FRONT PAGE

PROJECT FINAL REPORT

Grant Agreement number: 267042

Project acronym: TOXBANK

Project title: Supporting Integrated Data Analysis and Servicing of Alternative Testing Methods in Toxicology

Funding Scheme:

Period covered: 5 years from 2010 to 2015

Name of the scientific representative of the project's co-ordinator[1]: Emilio Benfenati

Title and Organisation: IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri"

Tel: +39-02-39014420

Fax: +39-02-39014735

E-mail: benfenati@marionegri.it

Project website Errore. Il segnalibro non è definito. **address: http://toxbank.net**

[1] Usually the contact person of the coordinator as specified in Art. 8.1. of the Grant Agreement.

4.1 Final publishable summary report

Executive summary

ToxBank established a dedicated web-based warehouse for toxicity data management and modelling, a „gold standards" compound database and repository of selected test compounds, and a reference resource for cells, cell lines and tissues of relevance for *in vitro* systemic toxicity research carried out across the FP7 HEALTH Alternative Testing Strategies SEURAT-1 program (http://www.seurat-1.eu/). The project developed infrastructure and service functions to create a sustainable predictive toxicology support resource going beyond the lifetime of the program. Specifically, based on an extensive requirements gathering from all SEURAT-1 consortia and an analysis of this data, a production version of the ToxBank data warehouse has been implemented that provides access to all experimental, processed data and protocols alongside relevant public information (https://services.toxbank.net/toxbank-ui/login). This includes the development of web-based interfaces for linking and uploading data, including raw and processed data, and model results. All steps of any experiments are linked to protocols describing the procedures. A web-based user interface for searching, browsing, and filtering the results has been implemented to provide access to all protocols and data across the cluster in a way that is sensitive of any intellectual property restrictions on access. Public access to the ToxBank data warehouse was established in Autumn 2014. Public data on reference compounds was incorporated into the warehouse supporting meta analysis and risk assessment being carried out on the SEURAT-1 case studies. A collaborative ToxBank Gold Compound database was established using the MediaWiki platform (http://wiki.toxbank.net/). It has been populated with a set of ca. 50 reference compounds, including information about chemical identities, adverse effects, toxicity mechanisms and therapeutic targets. These compounds were used as reference compounds by the SEURAT-1 cluster.

ToxBank Tutorial and Workshop proceedings have been captured and integrated into the ToxBank website (http://www.toxbank.net/). In 2015 ToxBank partners agreed to the continuation of ToxBank as a sustained OpenTox resource (http://www.opentox.net/) beyond the end of the project, including its extension and support of the EUToxRisk program (http://www.eu-toxrisk.eu/).

Work package No	Work package title	Type of activity	Lead participant No	Lead participant short name	Person-months	Start month	End month
WP1	Data Warehouse	RTD	4	IDEA	96	1	60
WP2	Compound Database	RTD	7	IST	72	1	60
WP3	Compound Repository	RTD	2	IRFMN	64	1	60
WP4	Cell and Tissue Bank	RTD	5	NIBSC	38	1	60
WP5	Dissemination	OTH	2	DC	30	1	60
WP6	Management	MGT	1	IRFMN	19	1	60
		TOTAL			319		

Table 1. Work package list

ToxBank upload status (*retrieved on 11 February 2016*):

- **Annex I** (Protocols and reports)
- **Annex II** (Data)

Summary description of project context and objectives

The primary goal of the FP7-HEALTH-2010-Alternative-Testing HEALTH.2010.4.2-9 program (SEURAT-1) was the development of human safety assessment strategies which may be used to replace, reduce or refine (3Rs principle) repeated-dose systemic toxicity testing historically carried out in animals. The target of ToxBank under the SEURAT-1 project pillar was the establishment of a dedicated web-based Data Warehouse (DW) for toxicity data management and modelling, a "gold standards" compound database and repository of selected model compounds, and a bank for cells and cell lines, including stem cells, and tissues of relevance for *in vitro* toxicity testing.

The objectives were the following:

a) Establishment of a dedicated web-based data warehouse
The ToxBank Data Warehouse (TBDW) has established a centralised compilation of information and data for systemic toxicity. Links to relevant public databases are provided for data import. All projects under the SEURAT-1 program uploaded their raw and processed data into the TBDW as soon as these become available. Data generated were analysed and the outcome integrated whenever possible into computerised models capable of predicting repeated-dose toxicity. The TBDW has been organised so that it provides a sustainable source of information for toxicological research going beyond the life-time of the research projects, through sustainability and business planning carried on throughout the project, including discussions with industry groups such as Cosmetics Europe to meet their requirements

b) Establishment of a database of selected model compounds
The ToxBank Gold Compounds were selected to meet the highest quality standards. Chemicals in the database have been selected based on the scientific literature, including review of mechanistic publications, high-quality repeated dose toxicity *in vivo* data from animal studies, and adverse event and epidemiological data from humans. The database covers cosmetic ingredients, industrial chemicals, and pharmaceuticals that meet high-quality selection criteria for reference compounds. In addition, a list of selected model compounds, standard operating procedures for data quality control, processing and analyses have been provided. Whenever compounds are needed for training or validation purposes, they can be selected from the Database in correspondence with targeted mode of actions in systemic toxicity. An extensive information resource on reference compounds was created for public dissemination through the ToxBank wiki (http://wiki.toxbank.net/).

c) Establishment of a repository for the selected model compounds
The ToxBank Chemical Repository ensures the availability of test chemicals accompanied by analytical quality control procedures to the research projects on the program. We have investigated service models so that the Chemical Repository could be maintain beyond the end of the program to provide ongoing services to further toxicology research and validation programs.

d) Setting up of a cell and tissue bank for in vitro toxicity testing
An important service to European scientists is the formation of a bank of cells, cell lines (including stem cells and stem cell lines) and tissues to be used in the program projects and beyond the end of the program. A Biomaterials information resource was developed and incorporated into the ToxBank wiki.

Description of the main S&T results/foregrounds

WP1 Data Warehouse

T1.1 User requirements gathering
Approach to collecting requirements
The ToxBank consortium used a methodology referred to as contextual inquiry/design for the collection of user information, from visits and direct interviews with many SEURAT-1 partners, to use in developing the system requirements for the TBDW[2]. An analysis of this data resulted in the user requirements for the TBDW. This included the need to develop a solution to manage, register, assign a status, comment, peer review, and sensitively share the diverse protocols being generated throughout the cluster as a high priority. Handling data presented a number of complex problems as a result of the diversity of the experiments being employed as well as the different workflows currently being adopted across the cluster. It was seen as essential that each step of an investigation be documented with a protocol and annotated with the resulting data, both the original results and any subsequent processed data. Providing information on the cells, reagents, and compounds was also highlighted as an important activity. It should be possible to search and download any protocols or investigation data.

To support the second phase development (integrated data analysis) ToxBank partners visited a further 10 SEURAT-1 partner sites and conducted interviews with ca. 20 investigators. The new requirements included the ability to precisely search for significant up or down regulated genes or proteins. In addition, chemical structure searching (exact, substructure and similarity) was added to support use cases such as read across. To understand how individual investigations, from a list of search results, were performed and what sort of data is available, a dashboard was implemented to summarize multiple investigations. This information allows users of ToxBank to understand both the experimental factors that were the basis for the investigations, but also the parameters and technologies used in producing the data. Data from the selected investigations can then be exported in a standardized way to enable combining data from different experiments. Since many tools were being used to perform data analysis and visualization across the cluster, it was decided not to replicate or build any of these specialized tools, but to enable their use through a variety of data export options. Specifically, linking the information to pathway tools is important to help understand the biological context.

T1.2 Design of system architecture
The TBDW architecture consists of a set of web services, providing access to protocols and data, a search service, and a Web GUI application, offering user-friendly access to the above functionality. ToxBank currently adopts the OpenTox framework design and incorporates the REpresentational State Transfer (REST) software architecture style, a formally defined common information model, based on the W3C Resource Description Framework (RDF) and authentication and authorisation based on OpenAM. All TBDW component and web service developments in this reporting period were based on these previously selected technologies.

T1.3 Incorporation of Systemic Toxicity Ontology
The ToxBank consortium created a keyword hierarchy that will be used in the TBDW. In addition to its use is facilitating collaborations, the keyword hierarchy is used to support searching, browsing

[2] *Karen Holtzblatt, Jessamyn Burns Wendell, and Shelley Wood, "Rapid Contextual Design: A How-To Guide to Key Techniques for User-Centered Design", 2005, Elsevier*

and linking of resources within the warehouse. When information is uploaded into the TBDW, terms are selected from this hierarchy and linked to protocols and investigation datasets in the warehouse. The keyword hierarchy is currently organized into six main branches: biomaterials, investigative techniques, data and readouts, adverse events, modes-of-action, and gold compound standards. In addition, the TBDW continues to incorporate existing life-science related ontologies through the use of ISAcreator data entry tools that create ISA-tab compatible archives, where concepts (e.g. cells, experimental unit, and so on) in the data are linked to existing ontology terms, and the continued development and extension of a cross-SEURAT-1 keyword hierarchy.

T1.4 Implementation of the Data Warehouse through a suite of distributed data marts

To handle all of the data generated in the diverse investigations being performed across the cluster, as well as relevant public data, ToxBank adopted the ISA-TAB universal data format to represent the experiments, including the toxicity studies, any chemical analysis, and omics experiments. Data access and upload procedures are defined by the Investigation API. Data is uploaded in ISA-TAB format; data queries are performed with the SPARQL query language. REST operations are available for accessing individual investigations, studies, assays and data files. Work has been ongoing throughout the project on extending the data warehouse framework to support data uploading and processing.

T1.5 Implementation of Data Warehouse operations using web services

The warehouse has a series of operations for managing protocols, data, and searching. These operations have been implemented as a set of distributed web services that make use of existing OpenTox APIs. The specific services implemented are based on the needs of the cluster, as defined in the requirements described earlier. ToxBank's REST resources are instances of the relevant RDF classes (e.g. https://services.toxbank.net/toxbank/protocol/SEURAT-Protocol-104-1 is an instance of the *tb:Protocol* class). ToxBank puts special emphasis on data confidentiality. The Authentication & Authorization infrastructure (AAI), in particular, builds upon what has already been developed and well tested in the OpenTox project and strives to further enhance it. Searching within the ToxBank system is provided as a separate web service that is deployable within an existing web container or as a stand-alone application. It was developed using Java and various open source technologies including Restlet[3] and elasticsearch[4]. The Search service is primarily accessed by the Protocol, Investigation, UI services and desktop applications such as ISAcreator[5]. When protocol or data resources are uploaded, the corresponding service notifies the Search service that a new resource is available. The search service then retrieves the resource and makes it available for indexing.

To support the precise searching of omics and other data, the isa2rdf tool has been extended to support conversion of microarray, mass spectrometry and protein assignment data files to RDF/XML in addition to converting the ISA-Tab metadata. The RDF representation of the data files is based on an extension of the OpenTox Dataset RDF representation and each data file item is linked to the relevant sample, described by the ISA-Tab metadata. The conversion to RDF is performed transparently for the user, who uploads an ISA-Tab archive. The server preprocesses the archive, using ISA-Tab validation and isa2rdf and imports the triples generated into a triple store[6]. Once all the information is available in the triple store, the relevant queries are defined as a set of predefined

[3] *Restlet [http://www.restlet.org/]*

[4] *elasticsearch [http://www.elasticsearch.org/]*

[5] *ISAcreator [https://github.com/ISA-tools/ISAcreator]*

[6] *http://4store.org/*

SPARQL queries and exposed as REST services in the general form of /investigation/sparql/{template_name}. The approach described allows a common data model for both metadata and data files, which is independent of a database technology.

To support searching by chemical structures, a dedicated ToxBank instance of OpenTox compliant web services from IdeaConsult[7] was installed on a ToxBank server. The content is updated on demand through the OpenTox dataset API. An ISAcreator plugin allowing to query the chemical structure services was developed[8]. It allows to search for chemical compounds (by identifier, similarity or substructure search) within ISAcreator and links the experiment metadata with the chemical structures in TBDW.

T1.6 Development of graphical user interface

Web-based graphical user interfaces have been designed, customised and implemented for loading the data into the TBDW as well as accessing the information and model results generated.

Data Entry

A series of forms-based user interfaces have been developed and/or customised for loading experimental data and related descriptions of experimental protocols. To collect investigation data in a consistent manner across the cluster, the ToxBank consortium selected to use ISAcreator, an open access tool (http://isatab.sourceforge.net/isahelp/ch03.html). ISAcreator provides a graphical user interface to create a consistently recorded series of data files that include the experimental design and information concerning the overall investigation, information on the experimental steps linked to both protocols as well as raw or processed data files.

