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

Identifying strengths and weaknesses of current human health risk assessment – a workshop report

RIVM report 050012002/2013

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Abstract

Strengths and weaknesses of current human health risk assessment of chemical substances

For several years, there has been a global need to innovate human risk assessment of chemical substances. The National Institute for Public Health and the Environment (RIVM) is responsible for the risk assessment of chemical substances and is therefore also involved in this innovation process. As a contribution to this process, the RIVM has evaluated the strengths and weaknesses of the current system, identifying gaps and limitations as well as essential elements that have to be retained. This evaluation shows that more insights are needed into the extent of human exposure to substances. This is necessary in order to be able to estimate the risk to humans and, subsequently, to ensure the safety of chemical substances. Moreover, the use of experimental animals should be kept to a minimum, without compromising human safety.

One of the strengths of current risk assessment procedure is that it enables identification of a wide range of toxic effects. The system also determines the dose causing this toxic effect, which is important information when determining toxicological reference values. Additionally, the current system makes it possible to estimate the extent to which people are exposed to a certain substance. One of the weaknesses of the current system is that useful information about human exposure is however not always available. Other weaknesses include the extensive use of laboratory animals and the lack of suitable methods for determining complex substances. It is not certain whether the current approach covers all adverse effects relevant to human health, and there is a lack of information on susceptible groups of the population, which may be at higher risk.

Key words:
Risk assessment, chemical substances, strengths and weaknesses, innovation

Rapport in het kort

Sterke en zwakke punten van de humane risicobeoordeling van chemische stoffen

Al enkele jaren is er wereldwijd behoefte om de risicobeoordeling van chemische stoffen te vernieuwen. Het RIVM is verantwoordelijk voor de risicobeoordeling van chemische stoffen en is daarom betrokken bij deze vernieuwing. Om hieraan bij te kunnen dragen heeft het RIVM geïnventariseerd wat de sterke en zwakke punten zijn van het huidige systeem. Op die manier worden beperkingen en hiaten duidelijk, evenals de essentiële elementen die behouden moeten blijven. Uit deze inventarisatie blijkt dat er meer inzicht nodig is over de mate waarin mensen worden blootgesteld aan stoffen. Dit is nodig om de risico's voor mensen te kunnen schatten en de veiligheid van stoffen te kunnen waarborgen. Bovendien moet zo min mogelijk gebruik gemaakt worden van proefdieren, zonder dat dit ten koste gaat van de veiligheid van mensen.

Een sterk punt van de huidige risicobeoordeling is dat een breed scala van schadelijke effecten vastgesteld wordt. Daarnaast maakt het systeem duidelijk bij welke dosis een stof schadelijke effecten veroorzaakt. Dit is belangrijke informatie om grenswaarden te bepalen. Verder biedt het huidige systeem de mogelijkheid om te schatten in welke mate mensen aan de desbetreffende stof zijn blootgesteld. Bruikbare gegevens over die blootstelling zijn echter niet altijd beschikbaar en dat is een van de zwakke punten van het huidige systeem. Andere zwakke punten zijn het gebruik van proefdieren en het ontbreken van geschikte methodieken voor complexe stoffen. Ook is niet zeker of het systeem álle nadelige effecten op de gezondheid afdekt en is er onvoldoende kennis over gevoelige groepen in de bevolking die mogelijk een hoger risico lopen.

Trefwoorden:
risicobeoordeling, chemische stoffen, sterke en zwakke punten, vernieuwing

Contents

Summary

Current human health risk assessment procedures are challenged by societal, political and legal demands as well as by scientific and technological progress. As a result, visions and concepts have been launched that plea for a paradigm shift in human risk assessment, of which the US National Research Council (NRC) report "*Toxicity testing in the 21st Century: a vision and strategy*" is the most well known example. According to all these initiatives human health risk assessment should shift from hazard-driven animal-based approaches to frameworks that incorporate innovative human-relevant methods that are based on our understanding of mechanisms of toxicity, and apply the 3R principles (replacement, reduction, refinement of animal testing). Our increased understanding of mechanisms of toxicity and progress made in the development of 3R test methods, is not yet incorporated in human health risk assessment procedures. To achieve innovation of these procedures a transition strategy will be required.

