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Summary and results from performing stakeholder interviews about ITS implementation and acceptance

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Summary and results from performing stakeholder interviews about ITS implementation and acceptance

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PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
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Summary of Stakeholder Interviews

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Summary

In order to investigate the stakeholders' perception on ITS implementation and acceptance, DIA and WUR performed stakeholder interviews with different target audiences (e.g. chemical industry, regulatory authorities, NGOs, scientific organizations). Both project partners have interviewed about 20 stakeholders. The results are documented here and provide insight into the stakeholders' views on ITS implementation and acceptance, reducing animal use in toxicity testing and the potential of ITS to contribute to this purpose. In addition, stakeholder-specific perceptions regarding core themes identified were examined by using qualitative data analysis methods.

This paper is, to the best of our knowledge, the first study examining the views of different stakeholder groups about Integrated Testing Strategies of Chemicals. By doing so our study complements and extends existing research about ITSs, which has focused mainly on the development of ITSs for hazard and risk assessment of chemicals from a purely scientific perspective.

By evaluating interviews with members from private enterprises, regulatory agencies, research organizations and NGOs we aimed to get better insight on stakeholders' perceptions regarding the definition of an ITS, its advantages and limitations, its acceptance, its potential for reducing animal testing and research needs.

Integrated Testing Strategies (ITSs) have received much attention as promising tools for more resource-efficient hazard and risk assessment of chemicals and for reducing animal use in toxicological testing. The usage of ITSs crucially depends on their acceptance and application by various stakeholder

groups, for example chemical industry, scientific organizations and regulatory authorities. However, we observe that little is known about stakeholders' views on the use and application of ITSs. In this study we present results from semi-structured interviews with different stakeholders groups. Interviewees were asked to express their personal views and opinions about what an ITS is or should be, about ITS advantages and limitations, about ITS implementation and acceptance and needs for further research. Using qualitative data analysis methods we identify a set of core themes that stakeholders considered most relevant with respect to these six topics. Our results illustrate that stakeholder perspectives differ considerably for the topics addressed. We find particularly diverging views across stakeholder groups with respect to ITS limitations and acceptance. This underlines that improving stakeholder integration and intensifying the dialogue about useful and successful ITS applications should receive more attention for strengthening ITSs as effective decision-support tools.

Analysing all results, the authors of this study conclude that the 19 interviewed stakeholders hold slightly positive, but mainly diffentiated opinion on Integrated Testing Strategies. ITS can serve as powerful tools to provide results quicker and to combine existing information and the wide range of methods into just one system that are in practise in chemical assessment. With the help of ITS, better risk assessment can be performed by using all available information in the position to perform better decisions.

The stakeholders see a huge potential on the reduction of classical tests with animals, which is an ethical issue and an aim in itself. ITS can save time and money. It is the different way of thinking an ITS promises. It leads away from the standardized testing batteries, to more sophisticated approaches. ITS can change toxicology and the normal way to handle chemicals completely. These are the main arguments expressed which should motivate to strengthen the efforts.

However, the stakeholders clearly express significant limitations do exist, which will partly function as huge barriers for the application. One limitation is the data and information accessability. Still a lot of data is stored in archives and not accessable for users and regulators. Another limitation is the uncertainty about wheather an ITS will be accepted by the regulating bodies.

Another line of discussion was the communication with stakeholders and other interested parties, which should be intensified. Lack of understanding, the shortage of experienced ITS experts, and the need for more training for unexperienced users are other limitating factors. Frequently the stakeholders ask for successful examples and cases that are really convincing. Further and better ITS should be developed. These would lead to a better awareness and wider use by industry and other users.

Results provide a picture about what the interviewed stakeholders considered relevant. This can be taken as guidance for targeting research efforts and points into the directions to which further studies should go.

Further activities in relation to this study

The results of this study have been worked out as a scientific paper, which will be offered to the peer-review Journal of Risk Research. The working title is: Gabbert, S.; Benighaus, C.: Quo Vadis Integrated Testing Strategies? Experiences and observations from the workfloor. Journal of Risk Research. Under review.

Silke Gabbert presented this study at the SETAC Conference in May 2011 (Title of the presentation: ITS implementation and acceptance: what do different stakeholder groups think?).

Activities in the future

A second scientific article will be worked out on other core themes identified in the study in 2011. This study will be presented during meetings, workshops and conferences.

The results will be made available to the other partners of the OSIRIS consortium, the stakeholders interviewed and other interested parties.

Contents

1 Introduction

There is growing recognition that risk assessment of chemicals has to be performed more transparently and efficiently in order to fill existing data gaps for several thousands of hazardous chemicals in use (Smith 2001, Schaafsma et al. 2009, Krewski et al. 2009). Motivated by recurrent dissatisfaction with the traditional "patchwork" or "box-ticking" approach to hazard and risk assessment of chemicals (Bhogal et al. 2005, Gibb 2008, Hartung 2010) that has been based on costly and time-consuming guideline animal-tests, in a new European regulatory framework for Registration, Evaluation, Authorization and Restriction of Chemicals (REACH, EC 2006, see also Foth and Hayes 2008) entered into force June 2007 (Holsapple et al. 2009, Hansen and Blainey 2006 and 2008). REACH calls chemical producers and manufacturers to submit comprehensive information about chemicals' hazard and risks. If existing data are insufficient to meet the requirements, information must be generated by using testing and non-testing methods. In addition, REACH emphasizes to apply animal experiments "only as a last resort" (EC 2006, Article 25).

