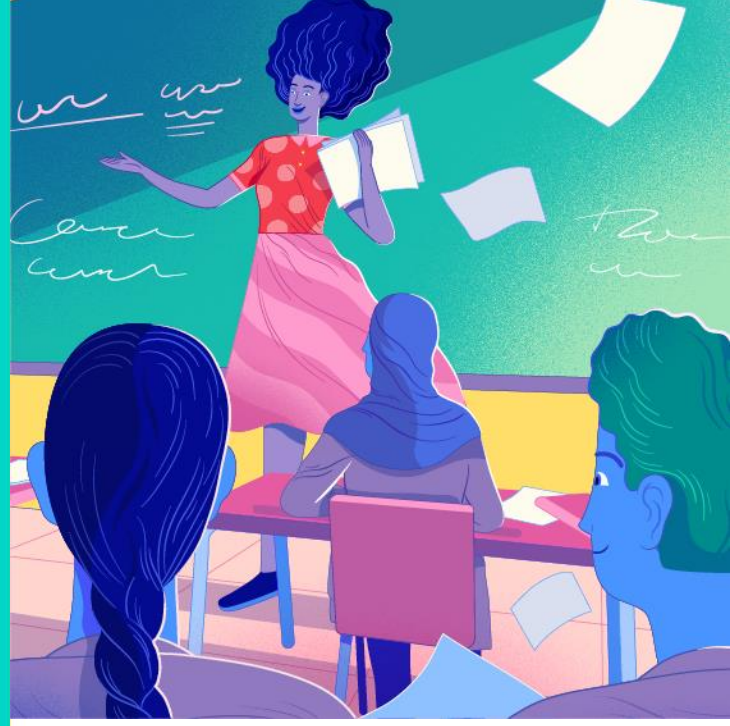
Scientific workshop on non-animal approaches for chemical safety in China: Current Progress and Outlook



Jin Li, Sandy Li, Paul Carmichael, Jie-Bing Zhu, Carl Westmoreland, Shuangqing Peng, Jiabin Guo, Chao Liu, Weidong Hao, Ping Xu, Feng Xu, Jingbo Pi, Shengnan Liu, Wei Sun, Yuan Pang, Aiqian Zhang, Rong Kuang, Lei Wen, Ying Yang, Erin Hill, Quanshun Zhang, Yongbo Lu, Jianhua Qin, Zhongyu Li, Xiaowei Zhang

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Changing world - towards non-animal approaches

Political: Regulations

Increasing regulatory restrictions on marketing ingredients that have been tested on animals

Social: Consumers/NGOs

Millennials demand cruelty free cosmetics

Low trust in safety of chemicals, foods & new innovations may cause rise in animal testing

Technology: 21st Safety Science

New technologies & scientific knowledge are transforming how we assess chemical safety

Unilever

Significant changes in Safety and Cosmetics

2021 in China

1st May: New regulation for the placing of cosmetic products on the market came into force in China. The Cosmetic Supervision and Administration Regulation (CSAR) now allows “general-use cosmetics” to be imported into China without the need for pre-market animal testing of those products

1. A safety assessment must be submitted for the cosmetic product to confirm the safety of product.

2. The manufacturer provides an official production qualification management certificate (e.g GMP or ISO) issued by competent authority in the country of origin.

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Recognition of NGRA in cosmetic safety assessment

Computational Toxicology 7 (2018) 20–26

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Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox

Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients

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Keywords:
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Cosmetics risk assessment

