国立感染症研究所
令和5年7月26日

動物実験の3Rsを取り巻く国際動向

国立医薬品食品衛生研究所
（一財）食品薬品安全センター

小島　肇

本発表は、個人的な見解であり、必ずしも
国立衛研や食薬センターの公式見解ではありません。
また、発表に利益相反はありません。

目次

動物実験の３Rs

経済産業省
Ministry of Economy, Trade and Industry

スリーアール
3R政策
リデュース・リユース・リサイクル

TOP　サイトマップ　関連サイト

3R Policies　English

３Ｒ（スリーアール）は、環境と経済が両立した循環型社会を形成していくための３つの取組の頭文 字をとったものです。３Ｒは、リデュース、リユース、リサイクルの順番で取り組むことが求められています。

1. Ｒｅｄｕｃｅ（リ デュース）・・・廃棄物の発生抑制
2. Ｒｅｕｓｅ（リ ユース）・・・・・・・・・・再使用
3. Ｒｅｃｙｃｌｅ（リ サイクル）・・・・・・再資源化

動物実験の３Rs

1. 実験動物を用いない試験法に置換える
   （Replacement　置換え）

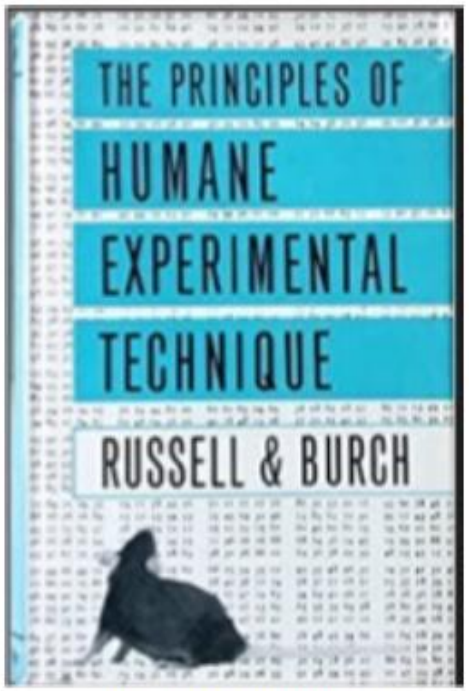
2. 実験で使う動物数を減らす
   （Reduction　使用数の削減）

3. 実験動物のストレス、痛みを減らす
   （Refinement　苦痛の軽減）

3 Rsの起源

Timeline for the 3Rs

- By 1955, the concept of the 3Rs was essentially present in a paper published by Russell
- The explicit term "The 3Rs" evolved sometime between 1955 and 1957 (Russell, 2005)
- The 3Rs were formally presented at a UFAW Symposium in May 1957 on *Humane Technique in the Laboratory*
- Russell and Burch published ***The Principles of Humane Experimental Technique*** in 1959



Russell WMS & Burch RL (1959)

Norecopa: *PREPARE for better Science*

Russell (2005); Hubrecht & Carter (2019)

3 Rsの変遷

Interest in the 3RS

- *A largely unknown concept for the first 20 years*
- *1969: The UK organisation FRAME (Fund for Replacement of Medical Experiments) was established, and also worked (independently of UFAW/Russell & Burch) on alternatives*
- *1991: The HSUS (Humane Society of the United States) instigated a Russell and Burch Award*
- *1995: ECVAM, CAAT and FRAME organised a workshop which Russell and Burch both attended*
- *2000: The European Science Foundation 'strongly endorses the principles of the Three Rs'*

FRAME

Rex Burch & William Russell in Sheringham, UK, in 1995

Norecopa: *PREPARE for better Science*

journals.sagepub.com/doi/abs/10.1177/026119299502300614

動物実験の３Rsに関する国際動向

DIRECTIVES

DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 22 September 2010

on the protection of animals used for scientific purposes

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 thereof,

Having regard to the proposal from the European Commission,

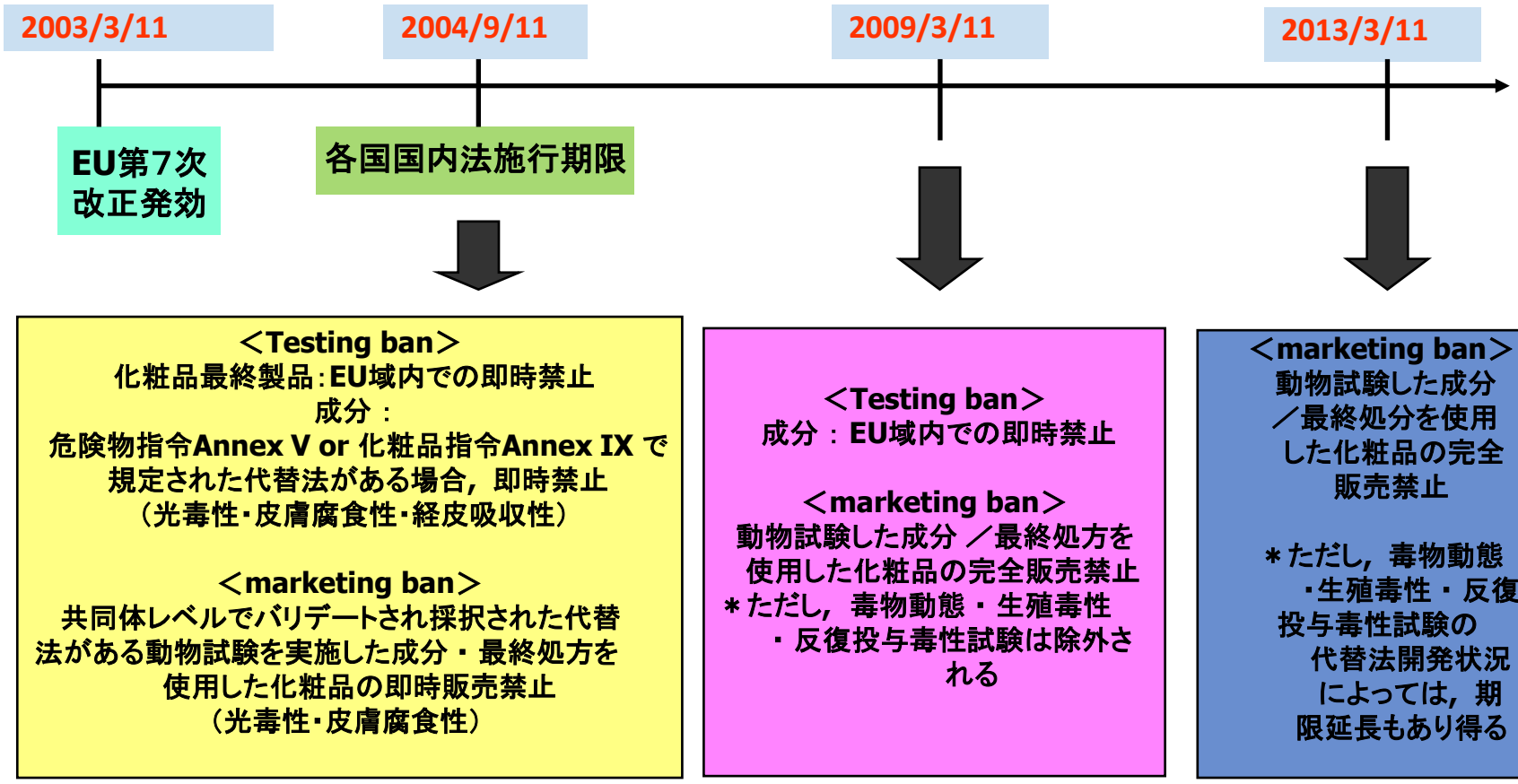
Having regard to the opinion of the European Economic and Social Committee ([1]),

After consulting the Committee of the Regions,

and other scientific purposes ([4]). By becoming party to that Convention, the Community acknowledged the importance of the protection and welfare of animals used for scientific purposes at international level.

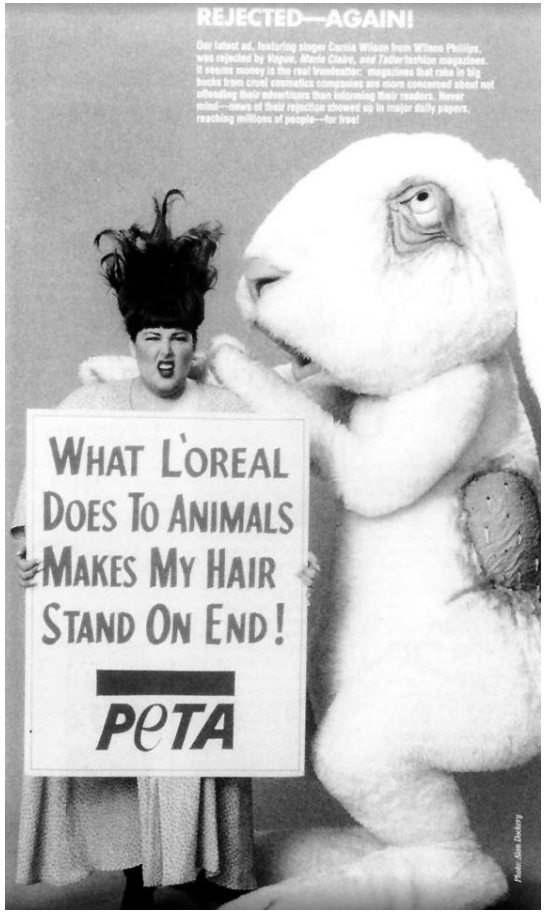
(4) The European Parliament in its resolution of 5 December 2002 on Directive 86/609/EEC called for the Commission to come forward with a proposal for a revision of that Directive with more stringent and transparent measures in the area of animal experimentation.