Risk assessment is the core business of the RIVM and involvement in the area of innovating risk assessment is therefore important. Since the topic is abstract, complex, and multidisciplinary, a step-by-step approach was chosen to determine how the RIVM might contribute. As a first step, innovation of risk assessment was discussed in a group of relevant experts. One of the recommendations was to identify the strengths and weaknesses of the current risk assessment paradigm. This evaluation was considered relevant since it would not only provide information about the limitations and gaps of the current procedures, but it would also highlight the strengths and thus the elements that should be included in a new risk assessment paradigm. For this, a workshop was organised bringing together risk assessors, toxicologist, and experts in the field of exposure assessment and alternative methods to animal testing.

Besides providing insight into the strengths and limitations of the current approaches, the workshop also yielded drivers and considerations for innovating human risk assessment. Elements from the current paradigm that were considered essential include: *i*) toxicity tests for a broad spectrum of adverse effects relevant to human health; *ii*) dose-response information; and *iii*) exposure assessment. Regarding toxicity tests, animal-based studies were discussed intensely. Advantages of *in vivo* studies include the ability to assess adverse effects of repeated exposure and to measure apical endpoints. Also, *in vivo* studies cover the toxicodynamic and toxicokinetic properties of chemicals. Despite these advantages, animal-based toxicity tests were also considered as a weakness because of the possible lack of human relevance. Other weaknesses and limitations identified are: *i*) lack of relevant exposure information; *ii*) risk assessment is hazard-driven and based on tick-boxing; *iii*) methods are not designed for "complex" substances or combined exposures; *iv*) not all human relevant adverse effects are (sufficiently) addressed; *v*) potential susceptible subpopulations are not always structurally addressed; and *vi*) the current approach does not meet the demands put forward from changes in risk governance.

A new approach should be more balanced between hazard and exposure, and incorporate mechanism-based human relevant test methods. It should be applicable to all types of substances, including complex ones and mixtures. Also, a new approach should cover susceptible subpopulations, and do justice to the 3R principles without being at the expense of safety to human health. Ultimately, this approach should meet the demands put forward by risk governance. As a next step in this project, the RIVM will design a conceptual framework in a top-down approach.

1 Introduction

Human risk assessment of chemical substances is required by legislation and is performed to determine whether chemicals pose a significant risk to human health and, if so, under which circumstances and at which dose. The risk assessment process is hazard-driven and consists of four basic elements: *i*) hazard identification, *ii*) dose-response assessment, *iii*) exposure assessment, and 4) risk characterisation (Figure 1). Information on hazard largely relies on information obtained in studies using animal (mostly rodent) models. The current system for assessment of risk has been in place since the 1970s and is the product of an approach that has addressed advances in science by incrementally amending available test protocols and by introducing new tests.

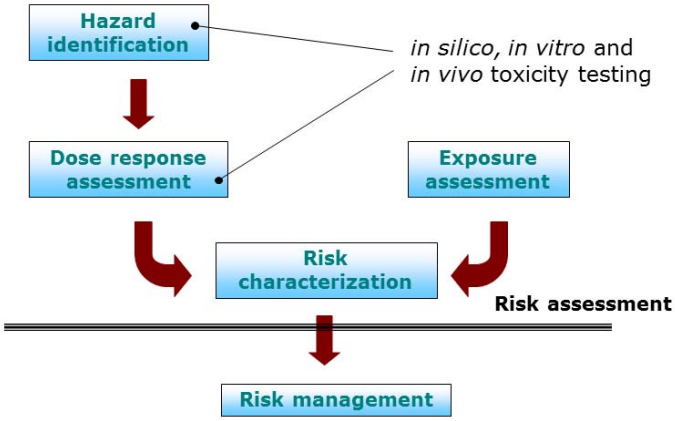

Figure 1. The four basic elements of risk assessment

Regulatory human risk assessment procedures evolve slowly, and may not always reflect the most recent developments in science. This is partly due to the fact that risk assessment procedures are internationally harmonised. Besides the numerous advantages, these legal frameworks appear difficult to change. Incorporation of novel scientific knowledge and tools is considered desirable, especially because it would facilitate the demands posed by society, policy makers, and legislative frameworks. For example, due to animal welfare considerations both society and policy makers demand a reduction or abolishment of animal testing for human risk assessment. From a legal perspective, there is a need for accepted, reliable non-animal approaches for the safety assessment of cosmetic ingredients, since animal testing is no longer allowed in the EU. Despite the progress made in the area of the development of 3Rs methods (replacement, reduction or refinement), risk assessment still predominantly relies on animal-based tests.

