Project no. 037017

OSIRIS

Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information

Integrated Project

Sub-Priority 1.1.6.3: Global Change and Ecosystems

Topic VII.1: Development of Advanced Methodologies for Risk Assessment
VII.1.1: Intelligent testing strategies for chemicals

D4.1.4
Report on the comparative review of stakeholder expectations, concerns, and proposals, including an assessment of the impacts of the results on the further structuring of the project

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PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

First Expert Workshop

Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information

SUMMARY OF RESULTS

November 28-29, 2007

Stuttgart, Germany

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Summary

The main aim of the first Expert Workshop of the OSIRIS project ("Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information") was to receive feedback from the participants on the overall scientific approach and the main framing of the research within Pillar 4. The principle results of the Group Delphi were the following:

- The participants agreed that it is highly important to develop integrated assessment strategies for (groups) of chemicals, using the different building blocks of ITS. Second place goes to the development and evaluation of individual ITS building blocks for physicochemical, (eco)toxicological and exposure data, followed by building a set of databases (with experimental and other data) that can be used for many purposes in and outside of OSIRIS.

- With respect to the output (products) of OSIRIS, operational ITSs for all endpoints, using a weight-of-evidence approach as well as operational overall ITS, also using a weight-of-evidence approach, should have priority. There was clear consensus that reproductive toxicity has the highest ranking because of the number of animals and costs involved. Local toxicity (skin, eye) got the lowest ranking from all four groups in the third Delphi round.

- Data obtained from in vivo studies were seen as very important for inclusion in the ITSs, but OSIRIS should not put effort in generating in vivo data. The innovation of ITSs should be realized through non-testing approaches. No consensus could be reached in prioritizing of the building blocks of ITS.

- Exposure and exposure categories, descriptions of categories of chemicals related to mode of toxic action and information of modes of toxic action (e.g. chemical reactivity) are the databases which were deemed most important in the future for (eco)toxicity and exposure assessment compared to today and should therefore be the focus of OSIRIS.

- The OECD (Q)SAR Toolbox as well as the RIP's should be considered by OSIRIS as being important ongoing international efforts and efforts should be made to link the various activities.

- There was high consensus among all four groups that data and model uncertainty should be included in a scoring system for data quality.

Introduction

The goal of the project OSIRIS ("Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information") is to develop integrated testing strategies (ITS) well suited for REACH that enable to significantly increase the use of non-testing information for regulatory decision making and thus minimise the need for animal testing. The project is funded by the European Commission within in the 6th Framework Programme under the theme "Global Change and Ecosystems", coordinated by Prof. Dr. Gerrit Schüürmann at the Helmholtz Centre for Environmental Research (UFZ) in Leipzig.

It is the task of DIALOGIK to explore the responses and reactions of different stakeholder groups (regulators, industry, members of society) with respect to the ITS developed and modified by the research team. In addition, DIALOGIK will prepare suggestions on how to integrate feedback from stakeholders into the testing strategies as well as design a targeted risk communication program as a means to initiate a constructive discourse between the research team and stakeholder groups. Several workshops with relevant stakeholder groups are envisioned during the research phase to meet this communication and consultation objective.

The first Expert Workshop took place in Stuttgart (Germany) at the Waldhotel Degerloch from 28th to 29th November 2007. 24 scientific experts from industry, academia, and regulatory agencies attended the workshop; 21 experts took part in the Group Delphi itself. A complete list of the participants together with their e-mail addresses can be found in the annex of this paper. This OSIRIS Stakeholder Workshop has been the first in a sequence of at least four workshops during the course of the project. In the main objective of the first workshop was to receive feedback from the participants on the overall scientific approach and the main framing of the research. For this purpose, representatives of Pillar 4 coordinated by Dr. J.J.M. (Han) van de Sandt, (TNO Quality of Life in Zeist) presented their research plans and asked for feedback from experts. This consultation was organized in the form of a Group Delphi.

This paper reports about the structure of the workshop and its results. The first section characterizes the Group Delphi method. Sections 2 and 3 describe the results of the individual and two group surveys in the context of the Group Delphi. Section 4 summarizes the outcomes of the workshop.