ＥＵ化粧品における動物実験規制



Fragrance journal, 2005-2

米国：消費者による不買運動

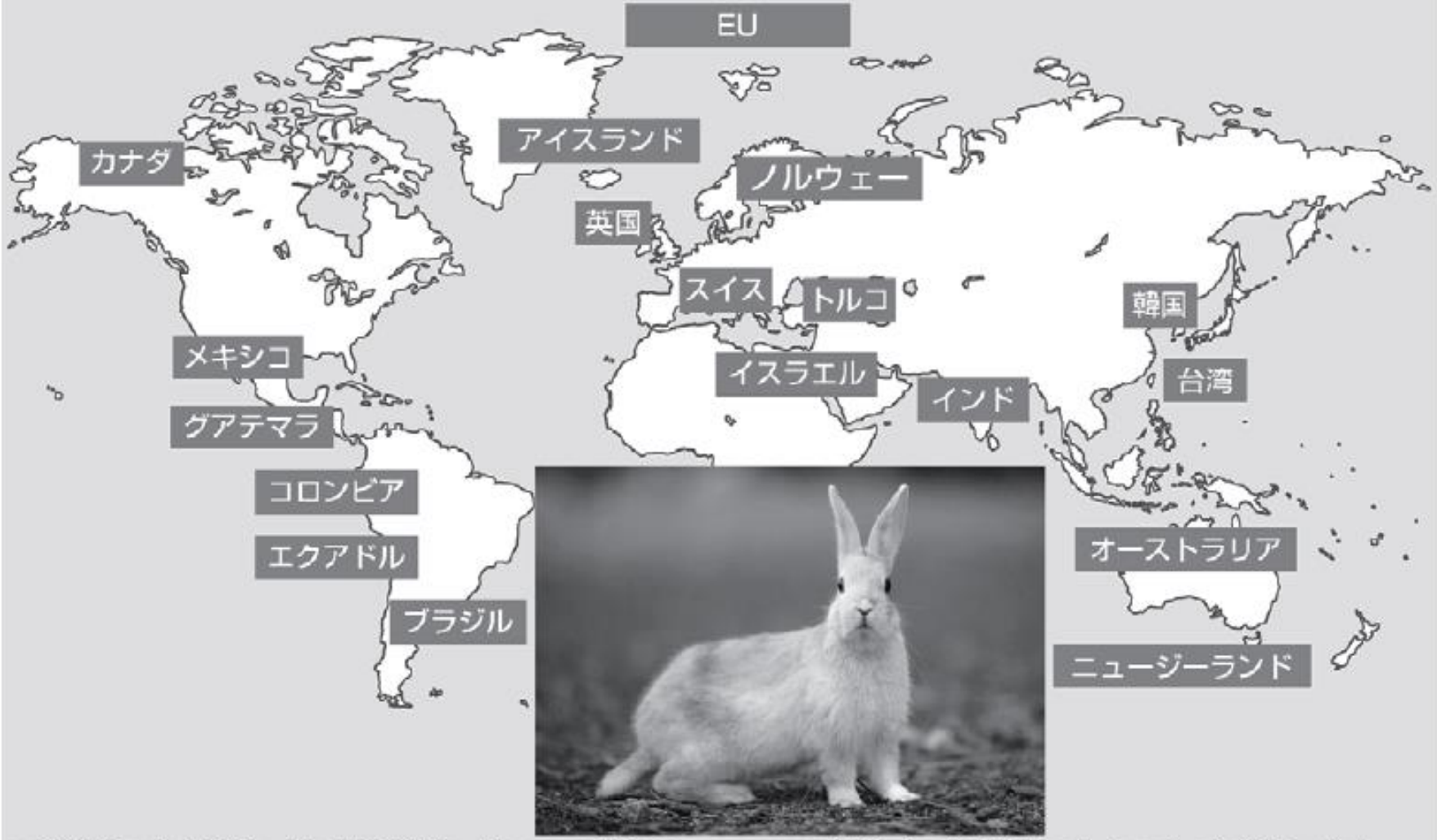


1990年代

欧州：企業によるキャンペーン

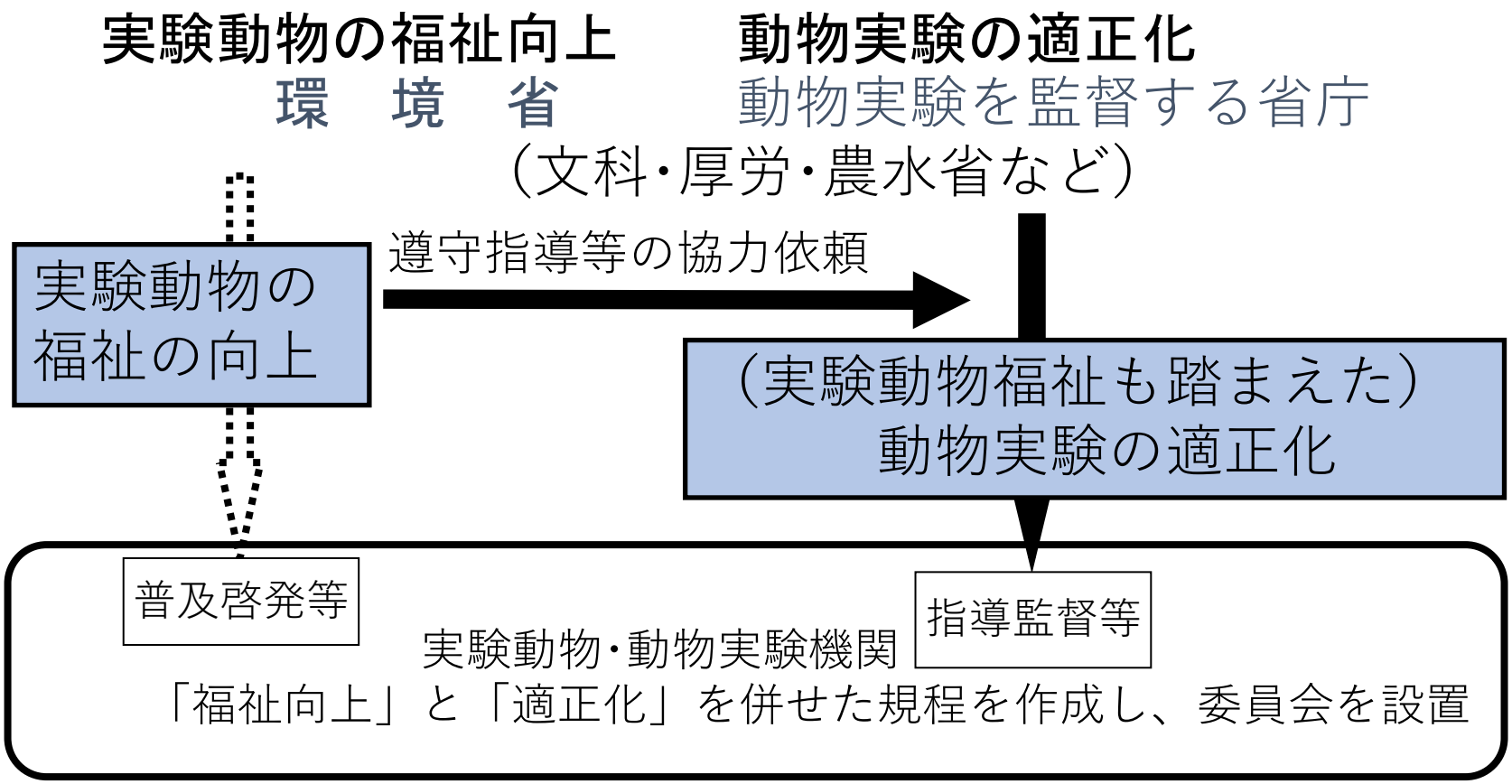
1990年代

化粧品の動物実験を法的に禁止している国・地域



※条件付きで実験を禁止したり、販売も禁止したりしている国もある。※PEACE・動物実験の廃止を求める会（JAVA）の資料を元に作成。

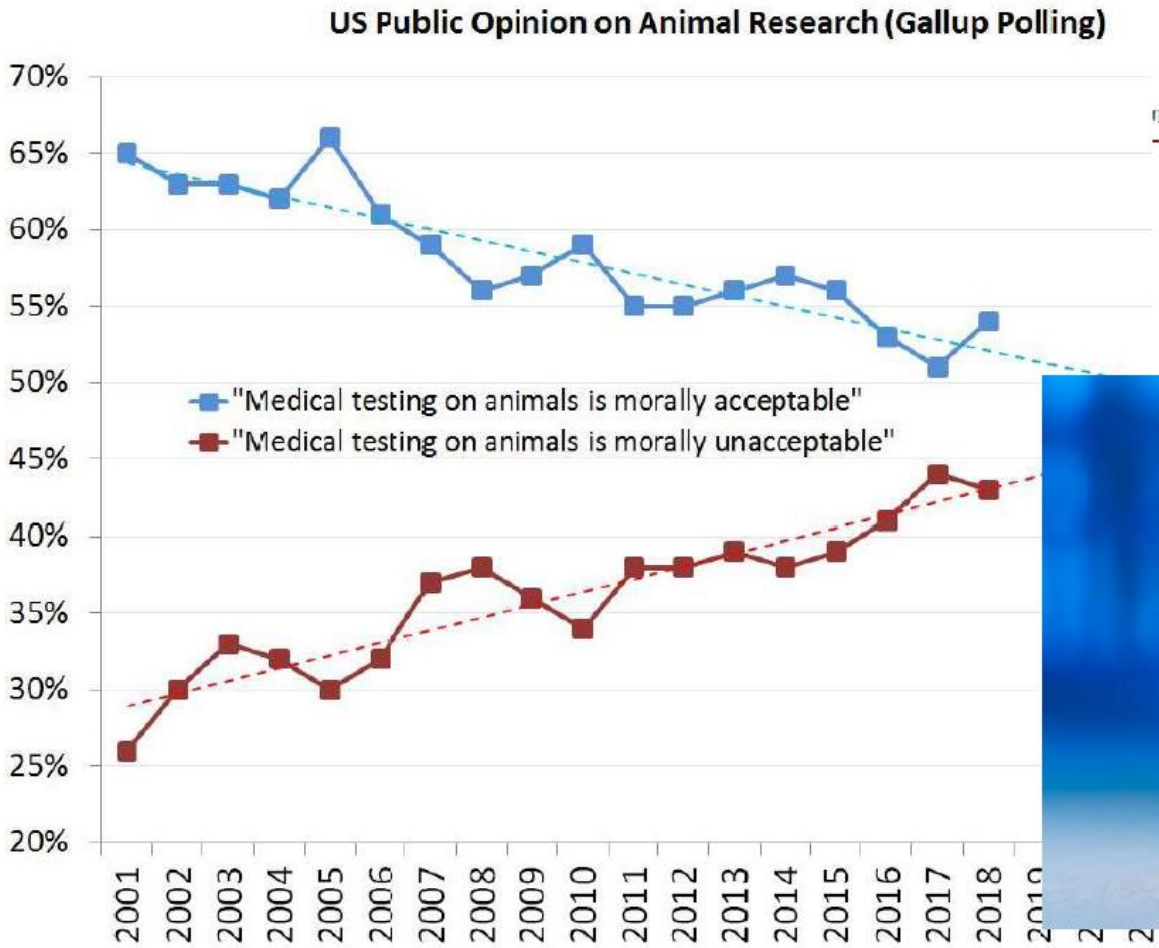
動物の愛護及び管理に関する法律
（動物愛護管理法）
平成１８年６月１日から施行



実験動物における３Rsの徹底

Public opinion

Animal testing less and less acceptable



Source: https://speakingofresearch.com/2018/08/30/52-of-american-public-opposes-the-use-of-animals-in-scientific-research/

charles ri

Annual Statistics of Scientific Procedures 2022: headline stats and trends

Great Britain's statistics record the **number of procedures** conducted, rather than the total number of animals used in procedures.

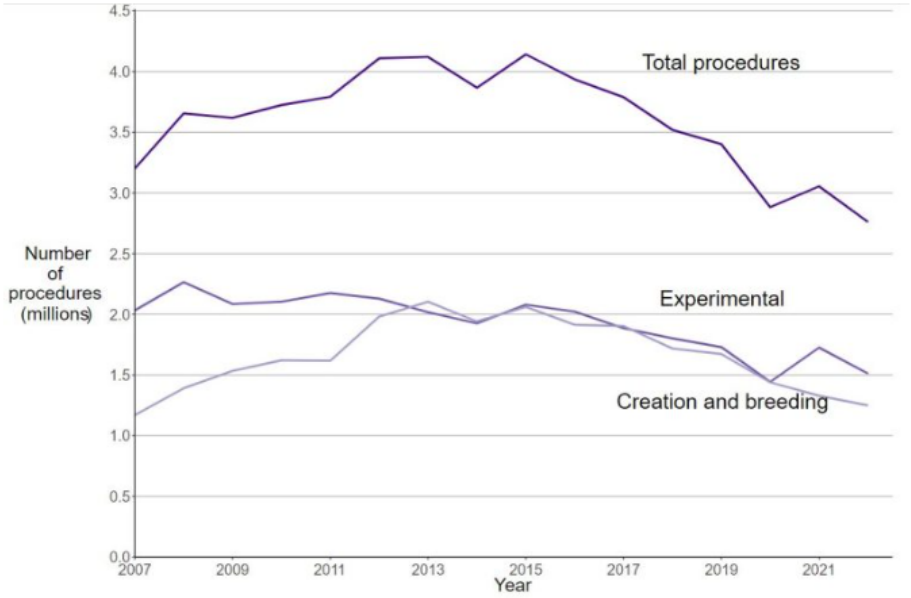


Figure 1: Total scientific procedures by type, 2007 to 2022

Source: The Home Office Annual Statistics of Scientific Procedures on Living Animals, Great Britain 2022

In total, 2.76 million procedures were conducted using live animals in Great Britain in 2022, a decrease from 3.06 million in 2021.

This is the lowest number of procedures records since 2002.

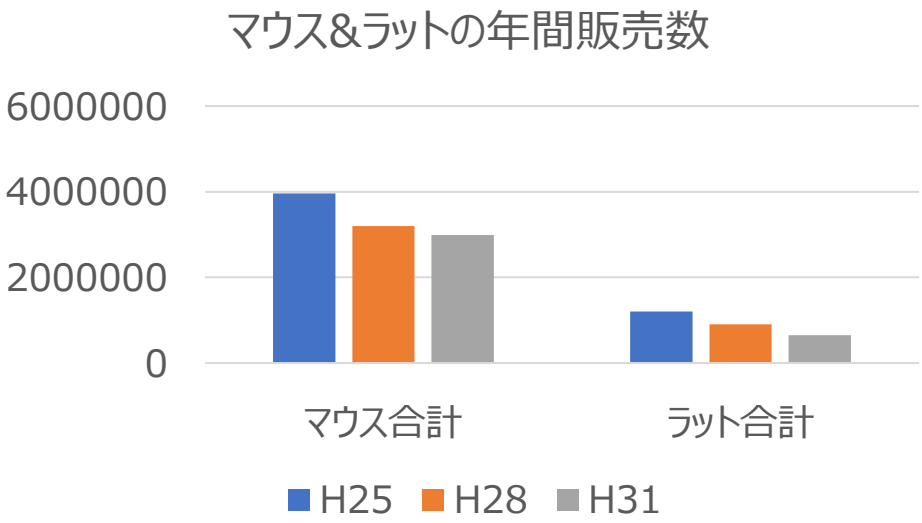
Of these 2.76 million procedures, 1.51 million (55%) were carried out for experimental purposes, and 1.25 million (45%) were carried out for the creation and breeding of **genetically altered (GA) animals** (Figure 1). Compared to 2021, experimental procedures have decreased by 13%, and GA procedures have decreased by 6%.