ABSTRACT

Consumer safety is a prerequisite for any cosmetic product. Worldwide, there is an ever-increasing desire to bring safe products to market without animal testing, which requires a new approach to consumer safety. 'Next Generation Risk Assessment' (NGRA), defined as an exposure-led, hypothesis driven risk assessment approach that integrates *in silico*, *in chemico* and *in vitro* approaches, provides such an opportunity. The customized nature of each NGRA means that the development of a prescriptive list of tests to assure safety is not possible, or appropriate. The International Cooperation on Cosmetics Regulation (ICCR) therefore tasked a group of scientists from regulatory authorities and the Cosmetic industry to agree on and outline the principles for incorporating these new approaches into risk assessments for cosmetic ingredients. This ICCR group determined the overall goals of NGRA (to be human-relevant, exposure-led, hypothesis-driven and designed to prevent harm); how an NGRA should be conducted (using a tiered and iterative approach, following an appropriate literature search and evaluation of the available data, and using robust and relevant methods and strategies); and how the assessment should be documented (transparent and explicit about the logic of the approach and sources of uncertainty). Those working on the risk assessment of cosmetics have a unique opportunity to lead progress in the application of novel approaches, and cosmetic risk assessors are encouraged to consider these key principles

SCCS/1628/21

Scientific Committee on Consumer Safety

SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION 11TH REVISION

Scientific Committees on Consumer Safety and on Health, Environmental and Emerging Risks

The SCCS adopted this guidance document at its plenary meeting on 30-31 March 2021

3-4 RELEVANT TOXICOLOGICAL TOOLS FOR THE SAFETY EVALUATION OF COSMETIC INGREDIENTS

The SCCS has been closely following the progress made with regard to the development and validation of alternative methods and updated its NoG on a regular basis taking progress into consideration.

Besides validated alternatives, the SCCS may also accept, on a case-by-case basis, methods that are scientifically valid as new tools (*e.g.*, "-omics" technology) for the safety evaluation of cosmetic substances. Such valid methods may not have necessarily gone through the complete validation process, but the Committee may consider them acceptable when there is a sufficient amount of experimental data proving relevance and reliability and including positive and negative controls.

According to the Cosmetics Regulation, the experimental studies have to be carried out in accordance with the principles of Good Laboratory Practice (GLP)laid down in Council Directive 87/18/EEC. All possible deviations from this set of rules should be explained and scientifically justified (SCCNFP/0633/02).

3-4.1 NEW APPROACH METHODOLOGY (NAM) AND NEXT-GENERATION RISK ASSESSMENT (NGRA)

Whereas the terminology of "Alternative Test Methods (ATMs)" does not cover all available tools *e.g.*, *in silico* methodology, the more general term, New Approach Methodology (NAM) has been introduced. As for cosmetics and their ingredients, testing and marketing bans apply with respect to animal use and also the obligation exists to only use validated replacement alternatives, the need for validated non-animal alternative methods for chemical hazard assessment is much more important in Europe for compliance with the Cosmetics Regulation than for other regulatory frameworks. NAMs may include *in vitro*, *ex vivo*, *in chemico and in silico* methods, read-across, as well as combinations thereof. Therefore, before any testing is carried out for safety evaluation, all information on the substance under consideration should be gathered from different available means. A set of criteria, universal across initiatives, to evaluate NAMs fit-for-purpose was developed by a multi-stakeholder group and may support greater consistency across different initiatives (Parish *et al.*, 2020).

Many efforts are ongoing to modernise toxicological safety evaluation and to look for non-animal methodology that can be used for the risk assessment of compounds that after long-term exposure could be at the origin of systemic toxicity. One of these approaches is referred to as NGRA (USEPA, 2014). The principles underpinning the application of an NGRA to cosmetics have been defined by the International Cooperation on Cosmetics Regulation (ICCR), a platform of regulators and cosmetics industry from the EU, the US, Japan, Canada and Brazil (Dent *et al.*, 2018). NGRA is a human-relevant, exposure-led, hypothesis-driven risk assessment designed to prevent harm. It integrates several NAMs to deliver safety decisions relevant to human health without the use of experimental animals. An NGRA should be conducted using a tiered and iterative approach, following an appropriate literature search and evaluation of the available data, and using robust and relevant methods and strategies. Given the novelty of NGRA and the current lack of regulatory guidance on the use of a variety of NAMs in decision-making, it is important that the assessment should be transparently documented and explicit about the logic of the approach and sources of uncertainty (Dent *et al.*, 2018). A general NGRA workflow is described in **Figure 5** (Berggren *et al.*, 2017). The tools useful for safety evaluation of cosmetic ingredients, which could also be used in case NGRA would be taken as a possible workflow in the future, are described in chapters 3-4.2 to 3-4.14. Treshold of Toxicological Concern (TTC) and internal TTC (iTTC) approaches as a risk assessment tools are described in 3-5.2.