It has been argued that the comprehensive data requirements outlined in REACH and the large number of industrial chemicals that are going to be tested require a "paradigm shift" of the current risk assessment and risk management regime for industrial chemicals from a hazard-testing to a risk-driven, context-specific and substance-tailored approach (Blaauboer and Andersen 2007, van Leeuwen et al. 2007, Schaafsma et al. 2009). Integrated Testing Strategies (ITSs) have been considered appropriate and powerful tools for this purpose (Bradbury et al. 2004, Grindon et al. 2006 and 2008, Van Leeuwen et al. 2007, Ahlers et al. 2008, Lilienblum et al. 2008). ITSs are expected to meet information requirements in a quicker way, at lower costs and with less animal use than standard tests and testing systems (Van Leeuwen et al. 2007, Lilienblum et al. 2008, Hartung 2010). Basically, an ITS is a tool for generating information about a substance's hazards or risks in a step-wise way, integrating information from various sources. Hence, the core aim of testing in general, and of applying ITSs in particular, is to guide and support the adoption of appropriate safety measures for chemcals' use. An ITS therefore serves as an "interface" or "briding tool" between science and (regulatory) decision-making.

Different definitions of an ITS offered in the literature describe the features and characteristics of an ITS in more detail. Whereas some focus mainly on the conceptual and methodological structure of an ITS, other definitions put more emphasis on possible ITS functions for risk assessment and risk management of chemicals (see Box 1).

Box 1: Definitions of ITS as proposed in the literature

"An ITS is any approach to the evaluation of toxicity which serves to reduce, refine or replace an existing animal procedure, and which is based on the use of two or more of the following: physicochemical data, in vitro data, human data (for example, epidemiological data, clinical case reports, animal data (where unavoidable), computational methods (such as quantitative structure-activity relationships (QSAR), and biokinetic models." (Blaauboer et al. 1999)

"(Integrated testing strategies) consist of a series of tests performed in a defined sequential manner. The tests selected in each successive level are determined by results in the previous level of testing in a stepwise process that leads to a decision. Testing strategies start by using existing data to enable in silico based predictions, including the application of (Q)SARs and decision models based on physicochemical data. In a successive step they also encompass the use of in vitro methods, and only if necessary they consider the application of in vivo tests." (Gallegos Saliner and Worth 2005)

"Integrated testing strategies are hierarchical in nature, and start by making use of pre-existing data and physicochemical properties, to enable predictions of toxicity to be made, where possible, based on computer (in silico) modeling. They can comprise the use of in vitro methods (subcellular and/or cellular systems), and culminate in the application of in vivo tests as requires, some of which have been subjected to reduction and refinement." (Grindon et al. 2006)

"Conceptually, an ITS is a hierarchical testing scheme consisting of a set of decision nodes, allowing for taking different routes for information gathering and inference for decision making about a chemical's hazard or risk. The overall aim of ITSs is to efficiently exploit and integrate existing information with new data, which can be generated by multiple testing and non-testing methods. In contrast to classic tiered testing schemes, exploiting information from various sources is considered to increase the safety assessment's quality, to maximize information gains, and to reduce testing costs, testing time and animal use. In addition, the information gained from a preceding test is considered to guide the choice of the next test, or battery of tests, at any particular stage in the testing sequence." (Jaworska et al. 2010)

These definitions, however, have predominantly been developed from an scientific perspective. Assuming that ITSs are tools for, most generally, generating information, their particular strength could be to link different stakeholder groups and to serve as interfaces, for example between science and policy. This presupposes that there exists some common understanding of different stakeholder groups on, for example, what an ITS is and for what purposes it can suitably be applied. So far, however, little is known about the views and opinions of stakeholder groups such as, for example, chemical industry or regulatory agencies. This is surprising since accounting for stakeholder perceptions has proven to be crucial for an effective science-policy interaction in many domains (Bryson 2004, van der Kerkhof 2004, Tuinstra et al. 2006, Gabbert et al. 2010, Assmuth et al. 2010).

The objective of this paper is, therefore, to explore the stakeholders' views on ITSs from a broader perspective. More specifically, we pursue two aims: Our first aim is to get better insights into what different stakeholders groupss ideas about what an ITS is or should be, where they see opportunities

and limitations for ITS usage in a regulatory risk management context, and which needs for further research they consider most relevant. To meet this aim we performed semi-structured interviews with members from chemical industry, research institutions, consultancies, NGOs, and regulatory agencies. The interviews were evaluated and analysed by using qualitative data analysis methods. This allows identifying core themes that stakeholders prioritize when reflecting about ITS. The second objective is to examine whether there exist stakeholder-specific patterns regarding these core themes and to identify areas of consensus and of disagreement across stakeholder groups. Our study complements existing research on ITS development (Van Leeuwen et al. 2007, de Wolf et al. 2007, Grindon et al. 2008a-f, Combes et al. 2007, Combes and Balls 2005, Benighaus 2009, Gabbert and Weikard 2010, Jaworska et al. 2010) and provides a more detailed picture on requirements and prospects for ITS usage in regulatory contexts such as REACH.

