actions at the same time in the whole improvement process.

The most important result of this analysis should be the so-called “**List of weak points**". Each “weak point” has an identifier consisting of a letter “S(urvey)” the chapter number on level 3 and a consecutive number.

This list does not contain all conclusions. ”weak points" should be understood as aspects whose improvement could potentially contribute to an improvement of these information flows / processes. However, this lists of “weak points" are neither sorted nor weighted.

What will be the part of the BfR in the further steps in this project? The BfR will prepare the following additional documents:

- Comparison of OHT58 „Basic toxicokinetics“ and DER Composer
- Analysis of components of the informational flow
- Proposals for the improvement of the informational flow

The results of the stakeholder survey were presented and discussed with the members of OECD Expert Group on the Electronic Exchange of Pesticide Data (EGEEPD).

These documents will be also published by the BfR. Knowing well that extensive changes can only be successfully implemented by involving all stakeholders, the BfR will submit a draft of the proposals drawn up to the Metapath User Group for discussion.

But the BfR is not in a role to implement and finance this improvement process later. The BfR can only be the initial engine for the pending improvement process.

3 Survey

The information flow from structured metadata of metabolism studies is not a machine-to-machine communication that runs automatically 24 hours a day. This information flow runs discontinuously via interfaces in packages that have to be compiled and processed by actors. For this reason, the "human" is the most important factor, which influences the quality of this information flow.

Weaknesses in the information flows/processes were identified in an as-is analysis in this report.

3.1 Organisation

The content of the survey and the addressees were agreed between BfR and EFSA. BfR was responsible for the technical implementation using the limesurvey-tool[1]. You will find the complete set of questions in Appendix (see chapter 4.3).

A public anonymous survey without a list of participants and without registration was created in order to reduce the barriers to participation as low as possible. However, this approach carries the risk of people misusing the survey so that the results of this survey could no longer be evaluated. Therefore it was decided not to publish the invitation link for the survey on the BfR website as originally planned.

The survey was circulated by the following actors across the following channels / groups:

- OECD
  - Expert Group on the Electronic Exchange of Pesticide Data (EGEEPD),
  - IUCLID User Group Expert Panel,
  - OHT Expert Group,
  - Residue Chemistry Expert Group (RCEG),
- EU Commission
  - Member states by the PAFF members
- ECPA / ECCA
  - Applicants by the member of these association’s
- ECHA
  - To stakeholders for biocides and chemicals

[1] https://www.limesurvey.org/de/

- EFSA
  - Contact points in all Member State authorities
  - ECPA / ECCA

- BfR
  - Members of the EFSA Technical IUCLID Group,
  - Metabolism User Group members,
  - Some greater international laboratories,
  - Some international institutes,
  - Official notice on the BfR website

The survey was opened from 05.01.2021 until 31.01.2021.

3.2 Participation and cleaning of the data

The BfR survey system registered 163 records out of which 58 were fully completed.

Many of the records that were not completed were caused by people who simply wanted to take a look at the surveys in order to assess the relevance of the questions for them. Besides there are also records which come from participants who may have been disturbed while answering the questions and therefore discontinued the survey. However, there are extensive textual comments in quite a few of these aborted data sets. For this reason, a group of "additional" data sets were formed, which were included in special considerations. The following table gives an overview of the different groups.

Group	Number	Remark
V(alide)	58	**Participant completed the survey with a final "Submit" button.** Used for statistical calculations in this report
A(dditional)	20	**Participant did not complete the survey with a final "Submit" button.** But at least 15 fields were completed. The results were excluded from statistical calculations in this report but used in special considerations
D(elete)	85	Delete the record because fewer than 15 fields were completed
Sum	**163**	

At the end of the evaluation of the results, it was recognised that the participant with id=67 had probably not finished the survey and then 30 minutes later he started the survey a second time (id=68). Identical textual comments of id=67 were not taken into account. This did not affect any of the calculations.

3.3 Questions and Results

You will find the complete set of answers in Appendix (see chapter 4.3).

The following chapters have the structure:

- **Question**
- Visualisation of the results in a **chart**.
- The results are presented under the heading **Findings**.
  In most of the cases, a mean value was calculated; however, it is clear that this value is of limited significance if a distribution is skewed.
  The following interpretation of the mean was used, if participants had to agree or disagree a statement.

Interval of mean	Interpretation
1 – 1,7	clearly contradicted
1,8 – 2,2	contradicted
2,3 – 2,5	tendency to “disagree”
2,6 – 3,4	undecided
3,5 – 3,7	tendency to “agree”
3,8 – 4,2	confirmed
4,3 – 5	clearly confirmed

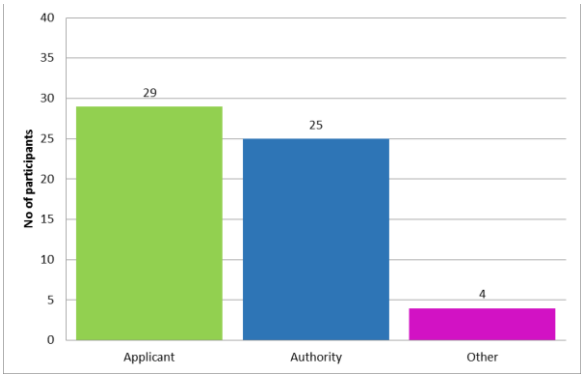
- If conclusions can be drawn from these results, they are listed under the heading **Conclusions**.
  If a conclusion would be “*A further analysis should be carried out*” it means – if one wants to have a much more clearer result, they have to invest into a further analysis. However, this lack of clarity is not an obstacle to the further work on this project.
- If a potential for possible improvement can be derived from these results, then these aspects have been listed under the heading **Weak point**.
  The list

3.3.1 Question group 1: Your position and your experiences

3.3.1.1 Which stakeholder group do you feel you belong to?

The empty stakeholder groups "NGO" and "Public", which were initially envisaged in the survey, were not included in the further evaluation, as the survey was only publicized via internal distribution circles.

Multiple choices of answers were possible.



Findings:

- There were only two survey participants who indicated that they belong to an independent laboratory. These two representatives of independent laboratories, however, cannot form a group of their own. 13 other participants from laboratories performing metabolic studies indicated at the same time that they should also be considered stakeholders for the applicants. Therefore, it seems to be possible to combine the survey participants of the group
  - “Laboratory which conducts metabolism studies”,
  - Applicant submitting metabolism studies in dossiers” and
  - Applicant using metabolism studies of other applicants”

  to the group "**Applicants**" with 29 participants.
- Only one survey participant from a management agency reported not performing evaluations of metabolism studies. For this reason, the groups "Authority assessing metab-

olism studies and using them to perform risk assessment" and "Authority utilizing metabolism studies for risk management decisions" are combined into one group "**Authorities**" with 25 participants.

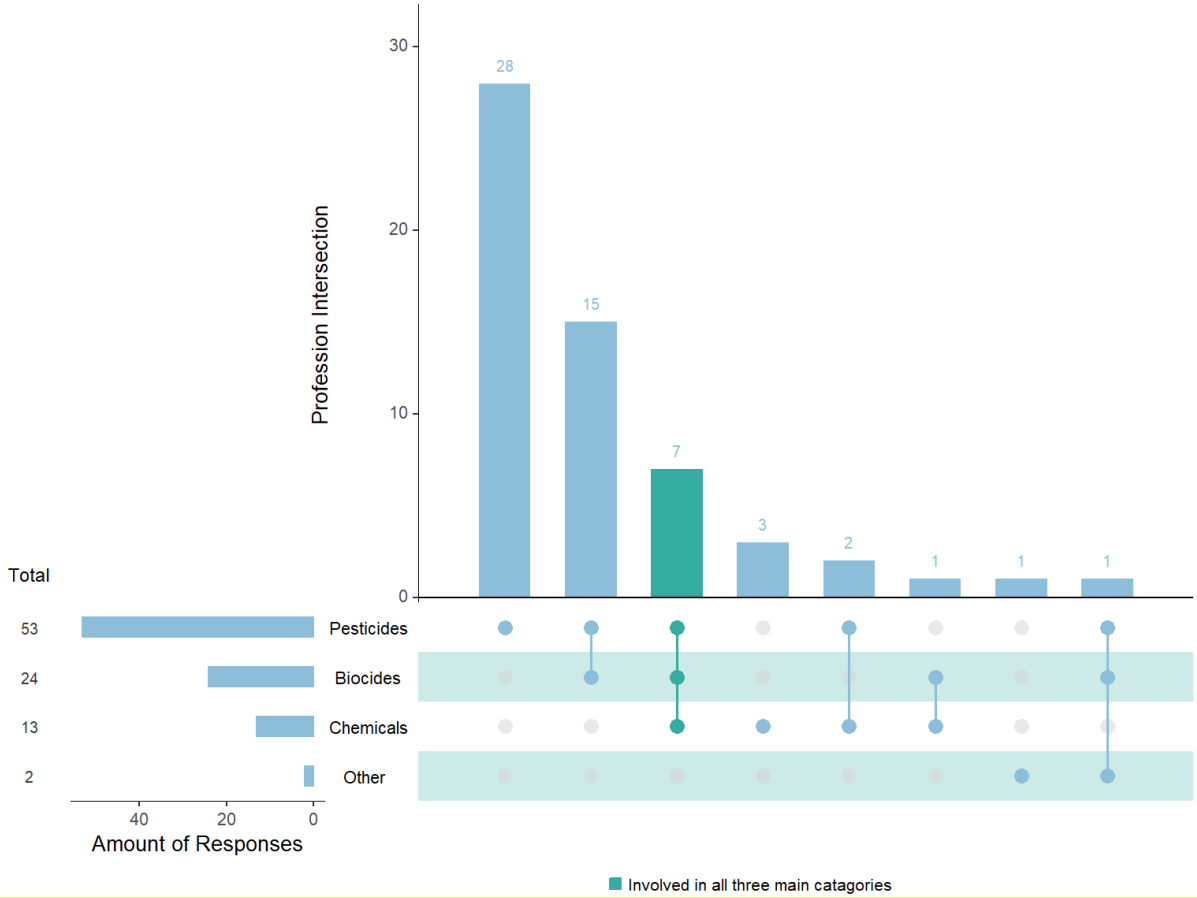
- There are only 3 participants who indicated that they are independent regarding the group of "Applicants" and independent regarding the group of "Authorities". Furthermore, one participant selected both the option of the applicants and the option of the authority at the same time. To avoid having to delete this inconsistent data record, this participant was assigned to the "Other" group. The group "**Other**" consists of 4 participants.
- The rate of participants is high enough to make some statistical analysis of the results and the respective contribution of applicants (29) and Authorities (25) is sufficiently balanced.

Conclusion:

- If analyses are necessary with respect to the origin of the stakeholder groups, use only the three groups mentioned above.

3.3.1.2 Responsible for / interested in

Multiple choices of answers were possible.



Findings:

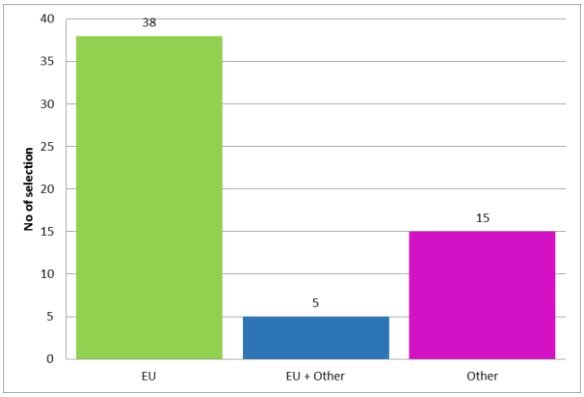
- There is a large overlap of areas of interest due to the way the invitation to the survey was distributed.
- In the knowledge area of pesticides 53 (=90%) out of the 58 participants were active. The survey is therefore very suitable for making statements for the area of plant protection products.

Conclusion:

- This grouping is not suitable for an analysis of the responses in terms of the field of interest. This report makes no such differentiation.

3.3.1.3 Affiliation to the economic area

The participants could be assigned to the economic area "European Union" to “Other” or to both.



Finding:

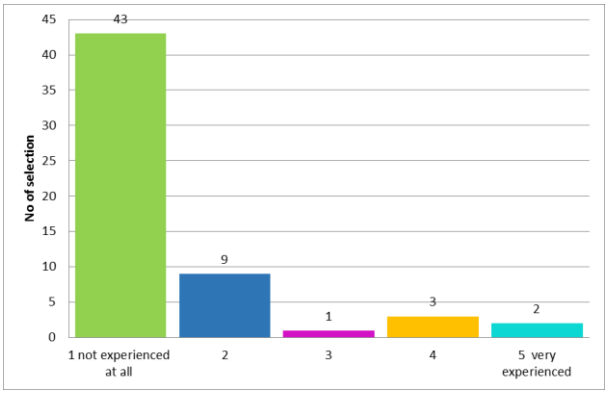
- Two-thirds of the survey participants assigned themselves to the "European Union" economic area. Thus, the results of this survey can be seen as "Europe-centered", but with 34% of the survey participants, there was also a strong international perspective as feedback.

Conclusion:

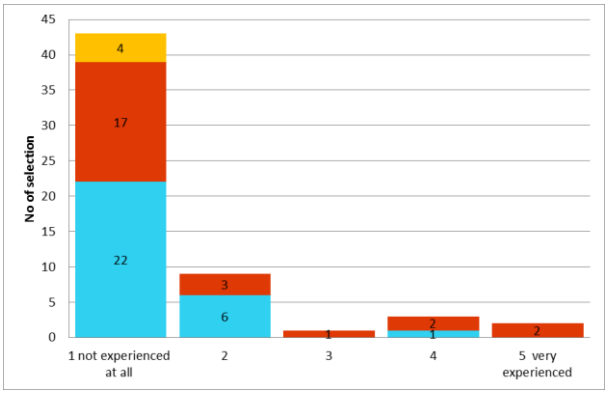
- This grouping allowed a stakeholder-specific analysis of the responses in terms of economic area affiliation.