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ICCR International Cooperation on Cosmetics Regulation

International Cooperation on Cosmetics Regulation (2018)

European Commission

European Commission: Scientific Committee on Consumer Safety (2021)

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2019: Workshop in Shanghai, China (10-11 April)

Brought together 70 scientists from across China and globally to

- Address challenges and gaps in China to maximise the impact of New Approach Methodologies (NAMs) in chemical safety
- Raise awareness and acceptance of NAMs to accelerate their uptake into regulations

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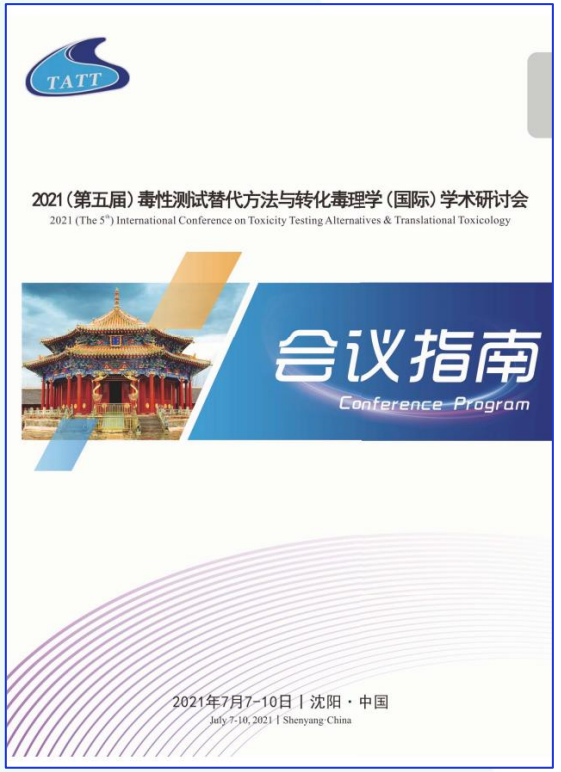
Breakout Groups

1. Group 1 – In vitro models
2. Group 2 – In silico models
3. Group 3 – Regulatory sciences
4. Group 4 – Education and training
5. Group 5 – Next Generation Risk Assessment

Talks from Chinese scientists

Prof ShuangQing Peng - Development and Application of Non-animal Toxicity Testing Alternatives in China

- Two scientific communities set up and organised annual China conferences from 2014 to 2021
- 3 books published in Chinese on NAMs
- Rising governmental funding on NAMs (in both chemical and food risk assessments)
- Challenges remain
  - Need for increased lab capability
  - Safety regulations need to evolve to adopt NAMs
- Perspectives
  - Willing to innovate
  - Science is advancing with the next generation of young scientists



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Talks from Chinese scientists

- Dr Jiabin Guo (AMMS) - A tiered pathway approach in an exposure-led framework for NGRA
- Prof Xiaowei Zhang (Nanjing Univ) - Dose-dependent transcriptomic approach for screening and prediction of chemical toxicity
- Prof Ping Xu (BPRC) - Multi-omics studies for chemical risk assessment- Ping Xu (Beijing Proteomics Research Centre)

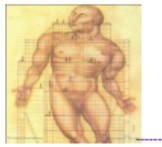
Li et al (2021) Toxicology in Vitro, **74**, 105171

Talks from Chinese scientists

- Organs-on-chips platform to advance chemical safety assessment – Prof Jianhua Qin (Dalian Institute of Chemistry Physics / CAS)

