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OECD Test Guidelines - Novel Developments and Perspectives from the UK

Miriam Jacobs

IGHRC/RSC
27 February 2019

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Overview of talk

1. **Intro and remit of OECD TGP**
2. **Overview of bottlenecks in the review/acceptance process**
3. Likely forthcoming validation work/TGs for approval on the OECD workplan: e.g.'s Genotoxicity; endocrine disruption
4. Growth of IATA development and applications: e.g. Non Genotox Carcinogen IATA work; Defined approaches (for skin sensitisation)
5. **New issues: Ethics in use of human serum/reagents in *in vitro* TGs** and IP guidance

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Relevance of the OECD Chemical Test Guideline Programme to society: **missions**

- To promote policies that will improve the economic and social well-being of people around the world.
- To provide a forum where governments can work together to share experiences and seek solutions to common problems.

The OECD chemicals test guideline programme (TGP) agrees harmonised validated methods and **frameworks to assess the safety of chemicals, enables the Mutual Acceptance of Data (MAD), avoiding duplicative testing across all OECD member countries.**

Aims:

- **To improve the predictive capacity of regulatory tests that are intended to protect public and environmental health from chemical harm**
- **To minimise the use of animals and develop alternative non-animal tests**
- **To incorporate new technologies**

The TGs are used in regulatory safety testing and subsequent chemical notification and registration. Also UN GHS.

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OECD
BETTER POLICIES FOR BETTER LIVES

Relevance to UK and global Public Health

Working within the OECD the chemical safety programme improves the quality of chemical safety assessment used to protect public health in the UK and internationally.

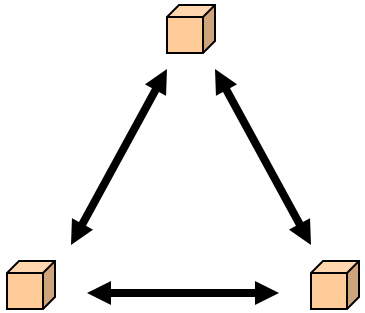
- **Prevention strategy: proactive front-end public health protection by <u>preventing</u> harmful chemicals coming onto the market**
- **Reduced animal use**
- **Supports innovation and green chemistry**
- **Economic benefit to UK industry**

Who drives OECD work?

Council

Oversight and strategic direction

Representatives of member countries and of the European Commission; decisions taken by consensus



Committees

Discussion and implementation

Representatives of member countries and countries with Observer status work with the OECD Secretariat on specific issues

Secretariat

Analysis and proposals

Secretary-General

Deputy Secretaries-General

Directorates

Annual budget 2017 : 374 million euros

Funded by 36 member countries + EC

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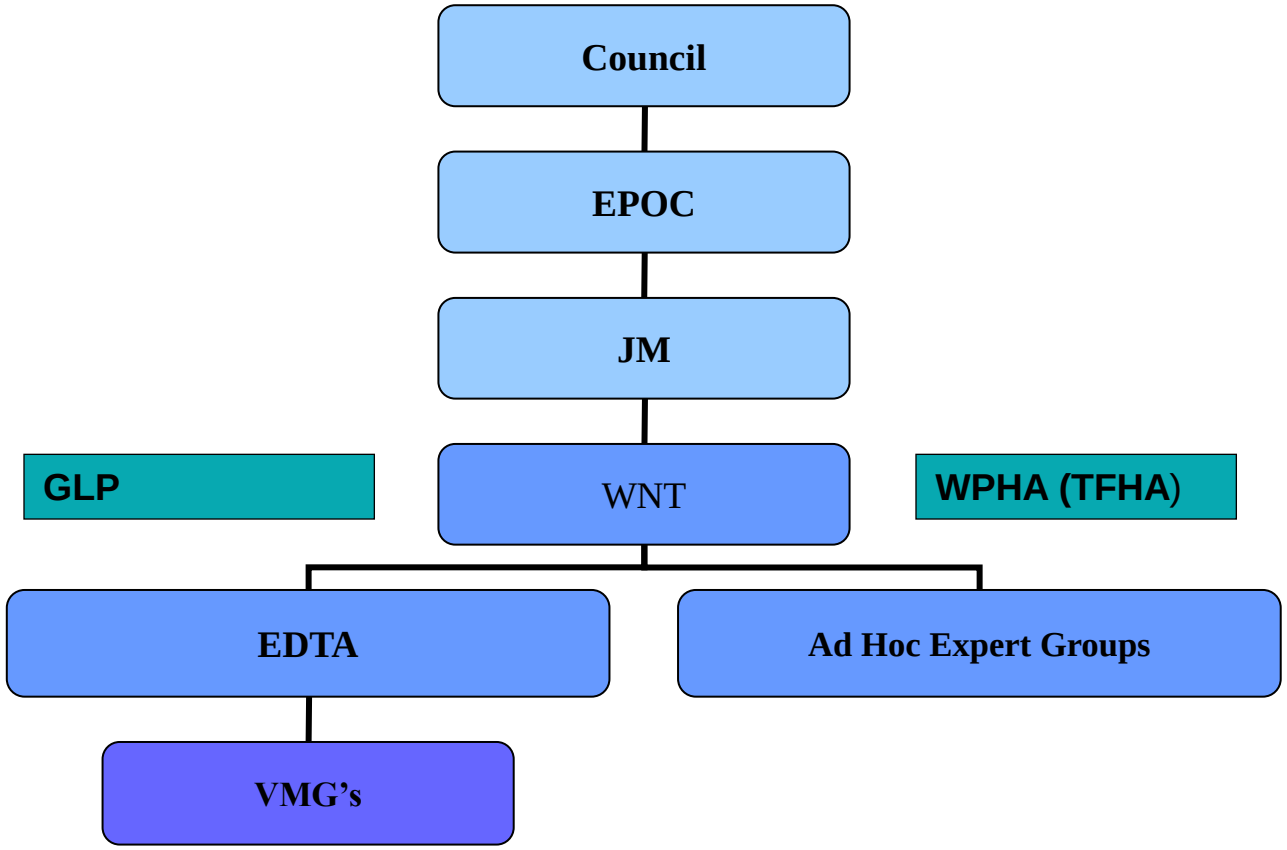
OECD Decision layers