Section 1: Methods of the Group Delphi

A Delphi process is aimed at obtaining a wide range of opinions among a group of experts (Turoff, 1970; Pill, 1971; Linstone and Turoff, 2002). The process is organized in four steps. In step 1, a questionnaire asks a group of distinguished scientists to rank or rate several items, in this case different methods for data collection, testing and verification. The scientists provide their best estimate and assign a confidence interval to their answers. In step 2, the organizing team feeds back to each participant the scores of the whole group, including medians, standard deviation and aggregated confidence intervals. Each individual is then asked to perform the same task again, but now with the knowledge of the responses of all other participants. In step 3, this procedure is repeated until individuals do not change their assessment any more. In step 4, the organizer summarizes the results and articulates the conclusions.

A variation of the classic Delphi method is the group Delphi (Webler et al, 1991). During a group Delphi all participants meet face to face and make the assessments in randomly assigned small groups of three or four. The groups whose average scores deviate most from the median of all other groups are requested to defend their position in a plenary session. Then the small groups are reshuffled and perform the same task again. This process can be iterated three or four times until no further significant changes are made. At the end of a Delphi process, one receives either a normal distribution of assessments around a common median, a two- or three-peak distribution (signalling a majority and one or more minority votes) or a flat curve (which means that knowledge is insufficient to make any reliable assessment).

The advantage of Delphi is that a serious effort has been invested in finding the common ground among the experts and in finding the reasons and arguments that cause differences in assessments. The disadvantage is that Delphis depend upon the quality and completeness of the expertise and information brought into the process. In general, DIALOGIK has had mostly positive experiences with Delphi processes, particularly group Delphi.

Literature

Linstone, H. A. & Turoff, M. (Hrsg.). (2002). The Delphi Method: Techniques and Applications. New Jersey: Science and Technology University.

Pill, J. (1971). The Delphi method: Substance, context, a critique and an anotated bibliography. Socio-Economic Planning Sciences, 5.

Turoff, M. (1970). The Design of a Policy Delphi. Technological Forecasting and Social Change, 2, 149-171.

Webler, T., Levine, D., Rakel, H., Renn, O.: “The Group Delphi: A Novel Attempt at Reducing Uncertainty,” Technological Forecasting and Social Change, 39 (1991), 253-263.

Section 2: Results of first round (Individual Delphi)

In the first Delphi round, a questionnaire was sent to each participant nine days before the workshop. It consisted of six key topics including one or more key questions each. The research team of DIALOGIK received 17 questionnaires. The results were summarized in an excel sheet which indicated the median value as well as the distribution of answers. This sheet together with a short presentation of the results formed the basis for the deliberations at the Group Delphi. Figure 1 gives a short overview of the results.

There was some **clear consensus** among the respondents on most topics. For example, on key topic 3 (3.1: Databases of Chemicals - Kind of databases) almost all experts fully agreed that all of the available databases should be included in the future for (eco)toxicity and exposure assessment. Also, the OECD toolbox and the RIP's were rated as very important or important by a vast majority of the participants. Almost every one agreed on the high importance of the OECD principles as part of key topic 4 (4.3: Quality of data – Criteria) for OSIRIS. Key topic 5 was also addressed in a similar fashion by almost all respondents. This section dealt with public access of results and the installation of an open website for ITS. With the exception of one single expert voice, all of them agreed that all scientific results should be made public available.

On other topics the answers of the respondents **differed, sometimes even dramatically.** For example, on key topic 2 (2.1: Tools and instruments for testing strategies of OSIRIS - Building blocks of ITS), hazard data from structurally related chemicals (read-across), (Q)SARs and Threshold of Toxicological Concern got very high rates of approval whereas in vitro methods, non-guideline animal data and animal data generated according to accepted guidelines were rated as less important by some experts and highly important by others. Responses to "non-guideline animal data" and "in vitro methods generated according to 'suitable' methodologies" varied considerably among the experts. There were five participants who believed in the usefulness of "non-guideline animal data" as a building block of ITS and six participants who believed in the usefulness of "in vitro methods generated according to 'suitable' methodologies", while the others felt them to be less useful.

There was only little variation in key topic 1 (1.1: Focus of OSIRIS). The development of integrated assessment strategies for (groups) of chemicals and generation of ITS procedures (IT-Tools and Guidance Documents) were rated by a vast majority as more important than the contribution to the generation of databases and development and evaluation of individual ITS building blocks. On key topic 4 (4.1: Quality of data - Quality parameters - Reliability), the identity, purity and source of substance, the availability of information on structural analogues and the substantiation of deviations from guidelines were top priorities in the eyes of most experts. Statistics, analytical methods and publication in peer-reviewed journals were rated as less important. The availability of the complete test report or exposure considerations shows more expert dissent: Some experts see them as very important while others rate them as only partly important.

