cdisc

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# SEND, The need for the implementation of the 3Rs in animal tests

Presented by Jiwon Kim, Senior Research Scientist
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# Meet the Speaker

## Jiwon Kim

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# Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author(s) have no real or apparent conflicts of interest to report.*

# My recent work (2022-2023)

# Agenda

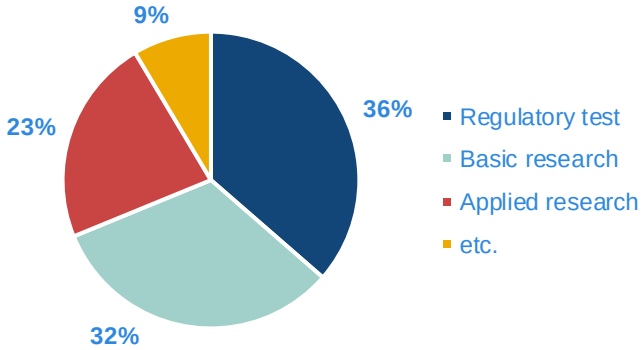
1. Alternatives to animal testing
2. Data-driven research environment
3. Virtual control groups in nonclinical studies
4. Small scale trial with KIT data
5. Requirements for the implementation of VCG and the role of KIT

# Alternatives to animal testing

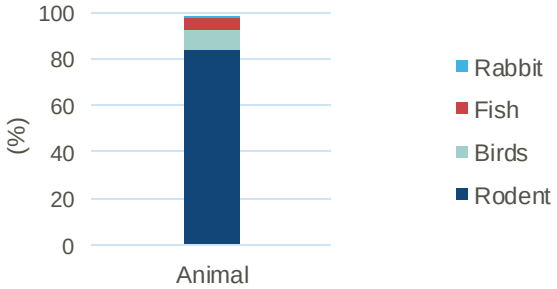
# Still increasing animal test in Korea


*Source: The Kyunghyan Shinmun, 2023. 7. 11*

**Animal usage by research field**




**Animal usage by species**



# Limitations of animal studies



High cost
Low efficiency

Animal
ethics

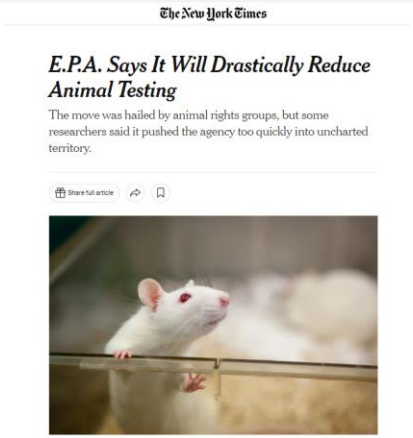

Biological
difference

VS

# Guidance to reduce animal testing

## EPA (September 2019)

- ✓ Amis to reduce the amount of studies that involve mammal testing by 30 percent by 2025
- ✓ Plans to eliminate the studies entirely by 2035



The New York Times

**E.P.A. Says It Will Drastically Reduce Animal Testing**

The move was hailed by animal rights groups, but some researchers said it pushed the agency too quickly into uncharted territory.

Share full article

## FDA (December 29,2022)

- ✓ Food and Drug Omnibus Reform Act (“FDORA”) was signed into law

• ***SEC. 3209. ANIMAL TESTING ALTERNATIVES.***

*(a)IN GENERAL.—Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) is amended*

*(1) in subsection (i)—*

*(A) in paragraph (1)(A), by **striking “preclinical tests (including tests on animals)”** and **inserting “nonclinical tests”**; and*

*(B) in paragraph (2)(B), by **striking “animal”** and **inserting “nonclinical tests”**; and*

*(2) by **inserting** after subsection (y) the following:*

*“(z) **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 nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test may include the following:*

*“(1) Cell-based assays.*

*“(2) Organ chips and microphysiological systems.*

*“(3) Computer modeling.*

*“(4) Other nonhuman or human biology-based test methods, such as bioprinting.*

*“(5) **Animal tests**.”*

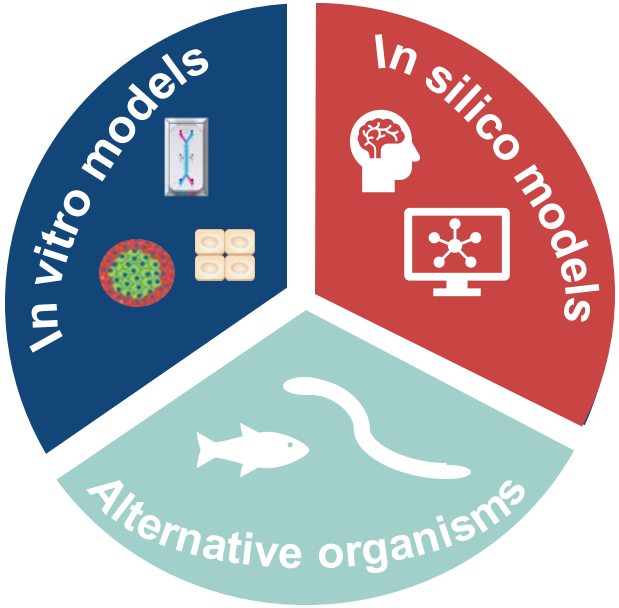
## Toxicity testing

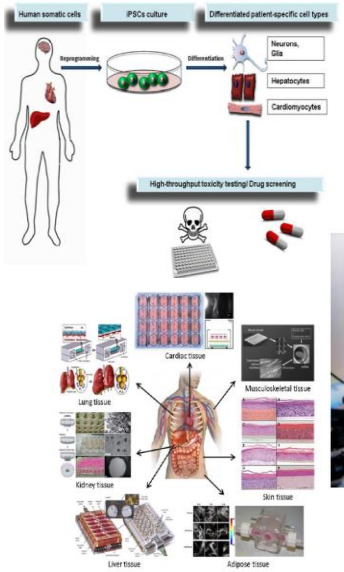
| ICH | OECD | ISO |
|---|---|---|
| Recommends prioritizing the priciples of the **3Rs** in non-clinical testing [M3(R2)] and safety assessment of biopharmaceuticals (S6) | Recommends prioritizing animal welfare and the priciples of the **3Rs** when developing toxicity testing guidelines | Recommends prioritizing animal welfare and the principles of the **3Rs** in the biological evaluation of medical devices |