Data Access & Analysis

The protocols and investigation housed in the TBDW are available from the web-based user interface. This GUI is a front-end user interface for the repository services defined by the ToxBank API. It is a standalone web application allowing users to log in, search and review existing protocols and investigations, and to upload new protocols and investigations. The interaction between the users' web browsers and the ToxBank UI server relies on standard HTML/CSS/Javascript content, generated dynamically within a Java-based web application framework (the Play Framework).

A series of user interfaces to support chemical searching as well as searches on genes and proteins have been developed. The chemical structure search user interface allows structure queries to be specified in order to perform an exact, substructure or similarity search. The query molecule is defined as either a SMILES string, a MOL file or is drawn within an integrated structure drawing editor. The search queries all investigations with chemical structures that are defined as experimental factors in ISA-Tab. A biomaterials search window was developed that allows a ToxBank user to define a precise query for different biological materials. An additional option to display a dashboard for a selected set of investigations is also provided. The new dashboard is being developed to help understand a specific list of investigations in terms of what experimental factors were considered, what was the source of the biological material, as well as what protocols, technologies, and endpoints were used. From these investigations, it is possible to download and combine specific data to use in external bioinformatics, chemoinformatics, advanced data analysis or visualization software as well as data mining applications .

[7] *http://ambit.sf.net*

[8] *https://github.com/vedina/opentox-isa-plugin*

T1.7 Integration of Tools for Data Analysis, Mining and Model Building

To support an integrated view of the derived or processed data generated from experiments across the SEURAT-1 cluster as well as outside the cluster, ToxBank uses preconfigured templates for assay metadata (as part of the ToxBank customised ISAcreator distribution) and proposed a standard file format for processed data. In this proposed standard, each type of experiment (e.g., transcriptomics, proteomics, and so on) has a different file format. The file containing this processed data is uploaded as part of an ISA-Tab archive (containing the experimental design, raw data, and links to the protocols) and can be used in ToxBank to support precise searching (e.g. identify all investigations where a specific gene has a fold change greater than 1.5) as well as a consistent integrated analysis of the data over the entire cluster. This standardization also supports effective integration with data analysis, data mining and model building applications.

T1.8 Data Warehouse Support Facilities

ToxBank has been supporting the preparation and upload of protocols and data into the data warehouse. To support the upload and use of the ToxBank data warehouse, a series of on-line tutorials have been generated. These include lectures on background material such as bioinformatics and tutorials to support the formatting of data, the upload of protocols, reports, and data as well as how to search, analyze and download information from the data warehouse. These tutorials are available through the toxbank.net website.

T1.9 Operation and Support of ToxBank Warehouse during the SEURAT-1 program

An interface to the COSMOS database via an API was developed and implemented in addition to approaches to integrate information on external resources with SEURAT-1 generated information. One of these projects was to integrate the ToxCast[9] and Tox21[10] data with the SEURAT-1 data to support a meta-analysis of the combined information.

T1.10 Scientific Coordination of WP work activities and their interaction with other WPs and all other related program activities

A number of tools have been adopted to support this task: Mantis, ToxBank wiki web-pages, Google Docs and the Jenkins integration server. Weekly technology focused meetings were held to discuss the ToxBank technical progress and the development and supported through ToxBank wiki web-pages. The web-pages developed outlining the APIs are made available publicly for other developers to build interfaces using the OpenTox/ToxBank web services.

T1.11 Sustainability Planning for resources developed within WP

The TBDW has been organised to provide a sustainable service for toxicological research beyond the lifetime of the research projects and resources set-aside such that the public reference data will be available for at least five years after the completion of SEURAT-1 as an OpenTox resource.

[9] *http://www.epa.gov/ncct/toxcast/*

[10] *http://ntp.niehs.nih.gov/results/hts/index.html*

WP2 Compound Database

T2.1 Establish Selection Criteria for ToxBank Gold Compounds

ToxBank was tasked to create a quality-controlled curated cheminformatics database for Gold Compound reference standards that can be used in the training and validation of *in vitro* assays and *in silico* models. Gold Compound selection criteria and standardized curation and operating procedures were established in the first half of year 1 in order to support the earliest possible creation of the database and its use in decision making on project and assay design across the SEURAT program. The SEURAT initiative addressed hepatic, cardiac, renal, neuronal, muscle, and skin toxicities, with the largest effort directed towards hepatotoxicity. The 6th Framework EU project, LIINTOP, identified the major hepatotoxicities of interest for development of *in vitro* testing methods. These included mitochondrial impairment, oxidative stress, apoptosis, and the lipid disorders of steatosis, cholestasis, and phospholipidosis (Gomez-Lechon et al. 2010). We therefore selected standards that are relevant to these pathologies, with the addition of specifically representing fibrosis with respect to cytotoxicity.

The SEURAT strategy encompasses "any substance". Thus, the reference compounds must cover a breadth of chemical classes that include cosmetic ingredients, agricultural and industrial chemicals, and pollutants, among others. Therefore the core criterion for acceptance was established to be a promiscuous mechanism of toxicity. While "mechanism" may refer to several possible aspects of the overall mode of action of a toxicant, compound selection was based narrowly on the molecular initiating event for the adverse outcome pathway. Promiscuity refers to lack of structural specificity in ligand binding, where the specificity may relate either to ligand or receptor structure. The concept derives from the observation that small, hydrophobic ligands tend to have binding affinity for multiple different proteins, and conversely, receptors with large hydrophobic pockets tend to bind multiple diverse ligand structures. Promiscuity is clearly relevant to a strategy that must span a broad chemical space. The following were identified as basic promiscuous mechanisms of toxicity: alkylation, redox, membrane disruption, and binding to (nonselective) nuclear hormone receptors. Additional standards were selected to represent especially well-characterized initiating events for the targeted pathologies.

To the mechanism-related criteria were added general criteria such as stability, solubility, and availability. The selection criteria were initially published in the deliverable D2.1, and are available at the ToxBank Gold Compounds Wiki site: http://wiki.toxbank.net/w/index.php/Selection_Criteria. Initial criteria also comprised non-idiosyncratic toxicity and relevance to repeated dose toxicity, but these criteria proved difficult to relate to objective standards of selection. There is no agreed frequency of occurrence that defines "non-idiosyncratic", for example; and these criteria had only secondary impact.

T2.2 Mine ToxBank Data Warehouse and select ToxBank Gold Compounds

In the original ToxBank conception, identification of the Gold Compounds was to be accomplished via computational data mining. Once the SEURAT consortium was constituted, however, it became apparent that only a small number of reference compounds was required and that manual selection and extensive curation were preferred.

An initial set of 24 compounds was selected and published in 2012 along with information about chemical identities, adverse effects, toxicity mechanisms and therapeutic targets. This compound set completed the selection of hepatotoxin reference standards. The list was reported in D2.2 and formally submitted to the cluster and approved at the 2013 annual meeting.

In 2013, the full compound set was completed by the addition of the full list of renal-, cardio- and neurotoxin standards. The complete list of compounds is available at wiki.toxbank.net/wiki/CompoundSummaryTable. Data associated with the Gold Compounds, especially the hepatotoxins, comprised in-depth textual analysis of the literature on mechanism of action.

T2.3 Verify availability and stability of selected ToxBank Gold Compounds

Selection criteria for the chemical standards included an evaluation of the highest purity available on the market, the reliability of information and traceability, suitability for cell culture application, ease of access and shipment availability in the different countries involved, and lot size and price. Standard compound suppliers and product numbers were provided to ensure that all labs were using a common compound source. Information on the stability of the chemicals was collected from the literature, and additional calculated biodegradation and metabolism properties were provided as a component of a data table that was constructed for each compound.

T2.4 Establish Standard Operating Procedures for data quality control, acceptance, processing and analyses of selected ToxBank Gold Compounds

The compound selection strategy evolved in consultation across the SEURAT-1 cluster. Each project team, the Scientific Expert Panel (SEP), and Colipa (now Cosmetics Europe) provided representatives at a kick-off meeting in Cascais, Portugal in February, 2011. An advisory Gold Compound Working Group with 18 members was assembled from the attendees at the Cascais meeting, and an evaluation team of 10 scientists was assembled from the SEP, industry, and academic labs to serve as the working Gold Compound Selection Team to evaluate specific compounds for acceptance. As a matter of process, it was agreed that compounds recommended as standards require unanimous agreement by the evaluation team and would be submitted to the working group for review and comment before being accepted as Gold Compound standards.

The selection strategy that emerged from the Cascais meeting was defined with respect to adverse events such as steatosis and cholestasis. The subsequent evolution to an MOA-based approach was endorsed by the SEP and developed in a series of monthly teleconferences with the Gold Compound Working Group starting in early August 2011. Explicit consideration of repeated dose toxicity was initiated at a meeting of experts organized by COACH in Ispra and a subsequent meeting with the SEURAT cardiotoxicity team in Cologne in November of 2011.

The final compound list was formally submitted to the Scientific Expert Panel and accepted in February of 2013. Compound selection efforts culminated in 2014 with the publication of a peer-reviewed review of the hepatotoxin reference compounds. This review assimilated information from the ToxBank Wiki data tables for individual compounds into an integrated discussion of mechanisms of toxicity and provided for peer review of the strategy and results.

T2.5 Build ToxBank Gold Compound Database including data import services and maintenance for SEURAT-1 program data passing curation evaluation and acceptance criteria
--And--
T2.6 Populate ToxBank Gold Compound Database with existing high-quality repeated-dose toxicity data from animal and human studies

Although it was originally envisaged that the Gold Compound Database would comprise a relational database, it was agreed with the Gold Compound Working Group in 2011 that a textual discussion of the rationale for selection of the compounds and their relevance to assay validation was preferred. Accordingly, a standard table of acceptance criteria was established and the data supporting compound acceptance was published as the ToxBank Gold Compound Wiki

(http://wiki.toxbank.net). The wiki format was selected because it supported incremental, rapid publication of compound data tables as they were developed and approved by the working group. This wiki ultimately became the primary repository for an extensively curated compilation of reference information on each Gold Compound.

Data associated with the Gold Compounds that was generated internally by the SEURAT cluster was then collected within the ToxBank Data Warehouse as described under the final report for WP1. Details about data import, maintenance, support, and curation for the Warehouse were reported in Deliverables 1.1 and 1.2. The core principle was to adopt existing standards and solutions, in particular OpenTox infrastructure and semantic web technologies (W3C Resource Description Framework - RDF3) to create an underlying database structure and then to provide data import and expose the data and functionality through web services. Data integration efforts were enhanced by establishing a database structure based on the ISA-Tab standard for uploading new biological data for to the Warehouse. This standard was proposed and adopted for use across the cluster. Finally, links from the Warehouse to external data sources were established as described below under T2.7.

T2.7 Establish procedures and analytical tools for selection of compounds for *in vitro* R&D programs, QSAR model building and training, integrated testing strategies, and model development and validation towards regulatory acceptance under REACH and the Cosmetics Directive

In the original ToxBank conception, identification of Gold Compounds was to be accomplished via computational data mining. Once the SEURAT consortium was constituted, however, it became apparent that only a small number of reference compounds was required and manual selection and curation were preferred. Therefore, the ToxBank data mining and analytical capabilities were redirected to two outcomes.

For the first outcome, efforts concentrated on supplementing the literature data in the Gold Compound Wiki with computed properties for the compounds. These properties were primarily physical properties such as solubility and predictions of elements of pharmacokinetics and can be accessed at the wiki (http://wiki.toxbank.net).

For the second outcome, efforts concentrated on integrating the ToxBank Gold Compound Warehouse with public databases and demonstrating proof of principle for data mining the linked data sources. These capabilities were then applied to developing methods for computationally relating chemical structure to mechanism of action in order support data mining efforts that address this future demand.

In order to support development of data mining tools, the Gold Compounds were associated with external mineable database collections in 2013, including the well-known TG-Gates and assay data from PubChem as well as the COSMOS database of the SEURAT cluster. The WP2 team then demonstrated application of analytical methods for Read Across, enriched meta-analysis of multiple omics and functional data, background knowledge from GO ontologies and Kegg pathways, and pathway visualization for SEURAT-1 Gold Compounds.