In essence, the first individual questionnaire demonstrated an astonishing degree of convergence for most issues. The variance was usually low and only few items were clearly controversial. The objective of the Group Delphi Rounds that were conducted after the individual data was displayed and explained was to investigate whether the response patterns remained stable under the condition of intensive discussions.

Figure 1: Results of first Delphi round (n =17)

Key Topic 1 (KT1): Focus of OSIRIS (1.1)

1.1 What should OSIRIS do?

	Very important	Important	Partly important	Not important at all
Contribute to the generation of databases	6	5	5	1
Develop integrated assessment strategies for (groups) of chemicals	11	4	2	0
Develop and evaluate individual ITS building blocks	7	9	1	0
Generate ITS procedures (IT-Tools and Guidance Documents)	11	5	1	0

KT1: Output of OSIRIS (1.1)

1.1 What should OSIRIS do?

	Very important	Important	Partly important	Not important at all
Summaries of evaluated experimental data following the OECD Guidelines for the testing of chemicals.	5	6	4	2
Estimates of individual fate and (eco)toxicity data including information about the uncertainty of the predictions.	5	8	3	1
Generation of PNEC and DNEL information.	3	4	7	3

KT2: Tools and instruments for testing strategies of OSIRIS - Building blocks of ITS (2.1)

2.1 Existing tools in OSIRIS: Which of the tools below for generating fate and (eco)toxicity information are important for the testing strategies in the REACH process and should be included in Pillar 4?

	Very important	Important	Partly important	Not important at all
Animal data generated according to accepted guidelines	6	7	3	0
Non-guideline animal data	5	5	5	1
In vitro methods generated according to validated methodologies	7	6	2	1
In vitro methods generated according to 'suitable' methodologies	6	5	5	0
Hazard data from structurally related chemicals (read-across)	9	5	1	1
(Q)SARs	9	6	1	0
Threshold of Toxicological Concern	10	4	2	0

Figure 1: Results of first Delphi round (continued)

KT3: Databases of Chemicals - Kind of databases (3.1)

3.1 Which databases should be included in the future for (eco)toxicity and exposure assessment?

	Fully agree	Partly agree	Partly disagree	Fully disagree
Exposure and exposure categories	12	3	1	1
Descriptions of categories of chemicals related to mode of toxic action	14	3	0	0
Physicochemical properties	13	3	1	0
Toxicity data	14	3	0	0
Ecotoxicity data	13	4	0	0
Information of modes of toxic action	12	5	0	0
Estimates of fate and (eco)toxicity data including an estimate of their uncertainty	11	4	1	1

KT3: Databases of Chemicals - International activities (3.2)

3.2 OSIRIS aims at being complementary to ongoing international efforts, such as the REACH Implementation Projects (RIP's) and further activities. How do you rate the importance of the RIP's, OECD QSAR toolbox and others? What other international activities are important for OSIRIS?

	Very important	Important	Partly important	Not import-ant at all
Reach implementation Projects RIP's	13	3	1	0
OECD QSAR toolbox	13	3	1	0

KT3: Databases of Chemicals - Databases needed (3.3)

3.3 What kind of databases has priority?

	Very important	Important	Partly important	Not import-ant at all
Local toxicity (skin, eye)	4	5	4	0
Reproductive toxicity	13	4	0	0
Aquatic toxicity	7	7	3	0
Chronic toxicity	11	5	1	0
Carcinogenicity	8	5	2	0
Repeated dose toxicity (90-d)	10	4	1	0

Figure 1: Results of first Delphi round (continued)

KT 4: Quality of data - Quality parameters (Reliability, 4.1)

4.1 What information about the data in OSIRIS is, according to you, needed from a scientific and regulatory point of view?

	Very important	Important	Partly important	Not important at all
Availability of complete test report	6	6	5	0
Substantiation of deviations from guidelines	8	8	1	0
In case of non-guideline studies: publication in a peer-reviewed journal	2	11	2	1
In case of non-guideline studies: interpretation of results (alone or in combination)?	7	5	3	0
Performance of the study according to GLP	1	7	9	0
Identity, purity and source of substance	10	7	0	0
Exposure considerations	4	10	3	0
Analytical methods	2	10	5	0
Statistics	1	11	5	0
Availability of information on structural analogues	9	4	3	1

KT 4: Quality of data - Quality parameters (Relevance, 4.1)

4.1 What information about the data in OSIRIS is, according to you, needed from a scientific and regulatory point of view?

