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In Silico Safety Assessment of Plant-Derived substances: a New Approach Methodology (NAM) strategy and its limits

Coline LAMOUR, **EXPERTOX**

Auteurs : L. GUILLEMIN, S. PIRNAY

Les New Approach Methodologies (NAMs) occupent aujourd'hui une place croissante dans l'évaluation de la sécurité des ingrédients cosmétiques, notamment dans le contexte de l'interdiction des tests sur animaux et de la recherche de méthodes alternatives. Ce travail a exploré l'application d'une stratégie NAM intégrée à la sarmentosine, un glycoside cyanogène présent chez certaines espèces de Kalanchoe. L'approche combine caractérisation physicochimique, prédictions QSAR, toxicologie mécanistique et recherche d'analogues pour le read-across. Les résultats suggèrent une faible préoccupation toxicologique globale, sans alerte de génotoxicité, mutagénicité, cancérogénicité ou activité endocrinienne. Cependant, un potentiel de sensibilisation cutanée ainsi que la présence d'un motif nitrile justifient des investigations complémentaires. Par ailleurs, l'absence d'analogues suffisamment proches a limité la robustesse du read-across et empêché toute dérivation fiable de PoD ou de marge de sécurité. Cette étude illustre à la fois l'intérêt des NAM pour le criblage précoce des substances végétales et les limites actuelles de ces approches lorsqu'elles sont appliquées à des composés naturels peu documentés.

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Preclinical 3D-Living System to dissect toxicity mechanisms in Central Nervous System and accelerate discovery of new drugs against neurological diseases.

Amandine ROUX, Research PIECES

Auteurs : Amandine Roux, Research PIECES

Research PIECES is a DeepTech Biotech on the campus of Poitiers & Paris-Saclay. The goals are to understand the Physiology & the Physiopathology of the Central Nervous System (CNS), through Research, Development and Treatment, to accelerate the discovery of drugs against neurological diseases (neurodegenerative diseases, cancer, infectious & rare diseases); and to understand the impact of the environment on the CNS with role of pesticides, endocrine disruptors, neurotoxins, biophysical parameters (frequencies, ultrasounds, UV), etc. For that, we provide innovative biological preclinical models to dissect molecular, cellular and tissular mechanisms in a physiological 3D-living tissue environment. Our intermediate models are dynamic (= in vitro), integrated (= in vivo), physiological (non-artificial), they maintain the complex 3D structure of the connections between all cell types (versus microfluidics) and the real lipid composition of the CNS (versus artificial alternatives, as Bioprinting or organoids). They are also considered as NAMS, by reducing animal testing (Winners of Challenge Innovation in Health of the Carnot 2025 Meetings-Servier France). Unlike previous models, our tailored-made organotypic+ of CNS, are kept alive in culture for long time (> 4-6 weeks), maintaining all functional cell types (including microglia) and preserving the physiological 3D structure of the CNS, which are fundamental for its function. Our robust and translatable 3D models reduce the risk of failure during the currently mandatory regulatory in vivo testing, allowing to accelerate the stages of early drug discovery (toxicity test, drug sensitivity, etc.) against neurological diseases (Forbes France 2026; Special report on Biotech 2025, Le Figaro).

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Comité scientifique Pro Anima : un hub scientifique pionnier dans le soutien et l'implémentation des NAMs

Jean-Pierre CRAVEDI, Comité scientifique Pro Anima

Auteurs : Courtot L, Cravedi JP, Gougeon E

Dans un contexte de transformation majeure de l'évaluation de la toxicité systémique, porté par l'essor des NAMs (New Approach Methodologies) et des approches NGRA (Next Generation Risk Assessment), le Comité scientifique de Pro Anima favorise le rapprochement entre acteurs académiques, industriels, réglementaires et institutionnels afin d'accélérer le développement et l'acceptation de méthodes prédictives innovantes. Ce poster présente les missions et initiatives du Comité, qui œuvre depuis 1989 à la promotion des NAMs dans le domaine d'évaluation de risques des substances chimiques : veille scientifique, réglementaire et législative internationale, sensibilisation, soutien à l'innovation et diffusion des connaissances. Les actions menées en réseau — notamment via son Conseil scientifique et sa participation au projet PARC — visent à encourager les dialogues, à fédérer et à accompagner les acteurs des secteurs dans l'anticipation des évolutions réglementaires européennes et l'intégration de stratégies prédictives pour l'évaluation des substances et produits finis. Le poster propose également un état des lieux non-exhaustif des outils NAMs, de leur niveau de maturité et leur capacité à contribuer à une évaluation du risque systémique plus prédictive, efficace et éthique.