The paper is structured as follows. In the next section we explain the setup and performance of the stakeholder interviews. In Section 3 we explain the application of qualitative data analysis methods for evaluating the interviews. Section 4, then, describes and discusses the results revealed from our analysis. Section 5 concludes.

2 Stakeholder interviews

A systematic investigation on the use and acceptance of ITSs has, to the best of our knowledge, not been conducted so far, performing interviews with members from various stakeholder groups seems to be most appropriate to approach the research objectives described in the introduction. Clearly, since interviews can usually cover just a small fraction of all stakeholders, they can only provide a snapshot of the total range of opinions and perspectives. The insights revealed, and the conclusions drawn from such analysis, therefore cannot be considered to be representative for all stakeholders. Nevertheless stakeholder interviews provide a valuable first step that illustrates the variety of perspectives and facilitates further research on ITSs.

Stakeholder interviews can be performed in many diffferent ways (Varvasovzki and Brugha 2000, Saffer 2010). We decided to conduct qualitative, semi-structured interviews where interviewees are consulted as experts. The participants are usually given a limited number of open, motivating and general topics or questions, but they are given the freedom to skip questions if they can't answer them, return later to them, and raise new issues which are not on the interviewer’s list of topics but are considered important by the interviewee. The objective was to provide a platform for expressing personal views, opinions

and experiences in an open way, without pre-directing or restricting the talks. For this purpose, interviewees were sent six working questions at least one week in advance of the interviews (see Box 2).

Box 2: Working questions and topics addressed during the interviews

1. What do you think is an ITS or what should it be? **(ITS definition)**
2. What do you think are the advantages of using ITS in a regulatory context? **(ITS advantage)**
3. What do you think are disadvantages and limitations of using ITS in a regulatory context (**ITS disadvantage/limitations**)?
4. Where do you see limitations for ITS application? **(ITS application)**
5. What would you recommend for improving the acceptance and use of ITS? **(ITS acceptance)**
6. What should be important further steps for ITS research and application? **(Research needs)**

The working questions framed the interviews and should stimulate interviewees to explain and elaborate their perspective regarding a certain topic (e.g. “ITS definition”). No time restriction was imposed in order to give participants a maximum of freedom and flexibility to express their views. Hence, the interviews differ across stakeholders with respect to their structure and overall length. The interviewer’s role was to ask, if necessary, questions for clarification (e.g. “could you please explain what you exactly mean?” or “can you think of an example?”) and to make sure that all topics were addressed. At the end of the interview participants were asked to briefly describe their professional background and how they have been involved in the REACH process.

In total 43 people belonging to private enterprises (chemical industry and consultancies), research organizations (universities and private research institutes), animal welfare and other interest groups, and regulatory agencies were invited by Email to participate in the interviews. Of these, 19 people were willing to participate and could be interviewed. Table 1 shows the number of participants within each stakeholder group.

Table 1: Interview participants across stakeholder groups

Stakeholder category	Number of participants
Private enterprises (P)	6
Regulatory agency (A)	4
Research organization (R)	6
NGO/interest groups (N)	3
Total	**19**

3 Qualitative data analysis

The interviews were conducted by phone and took approximately 30-45 minutes. Every interview was audio-taped and literally transcribed afterwards into a text file. The transcribed text files were analyzed with a software for qualitative text retrieval and analysis, MAXQDA (http://www.maxqda.com/), which has become widely used for text analysis in several disciplines such as Sociology, Psychology, Political Science, Public Health, Anthropology, Education, or Marketing (see, for example, Kronenwetter et al. 2005, Creswell and Zhang 2008, Remmers et al. 2010). Applying qualitative analysis tools has a number of advantages. First, it allows for a more systematic and sophisticated evaluation of text material. This is particularly important in cases where large amounts of qualitative data (e.g. essays, interviews, discussion records) need to be analyzed. Second, textual information can be structured more efficiently, which facilitates the extraction of key information. Third, it facilitates the exchange of information among analysts.

For evaluating and analyzing the interviews the transcribed text files have been coded. A "code" is defined a categorical phrase or a catchword that the analyst attaches either to a single word, to a part of a sentence, to complete sentences or to text passages transporting a particular content or meaning (Auerbach and Silverstein 2003, Saldaña 2009). The aim of the coding process is to transform and condense the textual data into analytic data to which then qualitative data analysis methods can be applied. "Coding" a text requires that the analyst, while reading through the transcribed interviews, assigns a code phrase to a marked text segment such that its content is appropriately described. This can either be done by literally adopting the terms used in the text ("in vivo coding") or by inventing suitable terms (free coding) in a more interpretative way. In this study both approaches to coding were applied. Depending on the text's content different codes can be attached to one and the same segment and coded segments are allowed to overlap.