	Very important	Important	Partly important	Not important at all
Animal species	3	13	1	0
Route of administration	6	10	1	0
Effect (with regard to target population)	6	10	0	0

KT 4: Quality of data - Quality aspect (4.2)

4.2 Do you believe that Klimisch (1997) is useful for this purpose? Which aspect do you consider important for a scoring system?

	Very important	Important	Partly important	Not important at all
Data uncertainty	8	5	0	0
Model uncertainty	5	7	1	0
Representativeness of results (generalisability)	6	7	1	0
Stochastic effects	0	6	5	0
Outlayers and surprises	2	9	3	0
Effects on specific ecosystems	2	4	4	1

Figure 1: Results of first Delphi round (continued)

KT 4: Quality of data - Criteria (OECD principles, 4.3)

4.3 OSIRIS aims at basing the (Q)SAR tools on the OECD principles. Do you agree?

	Fully agree	Partly agree	Partly disagree	Fully disagree
"a defined endpoint"	17	0	0	0
"an unambiguous algorithm";	15	2	0	0
"a defined applicability domain";	15	0	2	0
"goodness-of-fit, robustness and prediction power"	16	1	0	0
"a mechanistic interpretation, if possible"	14	3	0	0

KT 5: Public availability

5.1 OSIRIS aims at developing a webtool which is publicly available. Do you agree? Which elements need special attention with respect to confidentiality and ownership?

	Publicicly available	Should not be available
Methodologies	17	0
Databases	17	0
Webtool	16	1

KT 6: Support for industry and regulation

6.1 How can we support industry and regulators in providing effective and efficient testing methods and procedures in a timely manner?

	Very important	Important	Partly important	Not important at all
Demo version of the OSIRIS webtool	10	5	0	1

Section 3: Results of the two Group Delphi rounds (Group Delphi)

The first Group Delphi round took place after Dr. Dr. Han van de Sandt, Dr. Dinant Kroese and Prof. Dr. Ortwin Renn gave a short introduction to OSIRIS and explained the Delphi Method. In addition, Prof. Dr. C. J. (Kees) van Leeuwen presented the results of the individual Delphi round.

Five small groups were formed by random selection consisting of four individuals. Each of the group was asked to fill out the same questionnaire that they had individually responded to in the individual survey. The groups were encouraged to discuss the meaning of the question and deliberate about the most suitable answers. As expected the group discussion revealed first that many participants associated different connotations with each question. Secondly, by looking more closely into each question more variance and disagreement was produced. The five groups had about 1,5 hours time to discuss and give their ratings as a group vote. They were also free to add comments or refine the wording of the question. Once the groups had completed their task, the research team of DIALOGIK processed the data from the filled out questionnaires and provided a summary of the results for presentation during the plenary session.

During the plenary, the moderator asked groups that deviated most from the median value on each question to justify their judgments. This way the discussion focused on the differences not the similarities. Often differences were due to unclear formulation of the question or to different connotations of the terms used in the questions or in the list of standardized response categories. Occasionally differences were the result of calibration problems with respect to response categories such as very important versus important. There were only few questions where respondents had polarized views or were at the opposite end of the response scale. Yet there were quite a few significant variations in the middle range of the answer categories.

Those questions that did not produce any significant disagreement were scraped from the next round of deliberation. For example, the central role of the OECD principles as a basis for (Q)SAR tools in OSIRIS was unchallenged in all groups. There was also unanimous support for the desired public availability of methodologies, databases and the webtool for ITS. Both questions were therefore left out in the third round. The questions that seemed ambiguous were reformulated and many response categories were further specified. Several rating scales (from not important to very important) were transformed into ranking scales to force respondents to set priorities. Finally, additional questions were added where needed and new scales introduced. Once the new questionnaire was completed, a second group round was organized. This time the composition of the group was permutated so that each new group consisted of at least one member of the four groups in the first round. Since the total number of participants was 20, a complete permutation was not possible but this objective could be widely met by composing a total of four groups with five participants each.

