法規毒理測試(regulatory toxicology testing)

「應優先採用非動物替代方案」說明

The Preferential Use of Alternatives in

Regulatory Toxicology Testing

EAST/2019.9.12

一、 我國化學物質動物實驗簡介

Summary of animal testing on chemicals in Taiwan

(一) 法規與登錄現況

Regulatory and Registry Context

- 我國化學物質採登錄制度進行管理，分為「新化學物質」及「既有化學物質」，其中新化學物質的「標準登錄」及既有化學物質的「標準登錄」，須提供毒理、生態毒理資訊，涉及動物實驗。
- Taiwan's chemical substances registration system divides chemicals into 'new chemicals' and 'existing chemicals'. Standard registration for both new and existing chemicals requires the submission of toxicology and ecotoxicology data, which can involve animal testing.
- 截至 108 年 9 月 2 日，新化學物質登錄有效共 2,084 筆，既有化學物質登錄有效共 183,359 筆[1]，國內流通與運作的既有化學物質則有約 27,000 種[2]。
- As of September 2, 2019, 2,084 new chemicals and 183,359 existing chemicals were registered in the Toxic and Chemical Substances Bureau's (TCSB) chemical substances registration system. Approximately 27,000 existing chemicals are currently on the market or use in Taiwan.
- 化學局已指定第一期共 106 種既有化學物質應完成標準登錄，意即此 106 種既有化學物質，將於二至三年內，進行大量動物試驗。目前已完成標準登錄之新化學物質及既有化學物質，共計 36 筆。
- The TCSB has specified that a total of 106 existing chemical substances will complete the standard registration in Phase 1, meaning that a large number of animal tests will be conducted in the subsequent two to three years for these 106 substances. At present, a total of 36 new and existing chemical substances have completed the standard registration.

(二) 使用動物數量

Quantity of Animals Used in Animal Testing

- 進行化學物質毒理、生態毒理試驗的機構，屬動物科學應用機構中的「試驗研究機構」範疇。根據農委會 106 年《實驗動物人道管理年報》，試驗研究機構共 64 家，佔 31%。當年試驗研究機構使用動物總數 453,383 隻，其中齧齒類 308,523 隻，兔 10,722 隻，魚 76,884 隻。
- Bodies that conduct toxicology and ecotoxicology testing are classified as scientific research institutions (試驗研究機構) under the institutions with scientific application of animals (動物科學應

[1] 化學物質登錄資訊公開查詢平台 https://tcscachemreg.epa.gov.tw/Epareg/OpenData/content/Index.aspx
[2] 登錄制度沿革及政策目標 https://tcscachemreg.epa.gov.tw/Epareg/content/Introduction/Page1_2.aspx

用) umbrella. According to Council of Agriculture statistics contained in the *Humane Care of Laboratory Animals* 2017 annual report, there are 64 scientific research institutions, accounting for 31% of institutions with scientific application of animals. In 2017, scientific research institutions used a total of 453,383 animals in animal tests, including 308,523 rodents, 10,722 rabbits, and 76,884 fish.

- 由於化學物質登錄資料公開不完全，無法得知實際應用於化學物質測試的動物數量。
- Because the registration records of chemical substances are not entirely public, it is impossible to know the actual number of animals used in animal experiments for chemical testing purposes.

