



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport



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RIVM 3Rs Quarterly

July 2017

RIVM 3Rs Quarterly informs you on news and developments in the area of 3R methods that can be used for risk assessment of chemical substances and safety and efficacy assessment of pharmaceuticals, including vaccines.



ECHA Report on the use of alternative methods under REACH

The third report from the European Chemicals Agency (ECHA) on the use of alternative methods under REACH is published for which ECHA analyzed 6911 dossiers containing information on hazardous properties of 6290 substances. It was shown that many registrants use non-animal approaches for at least one toxicological endpoint in their dossier. The most commonly used method was read-across, in which existing toxicological information on similar substances is used (63% of the substances), followed by combining information from different sources (weight-of-evidence, 43% of the substances) and QSAR models (34% of the substances).

This ECHA report shows that mainly *in silico* approaches and existing data from previous animal studies are used, whereas the use of *in vitro* assays alone or combined in testing strategies is limited. The reason is that for the majority of toxicological endpoints no validated and accepted *in vitro* assays are available, except for genotoxicity, skin corrosion/irritation, serious eye damage/eye irritation and skin sensitization. An analysis of the use of *in vitro* assays for skin and eye irritation and skin sensitization showed that compared to the previous report, the total number of *in vitro* studies submitted increased, especially for skin and eye irritation. Information on skin irritation was based solely on *in vitro* assays for 10% of the

registered substances. For eye irritation, 7% of the substances was tested using only *in vitro* assays. The use of the novel *in vitro/in chemico* assays for skin sensitization is limited, although some registrants fulfill their information requirements using only these methods. It is expected that in the coming period the use of non-animal methods for these toxicological endpoints will further increase, due to the revision of the REACH requirements.

Source: <https://echa.europa.eu/nl/-/alternatives-to-animal-testing-widely-used>



Organ-on-a-chip technology for safety assessment

RIVM currently investigates how the organ-on-a-chip technology can be helpful in the transition to an animal-free, improved safety assessment of chemicals. For this purpose, a first workshop was organized on June 19, where needs and possibilities were exchanged between 30 risk

assessors and technology developers. The insights obtained during this workshop are currently further compiled and analyzed. This is in line with international developments investigating the applicability of organ-on-a-chip in safety assessment.

US FDA starts testing liver-on-a-chip for food safety

The journal Nature reports on its website that the US Food and Drug Administration (US FDA) has started testing whether liver-on-a-chip models can reliably be used in determining food safety for humans, as an alternative to animal data. The US FDA uses the chips of Emulate, the spin-off company of Wyss Institute in Boston, which were originally designed to test drugs. These chips contain

miniature liver tissue containing multiple types of cells and pump a blood-like fluid through the system.

Source: http://www.nature.com/news/miniature-liver-on-a-chip-could-boost-us-food-safety-1.21818?spJobID=1142140676&spUserID=MTc2NjQxMTEyOAS2&WT.ec_id=NEWS-20170413&spReportID=MTEoMjEoMDY3NgS2&spMailingID=53845786

EFSA OpenFoodTox database

EFSA recently launched its OpenFoodTox database of chemical hazards in food and feed. The database is a rich source of toxicological information for risk assessment that can potentially support the reduction of animal testing. Scientists at the Mario Negri Institute for Pharmacological Research in Milan, Italy, recently completed an EFSA-funded project aimed at developing alternative computer-based - *in silico* modelling tools based on data in OpenFoodTox. An external scientific report explains how these tools can help risk assessors to prioritise toxicological testing strategies and to carry out risk assessments for emerging contaminants when data are absent.