In 2014, links were extended to the Munro (2006) database of LO(A)EL and NO(A)EL data and HESS (Hazard Evaluation Support System) database from the OECD QSAR Toolbox and the EPA's Integrated Risk Information System (IRIS) database. Tools were then created to mine these databases to identify compounds chemically similar to the Gold Compounds, retrieve biological data for these compounds, and then predict biological targets for new compounds of interest, for example, in Read Across predictions and Adverse Outcome Pathway predictions. These tools and proof-of-principle

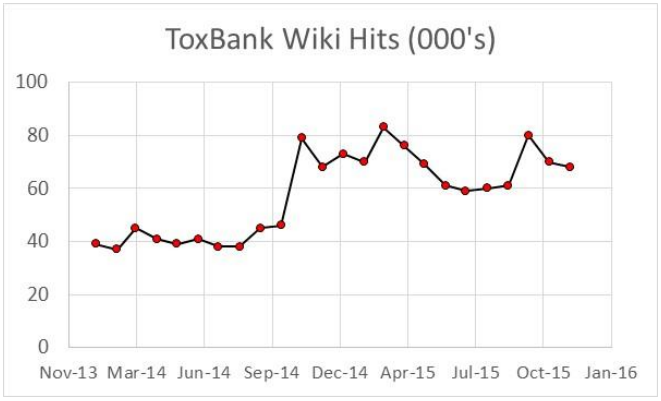
for their employment are exemplified by analysis of ToxCAST/Tox21 Phase II data for potential hepatotoxicity and analysis of the Munro, HESS and IRIS database for prediction of hepatotoxicity, prediction of repeated dose toxicity, and prediction of developmental and reproductive toxicity (see D2.4 and D2.5 reports).

T2.8 Define and enforce procedures for project-based and long-term ToxBank Gold Compound data submission, curation and maintenance, and support and training for ToxBank Gold users

As stated above, the primary relational database for the Gold Compounds is the ToxBank Warehouse, which was created and supported under WP1 and stores experimental data produced across the SEURAT cluster. Details of data IO processes, maintenance, and support are provided under the WP1 final report. Data submission was originally supported via the ISA-TAB standard for representation of final, curated data, and support for submission of preliminary, unformatted data was added in 2015.

T2.9 Operation and Support of ToxBank Gold Compound Database during the SEURAT-1 program

Since the primary Gold Compound data repository under WP2 was the Gold Compound Wiki, the primary effort was expended in collating the data that supported selection of compounds as reference standards, and building the wiki. Subsequent maintenance and support requirements were minimal. The successful support of the wiki is exemplified by the following graph of the number of hits on the wiki across 2014 and 2015.



Support requirements for the Gold Compound Data Warehouse for experimental data was extensive, however, and exemplified by a series of detailed video tutorials which are reported under D2.5. Further details are available from the final report for WP1.

A summary of the ToxBank gold compounds and associated datasets is provided in Table 1. In addition to SEURAT-1 datasets, discussions with the US EPA during the program resulted in the additional generation of ToxCast and Tox21 assay datasets, which were incorporated into ToxBank.

Adverse effect	CAS	SEURAT-1 Gold compounds	ToxBank	ToxCast	Tox21
Hepatotoxins	103-90-2	Acetaminophen	**Yes**	**ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]**	**Yes**
	144-48-9	Iodoacetamide	Yes	No	Yes
	107-18-6	Allyl alcohol	**Yes**	**ToxCast - 1800 [ph1 + ph2 + e1k]**	**Yes**
	6956-96-3	DMNQ	Yes	No	No
	56-23-5	CCl4	Yes	No	Yes
	1162-65-8	Aflatoxin B1	Yes	No	No
	642-15-9	Antimycin A	No	No	No
	1404-19-9	Oligomycin A	Yes	No	No
	83-79-4	Rotenone	**Yes**	**ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k], ToxCast - 300 [ph1]**	**Yes**
	370-86-5	FCCP	Yes	No	No
	99-66-1	Valproic Acid	**Yes**	**ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]**	**Yes**
	50-53-3	Chlorpromazine	Yes	No	Yes
	1951-25-3	Amiodarone	Yes	No	Yes
	59-05-2	Methotrexate	**Yes**	**ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]**	**Yes**
	147536-97-8	Bosentan	Yes	No	Yes
	481658-94-0	Dirlotapide	Yes	No	No
	54910-89-3	Fluoxetine	Yes	No	Yes
	31282-04-9	Hygromycin B	Yes	No	Yes
	293754-55-9	TO901317	Yes	No	No
	13292-46-1	Rifampicin	**Yes**	**ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]**	**Yes**
	50892-23-4	WY14643	No	ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]	Yes
	6051-87-2	β-Naphthoflavone	No	No	Yes
	10540-29-1	Tamoxifen	**Yes**	**ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]**	**Yes**
Nephrotoxins	7758-01-2	KBrO3	Yes	No	No
	303-47-9	Ochratoxin A	Yes	No	No
Cardiotoxins	23214-92-8	Doxorubicin	Yes	No	No
	642-15-9	Antimycin A	No	No	No
	113558-89-7	E4031	Yes	No	No
	51-83-2	Carbachol	Yes	No	Yes
	7683-59-2	Isoproterenol	No	No	Yes
	21829-25-4	Nifedipine	No	No	Yes
Neurotoxins	18228-17-6	Naphthol AS-E Phosphate	No	No	No
	66575-29-9	Forskolin	No	ToxCast - 1800 [ph1 + ph2 + e1k]	Yes
	208255-80-5	DAPT	No	No	No
	53123-88-9	Rapamycin	No	No	Yes
	1227911-45-6	GSK2334470	No	No	No
	?	Akt 1/2 inhibitor	No	?	?
	31430-18-9	Nocodazole	No	No	Yes
	109511-58-2	U0126	No	No	No
	79-06-1	Acrylamide	No	ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]	Yes
	2078-54-8	Propofol	No	ToxCast - 1800 [ph1 + ph2 + e1k]	Yes
	7758-95-4	Lead(II) Chloride	No	No	No
	2921-88-2	Chlorpyrifos	No	ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]	Yes
	333-41-5	Diazinon	No	ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k], ToxCast - 300 [ph1]	Yes
	60-57-1	Dieldrin	No	ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]	Yes
	?	Ni^{2+}	No	No	Yes
	4342-36-3 | 1461-22-9 | 2155-70-6	Tributyltin (TBT)	No	ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]	Yes
	1066-45-1	Trimethyltin (TMT)	No	No	No
	35065-27-1	PCB 153	No	No	Yes
	52663-68-0	PCB 180	No	No	Yes
	1499-55-4	Glutamate	No	No	Yes
Negative Control	69-65-8	*D* -Mannitol	No	ToxCast - 1000 [ph1 + ph2], ToxCast - 1800 [ph1 + ph2 + e1k]	Yes
			ToxBank Wiki	ToxCast	Tox21
SUMMARY		YES	25	16	33
		NO	27	36	19

Table 1. Summary of SEURAT-1 gold compounds and associated SEURAT-1, ToxCast & Tox21 data

WP3 Compound Repository

The main objectives within WP3 were the establishment of a physical repository of the test chemicals used, and the detailed characterisation of the chemical structure and relevant physico-chemical properties (including predictions on stability and binding properties) of the chemical used. We developed analytical methods for critical unstable test compounds, and the stability measurement under experimental conditions of doxorubicin, tamoxifen, amiodarone, bosentan, chloropromazine, valproic acid (and its liver metabolites), methotrexate and piperonyl butoxide. Particular attention was given to the measurement of the actual concentration of the substances within the *in vitro* assays. The measurement was made by LC-MS/MS in order to determine their stability during *in vitro* testing, at different time points. Furthermore, activities during the whole duration of the project aimed to direct the development of standard operating procedures (SOPs) for the test protocols and education on Good Chemical and Cell Culture Practice (see WP4).

A physical repository for test chemicals used within SEURAT-1 was established at Mario Negri Institute, Italy. Analytical methods were developed for doxorubicin, tamoxifen, amiodarone, bosentan, chloropromazine, valproic acid and its metabolites, methotrexate and pyperonil butoxide. Extraction procedures from cell culture medium were optimized for tamoxifen, amiodarone, bosentan, chloropromazine, valproic acid and its liver metabolites, methotrexate and pyperonil butoxide in order to measure their concentration during *in vitro* testing at different time points. Protocol guidelines were developed and uploaded in the ToxBank Data Warehouse providing definition, information on content, advices for the compilation, uploading and sharing within SEURAT-1 of research protocols and standard operation procedures.

Task 3.1. Establishment of a physical collection of test chemicals used within the SEURAT projects

The prime objective achieved within WP3 was the establishment of a physical repository for test chemical to be used within SEURAT-1. It addressed the availability and detailed characterization of the chemicals used within SEURAT-1 and was strictly related to the Data Warehouse established within ToxBank. According to the statement in the Description of Work the "Compound Repository" was established as a dedicated freezer at the partner institute in Milano (Mario Negri Institute), who held the responsibility for its maintenance and the associated chemical analysis facilities.

Task 3.2. Definition of a quality assurance framework for data inclusion on test chemicals to be used within SEURAT projects

A quality assurance framework for data inclusion on test chemicals to be used within SEURAT-1 was defined. This work was strictly related to the extensive assessment performed in WP2 for the selection of Gold Compounds for testing, since data on physico-chemical properties, purity and stability were gathered for the evaluation of the suitability of the standards in term of physico-chemical behaviour in test conditions.

The collected properties were those required for the characterization of the Gold Compounds proposed within WP2: testing within the US EPA ToxCast/Tox21; structure and isomeric form; stability to storage, light, freeze thaw; buffers and water solubility; dimethylsulphoxide solubility; binding to plasticware; availability commercially with highest purity; volatility.

The sources which were considered reliable and used were: scientific literature, official databases, material certification, information sheets and specification provided by the standard's suppliers and US EPA. For data confirmation, multiple sources were considered and compared contemporaneously, whenever available. For particular properties, such as water solubility and

volatility, if data were not available, they were calculated through commercially and freely available software for modelling, as planned in the Description of Work. The used software programs were ACD Labs (Advanced Chemistry Development, Inc., Canada) for the calculation of solubility and Episuite (EPA, USA) for the calculation of vapour pressure for volatility evaluation. Quality principles were established and followed in order to guarantee the reliability and completeness of the information collected.

All the data were reported in a standardized form (scientific unit, conditions, etc.) along with specification on how the data were generated (testing parameters and conditions, calculation methods) and with references.

Task 3.3. Development and distribution to the participants of the SEURAT projects of procedures for chemical handling during *in vitro* testing

The procedures for chemical handling during *in vitro* testing are strictly related to the specific test conditions (e.g. solvent, pH, temperature, duration, reactive conditions, other factors) and then to Standard Operating Procedures (SOPs) which describe how an experiment is performed. SOPs were developed within SEURAT-1 and published and shared through the ToxBank Data Warehouse. During the first year of the project the Data Warehouse was constructed within the ToxBank project and the SOPs were developed and applied within the cluster projects. Instructions on the correct handling of chemicals was transmitted through the indications reported in the "Stability" part of the "Physical properties" and in the "Storage" part of the "Recommended product and source" section on the wiki, where there is available specific information on the stability to light, storage, freeze-thaw, pH sensibility, etc.

Task 3.4. Data Warehouse entry of relevant information on test chemicals including source, purity, structure, isomers, and tautomers

The entry of the relevant physico-chemical information on already selected test chemicals in the Data Warehouse was achieved through the organization of these properties and those evaluated within WP2 in a wiki resource which will be linked to the Data Warehouse (ToxBankWiki, http://wiki.toxbank.net). The data are reported in the "Physical properties" section of each compound's table in the wiki. For each chemical all the properties collected for the evaluation of the criteria defined in WP2 are reported, including source, structure, purity and specification of the isomeric form.

Task 3.5. Calculation of stability of test chemicals

The calculation of stability for the Gold Compounds accepted has been made and all the results were reported in the deliverable D3.2 "Entry of structures, physico-chemical, stability and binding properties of test chemicals", due for M24. The calculation of biodegradation and metabolism properties was performed with the following software: Episuite (EPA, USA), Topkat (Accelrys, USA), MetabolExpert (CompuDrug, USA). These programs allow the estimation of several properties related to stability: atmospheric oxidation, Henry's law constant, melting point, boiling point, aerobic and anaerobic biodegradability, aqueous hydrolysis rate constant and half-lives (only for particular classes of chemicals), metabolites which may be formed in humans, animals or through photodegradation. These results contributed to the complete characterization of the Gold Compounds and to the evaluation of possible problems of stability in specific test conditions.

Task 3.6. Measurement and calculation of binding properties of test chemicals

The calculations on binding properties were performed on the accepted Gold Compounds and the results was reported according to the Description of Work in deliverable D3.2 "Entry of structures, physico-chemical, stability and binding properties of test chemicals", due for M24.

Task 3.7. Development and distribution to the participants of the other SEURAT projects of a template for preparing *in vitro* Standard Operating Procedure (SOP), education on GCCP, and continuous revision of SOPs

Partner IRFMN established contacts with the EC JRC, which is formalizing and disseminating the template for alternative methods within SEURAT-1 and also within a broader initiative of the EC. Partner Leadscope has been also actively involved in this task in order to harmonize the procedures used by SEURAT-1 partners and upload in the Data Warehouse within ToxBank.