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An Integrative NAM and PBPK Framework to Characterize Transporter-Mediated Drug-Pollutant Interactions of Synthetic Auxinic Herbicides

David MALNOË, [Université de Rennes](#)

Auteurs : David Malnoë, Clémence Meausoone, Pascal Le Corre, Olivier Fardel

Background: Assessing environmental chemical impacts on drug pharmacokinetics is a major challenge in next-generation risk assessment (NGRA). This study applies an integrative New Approach Methodology (NAM) framework to characterize transporter-mediated drug-pollutant interactions (DPIs) between synthetic auxinic herbicides (SAHs) and human renal OAT1/OAT3. Methods: Functional in vitro screening of 21 SAHs was performed using OAT-overexpressing HEK-293 cells. QSAR and dynamic molecular docking (DynamicBind) explored binding mechanisms. QIVIVE (ICH M12) and population PBPK modeling (PK-Sim®/R/opsuite) simulated interaction profiles with the OAT3 probe baricitinib under regulatory exposure limits to derive Benchmark Doses (BMDL10) and Margins of Exposure (MoE). Results: Six SAHs potently inhibited OAT1/OAT3 (K_i : 0.17–7.7 μ M) possibly through a conserved orthosteric mechanism. ICH M12 assessment indicated plausible in vivo inhibition. PBPK simulations revealed safety concerns for 2,4-DB under acute exposure ($MoE = 0.7$), and fluroxypyr increased baricitinib AUC by 19%, highlighting a tangible DPI risk for exposed populations. Conclusion: This work provides the first modeling proof-of-concept for transporter-mediated DPIs in humans, establishing a robust, mechanistically-informed workflow for incorporating transporter hazards into NGRA.

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Genotoxic assessment of 26 colorants based on experimental data, in silico predictions, and expert judgement.

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Auteurs : K.Zerdali, J.Leghait, P.Jenkinson.

This study addresses the regulatory requirement for acute oral toxicity assessment, which is traditionally performed using animal testing under OECD guidelines (420, 423, 425) for CLP classification purposes. In accordance with the 3Rs principle, a non-animal strategy based on New Approach Methodologies (NAMs) was developed for a UVCB substance. The approach combined in vitro cytotoxicity testing, in silico modelling, and read-across. An in vitro assay following OECD guidance 129 estimated an $LD_{50} \geq 1380$ mg/kg bw, indicating low acute toxicity potential. Chemical characterization by gel permeation chromatography showed that more than 90% of the UVCB consists of constituents with molecular weights between 500 and 2500. These constituents were grouped into five structurally similar families, and representative molecules were selected for modelling. In silico predictions using CATMoS and the OECD QSAR Toolbox consistently indicated LD_{50} values above 2000 mg/kg bw for all representative constituents. A read-across approach using a structurally similar UVCB analogue supported these results, with experimental OECD 423 data also showing $LD_{50} > 2000$ mg/kg bw. Although some minor constituents containing alcohol and acid functionalities were not present in the analogue, additional in silico evidence suggested no acute systemic toxicity concern. The integration of all evidence provided a consistent weight-of-evidence framework. Overall, the results indicate the absence of acute oral toxicity and support no classification under CLP criteria. This study demonstrates the applicability of NAM-based integrated strategies for regulatory hazard assessment of complex UVCB substances without additional animal testing.

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Microfluidic microwell array for parallelized spheroid formation and high-throughput chemo-immunotherapy screening

Anna SCHREIBER, **UPC**

Auteur : Anna Schreiber

Here we present a reusable two-level composite thermoplastic device for colorectal cancer spheroid studies. Micromilling on standard polystyrene forms microwells directly into 6-well plates, while a styrenic block copolymer layer defines the channel network. Each chip contains 600 microwells (200 μm depth/diameter) aligned alongside a serpentine channel (200 μm height) following each array of 60 microwells. The compact design maximizes space efficiency, and the short tunable working distance (~ 750 μm) enables both high-resolution microscopy and high-content screening workflows. Computational fluid dynamics modeling confirmed efficient convective transport, predicting complete filling in 0.3 s and medium renewal in 88 s. Using HCT116 and CT-26 colorectal cancer cell lines, 600 uniform spheroids (~ 150 μm diameter) were reproducibly formed per chip. Fluorescence staining of junction markers confirmed true spheroid formation rather than simple aggregation, and automated imaging of all 600 spheroids was achieved via a home made algorithm. Chip opening further enabled flow cytometry, yielding $\sim 70\%$ viable cells. Our methodology offers a comprehensive therapeutic research platform for screening standard or emerging therapeutic treatments

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Mise en place du modèle alternatif de membrane chorioallantoïdienne pour l'évaluation du potentiel irritant et pro-inflammatoire des NPs

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Notre équipe engage une démarche visant à remplacer, réduire ou raffiner (3R) l'utilisation de modèles animaux dans les études. C'est dans ce contexte que nous développons de NAMs (New alternatives models) pour la caractérisation et l'évaluation des nanoparticules (NPs). En effet, en raison des difficultés des modèles in vitro à prédire les performances des NPs in vivo, les NPs destinées à des applications thérapeutiques n'ont, dans l'ensemble, pas encore atteint leur plein potentiel clinique. L'embryon de poule et la membrane chorio-allantoïdienne (CAM) associée se sont imposés comme un modèle intermédiaire qui pourrait combler le fossé entre l'in vitro et l'in vivo. Ce modèle offre la possibilité d'étudier le comportement des NPs dans des conditions physiologiquement pertinentes tout en restant une méthode rapide, accessible, économique et plus éthique en vue d'une utilisation des NPs in vivo. La CAM, qui entoure l'embryon de poulet pendant son développement est richement vascularisée et les nanovecteurs peuvent être administrés directement sur la CAM permettant d'évaluer leur degré d'irritation et inflammation ou injectés par voie intraveineuse pour évaluer leur toxicité pour l'embryon. Nous menons actuellement l'évaluation du potentiel irritant et pro-inflammatoire des NPs sur le modèle in ovo.