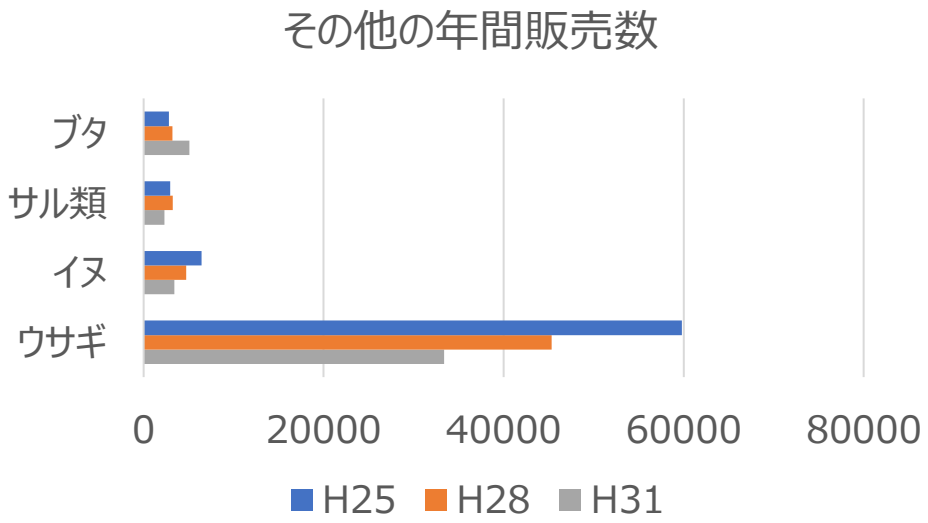
96% of all procedures used mice, rats, birds, or fish. Mice remain the most common, being used in 59% of experimental procedures, followed by fish in 14% experimental procedures, rats in 12% experimental procedures, and birds

Animal Research in Great Britain, 2022

実験動物の年間総販売数調査

（平成25年4月～31年3月）
平成31年9月　公益社団法人日本実験動物協会
（改変）





	ｺﾝｼﾞｪﾆｯｸ系	遺伝子改変
H25年	1,439	17,414
H28年	1,538	18,969
H31年	2,119	34,485

2021年　EU議会の更なる圧力

News
European Parliament

Headlines　Press room　Agenda　FAQ

Press room / MEPs demand EU action plan to end the use of animals in research and testing

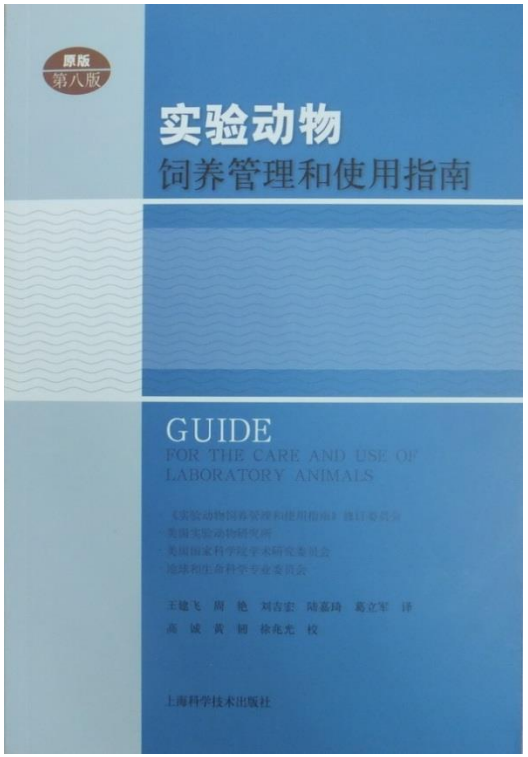
MEPs demand EU action plan to end the use of animals in research and testing

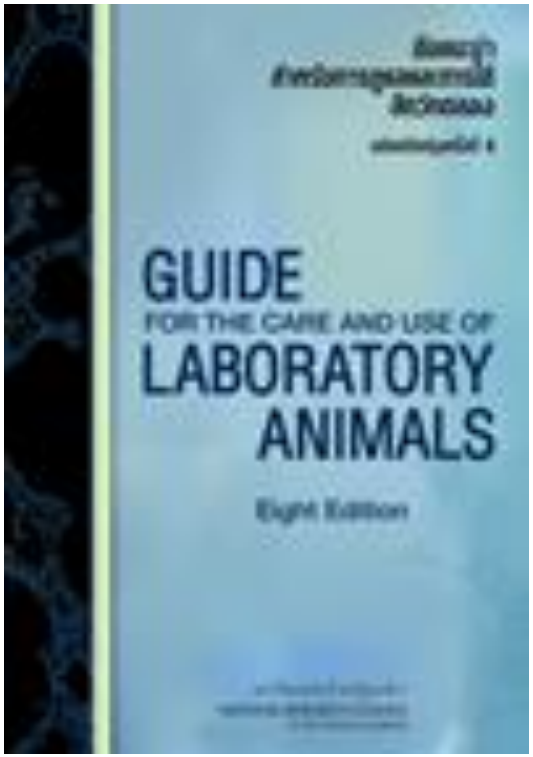
Press Releases PLENARY SESSION ENVI 16-09-2021 - 09:29

- Animal testing for cosmetic products prohibited in the EU since 2009
- 12 million animals were still bred and killed for other animal testing in 2017
- More funding for alternative testing methods needed
- Minimise pain, distress and suffering of animals when their use cannot be avoided

ILAR（Institute for Laboratory Animal Research） Guide

- The latest version of the *Guide* has been (or will be) translated into **a number of different languages** including





50か国あるいは地域　1,040施設、我が国の認証機関（公表を了承した機関だけ）28施設？

サービスの紹介
Services

動物実験実施施設外部検証・認証事業

英語版はこちら >

事業の概要

動物実験等の実施については、「動物の愛護及び管理に関する法律」（昭和４８年法律第１０５号、以下「動物愛護管理法」という。）第４１条により、３Rs (Reduction (使用動物数の削減), Replacement (代替法の活用), Refinement (苦痛の軽減)) が規定され、動物愛護管理法に基づく「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」（平成１８年環境省告示第８８号、以下「飼養保管基準」という。）により、実施機関における動物福祉に関する自主管理等が定められています。さらに、「研究機関等における動物実験等の実施に関する基本指針」（平成１８年６月１日文部科学省告示第７１号、以下「文科省基本指針」という。）、「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」（平成１８年６月１日厚生労働省大臣官房厚生科学課長通知。以下「厚労省基本指針」という。）及び「農林水産省の所管する研究機関等における動物実験等の実施に関する基本指針」（平成１８年６月１日農会第３０７号農林水産省農林水産技術会議事務局長。以下「農水省基本指針」という。）が策定されています。

認定施設一覧

認定番号(20)～はこちら
認定番号(40)～はこちら
認定番号(60)～はこちら
認定番号(80)～はこちら
認定番号(100)～はこちら

2016年9月現在

(1)	認定番号	14－001
	認定日	平成27年3月25日
	認定施設名	国立医薬品食品衛生研究所
(2)	認定番号	14－002
	認定日	平成27年3月25日
	認定施設名	国立感染症研究所
	認定番号	14－003

近年の動物実験に関する国際規約の新設、改訂

WOAH (World Organisation for Animal Health)

2018 Animal Welfare Code

2010 Laboratory Animal Welfare Code

CIOMS（Council for International Organisation of Medical Sciences）

2012 The International Guiding Principles For Biomedical Research Involving Animals

OECDのガイダンス

2000 No.19　Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Humane Endpoints

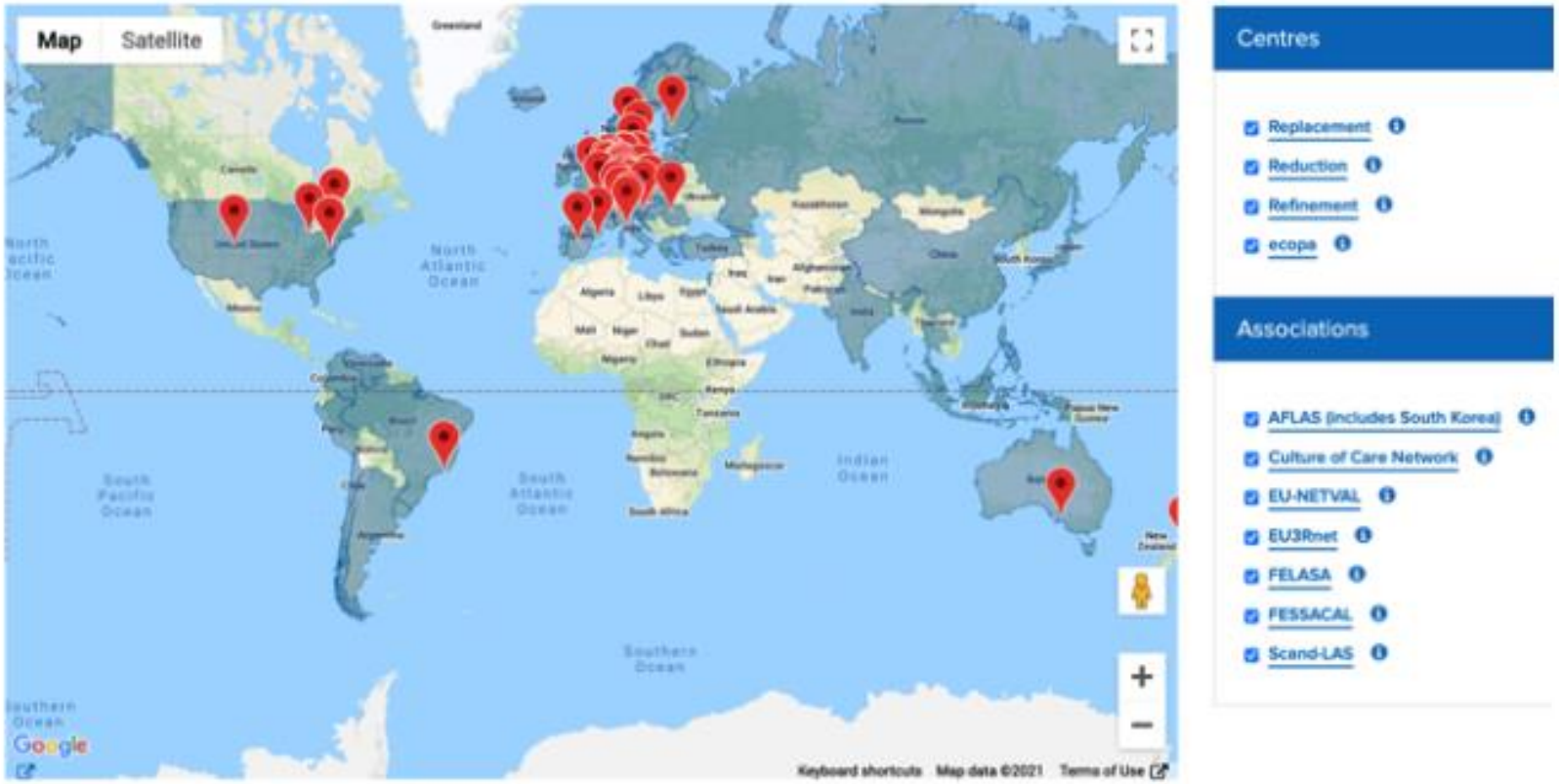
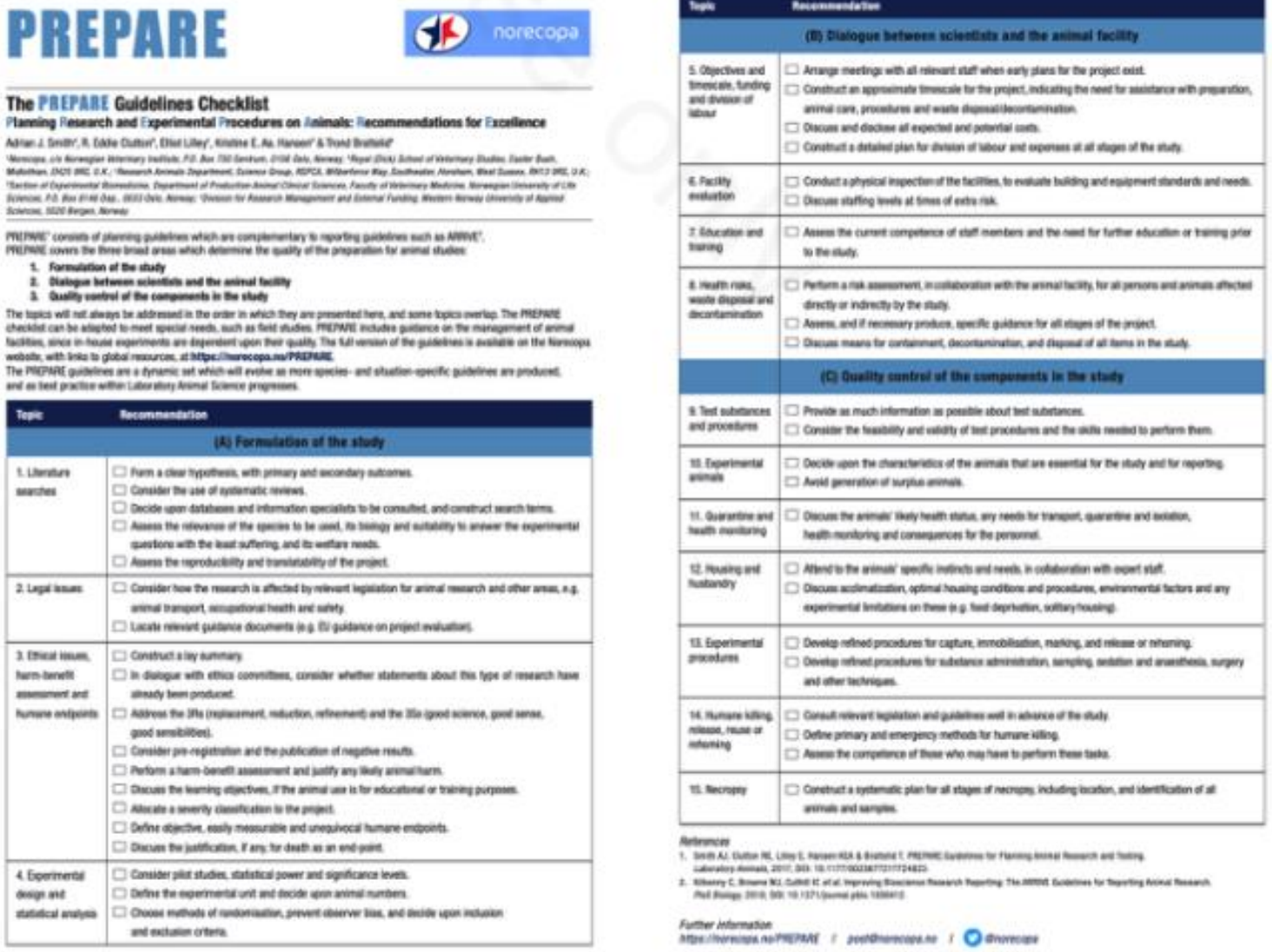


