SECTION 1 - User community

Europe is steadily increasing demands on the risk assessment of chemicals, drugs, cosmetics ingredients and nanomaterials to lead to safer products, resulting in a strong toxicology research community with sub-communities *e.g.* in the drug development, environmental, nanomaterial and rare-disease areas. Recent changes in European law for animal testing and new demands for testing of lower-volume chemicals and nanomaterials have triggered large-scale research into alternative testing approaches. These activities not only produce new biological and mechanistic insights, but also large amounts of new data, which have to be managed and shared for re-usage to avoid unnecessary duplication of experiments and, in this way, reduce animal testing. The goal is that the combination of data from integrated *in vitro* and *in silico* approaches will support (ultimately personalized) risk/benefit health analysis, safer drug innovation with fewer needs to withdraw after registration, a fact-based perception of chemical safety, safe-by-design nanomaterials and sustainable and safe economies.

The European Union supports toxicological and risk assessment projects with various funding programs. Recently, large collections of data have been released, resulting from research clusters, such as SEURAT-1[1], the EU NanoSafety Cluster (NSC) with NANoREG, EU-ToxRisk[2], the NORMAN network, and the EU Innovative Medicines Initiative (IMI) funded projects related to drug toxicology, including eTOX[3]. Data from these and other projects are becoming available, sometimes as Open Data (*e.g.* NANoREG) and sometimes as FAIR data. An example of the latter is European REACH data, which has recently been made FAIR by the Cefic-LRI-funded project AMBIT-LRI. Furthermore, FAIRplus is working on eTOX.

However, there are a few opportunities for data handling that need to be taken (see two recent roadmaps[4,5]). Recent studies show how powerful the combination of toxicology information and omics data is[6,7], but to be able to obtain the statistical significance to draw these conclusions, data from the US and Japan had to be combined. In contrast to large data sets like DrugMatrix, ToxCast/Tox21, and TG-GATEs from these countries, data from European projects is not often sufficiently integrated. There are also signs that the community is going in the right direction, e.g. the aforementioned data sets from diXa, NANoREG and REACH. With respect to the European Chemical Industry, TNO and others have been involved in various other Cefic-LRI activities related to data management (AIMT-3, AIMT-4).

In addition, the IMI-funded eTOX project[8] has established data integration approaches e.g. to enable the development of QSARs relating chemical structures to *in vivo* toxicopathological outcomes. As such, the project also delivered databases and approaches to ontology development, text mining approaches, and approaches for prediction of drug metabolism and pharmacokinetic features. Moreover, in 2017 the OECD performed an online survey underscoring the fact that data integration for safety is of global concern for ultimate risk assessment. The aim of the resulting knowledge base is the integration of eCHEMportal, IUCLID, and OECD QSAR toolbox supporting the development of Adverse Outcome Pathways and associated infrastructures (AOPWiki)[9]. The ‘data integration struggle’ from various perspectives (omics, computational chemistry and more ‘conventional’ toxicological data within REACH and pharma industry setting) will get even worse.

SECTION 2 - Roadmap

The above initiatives are mainly driven from user communities themselves (chemical industry, health research funding agencies, pharma, Member State organisations like OECD), but ELIXIR can contribute strongly to the existing infrastructure projects from a bioinformatics perspective, servicing the toxicology users.

For future risk assessment paradigms solely based on human-derived models, and in this way of higher relevance for human adverse effects[10], various data types will need to be integrated across the conventional boundaries of risk assessment. This involves external exposure assessment (*e.g.* via workplace or environmental modelling and detection), internal exposure characterisation (ADME-T *e.g.* via modelling and biomarker-based detection), toxicodynamics on a molecular level, and cell and systems biology. in this way more mechanism based evaluations and supporting data, can integrate into risk assessment used in regulatory toxicology. There will not only be more but also more diverse data as e.g. internal exposure data may be inferred from biomonitoring data and/or physiologically-based toxicokinetic modelling to estimate target dose available at the active sites involved in the molecular initiating events of Adverse Outcome Pathways.