The interviews were coded in three steps. First, codes reflecting the topics addressed in the working questions (see Box 2) were assigned to entire text blocks. For instance, a text section where the interviewee explained what she/he considered to be an advantage of an ITS, was assigned the code "ITS advantage". Other text segments were accordingly coded "ITS definition", "ITS limitation", "ITS application", "ITS implementation and acceptance", or "research needs". Second, within these text blocks codes were assigned as regards to content to single words, fragments of a sentence, complete sentences, or paragraphs. As a third step content-related codes were clustered into categories with a similar content. The categories characterize "core themes", i.e. key issues to which interviewees referred in their responses. Table 2 shows the complete set of core themes revealed from all interviews. A code category, for example "costs", "toxicological endpoint", or "uncertainty" (see Table 2), can include several sub-codes. Clearly, the content-related coding and the clustering of codes is based on plausibility considerations and largely depends on the analyst's subjective judgment. Different analysts may, therefore, suggest different categorizations (Sinkovics et al. 2008). To account for this subjectivity and to strengthen the reliability of the analysis the authors performed the content-related coding of interviews independently. In a subsequent step the two code systems were merged into a joint system. The same procedure was applied for the code categorization.

Table 2: Core themes (bold) and sub-codes revealed from coding all interviews

Costs
- Invest money
- Reduce costs
- Reduce testing time
- Efficiency

Toxicological endpoint
- All endpoints
- Human health endpoints
- Environmental endpoints
- Physicochemical properties

Information documentation
- How components are related to each other
- Data format
- Data completeness
- Registration dossier

Information requirement
- Target
- Evaluation whether information is sufficient
- Test requirement
- Identify data gaps and testing needs
- Complementarity of tests/conditional dependence

Information sources/methods
- Available information
- Historic reports
- Human data
- Expert judgment
- Mechanism/mode of action
- Alternative methods
- In vivo studies

Experimental animals
- Increased animal use
- Animal welfare considerations
- Political decision
- Reduce/refine/replace animal testing

Future challenges/perspectives
- Willingness to implement new tools
- Case studies
- Test/ITS development

ITS conceptual structure
- Check-box approach
- Decision-tree
- Combination of different types of information
- Iterative/ordered approach

ITS outcome target
- Effects assessment
- Hazard identification
- Risk assessment
- Risk characterization
- Exposure information
- Should lead to a decision
- Less standardized evaluations

ITS terminology
- Integrated testing strategy
- Intelligent testing strategy
- Alternative testing strategy

Knowledge
- About methods
- About substances

ITS functional characteristics
- Too narrowly focused
- High complexity
- Not user-friendly
- Not predictive
- Difficult to compare outcomes
- Assessment process facilitation
- More sophisticated/creative evaluation of information
- Paradigm change
- More transparent assessment
- Quicker assessment

Learning
- Gain experience/get familiar with
- Confidence and trust
- Expertise profile
- Lesson over time

Assessment and measurement
- Qualitative approaches
- Extrapolation
- Formal/automized approach
- Decision-analytic approaches
- Probabilistic methods

Stakeholder involvement
- Industry
- Regulators
- Public /customers
- Science
- Science-policy interaction
- Stakeholder communication

Data
- Conflicting data
- Data generation
- Data accessibility
- Data gaps
- About physiological pathways
- About reliability of in vivo methods
- About error propagation
- How to interpret data
- How to use alternative methods

Policy/regulation
- Policy reform
- Policy preference
- Regulation
- Toxicity testing in the 21st century
- Reversal of burden of proof
- REACH
- Identify most dangerous substances

Uncertainties
- Be aware of limitations
- Identify limitations of ITS
- Predictive accuracy
- ITS reliability
- Understanding of uncertainties
- Safety factors
- Validation
- Different interpretations
- Different perspectives
- Different results
- Policy uncertainty
- Regulatory acceptance
- Path dependency

Decision-making
- Decision-support
- Regulatory decision-making
- Harmonization/common procedure
- Traditional mode
- Guidance

Besides identifying the core themes and their respective sub-codes the frequency of code assignments was assessed. Table 3 shows the frequency of code assignments for all core themes and the whole sample of stakeholders (columns 1 and 2). In addition, the table gives an overview about relative code frequencies for different stakeholder groups (columns 3 to 7), which was revealed by dividing the absolute code frequency by the number of interviewees belonging to a certain stakeholder group. The figures illustrate that the themes “information sources”, “uncertainty” and “costs” were most frequently addressed by stakeholders. This is generally also true for individual stakeholder groups, though we observe that the exact rank positions of core themes can differ. For example, members from NGOs and other interest groups addressed more often issues subsumed under the category “costs” than issues clustered under “uncertainty” or “information sources/methods”, indicating that NGOs considered “costs” to be relatively more important.

Table 3: Frequency of core themes identified and relative frequency of code assignments across stakeholder groups

Core themes (code category)	Frequency of code assignments	Relative frequency of code assignments*				
		All	P	A	R	N
information sources/methods	162	8.53	8.3	12.5	7.5	6.0
uncertainty	154	8.11	6.5	8.3	6.8	7.7
costs	153	8.05	8.0	10.5	5.3	10.3
tox. endpoint	125	6.58	6.7	4.3	6.5	9.7
decision-making	121	6.37	5.5	8.3	6.0	6.3
learning	118	6.21	3.8	5.0	6.0	7.7
stakeholder involvement	118	6.21	4.3	5.8	7.5	9.0
experimental animals	99	5.21	5.7	5.5	3.7	7.3
future challenges	95	5.00	5.3	5.5	4.8	4.0
ITS functional characteristics	88	4.63	4.5	5.8	3.7	5.3
ITS conceptual structure	62	3.26	4.5	3.0	3.2	2.0
assessment and measurement	40	2.11	0.7	1.3	1.8	2.7
information requirements	30	1.58	1.8	1.3	1.2	2.3
policy/regulation	27	1.42	1.5	2.3	0.5	1.0
data	24	1.26	2.0	2.0	0.5	0.3
ITS outcome target	22	1.16	0.7	1.8	1.8	0.3
knowledge	17	0.89	1.3	1.3	0.5	0.3
information documentation	15	0.79	1.2	0.3	1.0	0.3
ITS terminology	12	0.63	0.2	1.5	0.5	0.7