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OECD Test Guideline Programme

Established 1981 (ENV DIR/EHS DIV)

MAIN TASK: Develop and revise Test Guidelines for the testing of chemicals for human health and the environment:

Mandate: Working Group of the National Coordinators to the TGP

MAD: Mutual Acceptance of Data

Original publication in 1981: 51 TG's

Today: 100+ new or updated Guidelines

At presently 80+ projects in the work-plan

- Special activities: EDTA (VMG repro tox , eco and non-animal)
- AOP and IATA, IATA for skin sensitisation, underway: NGTXC, DNT
- Defined Approaches TGs; Issues: IP, ethics and human serum

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TG development process

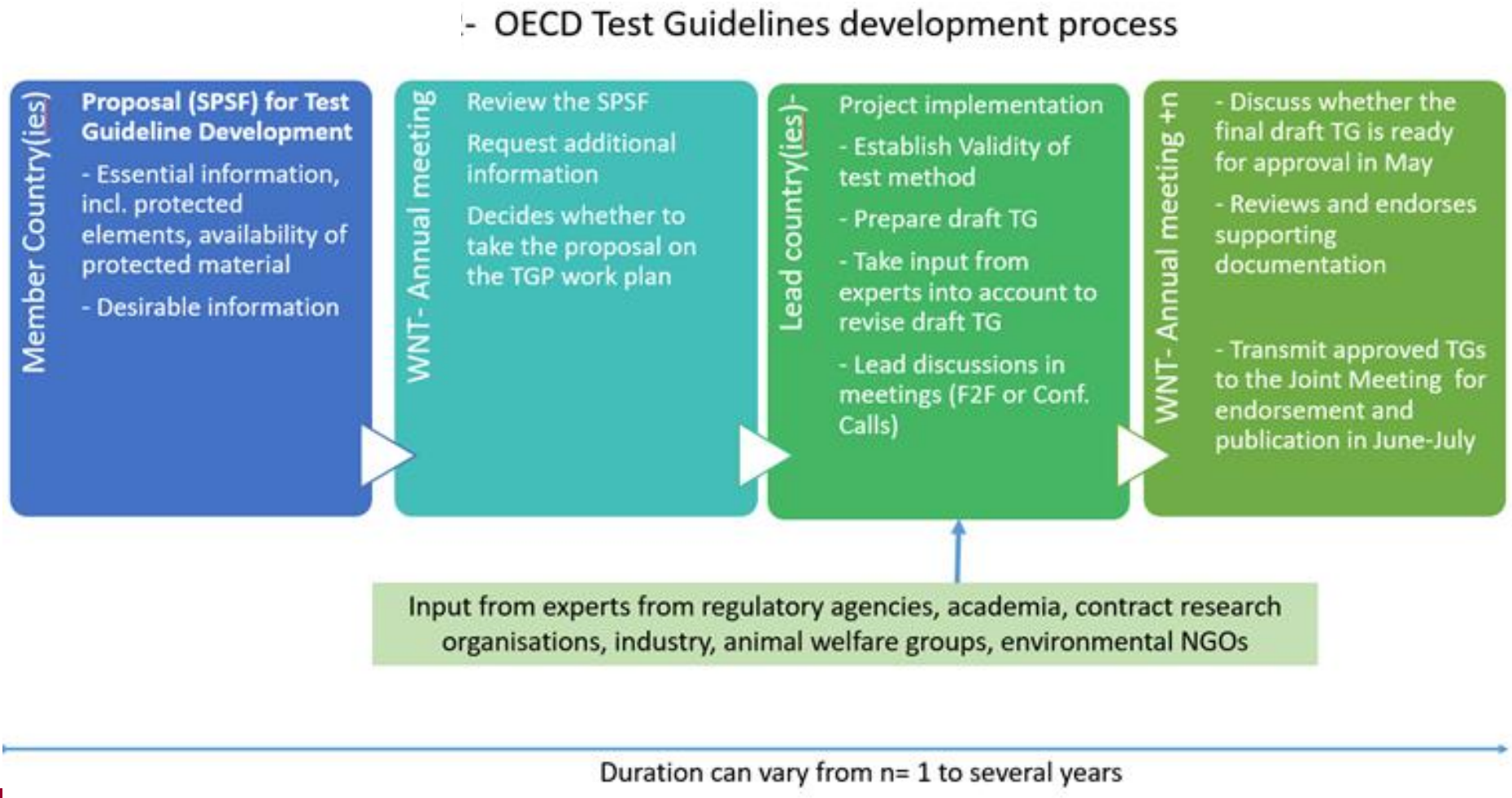

Figure taken from an early version of the OECD draft IP guidance 2018

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3. Likely forthcoming validation work/TGs for approval on the OECD workplan of interest: egs Genotoxicity: Toxtracker, mini Ames; endocrine disruption: performance based TG for androgen receptor agonism/antagonism
4. Growth of IATA development and applications: e.g. non genotox carcinogen IATA work; Defined approaches for skin sensitisation
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Common stumbling blocks in the OECD TGP process

- Material supporting the performance/validity of the test is not attached or of poor quality e.g. CTA
  - Statistical evaluations, scientific references, validation reports, peer review reports, etc.
  - Lack of adherence to validation criteria outlined in GD No.34
  - A poorly written draft Test Guideline
- A poorly defined/or changed regulatory purpose of the TG
- Low level of commitment by the lead country/ staff change
- Need for Expert Consultation or DRP
- Management of expert groups: Lack of briefing of (new) review experts by NCs e.g. TG 433