Telephone conference meetings and informal discussion with partner HPA-UKSCB led to development of a two tiered approach to protocol capture development of the terminology of "Research Protocol" for laboratory protocols provided by other SEURAT-1 partners and "SOP" where the protocol is produced in a standard form with a minimum data set and also supported by appropriate controls and qualifying data to demonstrate effectiveness of the SOP.

Partner HPA-UKSCB worked closely with Partner JRC in the first six months to establish a review of quality control issues and potential markers and tests which was published and selected as the journal editors' selection when published in the January 2012 edition of Expert Opinion On Drug Metabolism and Toxicology (F. Pistollato, S. Bremer-Hoffmann, L. Healy, L. Young and G. Stacey. (2012) Standardisation of pluripotent stem cell cultures for toxicity testing, Expert Opinion On Drug Metabolism and Toxicology, 8(2):239-57. Epub 2012 Jan 17). Partner HPA-UKSCB gave a presentation on the principles of Good Cell Culture Practice as part of the main SEURAT-1 scientific programme and provided a training session on stem cell culture for ToxBank partners at the SEURAT-1 first scientific meeting in Cascais, March 2011.

At the SEURAT-1 February 2012 scientific meeting Partner HPA UKSCB led a workshop on Quality Control for Stem Cells, which has been reported to COACH and is being developed as a cross-SEURAT-1 cluster activity. In addition, HPA-UKSCB has collaborated with the Karolinska Institute ToxBank partner to provide a Good Cell Culture Practice training session at the SEURAT-1 "Summer School" at IBET in Oeiras, Portugal, in June 2012. Partner HPA-UKSCB in collaboration with partner Leadscope, developed guidelines for preparing research protocols and Standard Operating Procedures, which is available to all SEURAT-1 partners in the ToxBank Data Warehouse.

Task 3.8. Development of analytical methods for critical, unstable test chemicals and

The development of analytical methods for critical, unstable test chemicals and the following measurement of stability properties of test chemicals were the tasks planned to start in a second part of the project course, in particular from months 19 and 25 respectively. Experiments were performed to determine the actual concentration of tamoxifen, amiodarone, bosentan, chloropromazine, valproic acid and its liver metabolites, methotrexate and piperonyl butoxide present in cell culture medium after different treatment times and in controls. The analyses were performed to support the request by a cluster project partner from NOTOX project. For this reason a specific analytical method based on acetonitrile extraction followed by centrifugation was developed and optimised for the extraction of each chemical from cell culture medium and the subsequent determination was performed by electrospray ionization liquid chromatography tandem mass spectrometry. Additionally, a chromatographic based method for the quantification of doxorubicin was developed on tandem mass spectrometry.

Task 3.9. Measurement of stability properties of test chemicals

The developed LC-MS/MS analytical methods were applied to the determination of the actual concentration of tamoxifen, amiodarone, bosentan, chloropromazine, valproic acid and its liver metabolites, methotrexate and piperonyl butoxide in cell medium samples from acute and long term toxicity studies on HepaRG cells. Analysis was performed both on medium incubated with cells and without cells to estimate the stability of the drug in cell medium under experimental conditions and to evaluate cellular uptake. Furthermore the stock solutions of the drug in cell medium maintained in the fridge have been analyzed. Valproic acid concentration was also measured in samples from different cultivation conditions: 2D and 3D HepaRG cultures; methotrexate and piperonyl butoxide was measured in samples from 3D HepaRG cultures. The measured concentration was compared with the nominal concentration; the partial loss of the active compound was related to different processes such as adsorption to containers, degradation, evaporation and absorption into cells.

Cells were exposed to the drugs dissolved in the culture medium for acute and long term (28 days) toxicity experiments, in which the medium was renewed every 48 h. Cells were treated with concentration in the micromolar range except for valproic acid which was tested in millimolar concentrations. After 48 h of incubation at 37°C, supernatants were collected in triplicates into 0.5 ml plastic reaction tubes and centrifuged for 10 minutes at 13k rpm (4°C). They were then transferred into glass vials with micro inlets and frozen at -20°C for storage. Before shipment from the NOTOX partner to ToxBank partner IRFMN, the samples were further thawed and aliquots were prepared. The samples for time points for days 6, 14, 20 and 28 were analyzed for chemical quantification, except for methotrexate and piperonyl butoxide where the experiment was a long term (21 days) toxicity experiment on 3D HepaRG cultures. Supernatant and cells were transferred in ice cold plastic tube and then the separation of supernatants from cells was obtained by sedimentation and consecutive relocation of supernatant. The calculated limits of detections for the developed analytical method were 0.001 ng/µl for tamoxifen, 1 nM for amiodarone and bosentan, 8 nM for chlorpromazine, 0.2 µM for valproic acid, 0.021 µM for piperonyl butoxide and 0.0042 µM for methotrexate.

Results showed that the analyzed compounds had different stability in the experimental conditions examined. Amiodarone was detected only in the acute toxicity test samples, when the tested concentration was higher than 10 µM, the measured concentrations were 1000 times lower than expected. The critical stability of amiodarone is probably related to its low solubility and binding properties towards plastic materials. Chlorpromazine was measured 3 to 27 times lower than the expected concentrations in the cell medium incubated for the long term toxicity experiments without cells. Bosentan measured in cell medium incubated for the long-term toxicity experiments without cells was about 50-70% of the expected concentration. Valproic acid was measured nearly at the expected concentrations. Methotrexate level was about 50-70% and the piperonyl butoxide was calculated 2-5% due to solubility problems and binding properties toward plastics. The protocols for extraction and LC-MS/MS analysis of the drugs have been uploaded on the ToxBank Data Warehouse and have been linked to the ISA-tab reporting the results on their concentration in cell medium samples.

Task 3.10. Scientific Coordination of WP work activities and their interaction with other WPs and all other related SEURAT program activities

The WP3 activities were strictly related to the selection of the Gold Compounds performed within WP2 and their characterization in terms of physical chemical properties. Collaboration with WP1 was achieved for the definition of the structure of the ISA-tab reporting data on mass spectrometry analysis.

The interaction with the other cluster projects was mainly achieved through the reported work performed in collaboration with the Saarland University, partner in the NOTOX project.

Task 3.11. Sustainability Planning for resources developed within WP

The repository of the substances will be maintained for 5 years. This is not demanding and critical, since it simply requires to keep the freezer on. The chemicals will be possibly available for other projects, such as, in particular, EU-ToxRisk. Similarly, the methodologies for the analyses of the chemicals will be available within others projects.

Significant Results WP3

- LC-MS/MS methods developed for doxorubicin, tamoxifen, amiodarone, bosentan, chlorpromazine, valproic acid and its metabolites, methotrexate and piperonyl butoxide.
- Determination of the actual concentration of amiodarone, bosentan, chlorpromazine, tamoxifen, valproic acid and its metabolites, methotrexate and piperonyl butoxide in cell medium samples from acute and long term toxicity studies on HepaRG cells (overall more than 1,000 samples measured).
- Protocol guidelines developed and uploaded in the Data Warehouse

Statement on the use of resources within WP3

The resources used, in terms of person months, to achieve the objectives within WP3 during the first part of the project were consistent with what was planned. In the last few months of SEURAT-1 a much higher amount of samples has been delivered, and with a sense of responsibility were carried out with anextensive amount of additional work, using personnel resources higher than expected in this final part of the project. For the evaluation of stem cells, input has been provided by the HPA-UKSCB partner staff in several cases at no cost to the project.

WP 4 Cell and Tissue Bank

T4.1 Determine Materials Requirements

The Biomaterials requirements for ToxBank were gathered as a cross-partnership collaboration following an initial scoping meeting (Milan, 2012) and subsequently through a combination of email, phone calls, web-based surveying and participation in the ToxBank Knowledge Café laboratory visits on user requirements (See WP5 D5.1). The developing materials requirements (D4.1 Report on Materials Requirements in Systemic Toxicity) were further updated and coordinated at ToxBank partner meetings organised around the SEURAT-1 consortia scientific meetings. This included fundamental criteria for acceptable characteristics of hPSC lines (D4.2 General quality and regulatory criteria for establishment and dissemination of hPSCs), which were established in a collaboration with the SEURAT-1 partner consortium Scr&Tox (Pistollato et al., 2012). Initiatives coordinating output from relevant national, regional or European activities (e.g. UK Stem Cells for Safer Medicine, California CIRM, International Stem Cell Banking Initiative) were also engaged in this process. Information requirements on Biomaterials were fed into WP5 (see Deliverable 5.1).

T4.2 Establish suppliers (biomaterials) virtual network and registry with user friendly information access for toxicologists

This goal was addressed by reviewing the general resources available in Europe (D4.3 Summary of existing European biobanks and biorepositories) and identifying those with special relevance to *in vitro* systemic toxicology and the detailed user requirements identified under T4.1. Based on information provided by suppliers and users, an evaluation procedure (T4.2, T4.3) was be set up to produce a web-based registry of suppliers that builds on existing registries focused on the central EC-funded database of hPSC lines hESCreg (www.hpscreg.eu/) (D4.5 First version of a virtual suppliers network, D4.6 Points to consider in gaining access to human tissues and cell lines and D4.7 Inventory and map of European suppliers: materials, resources, facilities and standards).

T4.3 Define a quality assurance framework

This activity was aimed to identify key quality criteria on which to base evaluation of suppliers (see T4.4, D4.4 Evaluation process for suppliers of hPSCs) and in addition provide advice on best practice for SEURAT-1 partners and ultimately to the broader toxicology field. These were based on key user criteria established in the earlier process of establishing biomaterials requirements (see D4.1, D4.2).

An additional and important development for this task was an active collaboration with the SEURAT-1 consortium Scr&Tox and the ToxBank WP4 lead coordinating the SEURAT-1 "Stem Cell Group" incorporating input from ECVAM. These interactions led to joint poster presentations at SEURAT-1 annual scientific meetings, peer reviewed publications (Pistollato et al 2012; Stacey et al., in press) and reports and guidance documents now available on the public ToxBank wiki. These dealt with accessing suitable human tissues and cell lines (D4.2 and D4.6) and key quality criteria for establishment and use of hPSC lines under Good Cell Culture Practice (D4.2). D4.6 identified critical issues to be addressed to enable compliance with legal, ethical and commercial requirements for use of stem cell lines in the SEURAT-1 programme and ongoing industry utility and involved the completion of an ethics review questionnaire developed in collaboration with partners in Scr&Tox.

T4.4 Establish an inventory of suitable cell culture passaging facilities and procedures

An evaluation process was created to invite feedback from suppliers of stem cell lines and other key reagents, indicating how they meet the quality criteria established for biomaterials in T4.2 and T4.3. This was developed to provide researchers with the ability to evaluate suppliers based on a standardised assessment based on information gathered using a standard questionnaire.

Securing satisfactory information from suppliers was a significant challenge and less than 50% of those suppliers contacted provided a response, or were able to provide sufficient information to use in the evaluation. All suppliers providing satisfactory responses were listed in a registry with details from their websites and their authorised response to the evaluation process (D4.3 & D4.5). These details included any quality standards or regulations under which they are inspected or to which they proposed to be compliant. A formal review and a registry of these suppliers was compiled and published (D4.5). These criteria were then utilised in the final registry of suppliers and a map with hyperlinks has also been developed for international suppliers of stem cell lines (D4.7). Whilst not identified as a formal commitment in T4.2, this activity has been extended to address the availability of biomaterials from outside Europe to identify international players in the biomaterials field with a special focus on human pluripotent stem cell lines (D4.9 Directory of suppliers of Materials for *in vitro* toxicology). The Deliverable Report 4.9 also contains the template questionnaire which was published on the ToxBank wiki, a questionnaire researchers can use for ongoing selection of biomaterials.

T4.5 Develop ongoing operations beyond the period of the project

Ongoing supply of Materials under the proposed framework could be delivered through a number of business models. A business case and service model were developed based on an options appraisal which concluded that a sustainable online Cell and Tissue Bank for provision of access to research materials and reagents for *in vitro* systemic toxicology was possible (D4.8 Options appraisal for coordinated supply of hPSCs via directory of suppliers). An estimate for the investment required to achieve this was also included in this report.

The WP4 activity has developed a significant virtual network engaging a range of stakeholder groups and an outline for a supply network for Materials for European *in vitro* systemic toxicology now available through the ToxBank wiki (D4.7, D4.9). These resources can be used to coordinate procurement of suitable research biomaterials and reagents for *in vitro* systemic toxicology procedures using stem cell lines which has ready capacity for expansion as a primary access conduit for users via a directory of suppliers (D4.9).

T4.6 Scientific Coordination of WP work activities and their interaction with other WPs and all other related 4.2.9 program activities

This task involved coordination of all the work activities and resources associated with the ToxBank Cell and Tissue Bank (achievement of implementation goals, requirements analysis, software development, delivery of services) including interaction with other SEURAT-1 projects and coordination of cross-project working groups.