In order to give an illustration of the changes that were made during the plenary, two examples are discussed here. The clear differences concerning the questions of key topic 1 were partly based on different comprehension in the terminology and the scaling that were used in the questionnaire. The specific role of databases in the project was not clear to the participants. Should databases be generated by OSIRIS? Should databases be generated only for the purpose to collect data or should they form the basis for ITS? Discussion showed that it is not the main purpose of OSIRIS to generate data, but to integrate existing data into ITS. Once this was understood, the questions in Topic 1 were reformulated with higher precision and clarity. Instead of simply asking for focus and output of OSIRIS, the new questionnaire asked respondents to assign priorities with respect of focus and output and rank the conditions for OSIRIS to be successful in their mandated tasks. Secondly, since the Building blocks of ITS (key topic 2) seemed to be all of high relevance, a ranking procedure was then included. Stating priorities and posteriorities was seen as a valuable assistance to the OSIRIS members in order to decide which of the building blocks should be developed preferentially for inclusion in ITS: A similar ranking procedure was inserted for prioritising the kind of databases that should be included in the future for (eco)toxity and exposure assessment (key topic 3).

For purpose of producing a good overview, consensus (➧) and dissent (✖) for the six key topics in the first, second and third round are given in Figure 2. One can see that in many cases agreements from the individual Delphi round turned into dissent during the first group discussions and were then later reconciled after the plenary and the second group Delphi Round (for example 3.1 and 3.2).

Figure 2: Overview over consensus and dissent in Delphi rounds 1 – 3 (consensus (✓) and dissent (✗))

			Individual Delphi (round 1, n = 17)	Group Delphi (round 2, n = 5)	Group Delphi (round 3, n = 4)
Key Topic 1: Focus and Output of OSIRIS	**Focus of OSIRIS (1.1)**	*What should OSIRIS do?*	✗	✗	-
		What should be the priorities for OSIRIS?	-	-	✓
		What are the conditions for the success of OSIRIS?	-	-	✗
	Output of OSIRIS (1.1)	*What should OSIRIS do?*	✗	✗	-
		What should have priority with respect to the output (products) of OSIRIS?	-	-	✓
Key Topic 2: Building blocks of ITS	**Building blocks of ITS (2.1) / Existing tools in OSIRIS:**	*Existing tools in OSIRIS: Which of the tools below for generating fate and (eco)toxicity information are important for the testing strategies in the REACH process and should be included in Pillar 4?*	✗	✗	-
		What building blocks should be developed preferentially for inclusion in ITS?	-	-	✗
Key Topic 3: Databases of Chemicals	**Kind of databases (3.1)**	*Which databases should be included in the future for (eco)toxicity and exposure assessment?*	✓	✗	-
		Which databases will be more important in the future for (eco)toxicity and exposure assessment than today?	-	-	✓
	International activities (3.2)	*How do you rate the importance of the RIP's, OECD QSAR toolbox and others? What other international activities are important for OSIRIS?*	✓	✗	-
		Which ongoing international efforts should be considered by OSIRIS?	-	-	✓
	Databases needed (3.3)	*What kind of databases has priority?*	✓	✗	-
		On what databases/endpoints should OSIRIS focus in order to reduce or replace vertebrate testing?	-	-	✗
Key Topic 4: Quality of data	**Quality parameters (Reliability, 4.1):**	*What information about the data in OSIRIS is, according to you, needed from a scientific and regulatory point of view?*	✗	✓	- (✓)
	Quality parameters (Relevance, 4.1):	*What information about the data in OSIRIS is, according to you, needed from a scientific and regulatory point of view?*	✓	✓	- (✓)
	Quality aspect (4.2):	*Which aspect do you consider important for a scoring system?*	✗	✗	-
		Risk assessors use scoring systems to assess the quality of the available information. Which aspect do you consider important with respect to a scoring system?	-	-	✓
	Criteria (OECD principles, 4.3):	*OSIRIS aims at basing the (Q)SAR tools on the OECD principles. Do you agree?*	✓	✓	- (✓)

Figure 2: Overview over consensus and dissent in Delphi rounds 1 - 3 (continued)