(三) 現況分析

Analysis of the Current Situation

- 化學物質毒理、生態毒理資訊，依法應採用 OECD 或環保署環檢所的測試規範為主[3]。然於母法「毒性化學物質管理法」及子法「新化學物質及既有化學物質資料登錄辦法」、「新化學物質及既有化學物質資料登錄工具說明第一版」中，均未提及須盡量避免動物實驗，優先採用替代方案，並且避免重複動物實驗。
- According to the law, toxicology or ecotoxicology testing should adopt guidelines from the OECD or the Environmental Protection Administration's Environmental Analysis Laboratory. However, neither the parent law (*Regulations of New and Existing Chemical Substances Registration*) or sub-laws (*Toxic and Concerned Chemical Substances Control Act* and *Guidance for New and Existing Chemical Substances Registration - Version 1*) make mention of a need to maximally avoid the use of animal testing, preference the use of alternatives, or avoid the repetitive animal tests.
- 部分試驗雖允許替代方案與動物實驗雙軌並行，或允許採「二階段試驗法」或直接進行動物實驗，但替代方案並不具有優先權，如此一來業者極有可能選擇慣行的動物模式進行毒理測試，於替代、減量並無助益。
- Although some experiments allow for the use of animal testing alternatives conducted in parallel to animal testing or so-called 'two-stage testing methods' or only animal testing, no preference is given to alternatives to animal testing. Because of this, most applicants will opt to use customary animal testing methods to conduct toxicology testing.
- 部分國際間已有替代方案的毒理試驗，例如「皮膚過敏性」試驗，OECD 至少已有二種非活體試驗方法(TG 442D 及 442E)，化學局卻規定必須進行動物試驗，明顯落後國際。
- In some parts of the world alternatives to animal testing are already being used for toxicology testing. For example, the OECD already accepts at least two types of ex vivo animal tests (TG 442D and 442E) for skin allergy tests, however TCSB regulations demand that animal tests be conducted, lagging behind its international counterparts.

二、國際推動化學物質以「替代方案」進行測試現況

Alternatives for Testing Chemical Substances in the International Arena

(一) 歐盟化學物質規範(REACH)

European Union REACH regulation

- 優先考慮替代方案：
- Preferential consideration is given to animal testing alternatives

[3] 新化學物質及既有化學物質資料登錄工具說明第一版

- 人類毒性試驗須優先採用非脊椎動物的替代方案，例如體外試驗、結構活性關係模式、相似化學物質資料(分類、交叉比對)[4]。若無替代方案，才可進行動物實驗。(Article 13)
- Human toxicology tests must preferentially make use of alternatives to vertebrate animal tests, such as in vitro methods, qualitative or quantitative structure-activity relationship models, or information from structurally related substances (grouping or read-across). Only when there are no suitable alternatives to animal testing can animal testing be used. (Article 13)
- 試驗方法須定期檢討，以減少動物數量，並符合動物實驗 3R。(Article 13)
- These methods shall be regularly reviewed and improved with a view to reducing testing on vertebrate animals and the number of animals involved, in line with the 3R principles. (Article 13)
- 主管機關歐洲化學總署(ECHA)辦理替代方案的教育訓練、發布相關指引
- The European Chemicals Agency (ECHA) has published a guide and conducted professional training in alternatives to animal testing.
- 化學物質資料公開
- Information relating to chemical substances is shared between registrants.

- 不允許重複進行動物實驗：
- Duplicate animal testing is not allowed.
  - 脊椎動物實驗是最後手段，也應避免重複實驗。(Article 25)
  - In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort. It is also necessary to take measures limiting duplication of other tests. (Article 25)
  - 已註冊過的化學物質，廠商可使用相關資料。(Article 13)
  - If a substance has already been registered, a new registrant shall be entitled to refer to the study summaries or robust study summaries, for the same substance submitted earlier… (Article 13)
  - 化學物質在過去 12 年內註冊過者，註冊者應向之前的註冊者要求提供動物試驗資料。(Article 27)
  - Any study summaries or robust study summaries of studies submitted in the framework of a registration under this Regulation at least 12 years previously can be used for the purposes of registration by another manufacturer or importer. (Article 27)
- 替代方案追蹤系統(TSAR)提供最新資訊：
- Tracking System for Alternative Methods towards Regulatory Acceptance (TSAR) provides the most up-to-date information on the application of animal testing alternatives:
  - TSAR (Tracking System for Alternative Methods towards Regulatory Acceptance)，完整匯集各驗證機構的資料，可查詢所有替代方案驗證進度與各國法規接受情況[5]。
  - TSAR brings together information from across certification bodies and provides a searchable database of the certification status of alternatives to animal testing and regulatory status in each country (i.e. whether or not the alternative method is accepted).
  - 只要在 TSAR 上顯示已被法規採用者，即可作為 REACH 化學物質毒性試驗的方法。
  - If a testing method is shown as being ‘adopted’ in the TSAR database, it can be used as a REACH

[4] Regulation (EC) No 1907/2006
[5] https://tsar.jrc.ec.europa.eu/test-methods

toxicology testing method.

