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

Roadmap
for animal-free innovations in regulatory safety assessment

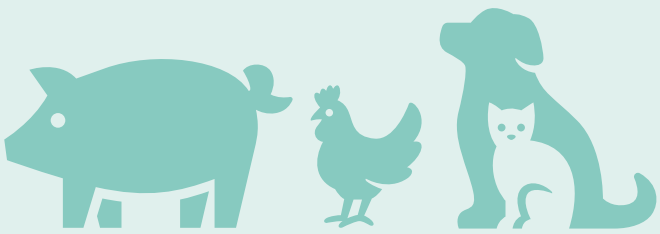
Contents

Foreword

The aim of this Roadmap is to describe the steps required to facilitate the transition to animal-free safety assessment. As the Roadmap was being developed, various national and international parties in government, scientific research and industry emphasised that it is not feasible to achieve safety based on animal-free safety assessment within the short term. In many areas, our current level of knowledge has not yet achieved the point where animal use can be abandoned entirely in assessing the safety of chemicals and medicines.

Accordingly, the focus of the Roadmap is to determine what is in fact possible. In other words, if we imagine that we have achieved our goal of animal-free safety assessment, looking back from that point, what steps were taken to get there? A structured approach to significant investments and wide-ranging collaborations in the activities described in this Roadmap would enable major achievements.

This Roadmap focuses on animal-free innovations as a complete replacement for animal studies. A focus on refinement and reduction of animal studies will remain necessary in the shorter term, since complete replacement is not yet feasible.



1. Introduction

Roadmap

"The Netherlands as a frontrunner in animal-free innovation in 2025". The transition to animal-free innovation is the primary ambition that will be pursued by the Ministry of Agriculture, Nature and Food Quality in collaboration with the team established to address the transition: the TPI core team. The objective of the transition to animal-free innovation has been defined as better science, safety assessment and health by developing animal-free concepts. RIVM is a member of the TPI core team and has been commissioned by the Ministry of Agriculture, Nature and Food Quality to design the Roadmap for Transition to Animal-free Innovations to improve safety assessment**. Improved safety includes improving predictability by achieving a better understanding of how exposure to chemicals and medicines affects humans, animals and the ecosystem. The Roadmap describes themes and conditions for the transition to better safety assessment based on animal-free innovations. These themes and conditions lead to activities that are interdependent and must be launched at different points in time.

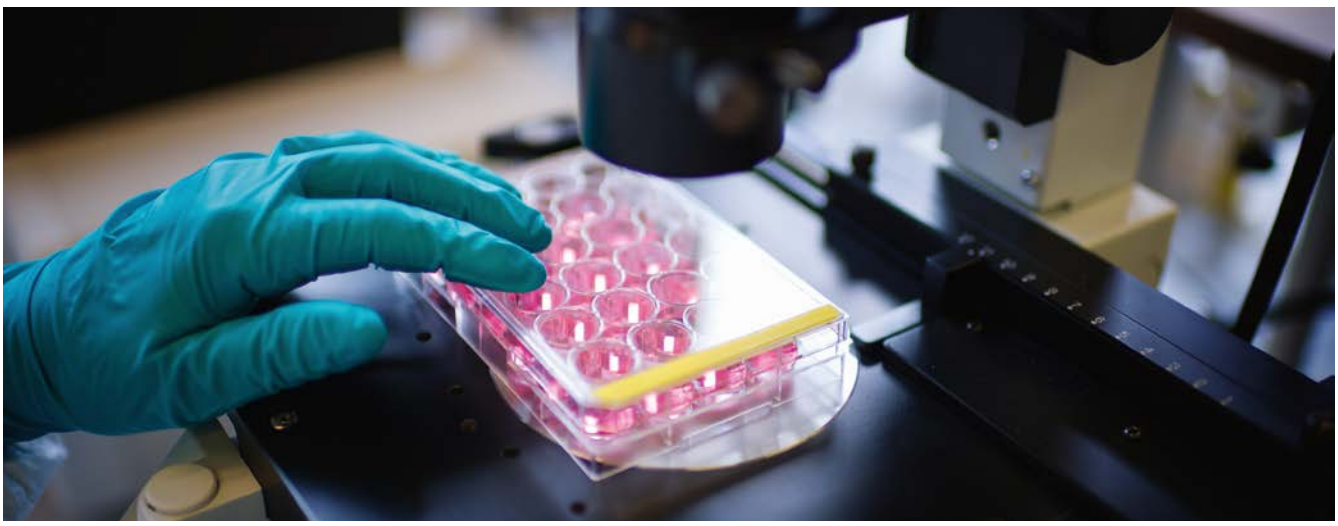
* *The TPI core team currently consists of the Ministry of Agriculture, Nature and Food Quality, the Royal Netherlands Academy of Arts and Sciences (KNAW), the Netherlands Organisation for Health Research and Development (ZonMw), the Netherlands National Committee for the protection of animals used for scientific purposes (NCad), the National Institute for Public Health and the Environment (RIVM), the Association of Health Foundations (SGF), the Top Sector for Life Sciences & Health, and the Dutch Society for the Replacement of Animal Testing. Various other members will be joining shortly, including industry representatives and/or sector organisations.*

** *For medicines, this also includes the transition to animal-free innovations for testing the potency of biological products, including vaccines.*

Guiding principles

The activities set out in this Roadmap have been defined in collaboration with Dutch representatives of private parties, NGO's, regulatory bodies, government organisations, knowledge institutes, and academia involved in the regulatory framework. The transition to animal-free innovations for safety assessment is unfolding in a **complex international regulatory** context. RIVM has worked on the Roadmap with Dutch representatives by looking at what can actually be done.
The key principles guiding the Roadmap are safety, animal welfare and innovation. By focusing on animal-free innovations, we aim to increase research quality in order to achieve a positive impact on health and safety for humans, animals and/or the ecosystem. This will result in reduced animal use and incentives for economic growth. It should be noted that animal-free innovations should only be used if the level of safety remains the same or higher. Animal studies are no longer the gold standard for safety assessment. For that reason, this Roadmap is based on the following concept:

"Safety, achieved by animal-free, innovative means."