3.3.1.4 How experienced are you in using the following tools regarding metabolism studies?

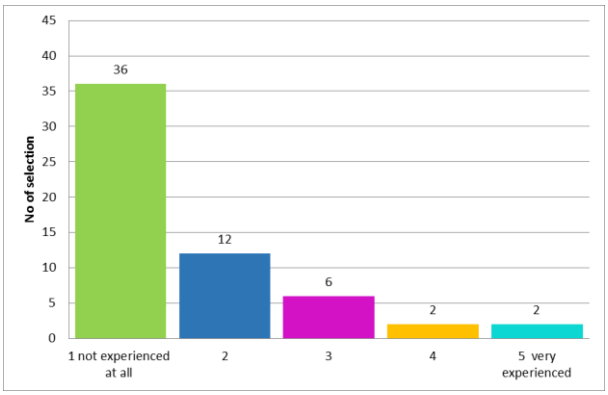
Used colours in the stacked bars: Other
Authority
Applicants



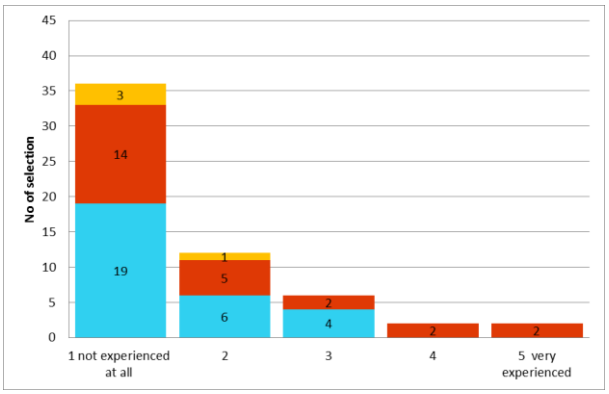
MSS Composer



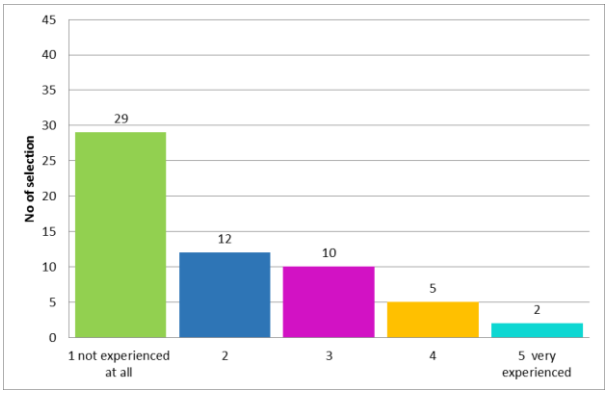
MSS Composer as stacked bars according the stakeholder group from chapter 3.3.1.1



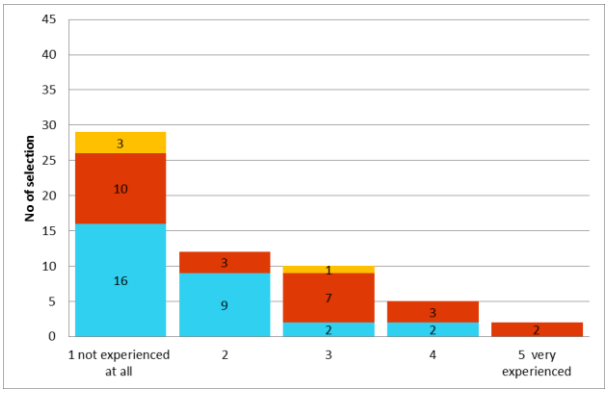
Metapath



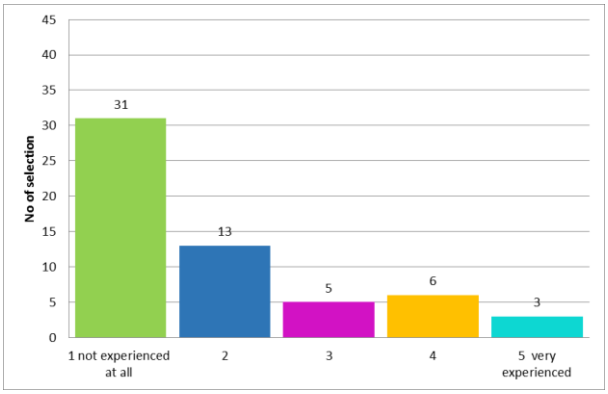
Metapath as stacked bars according the stakeholder group from chapter 3.3.1.1



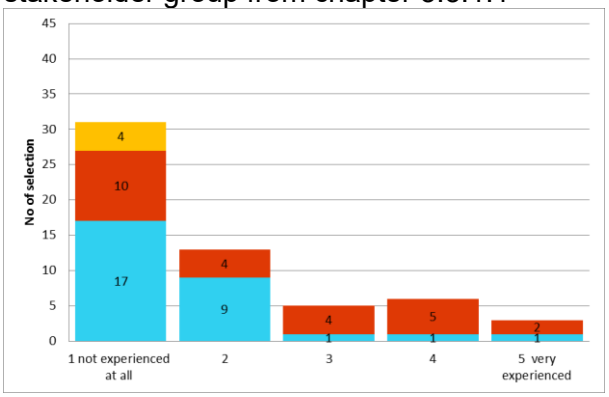
QSAR-Toolbox



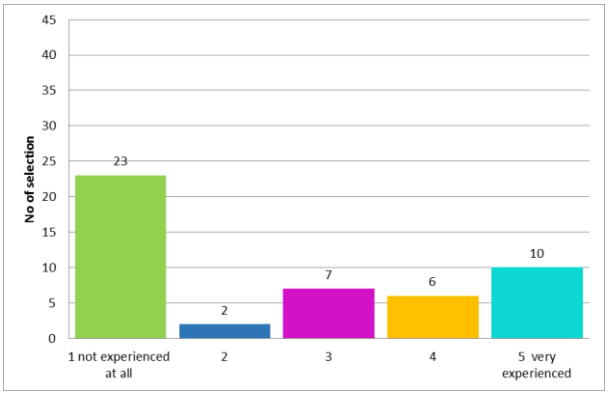
QSAR-Toolbox as stacked bars according the stakeholder group from chapter 3.3.1.1



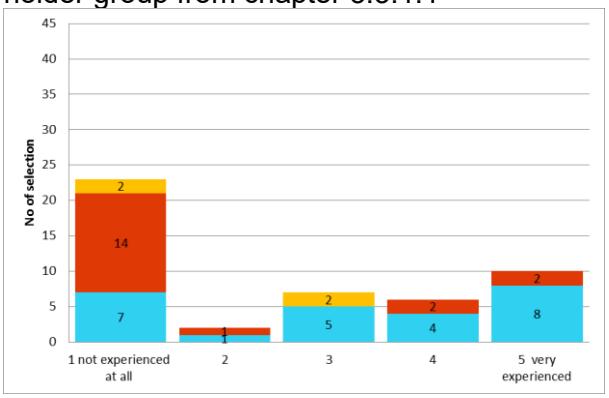
IUCLID



IUCLID as stacked bars according the stakeholder group from chapter 3.3.1.1



Other tools



Other tools as stacked bars according the stakeholder group from chapter 3.3.1.1

If those participants were excluded from the further calculations in the report, who are "not at all experienced" according to self-assessment, about 2/3 of the data sets would have had to be deleted. However, this was not done.

Findings:

- The figures above clearly show the reticence of the participants in the self-assessment regarding their skills / knowledge to use the listed IT tools. If this is correct, then the survey should reveal a knowledge gap.
- If one analyses the experiences in dealing with the MSS Composer, Metapath and QSAR-Toolbox then the few participants indicating themselves as "(very) experienced" with MSS composer, Metapath, QSAR, mainly belongs to Authorities. However, in the "not at all experienced" category, the ratio is quite balanced compared to the respective participation rates. Please compare the stacked bar for these tools above.
- A particularly large number of survey participants indicated that they are “very experienced” in using "Other tools to handle data of metabolism studies". It is noticeable that in this response option, applicants assigned themselves a higher level of knowledge.
- It seems that the authors of the survey are unaware of these additional essential tools related to metabolism studies used by applicants.

Conclusion:

- It is not clear whether the apparent lack of experience in using the IT tools mentioned leads to a distortion of the overall statement of this survey.

Weak point:

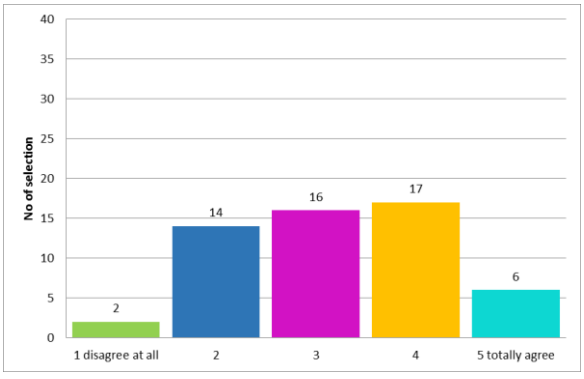
S 3.3.1-1 The identified knowledge gap that laboratories and applicants use appropriate but rather unknown IT tools to the authorities is an indication of a lack of exchanges of tools and practices between the different actors in this knowledge area.

3.3.2 Question group 2: Framework conditions

3.3.2.1 The term "metabolism study"

The purpose of this statement was to check whether serious discrepancies at the definitional level between members of the "scientific community" were known. It was not the goal testing participants´ understanding of the term “metabolism study”.

The participants had to respond to the statement:
“*All stakeholders have the same understanding regarding the term ‘metabolism study’*”.



Findings:

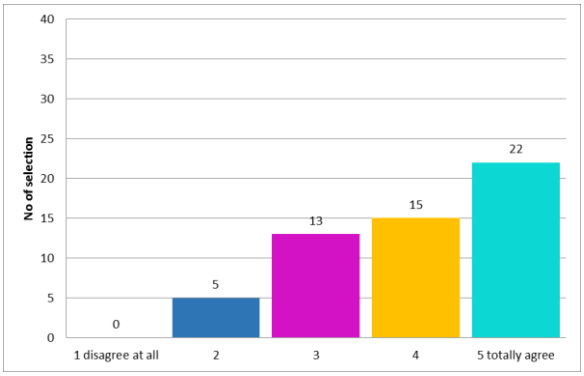
- The mean value is 3,2 which could be interpreted as “undecided”.
- There is a wide variation in the vote.
- The statement was not agreed with by 16 (2+14) of the participants (=30%) of 55 votes.
- Only 5% of the participants skipped this question.

Weak point:
S 3.3.2-1 A harmonised definition of the term “metabolism study” is needed.

3.3.2.2 The current data requirements …

The background of this question was to test whether participants recognized the current data requirements on metabolism studies as a uniform basis.

The participants had to decide about the statement:
“*The current data requirements for metabolism studies are a solid basis for the risk assessment*”.



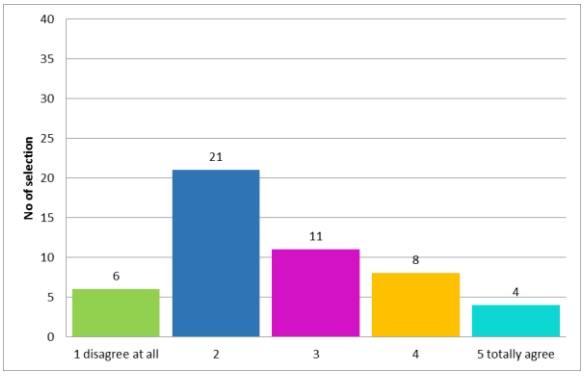
Findings:
- The mean value is 4,0. The statement was confirmed by the participants.
- Only 5% of the participants skipped this question.

Conclusion:
- There is no need for action regarding a revision of the data requirements for metabolism studies.
- The data requirements for metabolic studies form a stable basis for organising the required flow of information.

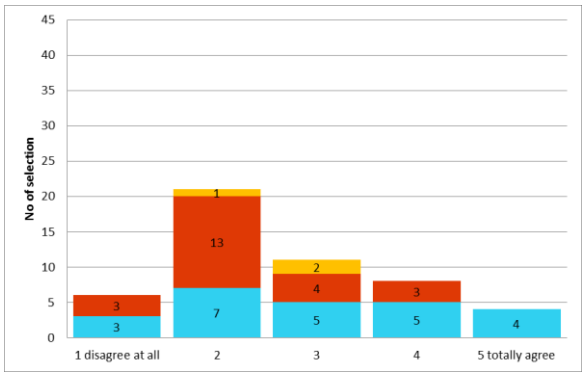
3.3.2.3 The current tools for …

The purpose of this statement was to get a high level picture of the suitability of existing tools for storage, processing, and publication of data on metabolism studies.

The participants had to decide about the statement:
“*The current tools for metabolism data storage, handling and dissemination are sufficient*”.



Used colours: Other
Authority
Applicants



Findings:

- The mean value is 2,7 which could be interpreted as “undecided”.
- There is a wide variation in the vote.
- Only 14% of the participants skipped this question.
- The survey result clearly showed that a relevant proportion of participants (6 +21 of 50 votes = 54%) are dissatisfied while only 12 (20%) are satisfied with the existing tools for storing, processing and publishing data from metabolism studies.

Conclusion:

- Comparing the satisfaction in the stakeholder groups, the applicants are rather dissatisfied with the current situation.
- Further analysis would be needed to clarify the different points of view.