As a consequence of this changing view on human risk assessment, several initiatives have been launched that propose a paradigm shift. In 2007, the US National Research Council (NRC) has published their vision on toxicity testing: *"Toxicity testing in the 21st Century: a vision and strategy"* (1). According to the NRC the current system, which is based on animal testing, should be transformed into a completely new system that makes uses of advances in science. For example, our increased understanding of the so-called 'toxicity pathways' should be incorporated in high-throughput *in vitro* tests that measure

perturbations in these pathways. It envisions a new, efficient, toxicity-testing system that integrates data from new methods in computational biology with a comprehensive array of *in vitro* tests based on human biology. A similar initiative that advocates a paradigm shift in risk assessment is ASAT (*Assuring Safety without Animal Testing*). This concept was first proposed in 2004 by a group of researchers from Unilever. ASAT envisions a new paradigm in human health risk assessment based on non-animal approaches (2). The Dutch government financially funds research projects to establish a proof-of-principle for this theoretical concept. In 2011, ILSI-HESI initiated the Technical Committee "*Risk Assessment in the 21st Century (RISK21)*" (3). This committee aims to stimulate the dialogue between various stakeholders in order to identify the main developments in risk assessment. The aim is to design better methods, and to bring forward applicable, accurate, and resource-friendly approaches for risk assessment. A commonality in these approaches is that they plea to use more human-relevant methods that are based on mechanisms of toxicity for hazard assessment and, as such, reduce or abolish the number of animal studies used for risk assessment.

Innovating risk assessment is also needed for other reasons besides incorporation of new technologies and methodologies, and reduction of experimental animal use. A comprehensive view on arguments for innovating risk assessment can be found in a recent opinion of the EU Scientific Committees on Health and Environmental Risks (SCHER), on Emerging and Newly Identified Health Risks (SCENIHR) and on Consumer Safety (SCCS). According to these committees, a new paradigm for human risk assessment is needed, which should consist of tiered approach that is more exposure-driven rather than hazard-driven (4). It is considered essential to develop more transparent, effective and efficient procedures for risk assessment, without putting unnecessary demands on available resources. The aspect of efficiency is also addressed by the advocated shift from a hazard-driven testing process towards an approach in which exposure is more important, *i.e.* a process in which decisions on the nature and extent of hazard testing are driven by exposure assessment. Important challenges that risk assessors face today should be covered by such a novel approach. Those include, amongst others, approaches that can be used for the safety assessment of complex materials, such as engineered nanoparticles and mixtures. The rapid developments in the manufacturing of engineered nanoparticles are driving new risk assessment strategies aimed at targeted, efficient testing and data gathering. The need for tools to assess the effects of mixtures or combined exposures was identified by both the EU Scientific Committees and the European Food Safety Authority (EFSA), since the available test methods were not designed for these purposes (5, 6).

Although the basics and outline as well as the main drivers for these new approaches have been described, developing an actual strategy remains a major challenge. Risk assessment, including evaluation of the applicability of 3R test methods for regulatory purposes, is part of the core business of the RIVM. We therefore consider it essential to identify and evaluate the main developments in risk assessment as well as the potential (strategic) role of the RIVM herein. The complexity of the topic, the global scope, the need for a multidisciplinary approach,the different stakeholders involved, and the need to at least keep the quality of human risk assessment at the current level, require a conscientious, stepwise approach. As a first step, in 2012 a brainstorm session was organised with RIVM experts to discuss how the RIVM should contribute to these developments. During this meeting it became apparent that innovating risk

assessment could be achieved in two possible ways: bottom-up versus top-down. Here, *bottom-up* refers to modifying the current risk assessment approach, by replacing elements of the existing system, as has been done by us and others over the last few decades. In a *top-down* approach, a new system is developed from scratch, without the constraints of current regulatory frameworks. The workshop participants concluded that a fundamental shift in risk assessment can only be achieved with the latter approach, but that it will take time. Another outcome of this meeting was that the strengths and weaknesses of the current risk assessment approach should be evaluated. Such an evaluation is not only useful to provide insight into the gaps and needs of the current system, but also to highlight its strengths. Furthermore, it may also serve as a reference when considering new approaches. This evaluation was undertaken in 2013, by organising a second workshop. Chapter 2 describes the format we employed for this workshop. The strengths and weaknesses that were brought forward are described in Chapter 3. Chapter 4 presents the main conclusions and recommendations and provides the outline for the activities in 2014.

2 Approach

To discuss the current paradigm for human health risk assessment, a workshop was organised, bringing together a group of RIVM toxicologists and risk assessors. The participants are active in various regulatory frameworks (see Acknowledgements for the list of participants and their background). In this workshop it was agreed that the term 'risk assessment' involved all elements of risk assessment, including hazard identification and characterisation, exposure assessment as well as quantitative risk assessment.

