NGTX - 21st Century Toxicology for Next Generation Tobacco and Nicotine Products (NGPs) Task Force 2020 Report

CORESTA Congress Online

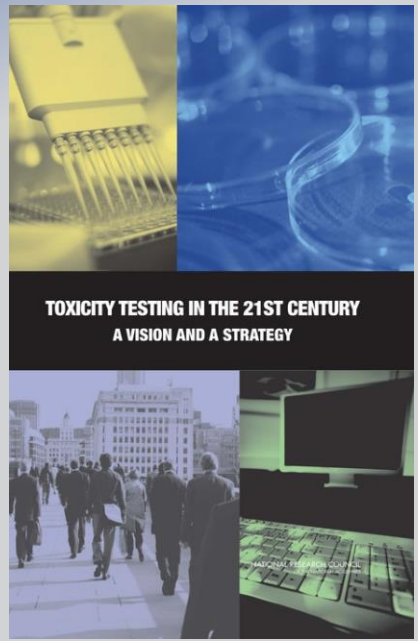
October 2020

Background

- Advances in molecular biology, biotechnology, and human tissue modelling are paving the way for major improvements in how scientists evaluate the health risks of novel consumer products
- These advances are making it increasingly possible to study the effects using cells, cellular components and tissues- preferably of human origin
- Current routine test methods were developed over 50+ years ago and some studies employ the use of laboratory animals.
  - High dose exposures
  - Apical endpoints, no consideration of mechanism
  - *In vivo* studies require extrapolation to human exposure
  - Uncertainty factors to translate and account for species difference
  - Expensive, time consuming, sometimes raises ethical issues

Ongoing innovation in cellular and molecular biology have facilitated a paradigm shift in toxicology testing away from the traditional heavy reliance on low-throughput animal data towards the greater use of medium- and high-throughput *in vitro* cellular screening approaches

New technologies can transform classical approaches



A framework for change: Toxicity Testing in the 21st Century (TT21C)

Applying 21C science and technology to transform human health risk - better understanding cellular and molecular effects levels (toxicity pathways)

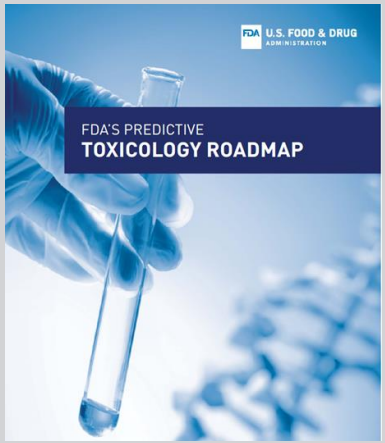
- Significant research investment from US, EU gov authorities - to underpin future regulatory changes for risk management; establishment of consortia

"envisions a new toxicity-testing system that evaluates biologically significant perturbations in key toxicity pathways by using new methods in computational biology and a comprehensive array of in vitro tests based on human biology"

21st century integration research

In line with US EPA, US FDA, EU-JRC and OECD Strategic Plans

- Last 10 years- developing/ exploring new scientific capabilities (computational toxicology, dosimetry, *in vitro*, 'omics,)
- Next 10 years- integration and application of new capabilities: AOP framework, bioinformatics, predictive modelling
- **Broader coverage of chemicals and endpoints, reduce cost and time of testing, use fewer animals**



Scope and Objectives of NGTX TF

To review, assess, apply and harmonize 21st century toxicology approaches to tobacco and nicotine products, including but not limited to screening approaches, AOP development, organs on a chip and systems biology to support quantitative risk assessment.

- To review emerging technologies and application to NGP testing- review document to be prepared (NWIP#221)
- To identify appropriate approaches and application of emerging technologies to NGP testing (Dec 2020)
- To provide guidance documents to support assay application for NGP testing using TT21C relevant assays (dates TBC, but an ongoing activity)

- January 2019 NWIP #199 21st Century Toxicology for NGP approved by CORESTA Scientific Commission
- March 2019 (London, England): Inaugural NGTX TF meeting
- October 2019 (Hamburg, Germany): 2nd NGTX TF meeting
- May 6th 2020, Belfast, hosted by Celerion - CANCELLED
- Autumn 2020 - virtual meetings - TBC

NGTX workshop, SSPT 2019 Hamburg

NGTX WORKSHOP		Chair: KEI YOSHINO (JT)	
16:00	NGTX TF	Report	Marianna Gaca (BAT)
16:20	STW01	The application of in vitro Toxicity Testing in 21 Century (TT21C) for Next Generation Products	Liam Simms (Imperial Brands)/ Edgar Trelles- Sticken (Reemtsma Cigarettenfabriken GmbH)
16:40	STW02	Contemporary high-content screening approaches to assess the biological impact of single compounds and complex mixtures in vitro	David Thorne (BAT)/Stefan Frentzel (PMI)
17:00	STW03	Organotypic in vitro models for assessment of biological impact	Shigeaki Ito (JT)
17:20	STW04	Multi-organ-on-a-chip platforms to assess the biological impact of toxicants as well as PBPK properties in vitro	Stefan Frentzel (PMI)
17:40		Discussion	