* Code assignments divided by number of stakeholders of a particular group

All = all stakeholders; P = private enterprises; A = regulatory agency; R = research organization; N = NGO/interest group

While the (relative) frequency of code assignments gives a first indication of thematic priorities across stakeholder groups, it does not provide insights into what stakeholders think when responding to specific topics such as, for example, “ITS advantages” or “ITS limitations”. This requires going further into depth and to examine stakeholder patterns across topics. We further elaborate this in the next section.

4 Stakeholder perceptions of Integrated Testing Strategies

In order to explore stakeholder patterns we examined intersections of topic-related and content-related codes, i.e. the frequency of content-related codes occurring within text blocks to which also topic-related codes were assigned. This revealed a matrix of code frequencies across stakeholder groups and topics, allowing to analyze areas of consensus and debate between stakeholder groups. Again, to account for different sample sizes code frequencies were divided by the number of participants in each stakeholder group.

Table 4 presents core themes addressed by stakeholder groups for every interview topic.

Table 4: Core themes addressed by stakeholder groups across interview topics

Core themes	All	P	A	R	N
ITS definition	information sources/methods	ITS conceptual structure	information sources/methods	information sources/methods	information sources/methods
ITS advantage	costs	ITS functional characteristics	costs	costs	costs
ITS application	tox. endpoint	tox. endpoint	tox. endpoint; information sources/methods	tox. endpoint	tox. endpoint
ITS limitation	uncertainty	tox. endpoint	information sources/methods; uncertainty	tox. endpoint; uncertainty	uncertainty
ITS acceptance	stakeholder involvement	costs learning	decision-making	uncertainty	stakeholder involvement
Research needs	uncertainty	uncertainty	uncertainty	stakeholder involvement	costs; decision-making; tox. endpoint; ITS functional properties; uncertainty

All = all stakeholders; P = private enterprises; A = regulatory agency; R = research organization; N = NGO/interest group

The table illustrates that core themes varied across topics. Moreover, we observe relative stronger consensus across stakeholder groups for the topics “ITS definition”, “ITS advantage” and “ITS application” compared to the topics “ITS limitations”, ”ITS acceptance” and “research needs”. Clearly, given the comprehensive set of codes in the code system, it would be beyond the scope of the paper to discuss all findings in every detail. Rather, we focus on the most interesting findings for each interview topic. Core themes and sub-codes as shown in Table 2 to which we explicitly refer to in our discussion are presented in quotation marks. Table 5 and 6, showing relative code frequencies of core themes for all interview topics and stakeholder groups, are presented in the Appendix.

4.1 Stakeholder perspectives regarding "ITS definition", "ITS advantage" and "ITS application"

Being asked what they think an ITS is or should be, stakeholders offered different terms ranging from "integrated-" and "intelligent testing strategy" to "alternative testing strategy". The core theme to which three stakeholder groups (regulatory agencies, scientific organizations and NGOs) predominantly referred was "information sources and methods", characterizing the type and origin of information that is integrated in an ITS. Within this category all three stakeholder groups frequently emphasized the use of all "available information" (including human data) and the application of "alternative methods" to be key characteristics of ITSs. Looking into text segments coded with "alternative methods" we find that *in vitro* methods, non-testing approaches such as QSARs, exposure-based waiving, information on a chemical's mode or mechanism of action and Weight-of-Evidence approaches were most often mentioned.

The private firm's understanding of ITSs differed from that of other stakeholder groups in that they considered the "conceptual structure of an ITS" to be most relevant. Within this thematic category they emphasized the "combination of different types of information" (testing and non-testing methods) into an "iterative, ordered assessment" or a "decision tree" that allows to stop the assessment at a certain stage, to be key ITS features.

In addition, our findings illustrate that all stakeholders, and in particular members of private firms, regulatory agencies and NGOs associated "ITS definition" with "decision-making". Analyzing their responses in more detail revealed that ITSs are commonly considered "decision-support tools", which is linked to "guidance" (e.g. on test selection) and to the development of a "harmonized or common procedure" on assessing a chemical's hazards or risks. Stakeholders from regulatory agencies and NGOs explicitly drew a connection to "regulatory decision-making in the REACH context". Members of private firms had also a clear association to "information requirements", stressing the identification of data gaps and testing needs and the evaluation whether available or generated information is sufficient to be important issues.