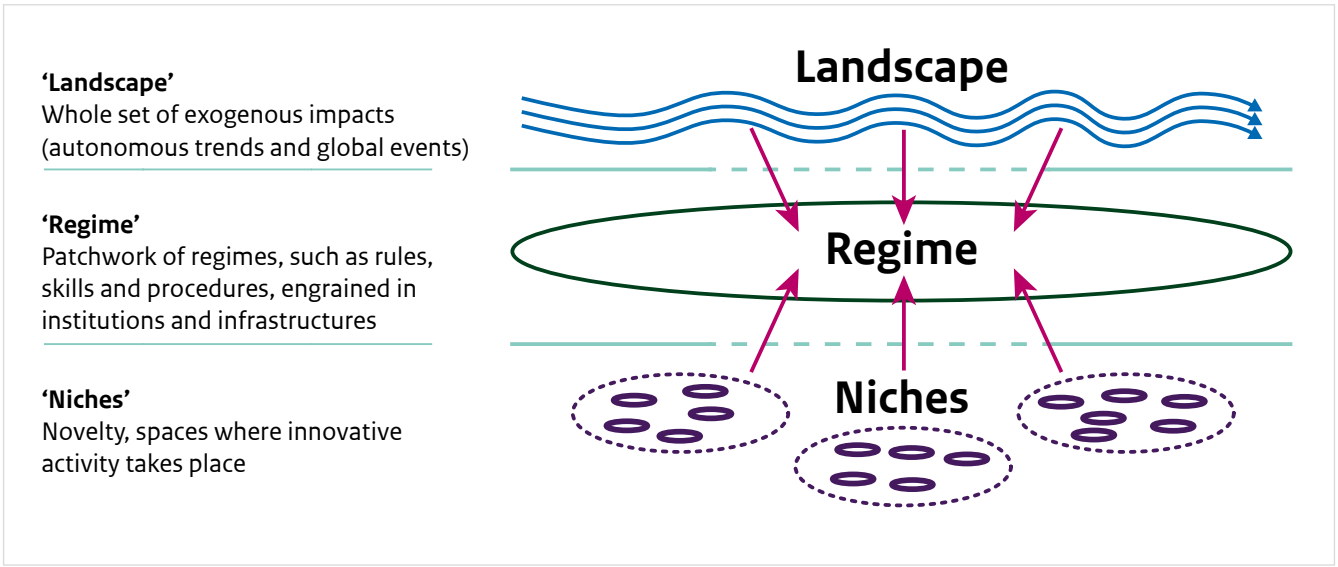
2. Process

Multi-level perspective

Transition research relies on multi-level perspectives to model the relevant surroundings. In this model, the transition is structured into 'landscape', 'regime' and 'niche'. The landscape describes major societal changes or values and characteristics that are not easily amenable to redirection. The regime consists of the structures that constitute the context of day-to-day practice. The niches are innovative developments that deviate from the regime and are separate from its structures. Developments take place in each structure that affect each other; this must be taken into account in order to achieve a successful transition.
In carrying out the commission for the Roadmap, the multi-level perspective model has been used to describe and analyse the transition to animal-free testing. When we translate this model to our central research question, we see that value-driven discussions about animal welfare, level of safety, and opportunities for innovation dominate the landscape. The animal-free innovations are being developed in the niches. The regulatory context (legal framework) is the day-to-day practice which is described in the regime; the landscape and the niches have an impact on this regime. In order to achieve an animal-free regime, the most promising innovations must be incorporated into the regime, which may or may not need to be adapted to accommodate them. The value-driven discussions in the landscape create the momentum for this incorporation.

The multi-level perspective model is a useful way to take the overall environment into account: the context of landscape, regime and niches. The various levels are intrinsically connected, requiring an integrated approach to the transition to animal-free safety assessment in the Roadmap. For that reason, themes and associated activities have been defined for each level in the multi-level perspective in order to accelerate the transition. These themes will be covered in the next chapter.

Figure 1. Multi-Level Perspective (Geels, 2002)



Approach

Domain working group (DWG)

The domain working group (DWG) consists of stakeholders representing private parties, NGOs, regulatory bodies, government organisations, and knowledge institutes (see Appendix 2). They met three times in 2017 to generate content for the Roadmap. The first working session of the DWG covered the conditions (the 5Cs); the resulting content was incorporated into the Roadmap. In the second working session, the DWG explored the knowledge and activities of the four themes in more depth. At its third and final meeting in 2017, the DWG provided feedback on a near-final draft of the Roadmap document.

Panel discussion in Seattle

The RIVM project leader gave a presentation in a session on roadmaps at the World Conference on Alternatives and Animal Use in the Life Sciences (August 2017). It was clear that the Netherlands is not the only country to be developing a roadmap for regulatory safety assessment. Particularly strong synergy was observed in relation to the Roadmap proposed by the US-based Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The contacts established there will be maintained to facilitate mutual learning.

Workshop at Economic Affairs conference in June 2017

In June 2017, a national conference on the transition to animal-free research was held', which included a workshop by RIVM. The workshop addressed the following question: "Imagine we have achieved the policy objective towards a transition to animal-free innovations for regulatory safety assessment in 2025; what have we done on the themes presented here (and when)?" The participants worked out a timeline for the themes, which has been incorporated into the themes of this Roadmap. Participants had the opportunity to sign up to receive updates on the progress being made on the Roadmap. The participants who were not represented in the DWG received the 80% draft of the Roadmap so they could provide their responses. They made ample use of this opportunity; the resulting feedback was incorporated into the Roadmap.