# 3R Principles

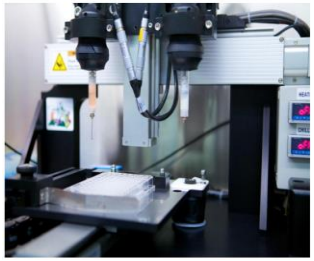
- **Replacing** the use of animals with non-animal methods where possible
- **Reducing** the number of animals used to a minimum while still obtaining scientifically valid results
- **Refining** practices to minimize the stress and improve the welfare of study animals used for regulatory purposes

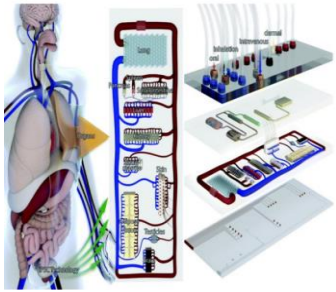
# Alternative methods







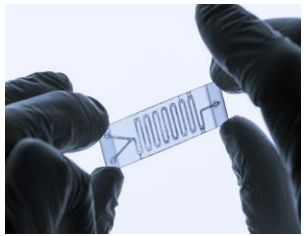


*Source: 2020-08, Technology Trends Brief, KISTEP*

# Industry trends in alternative animal testing

- Growing concern for animal ethics
- Avoiding unnecessary animal usage through the utilization of statistical methods and optimization of experimental design
- Efforts to apply various alternative test methods

- Increased growth in industries providing diverse materials and research tools, as well as the field of test services
  (Cell culture apparatus, culture vessels, 3D tissue culture containers, tissue cultureware, extracellular matrices, 3D bioprinters, image analysis equipment, machine learning-based toxicity prediction software, and more)

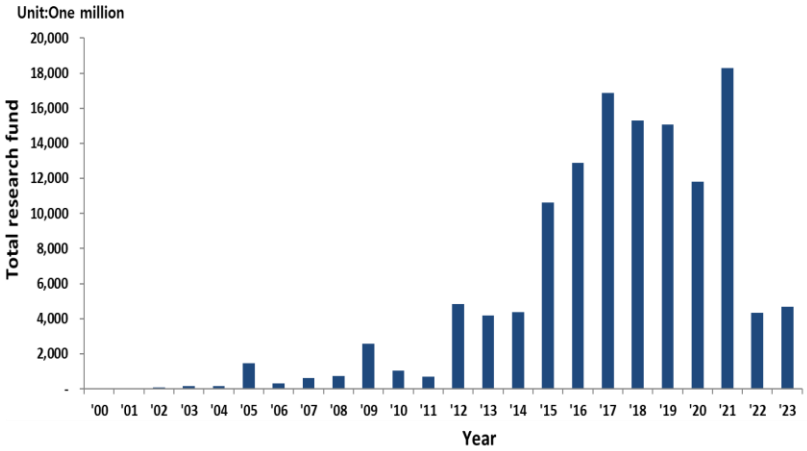


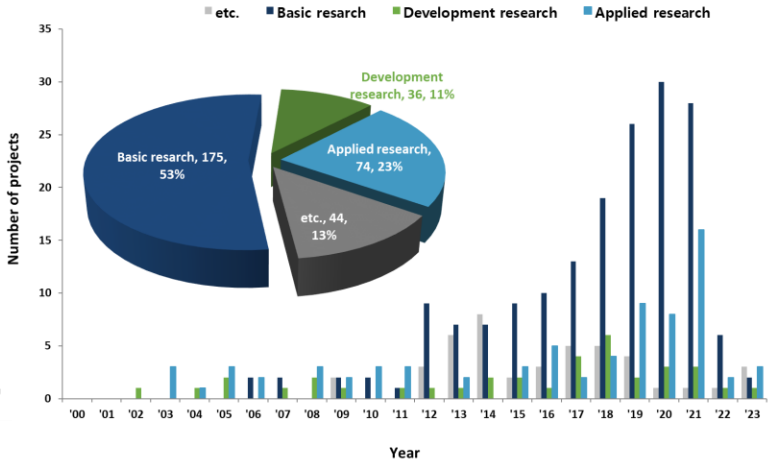
- In the field of alternative animal testing methods, organ chip technology is anticipated to be the future core technology, with the United States and Europe emerging as the major markets

***Source: 2020-08, Technology Trends Brief, KISTEP***

# Trend analysis of research projects on animal alternative testing technologies

| Data analysis | |
|---|---|
| Database | NTIS (National Science & Technology information Service), Korea |
| Method and Result | Keyword search formula, 2,340 cases |
| Effective data | 329 cases |



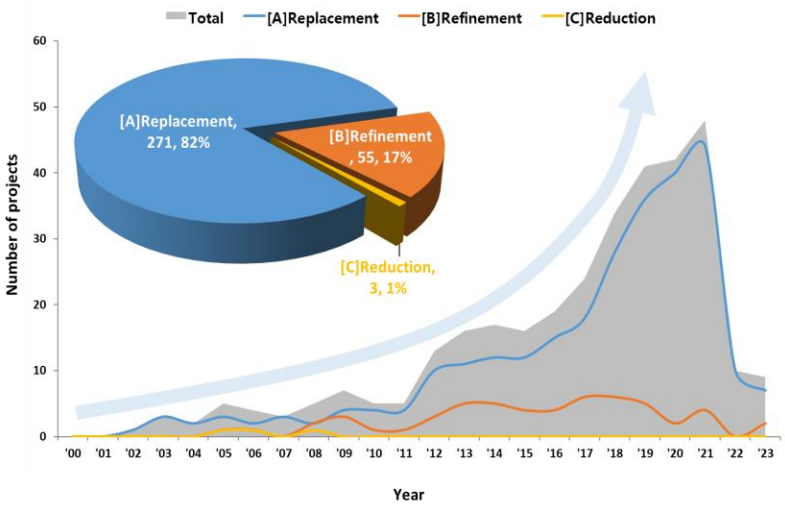



# Trend analysis of research projects on animal alternative testing technologies (Contiued)

| 3Rs | Number of projects based on the Technology Life Cycle-Characteristics of R&D | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Introduction | | | | | Growth | | | | | Maturity | | | |
| | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| Replacement | 85 | 21 | 21 | 43 | 7 | 28 | 14 | 16 | 21 | 1 | 5 | 1 | 0 | 7 | 1 |
| Refinement | 0 | 0 | 0 | 1 | 35 | 0 | 0 | 0 | 0 | 15 | 0 | 0 | 0 | 0 | 4 |
| Reduction | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Total | 85 | 21 | 21 | 44 | 43 | 28 | 14 | 16 | 21 | 17 | 5 | 1 | 0 | 7 | 6 |