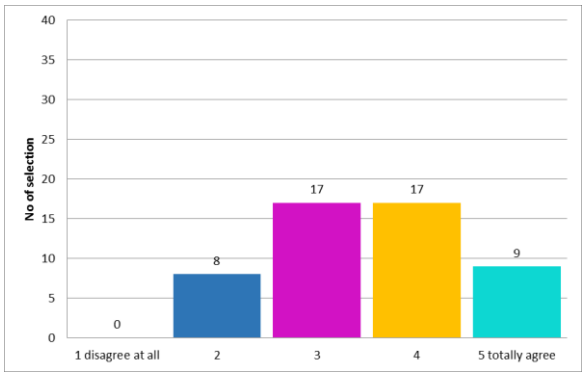
Weak point:

S 3.3.2-2 Dissatisfaction with current tools for storing, handling and disseminating metabolic data is an indication of improvements needed.

3.3.2.4 The summaries of the metabolism studies contain enough detailed information …

Only if a relevant percentage of survey respondents agree with this statement would it make sense to reorganize the way information flows to metabolism studies. Otherwise, a review of the information content to be transmitted would also be necessary.

The participants had to decide about the statement:
“*The summaries of the metabolism studies contain enough detailed information to assess them and to perform the risk assessment (for now and in the future).*”



Findings:

- The mean value is 3,5 which could be interpreted as a tendency to “agree”.
- Only 8 of 51 votes (=16%) for “disagree”.
- Only 12% of the participants skipped this question.

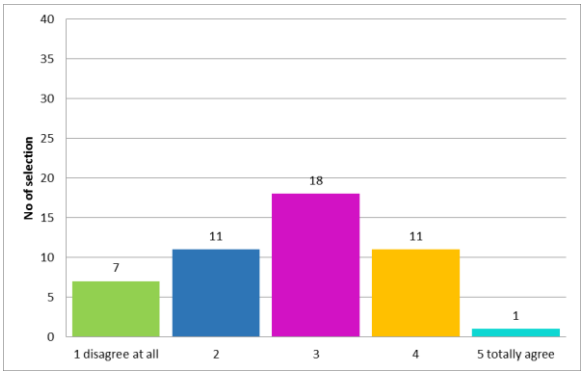
Conclusion:

- The current level of detail information provided in study summaries for metabolism studies seems to be a solid basis of the information flow and for an eventual reorganization.

3.3.2.5 The processes of the informational flow ...

This question was intended to determine the level of satisfaction / dissatisfaction with the organization of the process for the flow of information. If there is a significant dissatisfaction, there is need for a reorganisation.

The participants had to decide about the statement:
"*The processes of the informational flow on metabolism studies are optimally organized.*"



Findings:

- The mean value is 2,8 which could be interpreted as "undecided".
- There is a wide variation in the vote.
- Only 17% of the participants skipped this question.
- The result shows that more participants voted with "disagree at all" comparing with "totally agree".

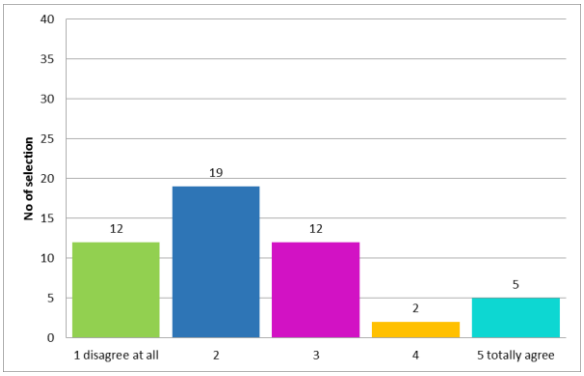
Conclusion:

- The current organization of the process seems to be a solid basis for an improvement of the information flow.

3.3.2.6 There is no duplication of work ...

This question was intended to determine if there is no duplication of work in the drafting of the metabolism study summaries

The participants had to decide about the statement:
"*There is no duplication of work in the drafting of the metabolism study summaries.*"



Findings:

- The mean value is 2,4 which could be interpreted as a tendency to "disagree".
- There is a wide variation in the vote.
- 12 + 19 participants (=62%) disagreed with this statement.
- Only 14% of the participants skipped this question.

Conclusion:

- Reduction of duplicate work should be a goal in redesigning the flow of information.

Weak point:

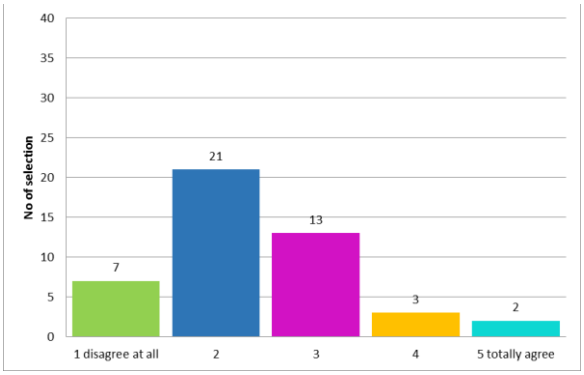
S 3.3.2-3 It seems that the current flow of information is connected with a relevant amount of duplication of work.

3.3.2.7 It is easy to visualize and check the raw results ...

The following question led to unintended confusion among the participants, as the concept of raw data was interpreted differently by the stakeholders.
The GLP raw data are subject to GLP rules, but do not usually leave the laboratories. These GLP data are not the content of the need information flow from applicants to authorities.

The following question did not refer to the GLP raw data.

The participants had to decide about the statement:
"*It is easy for the risk assessors to visualize and check the raw results of the metabolism studies*".



Findings:

- The mean value is 2,4 which could be interpreted as a tendency to "disagree".
- There is a wide variation in the vote.
- 7 + 21 participants (=61%) disagreed with this statement.
- 21% of the participants skipped this question.

Conclusion:

- A better visualisation of the aggregated data should be one goal in the improvement of the IT-tools.

Weak point:
S 3.3.2-4 The stakeholders have a different understanding ot the term "raw data".

3.3.2.8 Comments regarding the framework conditions

A large number of free text comments were submitted by the survey participants. The comments were documented in the table in chapter 4.1. If a survey respondent summarised several aspects in the comment field, these comments were divided according to the topic.

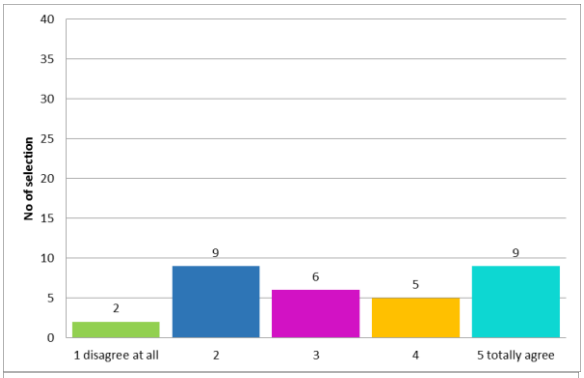
All text comments of all question groups were analysed in chapter 3.4.

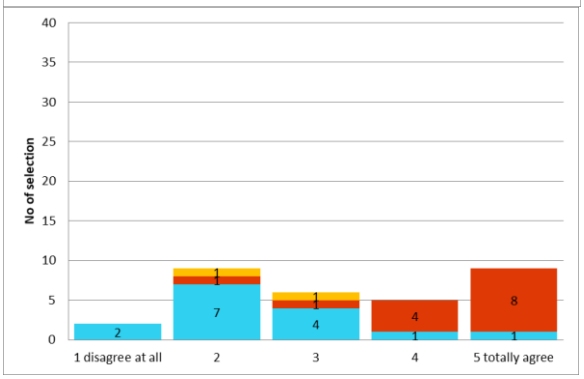
3.3.3 Question group 3: MSS-composers

In the following chapters, the participants were asked for their opinion on the IT tools used and on the possibilities for future development.

3.3.3.1 Creating metabolism pathway maps with the MSS-composers …

The participants had to decide about the statement:
"*I trust that creating metabolism pathway maps (xml files) with the MSS-composers is a good investment to improve the quality and the efficiency of risk assessment*".





Used colours: Other
Authority
Applicants

Findings:

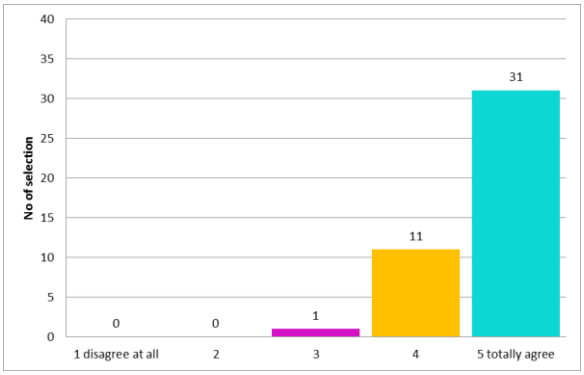
- The mean value is 3,3 which could be interpreted as "undecided".
- There is a wide variation in the vote.
- There exists a clear difference in the answer to this question depending on the stake-holder group. The representatives of the authorities agreed with the statement much more than the representatives of the applicants.
- 47% of the participants skipped this question.

Conclusion:

- There is no clear consensus in favour of this direction of development.

3.3.3.2 Additional information and tutorials on the MSS-composers …

The participants had to decide about the statement:
"*I would welcome an initiative for additional information and tutorials on the MSS-composers.*"



Findings:

- The mean value is 4,7. The statement was clearly confirmed by the participants.
- 26% of the participants skipped this question.

Conclusion:

- EFSA should meet this need for information within its area of responsibility in the short term. This happened in the meantime on 29/31 March with the webinar and the publication of the manual + setting up of a Q&A channel.

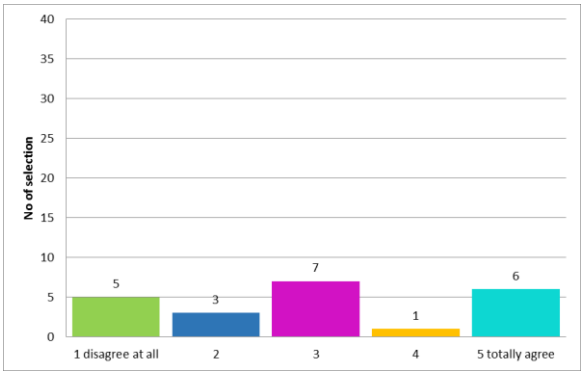
Weak point:

S 3.3.3-1 EFSA's March 2021 changes to the submission formats for metabolism studies do not appear to have been prepared with all stakeholders to the necessary extent.

S 3.3.3-2 The use of MSS Composer is necessary in the new information flow. Inadequate knowledge of how to use this IT tool poses a high risk for the implementation of this intermediary information flow.

3.3.3.3 MSS-Composers supports very detailed study descriptions

The participants had to decide about the statement: "*The current MSS-Composers supports very detailed study descriptions. This level of detail will also be needed in the future.*"



Finding:

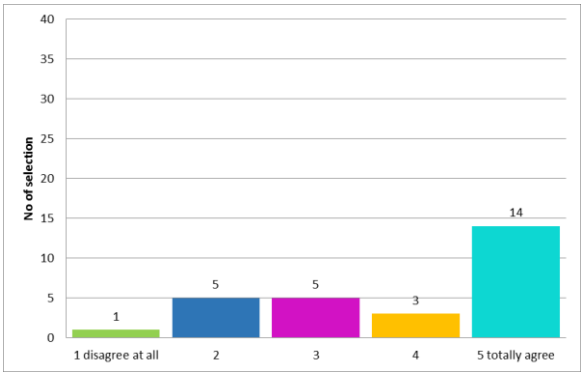
- The mean value is 3,0 which could be interpreted as "undecided".
- There is a wide variation in the vote.
- 62% of the participants skipped this question.

Conclusion:

- With this result, the above statement should not be used as an argument for decisions to be made.

3.3.3.4 One MSS-Composers should cover all OHTs …

The participants had to decide about the statement: "*One MSS-Composers should cover all OHTs relevant for metabolism studies.*"



Finding:

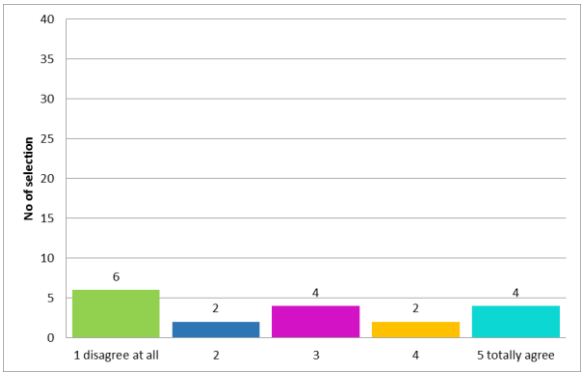
- The mean value is 3,9. The statement was confirmed by the participants".
- But 52% of the participants skipped this question.
- Those who did give an opinion are in favour of standardising the MSS Composer approach in an IT tool.

Conclusion:

- It could be that this limited statement is used in the argumentation for the improvement of the MSS Composer.

3.3.3.5 Confidentiality issues and the MSS-Composers

The participants had to decide about the statement: "*During the entry of the study data into the MSS-Composers, confidentiality issues are considered*"



Findings:

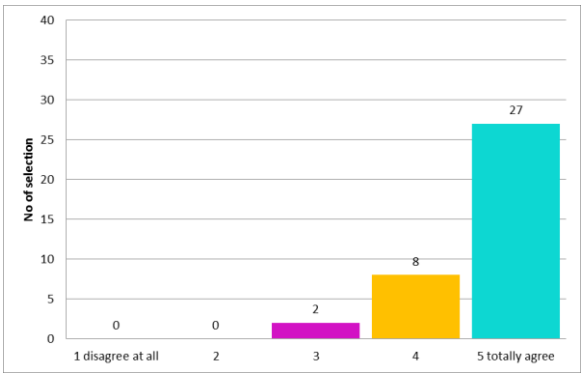
- The mean value is 2,8 which could be interpreted as "undecided".
- There is a wide variation in the vote.
- 69% of the participants skipped this question. This means that 2/3 of the participants could not / would not form an opinion on this question.