Interministerial consultation

Talks were conducted with all the ministries represented in the Interministerial Working Group on Alternatives to Animal Testing. The ministries' response to the core values of the RIVM project prompted interesting discussions regarding the desired level of safety in society for various groups; for instance, safety for humans is envisioned at a higher level than safety for animals in the environment.

Explanation:
The Roadmap for Animal-free Innovations was designed between March and December 2017 by means of a circular process with stakeholders. Every possible meeting, conference or gathering was utilised to seek knowledge and incorporate it into the Roadmap. As a result, this Roadmap was devised in collaboration with a wide range of individuals and organisations from every domain, within RIVM and beyond, within the Netherlands and beyond, in the private sector, the public sector, the research sector and amongst NGOs.

International: European Commission

A teleconference was conducted between RIVM and the European Commission. On this occasion, the project was presented and EC feedback was solicited. It was apparent that the EC primarily sees a role for itself in boosting communication. Although the project is viewed as a positive initiative, it seems apparent that more growth is needed in terms of commitment to the ideas from the Roadmap for Animal-free Innovations.

RIVM internal meetings

Employees from various domains and their managers are explicitly involved in the process. The project was developed by an RIVM core group that included representatives from the various RIVM departments involved in the Roadmap.

TPI core team
At the management level, the core team for transition to animal-free innovation meets once every 3 months. The TPI core team currently consists of the Ministry of Agriculture, Nature and Food Quality, the Royal Netherlands Academy of Arts and Sciences (KNAW), the Netherlands Organisation for Health Research and Development (ZonMw), the Netherlands National Committee for the protection of animals used for scientific purposes (NCad), the National Institute for Public Health and the Environment (RIVM), the Association of Health Foundations (SGF), the Top Sector for Life Sciences & Health, and the Dutch Society for the Replacement of Animal Testing.

Coordination group
At the employee level, the same organisations are represented in monthly consultations. Roadmap: conference preparations and steering group.

3. Themes

Societal perception of safety

When is something safe? How do we deal with risks and uncertainties? How do we quantify safety and risks? This is an international issue. Different groups in society may have different values and convictions regarding safety, animal welfare and innovation. Citizens are not the only factors here; this involves all those involved in the safety assessment system. An animal-free testing system will not necessarily be considered equally valuable in all cultures, either.
Moreover, perceptions of safety differ in relation to various chemicals and applications, particularly in terms of benefits and control measures; the contrast between chemicals and medicines is a case in point.
For that reason, it is vital to engage in dialogue with all parties. The main aim here is to promote awareness of what safety is and how safety is determined. A productive dialogue requires conscious consideration of local, regional, national and international differences in values and convictions – political as well as cultural. Differences in safety perceptions for various products and applications should also be taken into account. Unifying values should be identified in order to solicit commitment from various parties.

We have confidence in and experience with the current system used to assess safety, but we have neither of these for a new, animal-free testing system (see Box 1). The new system will be reliable in a different way. There is no such thing as 100% certainty or safety. How do people deal with this uncertainty? We need tangible examples to start a dialogue with all stakeholders to gain confidence in the new system.
All of this can be used to design a communication strategy.

Explanation:
The aim of this theme is to create awareness of the concept of safety and how it is perceived in society in relation to the current safety assessment system and an animal-free alternative.

Stakeholders:
Civil society (citizens, patient groups), NGOs, private parties, regulatory bodies, government, and knowledge institutes.

This theme is relevant at a landscape level.

Activiteiten

- Take stock of the values and convictions of various groups in society and seek to identify the unifying values.
- Define key talking points for the dialogue in society.
- Identify examples that illustrate confidence in the new system compared to confidence in the old system.
- Work with other ministries that are relevant to safety in the context of improving predictability by achieving a better understanding of how exposure to chemicals and medicines affects humans, animals and the ecosystem; these ministries include Infrastructure and Water Management (I&W), Social Affairs and Employment (SZW) and Health, Welfare and Sport (VWS).
- Establish a communication strategy at the national, European and global levels and align with existing initiatives.

Participants in action during the workshop at the Economic Affairs conference in June 2017.

Box 1. Confidence in an animal-free conceptual framework for safety assessment

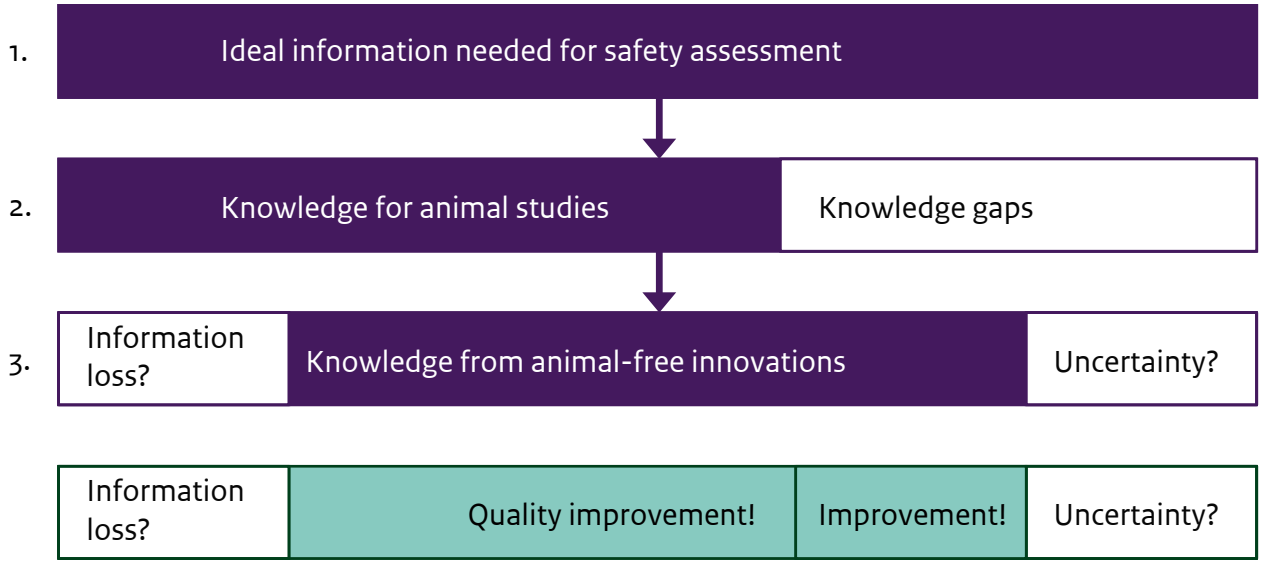
In the 20th century, animal studies were the best and most logical choice available, and that remains the case for most endpoints. A lot of time and effort is invested in reduction, refinement and replacement of animal studies. Most endpoints cannot yet be assessed in completely animal-free studies. In order to do justice to current safety assessment trends in scientific research and society, we need an innovative approach based on the mechanisms through which substances can cause damage, focusing specifically on human impact*. Viable avenues of exploration are available based on knowledge of human biology in combination with e.g. *in vitro* and *in silico* methods, supported by biomonitoring information and epidemiological data. The new approach could also incorporate such endpoints as immunological effects, cardiovascular effects, neurological disorders, etc. which are not (sufficiently) covered by the current system; these endpoints have a significant potential impact on the burden of disease and related costs.