Source: <https://www.efsa.europa.eu/en/press/news/170710>.
The report can be found here: <https://www.efsa.europa.eu/en/supporting/pub/1206e>

The OpenFoodTox Data Warehouse can be found here: <https://www.efsa.europa.eu/en/data/chemical-hazards-data>

Medicines



Opinion: Changing the field of carcinogenicity testing of human pharmaceuticals by emphasizing mode of action

The Dutch Medicines Evaluation Board, Leiden Academic Center for Drug Research, and TNO Innovation for Life published an opinion on changing the field of carcinogenicity testing of human pharmaceuticals by emphasizing mode of action. The opinion addresses the controversial issue of lifetime testing for carcinogenicity of pharmaceuticals in rodents. The authors discuss the utility of *in vitro* -omics approaches to identify involvement of signaling pathways in the mode of action (MoA) of human pharmaceuticals that might bear relevance for prediction of

carcinogenic properties. The ultimate research aim is to establish *in vitro* fluorescent reporters in human cells where individual key events that are functionally relevant in the signalling programs that drive cell proliferation are integrated. This would allow the qualitative and quantitative evaluation of key event activation as a predictive tool for the determination of the intrinsic carcinogenic potential of compounds. The opinion can be found here: <http://www.sciencedirect.com/science/article/pii/S2468202016300304>

Meeting report: Challenges and opportunities for the future of monoclonal antibody development: improving safety assessment and reducing animal use

In 2014, a workshop was held with experts in drug development, mechanistic toxicology and emerging technologies such as cell and tissue-based approaches, systems pharmacology and modeling. The 60 participants included current FDA and European Union (EU) regulators, including the Dutch Medicines Evaluation Board, and representatives from the pharmaceutical, biotechnology and contract research industries. In May 2017, the meeting report was published in the journal *mAbs*. During the workshop, challenges related to biotherapeutic monoclonal antibodies (mAbs) were discussed. The market for mAbs is large and growing rapidly. Due to species specificity,

non-human primates (NHP) are frequently the only pharmacologically relevant species for nonclinical safety and toxicology testing for the majority of antibody-based products. Therefore, as more mAbs are developed, increased NHP use is anticipated. The integration of new and emerging *in vitro* and *in silico* technologies, e.g., cell- and tissue-based approaches, systems pharmacology and modeling, have the potential to improve the human safety prediction and the therapeutic mAb development process, while reducing and refining animal use simultaneously. The meeting report can be found here: <http://www.tandfonline.com/doi/full/10.1080/19420862.2017.1324376>

Medicines



Scientific Committee European Commission has published its opinion on the need for non-human primates in biomedical research, production and testing of products and devices

In the last RIVMs 3Rs Quarterly (April 2017), it was announced that the preliminary opinion of the SCHEER was under public consultation. The public consultation involved 190 contributors from Academia, researchers, Member States, Non-Governmental Organisations and industry. Each submission was carefully considered by the SCHEER and the scientific Opinion has been revised to take relevant comments into account. The literature has been updated accordingly with relevant publications. The Commission had requested the SCHEER to review and update its 2009 Opinion, as foreseen by the Directive on the protection of animals used for scientific purposes (2010/63/EU). The 2017 Opinion addresses six main issues in the mandate of non-human primates (NHPs) studies and tests, such as areas of research where NHPs continue to be used today, opportunities for reducing and refining their use and

scientific viewpoints on when NHP use will no longer be necessary. It also considers potential implications an EU-wide ban of NHP use would have on biomedical research. The new opinion also highlights the many scientific approaches that could significantly contribute to the 3Rs for the use of NHPs, using alternative methods, training, improvement of techniques and protocols, sharing of knowledge, removal of barriers and research needs. The opinion was published on June 5, and can be read here: https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_004.pdf The opinion in a layman language can be found here: https://ec.europa.eu/health/scientific_committees/non-human-primates-testing_en

Vaccines



Workshop report: Drivers and barriers in the consistency approach for vaccine batch release testing

In 2015, RIVM organised a workshop which aimed to discuss and identify drivers and barriers for the implementation of the 3Rs in the consistency approach from three different perspectives/domains (industry, regulatory and science frameworks). Safety and potency assessment for batch release testing of established vaccines still relies partly on animal tests. An important avenue to move to batch release without animal testing is the consistency approach.

This approach is based on thorough characterization of the vaccine, and the principle that the quality of subsequent batches is the consequence of the application of consistent

production of batches monitored by a GMP quality system. Efforts to implement the consistency approach are supported by several drivers from industry, government, and research, but there are also several barriers that must be overcome. The workshop contributed to a better understanding of these drivers and barriers and resulted in recommendations to improve the overall regulatory processes for the consistency approach.