Further insight into stakeholders' perspectives on ITS is gained by comparing core themes addressed by interviewees with the explanations found in the scientific literature. Three of the four definitions presented in Box 1 (Blaauboer et al. 1999, Grindon et al. 2006, Jaworska et al. 2010) explicitly underline the reduction, replacement and refinement of animal experiments, and a reduction of monetary costs and testing time to be important requirements that an ITS should meet *besides* allowing

for a combination of different pieces of information. In our code system, these issues were clustered under the themes “costs” and “animal experiments” (see Table 2). As it can be seen from Table 5 in the Appendix, members from regulatory agencies did address neither of these themes.

Similar to “ITS definition” we observe considerable agreement regarding core themes subsumed under “ITS advantage”. Interviewees from regulatory agencies, scientific organizations and NGOs had clear associations to “costs”. In their responses they pointed to the potential of an ITS to “save costs”, for example by carefully evaluating the need for testing and by avoiding unnecessary tests. Furthermore, interviewees from science and NGOs explicitly considered the possibility to “reduce testing time” by avoiding long-term toxicity testing to be an advantage. This was also associated with the option to “increase the efficiency” of a hazard or risk assessment through a more careful resource planning and a more targeted testing of chemicals. Again, the views and opinions expressed by stakeholders from private enterprises differed from all other stakeholder groups by pointing to specific “functional characteristics” of ITSs. Here they repeatedly emphasized that ITSs may lead to “process facilitation” and a “more sophisticated and creative evaluation of information”. Moreover, all stakeholders considered the integration of “available information” in combination with “alternative methods”, leading to “reduce, refine and replace animal testing” and to improve “animal welfare” to be clear advantages of ITSs.

When talking about “ITS application” all stakeholder groups made clear reference to “toxicological endpoints”. Looking in more detail into content-related codes attached to their responses, however, we observe that stakeholders predominantly referred to specific human health endpoints, especially skin, lung and eye irritation, corrosion, skin and respiratory sensitization, carcinogenicity, and genotoxicity, while other endpoints such as, for example, repeated dose toxicity, acute chronic and systemic toxicity, or reproductive toxicity were not mentioned. Surprisingly, only interviewees from regulatory agencies and NGOs pointed to “environmental endpoints” (bioaccumulation and endocrine disruption in fish) and “physicochemical properties” as options for ITS application, but here the relative frequency of code assignments was much lower than for human health endpoints (see Table 5 in the Appendix). Members from regulatory agencies had equally strong associations to “information sources/methods”, emphasizing especially the use of alternative methods (*in vitro* methods and category approaches) in ITSs. This indicates that for regulators the application of ITSs is not detached from these methods (and the applicability of the respective methods). Moreover, regulators also put stronger emphasis on the theme “animal experiments” than other stakeholder groups, associating the application of ITSs with the goal to reduce, refine or replace animal testing. Finally, it is interesting to note that when talking about

ITS application all stakeholders point to “future challenges”, especially the development of (substance-specific) “case studies” of ITSs, creating useful and successful pilot examples. In addition, a link was made to the theme “learning” by gaining experience on ITS application and creating “confidence and trust” how to evaluate outcomes of an ITS. This illustrates that stakeholders also place the application of ITSs in a forward-looking perspective, clearly pointing to the scope and needs for improvement.

4.2 Stakeholder views regarding “ITS limitations”, “ITS acceptance” and “ITS research needs”

Compared to the topics “ITS definition”, “ITS advantage” and “ITS application” stakeholder opinions were much less homogeneous regarding the topics “ITS limitations”, “ITS acceptance” and “research needs”.

We find “uncertainty” to be a core theme addressed by all stakeholder groups when reflecting about ITS limitations. However, stakeholders had largely differing views regarding which uncertainties they assume to be most relevant. Interviewees from NGOs stated that uncertainties can be due to analysts ignoring the limitations of the methods included in an ITS, and by a lack of understanding of the type of information provided by a method and about its reliability. Moreover, they put strong emphasis on “learning”, addressing specifically the need to make analysts more familiar with probabilistic methods. Gaining a better understanding of the complexity and the functioning of an ITS was considered a prerequisite for creating “confidence and trust”, both on the experts’ and on the public’s side. Interviewees from private firms emphasized “policy uncertainty”, especially about what type of hazard and risk information will be accepted by regulators, to be highly important. Furthermore, NGO experts pointed out that uncertainty about a test’s predictive accuracy and applicability domain, and uncertainty due to the lacking validation of methods may limit the use of ITSs. Regulators and members of research organizations, to the contrary, regarded uncertainty caused by “different possible interpretations” of ITS outcomes and the associated costs of making errors, to be key limitations of ITSs. An interesting finding of our analysis is that researchers associated these uncertainties with specific human health endpoints (skin sensitization, skin irritation, carcinogenicity, reproductive and developmental toxicity), while regulators mainly talked about uncertainties in conjunction with methods or information sources (*in vivo* and *in vitro* tests, QSARs, WoE, category and grouping approaches). This illustrates diverging perspectives on what constitutes ITS limitations between these stakeholder groups.