ToxBank WP4 lead (partner NIBSC) also coordinated the SEURAT-1 “Stem Cell Group” which gathered SEURAT-1 partners together to discuss key issues of quality control for stem cell lines, formulated suitability criteria for cell lines used in SEURAT-1 workplans (D4.1) and published a consensus, with a number of SEURAT-1 partners, on quality assurance of hPSC lines and the development of stem cell-based toxicology assays (Pistollato *et al.,* 2012; Stacey *et al.,* in press).

T4.7 Sustainability Planning for resources developed within WP4

The current on-line facility is accessible at the ToxBank website (www.toxbank.net/) where the resources from WP4 described above are located with other elements of ToxBank. This system has a direct link with hPSCreg (www.hpscreg.eu) for access to scientific and ethics data on stem cell lines. ToxBank partners HPA-UKSCB and DC are also now partners in the IMI EBiSC project (European bank of iPSC lines), where DC leads the development of the information management system,

which in turn enables ongoing coordination and interoperability with ToxBank features and resources.[11]

WP5 Dissemination

The results obtained within te ToxBank project were presented in several national and international congresses and also published in peer-reviewed international scientific journals. A significant dissemination of resource information was provided through the website, tutorials, virtual seminars, workshops and working groups. More information about this activity is provided in Section 4.2.

WP6 Management

In order to plan and the check the status of the scientific and administrative work, the consortium regularly organized face-to-face meeting (at least one per year) and virtual meetings (usually every week).

Maintenance of ToxBank services and security updates at project end

At project-end the security of the ToxBank services were brought into state of the art condition. Secure communication between ToxBank web services and web clients are handled by HTTPS technology. HTTPS is a communication over HyperText Transfer Protocol within an encrypted connection by SSL or TLS. SSL, and its successor TLS, are cryptographic protocols to provide secure communication over the Internet. In the current server setup outdated and unsecure SSL protocols in version 1 to 3 are blocked and only newer TLS protocols 1.0, 1.1 and 1.2 are in use. TLS do support a large number of "cipher suites". Cipher suites are collections of symmetric and asymmetric encryption algorithms used by hosts to establish secure communication. Some offer better level of security than others. At the start of the connection between a web client and a web service the client sends a list of possible ciphers to the webserver. The webserver replies with the cipher suite that it has selected from this list. The ToxBank data warehouse server allows the use of a collection of 'latest' cypher suites that offers a good balance between security and the possiblity to connect with a variety of current web clients. The web server's configration was adapted and tested with the free online SSL test service from Qallys SSL Labs at https://www.ssllabs.com. The web services operating systems were upgraded to newest versions (Debian 8 with support until May 2018/May 2020 LTS) to ensure secure and "easy to update" operating system over the end of the project.

[11] *References*

Pistollato, F., Bremer-Hoffmann, S., Healy, L., Young, L. and Stacey, G. (2012) Standardisation of pluripotent stem cell cultures for toxicity testing, Expert Opinion On Drug Metabolism and Toxicology, 8(2):239-257.

Stacey GN, Coecke S, Price A, Healy L, Jennings P, Wilmes A, Pinset C, Sundstrom M. Myatt G. (in press) Ensuring the quality of stem cell derived models for toxicity testing. In: Validating Alternative Methods for Toxicity Testing. Eds Whelan M and Eskes C. Springer.

Potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results

We have uploaded numerous protocols, reports and datasets from the SEURAT-1 program activities (see Annex I and II). We have agreed as a consortium to maintain all ToxBank reference information as a public OpenTox resource for a minimum of 5 years beyond the end of the project, providing the scientific community access to the results of SEURAT at no charge for access. OpenTox was initially an FP7 project, but importantly has developed as a community around open resources and standards, and in 2015 was formed as an international member-based non-profit organisation (http://www.opentox.net/the-opentox-association).

During 2016 we will in collaboration with COACH and the EC JRC, continue to develop and extend case studies around the ToxBank resources. Part of the consortium (DC, IRFMN) will also be engaged in the new EUToxRisk program forming a bridge between SEURAT results and their extensions. We will continue to communicate with SEURAT-1 coordinators and data owners throughout the final reporting and review process, and beyond. Data Quality has been assured by continuing to support the best practices on data preparation as reported extensively in previous ToxBank reports and tutorials (www.toxbank.net).

To promote wider access, public registration and access to ToxBank is supported, and will continue to be supported throughout the next five years. We also plan to further develop the ToxBank resource as an important key reference resource interoperating with the growing set of OpenTox resources on data, algorithms, modelling, and analysis and visualization components.

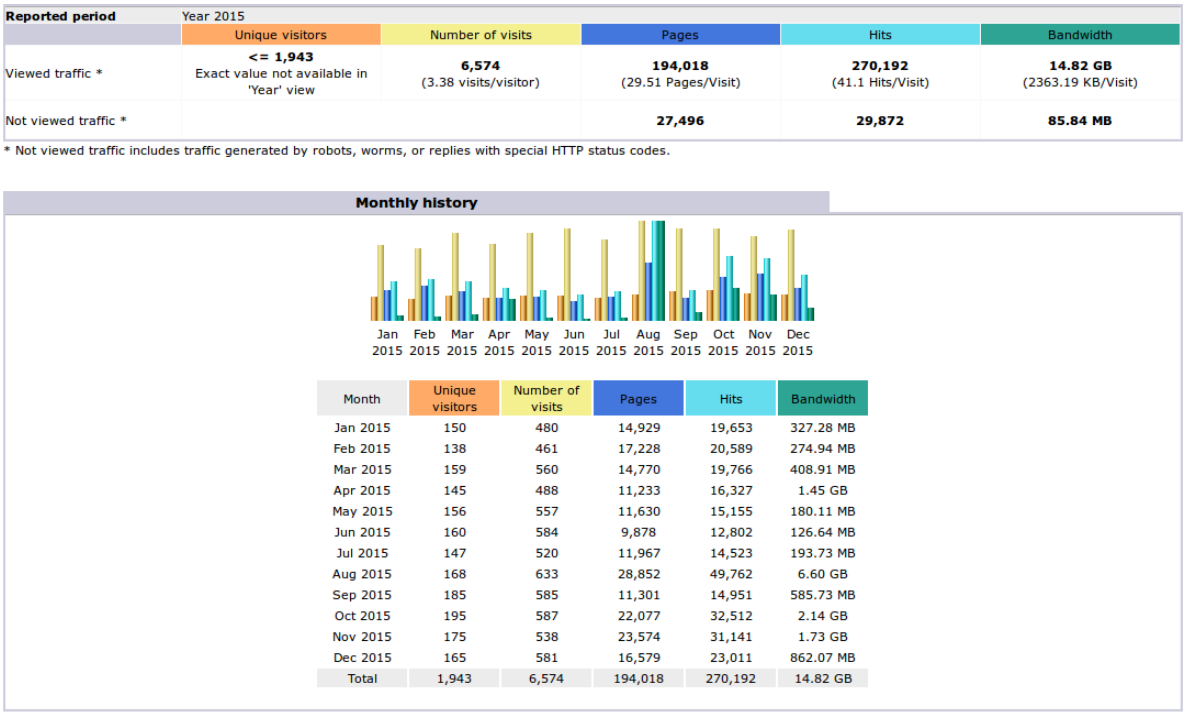
As data owners provide public access to their datasets and results, we will promote their availability to users registered on ToxBank, and more broadly to the scientific and general public

The address of the project public website, if applicable as well as relevant contact details

Public website: http://toxbank.net/
Subdomains:

- ToxBank Wiki: http://wiki.toxbank.net/wiki/
- ToxBank Data and Analysis services: https://services.toxbank.net/

Figure 1 provides an overview of statistics on access to the ToxBank Data Warehouse during the final year of the project.



Reported period	Year 2015				
	Unique visitors	Number of visits	Pages	Hits	Bandwidth
Viewed traffic *	<= 1,943 Exact value not available in 'Year' view	6,574 (3.38 visits/visitor)	194,018 (29.51 Pages/Visit)	270,192 (41.1 Hits/Visit)	14.82 GB (2363.19 KB/Visit)
Not viewed traffic *			27,496	29,872	85.84 MB

* Not viewed traffic includes traffic generated by robots, worms, or replies with special HTTP status codes.

Month	Unique visitors	Number of visits	Pages	Hits	Bandwidth
Jan 2015	150	480	14,929	19,653	327.28 MB
Feb 2015	138	461	17,228	20,589	274.94 MB
Mar 2015	159	560	14,770	19,766	408.91 MB
Apr 2015	145	488	11,233	16,327	1.45 GB
May 2015	156	557	11,630	15,155	180.11 MB
Jun 2015	160	584	9,878	12,802	126.64 MB
Jul 2015	147	520	11,967	14,523	193.73 MB
Aug 2015	168	633	28,852	49,762	6.60 GB
Sep 2015	185	585	11,301	14,951	585.73 MB
Oct 2015	195	587	22,077	32,512	2.14 GB
Nov 2015	175	538	23,574	31,141	1.73 GB
Dec 2015	165	581	16,579	23,011	862.07 MB
Total	1,943	6,574	194,018	270,192	14.82 GB

Figure 1. Visitors' history on the services.toxbank.net (2015)

ToxBank Partners

No.	Participant organisation name	Short Name	Org Type	Country	Contact person
1	Istituto di Ricerche Farmacologiche Mario Negri	IRFMN	RES	Italy	Emilio Benfenati
2	Douglas Connect	DC	SME	Switzerland	Barry Hardy
3	Leadscope Inc.	LEAD	SME	USA	Glenn Myatt
4	Ideaconsult Ltd.	IDEA	SME	Bulgaria	Nina Jeliazkova
5	National Institute for Biological Standards and Control	NIBSC	GOV	UK	Glyn Stacey
6	Pharmatrope	PHT	SME	USA	Jeffrey Wiseman
7	Karolinska Institute	KI	UN I	Sweden	Roland Grafström
8	In Silico Toxicology	IST	SME	Switzerland	Christoph Helma

Table 2. List of beneficiaries with the corresponding contact names

4.2 Use and dissemination of foreground

A plan for use and dissemination of foreground (including socio-economic impact and target groups for the results of the research) shall be established at the end of the project. It should, where appropriate, be an update of the initial plan in Annex I for use and dissemination of foreground and be consistent with the report on societal implications on the use and dissemination of foreground (section 4.3 – H).

The plan should consist of:

- *Section A*

  This section should describe the dissemination measures, including any scientific publications relating to foreground. ***Its content will be made available in the public domain*** *thus demonstrating the added-value and positive impact of the project on the European Union.*

- *Section B*

  This section should specify the exploitable foreground and provide the plans for exploitation. All these data can be public or confidential; the report must clearly mark non-publishable (confidential) parts that will be treated as such by the Commission. Information under Section B that is not marked as confidential ***will be made available in the public domain*** *thus demonstrating the added-value and positive impact of the project on the European Union.*

Section A (public)

This section includes two templates

- Template A1: List of all scientific (peer reviewed) publications relating to the foreground of the project.
- Template A2: List of all dissemination activities (publications, conferences, workshops, web sites/applications, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters).

These tables are cumulative, which means that they should always show all publications and activities from the beginning until after the end of the project. Updates are possible at any time.

TEMPLATE A1: LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS, STARTING WITH THE MOST IMPORTANT ONES

NO.	Title	Main author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Permanent identifiers[12] (if available)	Is/Will open access[13] provided to this publication?
1	*Ensuring the quality of stem cell derived models for toxicity testing.*	*Stacey G.*	*Validating Alternative Methods for Toxicity Testing*	*NA*	*Springer*	*-*	*In press*	*NA*	*NA*	
2	*In Silico Modeling for the Prediction of Dose and Pathway-Related Adverse Effects in Humans From*	*Maggioni S.*	*Toxicological Sciences*	*No 149, January 2016*	*Oxford Journals*	*-*	*2016*	*pp. 55 – 66*	*doi: 10.1093/toxsci/kfv218*	*No*

[12] A permanent identifier should be a persistent link to the published version full text if open access or abstract if article is pay per view) or to the final manuscript accepted for publication (link to article in repository).

[13] Open Access is defined as free of charge access for anyone via Internet. Please answer "yes" if the open access to the publication is already established and also if the embargo period for open access is not yet over but you intend to establish open access afterwards.