NWIP #221 'Report and Publication on 21st Century Toxicology for Next Generation Tobacco and Nicotine Products (NGPs)

- A review document outlining the emerging 21st century *in vitro* toxicology tools and their potential application for tobacco and nicotine product testing.
- Monica Lee (Altria), David Thorne (BAT), Marianna Gaca (BAT), Hitoshi Fujimoto (JT), Liam Simms (Imperial), Stefan Frentzel (PMI), Damian McHugh (PMI), Edgar Trelles- Sticken (Reemtsma Cigarettenfabriken GmbH), Gaddamanugu Prasad (RAI), Sarah Moses (Swedish Match)

  - CORESTA Technical report (CTR) (Dec 2020/ Jan 2021)
  - External Publication (CXP) (Q1 2021)

As the review will be quite comprehensive, it can provide content for NGTX webpage and also abstracts for future toxicology conferences

NWIP #221 'Report and Publication on 21st Century Toxicology for Next Generation Tobacco and Nicotine Products (NGPs)

- Introduction to Tox 21, 3Rs and high throughput approaches
- NGPs including oral products and lack of reference products
- Regulations and standards including CRM and HCI, oral standards
- Test articles (TPM, WA etc)
- Techniques available – Tox 21 programme
- Model systems, techniques that have been used for NGPs
- Challenges? Repeat dosing vs. acute exposure

Next steps (1)

- **Which approaches to take forward (practical)?**
  - **Use and application of high content screening**
    - Common test systems (cells),
    - common endpoints (cell health, oxidative stress, DNA damage),
    - applied to tobacco and nicotine products

Liam Simms (Imperial Brands)

Hitoshi Fujimoto (JT)

Stefan Frentzel (PMI)

David Thorne (BAT)

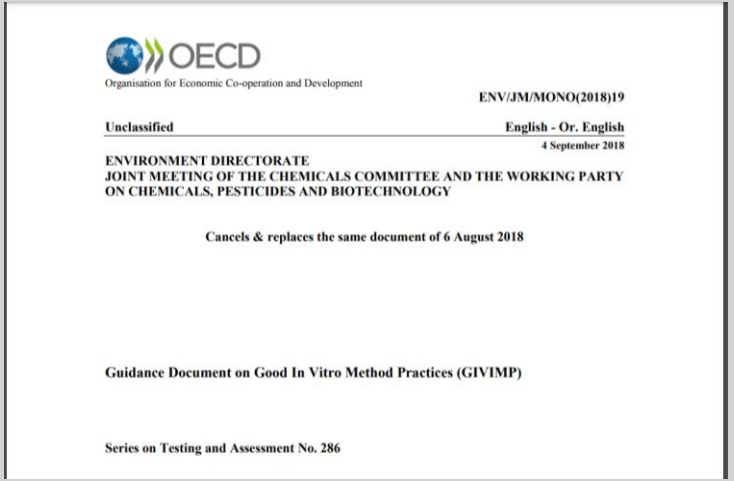
Next steps (2)

- **Guidance documents (theoretical)?**
  - **Recommendations**
    - Guidance Document on Good In Vitro Method Practices (GIVIMP)

    http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO%282018%2919&doclanguage=en

Tobias Krebs (Vitrocell)
Leon Stankowski (CRL)
David Thorne (BAT)
Elisabeth Weber (JTI Oekolab)
Michael Hollings (Covance)

Stefan Frentzel (PMI)
Hitoshi Fujimoto (JT)
Monica Lee (Altria)
Kubilay Demir (JUUL)
Damien McHugh (PMI)
Marianna Gaca (BAT)


OECD
Organisation for Economic Co-operation and Development

ENV/JM/MONO(2018)19

Unclassified — English - Or. English

4 September 2018

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Cancels & replaces the same document of 6 August 2018

Guidance Document on Good In Vitro Method Practices (GIVIMP)