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Relever le défi de l'hépatotoxicité : l'intégration des organes-sur-puce pour une prédiction précoce et robuste

Lucile RABIET, **Servier**

Auteurs : Lucile Rabiet, Aurore Mazurier, Nicolas Couvreur

L'hépatotoxicité demeure un obstacle majeur dans le développement pharmaceutique, entraînant des taux d'attrition élevés. L'émergence des New Approach Methodologies (NAMs) offre des perspectives innovantes pour une prédiction précoce des risques, tirant parti de l'évolution technologique en culture cellulaire et des modèles émergents toujours plus prédictifs. Ces approches sont encouragées par les agences réglementaires, notamment pour leur application aux nouvelles modalités thérapeutiques. Parmi ces avancées, les systèmes organes-sur-puce permettent la culture in vitro prolongée de cellules primaires hépatiques humaines dans un environnement contrôlé, mimant précisément la micro-physiologie du foie. Dans ce poster, nous présentons la caractérisation d'un système d'organe-sur-puce pour une utilisation en sécurité non-clinique ; ainsi que son application pratique à l'évaluation de l'hépatotoxicité d'oligonucléotides antisens (ASOs) retirés du marché. Nos résultats démontrent le potentiel des organes-sur-puce à se positionner comme un pont crucial entre le criblage haut débit et les études in vivo, et optimiser la sélection des candidats médicaments.

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Contextualizing Functional Off-Target Activity: An Imipramine Case Study Using AI-supported interpretation platform

Emilie DESFOSES, Eurofins Cerep

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Secondary pharmacology identifies off-target activities that may contribute to clinical safety liabilities. Their interpretation requires consideration of target biology, translational relevance, and anticipated human exposure. This study evaluated In Vitro Safety Insight (IVSI), an AI-supported platform for contextualizing secondary pharmacology data, using imipramine as a well-documented reference compound. Imipramine hydrochloride was tested in a functional panel covering 77 IQ-DruSafe-recommended targets. Concentration–response data were used to determine AC_{50} values for modulated targets, which were integrated with curated target–adverse event associations to generate Organ System Risk Profiles. Two unbound clinical exposure scenarios were assessed, corresponding to depression treatment and nocturnal enuresis, with and without a 10-fold desired safety margin. The two exposure scenarios produced distinct target- and organ-level risk profiles, while application of the desired safety margin identified additional target activities as potentially relevant and increased scores across several organ systems. By integrating program-specific parameters, IVSI enables secondary pharmacology findings to be weighted and presented within their development context, thereby supporting the anticipation of potential safety liabilities.

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Next Generation Risk Assessment (NGRA) In The Food Industry

Myriam COULET, Société des Produits Nestlé

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Next Generation Risk Assessment (NGRA) In The Food Industry Myriam Coulet¹, Danilo Basili¹, Elena Reale¹, Julie Mollergues¹, Martin Smieško¹, Marion Alriquet¹, Guitard Marjorie¹, Gina Montoya¹ ¹ Société des Produits Nestlé S.A., Nestlé Research, Institute of Food Safety and Analytical Sciences, Department of Food Safety Research - Lausanne, Switzerland New Approach Methodologies (NAMs) are driving the transition toward Next Generation Risk Assessment (NGRA), supporting human-relevant safety assessments while reducing reliance on animal testing. While NAMs are transforming risk assessment in the chemical, cosmetics and pharmaceutical sectors, food safety assessment offers unique opportunities to advance their application by considering food-related compounds, dietary exposure patterns and nutritional context. Building on EFSA and European Commission roadmaps, we developed an integrated framework combining in silico hazard identification, exposure modelling and targeted in vitro hazard characterization. Curated datasets, refined molecular descriptors and applicability-domain considerations were used to improve confidence in predictions for food-relevant compounds. Physiologically based kinetic (PBK) modelling was applied to estimate internal exposure and translate dietary exposure into biologically relevant dose metrics. Where required, targeted in vitro studies can be used for hazard characterization. This framework aims to prioritize biologically relevant effects and support the distinction between adaptive and adverse responses, acknowledging that biological activity is often an inherent characteristic of food compounds and may not necessarily be associated with harm. This approach enables interpretation of in vitro bioactivity data within a weight-of-evidence framework and supports the derivation of biologically relevant thresholds or points of departure. Together, these advances provide a practical and scientifically robust foundation for NAM-based food safety assessments, supporting innovation, regulatory confidence and consumer protection.

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The BioMAP® Platform: A New Approach Methodology (NAM) For Predicting Human Toxicity Liabilities In Vitro

Alastair KING, Eurofins Discovery

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The BioMAP® phenotypic platform enables an unbiased, target-agnostic evaluation of the effects of drugs on human cell biology. The platform uses different primary cell types, stimulated to accurately model a wide variety of tissue and disease states. Endothelial and epithelial cells, fibroblasts, PBMCs, and other cell types are used, often in co-culture, in models or systems that have been qualified using agents where their clinical effects are known. Evaluation of new test agents against twelve such models with the measurement of 148 translationally relevant protein biomarkers generates phenotypic “fingerprint” profiles. Comparison and statistical correlation of new test agent profiles with those previously generated for >4500 other agents allow mechanism of action characterization, efficacy indication, benchmarking with standard of care drugs, and potential toxicity prediction. By comparing profiles of different drugs that share similar clinical adverse effects, biomarker signatures common to acute, liver, organ, and vascular toxicities, immunosuppression, skin irritation, rash, and sensitization, and thrombosis have been defined. Analysis of new drug BioMAP profiles for these toxicity signatures thus provides a robust way of predicting potential toxicity risks in a highly translational human in vitro NAM platform.