*1; Idea development* *3; Product/process development* *5; etc.*

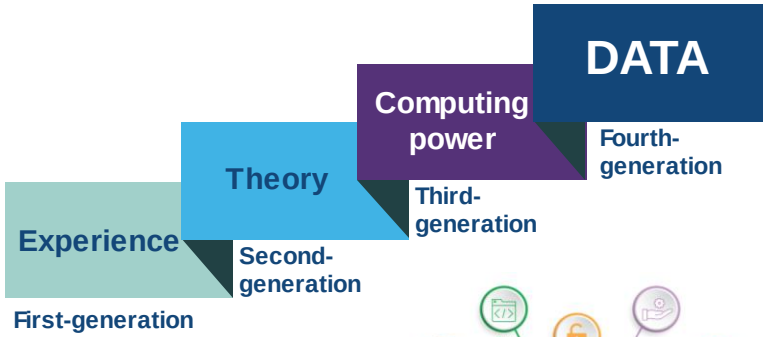
*2; Prototype development* *4; Test method validation/development*



# Data-driven research environment

# Data-driven research environment

## A shift in research paradigm




UNESCO adopted the 'Recommendation on Open Science' unanimously by all 193 member states during the 41st General Conference. (November 23, 2021)

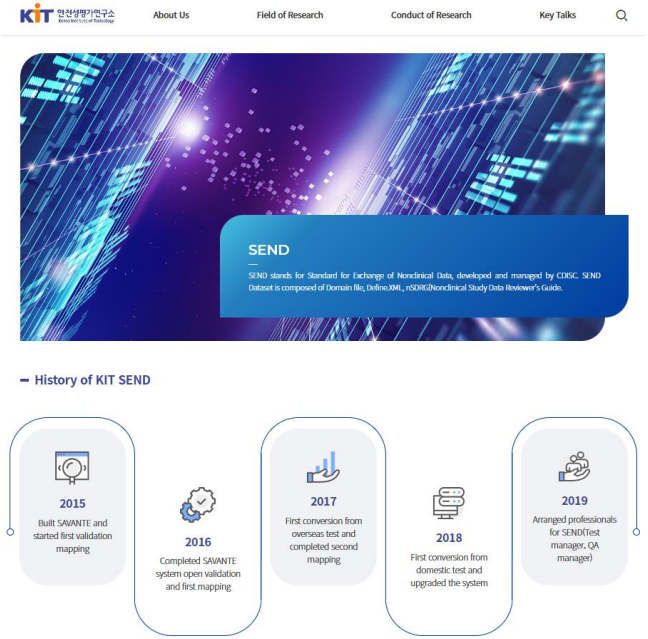

*Source: UNESCO, 2020*

## Preservation and utilization of research data

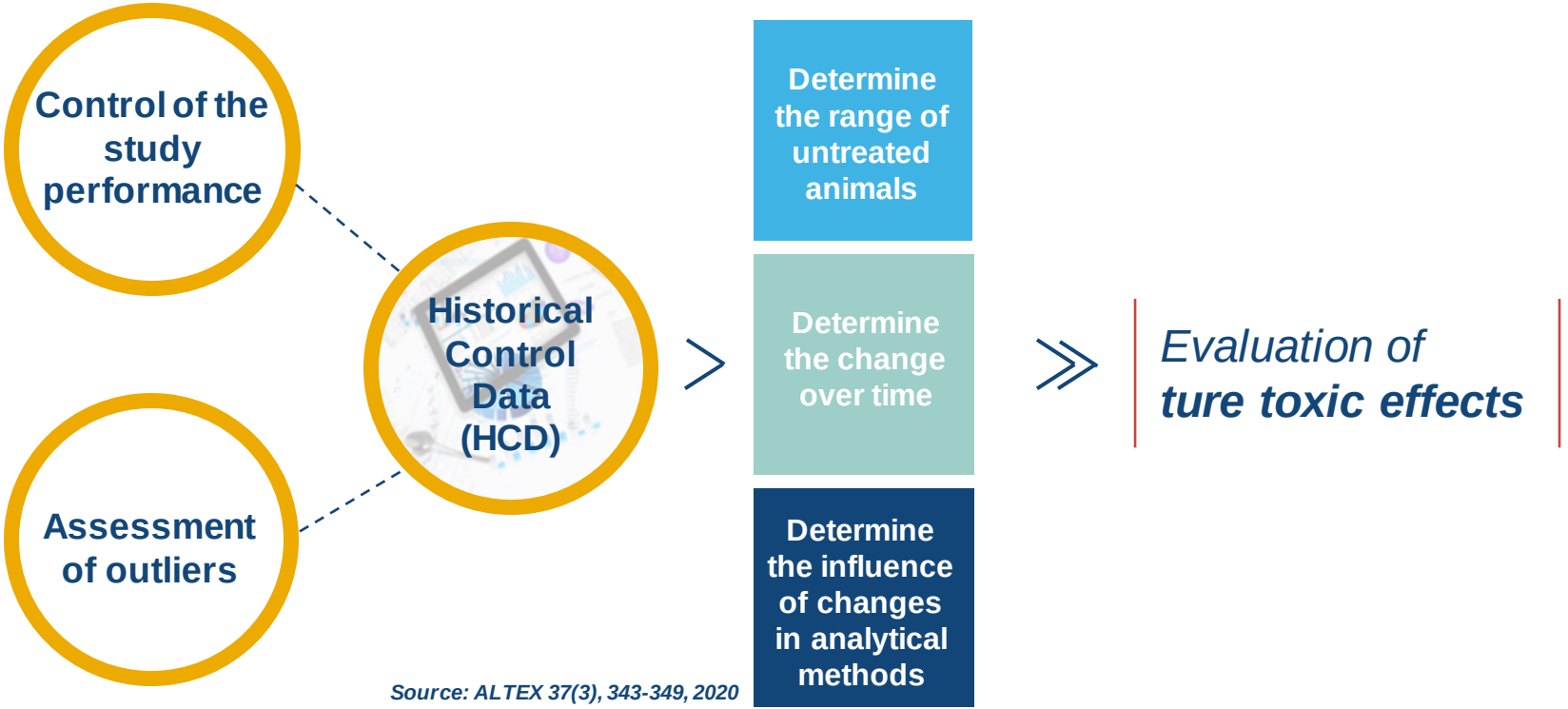

- Enactment of a bill promoting the management and utilization of national research data (국가연구데이터 관리 및 활용 촉진에 관한 법률안 제정)
- 입법예고 (‘23.9.27-’23.11.6) 후 법제처 심사 중

# Data from KIT

- **1987** — Establishment of safety Research Center, Korea Research Institute of Chemical Technology (KRICT)