Series on Testing and Assessment No. 286

Example of a publication- similar publications can be achieved in NGTX

An interlaboratory *in vitro* aerosol exposure system reference study

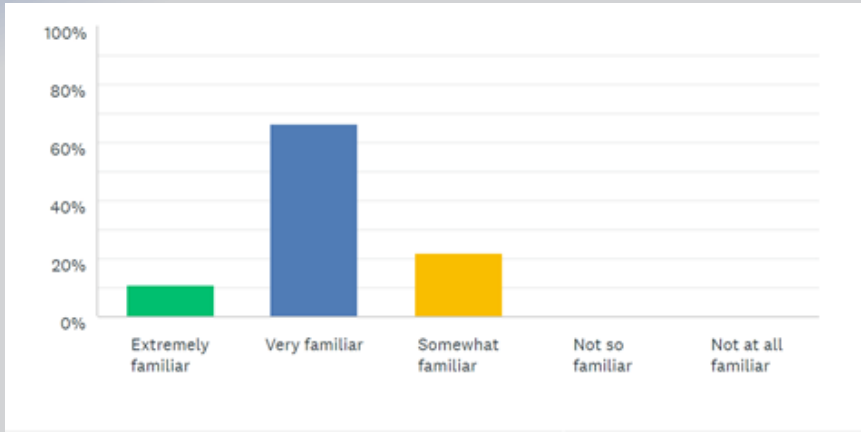
David Thorne[1]*, Jason Adamson[1], Edgar Trelles Sticken[2], Roman Wieczorek[2], Holger Behrsing[3], Sandro Steiner[4], Shoaib Majeed[4], Stefan Frentzel[4], Shinkichi Ishikawa[5], Shigeaki Ito[5], Liam Simms[2], Kei Yoshino[5], Julia Hoeng[4], Marianna Gaca[1]

[1] British American Tobacco, R&D, Southampton, Hampshire SO15 8TL, UK
[2] Imperial Brands, 121 Winterstoke Road, Bristol, BS3 2LL, UK
[3] Respiratory Toxicology, Institute for In Vitro Sciences, Inc., Gaithersburg, Maryland
[4] Philip Morris International R&D, Philip Morris Products S.A. (Part of Philip Morris International Group of Companies), Neuchatel, Switzerland
[5] Scientific Product Assessment Center, R&D Group, Japan Tobacco Inc., 6-2 Umegaoka, Aoba-ku, Yokohama, Kanagawa, 227-8512, Japan

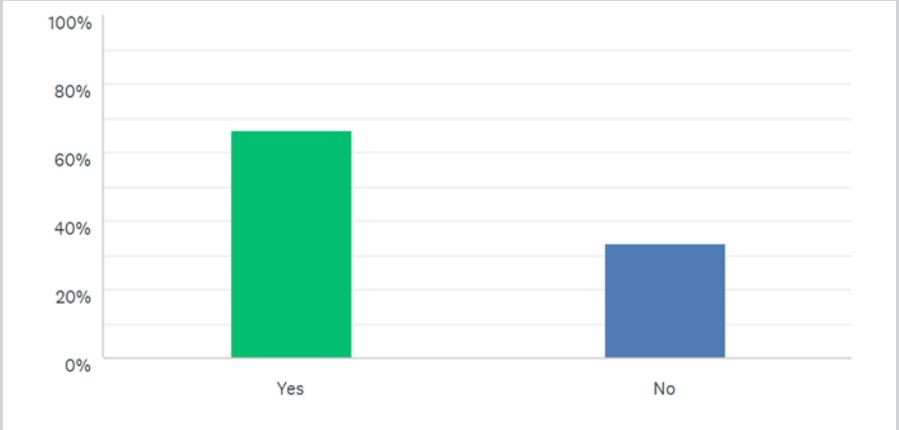
IN REVIEW

Survey of NGTX TF members

Q1. What is you understanding of 21st Century Toxicology



Q2. Are you currently using 21st Century Toxicology approaches for in vitro assessment



Survey of NGTX TF members

Q2. Are you currently using 21st Century Toxicology approaches for *in vitro* assessment?

Q3 What approaches?

Q4 Why?

Survey of NGTX TF members

Q5/Q6. What topics do you see as 'in scope'/ 'out of scope' for NGTX TF?

In scope
In vitro exposure systems
Dosimetry
Systems toxicology
High content screening
AOP
Organ on a chip
Non- regulatory toxicology assays
Reference products
Review of new assays
TOX 21 initiatives- alternative method roadmaps

Out of scope
Specialised assays, not used universally
Standard reg tox assays (IVTSG)
Device technology
Chemical analysis
Ringtrials (regulatory toxicology)

Survey of NGTX TF members

Q7. What topics should be addressed in future by NGTX TF?

1. Standardisation of *in vitro* whole aerosol exposure
2. Alignment of current methods
3. Reference products for NGPs
4. Standardisation of high content screening
5. Screening technologies for whole aerosols
6. Translation of data to human exposures
7. Dosimetry
8. New TOX 21 assays
9. Oral models (absorption, permeation)
10. Regulatory acceptance
11. AOPs
12. Adaptation of models for CROs

Summary

- **NWIP #221* – CORESTA Technical report (CTR) (Dec 2020/ Jan 2021)**
  External Publication (CXP) (Q1 2021)
- **Develop plan to share HCS data/ experiences and alignment a 'standardized' approach***
- **'Review' of OECD Guidance Document on Good In Vitro Method Practices (GIVIMP)***
- **Autumn 2020- virtual meetings- TBC**

***To review timelines and content at Autumn meeting**

Thank You