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EasyCard™ : une plateforme neuro-cardiaque innervée préclinique et compartimentée pour l'évaluation prédictive de la cardiotoxicité

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Auteurs : Nesrine Benslimane, Elisa Bounasri, Lamia Goual, Maxime Poinso

L'évaluation préclinique de la sécurité cardiaque repose aujourd'hui largement sur le criblage hERG, un test binaire à haute sensibilité et faible spécificité: environ 30 % des composés hERG-positifs sont cliniquement sûrs, tandis que 15 à 30 % des composés hERG-négatifs restent proarythmiques. Cette logique de filtre écarte de bons candidats et laisse passer des risques réels, faute de capturer les mécanismes intégrés, dont les interactions neuro-cardiaques, qui gouvernent le risque proarythmique. Le besoin de nouvelles méthodes prédictives (NAMs) humaines, mécanistiques et alignées sur le cadre réglementaire émergent, est aujourd'hui reconnu pour la sécurité cardiaque. Nous présentons EasyCard™, une NAM neuro-cardiaque associant cardiomyocytes dérivés d'hiPSC et neurones autonomes co-cultivés dans une puce microfluidique compartimentée, avec lecture fonctionnelle (imagerie calcique haute résolution et réseaux de microélectrodes). L'architecture compartimentée sépare fluidiquement le compartiment neuronal du tissu cardiaque : elle permet d'appliquer un candidat médicament sélectivement sur le compartiment choisi et de disséquer les effets directs et neuro-médiés du composé. Elle permet aussi de simuler des sympathetic surges, reproduisant les décharges sympathiques physiologiques et pathologiques qui modulent rythme, conduction et repolarisation. Sur un panel de composés de référence CiPA, la plateforme discrimine les profils à risque faible, intermédiaire et élevé au-delà de la seule logique hERG. Positionnée dans le cadre CiPA et alignée sur la NGRA et la feuille de route européenne de sortie de l'expérimentation animale, EasyCard™ fournit un outil humain de décision Go/No-Go précoce en pharmacologie de sécurité cardiaque.

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Apport d'un modèle de cellules dendritiques in vitro pour l'évaluation du potentiel sensibilisant de mélanges

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Auteurs : Z. Salmon, S. Jacquenet, A. Coiscaud, J. Mathiot, S. Muller, M. Mourof, S. Kerdine-Römer et F. Battais

Contexte : En milieu professionnel, de nombreux salariés peuvent être exposés à diverses substances chimiques ou biologiques, de manière simultanée ou séquentielle. Ces polyexpositions peuvent être à l'origine d'allergies professionnelles et ainsi altérer la santé des salariés. Dans ce contexte, un modèle in vitro de cellules dendritiques dérivées de la moelle osseuse (BMDC) a été développé dans notre laboratoire pour évaluer le potentiel sensibilisant des substances chimiques. L'objectif de cette étude est d'évaluer la pertinence du modèle BMDC pour l'évaluation du potentiel sensibilisant d'allergènes chimiques et protéiques, testés individuellement ou en mélanges binaires. Méthodes : Les BMDC ont été exposées à quatre substances : le chlorure de benzalkonium (BC), la N-(3-aminopropyl)-N-dodécylpropane-1,3-diamine (NNDD), la bêta-lactoglobuline bovine (BLG) et l'ovalbumine d'œuf (OVA), seuls ou en mélanges binaires. L'activation des DC a été évaluée par cytométrie en flux et l'expression des gènes de voies de signalisation d'intérêt (Nrf2, NF- κ B et p38 MAPK) par RT-qPCR. Résultats : Individuellement, toutes les substances induisent une augmentation concentration-dépendante de l'expression des marqueurs de surface. En co-exposition, les combinaisons de fortes concentrations entraînent 1/une expression des marqueurs membranaires significativement supérieure à celle des substances seules et 2/une tendance à la hausse de l'expression de certains gènes des voies Nrf2, NF- κ B et p38 MAPK comparativement aux substances seules. Conclusion : Le modèle BMDC semble être un outil sensible et pertinent pour évaluer le potentiel sensibilisant de substances chimiques ou biologiques, qu'elles soient testées seules ou en mélanges.