(二) 韓國 K-REACH

K-REACH (Korea)

- 2018 年 1 月 1 日起生效的修訂版，明定由主管機關制定法規，發展、使用替代方案(Article 4)。廠商須優先採用非脊椎動物替代方案(Article 5)。脊椎動物實驗應減到最低，盡量採用替代方案，同一化學物質不應重複進行試驗(Article 16-2)[6]。
- On January 1, 2018, revised regulations devised by the competent authority to advance the development and application of animal testing alternatives came into effect in Korea (Article 4). The regulations require that businesses prioritize the use of non-vertebrate animal tests by use of alternative testing methods, and demands that testing shall not be repeated for the same chemicals (Article 16-2).

(三) 美國毒性物質管理法(TSCA)

The Toxic Substances Control Act (TSCA)

- 2016 年修訂生效的新版 TSCA 明文要求美國環保署：
- Amendments to the Toxic Substances Control Act (TSCA) made in 2016 expressly require the US Environmental Protection Agency to:
  - 盡量減少、取代脊椎動物進行化學物質測試。
  - Reduce and replace animal testing of chemical substances.
  - 促進不使用脊椎動物的替代方案及評估策略等「新途徑方法」(NAMs)的開發與應用。
  - Promote the use of alternatives to tests on vertebrate animals, and the development and application of New Approach Methodologies (NAMs).
  - 制定減少動物實驗的策略計畫(strategic plan)，每五年向國會提交一次實施進度報告[7]，該策略計畫已於 2018 年公布[8]。
  - Publish a strategic plan to reduce and replace vertebrate animal testing, and submit a progress report to Congress every five years. This strategic plan was published in 2018.

三、規範優先採用替代方案之益處

Benefits of Prioritizing Animal Testing Alternatives

(一) 加快與聯合國「國際化學物質管理策略方針」接軌

Accelerate Unification with the UN Strategic Approach to International Chemical Management (SAICM)

- 以毒性預測軟體取代動物實驗，將是未來毒理研究的趨勢；甚至在化學物質被創造出來之前，就先以軟體做安全性篩選，確保只有無毒的物質才被會被製造[9]。
- The replacement of animal testing with toxicity prediction software is the future direction of toxicological research. Such software has the potential to conduct safety screenings even before a chemical substance has been developed, ensuring that only safe substances will be produced.

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[6] http://www.hsi.org/news/press_releases/2018/04/korea-k-reach-chemical-testing-040218.html

[7] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce

[8] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical

[9] Database analysis more reliable than animal testing for toxic chemicals. Jul 19, 2018. John Hopkins Bloomberg School of Public Health.
https://www.jhsph.edu/news/news-releases/2018/database-analysis-more-reliable-than-animal-testing-for-toxic-chemicals.html

- 例如美國約翰霍普金斯大學「動物實驗替代方案中心」(CAAT)發表的化學物質毒性預測軟體，比做動物實驗更加準確快速。目前該軟體已開始提供給民間做產品送審前的毒性篩檢[10]。
- For example, the chemical substance toxicity prediction software published by the John Hopkins University Center for Alternatives to Animal Testing is faster and more accurate than animal testing methods. The software has already been opened to private enterprises for the purpose of conducting toxicity screenings.
- 採用替代方案能加快我國朝聯合國化學品管理策略方針 SAICM 2020、2030 年的目標邁進，包括計畫性逐年推動化學品管理制度的建置與落實，減少有毒化學物質的釋出，鼓勵綠色安全產品，實踐全球公民責任的國家政策，發展創新經濟等[11]。
- Adopting alternatives can accelerate Taiwan's progress toward the United Nations Strategic Approach to International Chemical Management (SAICM 2020 and 2030), including promoting the establishment and gradual implementation of chemical management systems, reducing the release of toxic chemicals, encouraging the development of green, safe products, promoting global citizenship, and promoting economic innovation.