The workshop report was published in June 2017 and can be found here: <http://www.sciencedirect.com/science/article/pii/S1045105617300726?via%3Dihub>

Other news and developments



The Netherlands roadmap towards animal-free regulatory safety testing

As a follow up on the NCad advisory report “Transition to non-animal research” (see RIVM 3Rs Quarterly of April 2017 at <http://www.rivm.nl/3Vs>), RIVM was commissioned by the Dutch Ministry of Economic Affairs to draw up a roadmap towards animal-free regulatory safety testing. During a national conference on the subject, June 27th 2017, RIVM presented its work plan and held a workshop with 60 stakeholders from industry, academia, government, and society. A key principle for the discussion during the workshop was to maintain safety, but based on animal-free methods and strategies only. A main

challenge for the national ambition to succeed is to extend it to all levels of organization in the international field of regulatory testing. For this, collaboration with relevant international institutes and initiatives is needed. The results of the workshop will be presented during the Tenth World Congress Alternatives to Animal Use in the Life Sciences (Session IX-8, Wednesday, August 23, 2017, 11:00-11:15). The plenary presentations from the national conference can be viewed here (start after 30 min, RIVM at 2:38, in Dutch): <https://www.youtube.com/watch?v=laUZD-8-qKo&feature=youtu.be>

US Strategic Roadmap: New Approaches to Evaluate the Safety of Chemicals and Medicinal Products

A similar initiative is the US Strategic Roadmap. Here, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is coordinating the development of a strategic roadmap for incorporating new approaches into safety testing of chemicals and medical products in the United States. The US wants a national strategy to ensure the safe, effective, and timely

implementation of human-based, predictive approaches in toxicity testing, since scientific and technological advances in toxicology can significantly improve and protect public health.

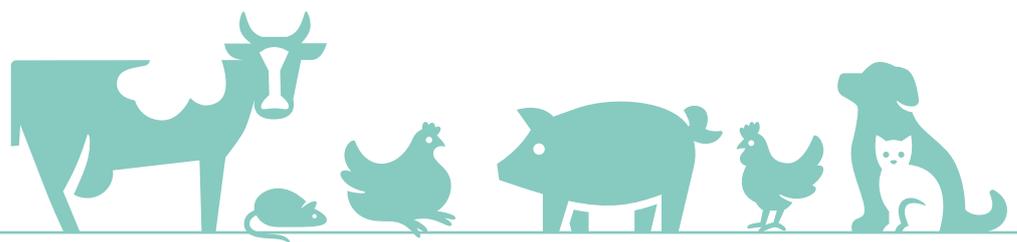
Source: <https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html>

Data warehouse on laboratory animal use and 3R alternatives

RIVM started a project to set up a data warehouse on laboratory animal use and 3R alternatives. This project is carried out in collaboration with the Netherlands Food and Consumer Product Safety Authority (NVWA), the Central Authority for Scientific Procedures on Animals (CCD) and the National Committee for the protection of animals used for scientific purposes (NCad). The project is financed by the ministry of Economic Affairs and based on two advisory reports by NCad to the ministry. With the data warehouse, the project partners aim to provide transparent information to the general public as well as help scientists find suitable 3R alternatives for their studies.

In the past six months of the project, RIVM and its partners explored the needs and possibilities from animal scientific, information technological, and legal angles. As a first stage (2017-2018), RIVM will build the

data warehouse and a website, which can show the publicly available NVWA and CCD data in a way that is suitable for a broad audience. After that, the data warehouse will be expanded stepwise with other data such as public non-technical summaries of experimental applications, studies on development of 3R alternatives, and information on implementation and use of alternative methods. This further growth of the data warehouse will especially help professionals such as scientists and policy makers to gain insight into the effectiveness of 3R alternatives and policies. More information can be found at: <http://www.ncadierproevenbeleid.nl/adviezen-ncad/uitgebrachte-adviezen>, and: http://www.rivm.nl/Onderwerpen/V/Vervangen_verminderen_en_verfijnen_van_dierproeven/3V_activiteiten_van_het_RIVM/Datawarehouse_proefdiergebruik_en_alternatieven



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