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DENDRITIC CELL-BASED IN VITRO APPROACH FOR IMMUNOTOXICITY SCREENING OF SYNTHETIC AMORPHOUS SILICA NANOMATERIALS

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Synthetic amorphous silica nanomaterials (SAS-NMs) are widely used in consumer and industrial applications, yet some have been reported to induce pro-inflammatory and adjuvant-like responses. This study aimed to identify physicochemical determinants of SAS-NM immunotoxicity and contribute to the development of New Approach Methodologies (NAMs) for nanosafety assessment. Six SAS-NMs with distinct surface properties were characterized and evaluated in human monocyte-derived dendritic cells (moDCs) and THP-1 cells. Cytotoxicity, activation markers, and cytokine/chemokine release were assessed by flow cytometry and Meso Scale Discovery multiplex assays. Functional consequences were further investigated by measuring CD4⁺ T-cell proliferation following co-culture with SAS-NM-primed moDCs. SAS-NMs displaying the highest surface reactivity induced the strongest phenotypic and inflammatory responses, whereas thermal treatment reducing surface silanol density attenuated DC activation. THP-1 responses were broadly consistent with those observed in primary moDCs. Moreover, a strongly DC-activating SAS-NM enhanced subsequent CD4⁺ T-cell proliferation. Overall, these results highlight the importance of surface properties in SAS-NM immunotoxicity and support DC-based approaches and THP-1 cells as complementary tools for immunotoxicity screening and safer-by-design strategies.

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Predicting ADC-induced hematotoxicity using in vitro safety data and quantitative systems toxicology

Davy GUIGNARD, Pierre Fabre Pharma - R&D center

Auteurs : Davy GUIGNARD, Omar HASSANI, Aurélie PETAIN, Isabelle SARTORI, Laurence DEL FRARI, Yannick AUSSAGUES, Fatima Ezzahra EL FADLE, Mark PRATT, Petra VINKEN, Ben-Fillippo KRIPPENDORFF, Guy BOUVIER

Hematotoxicity is a major dose-limiting toxicity of antibody-drug conjugates (ADCs), whose safety assessment still relies heavily on non-human primates (NHPs). To support the reduction of animal use, we developed a quantitative systems toxicology (QST) model to mechanistically predict human hematotoxicity. The approach was applied to two ADCs directed against different targets and carrying distinct but structurally related payloads. Neither target is expressed on hematopoietic progenitor cells. ADC1 is approved, whereas ADC2 is in development. Using pharmacokinetic and hematology data from NHPs and humans treated with ADC1, a QST model was established to describe the dynamics of reticulocytes, erythrocytes, neutrophils and platelets. Following calibration with ADC1, the model was used to predict ADC2-induced hematotoxicity in NHPs and humans at pharmacologically active doses. Both ADCs were assumed to share similar pharmacokinetic properties, while differing in cytotoxic potency according to IC50 values derived from in vitro colony-forming unit assays. This translational framework enabled prediction of ADC2 hematotoxicity using only in vitro potency data, supporting early human safety assessment while reducing reliance on animal studies.

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Multi-organ toxplate (motp) and incucyte live-cell imaging for high-throughput toxicity assessment in human kidney, intestinal, and liver models

Christian PELLEVOISIN, MatTek Now Part of Sartorius, Ashland, Massachusetts, and 2 Sartorius Stedim North America, Inc, Ann Arbor, Michigan

Auteurs : Seyoum Ayehunie, Joeseeph Finelli, Martha Mayo, Paul Keselman, Karetski Viktor, Pellevoisin Christian and Alexander Armento

Advanced primary cell-based 3D human tissue models are key components of New Approach Methodologies (NAMs) and provide an alternative to animal testing for hazard and risk assessment. We developed a 3D human Multi-Organ ToxPlate (MOTP) integrating small intestine, liver, and kidney human tissue models within a 96 well format compatible with the IncuCyte® for high-throughput imaging and automated live-cell analysis. This configuration enables simultaneous dose-range finding across three organ systems, reducing variability, timelines, and cost while providing real-time imaging with automated EC50 calculations. By combining IncuCyte® analytics with TEER, MTT, and histological endpoints, the workflow delivers comprehensive in vitro information on pharmacokinetics, pharmacodynamics, and toxicity and supports early detection of off-target effects. Cells representing liver, kidney, and intestine were seeded into a 96 well ToxPlate (32 wells per organ), cultured submerged for 1–3 days, then maintained at an air–liquid interface for 12 days. The workflow was first validated on a single-organ 3D kidney plate treated with Cisplatin (nephrotoxicant) and Oxaliplatin (non-toxicant), with cell death monitored using IncuCyte® Cytotox Green. The platform was then extended to a MOTP incorporating intestine, liver, and kidney tissues, imaged every 4 hours for 48 hours in an IncuCyte® S3; global mean green fluorescence was quantified, and non-invasive imaging enabled subsequent TEER, MTT, and histological analyses. Cisplatin induced a dose-dependent decrease in TEER in the kidney model, and IncuCyte®-derived EC50 values ranging from 11 to 25 μM were consistent with reported manual measurements, whereas Oxaliplatin did not cause acute kidney injury at tested concentrations. In the MOTP, Cisplatin was toxic to all three tissue models at higher doses, Fialuridine produced selective hepatotoxicity, and Troglitazone was toxic to liver and kidney with variable intestinal effects. A 48 hour, seven-dose range-finding study on kidney–intestinal ToxPlates showed clear dose-dependent reductions in TEER and MTT for Cisplatin, while Oxaliplatin did not elicit an MTT dose–response but reduced TEER, indicating TEER as a more sensitive endpoint. Overall, the integrated MOTP–IncuCyte® workflow provides a robust, economical trio-tox platform that accelerates in vitro toxicity prediction, enhances physiological relevance, and supports identification of organ-specific and off-target effects.