- Not addressing a key endpoint gap/Lack of lead countries coming forward to address OECD identified gap
- Conflicts of regulatory needs…
- Science - Cultural differences

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Expert group and evidence management: Refinement *in vivo* acute inhalation studies through the use of 'evident toxicity' as an endpoint: of the Fixed Concentration Procedure: TG 433 (2017)

Objective: To identify 'evident toxicity' and use it to predict severe toxicity

Societal impact: To reduce the number of animals used in *in vivo* TG inhalation studies, and to reduce the animal suffering, introduce more humane endpoints than 'death'.

Evidence background: Retrospective analysis of industry data, work led by UK (NC3Rs +NC).

Issues at OECD: Multiple data analyses conducted and published, but repeatedly NOT accepted by some OECD members. After **9 years** with lack of agreement, in 2016 WNT proposed to DROP the project entirely.

Actions to resolve the problems: **UK** assured OECD that all outstanding issues would be addressed and carefully managed to achieve consensus. Project given one more chance…otherwise deletion in 2017.

- UK NC coordinated with Secretariat to advise other NCs how to steer their experts and avoid tangential commenting
- Approp. selection of comments to be addressed, where further work was necessary, and how to explain this diplomatically; Appropriate briefings for the expert group and for the OECD, management of **off point comments**
- UK NC chaired all subsequent expert group TCs: additional data analysis/descriptive work conducted consensually agreed: all issues resolved
- **Turnaround: Successful adoption of April 2017 meeting!**

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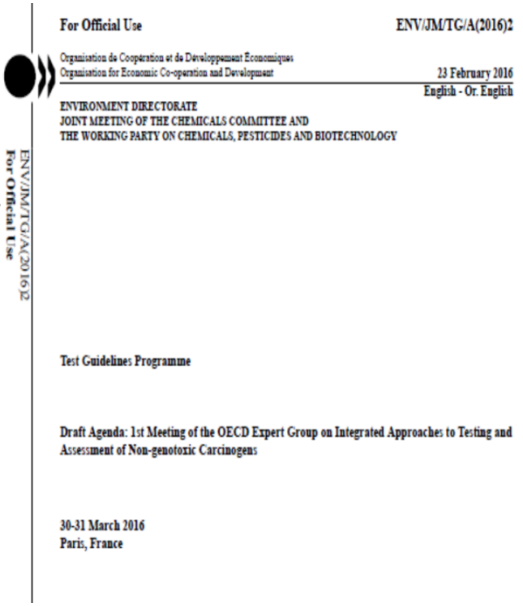
Failure of CTA as a TG: **solution:** OECD expert group: Integrated Approach to Testing and Assessment (IATA) for non-genotoxic carcinogenic chemicals