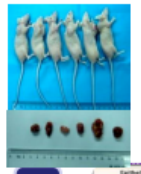
3DP In Vitro Model for Drug Testing

人体模型



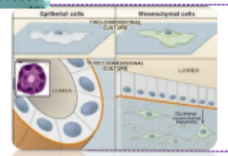
- **Limited human clinical trials**
- Not feasible for testing
- Ethic issues

动物模型



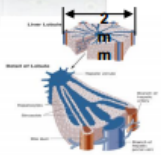
- Cell micro-environment different from human
- Different immune system
- **Different from human clinical trials**

二维模型



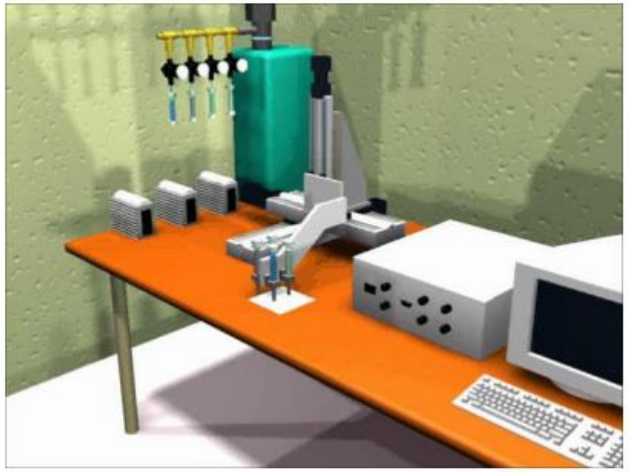
- Not a true physiological environment
- **Difficult to simulate 3D tissue**
- Not reliable to cancer drug testing

三维模型



- **Simulated physiological model**
- **More close to 3D human tissue**
- **Reduce using animals**

Bio-3D Printing



Using cells and/or other biological compounds as basic building blocks to 3D Printing in vitro biological models.

Bio-Printing *in vitro* Physiological Model for Drug Testing

生物3D打印体外组织模型及在药理毒理检测中的应用

Y. Li[1], SS Mao[1], Y. Song[1], Y. Zhao[1], Zhou[1], ZZ., Y. Pang[1], T. Zhang[1], W. Sun[1, 2]

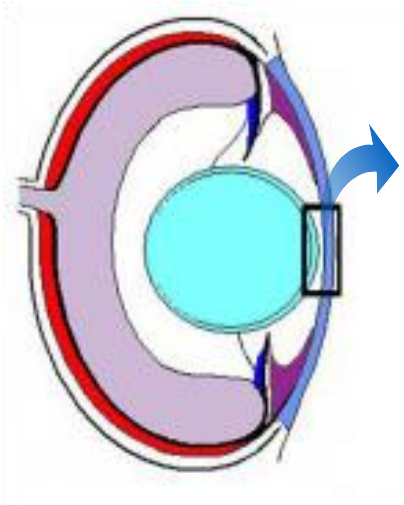
[1] Tsinghua University, China

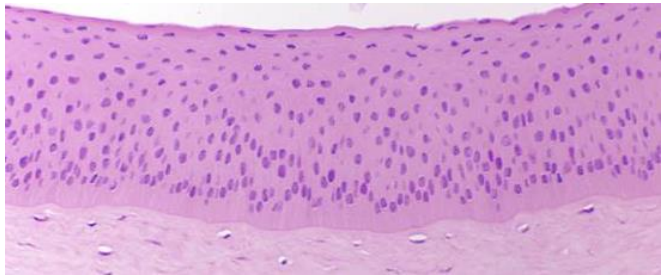
[2]Drexel University, USA

Chinese 3D models by BioCell™
(e.g. 3D Eye irritation test models for cosmetic products)