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Aerosol Application for Prediction of Respiratory Toxicity using a Human Airway Model

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Auteurs : Jo Wallace¹, Mary McElroy¹, Blane Stobbs¹, Anna Marshall¹, James Baily¹, Rossana Boni¹, Christian Pellevoisin², Viktor Karetski², Mitch Klausner², Seyoum Ayehunie²

Traditional in vivo inhalation toxicology studies are costly, require large numbers of animals, and often fail to translate effectively to human outcomes due to anatomical and physiological disparities between animal and human respiratory systems. Consequently, there is growing interest in human-relevant in vitro models for assessing inhalation toxicity. Human lung organotypic cultures are currently being used to assess direct toxicity of inhaled chemicals in a case-by-case basis. However, the absence of an OECD guideline limits their broader regulatory adoption. Establishing such a guideline would provide a standardized framework and promote regulatory acceptance of these models. The objective of this project is to develop an in vitro inhalation toxicity screening protocol for risk-based decision making. We show that an EpiAirway™ protocol has the potential to allow prediction of human hazard classifications for acute inhalation risk by applying chemicals directly to the epithelial surface at the air liquid interface in solution or suspension. We also re-evaluate a subset of chemicals using aerosol exposure to determine whether the mode of application influences the resulting toxicity profiles.

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Hepatotoxic Mechanisms by Drug-Induced Cholestasis and Reactive Metabolites in Human Hepatocyte Co-Culture System

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Hepatotoxicity is a critical concern in drug development because the liver is the primary organ responsible for drug metabolism and detoxification. Drug-induced cholestasis (DIC) represents a major subtype of drug-induced liver injury (DILI) that arises when compounds disrupt bile acid synthesis, uptake, or efflux in hepatocytes. This leads to bile acid accumulation and liver injury. Early detection of cholestatic potential is essential, as DIC is often species-specific and not reliably predicted by conventional animal models. Reactive drug metabolites are unstable intermediates formed during xenobiotic biotransformation, primarily mediated by hepatic cytochrome P450 (CYP) enzymes. These metabolites can covalently bind to cellular macromolecules such as proteins, lipids, and DNA, causing oxidative stress, mitochondrial dysfunction, and immune-mediated hepatocellular injury. Traditional liver toxicity assessments relying on animal models and isolated liver tissues have limitations including high cost, low throughput, interspecies variability, ethical concerns, and limited predictivity for human outcomes. We previously developed an advanced hepatocyte co-culture system that maintains long-term viability (>4 weeks) and stable metabolic function. These models (human, dog, and rat) were validated with 29 reference compounds, demonstrating dose-dependent hepatotoxicity, species-specific responses, and improved sensitivity (83-92%) compared to hepatocyte monocultures (50%). In the present study, we utilized the human hepatocyte co-culture system to evaluate compounds associated with DIC and determine the effect of reactive metabolites on hepatotoxicity.

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Mechanistic investigation of the immunotoxicity of synthetic amorphous silica nanomaterials using new approach methodologies

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Allergies represent a major public health challenge and could affect over half of the global population by 2050. Among environmental risk factors, synthetic amorphous silica nanomaterials (SAS-NMs), widely used in food and pharmaceutical products, remain insufficiently investigated. Recent studies suggest that SAS-NMs can activate dendritic cells and potentially exacerbate allergic responses, although the underlying early mechanisms remain poorly understood. This work aims to characterize the immunotoxic effects of SAS-NMs by identifying early key events and molecular initiating events using in vitro models aligned with New Approach Methodologies (NAMs). Human dendritic cells and THP-1 cells are used to investigate membrane perturbations and signaling pathway activation. These approaches are complemented by biomimetic membrane models, including GUVs and GPMVs, to assess direct nanomaterial–membrane interactions. Preliminary results show that SAS-NMs rapidly induce plasma membrane reorganization, including lipid raft formation, and activate Src- and Syk-dependent signaling pathways, supporting a membrane-driven activation mechanism. SEM observations also revealed morphological alterations and nanomaterial aggregates at the THP-1 cell surface. GUV and GPMV models have been optimized to further investigate these interactions.

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Hepoid®: une plateforme hépatique humaine 3D de sphéroïdes proliférants et hautement différenciés pour explorer toxicologie et physiopathologie

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Le foie est un organe clé de l'homéostasie de l'organisme, assurant des fonctions métaboliques essentielles ainsi que la biotransformation et la détoxification des xénobiotiques. La complexité de ces processus et leur étroite dépendance à l'espèce et au contexte physiologique soulignent la nécessité de développer des modèles humains in vitro capables de reproduire avec une haute-fidélité les fonctions, l'architecture et les réponses biologiques du foie in vivo. Hepoid® est un modèle innovant d'hépatocytes humains en 3D (primaires ou HepaRG) seuls ou en cocultures (cellules étoilées, cellules endothéliales, cellules immunitaires) reposant sur une culture cellulaire dans des matrices aux forces de tension bien définies. Hepoid® se caractérise par la formation de nombreux sphéroïdes de petite taille, creux et polarisés. Les hépatocytes sont capables, pendant plusieurs semaines, de proliférer et de maintenir un phénotype ainsi hautement différencié eu égard aux capacités métaboliques du foie. Les propriétés des sphéroïdes Hepoid® leur confèrent des avantages pour de nombreuses applications relatives à 1) la sécurité de composés (toxicité aiguë et chronique ; DILI ; génotoxicité et mutagenèse ; apoptose), 2) les fonctions hépatiques incluant le métabolisme des xénobiotiques (expression des ARNm et activités enzymatiques des enzymes de phase I, II et III), la sécrétion d'albumine et d'urée et 3) la modélisation de pathologies telles que la stéatose hépatique, la fibrose et la cholestase. Grâce à sa haute pertinence physiologique, le modèle Hepoid® s'impose comme une plateforme robuste et prédictive pour améliorer la transposabilité des études précliniques, de l'évaluation de l'efficacité et de la sécurité des médicaments à la caractérisation des risques liés aux contaminants chimiques environnementaux et tous produits chimiques.