Conclusion:

- With this result, the above statement should not be used as an argument for decisions to be made.

3.3.3.6 Governance model for the MSS-Composers

The participants had to decide about the statement:
"*It is important to define a transparent governance model for the MSS-Composers.*"



Findings:

- The mean value is 4,7. The statement was clearly confirmed by the participants.
- 36% of the participants skipped this question.

Conclusion:

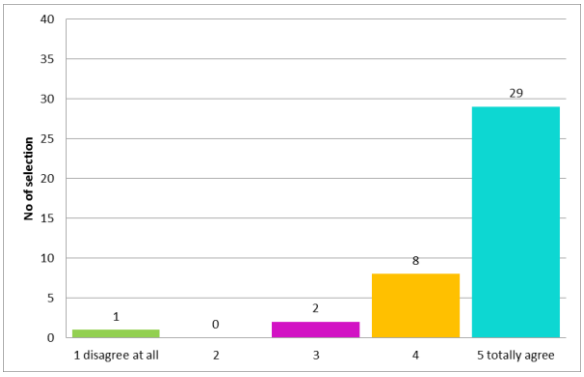
- The interested parties and the owner of the IT tool should develop and implement a transparent governance concept for the MSS Composers.

Weak point:

S 3.3.3-3 The current governance model of the MSS Composer could be a risk for the implementation of the MSS Composer in the European workflow.

3.3.3.7 MSS-Composers report formats

The participants had to decide about the statement: "*The MSS-Composers should be able to generate reports corresponding to the format of the Volume 3 of DAR/RAR.*"



Findings:

- The mean value is 4,6. The statement was clearly confirmed by the participants.
- 31% of the participants skipped this question.

Conclusion:

- The interested parties should make a concept of additional report formats corresponding to the format of the Volume 3 of DAR/RAR.

Weak point:

S 3.3.3-4 The MSS composers do not yet fully support the format of the Volume 3 of DAR/RAR.

3.3.3.8 Comments regarding the MSS Composers

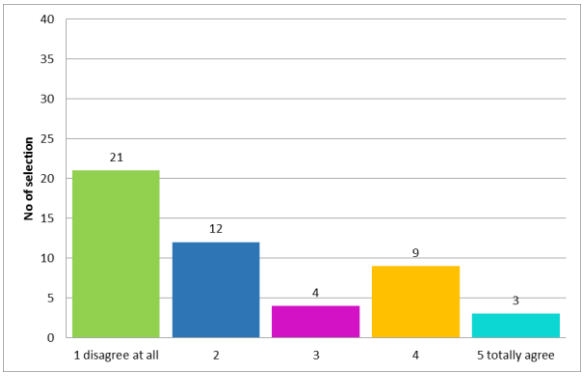
A large number of free text comments were submitted by the survey participants. The comments were documented in the table in chapter in chapter 4.1. If an author summarised several aspects in the comment field, however, these were divided according to the topic.

All text comments of all question groups were analysed in chapter 3.4.

3.3.4 Question group 4: MetaPath

3.3.4.1 I am aware of all the full package of MetaPath …

The participants had to decide about the statement:
"*I am aware of all the full package of functionalities offered by MetaPath and how it may be useful for the risk assessment.*"



Findings:

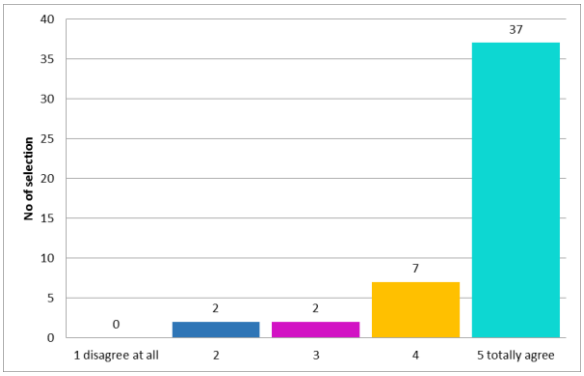
- The mean value is 2,2. The statement was contradicted by the participants.
- Only 16% of the participants skipped this question.

Conclusion:

- Combined with the high need for training (next chapter), this statement underlines that Metapath's functionalities are not widely known.
- From this statement, it must not be concluded that the functions of Metapath are not suitable.

3.3.4.2 Welcome a training on MetaPath

The participants had to decide about the statement: "*I would welcome a training/tutorial on MetaPath.*"



Findings:

- The mean value is 4,6. The statement was clearly confirmed by the participants.
- Only 17% of the participants skipped this question.

Conclusion:

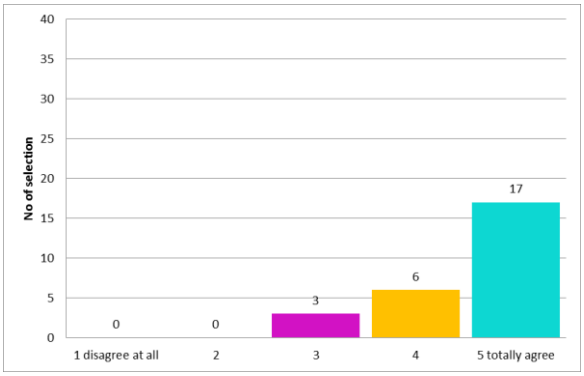
- There is a high need for training of Metapath.

Weak point:

S 3.3.4-1 The use of Metapath is necessary in the new information flow. Inadequate knowledge of how to use this IT tool poses a high risk for the implementation of this intermediary information flow.

3.3.4.3 Export function in MetaPath

The participants had to decide about the statement:
"*I need an export function in MetaPath to be able to use data in other IT-Tools.*"



Findings:

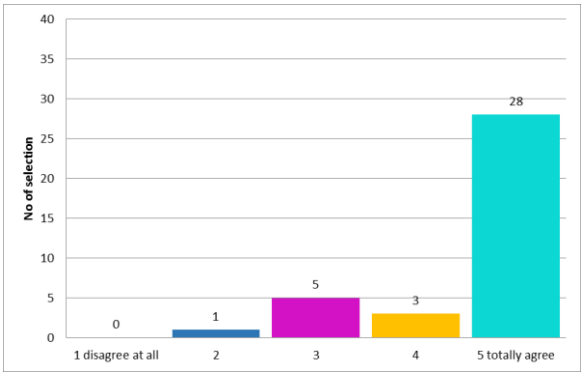
- The mean value is 4,5. The statement was clearly confirmed by the participants.
- 55% of the participants skipped this question.

Conclusion:

- It is not surprising that only a few participants had responded to this question. It is likely that participants clearly responded with a need for an export function when they were involved with Metapath.

3.3.4.4 MetaPath should be opened …

The participants had to decide about the statement: "*The IT-Tool MetaPath should be opened to access from other tools.*"



Findings:

- The mean value is 4,6. The statement was clearly confirmed by the participants.
- 36% of the participants skipped this question.

Conclusion:

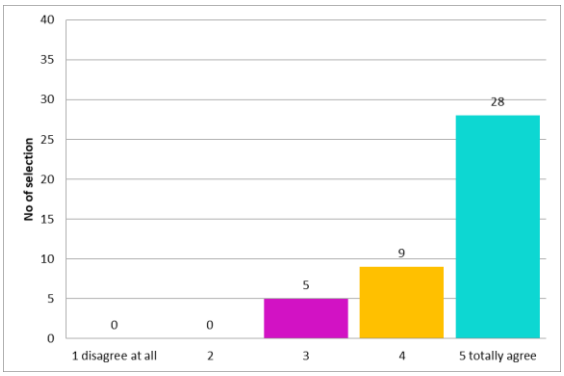
- This statement was answered far more clearly than after a possible export function (see chapter 3.3.4.3). So a better interoperability of Metapath would be very welcome.

Weak point:

S 3.3.4-2 There exists a need of more interoperability of Metapath with other IT tools.

3.3.4.5 Governance model of MetaPath

The participants had to decide about the statement:
"*It is important to define a transparent governance model for IT-Tool MetaPath.*"



Finding:

- The mean value is 4,5. The statement was clearly confirmed by the participants.
- 28% of the participants skipped this question.

Conclusion:

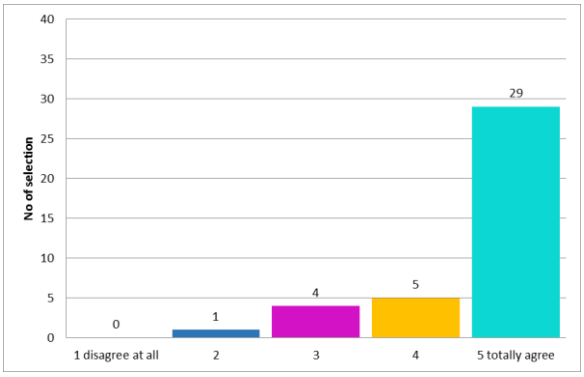
- This statement was answered far more clearly than after the interoperability of Metapath (see chapter 3.3.4.4). So a transparent governance concept of Metapath would be very welcome.

Weak point:

S 3.3.4-3 The current governance model of Metapath could be a risk for the implementation of the Metapath in the European workflow.

3.3.4.6 Governance model of the public Metabolic trees database

The participants had to decide about the statement:
"*It is important to define a transparent governance model for the public MetaPath "Metabolic trees databases"*"



Finding:

- The mean value is 4,6. The statement was clearly confirmed by the participants.
- 33% of the participants skipped this question.

Conclusion:

- A transparent governance model should be developed for both Metapath and for public metabolic trees database(s).

3.3.4.7 Comments regarding Metapath

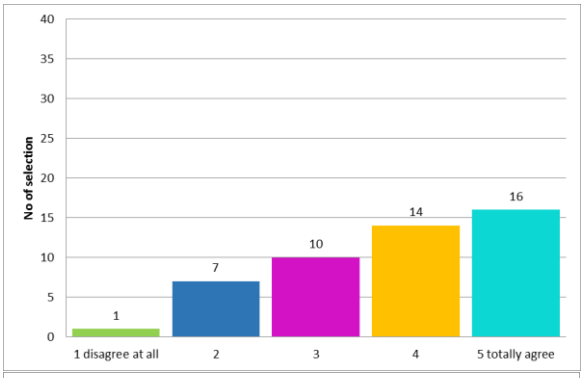
A large number of free text comments were submitted by the survey participants. The comments were documented in the table in chapter 4.1. If an author summarised several aspects in the comment field, however, these were divided according to the topic.

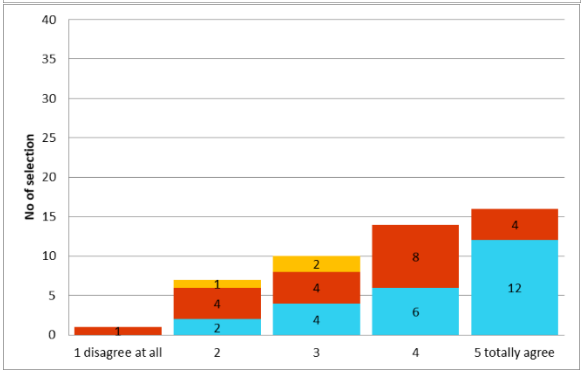
All text comments of all question groups were analysed in chapter 3.4.

3.3.5 Question group 5: OECD Harmonised Templates and IUCLID

3.3.5.1 A study is always assessed …

The participants had to decide about the statement:
"*A study is always assessed in the context of a specific application.*"





Used colours: Other
Authority
Applicants

Findings:

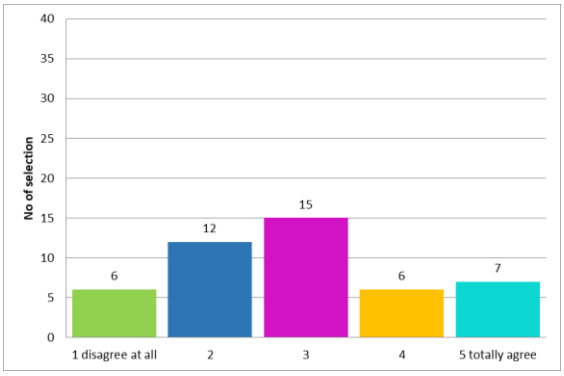
- The mean value is 3,8. The statement was confirmed by the participants.
- There is a wide variation in the vote.
- Applicants tended to agree with the statement more than representatives from the authorities.
- Only 17% of the participants skipped this question.

Conclusion:

- No comment field was available to justify disagreement of the statement in the survey. If needed, further analysis could clarify the different points of view.

3.3.5.2 The study summary … cannot become out of date

The participants had to decide about the statement:
"*The study summary without the administrative data and without the conclusions cannot become out of date.*"



Findings:

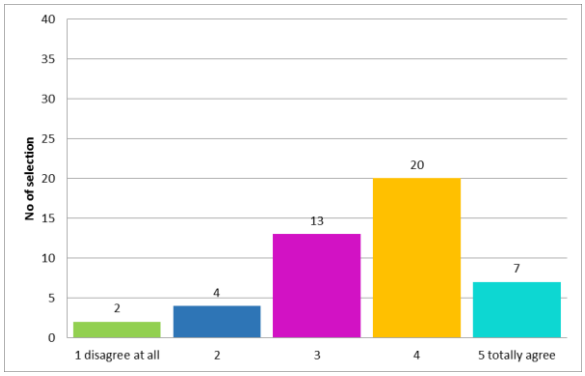
- The mean value is 2,9 which could be interpreted as "undecided".
- There is a wide variation in the vote.
- Only 21% of the participants skipped this question.