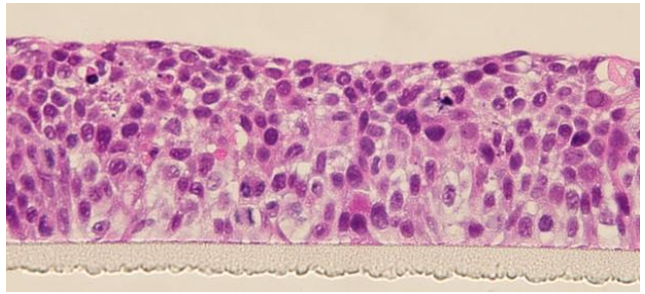
3D角膜上皮模型: BioOcullarTM

reconstructed 3D cornea epithelium model: BioOcullarTM

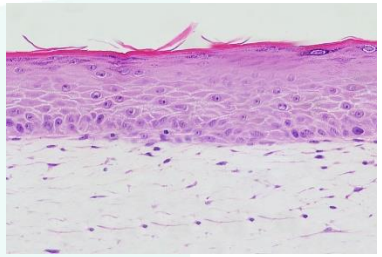




人角膜组织学结构,Native Cornea



角膜模型组织学结构, Histology of BioOcular



3D Skin Model

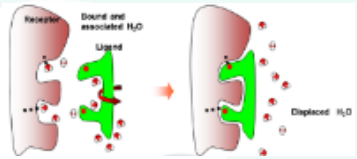
角膜模型（BioOcullar）高度接近于天然角膜

Talks from Chinese scientists

Predictive toxicology:

from and beyond structural basis

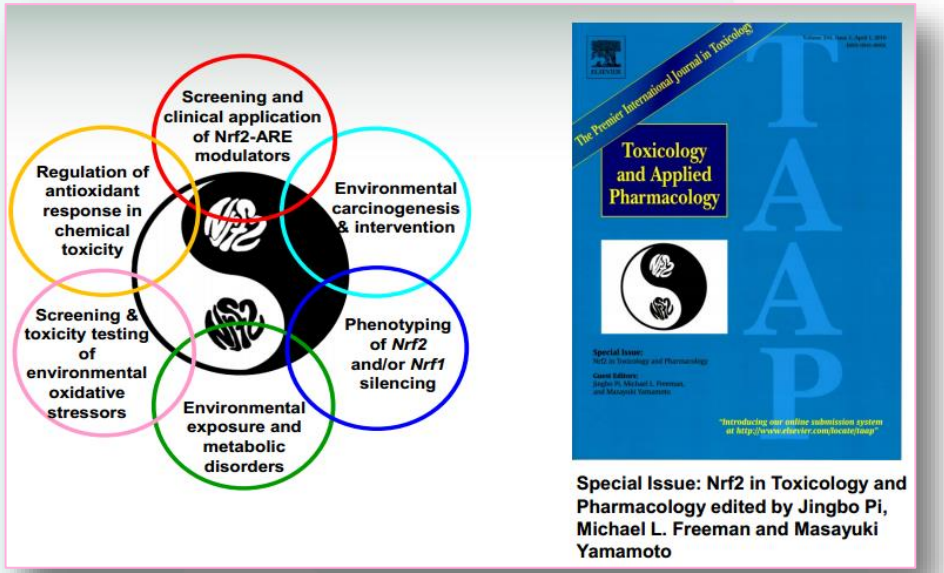
Prof Aiqian Zhang (Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences)



Molecular Simulation Investigation on Molecular Initiative Events

Assays for safety mechanisms: how to interpret the data on cellular adaptive stress responses?

Prof Jingbo Pi (China Medical University)



Special Issue: Nrf2 in Toxicology and Pharmacology edited by Jingbo Pi, Michael L. Freeman and Masayuki Yamamoto

Talks on China regulations by Dr Kuang Rong (ZJ-IFDC*) & Yang Ying (GD-CDC*)

- **Regulations rely mainly on animal testing**

- **Steps taken already**
  1. Cosmetics
     - no mandated animal testing for locally made general-use cosmetics and any imported cosmetics via online
     - No mandated animal testing for imported general use cosmetics (2021)
  2. Chemical: QSAR/Read-across can be used when appropriate
  3. Authority engagements with international organisations on future developments with New Approach Methodologies / Next Generation Risk Assessment (e.g. ICCR)