	In Vitro Repeated-Dose Studies.									
3	*Identification of structural alerts for liver and kidney toxicity using repeated dose toxicity data*	*Pizzo F.*	*Chemistry Central Journal*	*No 9, November 2015*	*BioMed Central*	*-*	*2015*	*pp. 151 - 167*	*doi: 10.1186/s13065-015-0139-7*	*Yes*
4	*CORAL: model for no observed adverse effect level (NOAEL)*	*Toropov A.*	*Molecular Diversity*	*No 19, April 2015*	*Springer*	*-*	*2015*	*pp. 563 - 575*	*doi: 10.1007/s11030-015-9587-1*	*Yes*
5	*A k-NN Algorithm for Predicting Oral Sub-Chronic Toxicity in the Rat*	*Gadaleta D.*	*Altex*	*No 31, July 2014*	*Altex*	*-*	*2014*	*pp. 423 - 432*	*doi: 10.14573/altex.1405091s*	*Yes*
6	*Cancer biology, toxicology and alternative methods development go hand-in-hand*	*Kohonen P.*	Basic Clin Pharmacol Toxicol	*No 115, July 2014*	*Wiley*	*-*	*2014*	*pp. 50-58*	*doi: 1111/bcpt.12257*	*Yes*
7	*SEURAT-1 liver gold reference compounds: a mechanism-based review*	*Jennings P.*	*Archives of toxicology*	*No 88, December 2014*	*Springer*	*-*	*2014*	*pp. 2099-2133*	*doi: 10.1007/s00204-014-1410-8*	*Yes*
8	*The ToxBank Data Warehouse: Supporting the Replacement of In Vivo Repeated Dose Systemic Toxicity Testing*	*Kohonen P.*	*Molecular Informatics*	*No 32, January 2013*	*Wiley*	*-*	*2013*	*pp. 47-63*	*doi: 10.1002/minf.201200114*	*Yes*
9	*Standardisation of pluripotent stem cell cultures for toxicity testin.*	*Pistollato*	*Expert Opinion On Drug Metabolism*	*8*	*Taylor and Francis*	*-*	*2012*	*239-257*	*doi: 10.1517/17425255.2012.639763*	*No*

			and Toxicology							

TEMPLATE A2: LIST OF DISSEMINATION ACTIVITIES

NO.	Type of activities[14]	Main leader	Title	Date/Period	Place	Type of audience[15]	Size of audience	Countries addressed
1	*Conference*	*IRFMN*	*QSAR 2014*	*16 - 20 June 2014*	*Milan (Italy)*	*Scientific Community*	*300 people*	
2	*Conference*	*IRFMN*	*EUSAAT*	*20 - 23 September 2015*	*Linz (Austria)*	*Scientific Community*	*200 people*	
3	*Conference*	*IRFMN*	*Cosmetovigilanza, garanzia di sicurezza del prodotto cosmetico.*	*3 December 2014*	*Milan (Italy)*	*Scientific Community and Industry*	*50 people*	*Italy*
4	*Conference*	*IRFMN*	*La realtà dei metodi alternativi: vantaggi e limiti.*	*30 September 2014*	*Milan (Italy)*	*Scientific Community*	*100 people*	*Italy*
5	*Course*	*IRFMN*	*Corso ed esercitazione sulla valutazione della sicurezza dei cosmetici*	*18 March 2014*	*Milan (Italy)*			
6	*Conference, Exhibition*	*DC, Leadscope*	*Society of Toxicology 2014*	*23-27 March 2014*	*Phoenix (USA)*	*Scientific Community and Industry*	*5000 people*	
7	*Conference*	*IRFMN*	*Making Cosmetics*	*25th-26th 2013*	*Milan (Italy)*	*Scientific Community*	*200 people*	

[14] A drop down list allows choosing the dissemination activity: publications, conferences, workshops, web, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters, Other.

[15] A drop down list allows choosing the type of public: Scientific Community (higher education, Research), Industry, Civil Society, Policy makers, Medias, Other ('multiple choices' is possible).

						and Industry		
8	Conference	IRFMN	Banca dati per le sostanze cosmetiche e oltre: NOAEL Project	23 November 2013	Milan (Italy)	Scientific Community and Industry	80 people	
9	Conference	IRFMN	Use of in silico models for cosmetic industry	16 July 2013	Rome (Italy)		80 people	
10	Conference	DC	OpenTox USA 2013	29-30 October 2013	Raleigh-Durham (USA)	Scientific Community and Industry	100 people	
11	Conference	Leadscope	American College of Toxicology, 2013	3-6 November, 2013	San Antonio (USA)	Scientific Community and Industry	1000 people	
12	Conference	Leadscope	Society of Toxicology Meeting	10-15 March 2013	San Antonio (USA)	Scientific Community and Industry	5000 people	
13	Conference	Leadscope	EuroTox Meeting	17-20 July 2012	Stockholm (Sweden)	Scientific Community and Industry	1000 people	
14	Conference	IRFMN	QSAR 2014	16 - 20 June 2014	Milan (Italy)	Scientific Community	300 people	
15	Conference	DC	OpenTox Euro 2013	Sep 2013	Mainz (Germany)	Scientific Community	100 people	
16	Conference	DC	OpenTox Euro 2014	Sep 2014	Athens(Greece)	Scientific Community	60 people	
17	Conference	DC	OpenTox Euro 2015	Sep 2015	Dublin (Ireland)	Scientific Community	60 people	
18	Conference, Exhibition	DC	Society of Toxicology Meeting	March 2015	San Diego (USA)	Scientific Community and Industry	8000 people	
19	Forum Meeting	DC, NIBSC	ToxBank Public Forum	October 2015	London (UK)	Public Audience	50 people	
20	Forum Meeting	DC, NIBSC	ToxBank Industry Forum	October 2015	London (UK)	Scientific Community and Industry	30 people	
21	Posters	All	See ToxBank Deliverable Report D5.14	2011-2015		Scientific Community and Industry		
22	Tutorials (41)	All	See ToxBank	2013-2015	www.toxbank.net	Scientific		

			Web site			*Community*		
23	*Stand, Exhibition, Posters*	*DC*	*Final SEURAT-1 meeting*	*4 December 2015*	*Brussels*	*Public Audience*	*200 people*	

Section B (Confidential[16] or public: confidential information to be marked clearly)

Part B1

The applications for patents, trademarks, registered designs, etc. shall be listed according to the template B1 provided hereafter.

The list should, specify at least one unique identifier e.g. European Patent application reference. For patent applications, only if applicable, contributions to standards should be specified. This table is cumulative, which means that it should always show all applications from the beginning until after the end of the project.

No patents were applied for during the project. Our approach to sustainability is that based around a community and framework supported by open standards, open source, open ontology, open interfaces and open data.

TEMPLATE B1: LIST OF APPLICATIONS FOR PATENTS, TRADEMARKS, REGISTERED DESIGNS, ETC.					
Type of IP Rights[17]:	Confidential Click on YES/NO	Foreseen embargo date dd/mm/yyyy	Application reference(s) (e.g. EP123456)	Subject or title of application	Applicant (s) (as on the application)

[16] Note to be confused with the "EU CONFIDENTIAL" classification for some security research projects.

[17] A drop down list allows choosing the type of IP rights: Patents, Trademarks, Registered designs, Utility models, Others.

Part B2
Please complete the table hereafter:

Type of Exploitable Foreground[18]	Description of exploitable foreground	Confidential Click on YES/NO	Foreseen embargo date dd/mm/yyyy	Exploitable product(s) or measure(s)	Sector(s) of application[19]	Timetable, commercial or any other use	Patents or other IPR exploitation (licences)	Owner & Other Beneficiary(s) involved
Reference Information Resource	ToxBank Data Warehouse	NO		Sustained Availability as a Public Reference Resource	Safety Assessment, Predictive Toxicology	2016 -	Open Licenses	All partners, OpenTox Community
Reference Information Resource	TOXBANK WIKI	NO		Sustained Availability as a Public Reference Resource	Safety Assessment, Predictive Toxicology	2016 -	Open Licenses	All partners, OpenTox Community

In addition to the table, please provide a text to explain the exploitable foreground, in particular:

- Its purpose
- How the foreground might be exploited, when and by whom
- IPR exploitable measures taken or intended
- Further research necessary, if any
- Potential/expected impact (quantify where possible)

[19] A drop down list allows choosing the type of foreground: General advancement of knowledge, Commercial exploitation of R&D results, Exploitation of R&D results via standards, exploitation of results through EU policies, exploitation of results through (social) innovation.
[19] A drop down list allows choosing the type sector (NACE nomenclature) : http://ec.europa.eu/competition/mergers/cases/index/nace_all.html

4.3 Report on societal implications

Replies to the following questions will assist the Commission to obtain statistics and indicators on societal and socio-economic issues addressed by projects. The questions are arranged in a number of key themes. As well as producing certain statistics, the replies will also help identify those projects that have shown a real engagement with wider societal issues, and thereby identify interesting approaches to these issues and best practices. The replies for individual projects will not be made public.

A General Information *(completed automatically when **Grant Agreement number** is entered.*	
Grant Agreement Number:	267042
Title of Project:	ToxBank
Name and Title of Coordinator:	Emilio Benfenati

B Ethics	
1. Did your project undergo an Ethics Review (and/or Screening)? • If Yes: have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final project reports? Special Reminder: the progress of compliance with the Ethics Review/Screening Requirements should be described in the Period/Final Project Reports under the Section 3.2.2 *'Work Progress and Achievements'*	***No***
2. Please indicate whether your project involved any of the following issues (tick box) :	***No***
RESEARCH ON HUMANS	
• Did the project involve children?	
• Did the project involve patients?	No
• Did the project involve persons not able to give consent?	No
• Did the project involve adult healthy volunteers?	No
• Did the project involve Human genetic material?	No
• Did the project involve Human biological samples?	No
• Did the project involve Human data collection?	No
RESEARCH ON HUMAN EMBRYO/FOETUS	
• Did the project involve Human Embryos?	No
• Did the project involve Human Foetal Tissue / Cells?	No
• Did the project involve Human Embryonic Stem Cells (hESCs)?	No
• Did the project on human Embryonic Stem Cells involve cells in culture?	No
• Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?	No
PRIVACY	
• Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	No
• Did the project involve tracking the location or observation of people?	No
RESEARCH ON ANIMALS	
• Did the project involve research on animals?	No
• Were those animals transgenic small laboratory animals?	No
• Were those animals transgenic farm animals?	No

• Were those animals cloned farm animals?	No
• Were those animals non-human primates?	No
RESEARCH INVOLVING DEVELOPING COUNTRIES	
• Did the project involve the use of local resources (genetic, animal, plant etc)?	No
• Was the project of benefit to local community (capacity building, access to healthcare, education etc)?	No
DUAL USE	
• Research having direct military use	No
• Research having the potential for terrorist abuse	No

C Workforce Statistics (included only sum from IRFMN, and NIBSC)

3. Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator	1	1
Work package leaders		7
Experienced researchers (i.e. PhD holders)	12	15
PhD Students		1
Other	3	3

4. How many additional researchers (in companies and universities) were recruited specifically for this project?	**2**
Of which, indicate the number of men:	1

D Gender Aspects

5. Did you carry out specific Gender Equality Actions under the project?	○ X	Yes No

6. Which of the following actions did you carry out and how effective were they?

		Not at all effective				Very effective
❑	Design and implement an equal opportunity policy	○	○	○	○	○
❑	Set targets to achieve a gender balance in the workforce	○	○	○	○	○
❑	Organise conferences and workshops on gender	○	○	○	○	○
❑	Actions to improve work-life balance	○	○	○	○	○
○	Other:					

7. Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed?

○ Yes- please specify

X No

E Synergies with Science Education

8. Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?

X Yes- please specify: workshop, open days

○ No

9. Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?

X Yes- please specify: websites

○ No

F Interdisciplinarity

10. Which disciplines (see list below) are involved in your project?

X Main discipline[20]: 1.1; 1.3

X Associated discipline[Errore. Il segnalibro non è definito.]: 1.5; 3.1 ○ Associated discipline[Errore. Il segnalibro non è definito.]:

G Engaging with Civil society and policy makers

11a Did your project engage with societal actors beyond the research community? *(if 'No', go to Question 14)*	X ○	Yes No

11b If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?

○ No

X Yes- in determining what research should be performed

○ Yes - in implementing the research

○ Yes, in communicating /disseminating / using the results of the project

[20] Insert number from list below (Frascati Manual).

11c In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?	○ X	Yes No

12. Did you engage with government / public bodies or policy makers (including international organisations)

	No
X	Yes- in framing the research agenda
X	Yes - in implementing the research agenda
X	Yes, in communicating /disseminating / using the results of the project

13a Will the project generate outputs (expertise or scientific advice) which could be used by policy makers?

- X Yes – as a **primary** objective (please indicate areas below- multiple answers possible)
- ○ Yes – as a **secondary** objective (please indicate areas below - multiple answer possible)
- ○ No

13b If Yes, in which fields?

Agriculture		Energy		Human rights	
Audiovisual and Media		Enlargement		Information Society	
Budget		Enterprise		Institutional affairs	
Competition		Environment		Internal Market	
Consumers		External Relations		Justice, freedom and security	
Culture		External Trade		Public Health	
Customs		Fisheries and Maritime Affairs		Regional Policy	
Development Economic and Monetary Affairs		Food Safety		**X** Research and Innovation	
Education, Training, Youth		Foreign and Security Policy		Space	
Employment and Social Affairs		Fraud		Taxation	
		Humanitarian aid		Transport	

13c If Yes, at which level?