(二) **提高安全性評估之準確性**，有效掌握化學物質毒性

Improve the Accuracy of Safety Assessments

- 國際間對動物實驗預測率低的批評不斷。例如根據 NIH 的統計，藥品、醫療器材從研發階段到上市，失敗率超過 95%[12]，其中有 30%是因為對動物無毒、對人類卻有毒而被淘汰[13]。
- Animal testing methods have come under continued criticism internationally for their low predictive value. For example, according to NIH (USA), the failure rate of pharmaceuticals and medical equipment tested on animals from R&D to market entry is in excess of 95%.
- 研究指出，替代方案等新途徑方法(NAM)比傳統動物實驗(TAM)出現偽陰性、偽陽性的機率較低，準確率較高，能夠更有效和快速的發現新化學物質、更準確的預測產品安全性、幫助製造出更好更安全的產品[14]。
- Research indicates that New Approach Methodologies (NAM) have a lower rate of false negatives and positives than Traditional Approach Methodologies (TAM), a higher accuracy rate, and are able to more quickly and effectively discovery new chemical substance, more accurately predict safety, and assist the manufacture of superior and safer products.

(三) 接軌國際法規，提升國際形象

Uphold International Standards and Taiwan's International Reputation

- 國際推動物實驗減量、替代，首要目標即是針對「法規實驗：安全性測試」，予以減量、廢除。The primary goal of the promotion of Reduction and Replacement is the reduction and abolition of mandatory safety testing requirements.

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[10] Software-based Chemical Screen Could Minimize Animal Testing. Jul 13, 2018. The Scientist. https://www.the-scientist.com/news-opinion/software-based-chemical-screen-could-minimize-animal-testing-64491

[11] 化學物質登錄制度的必要性 https://tcscachemreg.epa.gov.tw/Epareg/content/Introduction/Page1_1.aspx

[12] National Institute of Health. NIH-Wide Strategic Plan Fiscal Years 2016-2020. https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf

[13] National Center for Advancing Translational Sciences. About Tissue Chips. https://ncats.nih.gov/tissuechip/about

[14] Meigs L, Smirnova L, Rovida C, Leist M, Hartung T. Animal testing and its alternatives - the most important omics is economics. ALTEX. 2018;35(3):275-305. https://www.altex.org/index.php/altex/article/view/1134

- 我國法規參考歐盟、韓國、美國，此三國均明訂須優先採用替代方案進行化學物質毒性試驗，並要求廠商間資料共享，避免重複進行動物試驗。

Taiwan should refer to laws in the EU, Korea, and the United States. These three jurisdictions all expressly prioritize the adoption of alternatives to animal testing for the testing of chemical substances, and require businesses to share data to avoid the duplicative animal tests.

- 推動採用替代方案進行毒性試驗，將有助於與國際法規接軌調和，暢通國際貿易，並提升國際形象。
- Promoting the adoption of animal testing alternatives for toxicity testing will help to bring Taiwan's laws into line with international standards, facilitate international trade, and boost Taiwan's international reputation.