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Metabolomics analysis of human keratinocyte response to chemical sensitizers

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Allergic contact dermatitis (ACD) is a common skin disease caused by drugs and environmental chemicals acting as “chemical sensitizers”. Keratinocytes (KCs), the main component of the epidermal barrier, play a crucial role in initiating and developing inflammatory responses by releasing proinflammatory cytokines into the skin microenvironment. In this study, we investigated the impact of three chemical sensitizers - hydroxycitronellal (HC), cinnamaldehyde (CINA), and methylisothiazolinone (MIT) - on the metabolome of human primary KCs using a mass spectrometry-based metabolomics approach. A total of 181 endogenous metabolites were annotated with high or medium confidence levels (1 or 3 according to Sumner et al., 2007) after data processing and feature annotation using an in-house spectral database. Significant metabolic changes were observed in sensitizer-treated cells, showing time-, sensitizer-, and concentration-dependent variations. Although the three chemical sensitizers induced distinct modifications in the abundance of various intracellular metabolites, several key metabolic pathways were commonly affected across all treatments. These findings provide a strong foundation for further investigations into the role of metabolic remodeling in the inflammatory response of KCs to chemical sensitizers and may help to better understand the link between chemical reactivity and sensitizing potency for the development of new tools in skin sensitization testing.

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Assessment of EGFR inhibitors cytotoxicity in human intestinal organoids

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Background: Gastrointestinal (GI) toxicity of EGFR tyrosine kinase inhibitors is associated with inhibition of wild-type EGFR in the intestinal epithelium. Ranking of EGFR inhibitors for GI toxicity can be a decision criterion during drug development. Objective: Compare the epithelial safety profile of several EGFR Tyrosine Kinase inhibitors, including the approved EGFR TKIs afatinib and osimertinib using human iPSC-derived intestinal organoids (HIOs). Methods: HIOs were treated with two EGFR inhibitors structurally related, osimertinib or afatinib at clinically relevant exposure levels to assess cytotoxicity, Forskolin Induced Swelling (FIS) and cytokine profiling. Cytotoxicity was assessed in a static and dynamic (mimicking QD and BID regimens) condition. Results: Two structurally related EGFR inhibitors showed differentiated cytotoxicity profiles in human intestinal organoids when benchmarked against approved EGFR TKIs. Overall, cytotoxic effects appeared more closely associated with overall exposure than dosing schedule, while additional functional and cytokine readouts showed variability and should be interpreted with caution. Conclusion: This essay allows to distinguish EGFR inhibitors with an improved epithelial tolerability profile compared to afatinib and a profile comparable to osimertinib. HIOs provided a human-relevant model to characterize GI safety and may inform clinical development and dosing strategies.

Posters 25

Rat and Hamster Liver S9 Metabolic Activation: Comparative Performance in Miniaturized vs. Petri Dish-Based Bacterial Reverse Mutation Assays

Csaba BOGLÁRI, **Xenometrix AG**

Auteurs : Csaba Boglári, Cécile Koelbert

Phenobarbital- β -Naphthoflavone-induced rat and hamster liver S9 fractions are widely used for metabolic activation in bacterial mutagenicity testing, yet their performance can vary depending on assay format. This study compares rat and hamster S9 preparations in the Ames MPF, a miniaturized, 384-well fluctuation-based assay against the conventional Petri dish-based Ames test, using a panel of *Salmonella typhimurium* and *E. coli* tester strains. Reference mutagens requiring metabolic activation were evaluated across both platforms to assess sensitivity, mutagenic response magnitude, and reproducibility. Distinct S9-dependent differences emerged: the rat liver S9 showed altered dose-response profiles and shifted potency for several compounds relative to hamster liver S9, reflecting differences in metabolizing capability of the different microsomal fractions. Strain-specific differences were also apparent, with certain tester strains showing divergent sensitivity depending on the microsomal fraction applied. These findings highlight that S9 species selection and assay format are interdependent variables affecting genotoxicity outcomes, with practical implications for assay design, interpretation, and regulatory testing strategies relying on metabolic activation systems.