Similar to the current method, any innovative approach also inherently includes uncertainty about what we do not know. The guiding principle in society is to retain the same level of safety or higher. From a scientific perspective, the focus is on mechanism-driven research using human-based models that yield better predictions.

* *Where the text uses the term 'human', it could also be replaced with 'target animal', since the Roadmap also includes safety assessment of veterinary medicines and environmental impact.*

Figure 2. Confidence in an animal-free conceptual framework for safety assessment provides

1. *an indication of the ideal information needed for safety assessment*
2. *the current limited scope of knowledge from animal studies*
3. *an innovative animal-free approach focused on the objective for safety assessment (humans, animals, ecosystem), yielding benefits in terms of information and quality improvement, but possibly introducing other limitations; this leads to the cost-benefit analysis (bottom section) in which each approach also includes an undefined residual uncertainty..*



Please note: This figure is only intended to illustrate the point and has not been designed to scale; the size of the bars does not reflect the degree of uncertainty. The actual uncertainty cannot be quantified.

Implementation in legal frameworks

Methods that are used for safety assessment, including animal-free innovations, must be set out in guidelines (see Box 2).

Previous research has shown that there are generally no legal barriers to using animal-free innovations. The issue is ensuring that these methods are based on solid scientific research. Achieving international acceptance of new approach methodologies and strategies and ensuring they are incorporated into guidelines requires some form of validation. The implementation process demands compliance with clearly defined performance criteria, such as reproducibility in the lab and between multiple labs, clear definition of the applicability domain, relevance for humans, and a clear understanding of uncertainties and technical limitations.

Clear agreements also need to be made regarding the decisions taken based on the results of a test or testing strategy, in order to ensure that the legal consequences are clearly defined. The use of animal-free innovations is primarily restricted by the fact that these steps have not been taken, or that due diligence has not been performed.

One thing that will aid the implementation of animal-free innovations in legal frameworks is to ensure that test developers are aware of validation requirements from an early stage, and can therefore effectively incorporate validation factors into the tests and testing strategies.

A good set of positive and negative substances is needed in order to demonstrate the applicability of a new approach methodology. The current international validation processes are time-consuming and expensive. Accordingly, additional effort and resources will be needed in order to accelerate the process, and partnerships with international organisations (both regulatory agencies and industry representatives) must be established and maintained, both at the European level and globally (ECVAM, EFSA, ECHA, OECD, WHO, UN).

The term 'validation' is not used in relation to medicines. The guidelines for medicines must be flexibly defined, specifying the requirements that a test (or testing strategy) must meet. To achieve this objective, alliances will need to be forged with international partners (both regulatory agencies and industry representatives) to present a unified front at the European level, globally, in an ICH context, and towards EMA.

Explanation:
The aim of this theme is to utilise opportunities and mitigate obstacles in order to accelerate the adoption of animal-free innovations in the safety assessment regime.

Stakeholders:
Regulatory agencies, knowledge institutes, policy-makers, industry.

This theme is relevant at a regime level.

Activities

- Research the similarities and differences in animal-free methods that are accepted by various regulatory agencies and within various legal frameworks and promote mutual acceptance.
- Establish 'safe harbour' initiatives, initially for substances that are authorised, such as plant protection products. A safe harbour allows manufacturers to submit data on animal-free innovations in parallel to regular authorisation procedures, data that will not automatically be included in the assessment. Parallel to the regular process, the regulatory agency can then take a look at the decisions that can be reached regarding measures and consequences based solely on animal-free innovations. Plant protection products, which fall under the auspices of the Ministry of Agriculture, Nature and Food Quality in the Netherlands, can be used as a case study for this purpose.
- Put animal-free innovations on the political international agenda to promote implementation in legal frameworks for all domains.
- Strengthen targeted partnerships within the OECD, ICH and European Pharmacopoeia to develop harmonised guidelines and to promote and accelerate the robust testing batteries and/or strategies within the legal and regulatory frameworks.
- Ensure that agreements are made regarding measures and consequences of test results.
- Research options for requesting advice from the regulatory authorities regarding suitable test strategies at an earlier stage in the medicine development process. This could help prevent unnecessary animal studies.

Box 2. Laws and regulations

The safe application of chemicals in consumer products, in foods and medicines, and in relevant production chains is regulated by various legal frameworks. For instance, there is international legislation that specifically covers industrial chemicals (REACH), biocides, plant protection products, new foods, and veterinary medicines.