		Individual Delphi (round 1, n = 17)	Group Delphi (round 2, n = 5)	Group Delphi (round 3, n = 4)
Key Topic 5: Public availability	*OSIRIS aims at developing a webtool which is publicly available. Do you agree? Which elements need special attention with respect to confidentiality and ownership?*	✓	✓	- (✓)
Key Topic 6: Support for industry and regulation	*How can we support industry and regulators in providing effective and efficient testing methods and procedures in a timely manner?*	✓	✗	-
	How can we support industry and regulators in providing effective and efficient testing methods and procedures in a timely manner? Please be as specific as possible.	-	-	✓
Ratio of consensus / dissent total		**7 / 5 = 1,4**	**4 / 8 = 0,5**	**10 / 3 = 3**

Source: Individual and Group Delphi, n =17 persons for individual Delphi, n = 5 groups for first Group Delphi, n = 4 groups for second Group Delphi, ✓ = consensus, ✗ = dissent, - = question not posed in this round, - (✓) = consensus from round 2, because of that question not posed again in round 3

Overall, the ratio of consensus to dissent decreased from 1,4 to 0,5 between the individual and the first group round. This was mainly due to the discussion about the meaning of terms and the intention of the OSIRIS team. After carefully reformulating the ambiguous questions, generating new ones and introducing additional scales, the consensus/dissent-ratio increased to 3 indicating that consensual votes occurred three times more frequently than dissenting views. This comparison includes the consensual responses of round 1 which were deleted for the second Round of the Group Delphi. This is indicated by "– (⮟)". Also important to notice is that dissent does not necessarily mean substantive dissent or difference in judgments. Very often misunderstanding, misinterpretations, different connotations of terminology or ambiguities in the response categories were most frequently the source of the differences. Those problems could be resolved in the plenary discussion.

One can briefly summarize the final results after round 3 as follows:

- The participants agreed that it is highly important to develop integrated assessment strategies for (groups) of chemicals, using the different building blocks of ITS. Second place goes to the development and evaluation of individual ITS building blocks for physicochemical, (eco)toxicological and exposure data, followed by building a set of databases (with experimental and other data) that can be used for many purposes in and outside of OSIRIS.

- No definite statement on the conditions for success of OSIRIS could be formulated, but the actual use of the OSIRIS tool in practice (by industry and regulators) should be the main aim of the project.

- With respect to the output (products) of OSIRIS, operational ITSs for all endpoints, using a weight-of-evidence approach as well as operational overall ITS, also using a weight-of-evidence approach, should have priority. There was clear consensus that reproductive toxicity has the highest ranking because of the number of animals and costs involved. Due to its toxicological complexity, it was realized that developing an innovative ITS for this endpoint is a challenge, both from a scientific and regulatory acceptance point of view. Local toxicity (skin, eye) got the lowest ranking from all four groups in the third Delphi round.

- No consensus could be reached in prioritizing of the building blocks of ITS, but some conditional remarks came up during the plenary discussion which reduced the degree of dissent. For example, when high quality data is available for hazard data from structurally related chemicals (read-across), then all groups assigned a high degree of relevance to the building blocks; however if not, the relevance was seen as less pronounced. Data obtained from in vivo studies were seen as very important for inclusion in the ITSs, but OSIRIS should not put effort in generating in vivo data. The innovation of ITSs should be realized through non-testing approaches.

- Exposure and exposure categories, descriptions of categories of chemicals related to mode of toxic action and information of modes of toxic action (e.g. chemical reactivity) are the databases which were deemed most important in the future for (eco)toxicity and exposure assessment compared to today and should therefore be the focus of OSIRIS. This was the common judgment of tall four groups as the result of the third Delphi round.

- The OECD (Q)SAR Toolbox as well as the RIP's should be considered by OSIRIS as being important ongoing international efforts and efforts should be made to link the various activities.

- There was high consensus among all four groups that data and model uncertainty should be included in a scoring system for data quality.

The participants added many comments and specifications which were all recorded by the research team. The group results and comments are shown in Figures 3 and 4, respectively. Please note that for priority judgments the first digit indicates the number of the group, while the second digit indicates priority. For example "3,1" means that group number 3 gave this item first priority.