For Official Use ENV/JM/TG/A(2016)2

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development 23 February 2016
English - Or. English

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

ENV/JM/TG/A(2016)2
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Test Guidelines Programme

Draft Agenda: 1st Meeting of the OECD Expert Group on Integrated Approaches to Testing and Assessment of Non-genotoxic Carcinogens

30-31 March 2016
Paris, France

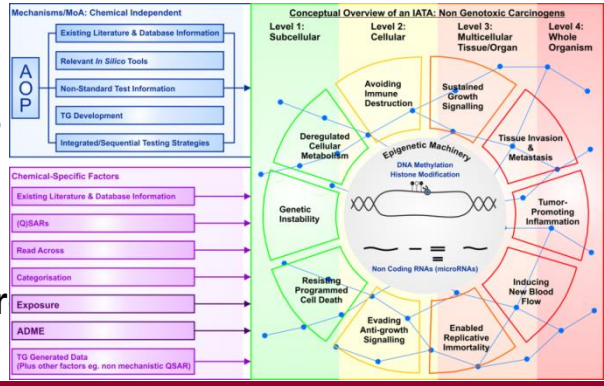
OECD meeting 2014: The only *in vitro* relevant NGTXC assay: Cell Transformation Assay FAILED to get approval as a TG.

No consensus on next steps.

UK led work within the group to achieve consensus on the way forward to develop an IATA for NGTXC. Publication (2016) and presentation to OECD: OECD basis for formation of expert group

Non genotoxic carcinogens contribute to an increased cancer risk by a variety of mechanisms, that are not yet included in international regulatory approaches.

To address this need, an IATA for non genotoxic carcinogens (NGTXC) is being developed at international governmental level.



Societal impact: Front end public health protection: Working towards impr hazard assessment of (potential) chemical carcinogens

So far 5 peer reviewed publications, another about to be submitted. Assay data base created and being further developed, 2 chapters of the guidance document drafted.

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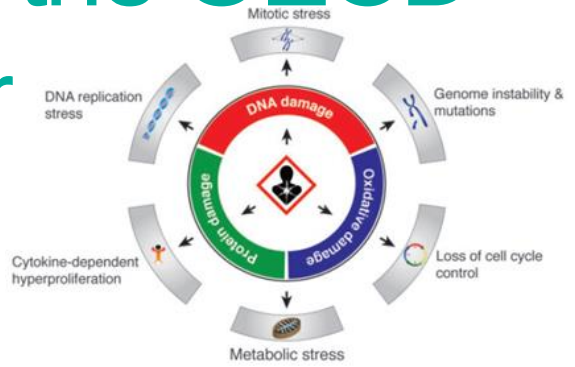
Genotox projects on the OECD workplan: Toxtracker



Stem cell-based reporter assay is an in vitro genotoxicity assay that can provide insight into the mechanism of genotoxicity.

Discriminates between induction of DNA damage, oxidative stress and protein damage.

Combination of these different MOA in a single assay, can be used in the NGTX IATA.

Mini-ames:

Recent call for data

Comparative analyses ongoing

Next meeting July 2019

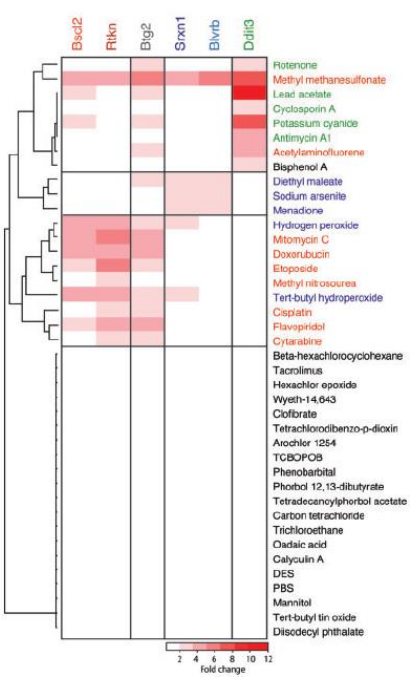


TABLE 1. Sensitivity and Specificity of the Conventional and ToxTracker *in vitro* Genotoxicity Tests

	Sensitivity (%)	Specificity (%)
Ames test[a]	46[b]	81
In vitro micronucleus test[a]	96	47
Chromosome aberration test[a]	94	50
ToxTracker assay	95	94

[a]Data obtained from Kirkland *et al.* (2008, 2011, 2014).
[b]Sensitivity increases to 62% when microtubule disrupting compounds were omitted from the calculations.