Figure 2. Norecopa's interactive map of 3R Centres and networks within Laboratory Animal Science and alternatives: https://norecopa.no/global3r

There are now over 30
3R centres in Europe alone...

norecopa.no/global3r



PREPARE

norecopa

The PREPARE Guidelines Checklist

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

Adrian J. Smith[1], R. Eddie Clutton[2], Elliot Lilley[1], Kristine E. Ae. Hansen[3] & Trond Brattelid[4]

[1]Norecopa, c/o Norwegian Veterinary Institute, P.O. Box 750 Sentrum, 0106 Oslo, Norway; [2]Royal (Dick) School of Veterinary Studies, Easter Bush, Midlothian, EH25 9RG, U.K.; [3]Research Animals Department, Science Group, RSPCA, Wilberforce Way, Southeater, Horsham, West Sussex, RH13 9RS, U.K.; [4]Section of Experimental Biomedicine, Department of Production Animal Clinical Sciences, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, P.O. Box 8146 Dep., 0033 Oslo, Norway; [5]Division for Research Management and External Funding, Western Norway University of Applied Sciences, 5020 Bergen, Norway

PREPARE[1] consists of planning guidelines which are complementary to reporting guidelines such as ARRIVE[2].
PREPARE covers the three broad areas which determine the quality of the preparation for animal studies:

1. **Formulation of the study**
2. **Dialogue between scientists and the animal facility**
3. **Quality control of the components in the study**

The topics will not always be addressed in the order in which they are presented here, and some topics overlap. The PREPARE checklist can be adapted to meet special needs, such as field studies. PREPARE includes guidance on the management of animal facilities, since in-house experiments are dependent upon their quality. The full version of the guidelines is available on the Norecopa website, with links to global resources, at **https://norecopa.no/PREPARE**.
The PREPARE guidelines are a dynamic set which will evolve as more species- and situation-specific guidelines are produced, and as best practice within Laboratory Animal Science progresses.

Topic	Recommendation
(A) Formulation of the study	
1. Literature searches	☐ Form a clear hypothesis, with primary and secondary outcomes. ☐ Consider the use of systematic reviews. ☐ Decide upon databases and information specialists to be consulted, and construct search terms. ☐ Assess the relevance of the species to be used, its biology and suitability to answer the experimental questions with the least suffering, and its welfare needs. ☐ Assess the reproducibility and translatability of the project.
2. Legal issues	☐ Consider how the research is affected by relevant legislation for animal research and other areas, e.g. animal transport, occupational health and safety. ☐ Locate relevant guidance documents (e.g. EU guidance on project evaluation).
3. Ethical issues, harm-benefit assessment and humane endpoints	☐ Construct a lay summary. ☐ In dialogue with ethics committees, consider whether statements about this type of research have already been produced. ☐ Address the 3Rs (replacement, reduction, refinement) and the 3Ss (good science, good sense, good sensibilities). ☐ Consider pre-registration and the publication of negative results. ☐ Perform a harm-benefit assessment and justify any likely animal harm. ☐ Discuss the learning objectives, if the animal use is for educational or training purposes. ☐ Allocate a severity classification to the project. ☐ Define objective, easily measurable and unequivocal humane endpoints. ☐ Discuss the justification, if any, for death as an end-point.
4. Experimental design and statistical analysis	☐ Consider pilot studies, statistical power and significance levels. ☐ Define the experimental unit and decide upon animal numbers. ☐ Choose methods of randomisation, prevent observer bias, and decide upon inclusion and exclusion criteria.
(B) Dialogue between scientists and the animal facility	
5. Objectives and timescale, funding and division of labour	☐ Arrange meetings with all relevant staff when early plans for the project exist. ☐ Construct an approximate timescale for the project, indicating the need for assistance with preparation, animal care, procedures and waste disposal/decontamination. ☐ Discuss and disclose all expected and potential costs. ☐ Construct a detailed plan for division of labour and expenses at all stages of the study.
6. Facility evaluation	☐ Conduct a physical inspection of the facilities, to evaluate building and equipment standards and needs. ☐ Discuss staffing levels at times of extra risk.
7. Education and training	☐ Assess the current competence of staff members and the need for further education or training prior to the study.
8. Health risks, waste disposal and decontamination	☐ Perform a risk assessment, in collaboration with the animal facility, for all persons and animals affected directly or indirectly by the study. ☐ Assess, and if necessary produce, specific guidance for all stages of the project. ☐ Discuss means for containment, decontamination, and disposal of all items in the study.
(C) Quality control of the components in the study	
9. Test substances and procedures	☐ Provide as much information as possible about test substances. ☐ Consider the feasibility and validity of test procedures and the skills needed to perform them.
10. Experimental animals	☐ Decide upon the characteristics of the animals that are essential for the study and for reporting. ☐ Avoid generation of surplus animals.
11. Quarantine and health monitoring	☐ Discuss the animals' likely health status, any needs for transport, quarantine and isolation, health monitoring and consequences for the personnel.
12. Housing and husbandry	☐ Attend to the animals' specific instincts and needs, in collaboration with expert staff. ☐ Discuss acclimatization, optimal housing conditions and procedures, environmental factors and any experimental limitations on these (e.g. food deprivation, solitary housing).
13. Experimental procedures	☐ Develop refined procedures for capture, immobilisation, marking, and release or rehoming. ☐ Develop refined procedures for substance administration, sampling, sedation and anaesthesia, surgery and other techniques.
14. Humane killing, release, reuse or rehoming	☐ Consult relevant legislation and guidelines well in advance of the study. ☐ Define primary and emergency methods for humane killing. ☐ Assess the competence of those who may have to perform these tasks.
15. Necropsy	☐ Construct a systematic plan for all stages of necropsy, including location, and identification of all animals and samples.

References

1. Smith AJ, Clutton RE, Lilley E, Hansen KEA & Brattelid T. PREPARE: Guidelines for Planning Animal Research and Testing. Laboratory Animals, 2017; DOI: 10.1177/0023677217724823.
2. Kilkenny C, Browne WJ, Cuthill IC, et al. Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. PLoS Biology, 2010; DOI: 10.1371/journal.pbio.1000412

Further information
https://norecopa.no/PREPARE / post@norecopa.no / @norecopa

Figure 1. The PREPARE checklist. Reprinted with permission from Laboratory Animals, published in Smith et al. (2018). Available in 25 languages at https://norecopa.no/PREPARE/prepare-checklist

小括

- 動物実験の３Rsは国際社会で拡大しつつある。
- 化粧品を初めとした動物実験代替法の利用は、種々の分野に広がりつつある。
- ＥＵはさらなる国際的な拡大を念頭に活動している。
- 動物実験継続を念頭に３Rsの教育も盛んである。

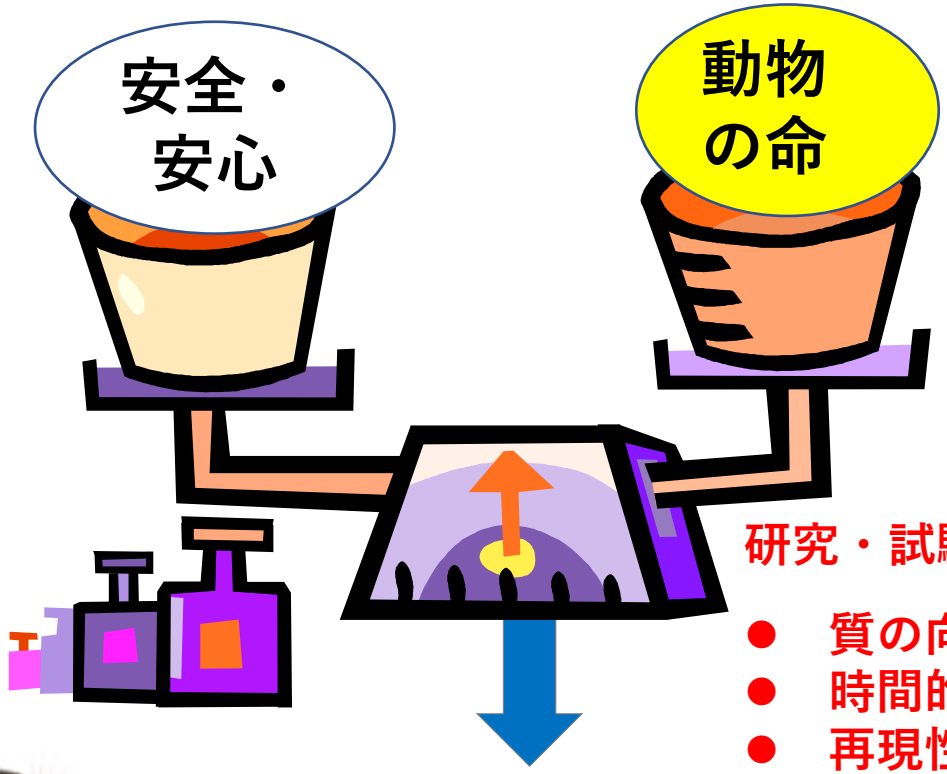
動物実験代替法に関する国際機関の動向

動物実験代替法とは？

- **Alternative test　＝　動物実験代替法**
  3R原則を実現する試験法
- **3Rs principle　＝　3R 原則**
  使用動物数を削減すること（reduction）、実験動物の苦痛軽減と動物福祉を進めること（refinement）、および動物を用いる試験を動物を用いない、あるいは系統発生的下位動物を用いる試験法に置換すること（replacement）、という原則。

