Tender Specifications

Open Procedure

No. ECHA/2013/109

**Title: Framework Service Contract
for the development of Phase 3 of the QSAR Toolbox**

Annex 5.1.1 – Technical Specifications

Contents

Overview of the technical specifications

This document is an integral part of the tender documentation for the "Framework Service Contract for the development of Phase 3 of the QSAR Toolbox", and constitutes the so-called technical specifications of the call for tenders.

This document is divided into several chapters as follows:

- Chapters 2-3 describe the overview of the required services and the technical context for the implementation of the FWC.

- Chapter 4 defines in detail the project organisation and specifications for the profiles foreseen in this FWC.

- Chapter 5 defines subjects which shall be specifically addressed by the tenderer in his technical offer, and describes the different types of services to be provided under the FWC.

- Chapters 6-7 define deliverables, as well as acceptance and handover procedures.

1. Glossary

Term	Definition
AoP	Adverse Outcome Pathway
ECHA	European Chemicals Agency
COM	Microsoft Component Object Model
DB	Database
FWC	Framework Contract
OECD	The Organisation for Economic Co-operation and Development
QSAR	Quantitative Structure Activity Relationship
UVCB	Unknown, of Variable Composition, or of Biological origin

Table 1: Glossary

2. Scope of the development of the Phase 3 of the QSAR Toolbox

There are various areas for the development of the Phase 3 of the QSAR Toolbox (also Toolbox in this document) that will have to be covered by the Framework Contract. These include:

2.1. Inception Phase

The aim of the Inception Phase is that the Contractor takes over from ECHA the Version 3 of the Toolbox including technical documentation, source code, methodology, and prepares production environments for further development of the Toolbox. Currently, part of the Toolbox functionality relies on third-party software modules what implies certain interdependencies and limits the Toolbox functionality. It is anticipated that in order to implement the new features foreseen in the scope of the QSAR Toolbox Phase 3 development, the Contractor will have to envisage replacement of these modules (the detailed list of donated modules is included in the QSAR Toolbox Technical Documentation).

As part of the Inception Phase related to the start-up of the project. The following activities are foreseen:

- Project kick-off

- Hand-over from ECHA of the Version 3 of the Toolbox and related documentation including the source code to the Contractor

- Definition of tools and versions of applications to be used

- Setting up of the development and test environments

- Assessment of general requirements related to scope of the Phase 3 development in order to provide input to a detailed Work Plan for further service requests under the Framework Contract.

2.2. Usability improvements

Feedback collected from users shows that the Toolbox is perceived as a complex tool. This complexity has been identified as a major impediment to its use. Users find that very significant time investment for initial training is required and that not enough post-training support is provided for the Toolbox to enable effective and efficient use of the tool. Therefore, one of the priorities in Phase 3 of the development of the Toolbox is to facilitate its use by making the Toolbox more intuitive. Issues for development in Phase 3 that directly relate to the improvement of the usability of the Toolbox include:

- Streamlining of workflows

- Further improvement of the user interface and addition of new help functions

- Expansion of the repertoire of guidance materials with new examples, and new tutorials

- Enhancement of the documentation describing the various profilers and databases

- Expansion and tailor the repertoire and implementation of databases

- Elaboration of a quality assurance protocol for inclusion of databases and applying it to existing and new databases

- Implementation of Ontology to merge databases for the same endpoint

- Improvement of the documentation format of the predictions

- Possibility for saving of the predictions

- Maintenance of the OECD QSAR Toolbox Discussion Forum

- Capacity building

2.2.1. Streamlining of workflows

The Toolbox can be used for data gap filling of many relevant environmental or human health endpoints. The selection of profilers and databases for the endpoint of interest requires expert judgement and might be difficult for the less experienced user. To provide better guidance into the Toolbox, the workflow to form chemical categories can be standardised and potentially partially automated for several endpoints for which generally QSAR predictions work well, without affecting the reliability of the predictions. The objective of this activity is to define workflows that could be standardised and, if possible even automated (partially or completely) as much as possible in order to yield a prediction without compromising the reliability or losing transparency. It is envisioned that for the less experienced users, the different strategies wrapped in a single workflow will be convenient for use and will also minimize the possibility of generating unreliable predictions and ultimately increase the confidence in the predictions generated by the Toolbox. The experienced user would have the flexibility to deselect the automated workflow and flexibly use of all the tools.

The Contractor will have to propose and implement new features to make the Toolbox more user-friendly without losing transparency over the predictions, as well as increasing the reliability of the predictions. Focusing the category formation on selected number of profilers and databases to be considered of relevance will increase the performance of the Toolbox by reducing the time needed to retrieve all the data. Endpoints of particular interest include, but are not limited to, in vitro mutagenicity and skin sensitisation, acute mammalian toxicity, acute and chronic toxicity to aquatic organisms.

2.2.2. Further improvement of the user interface and addition of new help functions

Toolbox Version 3 achieved significant improvement in the interface. However, there is a further scope for improvements, particularly in the area of reducing complexity. For example, at present all branches of the Toolbox data tree are active in the workflow, regardless of the presence of data. The users have to actively search branches with data and relevant information and have no possibility to inactivate empty or unwanted branches from the tree. This affects the representation of the information needed and the time frame for the analysis and decision making.

The interface and the usability of the Toolbox will have to be updated by the context help options (e.g. in the form of drop down boxes) that support the user in a more interactive way in the various workflows and the categorisation processes available in the Toolbox

2.2.3. Expansion the repertoire of guidance materials with new examples, and new tutorials

The release of Toolbox v.3.1 was accompanied with new guidance material and tutorials in different formats including video format. There is currently no feedback of how these new materials were used. However, the user survey in 2012 clearly indicated that new guidance documents and new format of tutorials are desired. The survey also indicated that these materials are crucial in the period following the initial training and as an on-going support and continuing capacity building tool for users.

The repertoire of guidance documents and tutorials in the existing and also in more interactive formats, such as video tutorials should be expanded. The guidance materials shall include structured examples for beginners, intermediary and advanced users. They shall include predictions processes for various endpoints, strategies for categorisation based on different purposes, formatting data in databases to be imported, introducing simple and more complex categories, docking QSARs, etc. These materials shall be updated with every new version of the Toolbox as they become available.

Consultation within the Toolbox management group also indicated that better description is needed for the existing functionalities for calculation of structural similarity. Therefore additional guidance on how to apply these functionalities for particular categorisation purposes will also have to be implemented.

2.2.4. Enhancement of the documentation describing the various profilers and databases.

While individual alerts are described in detail and supported by references that allow proper analysis, the profilers, databases and the metabolic simulators have only very generic descriptions. Yet, their choice is crucial in building a category for a given endpoint before the analysis of a particular alert is needed.

A strategy for reformatting and updating the "about" documentation for the profilers, databases, simulators and QSARs included in the Toolbox shall be developed and implemented. The information shall more precisely state the content, the relevance to particular endpoints, the sources and their quality assurance (QA) procedures and for similar profilers, databases and simulators, comparative statements should be included (e.g. how do liver and skin metabolic simulator differ, how do DNA binding by OECD and OASIS differ). This will aid the user to make more informed decisions about the choice of the profilers and databases and therefore improve usability and confidence in the predictions.

2.2.5. Expansion of the repertoire of databases

To enhance the empirical knowledge and improve the predictive power of the Toolbox it is of importance that the scientific and regulatory programmes that generate and collect data are continuously monitored and that the databases in the Toolbox are updated on a regular basis. This shall include data generated and collected by regulatory programmes in OECD Member countries. Upon request by the OECD member countries and stakeholders additional endpoints might need to be included.

An additional approach that will significantly contribute to the availability of high quality data will be a proposal to devise a data mining strategy for the data available in the eChemPortal. This portal contains an enormous wealth of data that can be used within the categorisation strategies in the Toolbox, however at present it is not in a format that can easily be used. Other sources of data with appropriate data mining strategies shall also be explored. Repeating data from the same original sources shall be avoided where possible.

2.2.6. Elaboration of a quality assurance protocol for inclusion of databases and applying it to existing and new databases

Currently, the databases that are included in the Toolbox vary in their quality as they have been donated and accepted without a quality assurance procedure. While some information about the quality of the data is given in the 'about' section in the description of the databases, there is a need to elaborate further the descriptions of the databases in this respect. Uncertainty about the quality of the data used for data gap filing affects usability of the Toolbox.