Because of the anticipated complexity of the subject, the workshop only focused on human health risk assessment of chemical substances. In this domain several different regulatory frameworks exist: *e.g.* for cosmetic ingredients, food additives, biocides and agrochemicals. Therefore, as a kick-off of the workshop, an overview of the risk assessment process in two of these arenas was presented, *i.e.* REACH and cosmetic ingredients, to illustrate possible commonalities and differences between various regulatory fields. The most important aspects of these frameworks within the present context are summarised in Boxes 1 and 2. The rationale for selecting these two legal frameworks was ample in-house expertise and experience. Furthermore, these examples are illustrative for the need for innovating risk assessment. For the safety assessment of cosmetic ingredients, the use of experimental animals is no longer allowed, as of March 2013, the European Union (EU) has banned the marketing of any cosmetics or cosmetics ingredients that have been tested on animals. REACH, the European policy framework for the risk management of dangerous chemicals, has been developed in such a way that it promotes the use of alternative test methods. One of the main reasons for developing and adopting the REACH Regulation was, however, to enable assessment of potential hazards and risks of a large number of chemical substances.

Subsequently, the strengths and weaknesses of the current approach were discussed in two breakout groups. To guide the discussion a set of questions was provided. These questions were as follows:

Q1: What are, in your view, the main drivers to change the current paradigm for risk assessment?

Q2: Which building blocks do you consider essential for human health risk assessment?

Q3: Are there toxicity endpoints or diseases lacking? If so, which ones?

The outcomes were then discussed in a plenary meeting and were used to identify the strengths and weaknesses of the current risk assessment approaches.

Box 1: Human health risk assessment within REACH

REACH (Registration, Evaluation, Authorisation and restriction of Chemicals) is the EU chemicals legislation that is operational since 2007. Under REACH, manufacturers, importers and downstream users have to ensure that the substances they manufacture, place on the market or use do not adversely affect human health or the environment. During the workshop an overview of the aspects of REACH was provided in the context of innovating human risk assessment. More detailed information on this regulation can be found on the website of the European Chemicals Agency (ECHA; http://echa.europa.eu).

In the framework of REACH the primary focus of human health risk assessment is on the classification and labelling of substances and on the derivation of levels of exposure above which humans should not be exposed (DNELs - Derived No-Effect Levels). REACH is strongly linked to the CLP Regulation (*i.e.* the EU legislation on classification, labelling and packaging of substances and mixtures). Which hazard information is required under REACH depends on the quantity in which a substance is manufactured or imported: the higher the tonnage, the more information also covering the more complex endpoints is required. An exposure assessment and risk characterization is only required for substances produced or imported in volumes over 10 tonnes/year and classified according to CLP or if they are PBT (Persistent, and Toxic) or vPvB (very Persistent and very Bio-accumulative).

Depending on the tonnage level, the following human health related toxic effects need to be addressed: acute effects, sensitisation, repeated dose toxicity and CMR (carcinogenic, mutagenic and reproductive) effects. When existing data do not cover all effects, REACH propagates ITS and the use of in vitro testing and non-testing methods (e.g. QSAR, read-across) over the use of animal testing in order to fill data gaps. Exposure-based waiving is a further possibility under REACH.

Aspects of REACH that were mentioned in the context of innovation of human health risk assessment include:

- Hazard and risk assessment is not performed for all chemicals, due to the tonnage-restrictions
- Only traditional toxicity endpoints are considered. Are these sufficient to ensure human safety, or should other toxicity endpoints be included?
- Kinetic information is not required and this impairs for instance *in vitro – in vivo* extrapolation.
- Guidance on how to extrapolate data from alternative methods to humans hardly exists. This impairs the use of alternative methods.
- Acceptance of new OECD test guidelines that are not legally anchored, for example the Extended One Generation Reproductive Toxicity test, is difficult.
- Even when required detailed and good quality exposure information is hardly provided.
- Exposure data are often based on worst-case scenarios, and details of the parameters used are often not available. How realistic and reliable are these exposure data and the subsequent risk characterization? DNEL is a new hazard metric, which is the result of the overall NOAEL or BMD divided by the overall assessment factors (AFs). In almost all cases default values are used for AFs. REACH guidance suggests using PBPK-modeling as an alternative for AFs, but this is not commonly applied due to the complexity, the amount of data and specific expertise needed.
- The industry is responsible for risk assessment and not the competent authorities. Compliance is however only checked for 5% of the substances in each tonnage band.