VMG-NA: Endocrine disruptor *in vitro* TGs

Thyroid:

EURL ECVAM: initiating validation of thyroid assays

based upon OECD thyroid scoping Doc 2014

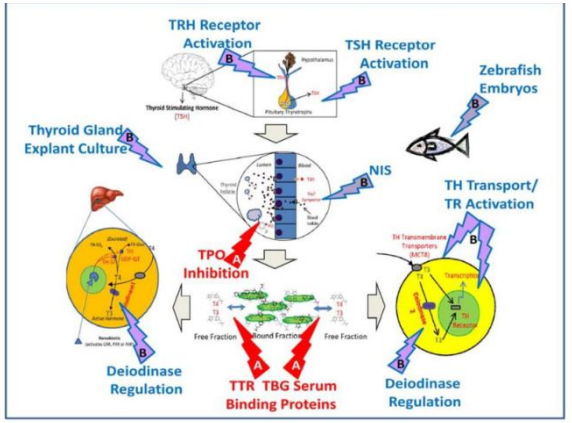
XETA assay: TG approval April 2019?

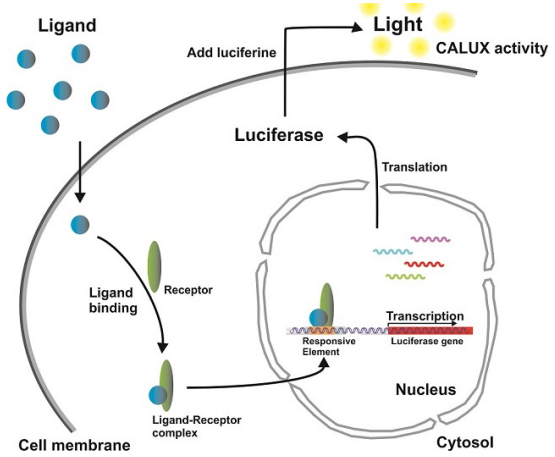
Androgen ag/antag TG 458 performance based TG (PBTG) update in 2020?

‘**Me-too’ assays**: ARTA: AR-CALUX and Korean TA validation completed 2018: peer review in summer 2019

AR-CALUX cells: Human osteosarcoma cell line U2-OS Stably transfected with cDNA for human AR Androgen responsive reporter gene (3 x ARE TATA luc)

22Rv1/MMTV_GR-KO AR TA human prostate cancer cell line, i.e. 22Rv1 endogenously expressed stably transfected with the pGL4-MMTV-Luc/Hygro plasmid, with glucocorticoid receptor knocked out by CRISPR-Cas9 system.