- **1988** — Certification as a GLP-compliant Testing Organization by the Ministry of Health & Welfare (Current. the Ministry of Food and Drug Safety)
- **2000** — OECD Mutual Visit and Evaluation
- **2002** — Inauguration of the Korea Institute of Toxicology (KIT) as an affiliated institute to KRICT
- **2005** — US FDA Inspection
- **2008** — Completion of the Jeonbuk Department of Inhalation Research Test Building
- **2012** — Completion of the Gyeongnam Department of Environmental Toxicology Chemistry
- **2013** — Accreditation as a Qualifying Testing Organization by the U.S. FDA with the Voluntary Action Indicated (VAI) Inspection Classification
- **Present**



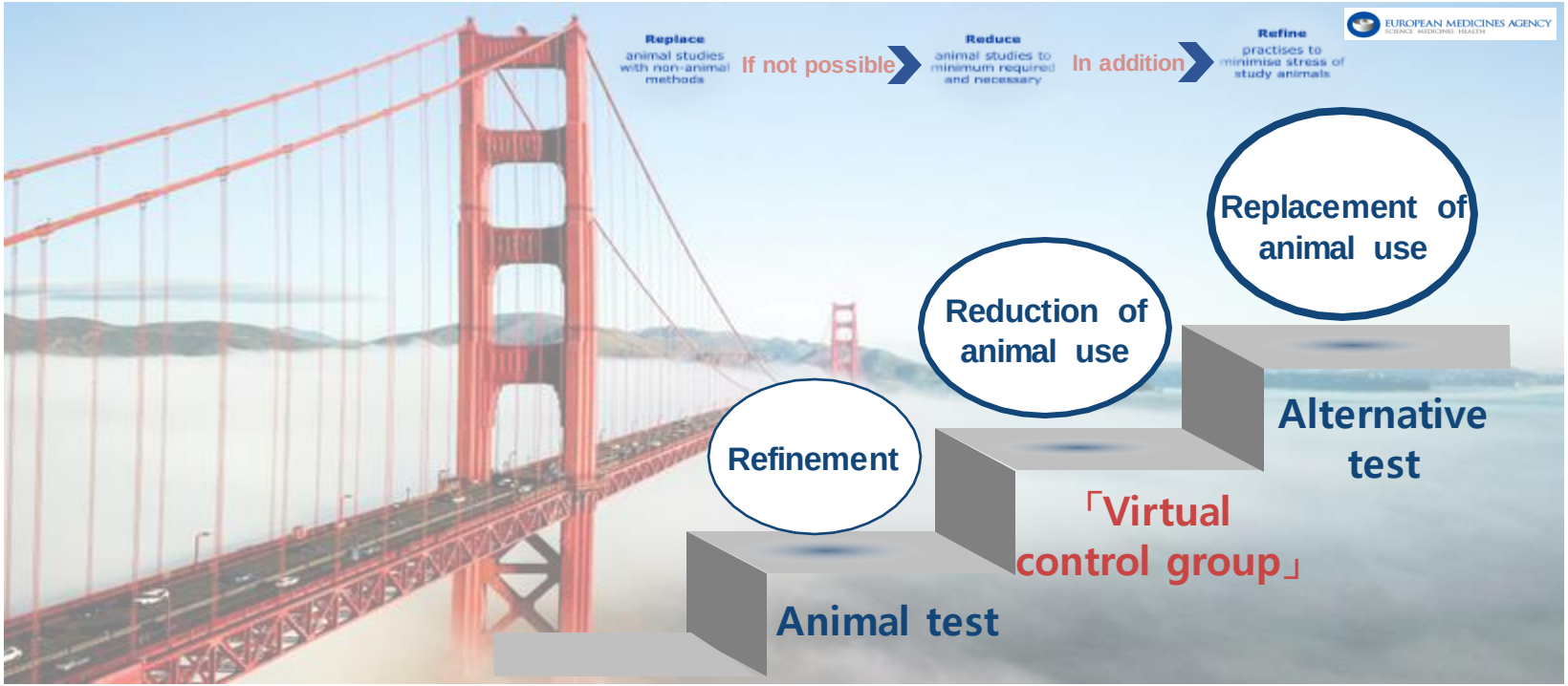
# Historical control data in nonclinical studies