Box 2: Human risk assessment for cosmetic ingredients

The Scientific Committee for Consumer Safety (SCCS) is a scientific advisory structure in the non-food area that is composed of independent scientists and is managed by the EU Directorate for Health and Consumers (DG SANCO). It provides advice to the European Commission on health and safety risks of non-food consumer products, including cosmetics. Their main focus is on risk assessment of cosmetic ingredients due to legal obligations of the Cosmetics Directive. During the workshop a summary of safety assessment of cosmetics was provided. More details can be found on the Notes of Guidance for the testing of cosmetic substances and their safety evaluation: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf

The Cosmetics Directive aims at ensuring the safety for human health for cosmetic products. Specific attention is given to substances for which some concerns exist with respect to human health. These substances are listed in the Annexes of Regulation (EC) and include e.g. colorants, preservatives and UV-filters. The SCCS is involved in safety evaluation of these cosmetics substances. Safety assessment includes both hazard assessment and exposure assessment. For hazard assessment, acute toxicity, dermal penetration, repeated dose toxicity (skin sensitization, sub-acute toxicity, sub-chronic toxicity, chronic toxicity, and carcinogenicity), reproductive toxicity and genotoxicity are considered. For exposure assessment, exposure via the dermal (and if relevant inhalation and oral) route needs to be evaluated. The resulting Margin of Safety is assessed to conclude on safe use of the ingredient.

Aspects of safety assessment for cosmetic ingredients in the context of innovation of human risk assessment include:

- Due to the testing and marketing ban, animal experiments are not allowed for cosmetic ingredients. There are no validated replacement alternatives available for repeated dose toxicity, reproductive toxicity and toxicokinetics.
- Extent of systemic exposure often not known and most of the time based on route-to-route extrapolation (with scarce, if any, information on kinetics).
- Dermal exposure studies often not adequate (different vehicles, large variation, few donors).
- Inhalation is an important route of exposure for sprays and should be considered as well (peak exposure, compare to which inhalation toxicity studies)
- Exposure scenarios might differ for certain sub-populations (relatively few exposure data available).
- Endocrine disrupting substances might be a cause of concern in case of systemic exposure (difficult to assess/ to interpret the available studies).
- Need to explore whether the TTC (threshold of toxicological concern) can be applied to cosmetic ingredients in a weight-of-evidence approach (challenging for dermal route).

3 Strengths and weaknesses – workshop summary

This chapter describes the outcome of the workshop as well as the most important strengths and weaknesses of present risk assessment strategies for human health within the respective frameworks, as put forward by the workshop participants.

3.1 Strengths

Essential elements
Over the past few decades, strategies for risk assessment have evolved and addressed advances in science. Some of the elements present in the current approaches in the respective legal frameworks have been proven to be essential for human health risk assessment, as was emphasized in the various discussions. These essential elements include *i*) toxicity tests for a broad spectrum of relevant adverse effects; *ii*) dose-response information; and *iii*) exposure assessments.

In vivo toxicity data
For risk assessment it is important to obtain information on the hazardous properties of a chemical and on dose-response information, including the highest dose at which no adverse effects are induced. The participants of the workshop agreed that, ultimately, for certain endpoints *in vivo* studies will be required for safety assessments of chemical substances. Animal studies yield information that currently cannot be obtained from *in vitro* tests alone, *e.g.* information regarding effects induced by repeated exposures. Also, toxicodynamic and toxicokinetic (including biotransformation) properties of a given chemical are implicitly accounted for in an *in vivo* experiment. As such, *in vivo* tests reveal whether potential hazardous effects can be expected, and they provide quantitative information about the dose-response relationship that is essential for the derivation of no-observed-adverse-effect levels (NOAELs) or benchmark doses. *In vivo* studies also allow for the assessment of apical adverse effects, *e.g.* by using histopathological analyses. All these aspects of *in vivo* toxicity testing were considered to be important for a quantitative safety assessment of chemical substances.

3.2 Weaknesses

Animal testing has its limitations
Currently, safety assessments predominantly rely on information obtained from studies performed in experimental animals. Despite its advantages (see section 3.1), the reliance on animal-based tests was at the same time considered a major weakness of the current approach. There are several ethical, legal and scientific arguments why the use of experimental animals for safety assessment is undesirable. The most important arguments identified during the workshop were mainly related to scientific and legal considerations. For example, in the EU there is, due to legislation, a clear need for validated and accepted non-animal testing methods for the safety assessment of cosmetic ingredients. Also, the anticipated number of animal experiments that is required to fulfil the requirements for REACH was recognized as an important driver to implement more methods based on the 3R principle.

