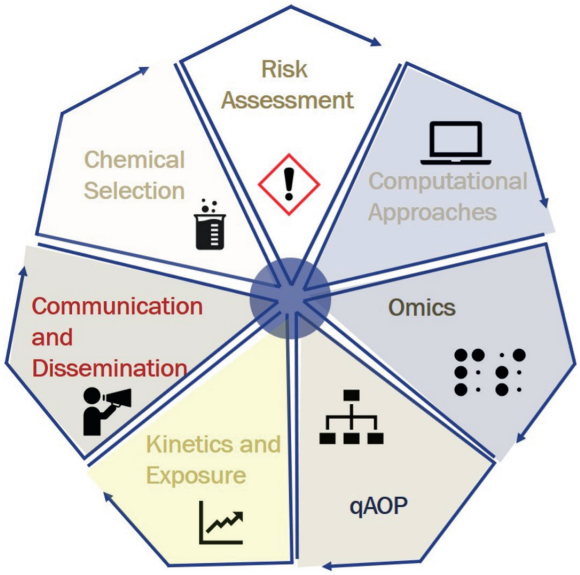
FIRST YEAR ANNUAL REPORT FOR ASPIS

ASPIS, Animal-free Safety assessment of chemicals: Project cluster for Implementation of novel Strategies, is the joint collaboration of the Horizon 2020 funded projects ONTOX, PrecisionTox, and RISK-HUNT3R. It represents Europe's €60M effort towards the sustainable, animal-free, and reliable chemical risk assessment of tomorrow. ASPIS includes more than 70 institutions across 16 European countries, the United Kingdom, and the United States.



ASPIS Working Groups

ASPIS was launched in July 2021; under the leadership of Bob van de Water, Leiden University, RISK-HUNT3R; and held its first annual meeting in November 2022. The cluster functions as seven Working Groups (WGs) composed of investigators from all three projects that specialise in activities that are relevant to the cluster's mission: Chemical Selection, Risk Assessment, quantitative Adverse Outcome Pathway, Omics, Kinetics & Exposure, Computational Approaches, and Communication & Dissemination. An eighth WG was later formed to establish a shared database for the F.A.I.R. management and sharing of project data. In March 2022, the position of ASPIS Working Group Coordinator (WGC) was created. The WGC plays a critical role in the development and reporting on ASPIS inter-working group projects. The WGC functions as a link among the WGs, ASPIS leadership, Scientific/ Regulatory Advisory Boards, and the Regulatory Forum. Additionally, the WGC maintains continuity and provides an historical perspective as new working groups are formed and old ones retire.

ASPIS is committed to improving the accuracy, speed, and affordability of chemical safety testing without the use of laboratory animals. Building on advances within the three consortia and close interactions with its stakeholders, it provides New Approach Methodologies (NAMs) to accelerate and improve chemical risk assessment. Through these activities, informed decisions that safeguard human health can be made to facilitate the development of safe and sustainable products. The goals of ASPIS are being met through international cooperation, method development, and guidance documents for chemical safety testing and risk assessment.

ASPIS-WIDE ACTIVITIES

The first year of ASPIS focused on establishing a formal organisational structure, WG formation, mission and goals development, and identifying areas for cross-consortia collaboration. To meet these goals, ASPIS has several regularly scheduled meetings:

- Coordinators meeting, which is attended by the ONTOX, PrecisionTox and RISK-HUNT3R coordinators, program managers, the WGC, and representatives from the European Commission (EC);
- WG chairs meeting, which includes project coordinators, managers, WGC, and chairs of each WG;
- Regulatory Forum (RF), which is composed of 27 policy and regulatory experts from across the European Commission (DG-JRC, DG-GROW, DG-ENV, DG-RTD, ECHA) plus 23 members of ASPIS are meeting on an ad hoc basis and chaired by the Joint Research Centre (JRC). The JRC is responsible for the organisation of the RF. The role of the RF is to discuss timely regulatory issues related to the Chemicals Strategy for Sustainability and revisions of REACH towards adopting NAMs. ASPIS supervisors, SRAB chair, and the ASPIS Coordination Team are invited to the RF. Meetings during 2022 were held on 10 May and 26 April resulting in a 'Group First, Regulate Better' whitepaper. The RF shares documents and communicates via a dedicated TEAMS channel hosted by the JRC.

Each WG is led by two or three co-chairs and includes members from each consortium and the JRC. WGs have regularly scheduled monthly virtual meetings and ad hoc meetings as needed. Meeting recordings and other ASPIS documentation are maintained on the ASPIS MS Teams/SharePoint site. Additionally, there are dedicated ASPIS Slack and GitHub sites.