Figures from OECD 2014 and BDS

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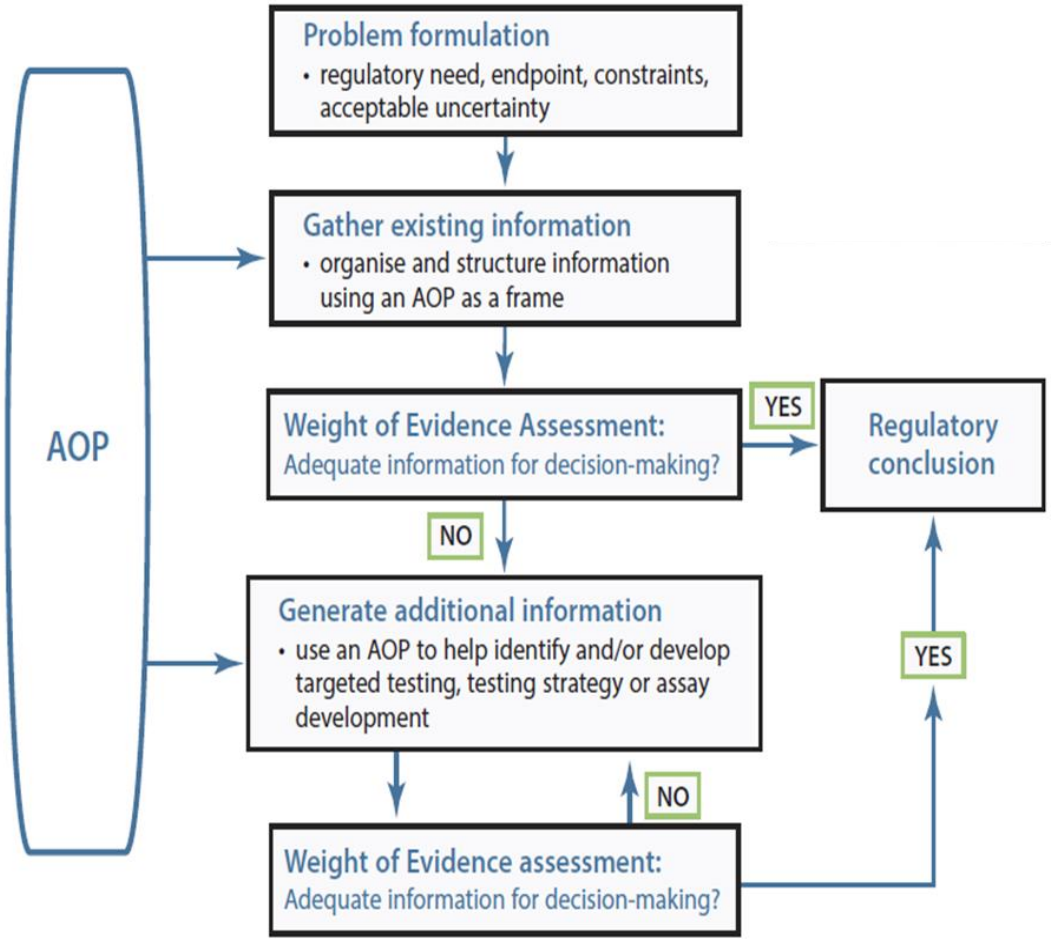
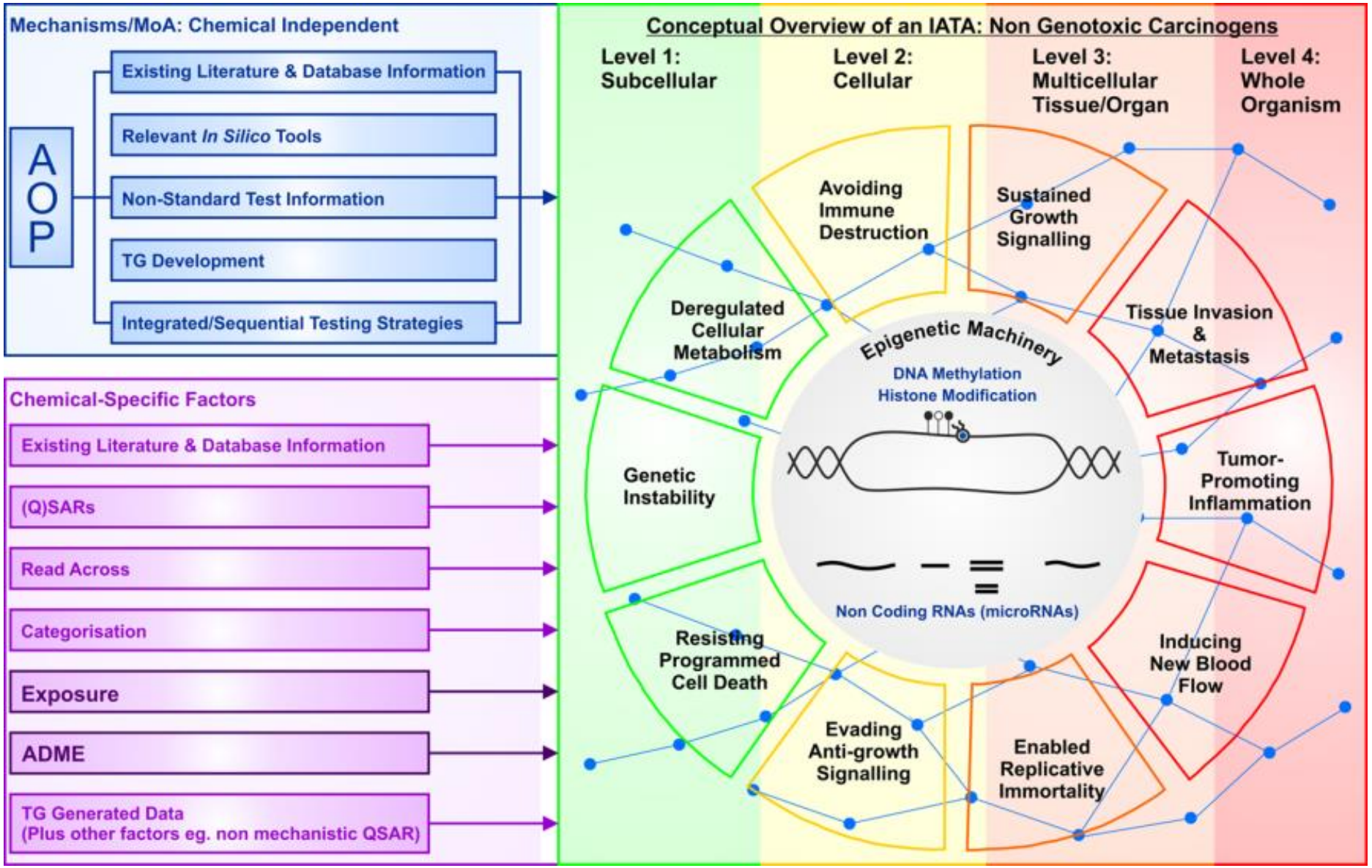
Integrated Approaches to Testing and Assessment (IATA)