JaCVAM用語集より

動物実験代替法と安全性



研究・試験データ

- 質の向上
- 時間的・金銭的な無駄が無い
- 再現性のある結果

国際的評価の高い
研究成果・論文・バリデーション

故池田卓也博士より

ECHA
EUROPEAN CHEMICALS AGENCY

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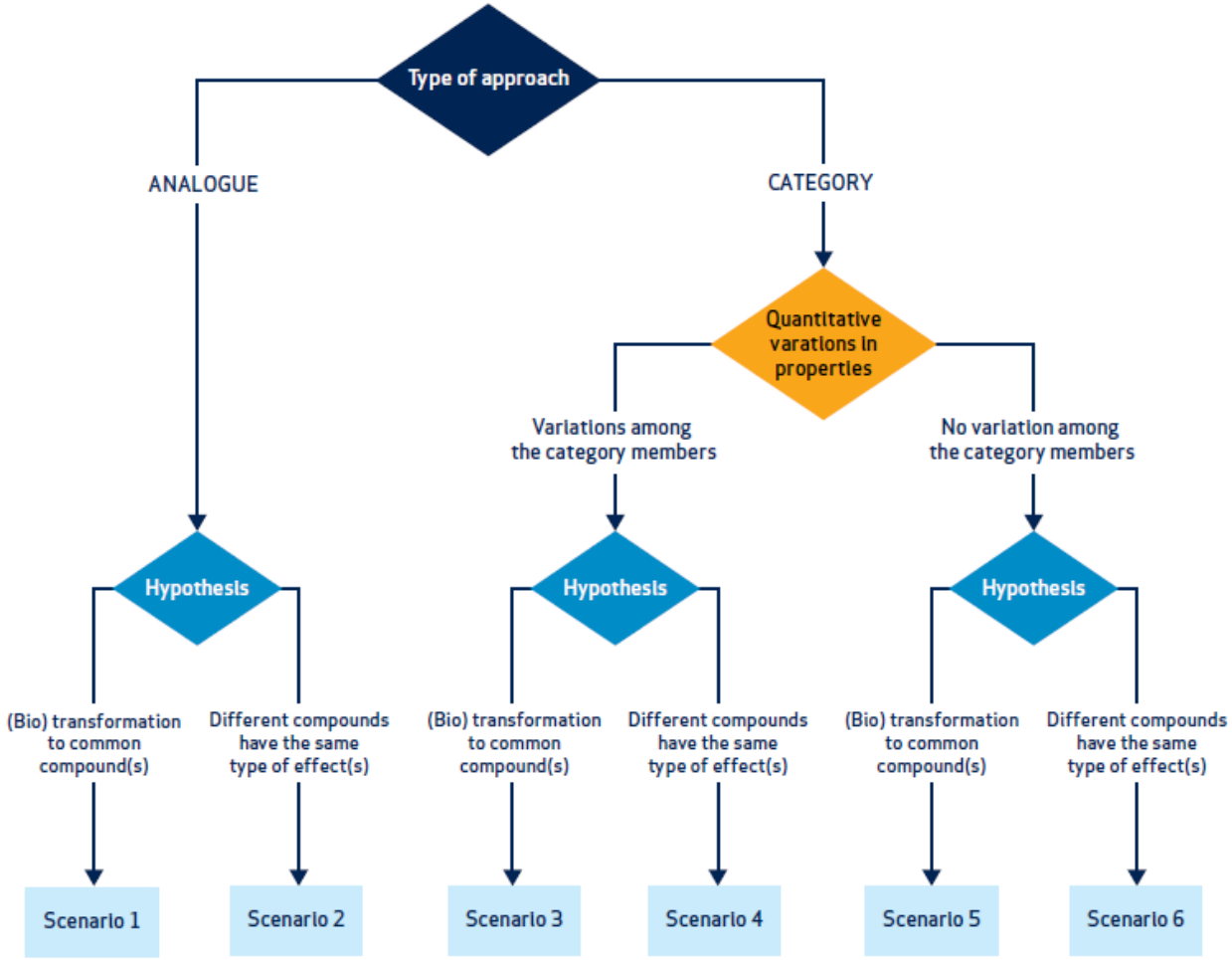
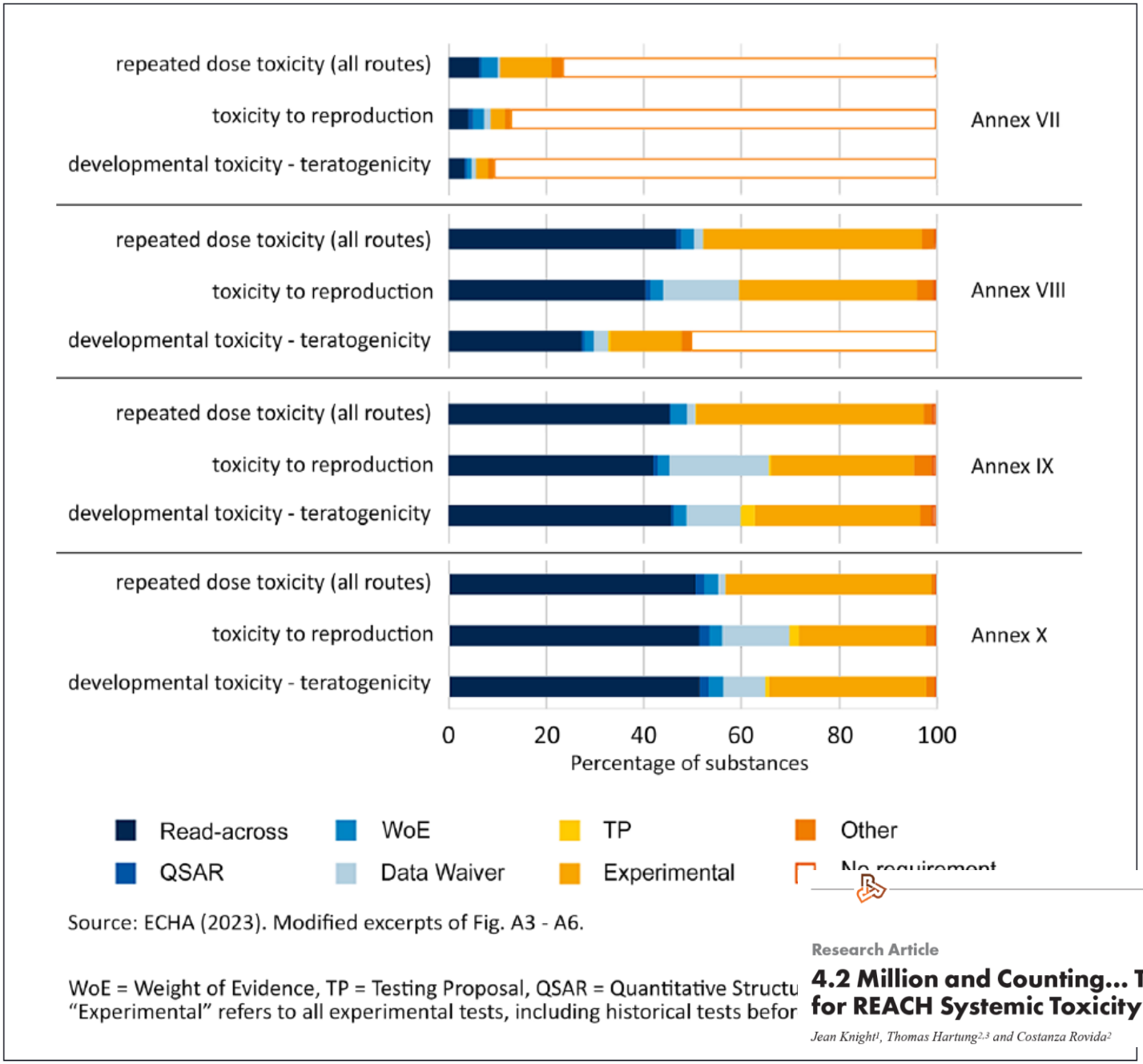


REACH (Registration,Evaluation,Authorisation, Restriction and Chemicals)

附属書のリスト

附属書 I	物質評価及び化学物質安全性報告書の作成のための一般的な規定
附属書 II	安全性データシートの編集に関する指針
附属書 III	1 トン～10 トンの量で登録する物質に関する基準
附属書 IV	第 2 条(7)(a)に従う登録の義務の免除
附属書 V	第 2 条(7)(b)に従う登録の義務の免除
附属書 VI	第 10 条に記す情報の要件
附属書 VII	1 トン以上の量を製造又は輸入する物質の標準的な情報の要件
附属書 VIII	10 トン以上の量を製造又は輸入する物質の標準的な情報の要件
附属書 IX	100 トン以上の量を製造又は輸入する物質の標準的な情報の要件
附属書 X	1000 トン以上の量を製造又は輸入する物質の標準的な情報の要件
附属書 XI	附属書 VII から附属書 X までに規定する標準的な試験計画の適合化に関する一般的な規定
附属書 XII	川下使用者が物質を評価し、化学物質安全性報告書を作成するのため一般的な規定
附属書 XIII	難分解性、生物蓄積性、毒性物質及び極めて難分解性で高い生物蓄積性を有する物質の特定のための基準
附属書 XIV	認可の対象となる物質のリスト
附属書 XV	一式文書
附属書 XVI	社会経済分析
附属書 XVII	ある種の危険な物質、調剤及び成形品の製造、上市及び使用の制限

REACH下における動物実験代替法の利用



Source: ECHA (2023). Modified excerpts of Fig. A3 - A6.

WoE = Weight of Evidence, TP = Testing Proposal, QSAR = Quantitative Structu
"Experimental" refers to all experimental tests, including historical tests befor

Fig. 2: Data retrieved from the latest ECHA report on the use of alternatives to testing on animals for the REACH Regulation (ECHA, 2023)
The experimental data include both existing historical tests and tests performed for REACH.

Research Article

4.2 Million and Counting... The Animal Toll for REACH Systemic Toxicity Studies

Jean Knight[1], Thomas Hartung[2,3] and Costanza Rovida[2]

TECHNICAL REPORT

APPROVED: 4 March 2016

PUBLISHED: 10 March 2016

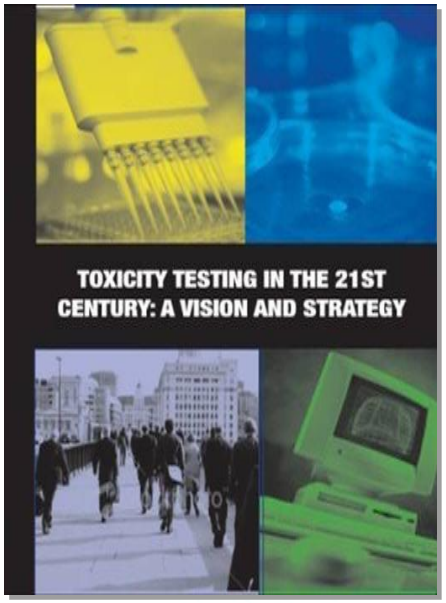
Outcome of a public consultation on the conclusions and recommendations of the EFSA–WHO workshop on the Threshold of Toxicological Concern approach

European Food Safety Authority and World Health Organization

Abstract

The European Food Safety Authority (EFSA) and World Health Organization (WHO) carried out a public consultation to receive input from the scientific community and all interested parties on the Draft Conclusions and Recommendations of the expert workshop on the Threshold of Toxicological Concern (TTC) approach held in Brussels on 3-5 December 2014. The written public consultation for this document was open from 12 February to 12 April 2015. A total of 99 comments from 14 interested parties were received. EFSA and WHO wish to thank all stakeholders for their contributions. The current report summarises the outcome of the public consultation, and includes all the comments received. The relevant comments were addressed and were taken into consideration in the finalisation of the event report that is to be published at the same time as the present report.

The Transatlantic Divide



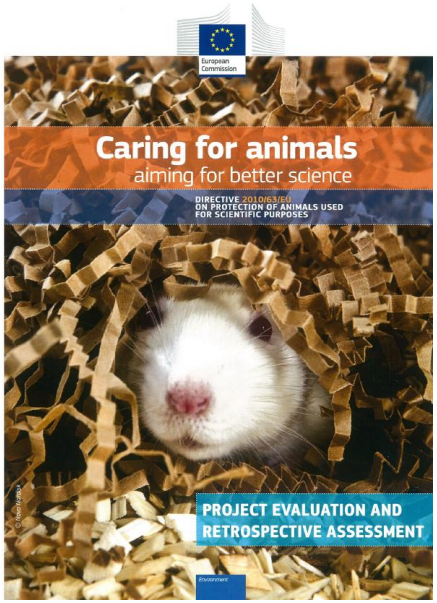
National Research Council
報告書（2007年）

Top-down development of new toxicological tools

Tox-21c

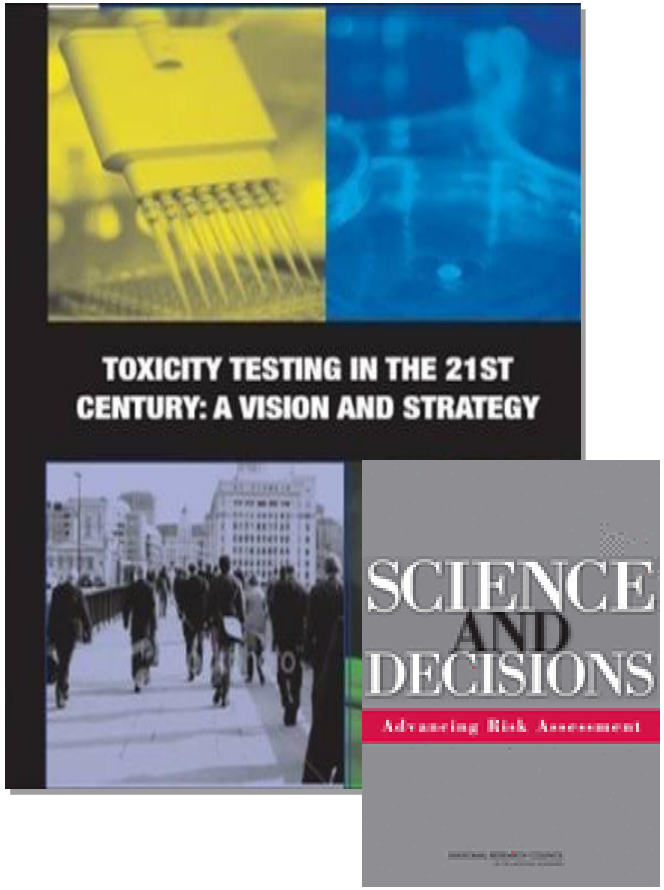
3Rs

Bottom-up support to alternative methods and legislative pressure



JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

The NTP Roadmap are consistent with the recent NAS Report



- **2007 NRC Report:**
  - Calls for transforming toxicology: *"from a system based on whole-animal testing to one founded primarily on in vitro methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin."*
  - Envisions pathway-based toxicology, where pathway perturbations are used to predict adverse effects
- **2009 NRC report**: *"the realization of the promise [of the 2007 report] is at least a decade away"*

National Research Council. 2007. Toxicity Testing in the Twenty-first Century: A Vision and a Strategy. Washington, DC: National Academy of Sciences. Available: http://books.nap.edu/catalog.php?record_id=11970