One of the first cross-consortia successes is the development of two case studies revolving around two toxicological endpoints: steatosis and developmental neurotoxicity (DNT). Initiated by the Chemical Selection Working Group, each WG is now actively engaged in the steatosis cases study. Steatosis was selected as the first case study for several reasons. First, it was included as a biological endpoint in several of the original consortia proposals. Second, there are large amounts of chemical, toxicological, and molecular data already available. This supports the development of pipelines for data/information gathering, qAOP and kinetic/exposure model building. Third, many of the steatotic chemicals have multiple, regulatory-relevant human health endpoints that may be identified through this project. Fourth, engagement in this case study shows that the three consortia can work together to quickly and efficiently address problems through their combined efforts. It also provides an opportunity to develop NAMs that can be used in future ASPIS-wide projects and by the risk assessment community. Additionally, it will help in the development of information pipelines for data generation and sharing among ASPIS WGs, stakeholders, and the public.

ASPIS is currently developing a second case study focused on DNT. The CSWG has collected lists of DNT chemicals from the three consortia and stakeholders including the JRC, National Toxicology Program (NTP), the EU co-funded Partnership for the Assessment of Risk from Chemicals (PARC), US Environmental Protection Agency (EPA), and the European Chemicals Agency (ECHA). Information on physical-chemical properties, in vivo and in vitro toxicity, and modes of action are being collected and incorporated into the ASPIS database.

One of the most recent successes of ASPIS is the development of a joint Next Generation Risk Assessment (NGRA) framework. This framework, called the ASPIS Safety Profiling Algorithm (ASPA), will establish approaches for the safety assessment of chronic adverse health effects associated with chemical exposure. ASPA is a tiered approach on tools and methods to be used, when to obtain and evaluate data, and how to put data into a context of a hazard or risk assessment scenario. ASPA defines a decision logic with multiple entry and exit points, activating/deactivating specific modules, and prioritising and filtering of information. In the future, ASPA will help define new ASPIS-wide case studies, ultimately guiding the activities of other WG to assist in evaluating the applicability of ASPA. Additionally, ASPA will strengthen collaborations within and outside ASPIS. This framework was at the centre of the Second Annual ASPIS meeting held in Sitges, Spain on 23-24 November 2022. In addition to consortia members, it included discussion panels with policy experts from the EU and the OECD. ASPA will next be presented at a PARERE – ASPIS Workshop to be held at the JRC – Ispra, 30-31 March 2023. This framework forms the basis of ASPIS case studies (focused on steatosis) that are guided by such exchanges and will be delivered as a whitepaper with scientific findings before the end of the project.

INDIVIDUAL WORKING GROUP ACTIVITIES

Chemical Selection Working Group

Co-chairs: Jonathan Freedman (PrecisionTox), Mathieu Vinken (ONTOX) and Sylvia Escher (RISK-HUNT3R)

The goal of the Chemical Selection Working Group (CSWG) is to coordinate chemical selection among the ASPIS partners. Members of this WG are responsible for collecting and distributing information on chemicals being used by the three consortia. Additionally, it leads the development of ASPIS-wide case studies, communication, and assisting other working groups by providing physical-chemical and toxicological information on individuals or groups of chemicals.
The CSWG has collected and combined chemical lists from the three consortia. Additionally, lists have been obtained from the JRC, US NTP, US EPA, ECHA, PARC, and several stakeholders. These chemicals and cognate information will be included in the newly developed ASPIS database. The CSWG led the development of the steatosis case study and is currently developing a DNT case study. A new formal Database WG (DbWG) was formed from the CSWG and other WG needs.
In the coming year the CSWG will focus its efforts in building the ASPIS database with the DbWG. It will also support the Risk Assessment WG in the development of ASPA. Additionally, it will assist other WGs regarding issues associated with chemical selection and characterization. The main issue facing the CSWG is its role in future ASPIS activities. At this point in time, most of the projects have selected their test chemicals and obtained necessary information. Additionally, future cases will be led by the needs of other WGs and not based solely on the types of chemicals. In the future, the CSWG may become an information resource for the other WGs on chemicals being used within their projects.

Communication and Dissemination Working Group (C&DWG)

Co-chairs: Francois Busquet (ONTOX/PrecisionTox) and Giorgia Pallocca (RISK-HUNT3R)