- ○ Local / regional levels
- ○ National level
- X European level
- X International level

H Use and dissemination

14. How many Articles were published/accepted for publication in peer-reviewed journals?	**9**
To how many of these is open access[21] provided?	**7**
How many of these are published in open access journals?	**7**
How many of these are published in open repositories?	**0**
To how many of these is open access not provided?	**2**
Please check all applicable reasons for not providing open access:	
❑ publisher's licensing agreement would not permit publishing in a repository ❑ no suitable repository available ❑ no suitable open access journal available ❑ no funds available to publish in an open access journal ❑ lack of time and resources ❑lack of information on open access ❑ other[22]: The paper has been handled mainly by another project within SEURAT……	

15. How many new patent applications ('priority filings') have been made? *("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).*		**0**
16. Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark	**0**
	Registered design	**0**
	Other	**0**
17. How many spin-off companies were created / are planned as a direct result of the project?		**0**
Indicate the approximate number of additional jobs in these companies:		

18. Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

❑	Increase in employment, or	❑	In small & medium-sized enterprises
X	Safeguard employment, or	❑	In large companies
❑	Decrease in employment,	❑	None of the above / not relevant to the project
❑	Difficult to estimate / not possible to quantify		

[21] Open Access is defined as free of charge access for anyone via Internet.
[22] For instance: classification for security project.

19. For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (*FTE = one person working fulltime for a year*) jobs:	*Indicate figure:* *11*
Difficult to estimate / not possible to quantify	❑

I Media and Communication to the general public

20. As part of the project, were any of the beneficiaries professionals in communication or media relations?

○ Yes X No

21. As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?

○ Yes X No

22 Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

❑	Press Release	❑	Coverage in specialist press
❑	Media briefing	❑	Coverage in general (non-specialist) press
❑	TV coverage / report	❑	Coverage in national press
❑	Radio coverage / report	❑	Coverage in international press
X	Brochures /posters / flyers	X	Website for the general public / internet
❑	DVD /Film /Multimedia	X	Event targeting general public (festival, conference, exhibition, science café)

23 In which languages are the information products for the general public produced?

X	Language of the coordinator	X	English
❑	Other language(s)		

***Question F-10*:** Classification of Scientific Disciplines according to the Frascati Manual 2002 (Proposed Standard Practice for Surveys on Research and Experimental Development, OECD 2002):

1.1, 1.2 and 1.5

FIELDS OF SCIENCE AND TECHNOLOGY

1. NATURAL SCIENCES

1.1 Mathematics and computer sciences [mathematics and other allied fields: computer sciences and other allied subjects (software development only; hardware development should be classified in the engineering fields)]

1.2 Physical sciences (astronomy and space sciences, physics and other allied subjects)

1.3 Chemical sciences (chemistry, other allied subjects)

1.4 Earth and related environmental sciences (geology, geophysics, mineralogy, physical geography and other geosciences, meteorology and other atmospheric sciences including climatic research, oceanography, vulcanology, palaeoecology, other allied sciences)

1.5 Biological sciences (biology, botany, bacteriology, microbiology, zoology, entomology, genetics, biochemistry, biophysics, other allied sciences, excluding clinical and veterinary sciences)

2 ENGINEERING AND TECHNOLOGY

2.1 Civil engineering (architecture engineering, building science and engineering, construction engineering, municipal and structural engineering and other allied subjects)

2.2 Electrical engineering, electronics [electrical engineering, electronics, communication engineering and systems, computer engineering (hardware only) and other allied subjects]

2.3. Other engineering sciences (such as chemical, aeronautical and space, mechanical, metallurgical and materials engineering, and their specialised subdivisions; forest products; applied sciences such as geodesy, industrial chemistry, etc.; the science and technology of food production; specialised technologies of interdisciplinary fields, e.g. systems analysis, metallurgy, mining, textile technology and other applied subjects)

3. MEDICAL SCIENCES

3.1 Basic medicine (anatomy, cytology, physiology, genetics, pharmacy, pharmacology, toxicology, immunology and immunohaematology, clinical chemistry, clinical microbiology, pathology)

3.2 Clinical medicine (anaesthesiology, paediatrics, obstetrics and gynaecology, internal medicine, surgery, dentistry, neurology, psychiatry, radiology, therapeutics, otorhinolaryngology, ophthalmology)

3.3 Health sciences (public health services, social medicine, hygiene, nursing, epidemiology)

4. AGRICULTURAL SCIENCES

4.1 Agriculture, forestry, fisheries and allied sciences (agronomy, animal husbandry, fisheries, forestry, horticulture, other allied subjects)

4.2 Veterinary medicine

5. SOCIAL SCIENCES

5.1 Psychology

5.2 Economics

5.3 Educational sciences (education and training and other allied subjects)

5.4 Other social sciences [anthropology (social and cultural) and ethnology, demography, geography (human, economic and social), town and country planning, management, law, linguistics, political sciences, sociology, organisation and methods, miscellaneous social sciences and interdisciplinary , methodological and historical S1T activities relating to subjects in this group. Physical anthropology, physical geography and psychophysiology should normally be classified with the natural sciences].

6. HUMANITIES

6.1 History (history, prehistory and history, together with auxiliary historical disciplines such as archaeology, numismatics, palaeography, genealogy, etc.)

6.2 Languages and literature (ancient and modern)

6.3 Other humanities [philosophy (including the history of science and technology) arts, history of art, art criticism, painting, sculpture, musicology, dramatic art excluding artistic "research" of any kind, religion, theology, other fields and subjects pertaining to the humanities, methodological, historical and other S1T activities relating to the subjects in this group]

2. FINAL REPORT ON THE DISTRIBUTION OF THE EUROPEAN UNION FINANCIAL CONTRIBUTION

This report shall be submitted to the Commission within 30 days after receipt of the final payment of the European Union financial contribution.

Report on the distribution of the European Union financial contribution between beneficiaries

Name of beneficiary	Final amount of EU contribution per beneficiary in Euros
Istituto di Ricerche Farmacologiche Mario Negri	
Douglas Connect	
Leadscope Inc.	
Ideaconsult Ltd.	
National Institute for Biological Standards and Control	
Pharmatrope	
Karolinska Institute	
In Silico Toxicology	
Total	

Annex I

Protocols and reports uploaded

[1] SEURAT-Protocol-59-1: Standard operating procedure for phospholipidosis and/or steatosis detection in cultured primary rat hepatocytes (LipidTOX assay) [DETECTIVE, HeMiBio]
[2] SEURAT-Protocol-61-1: Standard operating procedure for the measurement of reactive oxygen species in cultured primary rat hepatocytes [HeMiBio, DETECTIVE]
[3] SEURAT-Protocol-66-1: Wound healing migration assay with cultured human hepatic stellate cells [HeMiBio]
[4] SEURAT-Protocol-104-1: LC-MS/MS analysis of doxorubicin [ToxBank]
[5] SEURAT-Protocol-53-1: Standard operating procedure for the measurement of caspase 3-like activity in cultured primary rat hepatocytes [HeMiBio, DETECTIVE]
[6] SEURAT-Protocol-58-1: Standard operating procedure for the measurement of the extracellular release of lactate dehydrogenase in cultured primary rat hepatocytes [HeMiBio, DETECTIVE]
[7] SEURAT-Protocol-60-1: Standard operating procedure for cytotoxicity measurement in cultured primary rat hepatocytes (MTT test) [HeMiBio, DETECTIVE]
[8] SEURAT-Protocol-89-1: Drug extraction in cell medium and LC-MS/MS analysis [NOTOX/ToxBank]
[9] SEURAT-Protocol-103-1: Real-time polymerase chain reaction of RNA derived from pluripotent cell cultures and neural derivatives [Scr&Tox]
[10] SEURAT-Protocol-57-1: Standard operating procedure for the measurement of CYP3A activity in cultured primary rat hepatocytes [HeMiBio, DETECTIVE]
[11] SEURAT-Protocol-102-1: High content imaging to characterise the phenotype and functionality of H9 and IRM90 stem cells cultures and their derivatives. [Scr&Tox]
[12] SEURAT-Protocol-25-1: Information for UKSCB hES cell lines [ToxBank]
[13] SEURAT-Protocol-56-1: Standard operating procedure for the measurement of CYP1A1/2 and CYP2B1/2 in cultured primary rat hepatocytes [HeMiBio, DETECTIVE]
[14] SEURAT-Protocol-63-1: Standard operating procedure for the measurement of urea synthesis in cultured stem cell-derived hepatocyte-like cells [HeMiBio, DETECTIVE]
[15] SEURAT-Protocol-68-1: Transwell migration assay for cultured human hepatic stellate cells [HeMiBio]
[16] SEURAT-Protocol-99-1: Neuronal Differentiation [Scr&Tox]
[17] SEURAT-Protocol-126-1: LC-MS/MS analysis of valproyl-CoA in cell culture medium [ToxBank]
[18] SEURAT-Protocol-101-1: Cytotoxicity analysis on H9-hESCs and IMR90-HiPSCs [Scr&Tox]
[19] SEURAT-Protocol-82-1: Hepatotoxicity screening taking a mode of action approach using HepaRG cells and HCA [DETECTIVE]
[20] SEURAT-Protocol-106-1: Tamoxifen extraction and LC-MS/MS analysis in cell culture medium [NOTOX/ToxBank]
[21] SEURAT-Protocol-62-1: Standard operating procedure for Sudan Red III in situ staining of cultured primary rat hepatocytes [DETECTIVE/HeMiBio]
[22] SEURAT-Protocol-67-1: Isolation of human hepatic stellate cells (hHSC) [HeMiBio]
[23] SEURAT-Protocol-100-1: Reverse phase protein array (RPPA) assays [Scr&Tox]
[24] SEURAT-Protocol-108-1: Methyl-DNA immunoprecipitation [HeMiBio]

[25] SEURAT-Protocol-109-1: D-IMU-1 (Exposing RPTEC/TERT1 cells to KBrO3 and ochratoxin A) [DETECTIVE]
[26] SEURAT-Protocol-110-1: Labeling and hybridization of miRNA samples using Agilent microarrays[DETECTIVE]
[27] SEURAT-Protocol-111-1: Normalisation and pre-processing of Agilent miRNA Microarray data[DETECTIVE]
[28] Immunoprecipitation for DNA methylation analysis[DETECTIVE]
[29] SEURAT-Protocol-113-1: Labeling and hybridization of DNA samples using Nimblegen ChiP-chip microarrays [DETECTIVE]
[30] SEURAT-Protocol-112-1: Immunoprecipitation and DNA extraction for histone acetylation analysis[DETECTIVE]
[31] SEURAT-Protocol-115-1: Labeling and hybridization of DNA samples using Nimblegen microarrays[DETECTIVE]
[32] SEURAT-Protocol-116-1: Labeling and hybridization of mRNA samples using Affymetrix microarrays[DETECTIVE]
[33] SEURAT-Protocol-107-1: LC-MS/MS analysis of valproic acid liver metabolites in cell culture medium [ToxBank]
[34] SEURAT-Protocol-114-1: Immunoprecipitation and dna extraction for DNA methylation analysis[DETECTIVE]
[35] SEURAT-Protocol-120-1 : Preparation of samples for NMR analysis[DETECTIVE]
[36] SEURAT-Protocol-120-1: Collecting media samples for NMR analysis[DETECTIVE]
[37] SEURAT-Protocol-121-1: Collection of intracellular metabolite samples and derivitisation[DETECTIVE]
[38] SEURAT-Protocol-122-1: Analysis of metabolite samples using GC-MS[DETECTIVE]
[39] SEURAT-Protocol-118-2 (version 2): Collecting media samples for NMR analysis [DETECTIVE]
[40] SEURAT-Protocol-119-2 (version 2): Preparation of collected media samples for NMR [DETECTIVE]
[41] SEURAT-Protocol-120-2 (version 2): Preparation of collected media samples for NMR analysis. [DETECTIVE]
[42] SEURAT-Protocol-120-2 (version 2): Spectroscopic analysis of media samples by Nuclear Magnetic Resonance. [DETECTIVE]
[43] SEURAT-Protocol-120-3 (version 3): Spectroscopic analysis of media samples by Nuclear Magnetic Resonance.[DETECTIVE]
[44] SEURAT-Protocol-132-1 (version 1): Extraction of miRNA for analysis with Agilent arrays [DETECTIVE]
[45] SEURAT-Protocol-133-1 (version 1): Cell preparation for analysis with Nimblegen Chip-Chip arrays [DETECTIVE]
[46] SEURAT-Protocol-134-1 (version 1): 1. SOP for dual isotopic labeling –quantitative differential proteomic experiments [DETECTIVE]
[47] SEURAT-Protocol-136-1 (version 1): Whole genome transcriptomics of simvastatin treatment in Mesodermal Precursor Cells [Scr&Tox]
[48] SEURAT-Protocol-137-1 (version 1): Differentiation of mesodermal precursor cells (MPC) from human embryonic stem cells (hESC) [Scr&Tox]
[49] SEURAT-Protocol-149-1 (version 1): Dose response analysis of the toxicity of statins on hES-derived MPCs, hES-derived NSCs, human primary myoblasts and myotubes derived from primary myoblasts [Scr&Tox]
[50] SEURAT-Protocol-152-1 (version 1): Information for UKSCB hES cell lines [ToxBank]
[51] SEURAT-Protocol-153-1 (version 1): TG-GATEs Sample growth and treatment protocol [ToxBank]