EPA United States Environmental Protection Agency

ToxCast and Tox21 High Throughput Screening of Chemical Bioactivity

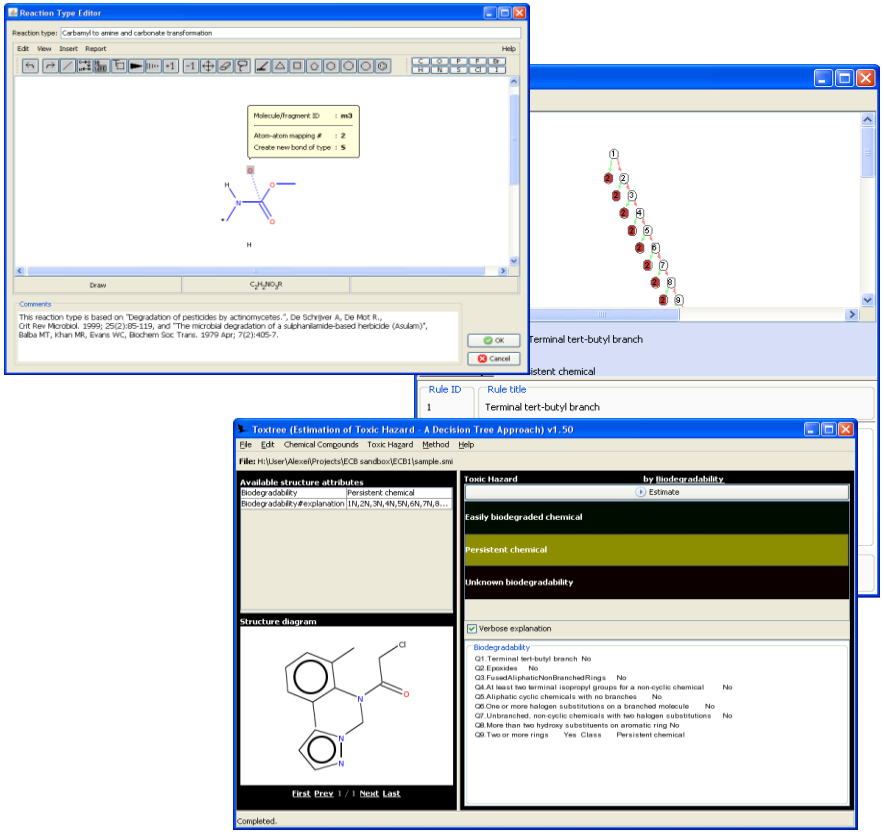
- Addresses chemical screening and prioritization needs for chemicals regulated by EPA

- Comprehensive use of HTS technologies to generate biological fingerprints and predictive signatures

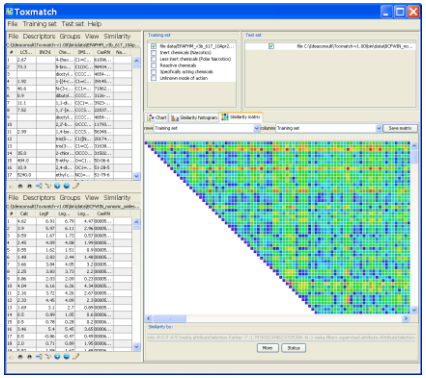
- Committed to stakeholder involvement and transparency
  - Communities of Practice- Chemical Prioritization; Exposure
  - Release of all data upon peer review publication

Computational Toxicology: physicochemical and reactivity profiling of compounds/metabolites

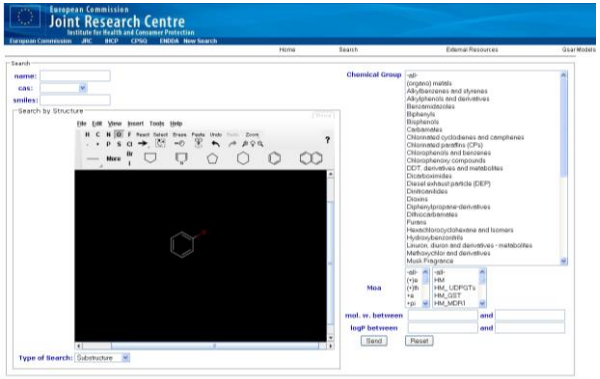
CRAFT - Chemical Reactivity And Fate Tool



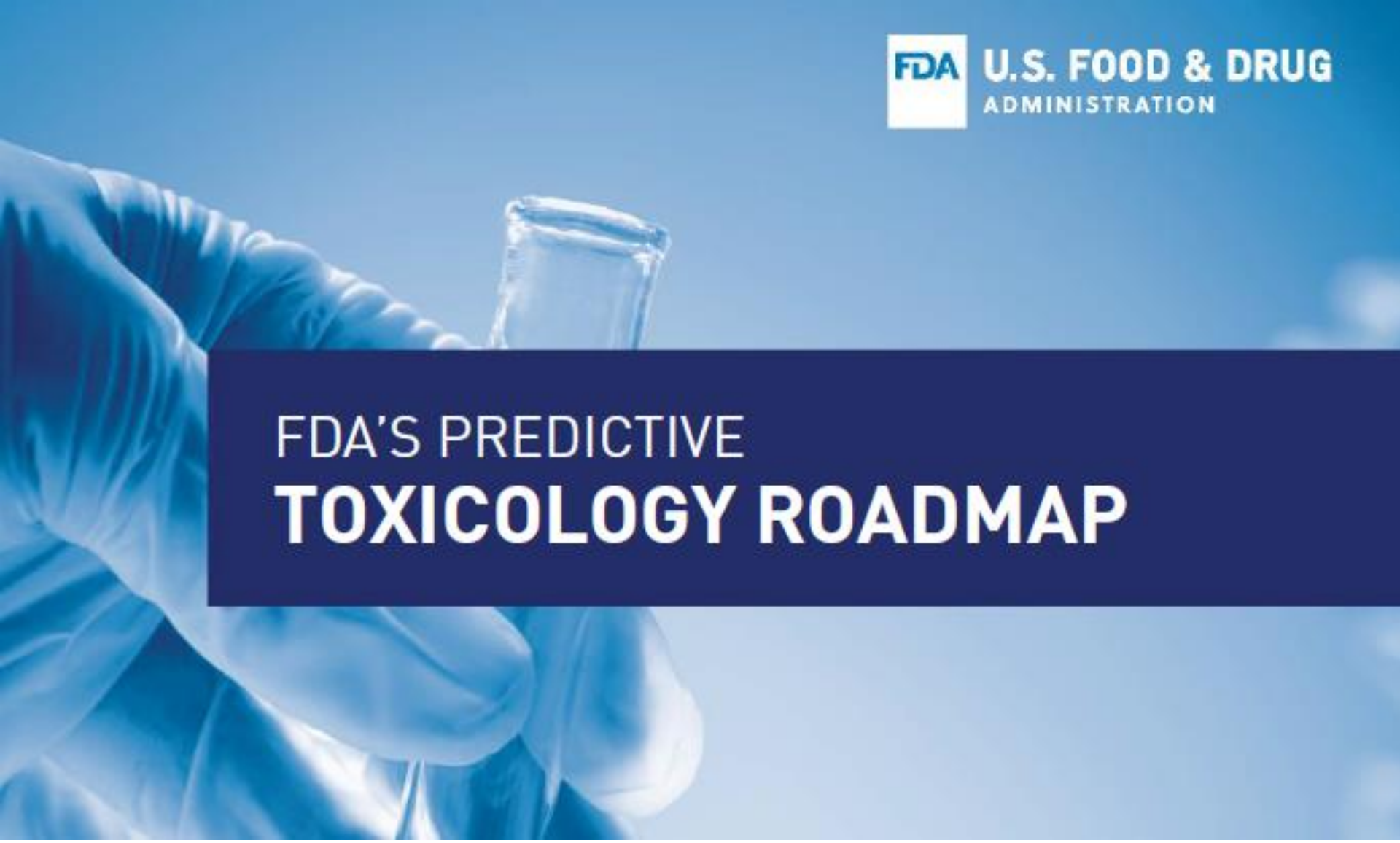
Toxtree – Hazard estimation



Toxmatch – Chemical grouping



Endocrine-Active Chemicals Database



Alternative test methods for reproductive toxicity testing

FDA's Center for Drug Evaluation and Research is working through the International Conference on Harmonisation (ICH) to consider the regulatory use of alternative test methods for reproductive toxicity testing, as outlined in the Step 2 draft guidance ICH S5(R3) available at www.ich.org.

ICH
harmonisation for better health

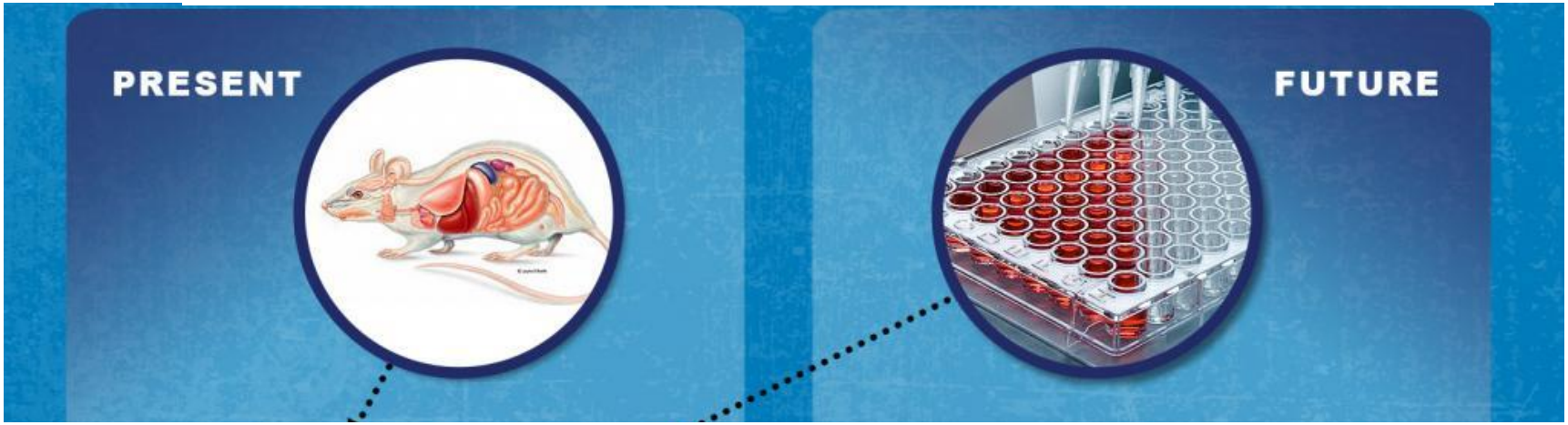
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

DETECTION OF REPRODUCTIVE AND DEVELOPMENTAL TOXICITY FOR HUMAN PHARMACEUTICALS

S5(R3)

Advancing Alternative Methods at FDA
FDA's Alternative Methods Working Group

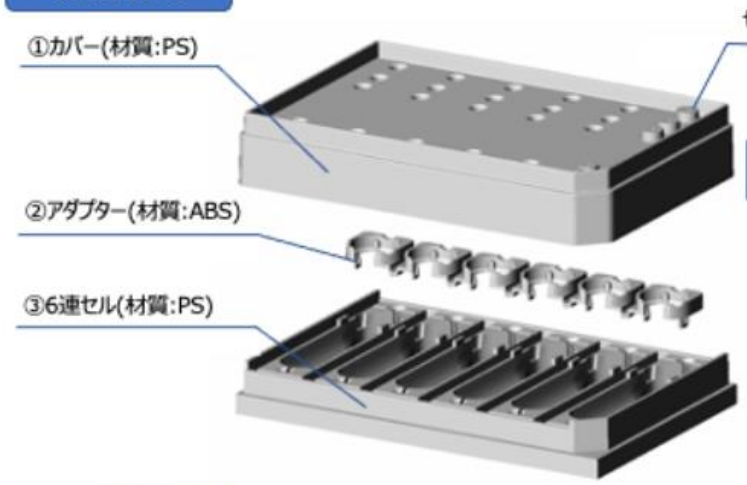


Objectives of FDA's Alternative Methods Working Group

- Discuss FDA-wide new in vitro, in vivo, and in silico methods, including research, training, and communication.
- Engage with U.S. Federal partners and global partners to promote discussion, development, and acceptance of regulatory performance criteria for such assays.
- Establish a dialogue and develop partnerships with FDA stakeholders to explore regulatory science applications for such technologies.
- Identify the performance criteria of microphysiological systems by engaging with FDA experts and FDA stakeholders through public-private partnerships.