The methods and strategies used to test, evaluate, manage and/or grant access for substances in all categories have been laid down in guidelines and directives. There are OECD guidelines in place for chemicals and substances in food, while medicines are subject to ICH/VICH, EMA and European Pharmacopoeia regulations. Biological products such as vaccines are covered by the medicines directives. These products are generally assessed by national control laboratories (NCLs). Before a batch of vaccines is released for use according to OCABR guidelines, it may be decided to retest the batch for safety and/or potency in the NCLs.

Laws and regulations are implemented and monitored at the national level by Bureau REACH, the Netherlands Food and Consumer Product Safety Authority (NVWA), the Board for the Authorisation of Plant Protection Products and Biocides (Ctgb), and the Medicines Evaluation Board (CBG). Implementation and monitoring at the European level are handled by the European Chemicals Agency (ECHA), the European Food Safety Authority (EFSA), and the European Medicines Agency (EMA).
International organisations operating in this field include the United Nations in cooperation with the GHS, WHO, FAO and Codex Alimentarius.

Future safety assessment

Explanation:
The aim is to collectively work towards a new design for safety assessment. This new design requires a paradigm shift, since it demands an entirely new perspective on safety, based on human or target animal biology. This theme is closely related to and dependent on the activities described in the theme on populating the toolbox.

Stakeholders:
Regulatory agencies, policy-makers, industry, scientists.

This theme is primarily relevant at a regime level.

To achieve animal-free safety assessment, it is necessary to draw up a conceptual framework that focuses on human physiology and biology and how they are affected by chemicals and other substances. This stands in contrast to the current framework based on toxicological endpoints and the animal study as the gold standard. New agreements, based on scientific knowledge, will need to be reached at an international level, regarding which changes at the molecular, cellular or tissue level are relevant - or predictive - for toxic effects and the emergence of diseases due to exposure to a substance. One advantage compared to the current system with animal studies is that it will also be possible to focus on events or changes that lead to specific health effects in humans, such as headaches or Alzheimer's.

This type of approach requires strategies (see the theme on populating the toolbox) that may consist of a combination of *in silico* and *in vitro* methods, biomonitoring data and epidemiological data. These strategies can be used on a case-by-case basis in order to ultimately fulfil the purpose of the safety assessment.

Safety assessment has a number of objectives, such as identifying the potential hazards of a substance in order to ensure safe transport, or regulating exposure (e.g. by defining standards). That means that less complex methods may be sufficient in some cases, while more complex issues may also require more complex methods. Besides the direct objective of the safety assessment itself, it is also important in designing these strategies to take into account that the outcome of the safety assessment may also have an impact in contexts beyond the legal or regulatory frameworks for the assessment (for instance in the context of crisis response, working conditions, or disaster control).

Ultimately, this conceptual framework must be firmly embedded in laws and regulations that provide the various legal frameworks; only then will it be possible to make decisions and institute measures regarding the safety of substances. Ensuring that laws and regulations provide a clear framework, and thus also developing a new safety

assessment, is an international matter; it does not take place within national borders. For that reason, it is important to ensure that the innovative knowledge available about future safety assessment is combined and developed at an international level, with the aim of arriving at a new design that provides consistency across borders. In addition, all stakeholders should be involved in the development process to ensure that the new approach methodologies are suitable for use and meet acceptable parameters. Finally, the new conceptual approach will have to be assessed in terms of legal feasibility and mutual acceptance. Targeted case studies can already address this point.

In the context of products such as medicines, every product has a different risk-benefit profile. Structuring case studies based on a single product makes it possible to engage in dialogue with the various stakeholders regarding feasibility and acceptance of animal-free safety assessment.

Participants in action during the workshop at the Economic Affairs conference in June 2017.

Activities

- Develop a conceptual framework for safety assessment based on human physiology and biology and how they are affected by exposure to substances. For that purpose, use international knowledge and initiatives regarding new conceptual frameworks for animal-free safety assessment.
- Regularly check the conceptual framework against the final goals of safety assessment. Also keep in mind that results of the assessment may well have an impact that extends beyond one single framework, potentially trickling down to affect multiple frameworks.
- Make clear agreements, based on scientific knowledge, at an international level, regarding which changes at the molecular, cellular or tissue level are predictive for toxic effects and the emergence of diseases due to exposure to a substance.
- Within this conceptual approach, develop strategies that could be viable that consist of *in silico* and *in vitro* methods, biomonitoring and epidemiological data, or combinations thereof, and could be adjusted on a case-by-case basis depending on the purpose of the safety assessment. Existing, relevant *in vivo* data can be used to support those decisions.
- Use targeted case studies to work on legal tenability and mutual acceptance of the new approach. Collaborate with all stakeholders to that end and propagate best practices.
- Develop a product-specific animal-free testing strategy for potency and safety assessment of biological products, particularly for medical use. Use in vitro, in silico, physical and immunochemical methods to develop the testing strategy.

Populate the toolbox

By toolbox, we mean *in silico* and *in vitro* methods and techniques such as biomonitoring and omics, which are required for safety assessment based on human physiology and biology. That toolbox is far from complete at this point. Within the current system, the tools at our disposal are primarily developed for acute toxic endpoints. However, there are hardly any animal-free methods available for systemic toxicity. It is important to establish an international overview of the animal-free innovations that are available and being developed. The various databases on animal-free innovations should be combined into a public-access information portal.

Based on the needs identified by the new safety assessment, it will be possible to determine which new approach methodologies are available and which still need further development. This could include new approach methodologies to determine more complex toxic effects, to determine kinetics, and to identify human-specific toxic effects related to burden of disease and public health. These new approach methodologies need to be developed based on human physiology, toxicokinetics and toxicodynamics.