Conclusion:

- No comment field was available to justify disagreement of the statement in the survey. If needed, further analysis could clarify the different points of view.

3.3.5.3 Administrative data and the conclusions … depend on the time point.

The participants had to decide about the statement:
"*The administrative data and the conclusions drawn from the study depend on the time point.*"



Findings:

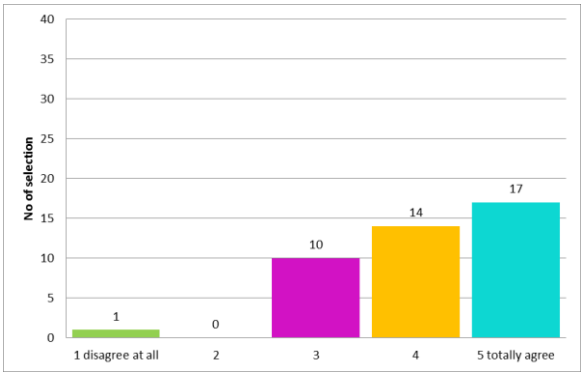
- The mean value is 3,6 which could be interpreted as a tendency to "agree".
- The median value of 4 indicates an agreement with the statement.
- Only 21% of the participants skipped this question.

Conclusion:

- No comment field was available to justify disagreement of the statement in the survey. If needed, further analysis could clarify the different points of view.

3.3.5.4 The OECD templates and IUCLID should be improved ...1

The participants had to decide about the statement:
"*The OECD templates and IUCLID should be improved to be the data source for Metapath regarding metabolism studies.*"



Findings:

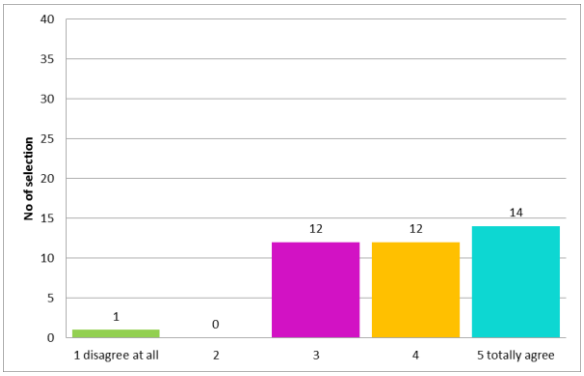
- The mean value is 4,1. The statement was confirmed by the participants.
- Only 28% of the participants skipped this question.

Conclusion:

- This result could form a basis for further consideration of improvements in the flow of information.

3.3.5.5 The OECD templates and IUCLID should be improved ...2

The participants had to decide about the statement:
"*The OECD templates and IUCLID should be improved to be the data source of the QSAR-Toolbox regarding metabolism studies.*"



Findings:

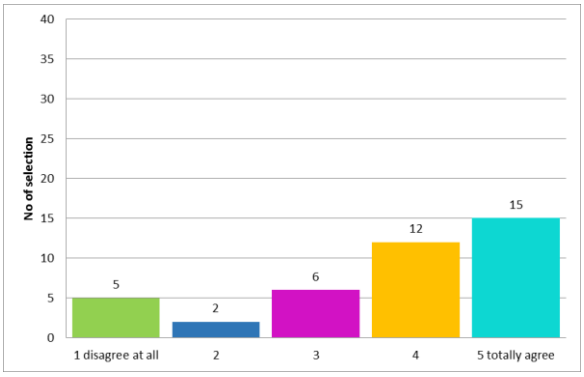
- The mean value is 4,0. The statement was confirmed by the participants.
- 33% of the participants skipped this question.

Conclusion:

- This result is not as clear as the result of the question from the previous chapter (see chapter 3.3.5.4). Therefore a further analysis should be carried out.
- This result could form a basis for further consideration of improvements in the flow of information.

3.3.5.6 OHT should be further developed to be able to …

The participants had to decide about the statement:
"*Although not currently possible, I believe that the OHT should be further developed to be able to submit the raw data of the metabolism studies.*"



Findings:

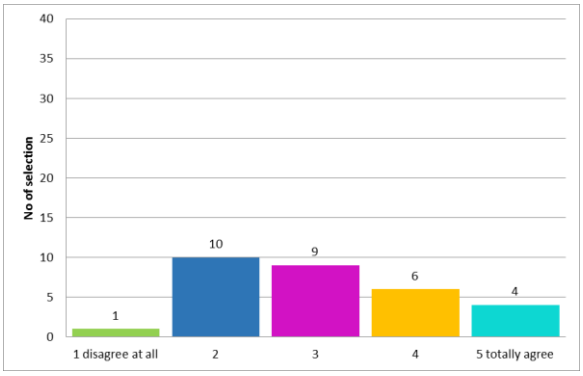
- The mean value is 3,8. The statement was confirmed by the participants.
- There is a wide variation in the vote.
- 31% of the participants skipped this question.

Conclusion:

- A further analysis should be carried out.
- This result could form a basis for further consideration of improvements in the flow of information.

3.3.5.7 OHT 85-2 and 85-3 are fit for purpose …

The participants had to decide about the statement:
"*The current OHT for metabolism in residues (85-2 and 85-3) are fit for purpose to report metabolism study results.*"



Findings:

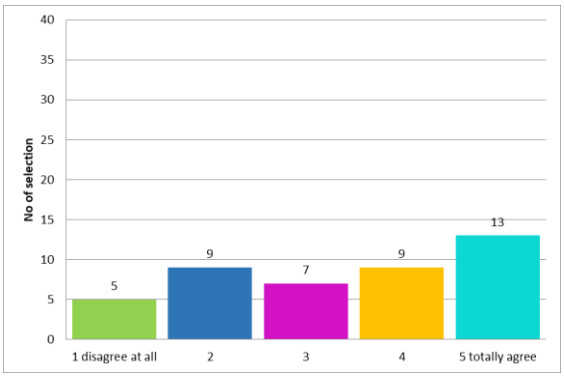
- The mean value is 3,1 which could be interpreted as "undecided".
- There is a wide variation in the vote.
- 48% of the participants skipped this question.

Conclusion:

- A further analysis should be carried out.

3.3.5.8 Generalize OECD templates related to metabolism studies …

The participants had to decide about the statement:
"*The OECD should generalize all OECD templates related to metabolism studies through a generic approach (including plants, livestock, toxicology, environment ...).*"



Findings:

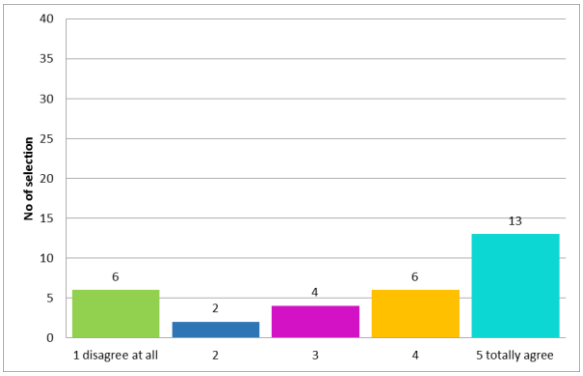
- The mean value is 3,4 which could be interpreted as "undecided".
- There is a wide variation in the vote.
- 26% of the participants skipped this question.

Conclusion:

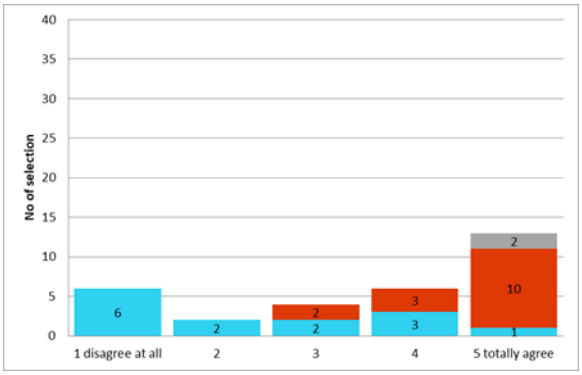
- A further analysis should be carried out.

3.3.5.9 Metabolism studies should be attached as MSS-Composer data files …

The participants had to decide about the statement:
"*As long as the OHT cannot be used as direct data sources for MetaPath, the results (raw data) of metabolism studies should be attached as MSS-Composer data files in the dossier.*"



Used colours: Other
Authority
Applicants



Findings:

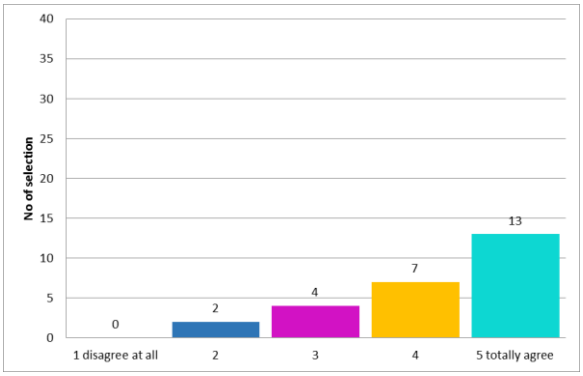
- The mean value is 3,6 which could be interpreted as a tendency to "agree".
- There is a wide variation in the vote.
- But 47% of the participants skipped this question.

Conclusion:

- The approach proposed by EFSA for 2021 on the use of the MSS-files is not supported by all participants.
- The position regarding this statement clearly differs between the stakeholder groups.

3.3.5.10 The OHT should mimic the MSS-Composers …

The participants had to decide about the statement:
"*The OHT should mimic the MSS-Composers and replace it on the long term.*"



Findings:

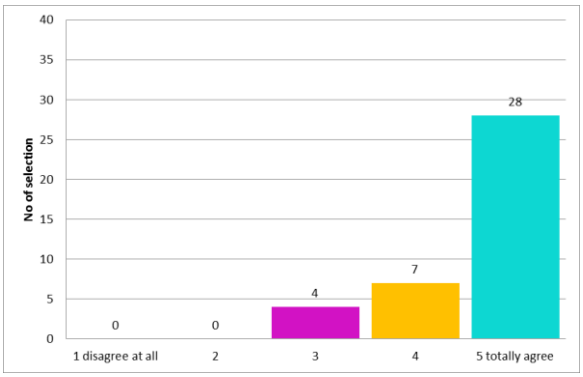
- The mean value is 4,2. The statement was confirmed by the participants who had provided an answer.
- But 55% of the participants skipped this question.

Conclusion:

- Based on the result of this question, one can only observe a tendency for possible changes.

3.3.5.11 IUCLID should be able to import a MSS-files …

The participants had to decide about the statement:
"*IUCLID should be able to import a MSS-Composers output into the corresponding OECD template.*"



Findings:

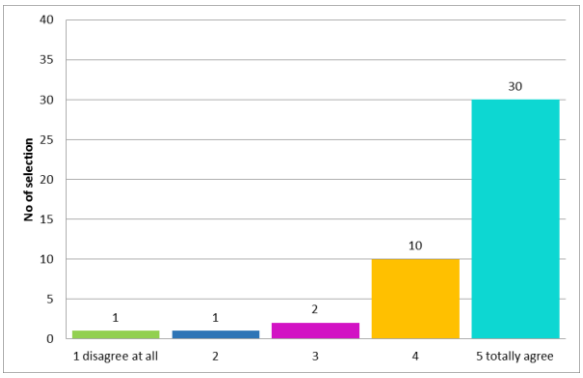
- The mean value is 4,6. The statement was clearly confirmed by the participants.
- 33% of the participants skipped this question.

Conclusion:

- The survey participants have thus clearly expressed their interest for better interoperability of the systems.

3.3.5.12 IUCLID should be able generate all needed reports …

The participants had to decide about the statement:
"*It should be possible to generate all needed reports regarding metabolism studies (eg. Study summaries for the Volume 3 of DAR/RAR, Appendix G) from IUCLID.*"



Findings:

- The mean value is 4,5. The statement was clearly confirmed by the participants.
- 24% of the participants skipped this question.

Conclusion:

- The survey participants have thus clearly expressed their interest for better interoperability of the systems.
- This vote is also a clear call to minimize duplication of effort.

Weak point:

S 3.3.5-1 Both IUCLID and Metapath (compare with 3.3.3.7) do not currently yet support the necessary reporting formats.

3.3.5.13 Comments regarding OECD templates for metabolism studies

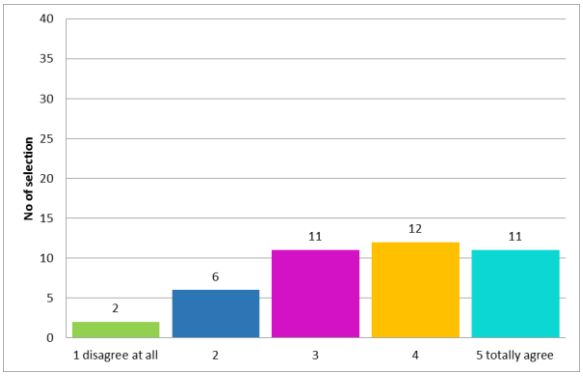
A large number of free text comments were submitted by the survey participants. The comments were documented in the table in chapter 4.1. If a survey respondent summarised several aspects in the comment field, however, these were divided according to the topic.

All text comments of all question groups were analysed in chapter 3.4.