MPS（生体模倣システム）とは？

部品構成

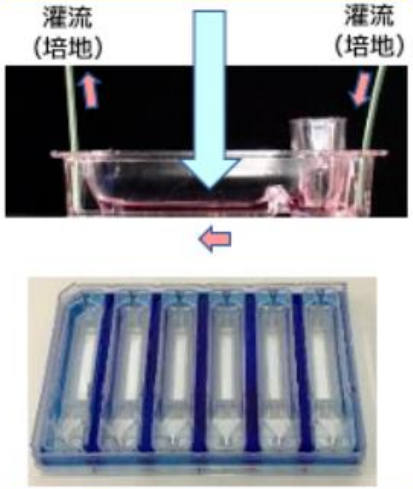


各社のインサートへの対応

アダプターにインサートを
セットした状態

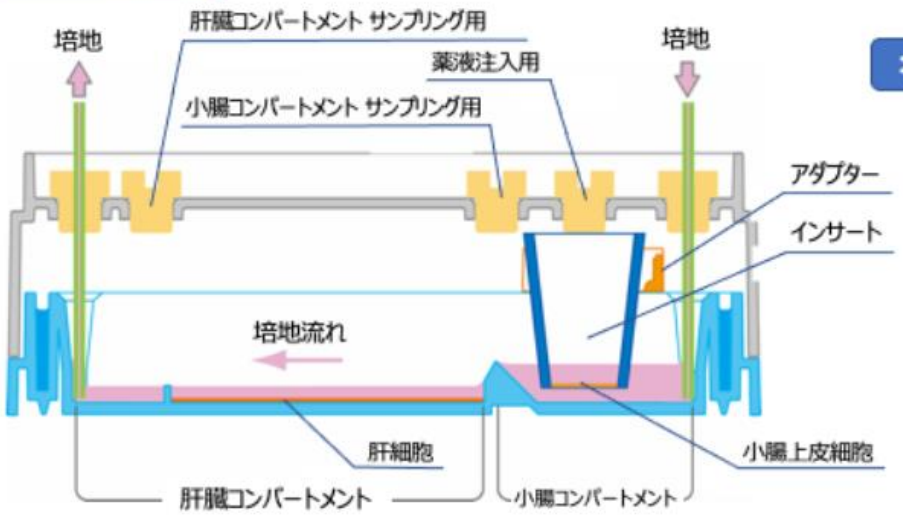
特 徴

肝臓部分の培地の深さ2～3 mm
(O_2供給と擦り応力増加)



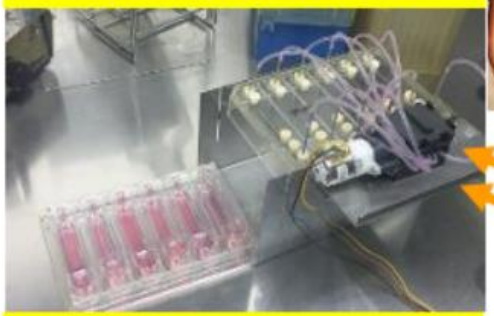
乾燥防止のプール付き(青い部分)

1well断面図



オプション

ホルダーにセット状態のデバイス



6連ポンプ
外部ホルダー

初心者も比較的容易に操作習得可能

特許出願済：特願2018-562427

IQ MPS Organotypic Manuscript Series 1.0

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Lab on a Chip

ROYAL SOCIETY OF CHEMISTRY

PERSPECTIVE

View Article Online

Check for updates

Cite this: Lab Chip, 2020, 20, 1049

Introduction to a manuscript series on the characterization and use of microphysiological systems (MPS) in pharmaceutical safety and ADME applications

Kristin Fabre,[a*] Brian Berridge,[a] William R. Proctor,[d] Sherry Ralston,[e] Yvonne Will,[f] Szczepan W. Baran,[g] Gorm Yoder[h] and Terry R. Van Vleet[i*]

Check for updates

Cite this: Lab Chip, 2019, 19, 3152

Microphysiological lung models to evaluate the safety of new pharmaceutical modalities: a biopharmaceutical perspective

Garrett R. Anslie,[a*] Myrtle Davis,[b] Lorna Ewart,[c] Linda A. Lieberman,[d] David J. Rowlands,[e] Andrew J. Thorley,[a] Gorm Yoder[f] and Anne M. Ryan[g]

Check for updates

Cite this: Lab Chip, 2020, 20, 199

Drug-induced skin toxicity: gaps in preclinical testing cascade as opportunities for complex *in vitro* models and assays

Rhiannon N. Hardwick,[a*b] Catherine J. Betts,[b] Jessica Whritenour,[c] Radhakrishna Sura,[d] Maike Thamsen,[e] Elad H. Kaufman[f] and Kristin Fabre†[g]

Check for updates

Cite this: Lab Chip, 2020, 20, 215

Liver microphysiological systems development guidelines for safety risk assessment in the pharmaceutical industry

Andreas R. Baudy,[a*] Monicah A. Otieno,[b] Philip Hewitt,[c] Jinping Gan,[d] Adrian Roth,[e] Douglas Keller,[f] Radhakrishna Sura,[g] Terry R. Van Vleet[h] and William R. Proctor[h]

Check for updates

Cite this: Lab Chip, 2020, 20, 697

Application of microphysiological systems in biopharmaceutical research and development

Norman C. Peterson,[a*] Prathap Kumar Mahalingaiah,[b] Aaron Fullerton[c] and Matteo Di Piazza[d]

Check for updates

Cite this: Lab Chip, 2020, 20, 448

Microphysiological systems for ADME-related applications: current status and recommendations for system development and characterization

Stephen Fowler,[a] Wen Li Kelly Chen,[b] David B. Duignan,[c] Anshul Gupta,[b] Niresh Hariparsad,[d] Jane R. Kenny,[e] W. George Lai,[f] Jennifer Liras,[g] Jonathan A. Phillips[h] and Jinping Gan[a*]

Check for updates

Cite this: Lab Chip, 2020, 20, 468

A pharmaceutical industry perspective on microphysiological kidney systems for evaluation of safety for new therapies

Jonathan A. Phillips,[a] Taraka Sai Pavan Grandhi,[b] Myrtle Davis,[c] Jean-Charles Gautier,[d] Niresh Hariparsad,[a] Douglas Keller,[e] Radhakrishna Sura[f] and Terry R. Van Vleet[a*]

Check for updates

Cite this: Lab Chip, 2020, 20, 1577

Developing *in vitro* assays to transform gastrointestinal safety assessment: potential for microphysiological systems†

Matthew F. Peters,[a*] Allison L. Choy,[b] Carmen Pin,[c] Derek J. Leishman,[d] Annie Moisan,[e] Lorna Ewart,[a‡] Peggy J. Guzzie-Peck,[f] Radhakrishna Sura,[g] Douglas A. Keller,[h] Clay W Scott[e] and Kyle L. Kolaja[a]

Cardiovascular microphysiological systems (CVMPS) for safety studies – a pharma perspective

Check for updates

Amy Pointon,[a] Jonathan Maher,[b] Myrtle Davis,[c] Thomas Baker,[d] Joseph Cichocki,[e] Diana Ramaiah,[f] Christopher Hale,[g] Kyle L. Kolaja,[h] Paul Levesque,[c] Radhakrishna Sura,[i] David M. Stresser[f] and Gary Gintant[a*]

Effort to Reduce Animal Testing at EPA

2018年6月：TSCAにおいて動物実験代替法の開発と実装を促すに戦略計画

↓

2019年9月：EPA長官Andrew Wheelerが動物実験を削減するため、2025年までに30%の哺乳類試験の助成削減、 2035年までに撤廃に関する指令に署名した。

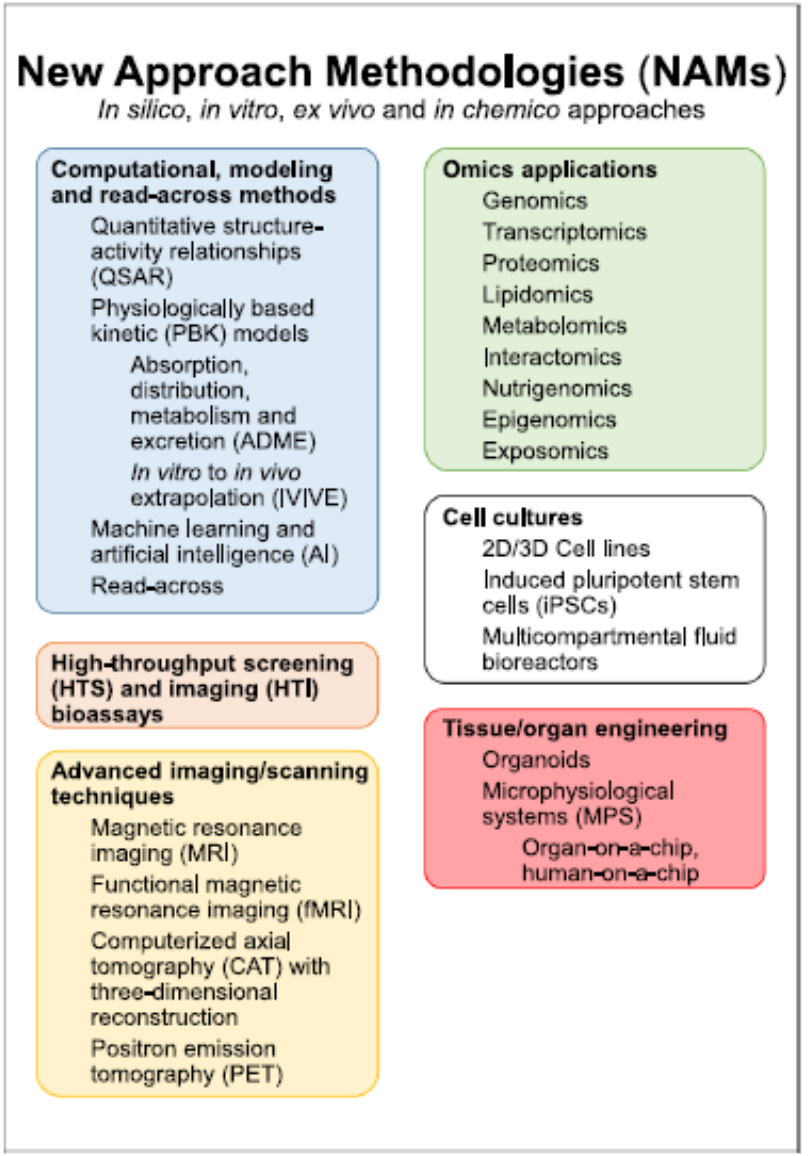
↓

2021年12月：化学物質試験における動物実験の利用削減に向けたNew Approach Methods Work Plan

Deliverable: *Reporting templates which may be used by EPA and stakeholders that capture the range of specific NAMs used for Agency decisions. An initial set of reporting templates will be delivered in the fourth quarter (Q4) of 2024.*

NAM(New Approach Methods)とは何か？

動物実験の利用を避けた化学物質の有害性およびリスク評価における情報を用いるための技術、方法、アプローチ、または組み合わせ *(USEPA)*



Environment International 178 (2023) 108082

Contents lists available at ScienceDirect

Environment International

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

Review article

New approach methodologies in human regulatory toxicology – Not if, but how and when!

Screening level assessment: combine NAMs for exposure, *in vitro* bioactivity, and toxicokinetics

- Conducted by Accelerating the Pace of Chemical Risk Assessment (APCRA)
  - *"international cooperative collaboration of government agencies convened to address barriers and opportunities for the use of new approach methodologies (NAMs) in chemical risk assessment" (Paul Friedman et al., submitted)*
- Two case studies including a large retrospective analysis and a prospective analysis
- A poster on these two case studies won the Top Abstract Award from the Risk Assessment Specialty Section at SOT 2019

(APCRA partners for these two case studies)

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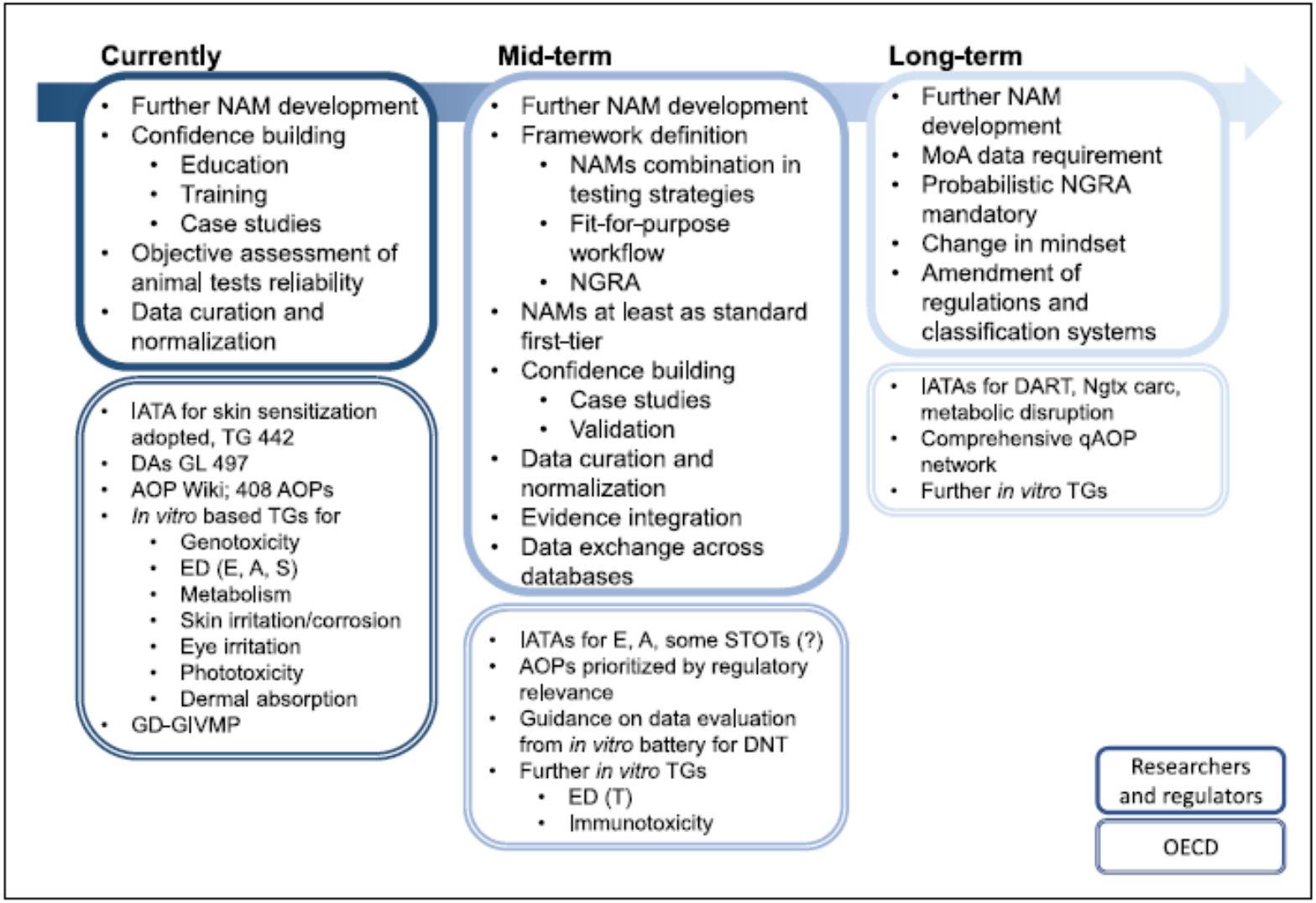
An Evaluation Framework for New Approach Methodologies (NAMs) for Human Health Safety Assessment

Publication Date : February 01, 2020

Publication Type : Journal Article

Author(s) : Stanley T. Parish, Michael Aschner, Warren Casey, Marco Corvaro, Michelle R. Embry, Suzanne Fitzpatrick, Darren Kidd, Nicole C. Kleinstreuer, Beatriz Silva Lima, Raja S. Settivari, Douglas C. Wolf, Daiju Yamazaki, Alan Boobis

Journal Name : Regulatory Toxicology and Pharmacology



Environment International 178 (2023) 108082

Fig. 2. ' stakehol left box. STOTs: s

Contents lists available at ScienceDirect

Environment International

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

NAM implementation into regulatory toxicology. Timeframe and IAMs established as OECD test guidelines are included in the bottom s; GD-GIVMP: guidance document on good *in vitro* method practices; and reproductive toxicology; Ngtx carc: non-genotoxic carcinogens.