A quality assurance strategy shall be devised and applied to all existing databases and all databases that will be added in the future versions. While this is not possible for each particular data entry a general description of the quality assurance process applied by the donators shall be provided and included into the Toolbox. This information could be used for determining the indicative reliability of the database. Also assurance of the appropriate forms used to describe test conditions/effects used in the databases, that the information is not lost due to editorials/spelling errors shall be included in quality assurance.

The quality assurance strategy proposed by the Contractor have to cover the entire process of database building: the source and type of collected data (open literature, web compilation, etc.), what were the criteria for inclusion into the database (review process, selection of the test methods, how the outcome was reported), any pre-processing of data (e.g. identification of synonyms and homonyms of test systems, aggregation of the results) and how conflicts in entries were solved, if possible.

2.2.7. Implementation of an Ontology to merge databases for the same endpoint

The QSAR Toolbox databases need standardisation and harmonisation of the terms used for reporting toxicity data for the complex endpoints. This will enable users to search for specific terms within all databases (e.g. specific effects), facilitate better reporting as well as group chemicals efficiently on the basis of specific properties and facilitate the use of AOPs within the QSAR Toolbox. Through a joint project, ECHA and OECD have developed ontologies for repeated dose toxicity, reproductive/developmental toxicity, and carcinogenicity (finalised December 2012), as well as for skin/eye irritation and sensitisation (to be finalised in December 2013). In particular the following aspects were developed for each endpoint:

- Definition of classes and hierarchical relationships in the ontology structure

- Compilation of terms related to the endpoint

- Definition of synonymous and homonymous

- Establishment of relationships, interactions and hierarchies between classes, object and numeric properties for each term and rules when existing (internal rules and restriction rules)

- Association of each attribute in a toxicological dataset with an entry in the ontology

The Contractor will have to implement the outcome from these ontology projects within the QSAR Toolbox. As a first step the existing databases of the QSAR Toolbox (for repeated dose toxicity, carcinogenicity and reproductive toxicity: ISSCAN, CPDB, ToxRef, RepDose, HESS, ILSI-DevTox) will need to be mapped to the preferred terms as developed by the ontology project (e.g. OHT terminology, INHAND terminology for repeated dose toxicity and Developmental toxicity vocabulary by Devtox.org). For a number of databases additional terms will need to be incorporated by the ontology project. In addition restructuring of the hierarchy trees for the specific endpoints will be needed.

2.2.8. Improvement of the report documentation

Once prediction from a read-across or a local Toolbox model has been accepted, there is a possibility for generating a report. The prediction report summarizes the final outcome, provides information for the group/category members, and indicates the boundaries of the applicability domain. In the current version, the Toolbox reporting format is built to address information required according to the OECD Guidance on grouping (QMRF and QPRF). Some information is generated automatically from the tool, and some requires manual input. Nevertheless, the length and the way of presentation still need to be improved. The steps of the category formation shall be depicted more clearly and the final prediction shall be better indicated (highlighted). The information about the group/category members, and in particular their structures, shall be rearranged to facilitate the user in justifying the group and interpreting the result. Moreover, a refined reporting format shall take into account new Toolbox features related to reliability of the profilers and databases used in the prediction process.

2.2.9. Possibility for saving the predictions

There is a strong demand from user's community to have in the Toolbox the possibility of saving the work done during the categorisation and data gap filling. The Contractor will have to address this request and implement this functionality.

2.2.10. Maintenance of the OECD QSAR Toolbox Discussion Forum

In order to provide further guidance there is an online OECD QSAR Toolbox Discussion Forum where users can exchange experience and seek guidance with using the QSAR Toolbox. This discussion forum will be maintained to provide direct answers to the questions raised. Suggestions for improved or new databases, profilers or QSARs could be received through this Forum. These will be forwarded to the Management Group for further consideration.

2.2.11. Capacity building

Training for the users of the Toolbox is foreseen on a regular basis. This is both to ensure that proper hands-on skills are developed, as well as to guarantee that the latest advances are reported by the developer and recognised by the users. One training every two years (or more often, depending on the progress of the project) might be needed, to be hosted by ECHA or OECD.

2.3. Scientific developments

Issues for development in Phase 3 that are directly related to the scientific development include:

- Activities related to the implementation of adverse outcome pathways (AOPs) into the Toolbox

- Activities related to the general scientific improvement of the Toolbox

2.3.1. Activities related to the implementation of adverse outcome pathways (AOPs) into the Toolbox

Systemic toxicity endpoints such as reproductive, developmental and repeated dose toxicity are particularly difficult to predict by using computational approaches. While the Toolbox now contains databases and profilers related to them and first experience is promising, it still remains challenging to make reliable predictions. One particularly promising way of improving these predictions is by using Adverse Outcome Pathways (AOPs), which allow incorporating mechanistic information in read-across and trend analysis for data gap filling. The OECD has developed this concept as a means of providing transparent mechanistic justification and weight-of-evidence to reduce uncertainty in the predictions for complex toxicological endpoints based on the Toolbox and it is considered to be the focal point of the future development of the Toolbox.

An AOP is the sequence of events from chemical structure through the molecular initiating event to the in vivo outcome of interest. AOPs are representations of existing knowledge concerning the linkage(s) between a molecular initiating event and an adverse outcome at the individual or population level. While AOPs may be initially depicted as linear procedures, the amount of detail and linear character of the pathway between a molecular initiating event and adverse outcome can vary significantly, especially for human health endpoints where effects are the result of multiple organ interactions (e.g. skin sensitisation), multiple events (e.g., repeat dose toxicity), which accumulate over time (e.g. neural toxicity), or are particular to a life stage of an organism (e.g. developmental toxicity).

AOPs take into account the fact that chemical interactions are at the molecular level and not at the whole animal level. Thus, adverse effects observed in vivo are the result of many biological responses, as well as the chemical structure of the toxicant. Hence, AOPs are designed to avoid mixing information from multiple mechanisms (i.e. different molecular initiating events which can cause the same in vivo outcome through different AOPs). When the molecular initiating event is closely linked to an observed in vivo response, one can easily develop a chemical category or derive a traditional quantitative structure-activity relationship (QSAR) between the in vivo endpoint and chemical structures (e.g. acute fish toxicity). As such AOPs shift the emphasis for category formations based on just intrinsic chemical activity to chemical activity plus the key events that occur across the different levels of biological organization. In this way, AOPs form a solid mechanistic reasoning to support the use of read-across and categories, thus reducing the need for toxicity testing of a substance.

Activities related to the implementation of AOPs into the Toolbox are:

- Software implementation of AOPs

- Review and development of IT functionalities for streamlining AOP implementation

• Further development of available profilers, expanding databases and adding new (AoP specific) profilers and databases

2.3.1.1. Software implementation of AOPs

The process for AOP development consists in the following main steps: 1) proposal by a stakeholder to develop an AOP, 2) drafting the document describing the AOP, 3) review and revision of the draft AOP document by OECD Extended Advisory Group on Molecular Screening and Toxicogenomics, and 4) approval by the sub-bodies of the Joint Meeting and declassification by the Joint Meeting. Once an AOP is published it can be implemented into the QSAR Toolbox after approval of the Task Force on Hazard Assessment.

The AOP for skin sensitisation was only recently adopted by OECD and implemented in the latest version of the Toolbox. Less progress is made for other endpoints. The development, assessment and acceptance of AOPs will be a continuous process and the OECD Molecular screening project is expected to deliver, on continuous basis, AOPs suitable for inclusion in to the Toolbox. For each published AOP, the Management group will need to decide whether the available information warrants an implementation of the AOP in the Toolbox.

2.3.1.2. Review and development of IT functionalities for streamlining AOP implementation

The AOP for skin sensitisation has been implemented in the Toolbox as a proof of concept which could serve as a universal model for other new AOPs. However, the design and presentation of the workflow to build categories and how the weight of evidence is indicated, has not yet been evaluated and agreed by the Management group. The usability of the workflow will be evaluated in 2013. The outcome of this analysis could serve as a valuable input for the Management Group to decide whether the functionalities of the workflow have to be adjusted and/or new functionalities have to be added. Once the design of the workflow has been agreed, a reporting template has to be developed and implemented into the Toolbox.

2.3.1.3. Further development of available profilers, expanding databases and adding new (AoP specific) profilers and databases

Based on available high quality data in the open literature, the profilers implemented in the Toolbox should be refined and extended to better cover the domains of the critical nodes of the AOP.