Lack of relevant exposure information
A main point that was raised referred to the fact that risk assessment approaches generally are hazard-driven rather than exposure-driven. There was general consensus that relevant and reliable information on exposure is limited or not available, mainly due to the high costs involved. This was considered a major caveat, as knowledge on the internal or external dose is crucial to relate dose-response toxicity data to health risks in humans. It is possible that the route of administration in the toxicity tests used is different from the most important human route of exposure, requiring route-to-route extrapolation. In case of insufficient or absence of exposure data, default assumptions that are often but not always worst-case are made, which in turn may lead to an under- or overestimation of the risk associated with exposure to a certain chemical. Other challenging aspects include frequency and duration of human exposure, which are not always mimicked properly in toxicity tests. Also aggregate and cumulative exposures, including exposure to mixtures should be taken into account, since it is likely that humans are exposed to chemical substances through different sources and via different routes, and to multiple (hazardous) chemicals at the same time.

Exposure assessment is not always legally required and therefore exposure data are often lacking. This illustrates that legal frameworks greatly determine which information should be provided. A complicating factor in this field is that the information requirements differ between the various legal frameworks. It is also noteworthy that regulatory frameworks, like REACH, offer the possibility to waive hazard information. However, although this possibility is regularly used, it is often not well-founded and lacking a sufficient scientific basis (7).

Hazard-driven testing strategy
The current system is based on generating data by performing a battery of toxicity tests, with mainly apical end points as the readout for toxicity. This approach provides to a (very) limited extent insight into the mechanisms underlying toxicity, due to which it is often referred to as a 'black box' approach. It is to a large extent hazard-driven rather than exposure-driven. This sometimes results in unnecessary testing because not all information is always required for accurate risk estimation, or extremely low human exposure would mitigate the need to know the hazard (*e.g.* when below the TTC). Furthermore, our increased understanding of toxicological mechanisms together with evolving new technologies is not reflected in the current framework for risk assessment.

Applicability of current approaches: substances
Another issue put forward was that the toxicity tests and the testing strategies described in the current test guidelines have not been developed for "complex" substances, such as engineered nanoparticles. Some of the existing toxicity tests may be suitable to assess the hazardous properties of these materials, whereas others may not. Proper risk assessment requires insight in the fate of these nanomaterials in the body, including toxicokinetics, and its relationship with their dynamic physico-chemical properties throughout exposure, such as size, shape, solubility and surface properties of the particle. The multitude of possible differences between these newly developed nanomaterials due to *e.g.* size, structure, or coating, poses an additional challenge. Unlike most regular substances, the risk of nanomaterials does not depend on chemical composition alone, but on a plethora of particle properties, complicating the extrapolation of safety data for risk assessment purposes such as deriving exposure limits from one material to another. Hence, to be able to assess the safety of these different types of materials a different approach is required.

In analogy, the current approach was not designed for risk assessment of adverse effects resulting from exposure to mixtures. Hazard assessment is generally aimed at and based on data derived for an individual substance. However, in daily life combined exposures from multiple sources are common practice. The issue how to deal with combined exposures was identified as a gap in the current risk assessment process. More research in this area is clearly needed.

Applicability of current approaches: relevance for human risk assessment
Since risk assessment aims at protecting human health, it is important to consider that the currently used *in vivo* animal toxicity assays have several limitations in terms of human relevance. Some toxic effects induced in rodents or dogs upon exposure to a given chemical are not relevant for humans,or not at the same dose level. Vice versa, not all possible adverse health effects in humans are addressed in and/or can be detected by *in vivo* rodent toxicity tests. For instance, subtle effects like headache or slight nausea are not picked up by animal tests. Animal experiments are designed to detect some clinical and pathological changes rather than the induction of human diseases. This lack of human relevance affects the predictive capacity of rodent assays not only in a qualitative, but also in a quantitative manner.

Further, not all toxicity endpoints relevant for humans are (sufficiently) addressed in the current approaches. For example, the current battery of toxicity tests does not cover all phases of the reproductive cycle, and predictive test methods for respiratory sensitization and autoimmunity are lacking. Also, it has been shown that exposure to environmental chemicals can induce adverse epigenetic effects, which may impact on human health later in life or on the health of future generations. Finally, certain diseases are not covered in the current frameworks, including neurodegenerative diseases (Alzheimer, Parkinson), neurological diseases (ADHD, autism), and cardiovascular diseases. It is not yet fully understood whether a causal relationship exists between these diseases and exposure to environmental chemicals. Obesity and ageing were also mentioned as endpoints of toxicity testing being possibly relevant for human risk assessment, although more research in this area is needed. Finally, special emphasis was given to endocrine disrupters and how to recognise the associated adverse health effects.