Review article

New approach methodologies in human regulatory toxicology – Not if, but how and when!

117TH CONGRESS
2D SESSION

S. 5002

To allow for alternatives to animal testing for purposes of drug and biological product applications.

IN THE SENATE OF THE UNITED STATES

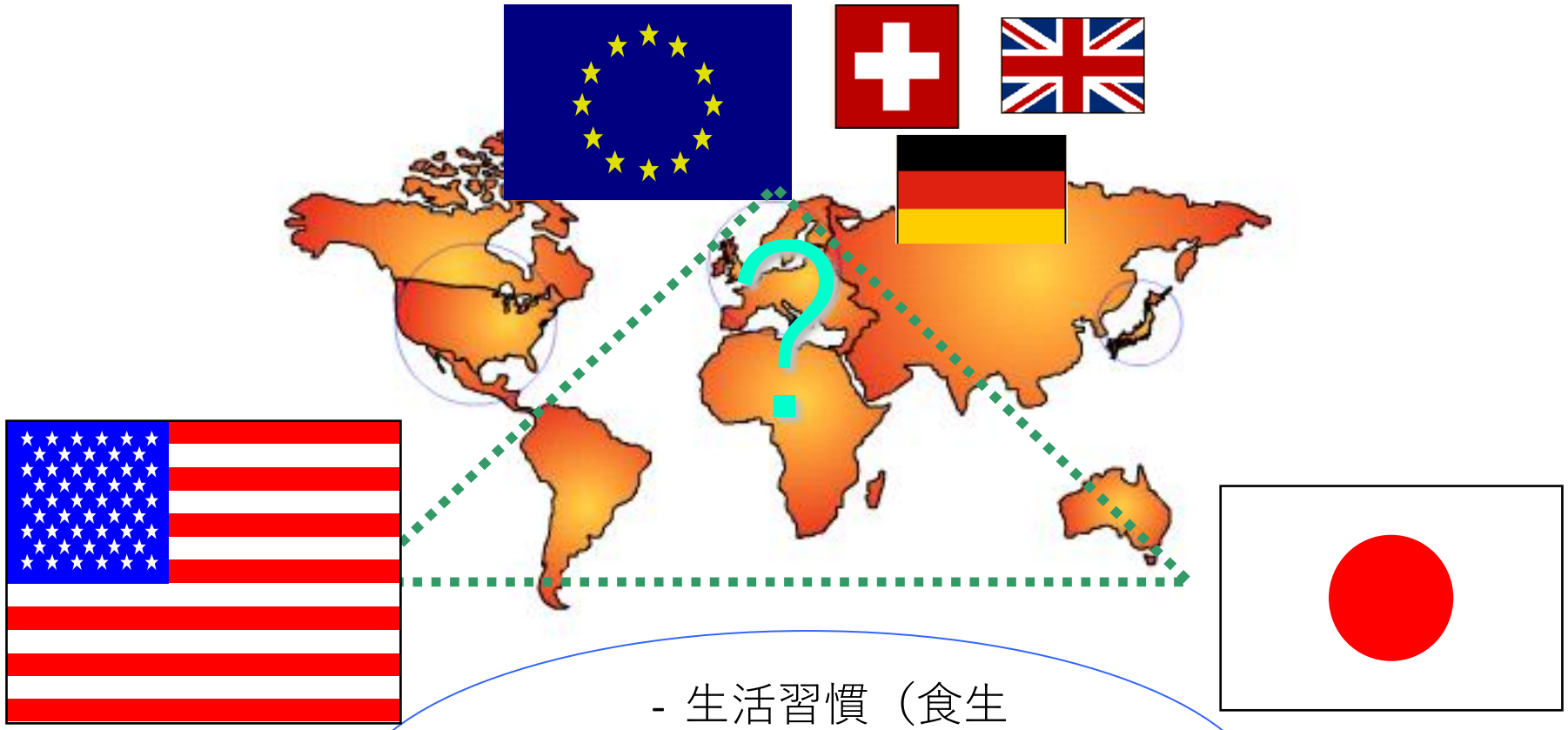
SEPTEMBER 29, 2022

Mr. PAUL (for himself, Mr. BOOKER, Mr. BRAUN, Mr. CRAPO, Mr. MARSHALL, Ms. COLLINS, Mr. KING, Mr. PADILLA, Mr. SANDERS, Mr. TUBERVILLE, Mr. LUJÁN, and Mr. SCOTT of Florida) introduced the following bill; which was read twice, considered, read the third time, and passed

NONCLINICAL TEST DEFINED.—For purposes of this section, the term 'nonclinical test' means a test conducted in vitro, in silico, or in chemico, or a non-human in vivo test that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug, and may include animal tests, or non-animal or human biology-based test methods, such as cell-based assays, microphysiological systems, or bioprinted or computer models.''.

ハーモナイゼーション・標準化

国際的な競争！、国際化！



ハードル

- 生活習慣（食生活）
- 宗教観・倫理観
- 社会的な関心
- 法律体系

故池田卓也博士より

国際規制組織との協調

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISO: International Organization for Standardization

OECD テストガイドライン ヒト健康に関する TGと動物実験を用いない試験法の割合（2023）

分類	TG数	*in vitro, in chemico* のTG数
腐食性	3	3
皮膚刺激性	2	1
光毒性	3	3
眼刺激性	10	9
皮膚感作性	8	4
経皮吸収	2	1
遺伝毒性	13	5
内分泌かく乱	6	4
その他	29	1
合計	76	31

OECD
BETTER POLICIES FOR BETTER LIVES

40%達成！

OECD:http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm

JaCVAMが成立・改定に寄与した日本発のOECD TG, GD, DRP

- ✓ Skin sensitization assay, LLNA：DA, TG 442A (2010)
- ✓ Skin sensitization assay, LLNA：BrdU-ELISA , TG 442B (2010)
- ✓ *In vivo* comet assay TG 489 (2014)
- ✓ Skin irritation assay with LabCyte EPI-MODEL 24, TG 439 (2013)
- ✓ Performance-based Test Guideline for stably transfected transactivation *in vitro* assays to detect estrogen receptor agonists and antagonist, Revised TG 455 (2015)
- ✓ Bhas 42 cell transformation assay (2016) Guidance document
- ✓ h-CLAT assay for skin sensitization testing, TG442E (2016)
- ✓ IL-8 Luc assay for skin sensitization testing, TG442E (2017)
- ✓ Eye irritation assay with LabCyte CORNEA-MODEL, TG492 (2018)
- ✓ LabCyte EPI-MODEL for skin corrosivity testing, OECD TG431 (2019)
- ✓ ROS assay for photosafety testing, TG495 (2019)
- ✓ Short time exposure (STE) assay for eye irritation testing, TG491 (2020)
- ✓ Stable transfected transcriptional activation (STTA) assay for androgen disruptor screening (AR-Ecoscreen), TG458 (2020)
- ✓ Vitrigel-EIT for eye irritation testing, TG494 (2021)
- ✓ ADRA for skin senstisation testing, TG442C (2021)
- ✓ Detailed Review Paper (DRP) for in vitro tests addressing immunotoxicity (2022)
- ✓ ADRA for skin senstisation testing, TG442C改定 (2022)
- ✓ IL-8 Luc assay for skin sensitization testing, TG442E改定 (2023)
- ✓ IL-2 Luc assay for immunotoxicity testing (2023)

赤字:2022年と2023年

「医薬品の臨床試験及び製造販売承認申請のための非臨床安全性試験の実施についてのガイダンス」について

１．背景

優れた医薬品の国際的な研究開発の促進及び患者への迅速な提供を図るため、承認審査資料の国際的なハーモナイゼーション推進の必要性が指摘されている。このような要請に応えるためＩＣＨが組織され、その合意に基づき、本ガイドラインが改正された。

２．改正の要点

動物実験の３Ｒ（使用動物数の削減／苦痛の軽減／代替法の利用）の原則に従って、各非臨床試験に関する見直しを行うとともに、新たに、一般毒性試験のための高用量の選択、早期探索的臨床試験のための非臨床試験、免疫毒性、光安全性試験、薬物乱用に関する非臨床試験及び配合剤のための非臨床試験等の考え方についての指針を示した。

ICH
harmonisation for better health

ICH S5（医薬品毒性試験法ガイドライン　生殖発生毒性試験）の試験戦略に、代替法の記述が追加

4.2.2 EFDリスクに対処するための代替アプローチ

4.2.2.1 代替法の利用

胚・胎児発生（EFD)に対する潜在的有害性を検出するために、*in vitro*、*ex vivo*や非哺乳類を用いた*in vivo*などのいくつかの代替法が開発されている。これらの代替法はEFDに対する有害作用に関する創薬スクリーニングに使用され、毒性作用機序の理解を深める一助となっており、（特にヒト特異的な標的について）非臨床データをヒトでのリスクに外挿する上で役立つ場合もある。これらの目的で代替法を継続的に利用することが推奨される。

VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

動物用医薬品の国際規制

VICH/07/038
Final
18 September 2007

Statement of Principle for VICH – Alternatives to Animal Testing

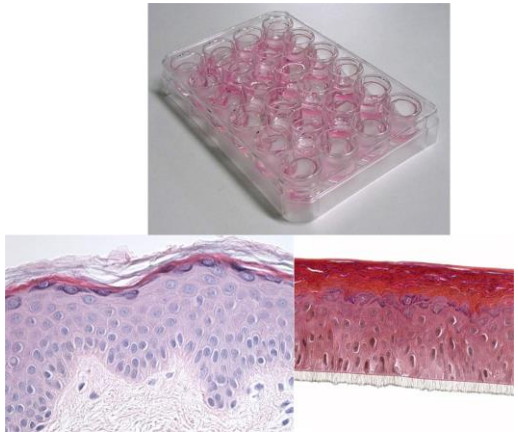
At its 19th meeting on 23-24 January 2007 in Washington D.C., USA, the VICH Steering Committee reiterated its ambition to minimise animal testing and specifically expressed its support for the 3Rs principle – replacement, refinement and reduction of animals in research.

VICH has always striven to eliminate repetitious and unnecessary testing through harmonisation of regulatory requirements for the registration of veterinary products, a goal that undoubtedly leads to a reduction in the number of animals used for product development and registration.

While the validation of alternative testing protocols[1] falls outside the remit of VICH, the Steering Committee recognises that the international status and influence of VICH provide a unique opportunity to encourage the use of validated alternative methods. To this end, Expert Working Groups developing guidelines involving animal experimentation have a specific responsibility to consider animal welfare, and particularly the possibilities for replacement, refinement and reduction of animal testing

ISO 10993-23（国際標準化機構が定める国際規格　医療機器における刺激性試験）

2021年1月、再構成ヒト皮膚モデルを用いる刺激性試験が取り入れられた。



ブラジル、カナダ、欧州連合、アメリカおよび日本の規制当局と業界で開催される、化粧品の規制と安全性に関する会議

4. Updated Inventory of validated alternatives to animal testing applicable for cosmetic products.

5. Integrated Strategies for Safety Assessments of Cosmetic Ingredients

- ICCR SC endorsed the "Paving the way for Application of Next Generation Risk Assessment to safety decision-making for cosmetic ingredients" report and will post to the website.
- ICCR SC agreed that a new Joint Working Group will be formed to work on other integrated strategies projects.

小括

- 全身毒性の代替に向けて、海外の機関のNAMへの取り組みが加速している。
- ただ、新しい試験法はまだ行政的な適用条件を満たしていない。
- それぞれの分野において、NAMを用いた事例研究が増えている。

課題

- 日本人は、動物実験の３Rsを尊重している国である。
- ただし、動物実験の存続に拘り、代替法開発分野の技術革新には対応しているものの、そのビジネスプランが欠ける。
- また、行政機関の支援や受け入れが後手に回っている。

ご静聴ありがとうございました