Implementation of new AOPs in the Toolbox will necessitate inclusion of new databases for relevant molecular initial and key events as well as consideration of IT applications that serve as collections of AOPs. Depending on the availability of high quality data, new profilers related to the key events have to be developed and described in terms of structural requirements and physical-chemical properties.

2.3.2. General scientific improvement of the Toolbox

Activities related to the general scientific improvement of the Toolbox are:

• Development of a reliability score for alerts and databases

• Improvement of predictions of covalent interactions

• Improvement of predictions of non-covalent interactions, especially interactions with receptors

• Improvement of the ADME predictive capabilities of the Toolbox and integration of PBPK functionalities

• Improvements of the QSAR models

2.3.2.1. Development of reliability score for alerts and databases

The categorisation schemes that can be applied within the Toolbox vary markedly in their development and expected purpose. Categories developed for filling data gaps are formed based on user defined choice of toxicologically meaningful and structurally sound profilers and alerts depending on the purpose of the category. The choice of the profilers and determination of the relevance of the particular alerts is also critical for profiling of chemicals and selecting analogues for various purposes. Evaluation of the robustness of the category is central to the assessment of the reliability of the prediction within a category. It is based on a number of factors including the quality of the data for the category members and the mechanistic basis underpinning the category for the particular endpoint.

Currently, the Toolbox does not provide any kind of quantitative reliability information. Similarly, the uncertainty associated with a choice of particular analogue(s) is only qualitatively defined by the user on a case by case basis. This was identified as one of the key areas that would need to be addressed in the future development of the Toolbox, based on the outcome of the 2012 CoCAM survey on the use of QSAR Toolbox.

Based on the current experience with the use of the category approach within the Toolbox it emerged that especially useful categories i.e. categories associated with least uncertainty or high confidence, are those based upon mechanistically well-defined and described structural alerts, particularly those based on chemical reactivity, such as protein and DNA-binding. These categories are numerous and diverse, and have proven useful in several environmental and human health endpoints. Well defined and described structural alerts not based on reactivity such as those for receptor binding have also been useful for the relevant endpoints.

Therefore, it appears that the development of a reliability score, possibly semi-quantitative, for alerts and databases, based on the quantity and the quality of the available information for a particular alert, its relationship to a particular endpoint and the quality of the databases used would help increasing the confidence in the final predictions.

The aim of this work is to support the assessment of the reliability for (eco)toxicological endpoints predicted using the Toolbox and the category approach. The quantity and quality of the existing knowledge relating to structural alerts (of existing and new profilers in the Toolbox) shall be gathered and reviewed. The review should also include the limits of applicability of the alert in terms of structural requirements and physico-chemical properties. Based on this analysis a (semi)quantitative reliability scale shall be developed and a reliability score shall be assigned for each alert. If possible, the reliability score of each alert shall be evaluated in the context of all the individual endpoints related to the alert.

Reliability scores for the databases shall be evaluated in the context of the elaboration of a quality assurance protocol for inclusion of databases (section 2.2.6.).

The review and the reliability scoring criteria will be agreed upon by the Management Group.

2.3.2.2. Improvement of predictions of covalent interactions

As mentioned above, the Toolbox currently performs well for endpoint predictions and categorisations derived using profilers based on covalent binding, such as DNA and protein reactivity. In phase 3, these profilers can be significantly improved if they are associated with reliability score(s) as described above. In addition, these profilers could be further improved through updates based on new relevant information that may become available, concerning new alerts or new information associated with the performance of the alert. Increasing the number of in chemico profilers for model electro- or nucleophiles and providing more quantitative information on the strength (potency) and rate of chemical reactions will improve the Toolbox further.

The exiting profilers should be improved and updated based on covalent binding using the already established protocols for inclusion of databases and the protocols that will be established for assigning reliability scores to individual profilers (described in the previous section).

2.3.2.3. Improvement of predictions of non-covalent interactions, especially interactions with receptors

A profiler for prediction of non-covalent interactions was incorporated in Version 3 of the Toolbox and covers only binding with estrogen receptors. The current profiler for ER binding is based on structural and parametric rules based on the analysis of information available in the open literature known for ER-binding chemicals. New profilers are needed for modelling of interaction with a number of other receptors important for other relevant endpoints (e.g. androgen receptor binding). In addition new approaches are needed where the features of the chemical ligands but also the features of the receptor binding sites are taken into account. One of the possibilities to be explored is developing profilers based on docking simulation approaches.

The aim of this work is to expand the profilers based on non-covalent interactions using the approach already employed for the estrogen receptor which can then also applied to other receptor interactions.

New approaches for modelling noncovalent interactions of chemicals with cellular macromolecules shall be identified. A proposal of how can the new approaches be incorporated into the Toolbox will be developed and implemented.

2.3.2.4. Improvement of the ADME predictive capabilities of the Toolbox and integration of PBPK functionalities

Read-across justifications can be considerably improved by taking into account ADME information and PBPK modelling. The current version of the QSAR Toolbox includes some simulators for abiotic transformation (e.g. hydrolysis, dissociation, auto oxidation) and some simulators for microbial and mammalian transformations (e.g. for liver and skin metabolism). The number of these profilers could be extended (e.g. simulator for fish metabolism). They all need to be improved by introducing quantitative aspects of the biotransformation prediction (e.g. by including probabilities, amounts and transformation rates). Understanding of the mechanisms of the biotransformations could also be improved by predicting which enzymatic systems could be affected and what would be the kinetic aspects of the enzymatic interactions. The absorption and distribution also should be targeted to the extent possible via existing data and surrogate models and data. This will not only improve the hazard assessment of individual substances but will help also enormously in preparing read-across justifications. The objective of this activity is to improve the way, in which the ADME information in the Toolbox is presented and to analyse how PBPK modelling could be integrated in the Toolbox.

2.3.2.5. Improvements of the QSAR models

The QSAR models in the Toolbox are an integral part of the data gap filling techniques. The current suite of models included covers only a limited number of endpoints, and these come almost exclusively from EPISUITE or the Danish QSAR database (generated with the MultiCASE methodology). The extension with more QSAR models, for predicting more endpoints (both (eco)toxicological) and for molecular initiating/key events within the AOPs) is expected to improve the tool's predictive capability, support better the grouping and read-across using mechanistic principles, and expand the chemical domains of the existing models. Particular attention should be given to the possibility of predicting some in vitro assays, such as the ones that can be used for the development of AOP pathways. Given the scarcity of test data for these assays, the capacity for generating predicted results for them would be highly useful, and could be essential for the future development and acceptance of this methodology.

Another point for improvement in this area is the possibility of implementing domain checks. For instance, the training sets and fragments are known for most of the EPISUITE models. An improvement will be to introduce warning, when a property is predicted for a molecule with fragments not represented in a given EPISUITE model. So far, the Toolbox simply warns that a model does not have a defined domain. Even for endpoints for which the Toolbox contains already some QSAR models, the usability of QSAR tools could be enhanced by adding models for specific chemical classes, with an indication of when they should be used (e.g. specific models for surfactants, pesticides, SNAr electrophiles etc).

This activity would seek to increase the number of models included in the Toolbox and when possible, their transparency and coverage. OECD MCs should be able to propose new, scientifically sound models to be considered by the Toolbox QSAR Management Group for improvement of both the predictions for endpoints already covered, and to cover new endpoints.

The new models should be transparent for the user. Ideally, these models should be feasible for implementation in the Toolbox, should allow a mechanistic interpretation and a domain check. If this is not possible, at least the training set should be known so that some judgement on their applicability would be possible. The automated check of the domain and reliability of the predictions should also be added to models already existing in the Toolbox when possible (e.g. for the EPISUITE models).

2.4. Development of Additional Functionalities

Issues for development in Phase 3 that directly relate to additional functionalities include:

• Use of the QSAR Toolbox as a prioritisation tool

• Extending the Toolbox capabilities for handling organometallic substances

• Extending the Toolbox capabilities for handling UVCB substances

• Extending the Toolbox capabilities for handling ionisable compounds

• Extending the Toolbox capabilities for handling nanomaterials

2.4.1. Use of the QSAR Toolbox as a prioritisation tool

The presence of predictive tools in the Toolbox can also be used for the prioritisation of substances for different purposes. The objective of this activity shall be to define and implement new functionalities that would allow the Toolbox to be used efficiently as a priority setting tool for different purposes for instance: prioritisation based on PBT criteria, prioritisation for evaluation based on hazard (observed and/or predicted), etc. The prioritisation strategy could be based in existing Toolbox functionalities (e.g. combination of experimental data, alerts for an endpoint, closest analogues with data, predicted values with a QSAR model, etc.), or in new features or modules. Implementation of some ranking techniques will facilitate the prioritisation activities in the Toolbox.