Risk assessors must be involved right from the start of the selection or development process in order to guarantee the applicability of new approach methodologies for safety assessment purposes. For instance, the new approach methodologies for most safety assessment objectives need to deliver quantitative readout parameters so appropriate measures can be implemented. In developing new approach methodologies, knowledge needs to be integrated from other fields than toxicology. Relevant knowledge may be derived e.g. from chemistry, biology, medicine (clinical practice, biomedical technology), mathematics, information science, and bioinformatics. In order to use these new approach methodologies for safety assessment purposes, they need to comply with clear performance criteria; see the theme on implementation in legal frameworks for more details.
In order to assess more new approach methodologies, and to do so faster, it will be necessary to increase the capacity of the validation/implementation process.

Explanation:
The aim is to generate a comprehensive overview of animal-free innovations that can be used in safety assessment, as well as identifying what is already available and what is still missing.

Stakeholders:
Test developers, risk assessors, users (industry, contract research organisations).

This theme is relevant at a niche level.

Activities

- Create an information portal in which information about animal-free innovations from all fields of work and disciplines are made publicly available in order to facilitate wide-ranging applicability of animal-free approaches and methodologies, amongst others regarding safety assessment. Connect to existing international information portals and databases.
- Based on the needs identified by the new safety assessment using the information portal, check which new approach methodologies are available and which still need further development. This could include new approach methodologies to determine more complex toxic effects, to determine kinetics, and to identify human-specific toxic effects related to burden of disease and public health.
- Encourage the design and further development of new approach methodologies by setting up platforms and network organisations at various levels (regional, national, international). Such initiatives could be fostered at the regional, national and/or international level, e.g. in a science park where stakeholders (developers, industry representatives, risk assessors) come together to work on animal-free innovations or regarding a specific theme (such as a toxic effect). Explicitly integrate knowledge from fields other than toxicology/pharmacology, such as chemistry, biology, medicine (clinical practice, biomedical technology), mathematics, information science, and bioinformatics.
- Work with all stakeholders to collectively and meticulously define clear performance criteria for the use of these new approach methodologies for the purpose of safety assessment. To that end, join discussions and initiatives in existing forums, such as EURL-ECVAM, OECD and ICH.
- Involve all stakeholders in interpreting the results in relation to the safety assessment to ensure that the new approach methodologies are suitable for use and meet acceptable parameters. These stakeholders could include toxicologists/pharmacologists, risk assessors and industry representatives, as well as new disciplines such as developers and bioinformaticists.

4. Conditions

Commitment

Commitment is vital in order to design and implement animal-free safety assessment. At the international level, politicians, regulatory authorities, academia, industry representatives and NGOs address the three values of the Roadmap for Animal-free Innovations in Regulatory Safety Assessment: safety, animal welfare and innovation. Determining a shared long-term vision that will reflect these values, as they are now identified by the core group for Transition to Animal-free Innovation, will contribute to attaining commitment. In particular, it will be key to achieve government commitment in order to unswervingly pursue, facilitate and monitor this long-term vision.
Commitment of the industry can be achieved in part by introducing incentives. For instance, in the medicines domain, an extension of the dossier protection period can be considered for applications where only animal-free innovations are used, provided that at least the same level of safety for humans is assured. This will generate costs for the government and for consumers. For biological products within the medicines domain, such measures can be considered as reducing the acceptance period for the change in the registration dossier, as long as suitable animal-free innovations are used.

Explanation:
Extensive debate and trials are emerging in terms of alternatives for animal studies for safety assessment purposes. Various forums have been established to explore those alternatives. This Roadmap is intended to accelerate this process by means of the activities described above.

The conditions that could contribute to the success of the transition can be summarised as the six Cs: Commitment, Coordination, Continuity, Communication, Cooperation and Cost. These conditions are key for the regulatory field, and each and every one must be addressed.

The current regime was built on 50 years of development. This means that the thought processes and interests of people have been solidly established in that regime. There is an intensifying awareness of safety in society (a sense of insufficient safety and a desire to be safer); the envisioned transition must continue responding to that sense of safety in society.

Coordination

Constant **coordination** at an international level is particularly key between industry representatives, the scientific forums and regulatory professionals. The activities in this Roadmap need to be coordinated with the activities within the coordinating organisations. Key coordinating international organisations include ECHA, EFSA, EMA, OECD, ICH and EURL ECVAM.

Continuity

Continuity must be provided by the government by establishing a long-term vision and formulating policies in line with that vision, ensuring continued deployment of the capacity and resources invested in this transition programme. One thing that could help achieve that long-term continuity is to appoint a strong spokesperson, ambassador or emissary who could convey that ambition (both in the Netherlands and internationally) and keep it on the political agenda.

Cooperation

Cooperation or collaboration between all stakeholders at an international level might sound obvious, but even so, it is not currently happening. Partnering with end users is particularly essential in the development of a new conceptual framework for safety assessment. Such collaboration can take place within the existing coordinating organisations. Case studies representing all stakeholders are often set up on an international scale for this purpose, such as within the Innovative Medicines Initiative (IMI) project known as VAC2VAC. An ongoing exchange of knowledge should be facilitated in order to promote collaboration. Pursue interdisciplinary approaches; in developing animal-free innovations, integrate knowledge from other fields than toxicology, such as chemistry, biology, medicine, mathematics, information science, and bioinformatics. Make all knowledge about animal-free methods available to the public. However, make sure to pay sufficient attention in this collaborative programme to the legal foundations and consequences, and seek consensus about the status of various results and about which decisions can be taken on that basis.

Communication

Communication is about interaction with society and about interaction between professional groups and different cultures. Communication with society entails conducting a dialogue about safety and the role of animal studies in that context. This could prompt mixed feelings on the one hand, citizens are aware that there is no such thing as complete safety, but they do want to see maximum safety achieved. Communication between professionals should be promoted, with the aim of improving mutual understanding of each other's motivations.