[52] SEURAT-Protocol-154-1 (version 1): Protocols for TG-GATEs gene expression data analysis and acquisition [ToxBank]
[53] SEURAT-Report-156-1 (version 1): Investigation of the fibrotic response induced by methotrexate and acetaminophen in the HeMiBio liver bioreactor [HeMiBio]
[54] SEURAT-Protocol-157-1 (version 1): SOP for derivation of neuronal precursors
[55] SEURAT-Report-159-1 (version 1): Developing Chemotypes for Mitochondrial Toxicity [COSMOS]
[56] SEURAT-Report-158-1 (version 1): Developing Chemotypes for Mitochondrial Toxicity [COSMOS]
[57] SEURAT-Report-160-1 (version 1): Development of an in silico profiler for mitochondrial toxicity [COSMOS]
[58] SEURAT-Report-161-1 (version 1): Developing Chemotypes for Mitochondrial Toxicity [COSMOS]
[59] SEURAT-Report-168-1 (version 1): Challenging the predictive power and robustness of an adverse outcome pathway construct from bile salt export pump inhibition to cholestatic injury [DETECTIVE]
[59] SEURAT-Report-169-1 (version 1): Mode of Action-based classification model for repeated dose liver toxicity [COACH]
[60] SEURAT-Protocol-174-1 (version 1): Toxic effect of APAP exposure on 3D HepaRG/HSC co-cultures [HeMiBio]
[61] SEURAT-Protocol-175-1 (version 1): APAP and MTX toxicity on HepaRG/HSC co-cultures upon Single and Repeated exposure [HeMiBio]
[62] SEURAT-Protocol-207-1 (version 1): Isolation of primary human hepatic stellate cells [HeMiBio]
[63] SEURAT-Protocol-206-1 (version 1): Cell culture of primary human hepatic stellate cells [HeMiBio]
[64] SEURAT-Protocol-205-1 (version 1): Standard operating procedure for cytotoxicity measurement in cultured primary rat hepatocytes (MTT test). [HeMiBio]
[65] SEURAT-Protocol-204-1 (version 1): Standard operating procedure for the measurement of reactive oxygen species in cultured primary rat hepatocytes. [HeMiBio]
[66] SEURAT-Protocol-203-1 (version 1): Standard operating procedure for phospholipidosis and/or steatosis detection in cultured primary rat hepatocytes (LipidTOX assay [HeMiBio]
[67] SEURAT-Protocol-202-1 (version 1): Standard operating procedure for the measurement of albumin secretion in HepaRG cells. [HeMiBio]
[68] SEURAT-Protocol-201-1 (version 1): Standard operating procedure for the measurement of cytochrome P450 3A activity in hepatic cell line cultures [HeMiBio]
[69] SEURAT-Protocol-200-1 (version 1): Standard operating procedure for the measurement of urea synthesis in cultured rat hepatocytes. [HeMiBio]
[70] SEURAT-Protocol-199-1 (version 1): Standard operating procedure for the measurement of caspase 3-like activity in cultured primary rat hepatocytes. [HeMiBio]
[71] SEURAT-Protocol-198-1 (version 1): Standard operating procedure for the detection of cholestasis-inducing agents in cultured primary rat hepatocytes. [HeMiBio]
[72] SEURAT-Protocol-197-1 (version 1): Assessment of central carbon metabolism in differentiating hepatocytes [HeMiBio]
[73] SEURAT-Protocol-196-1 (version 1): Adapting human Pluripotent stem cell differentiation to all three germ lineages for high through-put and high content screening (Restricted) [HeMiBio]
[74] SEURAT-Protocol-195-1 (version 1): Human Blood Outgrowth Endothelial Cell derivation and propagation [HeMiBio]

[75] SEURAT-Protocol-194-1 (version 1): Endothelial cell isolation from human liver biopsies [HeMiBio]
[76] SEURAT-Report-193-1 (version 1): VPA RAX case study: detection and verification of biomarker by using a RAX approach [DETECTIVE]
[77] SEURAT-Report-192-1 (version 1): Valproic acid case study: Detection and verification of biomarker by using a read across approach [DETECTIVE]
[78] SEURAT-Report-178-1 (version 1): Templates for reporting a read-across prediction of toxicity [COACH]
[79] SEURAT-Protocol-208-1 (version 1) Analysis of histone modifications via chromatin immunoprecipitation and sequencing (ChIP-seq) [NOTOX]
[80] SEURAT-Protocol-209-1 (version 1) DNA methylation analysis using HumanMethylation450 microarray [NOTOX]
[81] SEURAT-Protocol-210-1 (version 1) STANDARD OPERATING PROCEDURE (SOP) Seeding and cell culture of Ker-iPS #4603 cells [Scr&Tox]

Annex II

Data uploaded

Consortia	Data	Assay Technology	Experimental data
Scr&Tox	Analysis of pluripotency and neuronal related markers of H9 hESC and IRM90 hiPSC using HCI	High content imaging	Uploaded
Scr&Tox	Results of cytotoxicity analysis on H9-hESCs and IMR90-HiPSCs	Cytotoxicity	Uploaded
NOTOX/ ToxBank	Valproic acid concentration measured in samples from 2D and 3D cultivation	LC/MS	Uploaded
NOTOX/ ToxBank	Gold compound quantification in cell medium during acute and long-term toxicity test	LC/MS	Uploaded
NOTOX/ ToxBank	Quantification of valporic acid and its metabolites in cell culture medium from treated HepaRG cells	LC/MS	Uploaded
JRC	Hepatotoxicity Screening Taking a Mode-Of-Action Approach Using HepaRG Cells and HCA	Quantitative high-throughput screening	Uploaded
DETECTIVE	Multi-omics study where human proximal tubule cells RPTEC/TERT1 were exposed to potassium bromate and ochratoxin A at one sub-cytotoxic concentration in a 24h repeat-dose testing regime.	Trancriptomics	Uploaded
DETECTIVE	Multi-omics study where human proximal tubule cells RPTEC/TERT1 were exposed to potassium bromate and ochratoxin A at one sub-cytotoxic concentration in a 24h repeat-dose testing regime.	Histone modification	Uploaded
DETECTIVE	Multi-omics study where human proximal tubule cells RPTEC/TERT1 were exposed to potassium bromate and ochratoxin A at one sub-cytotoxic concentration in a 24h repeat-dose testing regime.	DNA Methylation	Uploaded

DETECTIVE	Multi-omics study where human proximal tubule cells RPTEC/TERT1 were exposed to potassium bromate and ochratoxin A at one sub-cytotoxic concentration in a 24h repeat-dose testing regime.	miRNA	Uploaded
DETECTIVE	Multi-omics study where human proximal tubule cells RPTEC/TERT1 were exposed to potassium bromate and ochratoxin A at one sub-cytotoxic concentration in a 24h repeat-dose testing regime.	Proteomics	Uploaded
DETECTIVE	Multi-omics study where human proximal tubule cells RPTEC/TERT1 were exposed to potassium bromate and ochratoxin A at one sub-cytotoxic concentration in a 24h repeat-dose testing regime.	Metabolomics	Uploaded
NOTOX	DNA methylation screening in 20h APAP-treated HepaRG cells	Epigenetics	Uploaded
NOTOX	Proteomics analysis of acetaminophen-induced toxicity using HepaRG cells*	Proteomics	Uploaded
NOTOX	Global gene expression analysis of HepaRG cells treated with APAP*	Transcriptomics	Uploaded
NOTOX	Systems toxicology approach to assess acute effects of acetaminophen on HepaRG in vitro cultures	Light microscopy	Uploaded
NOTOX	Systems toxicology approach to assess acute effects of acetaminophen on HepaRG in vitro cultures	Fluorescence microscopy (Live/Dead staining)	Uploaded
NOTOX	Systems toxicology approach to assess acute effects of acetaminophen on HepaRG in vitro cultures	GSH	Uploaded
NOTOX	Systems toxicology approach to assess acute effects of acetaminophen on HepaRG in vitro cultures	ROS	Uploaded
NOTOX	Systems toxicology approach to assess acute effects of acetaminophen on HepaRG in vitro cultures	Cell Viability	Uploaded
NOTOX	Systems toxicology approach to assess acute effects of acetaminophen on HepaRG in vitro cultures	CYP450	Uploaded
NOTOX	Systems toxicology approach to assess acute effects of acetaminophen on HepaRG in vitro cultures	Metabolic flux analysis	Uploaded

HeMiBio	Transcriptome analysis of human quiescent and activated Hepatic Stellate Cells and Hepatic Sinusoidal Endothelial Cells	Transcriptomics	Uploaded
HeMiBio	Promoter DNA methylation in three liver cell types	DNA methylation	Uploaded
ToxBank	TG-GATES for gold compounds	Transcriptomics	Uploaded
ToxBank	Mario Negri NOAEL data	NOAEL	Uploaded
Scr&Tox	48h dose responses curves of the toxicity of statins on different cell types	Cell counting/IC50	Uploaded
Scr&Tox	Whole genome transcriptomics of simvastatin treatment in Mesodermal Precursor Cells	Transcriptomics	Uploaded
DETECTIVE	Doxorubicin effects on human cardiomyocytes	NMR Spectrometry	Uploaded
DETECTIVE	Doxorubicin effects on human cardiomyocytes	Microarray	Uploaded
DETECTIVE	Doxorubicin effects on human cardiomyocytes	Additional technologies	Uploaded
DETECTIVE	Human skin-derived stem cells as a novel cell source for in vitro hepatotoxicity screening of pharmaceuticals.	Transcriptomics	Uploaded
DETECTIVE	Multiomics study where primary hepatocytes were treated with aflatoxin B1	DNA methylation profiling	Uploaded
DETECTIVE	Multiomics study where primary hepatocytes were treated with aflatoxin B1	DNA microarray	Uploaded
DETECTIVE	Multiomics study where primary hepatocytes were treated with aflatoxin B1	miRNA	Uploaded
DETECTIVE	Multiomics study where primary hepatocytes were treated with VPA	Transcriptomics	Uploaded
DETECTIVE	Multiomics study where primary hepatocyteswere treated with VPA	miRNA	Uploaded
DETECTIVE	Multiomics study where primary hepatocyteswere treated with VPA	Methylation microarrays	Uploaded
DETECTIVE	Challenging the predictive power and robustness of an adverse outcome pathway construct from bile salt export pump inhibition to cholestatic injury	High Content Screening	Data registered in ToxBank
DETECTIVE	High content imaging of adaptive stress response	Imaging data	Preliminary data

	BAC reporters treated with the gold compound library.		uploaded
DETECTIVE	Toxicogenomics map data	Transcriptomics	Uploaded
ToxBank	Tox21 and ToxCast Data	qHTS data	Integrated with ToxBank
COACH/COSMOS	Read across templates		Uploaded
NOTOX	VPA transcriptomics	Transcriptomics	Being prepared for upload
NOTOX	VPA proteomics	Proteomics	Being prepared for upload
NOTOX	Epigenomic profiling of the HepaRG cells from the VPA long term treatment experiment	Epigenetics	Uploaded
COSMOS	High content screening		Being prepared for upload
HeMiBio	Tools and Methods for testing drug-induced fibrosis in hepatic organoids		Uploaded
HeMiBio	APAP and MTX and Allyl alcohol toxicity and fibrotic response on HepaRG/HSC co-cultures upon Single and Repeated exposure		Uploaded
HeMiBio	Toxic effect of APAP exposure on 3D HepaRG/HSC co-cultures		Uploaded
DETECTIVE	In vivo data on VPA and its analogues		Uploaded
DETECTIVE	Biomarker repository		Uploaded
HeMiBio	Epigenetics of hepatocyte commitment of human pluripotent stem cells in vitro		Uploaded
HeMiBio	Integrative miRNA and Gene Expression Profiling Analysis of Human Quiescent Hepatic Stellate Cells		Uploaded
ToxBank	Developmental and reproductive toxicity database		Uploaded