2.4.2. Extending the Toolbox capabilities for handling organometallic substances

The Toolbox might need also to increase its capability to handle organometallic compounds. Organometallics are defined as compounds that contain at least one metal or metalloid covalently bonded to carbon. In several disciplines, and for the purposes of hazard or risk assessment, the working definition is expanded to include coordination complexes where the metal or metalloid has multiple and rather covalent-character bonds with carbon, oxygen, nitrogen, sulphur, and/or phosphorus. Dissociation of the metal is generally considered to be negligible; however, the metal may be liberated through various degradation pathways. Eventually, a profiler able to estimate the stability of the organometallic compounds and the rate of the metal release, when the bonds are not ionic will be of high value. Such profiler(s) could facilitate the hazard and fate assessment of the organometallics and organic-metal salts within a grouping context, and support the read-across for this class of substances.

2.4.3. Extending the Toolbox capabilities for handling UVCB substances

The substances of unknown or variable composition, complex reaction products or biological materials (UVCBs) constitute a significant part of every regulatory inventory. These pose a greatest challenge in a number of regulatory processes, in particular in the context of hazard identification, grouping and read-across, as well as in priority-setting activities. The objective of this activity is the implementation of a generic and flexible methodology for generating a computationally manageable number of representative structures that span the chemical space defined by the UVCB identifiers and their computational assessment with respect to physicochemical, fate and (eco)toxicological properties. The UVCB identifiers are usually related to the source of the substance and the process used for manufacturing. In addition, other identifiers, such as chromatographic and spectral fingerprints and physicochemical properties or conditions of the manufacturing process can be useful parameters. The combination of all these identifiers defines the chemical space of the UVCB, which may encompass a large number of individual constituents that often prevents their full enumeration. The ability to generate representative structures and predict their hazardous properties can be used in hazard and risk assessment of UVCB substances by pointing out the regions of chemical space of greatest concern. Moreover, it can point to the targeted analytical characterisation of constituents, as representative structures predicted to be hazardous should be analytically determined.

2.4.4. Extending the Toolbox capabilities for handling ionisable compounds

At present the Toolbox is not fully equipped to handle ionisable compounds. The fate, behaviour and toxicity of these compounds can be very specific with respect to their reactivity pattern (i.e. non-narcotic or even polar narcotic), their intrinsic bioavailability (e.g., ionisable, passive or active transport into cells), and their binding capability (protein, DNA, blood plasma, ER, that is non-lipophilic interactions). Consequently, the current in silico profiling implemented into the Toolbox would not capture these chemicals largely because of low logKow and thus low predicted toxicity and bioaccumulation) and/or just significant error with logKow prediction. In order to increase the capacity of the Toolbox to deal with ionisable compounds new profilers could be implemented, e.g. blood albumin binding, protein-water partitioning, liposome-water partitioning, internal transport mechanisms. For this purpose it would be useful to investigate software and tools used for the development and assessment of pesticides and pharmaceuticals.

2.4.5. Extending the Toolbox capabilities for handling nanomaterials

The understanding the hazards of the nanomaterials and their regulation poses increasing challenges to predictive methodologies. It is not deemed feasible nor possible to test every variety of shape, size and composition of different nanomaterials from a given bulk substance for every endpoint. Thus, of particular interest becomes the possibility for read-across between the bulk form and nanoform of the same substance, read-across between different forms of the same substance, and assessment of the options for the QSAR models. The effects of coating of the particles should be also considered. The capability for handling nanomaterials will include challenges for nano-form identification, description, collecting and handling of data by creating possibly a new original data model, extracting knowledge and providing it in a form of user-friendly profilers, similar to others already implemented in the Toolbox. It is anticipated that a large portion of the exploratory research related to this objective will be done outside the Toolbox development project but the practical implementation will be done within the project.

2.5. General improvements related to enhancements of IT technology

2.5.1. Introduction

The current version of the QSAR toolbox consist of modules recently developed during Phase 2, modules developed as a part of Phase 1 and many donated modules which were developed during the last 30 years. This combination of different features and modules in the current version of the Toolbox imply many technological constraints, which start to be a bottleneck both in terms of usability and performance. In addition, the core Toolbox architecture (Component Object Model- COM) has been recently replaced by WinRT. At the moment it will not affect Toolbox users as newer Windows operating systems are still able to use the features of COM. But in the longer perspective it might affect the lifetime of the Toolbox. Finally, current Toolbox users cannot benefit from the performance gains in the recent computer systems (e.g. bigger memory or new CPUs) as the Toolbox is not able to use these new features. All this constraints combined with the growing complexity of the Toolbox (both in terms of functionality and DB volume) are indicating the need for deeper refactoring of the Toolbox IT architecture. This conclusion is in line with the outcome of a Toolbox Code Review project carried out by ECHA after finalisation of phase 2.

It has to be stressed that improvements related to IT architecture shall be substantiated by scientific and user's needs and they have to be done only if there is also clear demand coming from user requirements or implementation of the new scientific features. Below some IT related usability improvements have been listed. All of them are related to the performance/usability improvements of the Toolbox which will directly benefit the users. Addressing them will also allow refactoring of existing Toolbox code.

Issues for development in Phase 3 that directly relate to information technology include:

- Optimisation of the data model and change of the database engine

- Refactoring of the calculations and I/O modules to increase Toolbox performance

- Implementation of the scripting capacity into the Toolbox

- Enhancement of the server component

2.5.2. Optimisation of data model and change of database engine

The size of the Toolbox database grew considerably for the last releases (size of v3.1 is approximately 3 times bigger than of v2.0). The large size of the databasestarts to be a problem for downloading and also for installation (especially in case of the standalone version). One way to reduce the size of the Toolbox database would be a further normalization of the data model to reduce unnecessary data duplications. Supplementing the current DB engine (Firebird) with another DB engines may be more suitable for big organisations which are using mainstream DBs and will help to increase the usability of the Toolbox server version. The Contractor will have to propose and implement data model optimisation.

2.5.3. Refactoring of the calculations and I/O modules to increase Toolbox performance.

The code review project reported that the way the data are processed in the Toolbox is not optimal. One of the consequences is a reduced responsiveness during data extraction or category building process. Further optimizing the Input/Output (I/O) operations and the way the Toolbox performs calculations should significantly increase the performance of the Toolbox. In addition (as it was stated before) the current communication protocol (COM, DCOM) shall be adapted to the recent technology in order to extend the life time of the Toolbox.

2.5.4. Implementation of the scripting capacity into the Toolbox

Scripting capacity is very useful for any kinds of tasks that need batch mode processing. This is an important feature to support prioritization projects where a high number of substances needs to be processed in a consistent (preferably automated) way. Furthermore scripting might be very useful for streamlining predictions for certain (less complex) endpoints and for building 'prediction macros' which can be later on exchanged within the Toolbox community. Therefore the Contractor will have to address this request and implement this functionality.

2.5.5. Enhancement of the server component

At the moment server functionalities are quite limited, the application server does not provide user management options, has relatively low data throughput, limited performance and duplicates many functionalities with the Toolbox client component. By addressing these limitations, the Toolbox usability will increase substantially and as a consequence the Toolbox might be used more efficiently in bigger organisation where one Toolbox installation serves a bigger user group. During the implementation of the Framework Contract, the Contractor will have to propose an approach to enhance the server component of the Toolbox.

2.6. Corrective Maintenance

During Phase 3 Toolbox development corrective maintenance tasks of the Contractor shall focus on:

- bug fixing

- assuring compatibility with the new versions of IUCLID

- updating of external modules (once needed)

- updating of databases (once needed)

- provision of the download repository for installation packages and additional documentation

- direct users' support.

2.6.1. Bug fixing

Adjustments which become necessary over time due to e.g. spotted functionality error, incorrectly implemented features and performance deficiencies.

2.6.2. Assuring compatibility with the new versions of IUCLID

To assure that functionalities related to data exchange with IUCLID (both via *.i5z files and Web Services) are compatible with the current version of IUCLID available for registrants.

2.6.3. Update of external modules

Update of the modules developed by external Toolbox partners and donated into the Toolbox (EPISuite, pKa, toxtree…). Such updates shall be done on demand from module owner after authorisation by the OECD and ECHA.