Our findings show a clear divergence of stakeholders' opinions and views with respect to what improves "ITS acceptance". Members from regulatory agencies most frequently stressed pointed to "guidance", in particular on how different testing and non-testing methods in an ITS should be performed, and on how the process of drawing conclusions from ITSs can become more standardized. Interviewees from private firms prioritized the theme "costs". They expressed the view that ITSs have currently only limited potential to "save monetary costs" and to "reduce testing time". They argued that cost reduction, for example through the use of information across endpoints, could support the implementation of ITSs. Likewise, researchers put considerable emphasis on the theme "learning". They stressed that ITS may become more widely accepted by "gaining more experience" in using ITSs. In addition, "confidence and trust" in ITSs could be built by offering additional "training" to stakeholders from regulatory agencies, industry and academia. NGOs, finally, linked ITS acceptance predominantly to "stakeholder involvement". It should be noted that this theme was addressed by all stakeholder groups, but members from NGOs put much stronger emphasis here (see Table 6 in the Appendix). They stressed the need for stimulating the inter-stakeholder dialogue between chemical industry, regulatory agencies and the public as a requirement for implementing ITSs. Even stronger, NGO experts explicitly regarded public acceptance of ITSs to be a major "future challenge" since, in their view, the majority of consumers is not aware of the complex assessment procedures in an ITS but expect chemicals to be "safe".

NGO experts did not show clear priorities regarding needs for further research on ITSs. Relative code frequencies were generally low and equal for different themes ("costs", "decision-making", "toxicological endpoint", "ITS functional characteristics", "uncertainty", see Table 6 in the Appendix). Key topics addressed were the assessment of ITSs' monetary costs and how information can be used across endpoints in order to better contribute to an overall reduction of costs. Likewise, they argued that more attention should be given to improving the "efficiency". More specifically, the scientific complexity of ITS needs to be better broken down to the practical needs of decision-makers. For ITSs being "decision-support tools" interviewees from NGOs emphasized the need for more research on how to develop generic, performance-based guidelines for methods incorporated in an ITS. Finally, reducing the uncertainty by extending the "validation" and "regulatory acceptance" of alternative methods incorporated in an ITS were stated important areas for further analysis.

Interviewees from private firms and regulatory agencies, to the contrary, argued that research should focus on reducing "uncertainty" inherent to the "predictive accuracy" of test information, giving more attention to exploring the applicability domain of methods incorporated in an ITS, and to the

comparability of information from different tests. In addition, they pointed to the need for more research on reducing "policy uncertainty" in terms of what information will be regarded sufficient and acceptable by regulators. Related to their views expressed about the application of ITSs, stakeholders pointed to research needs in conjunction with "future challenges". In particular, researchers assumed a better "involvement of stakeholders" in the risk management of chemicals to be a key need for further research. In their responses they raised the question how science-policy interaction can be improved and what type of regulatory incentives could stimulate such interaction. Another issue brought forward by members from private firms was how the implementation of new concepts and methods, for example probabilistic methods, decision-theoretic approaches or data mining techniques, could become used on a broader scale by chemical industry.

5 Conclusions and discussion

Much attention has been paid on the conceptualization and development of Integrated Testing Strategies (ITSs) as tools for more efficient hazard and risk assessment of chemicals. Since the use and implementation of ITSs for scientific and regulatory purposes largely depends on their acceptance by various stakeholders, we need to better understand what they find relevant for using ITSs in their respective working environment.

This is, to the best of our knowledge, the first study examining and comparing the views of different stakeholders groups regarding the topics "ITS definition", "ITS advantage", "ITS application", "ITS limitation", "ITS acceptance", and "research needs". Using qualitative data analysis methods we identified a set of core themes reflecting what stakeholders considered most important with respect to these topics. In addition, we analyzed areas of consensus and debate across stakeholder groups. Given the sample size, the outcomes of this analysis cannot be interpreted in terms of statistical significance and representativeness. Rather, they provide a first and preliminary snapshot of stakeholder perceptions. In this respect, however, our study reveals some interesting insights.

First, we observe that stakeholders addressed a large variety of themes that are related to the methodological and conceptual characteristics of an ITS, but also to political, regulatory and administrative aspects underlying the use and implementation of ITSs. Second, our findings illustrate that stakeholder opinions differ considerably across topics. In particular, experts from private enterprises and regulatory agencies showed differing thematic priorities for all topics except "ITS research needs". This indicates fundamentally different decision-making perspectives regarding

chemicals' hazard and risk assessment. Furthernore, there is no common agreement across stakeholder groups regarding what triggers and improves ITS acceptance. Even if we keep in mind that the development and use of ITSs in regulatory contexts is still in an early phase, it underlines that stakeholder communication and integration deserves more attention. Assuming that ITSs can, most generally, be used both for scientific assessment and for regulatory decision-making purposes they serve as interfaces, i.e. as tools for generating and exchanging information between stakeholders. The transmission and exchange of information can, however, only be effective if stakeholder groups have a common understanding on key determinants. In this context our findings can guide further research efforts on ITSs and contribute to a better targeting of scarce resources for improving risk assessment and risk management of chemicals.