*Source: ALTEX 37(3), 343-349, 2020*

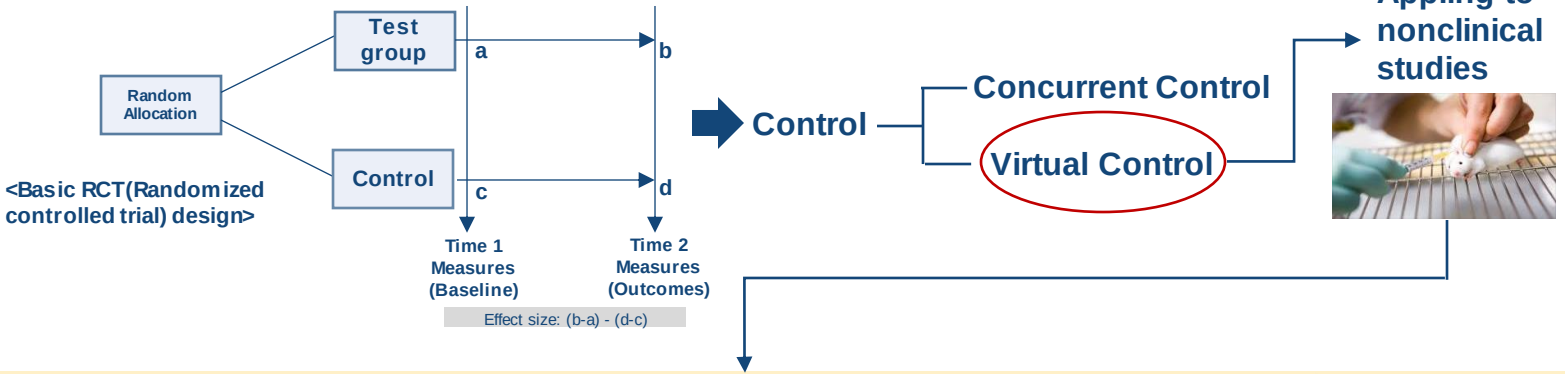
# Virtual control groups in nonclinical studies

# First, reduction of animal use

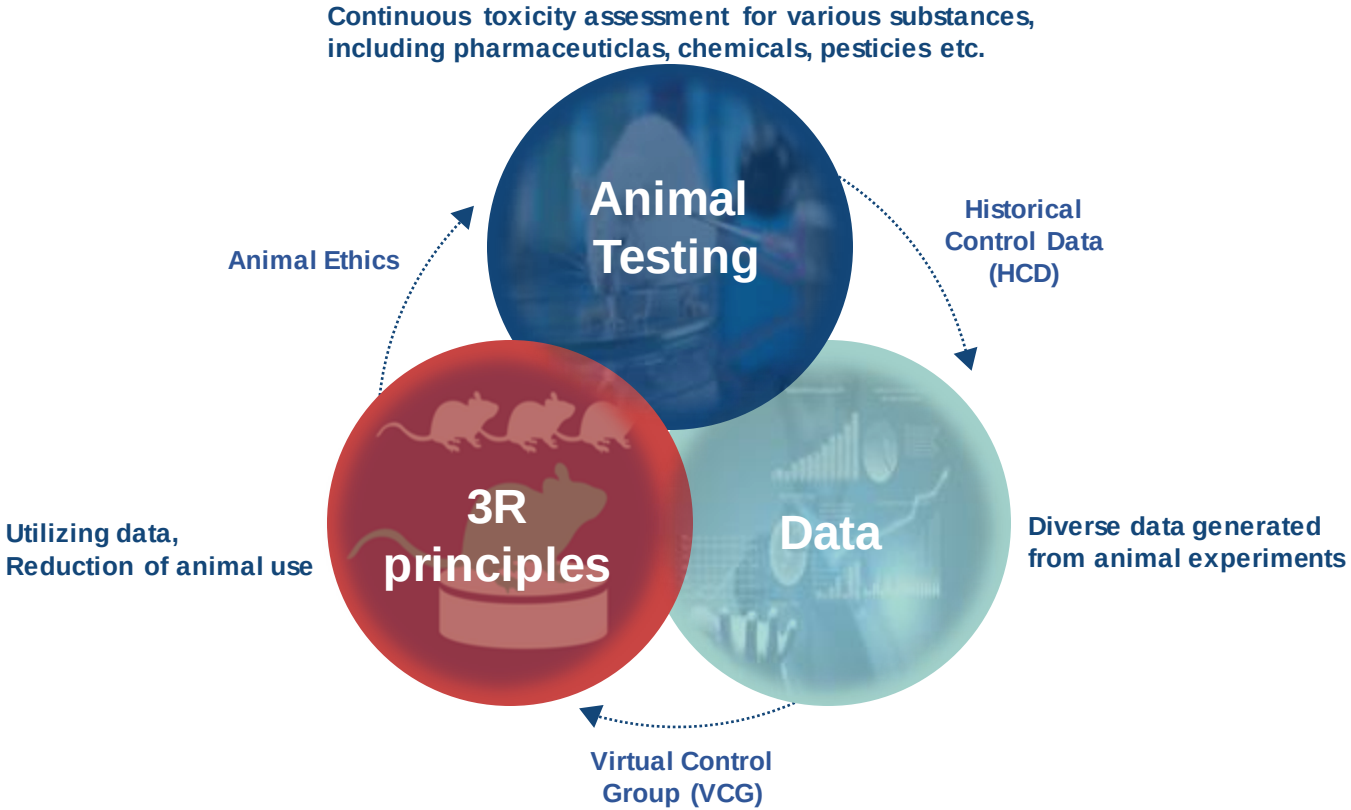


# Virtual Control Group (VCG)

Concept of the virtual control group, which is well established in clinical trials