* Zhejiang Institute for Food and Drug Control
Guangdong Provincial Center for Disease Control

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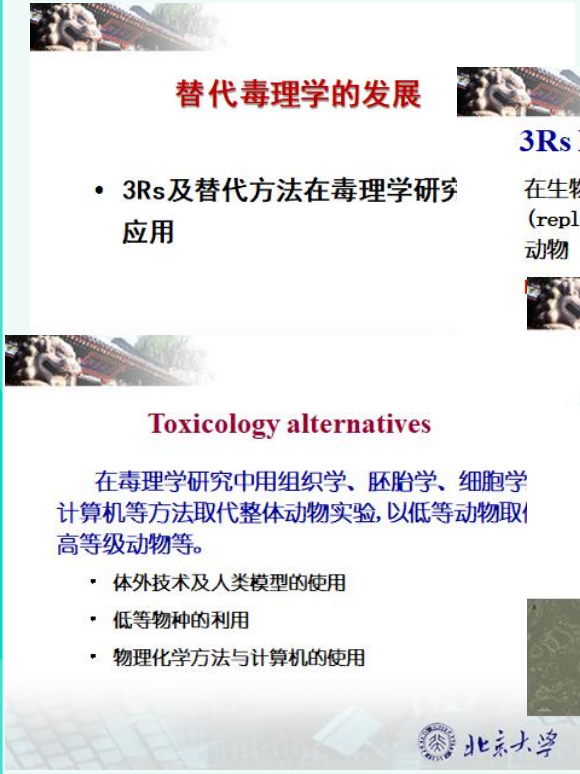
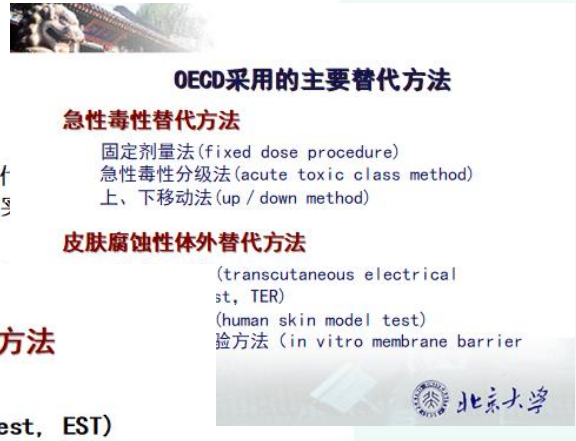
NAMs in education in China by Prof Weidong Hao (Peking Univ.)

Overview of content of undergraduate and graduate toxicology education





Student Poster Awards

Name	Poster title	Organization
Chi Zhang	Integration of in vitro data from 2D/3D culture HepaRG cells and PBPK-based simulation for predicting acetaminophen hepatotoxicity	Academy of Military Medical Sciences
Yuan Pang	Personalized tumor model: from patient tumor to three-dimensional printing of in vitro model and drug testing	Tsinghua University
Bayindala Xiagedeer	Mode of action of androgen receptor antagonists on HepG2 cells based on ToxCast open source data	Peking University
ZhongYu Li	Organ-on-a-chip to advance the assessments of chemical and product safety	Chinese Academy of Sciences
YuanYuan Yin	Nrf2 deficiency disrupts autophagy and sensitizes ZnO nanoparticles induced cytotoxicity in HaCat cells	Academy of Military Medical Sciences
Liu Shengnan	Hyperoxidation of peroxiredoxin renders bistable H_2O_2 signalling and nonlinearity for redox circadian oscillation	China Medical University

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Conclusions and next steps

Significant advances in China on NAM science (*in silico* and *in vitro* methods as well as application in risk assessment)

Uptake and progress with NAMs is a multi-stakeholder process

Programmes of training and educations on non-animal approaches to chemical safety Assessment and application of NAMs

Discussion of regulatory developments and approval of alternative methods in China (including recent adoption of OECD non-animal methods into Chinese technical guidance).

Workshop report in preparation for publication

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Thank you!

谢谢!

#UseScienceNotAnimals