Another relevant topic is the concept of the exposome, which aims at characterising lifetime exposure (not only to chemicals in the narrowest sense, but also dietary components, lifestyle factors, environmental exposures, etc) or at least during vulnerable periods of life (infancy, childhood, and old age), in relation to health outcome and the evaluation also integrates epidemiology. This is one clear demonstration of the trend that the previously distinct areas of toxicology, drug and product design and personalized/precision medicine are moving closer together. Data sharing will be increasingly necessary across these disciplines.

The toxicology community is large and well established and the current list of proposers only reflects a subset of a much larger community with a lot of Open collaboration. It has clear omics and knowledge management needs to accommodate the increasing wish to predict toxicology without animal testing (e.g. in SEURAT-1, EU-ToxRisk, eTOX). Foreseeing this need for better infrastructures, the community has previously contacted ELIXIR for collaboration. Various domain specific projects exist that service the toxicology community with computational and database knowledge (OpenRiskNet, NanoCommons) that can translate ELIXIR knowledge to the respective communities. These infrastructure projects are the successors of research projects focusing on data management, including diXa[11], ToxBank[12] and eNanoMapper[13].

To benefit the research community, SMEs and larger industry, and to enable further future support to regulatory applications, we need to reach an inclusive ecosystem of data and evaluation and modelling tools. The currently separate consortia from different toxicity-related and neighboring disciplines already work towards data and knowledge that is findable, accessible, interoperable, and reusable (FAIR)[14]. After all, these aspects are essential to efficiently assess the risk of new compounds and materials, as well as combined risks of current stressors (e.g. under the exposome concept). To further accelerate these activities, more toxicology-related data and knowledge needs to be linked, such as on physiologically based pharmaco kinetic (PBPK)

modelling (including parameter estimates), biological pathways describing affected metabolism and cell biology processes, metabolism, metabolic models and metabolism predictions, drug-response, omics (*biological identity*), chemical structures, QSARs, Adverse Outcome Pathways, REACH dossiers, etc. Simultaneously, an extension towards the human (preclinical toxicology) discipline should be initiated, in which exposure data are combined with internal exposure data (e.g. data from the European Biomonitoring Initiative (HBM4EU) and environmental data from NORMAN) towards pathways of toxicity.
However, to reach such interoperable toxicology, resources need to be integrated better. Despite the work of many projects, their FAIR features can still be improved and applying newly developed FAIR metrics will help steer this. Example key needs that are unresolved, overlap with other ELIXIR communities but require innovative integration approaches for risk assessment needs include (see the aforementioned roadmaps by Haase and Karcher[4,5]):

- chemical structure interoperability challenges (e.g. links to ELIXIR metabolomics community)
- metadata, open standards (e.g. links to ELIXIR interoperability platform, and TeSS)
- continued ontology development (e.g. links to ELIXIR interoperability platform and ontology lookup service)
- interoperable computation (e.g. links to the Galaxy and bio.tools communities)
- interactions with other ELIXIR core resources
- interactions with other communities, including nanomedicine and health
- deployment of existing tools and modelling approaches on ELIXIR compute infrastructure (also allowing future growth towards risk estimations needing monte carlo approaches)
- integration of ELIXIR AAI

The concrete steps forward proposed in this roadmap include:

1. leverage from Open solutions (models, ontologies, educational material, standards etc) developed by past and ongoing toxicology and ELIXIR projects
2. connect more closely with the core ELIXIR resources (FAIR data, database interoperability, etc)
3. strengthen and connect the inclusive communities that have evolved over the past few years (OpenTox, eNanoMapper, diXa, OpenRiskNet, REACH, NORMAN) and older communities like the European Society of Toxicology and EEMS)
4. develop open community standards to support common interest (ontologies, application programming interfaces, data formats)