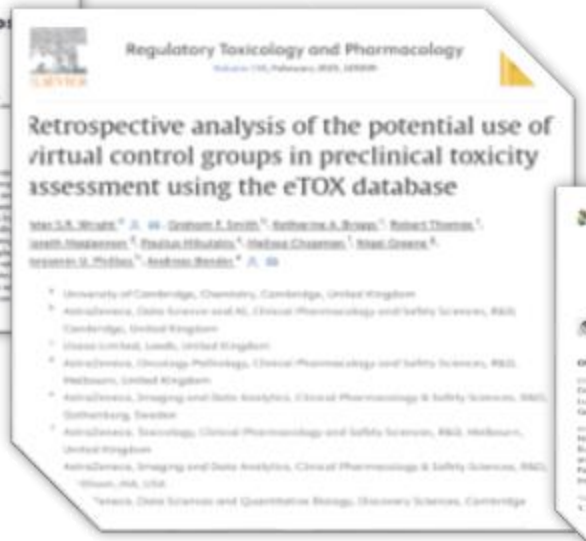


# Sustainable Animal Testing

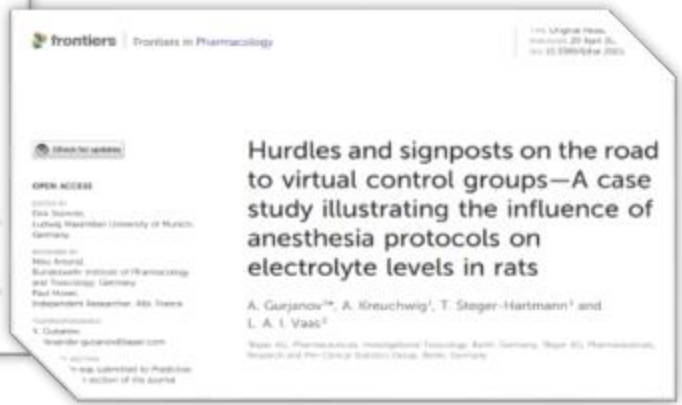


# Recent research on the VCGs in nonclinical studies


2020.2

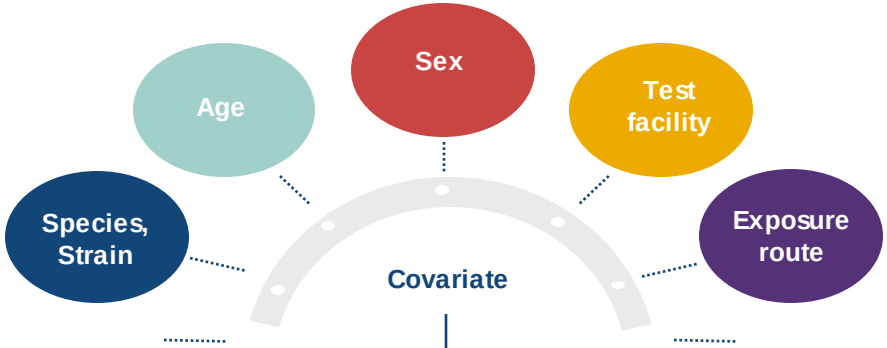



2023.2




2023.4

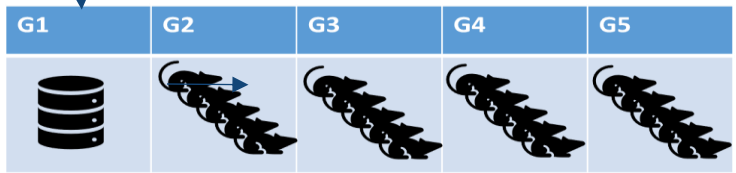
# Verifying the feasibility with KIT data




**KIT Historical Control Data (HCD)**

Data collection and standardization

Ex) FDA SEND

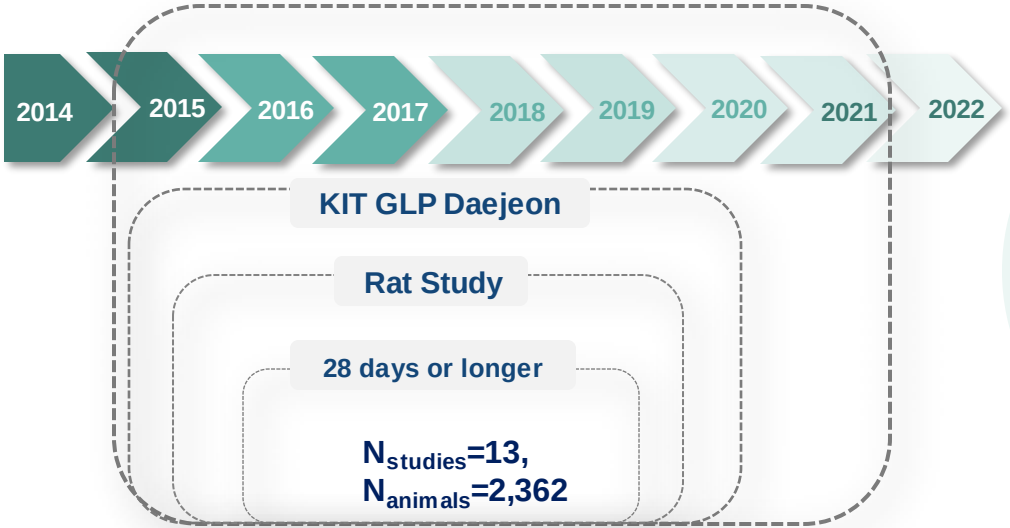


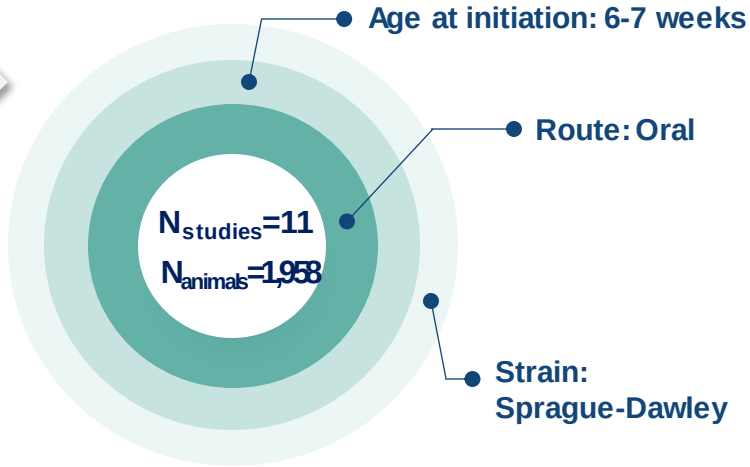
# Small scale trial with KIT data

# VCG with KIT Data_Dataset

## ❖ Small scale trial

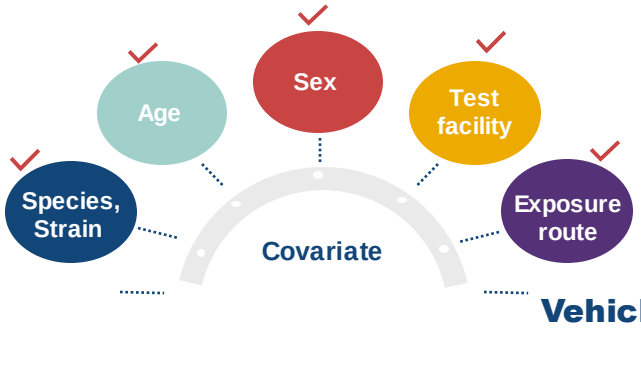
- ✓ Collection of harmonized data (SEND format)
- ✓ Data selection for generating VCG