The Communication and Dissemination Working Group (C&DWG) aims to harmonise dissemination activities and maximise the impact of ASPIS. Communication and dissemination activities are coordinated by the three consortia with the shared mission to unbiasedly inform on how NAMs-based strategies can rapidly accelerate and improve chemical risk assessment. The objective of the C&DWG is to build beyond projects' specificities, a single ASPIS to have a stronger voice to vehicle its outcome to regulatory stakeholders, policy-makers, non-governmental organisations, and the lay public.
The C&DWG has successfully created a visual identity for ASPIS and increased its international recognition. ASPIS activities including; open letters supporting the motion of resolution voted by the European Parliament[1] towards a transition to animal-free testing or the EC public consultation for CLP[2], symposia, webinars, and news releases: are listed on the ASPIS website (https://aspis-cluster.eu/). Through joint training and dissemination, the C&DWG has created a feeling of cohesively among ASPIS members. In the future, it will utilise opportunities to amplify the message of developing a sustainable, animal-free and reliable chemical risk assessment. A major focus of the C&DWG is the ASPIS Academy, which was launched in 2021-22 following a survey completed by the ASPIS ESRs (Early Stage Researchers). Activities performed under the umbrella of the Academy include training courses, research exchanges, organisation of dedicated discussion fora, and tailored sessions at open symposia. Additionally, they will be led by the needs and interests of the ASPIS ESRs. The first ASPIS Academy events were held at the Annual meeting in Sitges, including an ESR poster session, networking opportunities, and a training workshop. One training workshop on science communication[3] took place in Sitges where participants explored the most common tools that will help them achieve their goals in scientific communication, without wasting time and/or money. Another was dedicated to Artificial Intelligence. The overarching purpose of these activities is to build a sustainable platform for ESRs, comprehensively educated in NAMs and its functioning ecosystem. This action represents an efficient dissemination tool, allowing the integration of ESRs expertise in diverse organisations when entering the job market. Three training events are being planned for 2022-23 and dedicated webpages are being created for the benefit of ESRs with content being driven by this community within ASPIS. Two practical trainings are foreseen on data management, omics, and science

[1] https://aspis-cluster.eu/article-1/
[2] https://aspis-cluster.eu/aspis-statement-clp-public-consultation/
[3] https://aspis-cluster.eu/science-communication-tips/

communication to deepen participants knowledge after the Sitges session.
It is foreseen that in 2023 the C&DWG will pursue on an ad hoc basis op-eds and joint letters as well as joint representation with booths at scientific conferences. Under the new ASPIS chairmanship, the ASPIS Academy will be further elaborated with similar training and networking activities. Moreover, the Horizon Results Booster will be used to generate and deliver new communication material such as videos of the cluster and infographics.

Computational Approaches Working Group (CAWG)

Co-Chairs: Emilio Benfenati (ONTOX), Gerhard Ecker (RISK-HUNT3R) and Joseph Shaw (PrecisionTox)

The goal of the Computational Approaches Working Group (CAWG) is to organise activities related to computational methods used in ASPIS. As a part of the first case study, the CAWG focused on steatosis. The results of this case study will be shared with the Regulatory Forum, during the ASPIS Annual meetings, at international conferences, and ultimately as publications in scientific and policy peer reviewed journals.
To that end, a core group of members have been identified that are actively participating in the steatosis case study. They have compiled relevant datasets and have been assigned specific computational tasks.
The combination of different expertise within this WG provides the opportunity for consensus modelling, pooling of datasets to broaden the chemical space, and interpretations of models. The CAWG is utilising the ASPIS GitHub and interacting with the DbWG. The CAWG will establish a panel of in silico tools for steatosis and will address developmental neurotoxicity as the next use case. The CAWG will liaise with the RAWG to contribute to the ASPA.

Kinetics & Exposure Working Group (KEWG)

Co-chairs: Nynke Kramer (ONTOX), Sylvia Escher (RISK-HUNT3R)

The Kinetics & Exposure Working Group (KEWG) consists of investigators from each of the three consortia with a common goal of defining chemical exposure levels in the environment, human populations, target organs, and in vitro. The KEWG has finalised its membership; which includes individuals from ASPIS and associated organisations interested in activity participating in the WG and being updated on the content discussed by the working group; and established regular meetings. As first steps, each consortium introduced their kinetic models and exposure approaches to identify synergies and complementary strategies within ASPIS. The work of the KEWG is not targeting a specific toxicological endpoint. As part of the overarching ASPIS steatosis case study, a group of conazoles was identified, by comparing the already selected compounds in the three consortia. The KEWG is using this case study to further develop and improve the kinetics assessment of the ASPA workflow.
In the coming year, the KEWG will compare in vitro biokinetic modelling approaches using the conazole case study to calculate free and cell-associated concentrations from nominal concentrations in vitro. It will start with the development of a tiered testing and assessment strategy for in vitro ADME data to be integrated into PBK models. It will also demonstrate feasibility by using the conazole case study and NAM data from the three ASPIS consortia.
Additionally, the KEWG aims to develop a tiered testing strategy starting with in silico predictions and then progressing to a tiered experimental approach to address the absorption (passive vs. active transport), metabolism, and excretion of chemicals. This WG is using the opportunity to work across the three consortia to exchange best practices. Additionally, they are introducing ecotoxicity exposure and bioaccumulation test strategies into ASPA. Milestones, deliverables and timelines across projects will be defined to realise the ambitious goal of the KEWG. A discussion on a work plan with members of KEWG is scheduled for February 2023.