For the extrapolation of animal data to humans, the current approaches use as default an interspecies factor that is not chemical specific to address (part of) the uncertainties associated with this extrapolation. Interspecies differences may however depend on the endpoints measured as well as on the chemical of interest. Consequently, in some cases this factor may be insufficient to cover interspecies differences, whilst in other cases it may result in overprotective risk management measures. Also, the interspecies assessment factor has to account for the possibility that humans might be more susceptible to the most critical effect observed in animals. Lastly, the possibility that the critical effect in humans might be *different* from that in experimental animals is not taken into account in the default assessment factor for interspecies differences.

Applicability of current approaches: Susceptible subpopulations
There was a clear consensus among the participants that potential high-risk groups, such as children or elderly, are not structurally addressed by the strategies currently in place. This is most likely due to insufficient knowledge about fundamental issues underlying age-dependent differences in sensitivity to toxicants, *i.e.* biochemical differences or physiological maturity. The current approaches do not include identification of potential susceptible subpopulations. In general, a default safety factor is applied to account for potential differences between individuals of the human population but its adequacy is highly uncertain.

Risk governance
The abovementioned issues in the current approaches for human health risk assessment, imply the necessity of a shift in the risk assessment paradigm and, therefore, will also mean a challenge for risk governance. New developments are not only accompanied by potential benefits and opportunities, but also by potential risks. Today's world requires a different way for dealing appropriately with risks. For instance, introduction of probabilistic methods has raised the issue how to deal with uncertainties in risk management and risk communication. It is also anticipated that risk managers will more often evaluate risks in the context of the benefits for society. Therefore it is important to be aware timely of the implications of changes in risk assessment approaches for future risk governance and to be prepared for discussions with relevant stakeholders.

3.3 Drivers for innovating human health risk assessment

Based on the strengths and weaknesses put forward in the various discussions, the participants of the workshop identified several drivers for innovating risk assessment, listed in Table 1.

Table 1: Main drivers for innovation of human health risk assessment

Hazard assessment
Relevance of effects in animals for the prediction of human adverse effects • Relevance of animal model for humans is uncertain • Incomplete coverage of human endpoints
Unknown level of uncertainty in the extrapolation of animal data to humans
Need for shift from black-box testing to mechanism-based toxicity testing
Animal welfare considerations (3R principles)
Approaches are not developed for "complex" substances, such as engineered nanomaterials, and mixtures
Unknown whether current approaches are adequate for susceptible subpopulations since these are not systematically identified
Insufficient insight in impact of chemical exposure on adverse epigenetic effects
Exposure assessment
Exposure data are often not available or limited (only defaults, no distribution)
Need for data that are relevant for the route and duration of exposure (*i.e.* geared to actual human exposure scenarios)
Need for adequate estimation of systemic exposure • Need for relevant kinetic information
Risk assessment
Need to shift from hazard-driven to an exposure-driven framework
Risks from combined exposures (multiple chemicals and/or multiple sources) are not addressed
Need to shift from a rigid system based on 'tick-box testing' to a flexible integrative and efficient risk assessment strategy
Need for more flexibility in legal frameworks towards methods for hazard and exposure assessment
Need for harmonization between different legal frameworks
Changes in risk governance: from risk assessment towards risk-benefit analysis

4 Conclusions and future perspectives

It can be concluded from this workshop that there are several drivers for innovating human risk assessment. We identified various important aspects and considerations that need to be taken into account when designing a new risk assessment strategy (Table 2). The conclusions are based solely on the outcomes of this workshop. They are in line with the challenges for human risk assessment as described, for instance, in the report of SCHER, SCENIHR and SCCS (4). Therefore, it is felt that the most important strengths and weaknesses of the existing approaches have been identified and, as such, the main drivers for changing the current paradigm. Ultimately, innovation of the human health risk assessment process should bring forward a more transparent, effective, and more efficient approach, in which decision-making is based on human-relevant exposure and hazard information. It should be based on the best available scientific knowledge using state-of-the-art tools, and should be designed in such a way as to avoid unnecessary toxicity testing. Preferably, a new conceptual framework will consist of a tiered targeted approach that is exposure-driven, mechanism-based, flexible, and cost efficient.