# VCG with KIT Data_Vehicle type

✓ Data classification based on types of vehicles



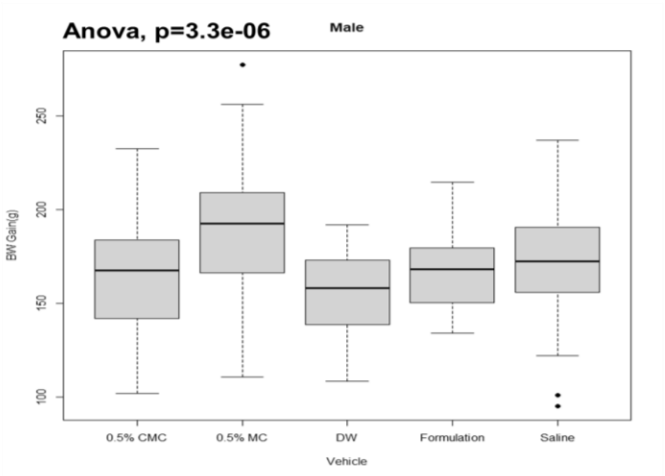

| | | |
|---|---|---|
| 0.5% MC | $N_{studies}$=4 | $N_{animals}$=826 |
| | $N_{vehicle\ animals(M)}$=62 | |
| | $N_{vehicle\ animals(F)}$=62 | |
| Saline | $N_{studies}$=3 | $N_{animals}$=420 |
| | $N_{vehicle\ animals(M)}$=45 | |
| | $N_{vehicle\ animals(F)}$=45 | |
| 0.5% CMC | $N_{studies}$=2 | $N_{animals}$=404 |
| | $N_{vehicle\ animals(M)}$=39 | |
| | $N_{vehicle\ animals(F)}$=39 | |
| DW | $N_{studies}$=1 | $N_{animals}$=140 |
| | $N_{vehicle\ animals(M)}$=15 | |
| | $N_{vehicle\ animals(F)}$=15 | |
| Formulation; 10% LM 2125 CS in LLW solution + 0.5% MC in DW (35:65(v/v)) | $N_{studies}$=1 | $N_{animals}$=168 |
| | $N_{vehicle\ animals(M)}$=15 | |
| | $N_{vehicle\ animals(F)}$=15 | |

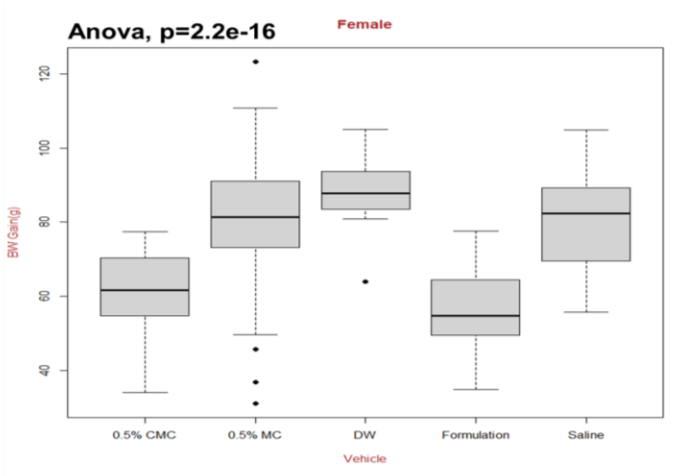
# VCG with KIT Data_The impact of the vehicles

✓ **Analysis of the impact of vehicle types on key endpoints**

**Weight gain (Day1-Day29)**

ANOVA analysis after confirming normality and equal variance (R software, version 4.3.1)



# VCG with KIT Data_ The impact of the vehicles

## ✓ Analysis of the impact of vehicle types on key endpoints (*contiuned*)

### Microscopic findings

-SEND parameter, “MISTRESC”
-Incidence: The frequency of the finding per total animals

| KIDNEY | Incidence (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5% MC | | Saline | | 0.5% CMC | | DW | | Formulation | |
| Microscopic Finding (MISTRESC) | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| BASOPHILIA | 13 | 13 | 36 | 11 | 31 | 6 | 20 | 0 | 47 | 7 |
| INFILTRATE | 27 | 27 | 36 | 22 | 56 | 24 | 47 | 27 | 60 | 20 |
| MINERALIZATION | 2 | 24 | 9 | 29 | 10 | 21 | 0 | 20 | 0 | 7 |
| CAST | 3 | 11 | 13 | 13 | 10 | 0 | 0 | 0 | 13 | 0 |
| DILATATION | 0 | 0 | 24 | 13 | 21 | 6 | 7 | 0 | 0 | 0 |

| LIVER | Incidence(%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5% MC | | Saline | | 0.5% CMC | | DW | | Formulation | |
| Microscopic Finding (MISTRESC) | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| INFILTRATE | 13 | 71 | 64 | 58 | 64 | 56 | 80 | 107 | 67 | 67 |
| VACUOLATION | 18 | 15 | 13 | 7 | 23 | 9 | 20 | 7 | 7 | 0 |
| TENSION LIPIDOSIS | 0 | 0 | 27 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |

# VCG with KIT Data_ The impact of the vehicles

✓ **Analysis of the impact of vehicle types on key endpoints (*contiuned*)**

**Microscopic findings**

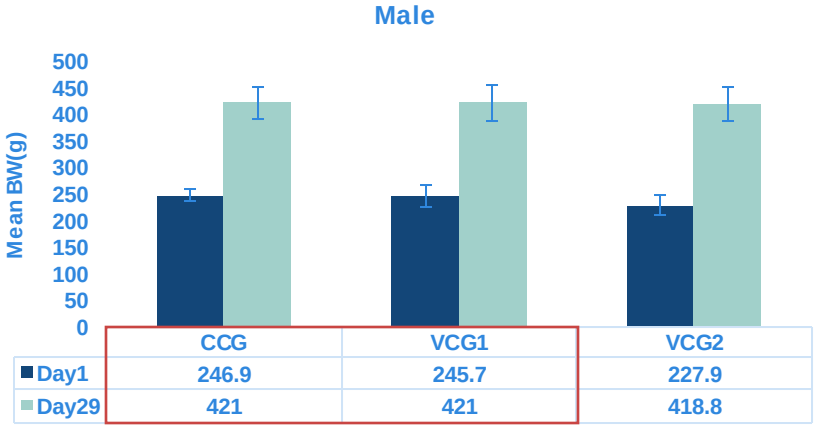
-SEND parameter, “MISTRESC”
-Incidence: The frequency of the finding per total animals

| PANCREAS, LUNG/BRONCHUS, LARGE INTESTINE | Incidence(%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5% MC | | Saline | | 0.5% CMC | | DW | | Formulation | |
| Microscopic Finding (MISTRESC) | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| PANCREAS/INFILTRATE | 31 | 6 | 22 | 9 | 8 | 15 | 7 | 20 | 7 | 7 |
| PANCREAS/ATROPHY | 5 | 0 | 13 | 0 | 3 | 12 | 7 | 0 | 0 | 0 |
| LUNG/BRONCHUS/ AGGREGATE | 3 | 2 | 24 | 13 | 0 | 0 | 7 | 13 | 0 | 0 |
| LUNG/BRONCHUS/ INFILTRATE | 0 | 8 | 31 | 11 | 10 | 12 | 7 | 0 | 0 | 0 |
| LARGE INTESTINE/ CECUM/INFILTRATE | 0 | 0 | 0 | 0 | 26 | 18 | 0 | 0 | 0 | 0 |
| LARGE INTESTINE COLON/INFILTRATE | 0 | 0 | 0 | 0 | 10 | 12 | 0 | 0 | 0 | 0 |

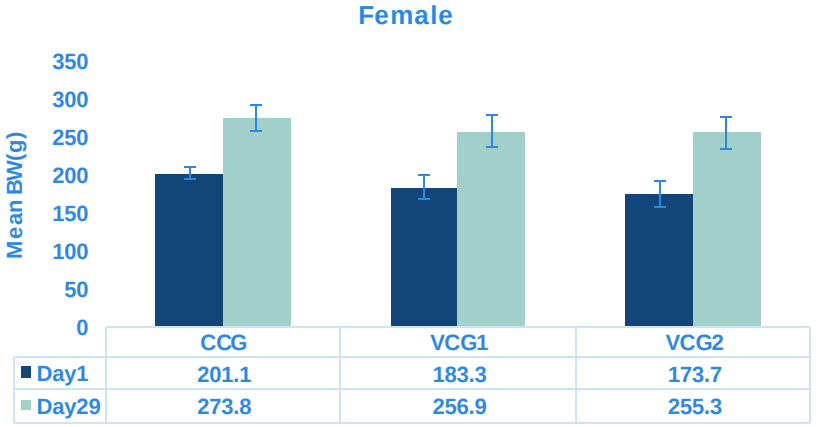
| HEART, GLAND,THYROID/PARATHYROID, LYMPH NODE, MESENTERIC | Incidence(%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5% MC | | Saline | | 0.5% CMC | | DW | | Formulation | |
| Microscopic Finding (MISTRESC) | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| HEART/INFILTRATE | 5 | 2 | 49 | 11 | 31 | 9 | 13 | 7 | 40 | 0 |
| GLAND, THYROID/ GLAND, PARATHYROID/ CYST | 0 | 8 | 0 | 0 | 0 | 0 | 20 | 13 | 0 | 0 |
| LYMPH NODE, MESENTERIC/ CELLULARITY, INCREASED | 2 | 0 | 0 | 2 | 5 | 3 | 0 | 0 | 13 | 20 |

# VCG with KIT Data_Feasibility of replacing CCG

**Vehicle of CCG; 0.5% MC, Number of animals; 15/sex/dose**




| | CCG | VCG1 | VCG2 |
|---|---|---|---|
| Day1 | 246.9 | 245.7 | 227.9 |
| Day29 | 421 | 421 | 418.8 |




| | CCG | VCG1 | VCG2 |
|---|---|---|---|
| Day1 | 201.1 | 183.3 | 173.7 |
| Day29 | 273.8 | 256.9 | 255.3 |

※ VCG1: Selection from the entire individual data (n=176)
VCG2: Selection from the individual data administered with the same vehicle (n=62)

※ VCG generation: Perform random sampling(n=15) 10 times in succession

# Requirements for the implementation of VCG and the role of KIT

# Strategies for implementing VCG in KIT

## Construction of harmonized database

-Investigation of the accumulation and managemen status of KIT
-Data harmonization
-DB construction and establishment of data management

## VCG Generation

-Identification of data requirements for VCG
-Establishment of criteria and procedures for dataset selection
-VCG generation (resampling, simulation etc.)

## Perfomance verification and applicaton of VCG

-Performance evaluation through retrospective analysis
-Internal and external validation
-Stepwise application

# For the successful implementation

## Criteria for the use of VCG

Reduction of animal use

- ✓ Construction of dataset for the variables affecting control animals
- ✓ Investigation of other toxicological endpoints for the utility of the VCG


## Increase of harmonized data (SEND data)

- ✓ Standarization and quality management of nonclinical data
- ✓ Suggesting the required amount of data for meaningful VCG
- ✓ Improve statistical power

# In the future, hopefully

OECD/OCDE **407**

Adopted:
3 October 2008

**OECD GUIDELINES FOR THE TESTING OF CHEMICALS**

**Repeated Dose 28-Day Oral Toxicity Study in Rodents**

3p.

**Preparation of animals**

Healty young adult animals are randomly assigned to the control and treatment groups. **Where feasible, a virtual control group can be used as a substitute for the concurrent control group.** Cages should be arranged ~

# Do what you can do now

**Thank You!**

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