2.6.4. Update of databases

Update and inclusion of the new databases donated into the Toolbox. Such updates shall be done on request of data owner after authorisation by the OECD and ECHA.

2.6.5. Provision of the download repository for installation packages and additional documentation

This task is to assure the availability of the download packages for the latest version of the QSAR Toolbox installation packages (for standalone and distributed versions) and all supporting documentation.

2.6.6. Direct user's support

This task will include support for technical questions (installation process, etc...) to QSAR Toolbox registered users.

3. QSAR Toolbox Architecture

The QSAR Toolbox is a Delphi application consisting of:

- Toolbox chassis

- interface modules (based on Microsoft COM)

- precompiled libraries with calculating modules (QSAR predictors, metabolism simulators, etc…)

- chemical Profilers (predefined filters for grouping chemicals)

- database (firebird) containing data about chemical structures and a wide range of properties.

The software is developed in two versions: standalone and client-server.

The Toolbox chassis architecture is based on Microsoft Component Object Model (COM) platform. This allows connection (docking) with external software. As an example of such docking, a dedicated Toolbox module was developed to allow for direct communication between the QSAR Toolbox and IUCLID 5. Using either XML files or WebServices, users of the Toolbox and IUCLID can:

- download substance datasets together with the corresponding endpoint study records from an IUCLID 5 database to the QSAR Toolbox

- upload endpoint data in the form of templates from the Toolbox to an IUCLID 5 database.

For the WebServices method, the Toolbox connects to IUCLID over a SOAP environment and uses predefined WS functions for session establishment and then data communication. The retrieved data in the form of XML is then passed to the XML processing engine and imported into a Toolbox database.

Further to the docking to IUCLID 5, the OECD Harmonised Templates were mapped for the QSAR Toolbox to facilitate the exchange of data with other systems compatible with the OECD Harmonized Templates.

General schema of Toolbox internal architecture is presented in Figs.1-3.
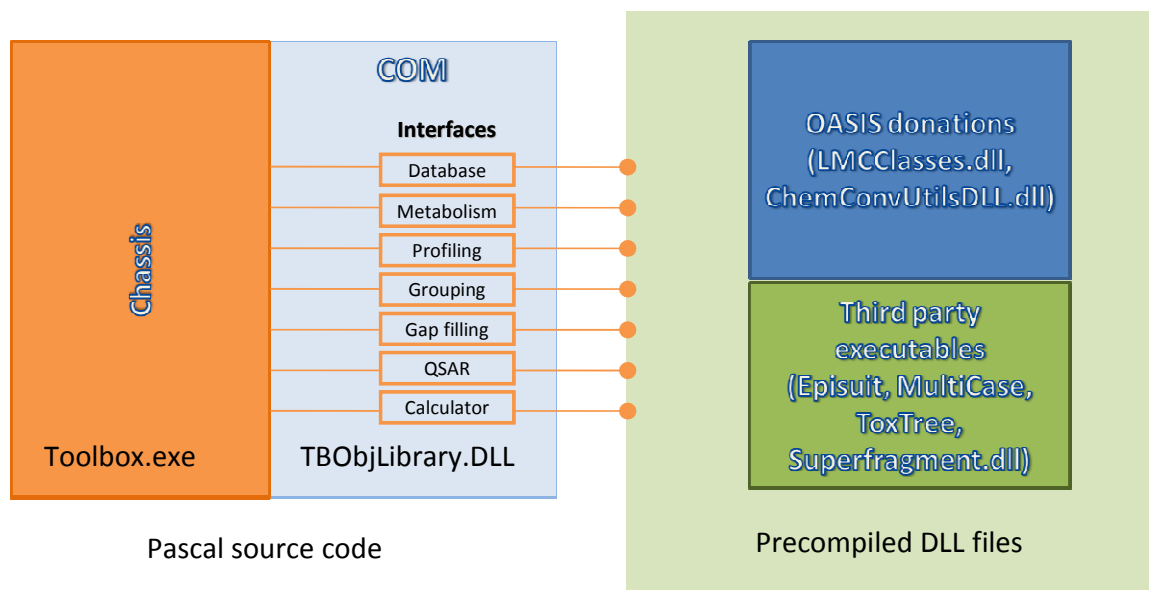
Fig.1. Toolbox system architecture: interface model.
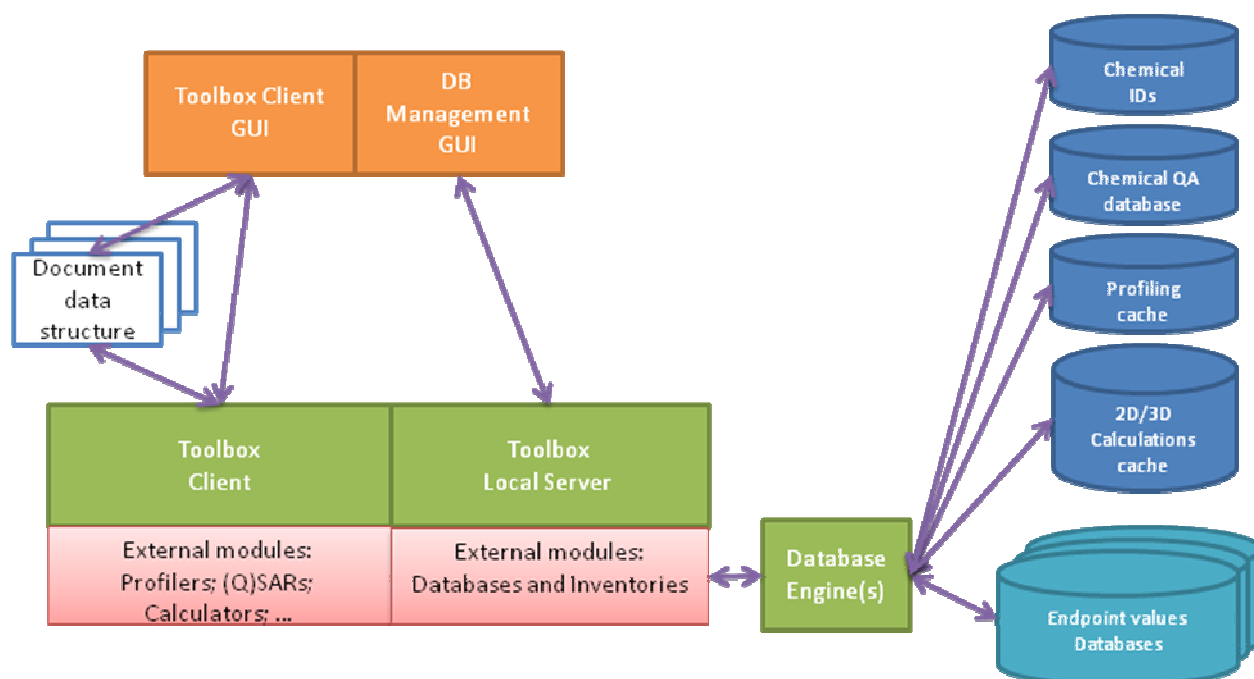
Fig.2. Toolbox system architecture: logical view of standalone version.
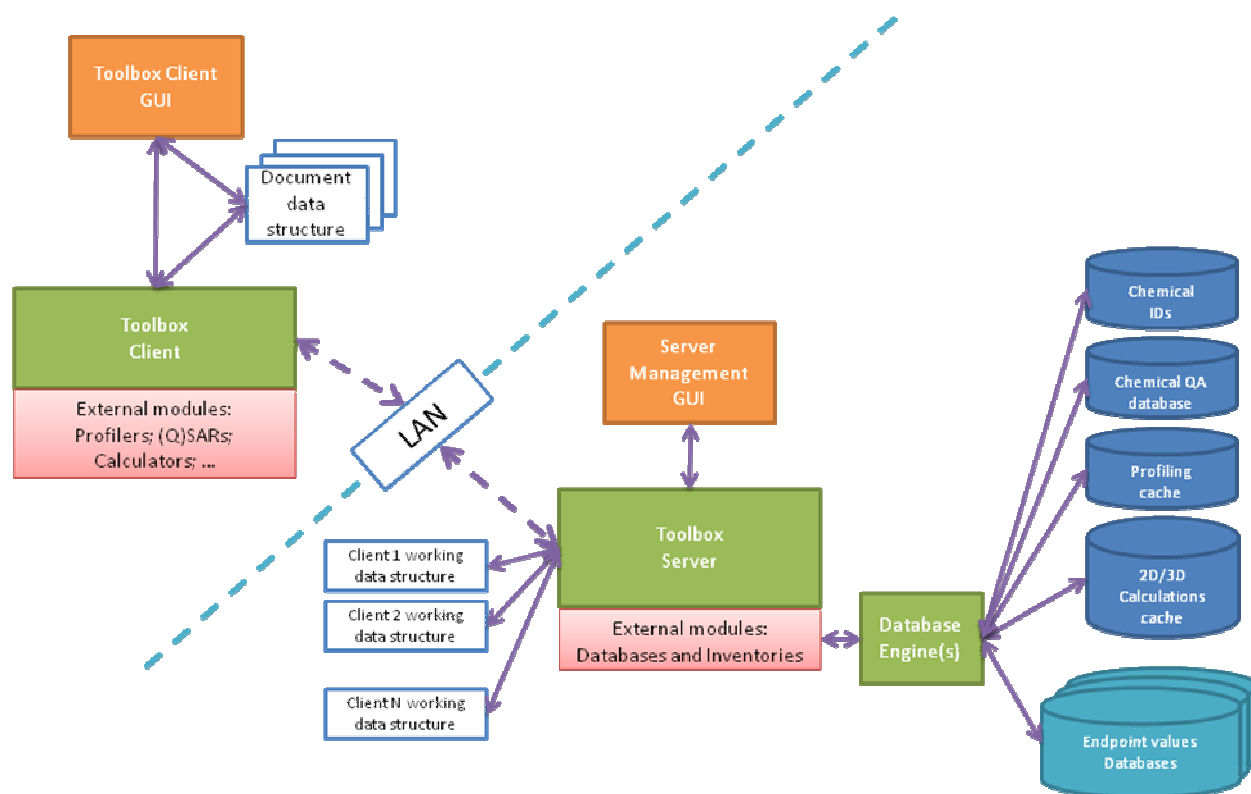
Fig.3. Toolbox system architecture: logical view of client-server version.