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Appendix

Table 5: *Relative code frequencies across stakeholder groups for the topics "ITS definition", "ITS advantages", and "ITS application"*

Core themes	Topics addressed in the interview											
	ITS definition				ITS advantage				ITS application			
	P	*A*	*R*	*N*	*P*	*A*	*R*	*N*	*P*	*A*	*R*	*N*
costs	0.17	0.00	0.83	1.00	0.83	3.75	1.17	3.33	0.67	0.50	0.17	1.33
data	0.00	0.25	0.00	0.00	0.17	0.25	0.00	0.00	0.00	0.00	0.00	0.33
decision-making	1.50	1.75	0.50	1.67	1.00	0.00	0.00	0.67	0.67	0.00	0.00	0.67
tox. endpoint	0.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.33	2.25	3.50	8.00
experimental animals	0.33	0.00	0.33	1.00	0.50	0.75	0.67	1.33	0.67	2.00	0.17	0.00
future challenges	0.17	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.50	0.75	0.17	1.00
information documentation	0.00	0.00	0.17	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
information requirement	1.00	0.50	0.50	0.33	0.00	0.25	0.17	0.33	0.00	0.00	0.00	0.00
information sources/methods	2.00	4.00	2.83	2.00	0.67	1.50	1.00	0.33	1.00	2.25	0.50	0.67
ITS conceptual structure	2.83	2.25	2.00	1.33	0.50	0.50	0.00	0.00	0.00	0.00	0.00	0.67
ITS functional properties	0.17	0.75	0.67	0.00	1.50	1.50	0.33	1.67	0.67	0.25	0.33	0.33
ITS outcome target	0.67	1.00	1.50	0.00	0.00	0.00	0.33	0.33	0.00	0.25	0.00	0.00
ITS terminology	0.17	1.25	0.50	0.67	0.00	0.25	0.00	0.00	0.00	0.00	0.00	0.00
knowledge	0.17	0.00	0.00	0.00	0.17	0.00	0.00	0.00	0.50	0.25	0.00	0.00
learning	0.50	0.00	0.50	1.00	0.00	0.00	0.33	0.00	1.17	0.25	1.00	0.67
assessment and measurement	0.17	0.00	0.33	0.33	0.17	0.00	0.33	0.00	0.00	0.00	0.33	0.00
REACH/regulation	0.33	0.25	0.33	0.67	0.00	0.00	0.00	0.00	0.50	0.25	0.17	0.00
stakeholder involvement	0.00	0.00	0.17	0.00	0.17	0.00	0.00	0.33	0.17	0.25	0.50	0.00
uncertainty	0.00	0.00	0.00	0.33	0.17	0.00	0.17	0.00	0.50	0.25	1.00	1.33

P = private enterprises; A = regulatory agency; R = research organization; N = NGO/interest group.

Table 6: *Relative code frequencies across stakeholder groups for the topics "ITS limitation", "ITS acceptance", and "ITS research needs"*

Core themes	Topics addressed in the interview											
	ITS limitation				ITS acceptance				ITS research needs			
	P	*A*	*R*	*N*	*P*	*A*	*R*	*N*	*P*	*A*	*R*	*N*
costs	0.33	1.25	0.17	0.33	2.17	0.00	0.67	0.33	0.33	0.50	0.50	0.67
data	0.17	0.00	0.33	0.00	0.00	0.00	0.00	0.00	1.33	1.50	0.17	0.00
decision-making	1.00	0.75	0.83	0.67	0.50	4.00	0.50	3.00	0.50	0.75	1.83	0.67
tox. endpoint	2.17	0.00	2.33	0.67	1.00	0.25	0.17	0.00	0.00	0.00	0.33	0.67
experimental animals	0.00	0.00	0.17	0.00	0.17	0.00	0.00	0.00	0.00	0.00	0.33	0.00
future challenges	0.67	0.00	1.00	0.33	1.33	2.25	0.33	3.33	2.50	1.25	2.00	0.00

information documentation	0.00	0.00	0.00	0.00	0.50	0.00	0.00	0.33	0.33	0.00	0.83	0.00
information requirement	0.17	0.00	0.00	0.67	0.50	0.75	0.33	0.67	0.00	0.00	0.17	0.33
information sources/methods	1.17	2.25	0.50	1.33	0.83	0.25	0.33	0.33	0.33	1.75	1.33	0.33
ITS conceptual structure	0.33	0.25	0.00	0.00	0.00	0.00	0.50	0.00	0.50	0.50	0.33	0.00
ITS functional characteristics	1.50	0.50	1.00	2.67	0.50	1.50	0.83	0.33	0.50	0.25	0.83	0.67
ITS outcome target	0.00	0.25	0.00	0.00	0.17	0.00	0.00	0.00	0.00	0.25	0.00	0.00
ITS terminology	0.00	0.00	0.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
knowledge	0.33	0.75	0.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.17	0.00
learning	1.00	1.25	1.33	4.00	2.17	1.25	2.83	2.33	1.33	1.00	1.00	0.00
assessment and measurement	0.00	1.25	0.33	2.33	0.83	0.00	0.50	0.33	1.17	0.25	0.33	0.33
REACH/regulation	0.17	0.25	0.00	0.00	0.67	1.00	0.00	0.00	0.00	0.00	0.00	0.00
stakeholder involvement	0.00	0.50	0.50	2.67	2.00	1.50	2.17	6.00	0.67	1.50	3.17	0.00
uncertainty	1.83	2.25	2.33	4.33	1.83	1.75	3.00	4.00	2.67	2.50	1.17	0.67

P = private enterprises; A = regulatory agency; R = research organization; N = NGO/interest group.