3.3.6 Question group 6: OECD QSAR-Toolbox

3.3.6.1 Missing information about using …

The participants had to decide about the statement:
"*I was missing information about the possibility of using QSAR-Toolbox for this topic.*"



Findings:

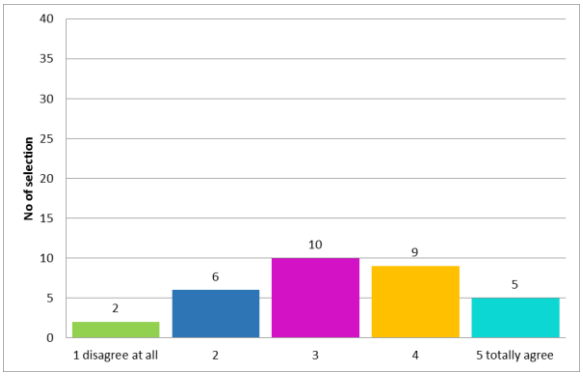
- The mean value is 3,6 which could be interpreted as a tendency to "agree"
- 28% of the participants skipped this question.

Conclusion:

- Since it can be assumed that only interested stakeholders participated in the survey, the wide spread of responses shows that there are deficits in public relations regarding the QSAR-Toolbox.

3.3.6.2 I know the advantages of the QSAR-Toolbox …

The participants had to decide about the statement:
"*I know the advantages of the QSAR-Toolbox and would like to use this tool in the future.*"



Findings:

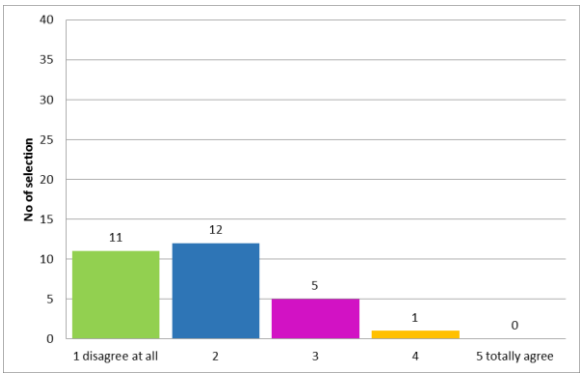
- The mean value is 3,3 which could be interpreted as "undecided".
- There is a wide variation in the vote.
- But 45% of the participants skipped this question.

Conclusion:

- The advantages of the QSAR-Toolbox in terms of applicability in the field of metabolism are not sufficiently known or convincing enough.

3.3.6.3 QSAR models are of sufficient quality …

The participants had to decide about the statement:
"*The pesticide-related QSAR models are of sufficient quality for predicting metabolism pathways.*"



Findings:

- The mean value is 1,9. The statement was contradicted by the participants.
- But 50% of the participants skipped this question.

Conclusion:

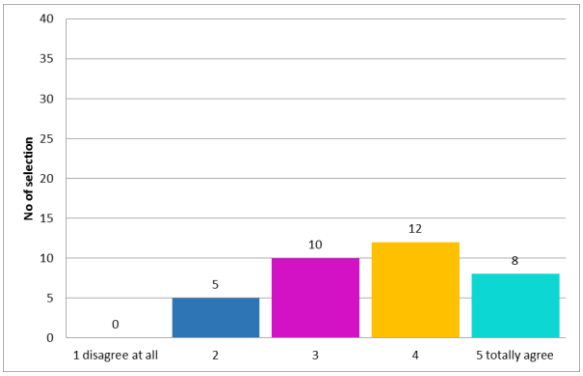
- It seems that the QSAR-Toolbox is not sufficient for predicting metabolism pathways.
- It was not the aim of the survey to find possible reasons for the rejections of a statement. Nevertheless, some reasons can be found in the comments (see chapter 3.4)
- If one wants to improve the quality of the QSAR-Toolbox, a further analysis should be carried out.

Weak point:

S 3.3.6-1 The rejection of the statement "*The pesticide-related QSAR models are of sufficient quality for predicting metabolism pathways*" suggests that the QSAR-Toolbox has weaknesses in this area.

3.3.6.4 Collections from MetaPath could be important data sources …

The participants had to decide about the statement:
"*Collections from MetaPath could be important data sources of the QSAR-Toolbox regarding metabolism studies.*"



Findings:

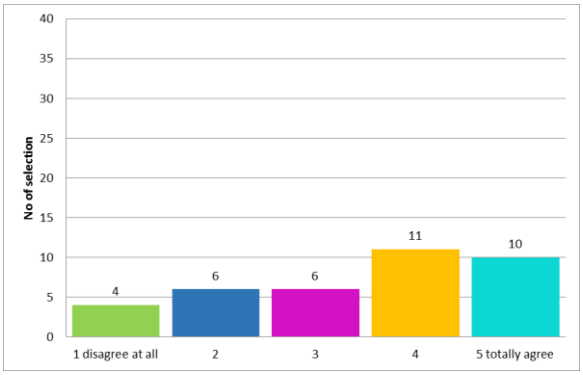
- The mean value is 3,7 which could be interpreted as a tendency to "agree"
- There is a wide variation in the vote.
- 40% of the participants skipped this question.

Conclusion:

- Since the participants are of the opinion that the QSAR-Toolbox is not sufficient for predicting metabolism pathways, the weak agreement with the above thesis is not surprising.

3.3.6.5 QSAR-Toolbox should be the publicly available reference model …

The participants had to decide about the statement:
"*The QSAR-Toolbox should be the publicly available reference model for predicting the metabolism of pesticides.*"



Findings:

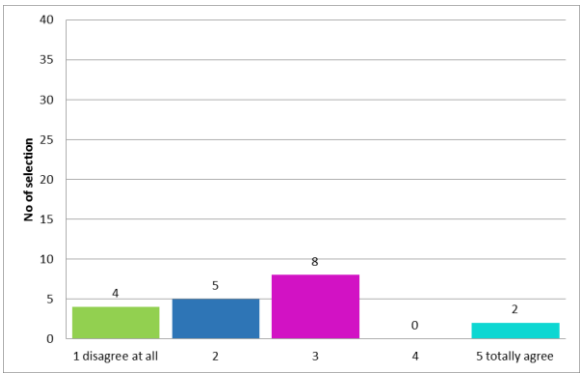
- The mean value is 3,5 which could be interpreted as a tendency to "agree"
- The median value of 4 indicates an agreement with the statement.
- There is a wide variation in the vote.
- But 36% of the participants skipped this question.

Conclusion:

- The weak agreement with the above thesis could be interpreted as the hope of the participants to improve the QSAR-Toolbox to a publicly available reference model.

3.3.6.6 Confidentiality aspects of studies into QSAR-Toolbox …

The participants had to decide about the statement:
"*Confidentiality aspects have been clarified for including data of studies into QSAR-Toolbox.*"



Findings:

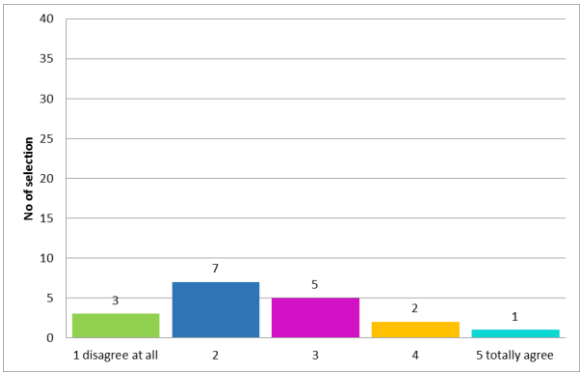
- The mean value is 2,5 which could be interpreted as a tendency to "disagree".
- But most of the participants (67%) skipped this question.

Conclusion:

- It seems that participants do not have enough information regarding confidentiality rules.

3.3.6.7 The principles for the reuse of the information …

The participants had to decide about the statement:
"*The principles for the reuse of the information (data access) available in the QSAR-Toolbox have been clarified.*"



Findings:

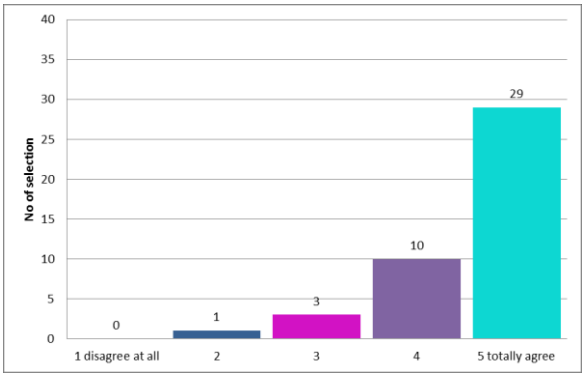
- The mean value is 2,5 which could be interpreted as a tendency to "disagree".
- But most of the participants (69%) skipped this question.

Conclusion:

- It seems that participants do not have enough information regarding the reuse of the information (data access) available in the QSAR-Toolbox.

3.3.6.8 Training/ tutorial on QSAR-Toolbox …

The participants had to decide about the statement:
"*I would welcome a training/tutorial on QSAR-Toolbox.*"



Findings:

- The mean value is 4,6. The statement was clearly confirmed by the participants.
- 26% of the participants skipped this question.

Conclusion:

- There is a high need for training for the QSAR-Toolbox.

3.3.6.9 Comments regarding OECD QSAR-Toolbox

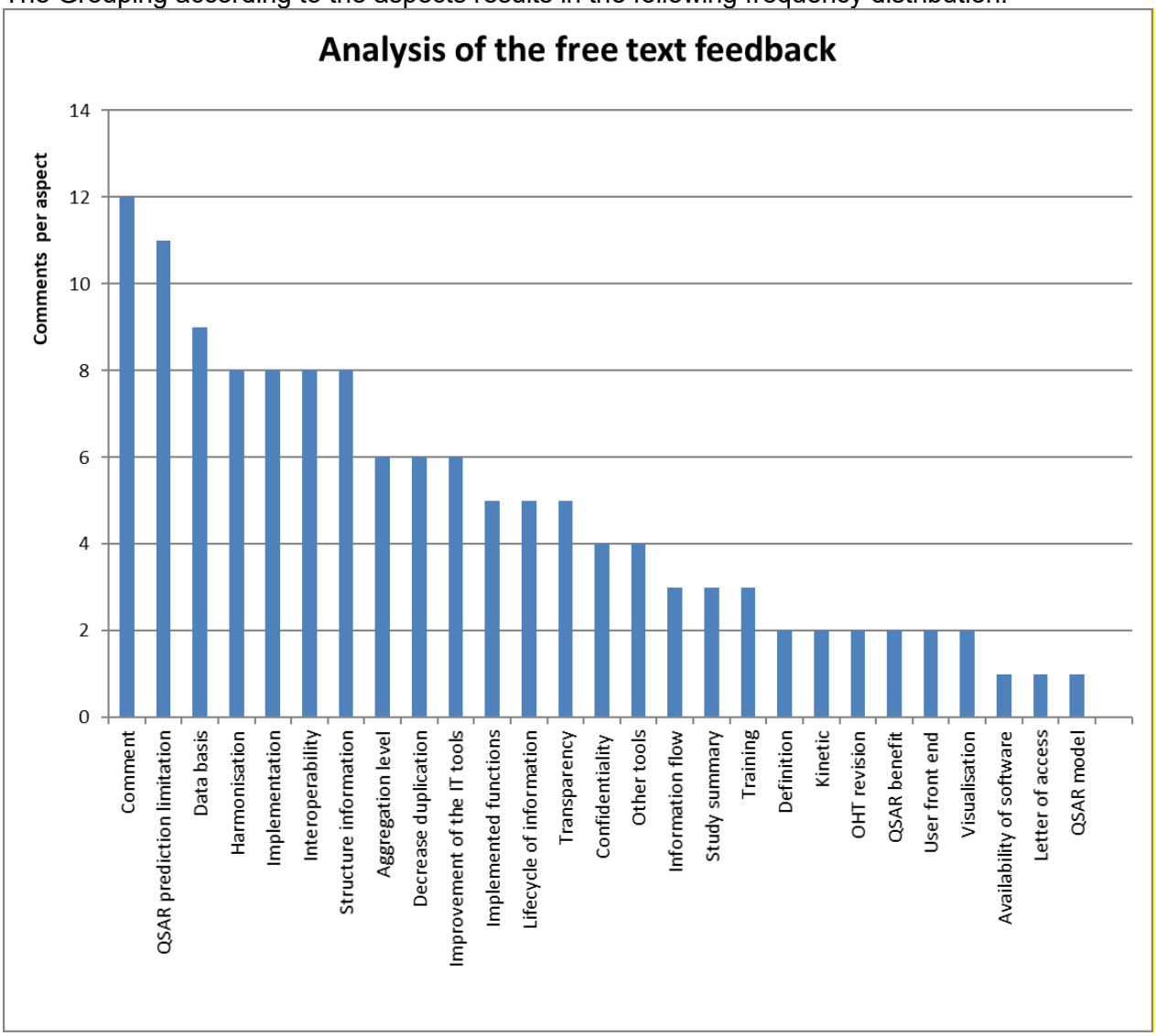
A large number of free text comments were submitted by the survey participants. The comments were documented in the table in chapter 4.1. If an author summarised several aspects in the comment field, however, these were divided according to the topic.

All text comments of all question groups were analysed in chapter 3.4.

3.4 Analysis of the text comments

The textual comments (chapter 4.1) were grouped according to different aspects. It should be noted that long textual comments that could be assigned to several aspects were divided.

The Grouping according to the aspects results in the following frequency distribution:



From the BfR's point of view, the **most important weak points** from the textual comments of the participants are listed below. But it should be emphasised that this list summarized not all topics. Stakeholders should be invited to participate in the improvement process and to prioritise the necessary efforts from their perspective.

3.4.1 Structure information

S 3.4.1-1 There are elementary difficulties in encoding of structures (generic structures; stereochemistry). As long as these difficulties exist, IT tools for storing results from metabolism studies, searching for structure-like and predicting metabolic pathways will be imperfect.

S 3.4.1-2 As long as there are elementary difficulties in encoding of structures, the IT tools provided will also only be of limited use.

3.4.2 Harmonisation, Interoperability, IT tools

S 3.4.2-1 There seems to be a discrepancy between the wealth of information required for a risk assessment of metabolites and the suitability of the IT tools provided.