A more detailed description of the Toolbox software architecture can be found in QSAR Toolbox Software Architecture Document (SAD) which is a part of the **QSAR Toolbox Technical Documentation**. A password for the opening of the Technical documentation will be provided upon written request of the tenderer, submitted to procurement@echa.europa.eu. The request must be accompanied by a signed non-disclosure agreement (NDA) in PDF format (See Annex).

In addition the QSAR Toolbox application, user's manuals, examples and guidance's can be downloaded from www.qsartoolbox.org and http://www.oecd.org/env/ehs/risk-assessment/theoecdQSARtoolbox.htm.

4. Specifications for teams and resources

It is necessary that the Contractor establishes a proper organisation for the implementation of all service types of the Framework Contract. The requirements for this are described below.

4.1. Project organisation

The project language is English. All deliverables in the context of this project must be drawn up in English.

4.1.1. ECHA and OECD Project Managers and Coordination Group

Administrative Project Management

The implementation and execution of this Framework Contract will be formally managed by ECHA Project Manager nominated by the Agency since ECHA will exercise all responsibilities a as Contracting Authority. The ECHA project manager will represent the Agency in contacts with the Contractor and the OECD on matters related to the scope and implementation of the Specific Contracts to ensure that the Contractor meets his obligations within the limits and the terms of the Framework Contract.

Technical and Scientific Project Management

The OECD Secretariat will nominate an OECD Project Manager who will be responsible for the day to day contact and monitoring of the technical and scientific work to be achieved under the build contract. He/she will ensure a structured dialogue between all members of the project team in the form of regular meetings, teleconferences and progress updates. He/she will report on progress at regular intervals to the ECHA Project Manager.

Coordination Group

A Coordination Group will be put in place, comprising staff from ECHA and the OECD. This team will encompass scientific and technical expertise with members having experience in (quantitative) structure-activity relationships and managing chemical data information systems.

By default ECHA and OECD project managers will be a members of the Coordination Group. Other members will provide scientific and technical input in particular for detailing with the functional specifications of the system. They will also be in charge of reviewing and accepting the deliverables and testing the system.

4.1.2. Contractor's Project Manager and Project Management Team

The Contractor shall nominate a Project Manager to act as counterpart of ECHA/OECD for the general management of the Contract. The Project Manager shall be responsible for the execution of the project, including internal coordination of the activities and day-to-day contacts with the OECD and ECHA Project Managers. He/she should be the single point of contact for the Coordination Group. Any delays or changes to the timing or scope should be duly reported to the Coordination Group and has to go through a change request procedure as outlined in the change management plan before it can be accepted by the Coordination Group. Any agreed revision to the project schedule should be reflected in the project plan.

The Project Manager should be supported by a Project Management Team, which shall consist of Project Leaders in the main project areas:

- Usability improvements (as described in Section 2.2)

- Scientific developments (as described in Section 2.3)

- Development of additional functionalities (as described in Section 2.4)

- General improvements related to enhancements of IT technology and System Maintenance(see Sections 2.5-6)

The Project Manager can also act as a Project Leader. The Project Manager or one of the Project Leaders also needs to be responsible for issues related to training.

The Contractor needs to clearly specify how the project will be managed and what the specific roles and responsibilities in the Project Management Team will be.

4.1.3. Stakeholders: QSAR Toolbox Management Group

During the project, the QSAR Toolbox Management Group will be consulted regularly by the Coordination Group. Reasons for consulting the QSAR Toolbox Management Group can be, for example, the recommendation for the acceptance of deliverables or the involvement in system usability/functionality tests. The QSAR Toolbox Management Group will also provide scientific and technical input to the project, especially on incorporation of databases and QSARs as described in Toolbox governance.

4.2. Contractor's technical team

The day-to-day work related to any Specific Contract or Order Form under this FWC will be carried out by the contractor's team and managed by the contractor Project Manager and Project Leaders.

The contractor shall provide the necessary resources to implement the services under this Framework Contract. Every resource provided shall comply with the profiles described below.

The requirements for the profiles indicated hereafter shall be applicable to all resources involved in the implementation of the Framework Contract. These requirements may be further defined, without substantially deviating from the profiles as defined in the Framework Contract, in the service requests for the specific contracts.

4.2.1. Requirements for Project Manager

Responsibilities

The Project Manager is responsible for the management of all aspects of the Phase 3 development of the QSAR Toolbox Framework Contract services to meet identified business needs, acquiring and utilising the necessary resources and skills, in line with cost, time, and quality criteria. Also acting as the service manager for specific contracts or orders related to end-user support and application maintenance, and platform configurations and operations services.

More specifically, the Project Manager will contribute to the following deliverables:

- Project plans, reports, project management tools

- Project/team resources management

- Management of the delivery of all project/service deliverables and products

- Quality assurance

- Project communications

- Liaison with ECHA users and other stakeholders

Qualifications and experience

- At least 6 years of experience as a Project Manager or Programme Manager

- At least 4 years of the above must be in relation to the tasks described in section 2 of this document

- At least 10 years of overall scientific or IT experience

- Experience in management of the IT/scientific projects (at least 4 projects)

- Experience in management of the projects with governmental agencies

- Oral and written English language skills (minimum B2)

Knowledge

The Project Manager must have practical knowledge of the following:

- Computational Chemistry, QSARs or Computational Toxicology

- Hazard Assessment of Chemicals

- Application of IT tools to support public organizations with one of the following topics: substance prioritization, hazard assessment, hazard screening

4.2.2. Requirements for Senior Scientist / Scientist

Responsibilities

The (Senior) Scientists are responsible for the providing scientific input for the project

More specifically, the (Senior) Scientists will contribute to the following deliverables:

- Analysis of the problem in collaboration with Product managers from OECD and ECHA

- Documentation of the user requirements

- Preparation of the specifications for IT developer

- Preparation of the scientific/technical documentation

- Writing reports/ scientific papers.

Qualifications and experience

- Ph.D. or M.Sc.

- At least 5 years of experience in chemistry, biochemistry, biology, (eco)toxicology or pharmacology (Senior Scientist)

- At least 3 years of experience in chemistry, biochemistry, biology, (eco)toxicology or pharmacology (Scientist)

- Participation in at least 5 scientific projects[1] (Senior Scientist)

- Participation in at least 2 scientific projects (Scientist)

- [1]This definition is valid for all profiles where term 'scientific project' have been used. Scientific project is a project where staff member was involved for equivalent of at least 30 working days. In addition, the project has to be related to at least one area listed under professional capacity in selection criterion 2.2 of Tender Specification.