An IATA integrates & weights all relevant existing evidence & guides targeted generation of new data where required to inform regulatory decisions



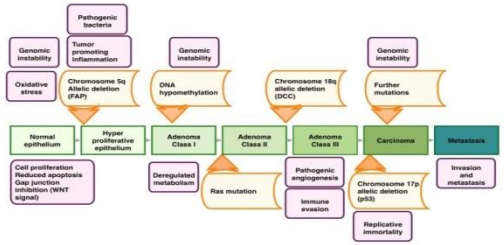
NGTXC IATA Conceptual overview

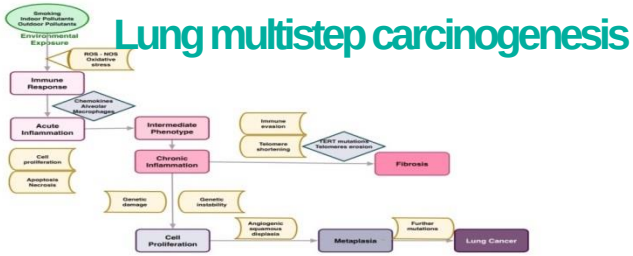


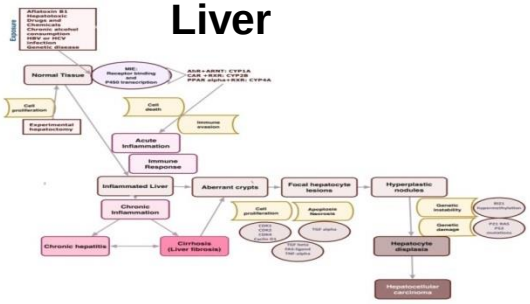
Development of an IATA backbone

- ✓Begin at a more basic level by developing a **general** IATA
- ✓**Assessment of commonalities and differences between cancer models** for NGTxC aspects
- ✓Subsequently move towards a **comprehensive** IATA

Colon multistep carcinogenesis



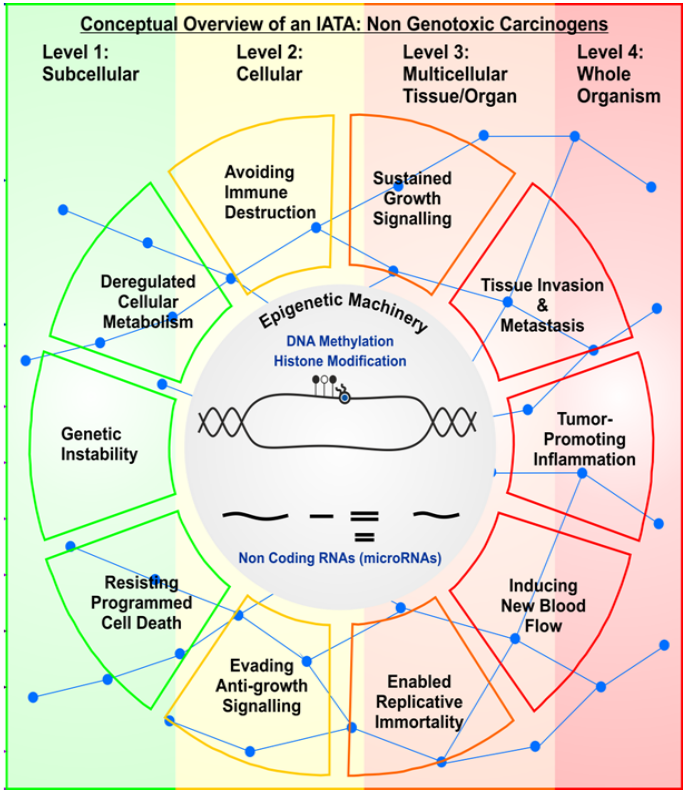




Jacobs et al ALTEX 2016

Roadmap IATA NGTXC

1. Establishment of remit of expert group, and scope of work programme (2016)
2. Nomination of international scientific experts to cover all endpoints identified so far in Table (2016)
3. Global regulatory approaches for NGTXC
4. Conceptual overview of IATA and cancer models
5. Uncertainty analysis of RCB
6. **Assessment of assays' appropriateness & readiness to enter the TGP**
7. **Preliminary IATA**
8. Application of uncertainty analysis and weight of evidence to refine IATA & development of decision trees
9. Case study testing of IATA
10. OECD consultation workshops
11. Final guidance document for WNT approval rounds



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Why use human serum?