S 3.4.2-2 An insufficient degree of harmonisation in the templates to be completed, the variety of IT tools to be used and the lack of data interfaces are the cause of duplication.

S 3.4.2-3 The orientation towards EU specific requirements / formats complicates the efforts for a global harmonisation.

3.4.3 Risk assessment and the silico limitations of predictions

S 3.4.3-1 Due to the modern analytical methods, the data basis to be provided for metabolism studies is growing to a level that risk assessors cannot cope without IT support. Technical limitations of the IT tools, difficulties in data exchange between systems and in the visualisation of the results can lead to an excessive demand on the risk assessors.

S 3.4.3-2 The QSAR tools currently available on the basis of the existing models and the existing database can only be used to a limited extent in the field of metabolic pathway prediction.

S 3.4.3-3 The OECD QSAR-Toolbox is limited in the prediction of the kinetics in different "objects of investigation" (species, crops, and environment) of a certain metabolite at different time points.

4 Appendix

4.1 Compilation of the textual comments survey

Question Group /Number	Comment	Topic	Additional Topic	Additional Topic
2 01 a	More clear studies description in official reviews, make it more transparent and easier for interested parties to understand the idea and results of metabolism studies.	Study summary		
2 01 b	There should be more emphasis on the obligatory data sharing of metabolism studies among interested parties.	Letter of access		
2 02 a	A lot of duplication from the raw results from the labs to the risk assessment conclusions. Ideally raw results should be inserted only once by the labs and the level of aggregation of the results should increase when we get closer to the risk assessment	Aggregation level		
2 02 b	Visualisation of the raw results is not easy, available in the DAR/RAR in tables but it's already a summary.	Visualisation		
2 02 c	Impossible to compare several studies in one single table in the DAR/RAR, without doing additional manual data management (e.g. excel Appendix G) while the data were previously probably entered in excel files of other electronic formats.	Interoperability		
2 03	A metabolism study can be extremely complex. Database systems which are working on the basis of harmonised tables and templates are therefore of limited use and bearing the risk that important information is not reflected properly or not seen in the right context.	Harmonisation		

2 04 a	Currently EFSA requires MSS Composer to be filled out for livestock metabolism, plant metabolism, confined rotation crop for dossier submissions in July 2021. The Rat MSS Composer is under development. No public MetaPath and Composer Versions are available yet (January 2021) on a web-site for a download. Not enough experience has been collected to work with the tools.	Availability of software		
2 04 b	Confusion is there where to enter the data for metabolism in IUCLID and the MSS Composer.	Information flow		
2 05	Include tables of raw data with all metabolism study summaries published (as in data points/results to allow calculations as per the authority's own standards, not full study details).	Aggregation level		
2 06 a	Information flow question is unclear if it pertains to pre-submission, regulatory review, post registration in first country, post registration in many countries.	Comment		
2 06 b	It is unclear what is meant by "easy" to check "raw results"--> detailed EXCEL spreadsheets for metabolites based on %TRR and absolute levels are quite possible but they are not standardized.	Harmonisation		
2 07 a	OECD summaries are designed as such, that human experts can easily follow the argumentation, judge reliability of conclusions drawn and see the relevant processed data in a transparent way. All data needed to judge the reliability of the presented data are given in the study report, being part of the dossier submitted.	Aggregation level		
2 07 b	Raw data in the sense of read-outs of analytical machines are typically not of interest in this context, as the reliability of the process of transforming raw data to data to processed data, is regulated under GLP, which is claimed for such studies.	Aggregation level		
2 07 c	The machine readability of chemical structures thus is important for the generation of machine-readable data for metabolism studies. However, there is no language (neither SMILES nor InChI) being able to handle the complexity of stereo chemistry and Markush-structures covering the complexity of structural information being generated in metabolism studies.	Structure information		

2 08	Need to decrease duplication of effort / rework for compiling various summary documents for regulatory submissions.	Decrease duplication		
2 09	Studies are done under GLP and the reported data is always an Finding of raw data. The original raw data is not reported but available upon request. I has to be kept in mind that for example MS raw data can only be interpreted using special software and that the size of the raw data surpasses the gigabyte range. Furthermore raw data is only interpretable if meta information like experiment setup, workup strategy is available - this would lead to the need to include the LIMS data and software. Therefore this approach would be very resource demanding and is deemed unnecessary by me as all studies are done under GLP and under strict adherence to the published guidance documents.	Aggregation level		
2 10 a	The OECD dossier summaries, applicants are submitting are prepared from the metabolism reports. Today's metabolism reports are written in a way that it is easy to extract the relevant data into the dossier. They are human readable and contain metabolite structures. The guidelines for these metabolism studies are widely harmonized by OECD and also accepted by global authorities.	Study summary		
2 10 b	As the studies are done under GLP conditions, it might not be needed to check individual raw data results (e.g. counts from LSC equipment). The relevant calculation procedures are validated.	Aggregation level		
2 11	We do have harmonized guideline for metabolism studies by OECD and also accepted by international authorities. The study reports are written in a way that they are easy to handle and the relevant data for inclusion into dossiers can be extracted straight-forward. Also, they are human readable and contain metabolite structures.	Study summary		
2 12 a	All current regulatory decisions already rely on the metabolism data "as a solid basis for the risk assessment". It is difficult to interpret the question on organizational informational flow because the stages of pre-submission versus initial regulatory review versus registered products need consideration.	Information flow		
2 12 b	It is unclear what last question means by visualizing raw results, but generally some detailed Excel tables with %TRR and absolute amounts can be organized to provide a good	Visualisation		

	overview across multiple studies. Standardization of overview tables could be improved however.			
2 13	I can only speak about my experience here of course working in this area for 30 years. Changes and lack of globally harmonized approaches/ guidelines are in my opinion the biggest hurdle	Harmonisa-tion		
2 14	If it is presumed that Metapath is widely used by US registrants to submit data to EPA that is not accurate. We summarize data in Excel tables first translate it to Tables in Word and create figures in structure drawing programs such as Biovia based on SMILES codes.	Comment		
2 15 a	The current data requirements for metabolism studies are a solid basis for the risk as-sessment. I would agree with the current OECD requirements. The current tools for me-tabolism data storage, handling and dissemination are sufficient. I suspect different or-ganizations do things differently to suit their purposes. But the question seems to indicate someone thinks there is an issue. Of course there can always be improved processes.	Comment		
2 15 b	The summaries of the metabolism studies contain enough detailed information to assess them and to perform the risk assessment (for now and in the future). Since this is a sur-vey starting in EU, I will assume the overarching questions refer to the EU. If you want to perform more sophisticated risk assessments in the future start with the design of risk as-sessment. As an example there are new guidelines for the metabolism in fish from fish farms yet I don't believe the consumption data in the EU risk assessment differentiates between farm raised fish and wild caught fish, let alone crustaceans and mollusks, in the absence of appropriate consumption data the risk is now overestimated.$The processes of the informational flow on metabolism studies are optimally organized. There is always room for improvement.	Comment		
3 01 a	Currently information about the MSS composer is hard to find, and information available on the internet seem to be old. Although being available for a long time, obviously it was not used, which shows that there must be limitations in the functionality, limiting its use-fulness.	Implemented functions		

3 01 b	The basis for using MSS composer is a language covering the complex structures recovered in metabolism studies, including stereochemistry and generic structures (which cannot be avoided due to complex matrices and low concentrations of the metabolites found).	Structure information		
3 02 a	Entering data in the composers is a tedious manual process.	User front end		
3 02 b	The many free text fields make re-use of the data difficult.	Interoperability		
3 03 a	Given that we have not yet had the possibility to work with MSS-composers, it is not really possible to judge if for example "creating metabolism pathway maps with the MSS-composers is a good investment to improve the quality and efficiency of the risk assessment" or to know if "one MSS-composer should cover all OHTs relevant to metabolism studies". Additionally, I believe that MSS-composers are not yet available for all types of metabolism studies. It is thus not possible to emit an opinion if the tool will be adapted to the submission and evaluation of metabolism data for pesticide registration.	Implemented functions		
3 03 b	If MSS-composer's and MetaPath shall be used in the future for the regulatory submissions of pesticides, the development of the MSS-composer's should be carefully done (and maybe involve all stakeholders) to make sure we keep high quality standards for the reporting of metabolism data.	Improvement of the IT tools		
3 04 a	I skipped question on confidentiality because it is unclearly written. However both confidentiality and transparency need careful consideration and polices and specific attention needs to be paid to different needs during development/ presubmission, regulatory review and post registration - but also the fact that submission into all countries rarely happens simultaneously so a global timeframe should be considered.	Confidentiality		
3 04 b	The survey intro seems to assume that the system was developed by EPA and therefore registrants will already have experience. However the branch of EPA that developed it is not EPA OPP and the tools have not been a requirement in the US submission process for pesticide registrants.	Comment		

3 04 c	The question on Volume 3 of the DAR/RAR is very EU centric and may not make sense to survey participants outside of EU. OECD and international terminology should be considered.	Harmonisation		
3 05 a	… and ends with the antiquated user interface.	User front end		
3 05 b	In the current stage the composers are neither publically available, nor easy to use or able to provide the same quality of study summaries compared to an oecd summary. They can only be used to attach quantification data and some additional information for metabolic pathways under ideal conditions. For complex studies or molecules showing complex metabolic processing the Composer are not able to reflect this accurately. This starts with the limitations of the composer framework, the handling of generic structures, stereochemistry …	Implemented functions	Structure information	
3 06 a	While I totally agree with the need of providing curated metabolism data for chemical compounds I strongly suggest to further develop these tools before doing a roll out.	Improvement of the IT tools	Implementation	
3 06 b	Especially the good support of generic structures is essential for risk assessment. Furthermore, due to the huge differences in the different metabolism study designs (rat vs plant vs rotcrop vs comp. in vitro vs livestock). I do not think that one composer can be used to generate all of these. They should be tailored. Especially if you consider to contain kinetic information like for example in efate studies.	Implemented functions	Structure information	
3 06 c	The confidentiality topic is in my opinion not so much a composer topic but a data ownership topic which can be addressed elsewhere (eg IUCLID).	Confidentiality		
3 07	MSS composers are good tools to report study results. The same fields could be in the OHT in the future. However, OHT should be used only if we are sure that the data can be read in Metapath. MSS composer can always be improved (just like the OHT) but there are already used and demonstrate their efficiency to capture detailed study results.	Harmonisation		

3 08	Proper training should be implemented for registrants prior to requiring use of the MSS composers for generation of IUCLID or any other study summaries. Duplication of effort/work needs to be avoided.	Implementation		
3 09 a	Based on my metabolism experience and driven by complexity, it is hard to believe that there is only one composer for all study types (rat, livestock, fish, crops, rotational crops, hydrolysis at exaggerated temperatures) allowing and facilitating an accurate risk assessment. The known technical limitations (handling of generic structures, isomers, user interface) must be solved FIRST and prior to any use; any confidentiality question should be handled with the incorporation into IUCLID.	Implemented functions	Implementation	Structure information
3 09 b	The public information available today about the MSS Composer is too limited for any judgement about its potential use in the registration process. Despite the tool was developed by EPA it is not part of any pesticide US submission. There are also no worked-out case studies in public literature.	Comment		
3 10	I have zero understanding of what MSS-composer does at this point in time. My main job responsibility is generating GLP OECD 417 like metabolism data in rats, and helping prepare section specific dossier information.	Implementation		
3 11	I have no direct experience yet with MSS-Composers.	Comment		
3 12	I have been unable to answer most these questions. In common with the vast majority of my colleagues, I have no experience with MSS composer or Metapath and have only seen a few screenshots. Applicant metabolism departments have not been using this system at all for summarizing their studies and are generally only experienced with standard OHT based summaries and the Appendix G spreadsheet. It may well be that this represents and great step forward, but it is impossible for us to judge on the proposed timescale. Releasing guidance only a month before a new system comes into force is not sufficient time for applicants to upskill themselves in a new system and embed the system into their dossier preparation processes (writing, QC checking and internal review). It is also the case that many applicants outsource the production of study summaries to CROs/Consultants who will likely have even less experience than the applicants	Implementation		

4 01	"Open access" needs careful consideration relative to data protection needed for registrants prior to regulatory approval. Please see previous comments as well. Each stage (presubmission, regulatory review, post approval) needs consideration for intellectual property data protection.	Confidentiality		
4 02	Again, I am unable to answer most of these questions and want to highlight that the proposed timescale is too short for an organization to familiarize itself with a complex new system and properly evaluate it and incorporate it into its dossier preparation processes	Implementation		
4 03	As stated before I support the availability of metabolic data in the public domain. To achieve this goal I would welcome if this data is gathered using opensource tools and is distributed in a open file format (human and machine readable like xml) which can be imported into various tools and can be created without the need for metapath or the composers (one could envision to create maps using for example LIM systems). Therefore I support all the aforementioned questions as long as they lead to an open data structure which will be of great use for everyone working on metabolism and risk assessment (authorities, NGOs, academia, applicants). To achieve this the data structure has to support all the properties relevant for structural characterization of compounds (sum formula, generic structures (markush), isotope patters, stereogenic centers) and has to be flexible enough to accurately reflect all types of metabolism studies.	Structure information		
4 04	I have zero experience with MetaPath	Comment		
4 05	I would emphasize that the process for generating summaries. One main concern of this initiative is that multiple formats/entries will be required. The use of the MSS composer should streamline the process vs. resulting in additional work for registrants.	Implementation	Decrease duplication	
4 06	In cases of MSS composer and Metapath it must be ensured that information will be human AND machine readable. Based on the complexity of metabolism studies it will be hard to find only one MSS composer and tool (like Metapath) that allows for an accurate risk assessment. There are obvious difficulties, like the handling of generic structures, that need to be solved first.	Structure information		