Cost

The activities in this Roadmap involve exceptionally high **costs**, estimated in the order of billions. These costs will have to be borne by the government, the industry and society. Each specific action will have to undergo close scrutiny as to the extent to which it can be implemented with existing resources, and whether additional investments will be needed. A coordinated effort will already boost the return on investment. Additionally, a close look will have to be taken as to whether activities in national or international subsidy projects can be included. Examples include the National Research Agenda, institutional funds for animal-free innovations, the Innovative Medicines Programme and the Horizon2020 Programme.

5. Conclusion

The transition to animal-free innovation for safety assessment of chemicals and medicines requires:

1. A paradigm shift embracing a different approach to safety assessment. Achieving a paradigm shift requires:
2. Unifying various interests, various perceptions of safety, various degrees of acceptance. A social dialogue needs to be initiated on this subject. At the same time, we need:
3. Continued development of *in vitro* and *in silico* tests, including other or additional endpoints, in which the sequence or 'workflow' of these tests in the new system needs to be considered, as well as how the tests comply with the objectives of safety assessment. In this context, the following aspects need to be taken into account:
4. The implementation of these new approach methodologies for animal-free tests in the regulatory context, preferably in an overarching framework that supersedes sectors and disciplines, and an awareness of how to attach measures and consequences to these tests.
5. Lastly, considerable capacity is needed to accelerate the transition to animal-free innovation in order to ensure safety margins. This Roadmap indicates that this needs to be undertaken on an international level, with due consideration of the 6 Cs: Commitment, Coordination, Continuity, Communication, Cooperation and Cost.
6. To make the Netherlands a frontrunner in animal-free innovations in 2025, the country will need to invest in establishing innovation networks surrounding these actions. The members of the domain working group (Appendix 2) form an initial group that can be approached for assistance in setting up these innovation networks.

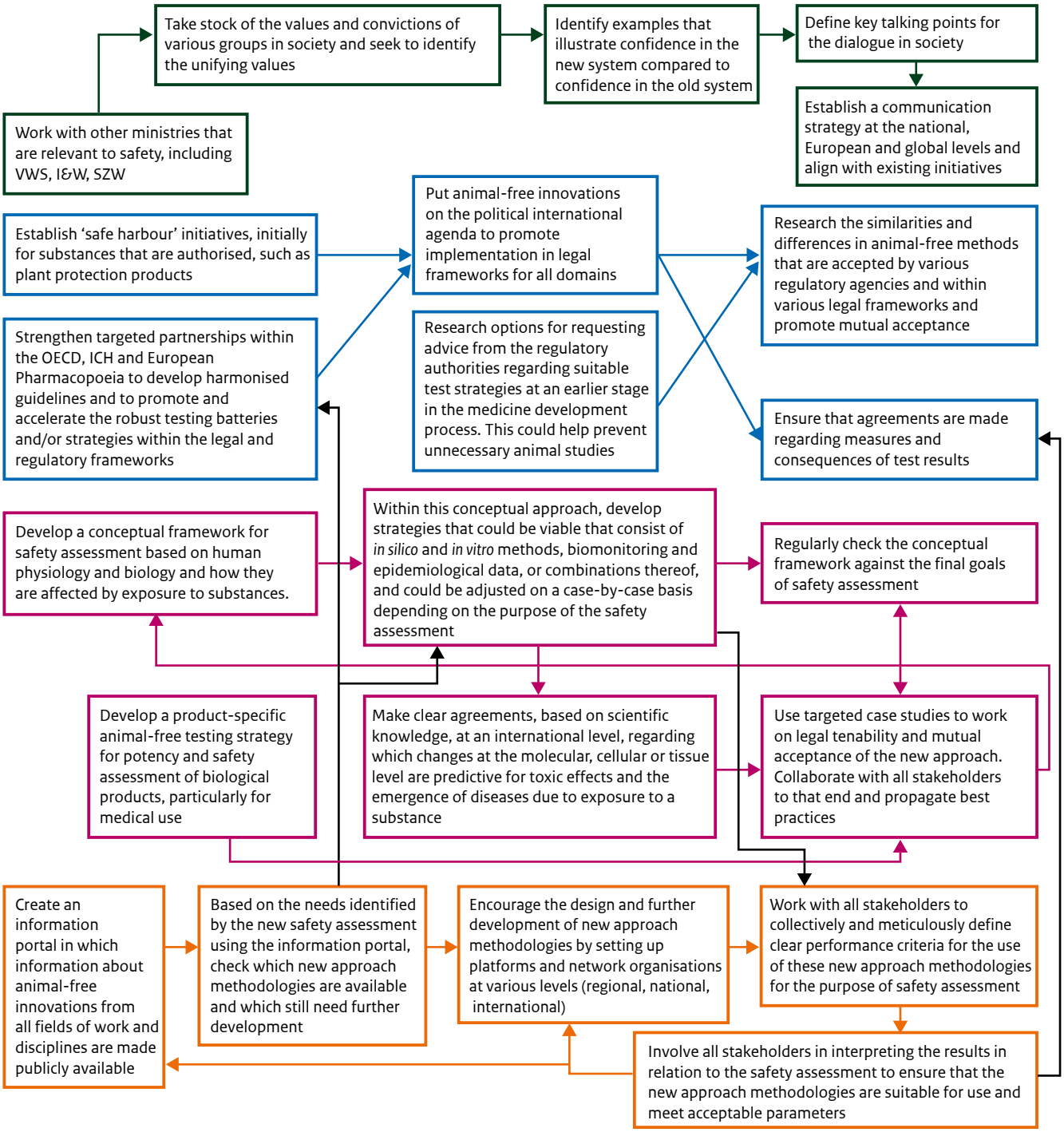
FOCUS!