Specifically, we will continue to grow the list of involved toxicology research groups, projects, and Node activities. A joint meeting to select the key priorities and use cases (*e.g.* toxicogenomics, AOPs) is planned as well as a positioning paper.
By bootstrapping from Open Science approaches developed in aforementioned projects, the new community will focus on mutual benefit, an open and inclusive community, solving practical community problems. The goal is not to design a domain specific solution, but a pragmatic approach that provides FAIR and Open solutions from month one, allowing all toxicology and neighboring communities, to benefit from these harmonized solutions. The inclusive community will involve the existing sub-communities in pharmaceuticals, *e.g.* from eTOX, transQST, and eTRANSAFE, cosmetic ingredients, *e.g.* from SEURAT-1, high and low-volume chemicals, *e.g.* from

different Cefic-LRI projects, and REACH supporters, and nanomaterials, via the NSC, building on shared needs and community solutions and strongly aligned to other ELIXIR communities. Open licensing and interfaces (ontologies, standards, formats) will encourage new solutions and collaborations, which will be accessible to any organisation and every project within and outside Europe. This will allow close interoperability with toxicology communities outside Europe that also use open approaches, while at the same time allowing compatibility with closed approaches too. This dual model has been demonstrated successfully in recent projects. A prioritized roadmap is essential; the label "ELIXIR Community" enables us to set priorities at a level above the individual projects.

Existing component that will give this community an initial boost, include, software (e.g. AMBIT with OpenTox API[15]), databases (*e.g.* diXa, eNanoMapper, AMBIT-LRI), ontologies (*e.g.* the eNanoMapper ontology[16], AOP ontology[17]), interoperability concepts (*e.g.* annotation of OpenAPIs, in collaboration with bio.tools), teaching/education material (Bioschemas annotation of outreach activities, in collaboration with TeSS), and virtual infrastructures (*e.g.* OpenRiskNet Virtual Research Environment, the NORMAN Digital Sample Freezing Platform). However, each of these approaches would benefit from integration in the ELIXIR Platforms (see examples in Table 1) and with Core Resources. Various existing ELIXIR Communities need similar solutions, *e.g.* for chemical structure handling, toxicology needs proteomics and metabolomics, toxicology involves human data, and ecotoxicology has significant impact on crops and health.

Table 1: Examples of existing and anticipated collaboration.

	Existing collaboration / Reuse	**Anticipated collaboration**
Tools	Semantic annotation of services (e.g. bio.tools)	Alignment met BioContainers of toxicology workflow efforts (e.g. OpenRiskNet)
Data	diXa was co-developed by the CHEMBL-EBI team, and builds on ArrayExpress an ELIXIR CDR	Better adoption of the core resources
Compute		Better and more sustainable compute infrastructure reuse of core elements (ELIXIR AAI, modelling toolsets)
Interoperability	FAIR and RDM standards have already been adopted by various projects	Registries of toxicology tools need integration with FAIRsharing; There is a huge identifier, mapping service need (also for ontology mapping and chemical (sub)structures)
Training	Bioschemas annotated tutorials	Several projects have training tasks, listing in TeSS would be great. Automation of some of that was done already

The following projects have been adopting and integrating FAIR toxicology concepts, but need integration with ELIXIR Platforms and Communities: eTOX, NanoCommons (NSC), EU-ToxRisk (69 partners), OpenRiskNet (11 partners), OpenTox Foundation, Open PHACTS Foundation, and the diXa platform. Many other projects have a specific scientific focus but also need integration. A non-exhaustive list is ACEnano,

SmartNanoTox, HeCaToS, NewGeneris, EnviroGenoMarkers, Exposomics, HELIX, ASAT, PATROLS, and HEALS.

Companies and organisations that will profit from this Community either as users or as providers of services on top of the infrastructure, including ECHA (FI), Douglas Connect (CH), IdeaConsult Ltd (BG), Misvik Biology (FI), TNO (NL), and SweTox (SE). Industries showed a strong interest in toxicology, demonstrated by their activities: Cosmetics Europe was participant in the SEURAT-1 cluster; chemical industries (NIA) are participant of the NSC; chemical branch organisation (Cefic) funds LRI projects around toxicology; and pharmaceutical industries funds toxicology research via IMI projects like eTOX and Open PHACTS. The Research Data Alliance organized a workshop recently about integration of toxicogenomics resources[18], and collaboration with international organizations has already been established with, for example, the CompTox Chemistry Dashboard team of the US EPA[19].

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