(四) 幫助產業轉型，創新經濟

Support Industry Transition and Economic Innovation

- 根據 MarketsandMarkets 統計，2017 年體外毒理試驗(in vitro toxicology)的市場為 63 億美元，已超過動物毒理試驗(in vivo toxicology)的市場(44 億)。
- According to MarketsandMarkets figures. The market for in vitro toxicology was USD $6.3 billion in 2017, exceeding the market for animal in vivo toxicology testing (USD $4.4 billion).
- 預估到 2022 年，體外毒理試驗的市場為 87.4 億美元，動物毒理試驗的市場則為 61.4 億美元。
- It is estimated that by 2022, the market for in vitro toxicity testing will exceed USD $8.74 billion, compared with USD $6.14 billion for conventional animal testing.
- 數據顯示，替代技術已形成一經濟體系，且已超越傳統動物實驗市場[15]。
- The data shows that alternative technologies have already formed a sector of their own, with the market for alternative to animal testing surpassing that of animal testing.

四、建議

Recommendations

(一) 修正「毒性及關注化學物質管理法」第30條，新增一項：「登錄化學物質需提供毒理、生態毒理資料時，應優先採用國際認可之動物測試替代方法，經舉證無替代方法時，才可使用活體動物進行測試。」

That the following clause be added to Article 30 of the *Toxic and Concerned Chemical Substances Control Act*: 'When submitting information on toxicity and ecotoxicity, all registrants must prioritize OECD-approved alternatives for animal testing. Live animal tests should only be used where it has been demonstrated that no suitable alternatives are available.'

(二) 配合修訂「新化學物質及既有化學物質資料登錄辦法」第10、17條及其附表二、七，「新化學物質及既有化學物質資料登錄工具說明第一版」：

In accordance with this change, that Articles 10 and 17 of the *Regulations of New and Existing Chemical Substances Registration* and Appendixes 2 and 7 of the *Guidance for New and Existing Chemical Substances Registration - Version 1* be amended as followed:

1.修訂「新化學物質及既有化學物質資料登錄辦法」第10條第1項、第17條第1項，增列「**登錄須**

[15]Meigs L, Smirnova L, Rovida C, Leist M, Hartung T. Animal testing and its alternatives - the most important omics is economics. ALTEX. 2018;35(3):275-305. https://www.altex.org/index.php/altex/article/view/1134

提供毒理、生態毒理資料時，各登錄人應協議共同使用資料，或以國際認可之動物測試替代方法進行測試；不得重複進行動物試驗。」

That the following clause be added to Appendixes 2 and 7 of the *Regulations of New and Existing Chemical Substanc*es Registration: 'When submitting information on toxicity and ecotoxicity, all registrants must sign an agreement permitting the sharing of submitted information with other registrants, or must use internationally-approved alternatives to animal testing, and must not conduct duplicative animal tests.'

2.修訂「新化學物質及既有化學物質資料登錄辦法」附表二、附表七，新增「**登錄須提供毒理、生態毒理資料時，應優先採用國際認可之動物測試替代方法；經舉證無替代方法時，才可使用活體動物進行測試。**」

That the following clause be added to Appendixes 2 and 7 of the *Regulations of New and Existing Chemical Substances Registratio*n: 'When submitting information on toxicity and ecotoxicity, all registrants must prioritize the use of internationally-approved alternatives to animal testing. Live animal tests should only be used where it has been demonstrated that no suitable alternatives are available.'

3. 修訂「新化學物質及既有化學物質資料登錄工具說明第一版」，增列「毒理、生態毒理試驗如涉及動物試驗，應優先採用OECD認可之動物測試替代方法；經舉證無替代方法時，才可使用活體動物進行測試。」並配合修正測試相關要求、資料繳交規定、評估終點與測試規範建議（表3.3.3、3.3.5、3.4.2、3.4.3）

That the following clause be added to the *Guidance for New and Existing Chemical Substances Registration - Version 1*: 'For toxicological and ecotoxicological tests, where animal testing is involved, all registrants must prioritize OECD-approved alternatives for animal testing. Live animal tests should only be used where it has been demonstrated that no suitable alternatives are available.', and the test-related requirements, regulations governing information and payment, evaluation end points, and guidance recommendations be amended in accordance with these changes (Appendixes 3.3.3, 3.3.5, 3.4.2, & 3.4.3).