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Mitochondria-enriched extracellular vesicle signatures as biomarkers of PAH-induced toxicity: towards a NAM-based approach

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Polycyclic aromatic hydrocarbons (PAH) are persistent environmental contaminants associated with mitochondrial dysfunction and systemic toxicity. In the context of NAMs and NGRA, human-relevant tools providing mechanistic and predictive information are needed. We investigated whether mitochondria-enriched extracellular vesicles (Mito-EV) released by endothelial cells could provide biomarkers of PAH-induced stress and contribute to the assessment of systemic toxicity. Human microvascular endothelial cells (HMEC-1) were exposed to benzo[a]pyrene, a 4-PAH regulatory mixture, or an 18-PAH mixture representative of human dietary exposure. EVs were isolated, fractionated by density-gradient centrifugation, and characterized using complementary biophysical, molecular and multi-omics approaches. All PAH exposures increased total EV and Mito-EV release, with the strongest response induced by the 18-PAH mixture. PAH exposure also altered Mito-EV mitochondrial content, including mitochondrial proteins, lipids and mtDNA, and generated distinct Raman signatures. EV surface interaction profiles further discriminated exposure conditions. Overall, PAH-induced changes in Mito-EVs provide mechanistic signatures of exposure and cellular stress, highlighting their potential as candidate biomarkers to support NAM-based predictive assessment of systemic toxicity.

Flash Poster

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Implementation and Validation of the In Vitro Comet Assay on Human Lymphocytes with Future Perspectives on Hepatocyte Models

Corina CUCEU-PETRENCI, **GenEvolutionN**

Auteurs : Corina Cuceu-Petrenci, Gautier Decock

Le test des comètes permet de détecter les dommages primaires à l'ADN sur lymphocytes humains (PBMC). Cette étude visait à implémenter et valider ce protocole au sein du laboratoire, en utilisant des composés de référence positifs (MMS, EMS, BaP, cyclophosphamide) et négatif (DMSO), à plusieurs concentrations, avec et sans activation métabolique S9. La lecture automatisée par le système Metafer a permis une quantification standardisée du %Tail DNA, éliminant les biais de sélection manuelle. Les résultats montrent une augmentation dose-dépendante du %Tail DNA pour l'ensemble des composés positifs testés, avec un dommage à l'ADN atteignant 4 à 5 fois le niveau du témoin négatif pour le MMS à 25 µg/mL. La reproductibilité de l'essai a été confirmée sur trois expériences indépendantes. Ce travail établit une méthode fiable pour les évaluations futures de toxicité. Les perspectives incluent l'extension du protocole aux modèles hépatocytaires (HepG2 2D et 3D), afin de proposer un outil de criblage génotoxicologique plus pertinent sur le plan physiologique pour les applications industrielles.

Posters 29

Smarter Safety Testing: Miniaturized Ames Assays and Mechanistic FISH-Complemented In Vitro Micronucleus Assay as NAMs for Nitrosamine Genotoxicity Evaluation

Corina CUCEU-PETRENCI, **GenEvolutionN**

Auteurs : Csaba Boglári, Cécile Koelbert, Joana Raposo, Corina Cuceu Petrenci

La détection des impuretés génotoxiques dans les produits pharmaceutiques et industriels requiert des méthodes d'évaluation robustes, notamment pour les nitrosamines dont le potentiel mutagène est évalué via l'Enhanced Ames Test (EAT) recommandé par la FDA et l'EMA. Cette étude compare deux versions miniaturisées du test d'Ames (MicroAmes6 sur plaque 6 puits et Ames MPF en microplaque de fluctuation) avec les souches TA100, TA1535 et E. coli uvrA[pKM101], en présence de S9 hépatique de hamster, sur quatre nitrosamines (NDMA, NDEA, NDEthA, EIPNA). Un test du micronoyau in vitro avec sondes FISH télomère/centromère a également été réalisé pour déterminer le mode d'action (clastogène vs aneugène) de la NDMA. Les résultats des tests d'Ames miniaturisés sont concordants avec les données historiques obtenues en boîtes de Petri, tout en nécessitant moins de ressources (S9, plastique, déchets). Le test du micronoyau avec FISH apporte une réponse rapide (3h) sur le mode d'action génotoxique. Ces travaux renforcent la boîte à outils NAMs pour l'évaluation de la sécurité des nitrosamines dans les industries pharmaceutique et chimique.

Posters 30

Interest of the Micronucleus test on Reconstructed Skin and skin organoids for cosmetic products

Corina CUCEU-PETRENCI, **GENEVOLUTION**

Auteurs : Corina Cuceu Petrenci, Joana Raposo, Theo Lacour, Isabelle Mouche

Le test du micronoyau sur peau reconstruite (RSMN), utilisant le modèle EpiDerm, permet de détecter les dommages à l'ADN dans des conditions mimant une exposition réaliste, particulièrement pertinentes pour l'évaluation du risque génotoxique des produits cosmétiques et des médicaments topiques/transdermiques. Début 2025, l'ESAC a conclu à la validité scientifique de la méthode RSMN. Cette étude a exploré l'intégration d'un marquage FISH télomère/centromère afin de distinguer les effets clastogènes (Mitomycine C) des effets aneugènes (Vinblastine), confirmés aux temps de traitement 48h et 72h. Les résultats démontrent que ce marquage complémentaire permet une discrimination fiable du mode d'action génotoxique directement sur le modèle 3D de peau reconstruite. Le RSMN constitue ainsi un outil de seconde intention pertinent en stratégie de test par paliers, conforme aux principes des New Approach Methodologies (NAMs) et aux exigences du règlement cosmétique européen, réduisant le risque de classifications de danger trop conservatrices. Les perspectives évoquent l'intégration de technologies d'organoïdes multicellulaires (épiderme, derme, follicules pileux, neurones, adipocytes) pour des évaluations plus dynamiques et individualisées du risque génotoxique.



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NAMs & NGRA pour
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