- Writing skills to produce reports, scientific papers and training materials

- Oral and written English language skills (minimum B2)

Knowledge

The (Senior) Scientist must have practical knowledge of the following:

- Model building and validation proven by scientific publications about models for predicting environmental fate or (eco)toxicity of chemicals (senior scientist)

- Computational Chemistry, QSARs or Computational Toxicology

- Hazard Assessment of Chemicals.

4.2.3. Requirements for Business Analyst

Responsibilities

Business Analyst analyses requirements (e.g. business, user, functional, non-functional requirements) for the Phase 3 development of the QSAR Toolbox in a form (such as process/workflow models, solution specification documents) understandable for both users and technical persons designing, developing, and maintaining the solutions. As part of the requirements analysis, Business Analyst e.g. conducts and facilitates workshops, helps creating prototypes, collects, reviews and validates business information items, etc.

Qualifications and experience

- At least 6 years of experience in related field (chemistry, biochemistry, toxicology).

- At least 6 years of IT experience in relation to the tasks described in section 2 of this document.

- At least 4 years of experience in the business analysis of the scientific projects related to the scope defined in section 2 of this document.

- Writing skills to produce and review scientific papers, reports, documents.

- Oral and written English language skills (minimum B2).

Knowledge

The Business analyst must have practical knowledge of the following:

- Computational Chemistry, QSARs or Computational Toxicology

- Hazard Assessment of Chemicals

- Creating functional diagrams and flowcharts.

4.2.4. Requirements for Analyst / Programmer (Senior and Junior)

Responsibilities

The Developer produces software artefacts in line with the specifications and quality criteria identified in each individual assignment.

Qualifications and experience

- At least 3 years of overall IT experience (Senior).

- At least 1 year of overall IT experience (Junior).

- Oral and written English language skills (minimum B2).

Knowledge

The Developer must have practical knowledge of the following:

- Java and J2EE technologies **or** .NET and Microsoft Solutions Framework

- Delphi

- Change management processes.

4.2.5. Requirements for Knowledge Analyst

Responsibilities

Knowledge Analyst is responsible for extracting information/knowledge from various external sources like: scientific publications, databases, expert meetings, reports.

Qualifications and experience

- At least 5 year of experience in chemistry, biochemistry, biology or toxicology.

- Participation in at least 5 scientific projects.

- Participation in the research phases of the projects, such as design and implementation of relevant studies and surveys.

- Technical expertise, data codification and normalisation.

- Preparation of the training materials and reports.

- Oral and written English language skills (minimum B2).

Knowledge

The Knowledge Analyst must have practical knowledge of the following:

- Analysis and compilation of textual and numerical information

- Repositories of Scientific papers (e.g. Science Direct)

- Creating functional diagrams and flowcharts

- Computational Chemistry, QSARs or Computational Toxicology.

4.2.6. Requirements for User Interface Specialist

Responsibilities

User Interface Specialist is responsible for design and implementation of UI elements. He must have a good understanding of functional requirements. User Interface Specialist shall be aware of problems and challenges in the field of chemo-informatics and needs to have experience in working with scientists.

Qualifications and experience

- 6 years of professional experience including a minimum of 3 years as User Interface Specialist.

- Participation in at least 5 scientific projects.

- Good communication skills and the ability to lead and influence decisions about UI design.

- Oral and written English language skills (minimum B2).

Knowledge

The User Interface Specialist must have practical knowledge of the following:

- Recent web interface standards

- Recent UI standards and UI solutions.

4.2.7. Tester

Responsibilities

Tester is responsible for creation and execution of test cases.

Qualifications and experience

- 3 years of professional experience as tester.

- Ability to quickly grasp business scenarios related to complex software applications.

- Some familiarity with test planning and coordination.

- Oral and written English language skills (minimum B2).

Knowledge

The Tester must have practical knowledge of the following:

- Testing technologies and test automation.

5. Specific topics which are critical for further development of the QSAR Toolbox

This section provides information which will be used as the basis for assessment of the quality of the offer in light of the qualitative award criteria (AW2, AW3) related to the tasks critical for the future development of the QSAR Toolbox. The tenderers have to address all topics presented in this section and propose an organisational setup of the team suitable to deal with them.

5.1. Further improvement of the user interface and addition of new help functions

As mentioned in section 2, the complexity of using the Toolbox could still be reduced by arranging better the information and showing only the minimum necessary for each situation, as well as adding context help options that support the user in a more interactive way in the various workflows.

The workflows themselves are prone to further improvement and streamlining, by adding functionalities that would guide the user or automating parts of the data gap filling or category formation processes.

Based on the current Toolbox implementation (v3.1), Toolbox guidance's and examples available on the QSAR Toolbox and OECD website, the tenderer shall:

- Propose strategies for improvement of the interface to overcome the complexity of the information displayed in the screen

- Propose options for the addition of contextualised help functionalities

- Provide at least one example of the streamlined prediction workflow for one of the following endpoints: fish toxicity, skin sensitization, genotoxicity or bioaccumulation.

The tenderer shall also address modifications needed in the user interface to improve its clarity of use. Specifically:

- How to display the profilers and the associated information about them so that is visually apparent to the user in which context they can be used and where to find additional information about them

- How to display the model and the associated information about them (model description, list of endpoints they refer to, applicability domain and additional info) so that is visually apparent to the user in which context they can be used and where to find additional information about them

- How to inform the user about the current status of the prediction process and suggest the next step(s).

While addressing the questions related to these usability improvements the tenderer is strongly advised to provide schemas or mock-ups of the proposed modifications to the visual interface of the Toolbox.

5.2. Reliability score for alerts and databases

During the development of a reliability score for alerts and categories would be essential to evaluate and describe in the quantitative and qualitative manner the reliability of the available information associated with the particular alert and its relationship to a particular endpoint. Issue

In its tender, the tenderer shall propose strategies for developing a reliability score for databases and alerts. It is envisaged that this score will be of a semi-quantitative nature, but other possibilities can also be suggested, and different types of scores for different profilers/databases can be considered. In addition, an example of how to assign a reliability score shall be elaborated for **one** alert and one database.

The proposal for potential strategies for the reliability score for alerts shall describe:

- How to establish a reliability scale for a profiler or alert
- How to evaluate positive predictivity of individual alerts for a specific test or an endpoint
- How to evaluate overall (average) positive predictivity of the profiler for a specific test or an endpoint
- How to relate the predictivity of alerts to the characteristics of their underlying database.

The proposal for potential strategies for the reliability of databases shall take into account, for each database:

- Source and characteristics of data (e.g. literature on journals, web compilation)
- Type of data collection and curation of data
- Selection of test system in relation to the endpoint (e.g. addressing an apical endpoint vs a critical step)
- Treatment of results (e.g. individual or collapsing data into an "overall")
- Quantity of data for similar databases (containing different tests or combination of tests for a particular endpoint).

5.3. Improvement of the ADME predictive capabilities of the Toolbox and integration of PBPK functionalities

This issue shall be addressed by the tenderer in two separate parts: extension of ADME functionalities and inclusion of PBPK capabilities.

The tenderer shall first make a proposal on how to improve ADME capabilities of the Toolbox, specifically:

- Where and how to place ADME information in the workflow of the Toolbox, and in the user interface, in order to make it more clearly visible. This shall include suggestions on visual elements to highlights this information (changes in font type or colouring)

- How to incorporate this functionality so that it becomes apparent when it might be useful. (e.g. the metabolic simulator might not be as relevant in the context of a trend analysis as during the category formation process)

- How to re-arrange information related to metabolism so that it becomes more useful, e.g. changes in the way the metabolites are displayed

- Identification of additional elements to be incorporated within the metabolic simulator

- Identification of additional elements to address other components of ADME that are currently missing in the Toolbox (e.g.: adsorption, distribution), including a suggestion on where to place them in the Toolbox interface.

Additionally, the tenderer shall include a proposal on how to add PBPK capabilities to the Toolbox, addressing:

- What PBPK related elements or models could be added into the Toolbox

- In which step of the Toolbox workflows those elements would be useful

- In what part of the Toolbox interface should be placed the access to those elements.

5.4. Extending the Toolbox capabilities for handling UVCB substances

The handling of UVCB substances poses two main challenges: how to store that information, and how to use it in a meaningful way during the data gap filling process.

Hence, the tenderer will have to address this topic in two aspects:

- Propose a way in which the Toolbox can store information on UVCB substances, so that a UVCB substance can be represented with a variety of possible constituents and that information can be stored without necessarily encoding all of them by hand. This proposal shall take into account the different types of UVCBs that exist (e.g.: biological products, reaction products, petroleum substances, etc.)