Omics Working Group (OWG)

Co-chairs: John Colbourne (PrecisionTox), Florian Caiment (ONTOX) and Giulia Callegaro (RISK-HUNT3R)

The ASPIS Omics work group (OWG) is dedicated to promoting the transition of omics into NGRA. For this, all data produced by ASPIS will be made compliant with the OECD Transcriptomics and Metabolomics Report Framework (TRF and MRF, respectively). The OWG has successfully promoted the OECD Reporting Framework and R-ODAF within ASPIS. It is maintaining active discussions among omics experts on the collection and analysis of omics data, with a focus on transcriptomic data associated with the steatosis case study. The OWG is leveraging opportunities to share omics datasets generated with the three consortia to harmonise data analysis pipelines.
The steatosis case study will be the main focus of 2023. A steatosis dataset will be assembled from public and private datasets, starting with transcriptomics. All assays will be normalised and analysed by a common pipeline and circulated among the members of the OWG. Starting from this common data input, each member (or sub-team) will have the freedom to perform any relevant analysis scheme to answer a common research question: Can heterogeneous transcriptomics datasets identify the steatosis state of a compound? The results of the different proposed strategies will be presented in at scientific conferences and through publications.

Quantitative Adverse Outcome Pathway Working Group

Co-chairs: Mark Cronin (RISK-HUNT3R) and Huan Yang (ONTOX)

The scope of the quantitative Adverse Outcome Pathway Working Group (qAOPWG) is to support the development of qAOPs across ASPIS. Specifically this WG aims to investigate models that quantify Molecular Initiating Events (MIEs) or Key Event Relationships (KERs) within existing AOPs using non-confidential data, as well as identifying and sharing good practice. The qAOPWG is actively developing a steatosis qAOP through data and model sharing. They have explored systems modelling approaches to simulate steatotic KEs and have prototyped a QST model to integrate steatosis qAOP and (toxico)kinetics. Additionally, they have established a framework for validation of qAOPs. Working with the CAWG provides the opportunity to build and present models for MIEs and coordination of qAOP model development. Ultimately, these models will provide input into regulatory decisions and ASPA.
There will be two main collaborative projects in 2023. The first is the continuation of the development of a qAOP for steatosis to support the case study. Data for KEs related to the steatosis AOP will continue to be shared between members of the qAOPWG to assist in the creation of models. It is likely that a variety of modelling approaches will be applied in response to the different endpoints and types of data. The second collaborative project will be to develop a framework for the evaluation of qAOPs while engaging with our external stakeholders. The framework is intended to promote the use of qAOPs and create greater understanding and confidence. The overarching aim of the activities of the qAOPWG is to demonstrate the possibility of using qAOPs to support the risk assessment process. There is an inherent uncertainty in all of the qAOP models. Additionally, there is not a firm plan to move qAOPWG activities from a modelling exercise to practical tools with uptake and acceptance by the regulatory community. To address this last issue, the qAOPWG intends to develop a tangible product that will directly support interaction with the RAWG.

Risk Assessment Working Group (RAWG)

Co-chairs: Stefan Scholz (PrecisionTox), Erwin L. Roggen (ONTOX), and Mirjam Luijten (RISK-HUNT3R)

The three ASPIS consortia have complementary approaches on how to use NAMs for the hazard and risk assessment of chemicals including prioritisation, grouping/read-across, and hazard characterization. The ASPIS risk assessment working group (RAWG) intends to share and link different approaches, coordinate joint activities, and critically review ASPIS research in comparison to previous activities for promoting NAMs with reference to the EU-ToxRisk project. The RAWG has had several major successes during its first year. Following a mid-year change among co-chairs, they established regularly scheduled inter-project meetings. They supported discussions, development, and presentations of ASPA. With the ongoing development of ASPA, the RAWG will strengthen its interactions with the other WGs to develop future case studies and begin collaborating with other European projects. Additionally, the RAWG will map case studies to the goals and mission of other WG, and draw from activities conducted in EUToxRisk and under auspices of OECD. To remain agile, the RAWG plans to begin smaller, focused meetings, define internal deliverables, and carefully consider future collaborations

In 2023, the RAWG will evaluate the ASPA workflow against ASPIS case studies to assess its flexibility and identify gaps. Integrating the Probabilistic Risk Assessment approach, once sufficiently mature, with the ASPA workflow with help to achieve a reliable, economically feasible tool to assess the risk of chemicals in their context of use. The RAWG will also identify new ways to engage regulatory authorities at national and international levels. Driving dissemination, while the integrated concept is maturing, to allow adjustments based on the input from the end-users. This interaction should result in the 'final' product that can be delivered at the end the project(s). PARC activities will also be taken into consideration.