Table 2: Considerations for a new approach

Exposure assessment
Use of kinetic tools that allow accurate (internal) exposure assessment for the relevant route of exposure
Insight in uncertainties associated with interspecies and *in vitro-in vivo* extrapolation
Definition of criteria for waiving of toxicity testing
Definition of decision criteria for the appropriateness of subsequent testing
Hazard assessment
Start with available data (*in silico*, *in vitro* and human and animal data). When insufficient, add information from toxicity tests (from simple to complex)
Include tests that measure relevant parameters (based on Adverse Outcome Pathways or mechanisms of toxicity)
Apply the 3R principle as much as possible
Gather dose-response information to allow a quantitative assessment
Weight-of-evidence approach (incl. decision criteria) to integrate a broad spectrum of toxicity data
Risk characterisation
Addition of an analysis of the level of uncertainty (*e.g.* on uncertainty factors) to inform risk managers about the accuracy of the risk assessment outcome (risk estimate)
Legal requirements
Short-term: design (modules of) a new approach that fits within current legislation
Long-term: modify legal frameworks to align information requirements with the needs for each element in the risk assessment process
Risk governance and risk communication
Develop a strategy for risk communication towards society Involve risk governance

In 2014, RIVM will continue working on this topic in several ways. First, the focus will be on a pragmatic path forward by designing a conceptual framework for a more balanced (human exposure and human hazard) risk assessment strategy. The foundation, obviously, has been laid by the outcome of the workshop: the identified strengths and weaknesses as well as the

abovementioned considerations. In addition, the developments and progress made in the initiatives mentioned in Chapter 1 will be considered and taken into account. An important aspect of the future framework will be defining decision criteria that determine which information and test methods are needed and in what order. In the process of designing this conceptual framework (knowledge) gaps will be identified, which in turn will serve as guidance for the development of toxicity test methods, kinetic instruments and statistical tools to bridge these gaps. Furthermore, it is foreseen that both complex tools and complex information may become more important in a new framework. Since it is anticipated that these new developments and tools will influence future risk assessment, RIVM will have to gain the knowledge to judge these new tools on their merits. In addition, implications for adequate risk governance should be considered. A transition from existing towards innovative approaches will require a shift in thinking and risk perception, by toxicological risk assessment and management communities, policy makers and possibly societal organizations. Proper risk communication will facilitate this transition and should be taken into consideration in this process.

Innovating risk assessment is a difficult and complex task that requires time and international collaboration and engagement. The RIVM participates in several international projects on transitioning the current risk assessment process. These include the EU-FP7 projects 'MARINA' (*Managing Risks of Nanomaterials)* and 'NANoREG' (*A common European approach to the regulatory testing of nanomaterials*), and the working group "Clean Sheet Testing Strategy" of the ILSI-HESI Genetic Toxicology Technical Committee. By actively participating in these projects, RIVM not only contributes to the shared goal of a paradigm shift, but it also ensures that the future RIVM strategy in this respect is aligned with other efforts in this field. Additional collaborations with institutes and organizations involved in other programmes related to this topic will be sought. Finally, it is important to note that, given existing pragmatic barriers in acceptance of novel methods in the regulatory frameworks, an actual transition strategy will be required. The outcome of the workshop presented here may serve as reference, which is instrumental in a strategy to ensure acceptation and meaningful implementation of a new approach. This aspect of innovating the current risk assessment process will be given more attention in the coming years.

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References

1. National Research Council. Toxicity Testing in the 21st Century: A Vision and a Strategy. Washongton DC: The National Academies Press; 2007.
2. ASAT: Assuring Safety without Animal Testing. 2008. http://www.asat-initiative.eu/ASAT%20Final%20Report.pdf
3. ILSI Health and Environmental Sciences Institute. Risk assessment in the 21st century (RISK21).
4. EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR); EU Scientific Committee on Consumer Safety (SCCS); EU Scientific Committee on Health and Environmental Risks (SCHER). Addressing the New Challenges for Risk Assessment. 2013. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_037.pdf
5. EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR); EU Scientific Committee on Consumer Safety (SCCS); EU Scientific Committee on Health and Environmental Risks (SCHER). Toxicity and Assessment of Chemical Mixtures. 2011. http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf
6. EFSA Panel on Plant Protection Products and their Residues (PPR). Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile. EFSA Journal. 2013;11(7).
7. European Chemicals Agency CHA. The Use of Alternatives to Testing on Animals for the REACH Regulation. 2011. http://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2011_en.pdf)

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