Figure 3: Results of second Delphi round (n = 5)

Key Topic 1: Focus and output of OSIRIS, What should OSIRIS all about?				
Focus of OSIRIS	**Very important**	**Important**	**Partly important**	**Not important at all**
to contribute to the generation of databases (experimental and estimated data)	2 (?)	3/1/ 4	5	4
the development of integrated assessment strategies for (groups) of chemicals, using the different building blocks of ITS	3/1/2/ 4/ 5	1		
to develop and evaluate individual ITS building blocks for physicochemical, (eco)toxicological and exposure data	1/ 2/ 4	3/1/ 5		
to generate ITS procedures (IT-Tools and Guidance Documents) for integrating these building blocks into integrated strategies to estimate fate, effects and exposure information.	1/ 2/ 4/ 5	3		
Output of OSIRIS	**Very important**	**Important**	**Partly important**	**Not important at all**
We want to have summaries of evaluated experimental data following the OECD Guidelines for the testing of chemicals		5	1/2/ 4	3/2
We want to generate estimates of individual fate and (eco)toxicity data including information about the uncertainty of the predictions	2/ 4/ 5	3/1		
We want to generate PNEC, and DNEL information		4	3/1/ 5	2
Comment: yes (3), yes (2), yes (4)				

Note: Numbers indicate group positions.

Key Topic 2: Tools and instruments for testing strategies of OSIRIS

Existing tools in OSIRIS: Which of the following tools for generating fate and (eco)toxicity information are important for the testing strategies in the REACH process and should be included in Pillar 4?

Building blocks of ITS	Very important	Important	Partly important	Not important at all
Animal data generated according to accepted guidelines	3,1/2/ 5			1
Non-guideline animal data	3,2/2	1		
In vitro methods generated according to validated methodologies	3,4/2	1		
In vitro methods generated according to 'suitable' methodologies	3,6/2	1		
Hazard data from structurally related chemicals (read-across)	3,3/2/ 5	1		
(Q)SARs	3,7/2	1		
Threshold of Toxicological Concern	3,5/2	1		
Comment: yes (3), yes (2), yes (4), yes (5)				

New tools: Should new tools be developed for the REACH process? And if so which ones do you have in mind? Exposure tools for low exposure situation (3)

Additions to OECD toolbox (3)

TTC (3)

Focus on sensitivity of tests (3)

Key Topic 3: Databases of Chemicals

Which databases should be included in the future for (eco)toxicity and exposure assessment?

Kind of databases	Fully agree	Partly agree	Partly disagree	Fully disagree
Exposure and exposure categories	3,1/ 2/4/ 5	1		
Descriptions of categories of chemicals related to mode of toxic action	3,2/1/ 2/4/ 5			
Physicochemical properties	3,3/1/2/4/5			
Toxicity data	3,4/1/2/4/5,1	1		
Ecotoxicity data	3,5/1/2/4/5	1		
Information of modes of toxic action	3,2 (?)/1/2/4/5			
Estimates of fate and (eco)toxicity data including an estimate of their uncertainty	3,6/2/4/5	1		
Comment: yes (4)				

OSIRIS aims at being complimentary to ongoing international efforts, such as the OECD QSAR toolbox. Do you agree and which efforts are relevant to OSIRIS according to you?

International activities	Very important	Important	Partly important	Not important at all
OECD QSAR toolbox (steering group 3)	3/1/2/4/5			
RIPs	3/1/2/5			
Fobig ECVAM data quality		3		
Health Canada	1/ 2	3		
Comment: Toxcase partly important (3), EU CESAR (2), Predictonics (2), EU projects (2), EPAA (2), industry projects (2), US PMV activities (4), Testguidelines OECD (5)				

What kind of databases has priority, considering that the OECD Toolbox is already strong in aquatic toxicity and some mammalian toxicity endpoints (e.g. Ames test and sensitization).

Databases needed	Very important	Important	Partly important	Not important at all
Local toxicity (skin, eye)	4		3/1/2	
Reproductive toxicity	3/1/2/4/5			
Carcinogenicity	4/5	1/ 2	3	
Repeated dose toxicity (90-d)	4/5	3/1/ 2		
Sensititation	3/1	2		
Comment: Aquatic tox (BCF, 3), Aquatic tox (1,very important), chronic tox (1, very important), mutagenicity (2), yes (4)				

Key Topic 4: Quality of data

What information about the data in OSIRIS is, according to you, needed from a scientific and regulatory point of view?