- Provide a proposal on how the Toolbox standard workflow could be adapted for the categorization and data gap filling of UVCBs, taking into account how to handle the large amount of constituents (e.g. making predictions for all of them versus generating strategies to identify the relevant ones) and how to combine those results in a meaningful way to reach an overall prediction.

At least one example illustrating practical implementation for both cases is required.

5.5. General enhancements of IT technology

The tenderer will have to describe the way to address the improvements to the Toolbox IT technology, especially those specified in Sections 2.5.2 – 2.5.5:

- Optimization of data model and change of database engine in order to increase Toolbox performance and (preferably) reduce the size of database.

- Refactoring of the calculations and I/O modules to increase Toolbox performance.

- Implementation of the scripting capacity into the Toolbox.

- Enhancement of the server component.

The described approach has to take into account the documentation of the current Toolbox architecture available in Toolbox Technical Documentation. In the proposed approach the tenderer shall also consider that IT refactoring will need to be done in parallel to scientific developments, therefore a proposal to combine IT improvements with the development of other features is needed.

6. PROCEDURE FOR ACCEPTANCE OF DELIVERABLES

6.1. General acceptance procedure

If not specified otherwise in the order forms or specific contracts, the acceptance procedure below will apply by default.

6.1.1. Phase 1: Review and tests by the Contractor, Factory Acceptance Test (FAT)

All project deliverables shall undergo thorough reviews and tests by the Contractor before being released to the Coordination Group and the QSAR Toolbox Management Group.

Concerning software releases foreseen in the Specific Contracts, before they are delivered by the Contractor, the Coordination Group needs to ensure that all tests required by the development cycle have been executed and completed successfully by the Contractor.

For this purpose, the Contractor will conduct a Factory Acceptance Test (FAT) in order to verify that the software meets its specifications and that all development activities are completed and finally that the test scripts to be run during the Site Acceptance Test (SAT) passed successfully. After the Coordination Group has accepted the results of the FAT the Contractor will be allowed to deliver its software for acceptance.

Documentation, including release notes, installation notes and the Contractor's FAT report, should be provided to the Coordination Group and the QSAR Toolbox Management Group.

With the exception of the deliverables of the Inception Phase for each Specific Contract, not subject to an acceptance procedure by the Stakeholders' groups, the Contractor shall send all deliverables (documents and software) to the Coordination Group 10 working days before the QSAR Toolbox Management Group.

6.1.2. Phase 2: First Review by the Coordination Group

A review cycle will then apply, where:

- The Coordination Group will have 5 working days to review the deliverables and provide the Contractor with preliminary comments.

- The Contractor will have 5 working days to analyse the consequences of these preliminary comments and either incorporate them in the deliverables, if possible, before the Stakeholders' meeting (e.g. for document deliverables) and/or present them at the meeting.

6.1.3. Phase 3: Review by the Coordination Group and the QSAR Toolbox Management Group, Site Acceptance Test (SAT)

- After the presentation at the QSAR Toolbox Management Group meeting, the Stakeholders will have 20 working days to provide their comments to the Coordination Group who will review and consolidate them within 5 working days before they are sent to the Contractor.

- During these 20 working days, the Coordination Group will conduct the Site Acceptance testing (SAT). It will run the test scenarios specified in the Test Plan made available to the Coordination Group before the start of the SAT. The Contractor shall provide assistance to the Coordination Group personnel in order to set up the test environment.

The Coordination Group will decide whether the software under test can be accepted as is or can be accepted with reserves (which will be implemented in future releases of the application) or cannot be accepted. In the latter case, necessary changes will first be agreed between the Contractor and the Coordination Group before their implementation and a new SAT cycle will be planned.

The number of defects that can be accepted and their criticality must be formally agreed between the Contractor and the Coordination Group before the SAT starts

By default:

When one (1) critical issue is raised during the SAT, the SAT may be interrupted and the software may be rejected.

When more than three (3) major issues are raised during the SAT, the SAT may be interrupted and the software may be rejected. For any of the major issues identified raised during the SAT, provided that the Agency accepts the SAT Acceptance Test Script, the Agency shall be entitled to withhold an amount of 20% per major issue on the related payment.

When more than seven (7) minor issues are raised during the SAT, the SAT may be interrupted and the software may be rejected.

A critical issue is: a defect that prevents the user to use the software for its purpose.

A major issue is: a defect that will prevent the user to use one or more functionalities of the software.

A minor issue is: a defect that will not prevent the user to use any functionality. However the implementation of the functionality is considered faulty and requires a modification.

The decision on acceptance of software is made by Coordination Group based on the outcome from the Site Acceptance Test.

6.1.4. Phase 4: Incorporation of changes by the Contractor and Acceptance by the Coordination Group

- The Contractor will have then 10 working days to incorporate the comments received into the Documents deliverables or, for comments on the software itself, indicate its position (e.g. "to be implemented", "to be discussed") and plan on how the changes will be incorporated into the next release.

- The Coordination Group will have then 5 working days to verify the correct implementation of the reviewers' comments and/or to formally accept the Contractor's plan on how to incorporate the changes into the software. These will be reviewed at the next release.

The Coordination Group can reject a deliverable by interrupting the review cycle when there is evidence that the quality of the deliverable is too low or when there is evidence that the objective is missed.

No deliverable is accepted by default. When the responsibility of a delay in the review process is clearly identified on the Coordination Group side, the Contractor must alert the Coordination Group.

The payment of deliverables at the end of each work period is linked to the formal Acceptance by the Coordination Group in Phase 4.

6.1.5. Simplified procedure for the Inception Phase

Deliverables of the Inception Phase are not subject to the review procedure by the Management Group. Consequently, the following review cycle will apply:

- The Contractor shall send his deliverables to the Coordination Group 2 working days before the Coordination Group meeting.

- The Coordination Group will have 10 working days to review the deliverables and provide the Contractor with comments.

- The Contractor will have 5 working days to incorporate these comments and release an updated version of the deliverables.

- The Coordination Group will within 5 working days formally accept or reject the deliverables.

6.1.6. Final Acceptance

Although some deliverables may be accepted at the end of a work period to allow project subsequent steps to be executed, there will be a Final Acceptance at the end of the project.

A provisionally accepted deliverable may be rejected during final acceptance of all deliverables. In such case, a review cycle (10 working days by the Contractor to incorporate the changes, 10 working days by the Coordination Group to review the updated version) must re-apply to the deliverable and if satisfactory, another final acceptance procedure must be called.

If after three attempts at acceptance, the Toolbox still fails to meet the terms of the contract, the Agency shall have the following options:

• To require the Contractor to supply, without charge, a replacement or additional set of software;

• To accept and retain part of the software, at a reduced price agreed between the Agency and the Contractor;

• To refuse the software and cancel the contract on reimbursement of sums unduly paid.

In the case the tests have been satisfactory, the Agency shall deliver a Certificate of acceptance that shows the acceptance date and mentions any reservations it may have regarding the services.

A copy of the Certificate of acceptance shall be attached to the final invoice.

7. Handover

At the end of the FWC the following activities are foreseen as obligations for the Contractor:

- Preparing presentation and training material and giving presentations and training, as needed.

- Transfer of the contents of any development time repositories to ECHA and OECD, such as issue tracking and Contractor test case repositories.

- Set-up of a fully working development environment at ECHA premises.

- Cooperation with a new Contractor to ensure smooth transition between implementation phases, if ECHA decides to further develop the Toolbox under a new contract.

Any other activities that are related to knowledge transfer and handover of the development work, covering not only the software and related software assets, but also the development tool chain and the development and test time repositories. ECHA, together with OECD, will define the extent to which this work will be performed.

The following deliverables are initially anticipated during the handover:

- Up-to-date documentation.

- Up-to-date training material.

- Training sessions.

- Fully working development environment at ECHA premises.

- Fully transferred software assets to ECHA and OECD.

- Fully transferred contents of the repositories used during development and test time to ECHA (including test plans, test cases, defect reports and test reports).

The following delivery schedule is foreseen for the handover materials:

- Handover deliverables during the last twelve months of the contract as decided by ECHA.

- First version of the up-to-date documentation ready for review by ECHA latest one month before the end of the contract.

ECHA will have the final decision, previous discussion with the Contractor, on any delivery schedule related issues.

8. Annexes

QSAR Toolbox Technical Documentation

Non-Disclosure Agreement