- ***Fetal calf serum (FCS)*** *most commonly used for the maintenance and growth of cells in in vitro cell culture used in many of the in vitro* TGs.
- **Animal welfare**, FCS documented to be of particular concern due to manner in which sourced, and pain it causes the animal

(van der Valk *et al.,* 2017 and refs therein, More et al 2017, and contested by slaughter and serum industry).

- **Animal welfare concerns** ➔cosmetics industry (2) to encourage modification of existing skin sensitisation *in vitro* TGs to use human reagents to achieve **xeno-free culture or human-based culture conditions instead of animal based reagents, including human serum.**
- Human based sources: **human serum, human platelet lysate (hPL) and human serum albumin (HSA)**
  - added benefit of being completely human relevant,
  - But concerns i) the **ethics in obtaining the serum from human donors**, and ii) the **potential for there to be a limited number of suppliers**, with respect to OECD *in vitro* TG applications.

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What are the ethical needs and concerns with use and sourcing of human serum ?

1. **Health-related aspects of the donation procedure: tissue screening**
2. **Permission from the donor for commercial use**
3. **Payment of the donors and the potential for exploitation of low income populations**
4. **Supply /availability/competition with clinical needs**
5. **Data protection of the donors**
6. **Traceability**

OECD workshop 18-19 March 2019

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Human serum supply: Europe

Standardised approach to informed consent.

France: e.g.s of collection as part of medical waste,

Sweden, and Austria: products are generated from out of date blood donations.

Germany: collection centres exists in Germany, for which one consent form, which is known to comply to the European standard, states about the donated blood: "*its components are used in the context of patient care; in* ***rare cases the blood or the components are used for standardization purposes as well as for quality control or for research and development projects***."

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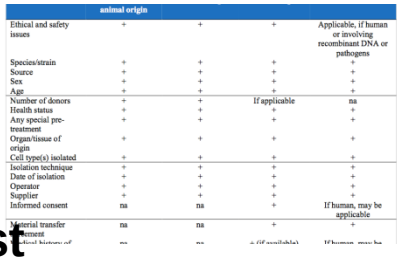
Annex to TG: Development of Ethical check list for TGs using human serum

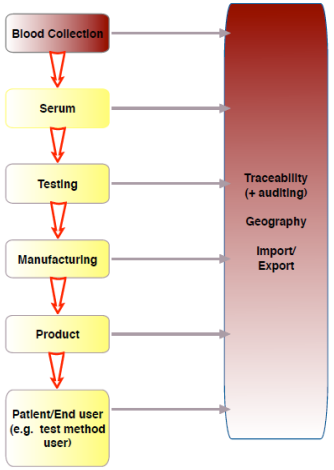


	animal origin			
Ethical and safety issues	+	+	+	Applicable, if human or involving recombinant DNA or pathogens
Species/strain	+	+	+	+
Source	+	+	+	+
Sex	+	+	+	+
Age	+	+	+	+
Number of donors	+	+	If applicable	na
Health status	+	+	+	+
Any special pre-treatment	+	+	+	+
Organ/tissue of origin	+	+	+	+
Cell type(s) isolated	+	+	+	+
Isolation technique	+	+	+	+
Date of isolation	+	+	+	+
Operator	+	+	+	+
Supplier	+	+	+	+
Informed consent	na	na	+	If human, may be applicable
Material transfer agreement	na	na	+	+
Legal history of	na	na	+ (if available)	If human, may be

All use of human serum in this TG needs to include evidence of ethical considerations focusing on sourcing of the human blood derived products such as serum, to be included with test report

Failure to adequately and satisfactorily address and meet the criteria will result in non acceptance (non compliance) of the test method results

- ✓ Demonstrated membership of traceability audit scheme
- ✓ Provision of certificate of origin of human serum specifying:
  - ✓Donor permission freely given
  - ✓Any compensation received by the donor (e.g. payment)
  - ✓Source (i.e. preference: out of date blood product/ medical waste not fresh, that has been sourced primarily for medical needs)



Jacobs, M., Versteegen, R., Treasure, C. and Murray, J. 2019. Addressing potential ethical issues regarding the supply of human-derived products or reagents in in vitro OECD Test Guidelines. *ALTEX - Alternatives to animal experimentation*. (Feb. 2019). DOI:https://doi.org/10.14573/altex.1901281.

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Thank you for your attention !
Contact: Miriam.Jacobs@phe.gov.uk

Acknowledgments:

TG 433: NC3Rs

TG 402: Tina Mehta (when at Dow)

NGTXC IATA expert group: a unique

OECD expert group paving the way for

C21st globally harmonised carcinogenicity

hazard assessment

OECD WNT

Ethics and human reagents/serum: ISIA Rosie Versteegen, Jenny Murray, Carol Treasure XCellR8

OECD secretariat