In the Transition to Animal-free Innovation, the Netherlands intends to be a frontrunner in animal-free innovation in 2025.
This Roadmap describes four themes, six conditions and various activities designed to achieve that objective.
A structured approach to significant investments and wide-ranging collaborations would enable major achievements in the regulatory context. For that reason, it is vital to establish networks surrounding these activities that involve the various stakeholders. This Roadmap has not yet defined which stakeholders need to be involved in which activities.
This focus outlines four activities that can be started immediately in 2018 in order to get this transition off to a vigorous start. However, the other activities referenced in this document must proceed as well, as should the 3R activities: the established framework of replacement, reduction and refinement.

1. **Develop a conceptual framework for safety assessment based on human physiology and biology and how they are affected by exposure to substances.** For that purpose, use international knowledge and initiatives regarding new conceptual frameworks for animal-free safety assessment. Regularly check these frameworks against the final goals of safety assessment.
2. **Establish 'safe harbour' initiatives, initially for substances that are authorised, such as plant protection products.** Parallel to the regular process, the regulatory agency can then take a look at the decisions that can be reached regarding measures and consequences based solely on animal-free innovations. Plant protection products, which fall under the auspices of the Ministry of Agriculture, Nature and Food Quality, can be used as a case study for this purpose.
3. **Create an information portal in which information about animal-free innovations from all fields of work and disciplines are made publicly available in order to facilitate wide-ranging applicability of animal-free approaches and methodologies, amongst others regarding safety assessment.** Connect to existing international information portals and databases.
4. **Encourage the design and further development of new approach methodologies by setting up platforms and network organisations at various levels (regional, national, international).** Explicitly integrate knowledge from fields other than toxicology/pharmacology, such as chemistry, biology, medicine (clinical practice, biomedical technology), mathematics, information science, and bioinformatics.

Cohesion

The activities in this overview originate from the four themes.
On this page, the cohesion between the activities is presented.



Legend:

- *Activities in green boxes belong to the theme Social perception of safety*
- *Activities in blue boxes belong to the theme Implementation in legal frameworks*
- *Activities in violet boxes belong to the theme Future safety assessment*
- *Activities in orange boxes belong to the theme Populate the toolbox*

Appendices

Appendix 1: References

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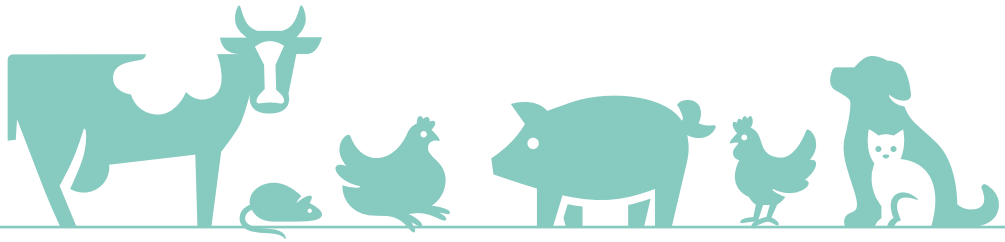
Appendix 2: Members DWG

The members of the DWG consist of stakeholders representing private parties, NGOs, regulatory bodies, government organisations, and knowledge institutes. Members are:

- The Association of the Dutch Chemical Industry (VNCI)
- Association Innovative Medicines
- Charles River
- Shell
- Intravacc
- Dutch Society for the Protection of Animals
- Dutch Society for the Replacement of Animal Testing
- Dutch Collaborating Health Foundations (SGF)
- Bureau REACH
- Dutch Board for the Authorisation of Plant Protection Products and Biocides (Ctgb)
- Medicines Evaluation Board (CBG-MEB)
- Netherlands Food and Consumer Product Safety Authority (NVWA)
- National Institute for Public Health and the Environment (RIVM)
- The Netherlands Organisation for applied scientific research (TNO)
- Leiden University
- Wageningen University
- University of Applied Sciences Utrecht (HU)

Appendix 3: Abbreviations

CBG	Medicines Evaluation Board
Codex Alimentarius	The Codex Alimentarius (Latin for "Food Code") is a collection of internationally recognized standards, codes of practice, guidelines, and other recommendations relating to foods, food production, and food safety.
Ctgb	Dutch Board for the Authorisation of Plant Protection Products and Biocides
DWG	Domain working group
EC	European Committee
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESAC	European statistical advisory committee
EURL ECVAM PARERE	Network for Preliminary Assessment of Regulatory Relevance
EURL-ECFAM	European Union Reference Laboratory for alternatives to animal testing
FAO	Food and Agriculture Organisation (UN)
GHS	Globally Harmonised System of Classification and Labelling
I&W	Ministry of Infrastructure and Water Management
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICH	International Council for Harmonisation of Technical Requirements
ICT	Information and communication technology
KNAW	Royal Netherlands Academy of Arts and Sciences
LNV	Ministry of Agriculture, Nature and Food Quality
MLP	Multi-Level Perspective
NCad	Netherlands National Committee for the protection of animals used for scientific purposes
NVWA	Netherlands Food and Consumer Product Safety Authority
OCABR	Official Control Authority Batch Release
OECD	The Organisation for Economic Co-operation and Development
OMCL	Official Medicines Control Laboratories
QSAR	Quantitative structure-activity relationship
REACH	Registration, Evaluation and Authorization of CHemicals
RIVM	National Institute for Public Health and the Environment
SGF	Dutch Collaborating Health Foundations
SZW	Ministry of Social Affairs and Employment
TPI	Transition to animal-free innovation
3R	Replacement, reduction, refinement
VAC2VAC	Vaccine batch to vaccine batch comparison by consistency testing
UN	United Nations
VWS	Ministry of Health, Welfare and Sport
WHO	World Health Organization
ZonMw	The Netherlands Organisation for Health Research and Development



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