4 07 a	It is important, that the information collected with both, Metapath and MSS Composer are both, human and machine readable. Furthermore, transparency can only be achieved, if open formats like XML are used to exchange data between systems.	Interoperability		
4 07 b	This includes the use of descriptive languages for chemical structures being open source. Allowing to create a workflow based on automatic data exchange from the instrument in use to the dossier compiled, without the need for re-entering already existing information is essential to avoid unnecessary duplication of work.	Structure information	Decrease duplication	
4 08	Similar comment as for MSS-composers: Given that we have not yet had the possibility to work with MetaPath, it is not really possible to judge if the tool will be adapted to the submission and evaluation of metabolism data for the risk assessment of pesticides.	Comment		
4 09	The same comments (MSS Composer) are also applying to Metapath. The future tool should adequately cover the complexity of all metabolism studies allowing an adequate and accurate risk assessment. The general goal to have data with high importance for risk assessment in the public domain is fully supported (but also part of the Transparency Regulation). As in case of the MSS composer it must be ensured that the information will be human (and Maschine) readable.	Interoperability		
4 10	Again, though I am not fully aware of all functionalities, I do know that transparency policies will be important in any implementation.	Transparency		
4 11	These questions already assume that there is a distinction in place between public and private data sets, but it is unclear to the registrant community that data protection and access rules for global presubmission is sufficiently developed yet.	Confidentiality		
4 12	Transparency is paramount.	Transparency		

5 01	"A study is always assessed in the context of a specific application." Yes, generally true, however, trade implications should be considered when conclusions are changed over time (e.g. related to MRL for example or groundwater levels). "The study summary without the administrative data and without the conclusions cannot become out of date." Study description (summary, method, results) with study director conclusion should be consistent over time. However, it is accepted that certain study type, data Finding criteria may change over time; this should not change the content of the summary; A proposal is to clearly have a post-study assessment area where applicant or receiving authority can assess the study at a given point in time according to local guidance (geography- and time- dependent assessment).	Lifecycle of information		
5 02	Again, difficult to answer from a position of zero experience with Metapath and MSS Composer	Comment		
5 03	Fully trust that the OHT should be used as the unique standard format to report studies and study results in the future. In the meantime, as they did not prove their efficiency to report metabolism study complex results, the OHT can be used in combination with the MSS composers.	Harmonisation		
5 04 a	Given that no submission for pesticide registration has yet taken place in IUCLID and given that we have not yet started to work on MSS-composers, it is, here again, difficult to emit an opinion on the future developments necessary.	Implementation		
5 04 b	As a general comment on OHTs: Based on our experience with IUCLID pilot projects, the OHTs for metabolism studies are, in their current status, suboptimal and do not allow to report properly metabolism data. To take one concrete example, in the OHT for soil metabolism, it is currently not possible to rationally report data for several radio-labels. Using several radio-labels to characterize the metabolism scheme is a core feature of metabolism studies. Seeing this, it seems ambitious to use, in a short term, solely OHTs to submit metabolism data.	OHT revision		
5 05 a	I would emphasize that the process for generating OECD templates should be harmonized. One main concern of this initiative is that multiple formats/entries will be required.	Harmonisation	Decrease duplication	

	The use of the MSS composer should streamline the process vs. resulting in additional work for registrants.			
5 05 b	I believe that MSS-composers and MetaPath are great tools that will allow us to report metabolism data more efficiently and transparently. But the tools currently available are not fully adequate and need further development to reach the high quality standards in place for the regulatory submissions of pesticides.	Improvement of the IT tools		
5 06	It is not clear what is meant by raw data. Data should flow from MetaPath to IUCLID. The data flow is still unclear.	Interoperability		
5 07 a	Lifecycle of study summaries: Studies are always assessed in context of a submission. For that reason, most of study summaries submitted within Renewal Dossiers have been rewritten. Further details (-> GLP raw data) required by today's guidelines but also comparisons to other newer studies have been added to previously prepared summaries.	Lifecycle of information		
5 07 b	In case of changes in the ownership of studies, it will be mandatory to revise e.g. metabolite codes.	Lifecycle of information		
5 07 c	OHTs for metabolism studies (mainly 85-2 and 85-3): The OHTs which are implemented in IUCLID 6.5 have never been used for any regulatory submission. Consequently, there is no practical experience whether they are fit for purpose or not. Missing data fields and the general lack of OHTs for fish metabolism studies and comparative in-vitro studies (human, tox species) have been addressed in 2020, but the issue is not solved.	OHT revision	Data basis	
5 07 d	The most important deficiency is caused by IUCLID which does not allow to directly import structural formula in OHTs, For that reason, my preferred option for April 2021 would be to use IUCLID, today's OHTs and a broad upload possibility for attachments. As this solution is resource demanding, next step would be to program a standardized tool which is globally accepted (EU, USA, JMPR, etc.)	Improvement of the IT tools	Interoperability	
5 08	Once again, zero experience at this level.	Comment		

5 09	The fundamental problem with IUCLID is that it typically contains uncurated data from IND as submitted to the authority. Such uncurated data is not acceptable as a data source for Metapath and OECD Toolbox. The information flow should be: 1. submission of raw data by IND in an editable format (currently not foreseen in IUCLID, annotation only by authority) 2. data curation including revision by authority as needed (as done currently in DAR/RAR for summary data)$3. publication of all data in a suitable format	Information flow		
5 10	The need of generating OHT based on IUCLID data input is given, to make use of the same data source for any application in any country, independent if human or machine-readable data is required. Thus it is important to streamline IUCLID, OHT and MSS-composer (or whatever other solution being more suitable) to avoid duplication of work.	Improvement of the IT tools	Interoperability	Decrease duplication
5 11 a	While its rather improbable that the overall conclusion of a study is changing, a study is always assessed in the context of an application and the details of a conclusion will change as time progresses, due to new data, due to reinterpreatation of the results and an ever progression of that what is considered to be state of the art. Additionally due to evolution of the guidelines for the conduct of studies additional data which was not reported in the original study report is sometimes included or leads to an update. Therefore I am not of the opinion that a summary can be considered as static statement.	Lifecycle of information		
5 11 b	Every step which can streamline the reporting of metabolism studies and prevents double work is a good step. At the time of writing I consider the information summarized in the OHTs to be far superior compared to the MSS composers as it gives more flexibility in reporting studies which are not really fitting into the standard framework imposed by the composers. I would like to end up with OHTs which give me the flexibility in reporting combined with the ability to connect meta information for the different compounds in a form which is human and machine readable. By this one could fill IUCLID and Metapath and would still be able to disseminate the summary to parties which are not using these systems. On the other hand it will greatly reduce the resource drain of trying to fulfill the demands of 3 different frameworks - this should be done in a standardized way globally.	Improvement of the IT tools	Interoperability	Decrease duplication
5 12 a	Top set of questions are difficult to answer - yes every study is assessed in light of a specific submission. The ultimate question here is what are the information blocks to reuse	Lifecycle of information		

	in additional submissions. The data will always be useful as part of a core package, but overtime it will age and newer studies and studies in additional crops or animals may be added. Likewise, it is not always possible to set a residue definition at only once - the residue definition may need to change as additional information becomes available or use patterns are expanded.			
5 12 b	These questions are asking about a specific implementation process for which I don't have specific practical experience and there may not be global consensus on yet?	Comment		
5 12 c	GLP "raw data" is not easily submitted - terminology of "raw data" should be better defined.	Definition		
5 12 d	Again focus at the OECD level should not be on DAR/RAR templates specifically but instead the DAR/RAR should use global OECD language and standards.	Harmonisation		
6 01	You cannot offer the QSAR toolbox as a way of predicting metabolites without sharing the rules or methods used in generating a prediction. It is essential that someone using the QSAR toolbox to predict metabolites understands what has been predicted and why. What is the underlying data and how does the prediction work?	Transparency		
6 02	Training/Tutorial on the QSAR Toolbox general but also in the context metabolism studies and use of IUCLID and Metapath.	Training		
6 03	Training in the context of metabolism studies and use of IUCLID and Metapath would be welcome!	Training		
6 04 a	The QSAR models in the QSAR toolbox are of limited use for pesticide risk assessments. They suffer from low reliability, low applicability, and too often make crude mistakes. This compromises the trust in other reliable models that do exist outside the toolbox.	QSAR prediction limitation	Data basis	
6 04 b	Metabolism pathway prediction models are not fit for the purpose of regulatory risk assessments, yet. Their data basis is often too limited, their reliability is largely unknown, and the applicability domain cannot be assessed with current tools.	QSAR model		

6 05 a	The prediction of metabolite structures might be helpful when deciding which of the many possibilities of a generic structure is the most probable one, or supporting a pathway suggestion, in which a metabolite in a line of metabolisation steps is missing.	QSAR benefit		
6 05 b	The limitation of the prediction is that neither the kinetics of formation and degradation nor the actual concentrations of a certain metabolite can be predicted.	QSAR prediction limitation	Kinetic	
6 05 c	It rather opens the question what efforts are required to proof a predicted metabolite cannot be confirmed experimentally. Thus, prediction of metabolite structures may rather result in an increase in animal experiments than in a reduction.	Data basis		
6 06 a	The prediction of metabolic pathways is a great goal but in practice hard to achieve. While different steps can be predicted, other information and especially quantities of individual metabolites in different departments / matrices (species, crops) strongly depend on kinetics, uptake, excretion / translocation.	QSAR prediction limitation	Kinetic	
6 06 b	For that reason the OECD tool box can assist decision making at early project stages but would not replace experimental studies. More research should be spent to replace vertebrate studies by suitable and in-vitro test systems (being accepted globally!).	Data basis		
6 07 a	My main concerns with the OECD Toolbox are - easily manipulated to generate the desired output (does not apply to profiler functionalities) - largely uncurated database with obviously large number of incorrect entries (every time I use it I come across about entries that are wrong or rely on outdated study protocols / are not reliable) - poor reporting functionalities in particular when compared to other tools - information on validation for most prediction models obscure or hard to find I use the toolbox only to generate a first overview / gather information from a wide range of databases and develop hypotheses. In depth analysis is done in other tools or manually.	QSAR prediction limitation	Data basis	Transparency

6 07 b	Comment on Q3: I am not aware of any "pesticide-related" QSAR model for metabolism. General comment: use of terminology "tool" vs. "model" is very confusing in this survey and seems to be mixed up in part.	QSAR prediction limitation	Definition	
6 08	In general, Regular training/tutorial on OECD maintained tools (toolbox, metapath, others...) should be regularly organised: this would allow developing common global use practices.	Training		
6 09 a	I have troubles to understand the point of the question. While the prediction of metabolism is certainly a goal worth striving for one has to differentiate what one wants. The prediction of the different pathways for metabolizing chemicals is certainly interesting but what is missing in these models is the quantification.	QSAR prediction limitation		
6 09 b	The whole concept of risk assessment is based on the identity and the amount of a metabolite. In silico prediction can (state of today) not predict the amounts found in organisms due to kinetics, combinatorial explosion, formulation, target crop etc. So all of these results come with a high degree of uncertainty - the question is which kind of uncertainty is one willing to accept? By running metabolism studies the quality of data we have for a certain compound is much higher compared to that an in silico evaluation can deliver. Another important point is the sheer number of different species we're investigating.	QSAR prediction limitation		
6 09 c	To develop an in silico model covering all these the amount of valid training data needs to be huge - something which will be rather difficult to achieve. To sum it up - while the prediction of transformation pathways is worthwhile during the development of a compound its rather hard to see the advantage of applying it to risk assessment purposes in the near future. I would rather invest in technologies resulting in the reduction of animal experiments (organ an a chip) or QSAR systems predicting a single endpoint (e.g. genetox, ED) than in modelling the metabolism.	QSAR benefit	Data basis	
6 10	General use of QSAR tools are important to develop. While this survey has focused on the benefits of improved storage of metabolism information, overreliance on automated IT tools and theoretical outcomes must be avoided; these can't replace expert judgement and real world experiments. Again careful consideration of policies for public release of information relative to IP and data protection rights is needed.	Transparency		

7 01	Preference is to use in-vitro studies.	Data basis		
7 02	Predictive expertise can't replace experimentation and confirmation at this time.	QSAR prediction limitation		
7 03	None. For reasoning see above.	QSAR prediction limitation		
7 04	None, for the reasons mentioned above in vitro systems are preferred.	QSAR prediction limitation	Data basis	
7 05	None - clear preference is to use in-vitro systems!	QSAR prediction limitation	Data basis	
7 06	for metabolism: Nexus METEOR (Lhasa)	Other tools		
7 07	Expert knowledge, in-house models.	Other tools		
7 08	EnviPath	Other tools		

4.2 List of weak points

S 3.4.2-2	An insufficient degree of harmonisation in the templates to be completed, the variety of IT tools to be used and the lack of data interfaces are the cause of duplication.	31
S 3.4.2-3	The orientation towards EU specific requirements / formats complicates the efforts for a global harmonisation.	31
S 3.4.3-1	Due to the modern analytical methods, the data basis to be provided for metabolism studies is growing to a level that risk assessors cannot cope without IT support. Technical limitations of the IT tools, difficulties in data exchange between systems and in the visualisation of the results can lead to an excessive demand on the risk assessors.	31
S 3.4.3-2	The QSAR tools currently available on the basis of the existing models and the existing database can only be used to a limited extent in the field of metabolic pathway prediction.	31
S 3.4.3-3	The OECD QSAR-Toolbox is limited in the prediction of the kinetics in different “objects of investigation” (species, crops, and environment) of a certain metabolite at different time points.	31

4.3 Attachment

Survey template	Survey_quexmlpdf_877585_en.pdf
Full result list	results-survey877585.xlsx