Quality parameters	Very important	Important	Partly important	Not important at all
Reliability				
Availability of complete test report	2	3/5	1/ 4	
Substantiation of deviations from guidelines	3/2	1/ 4/5		
In case of non-guideline studies: publication in a peer-reviewed journal		1/5	3/ 4	
In case of non-guideline studies: interpretation of results (alone or in combination)?	3	4/5	1	
Performance of the study according to GLP		5	3/1/ 2/ 4	
Identity, purity and source of substance	3,1/ 4,1	1/5		
Exposure considerations	3,1/ 4	1/5	1	
Analytical methods		3/1/ 4/5		
Statistics			3/1/ 4	
Availability of information on structural analogues	3/1	4/5		
Relevance				
Animal species	2/ 4,1	3,3/1/5		
Route of administration	2/ 4	3,2/1/5		
Effect (with regard to target population)	3,1/ 2	1/ 4/5		
Comment: yes (3)				

In practice, risk assessors in industry, academia and governmental organizations may not have time to read all the details about the data sources and quality and may wish to use simple scoring systems for reliability. Do you believe that the Klimisch (1997) is useful for this purpose? Which aspect you consider important with respect to a scoring system?

Quality aspect	**Very important**	**Important**	**Partly important**	**Not important at all**
Data uncertainty	3,1/ 2/5	1/ 4		
Model uncertainty	3,3/ 2	1/ 4/5		
Representativeness of results (generalisability)	3,4/ 2/ 4	1	5	
Stochastic effects	?? 3, 2/ 4	1	1	
Outlayers and surprises	3,2/ 2/ 4/5	1	1	
Effects on specific ecosystems	4		1/5	3
Comment:				

OSIRIS aims at basing the (Q)SAR tools on the OECD principles. Do you agree?

Criteria (OECD principles)	**Fully agree**	**Partly agree**	**Partly disagree**	**Fully disagree**
“a defined endpoint”	3/1/2,1/ 4/5			
“an unambiguous algorithm”;	1/ 2/ 4/5	3		
“a defined applicability domain”;	1/ 2,1/ 4/5		3*	
“goodness-of-fit, robustness and prediction power”;	3/2/5	1/ 4		
“a mechanistic interpretation, if possible”.	3/2/ 4/5	1		
Comment: yes (3)				

Key Topic 5: Public availability

OSIRIS aims at developing a webtool which is publicly available. Do you agree? Which elements need special attention with respect to confidentiality and ownership?

Information	Publicicly available	Why not?
Methodologies	3/1/ 2/ 4/5	
Databases	3/1/ 4/5	Industrial restrictions
Webtool	3/1/ 2/ 4/5	
Comment: yes (2)		

Key Topic 6: Support for industry and regulation

How can we support industry and regulators in providing effective and efficient testing methods and procedures in a timely manner?

Effort	Very important	Important	Partly important	Not important at all
Demo version of the OSIRIS webtool to get feedback and enhance implementation	1/ 2/5	3/ 4		
Training	3/ 2			
Communication	3			
Comment:				

Figure 4: Results of Third Delphi Round (n = 4)

Key Topic 1: Main Focus of OSIRIS: What should be the priorities for OSIRIS?

Priorities of OSIRIS	**Rank 1**	**Rank 2**	**Rank 3**	
To build a set of databases (with experimental and other data) that can be used for many purposes in and outside of Osiris			3/ 2/ 4/ 1	
To develop and evaluate individual ITS building blocks for physicochemical, (eco)toxicological and exposure data		3/ 2/ 4/ 1		
To develop integrated assessment strategies for (groups) of chemicals, using the different building blocks of ITS	3/ 2/ 4/ 1			
Others: yes (3), yes (2) Identify existing databases and see if they are suitable for the purpose of Osiris Comment: sequential ranking		x		
What are the conditions for the success of OSIRIS?	**Rank 1**	**Rank 2**	**Rank 3**	**Rank 4**
To have existing testing data on relevant endpoints (in database format)	3/ 2		4/ 1	
To have existing databases operational which are relevant for ITS	3/ 4/ 1	1	2	
To have harmonized templates for quality assessment of data	1	3/ 2/ 4		
Others: yes (3), Here conditions related to data More success criteria such as acceptability, timeliness, easy implementability, communicability Integrate item 1 and 2 (very high rank)				

What should have priority with respect to the output (products) of Osiris?	Rank 1	Rank 2	Rank 3	Rank 4
Operational ITSs for all endpoints, using a weight-of-evidence approach.	3/ 2/ 1	4		
Operational overall ITS, using a weight-of-evidence approach.	3/ 2/ 4	1		
Summaries of assessment of adequacy of available information based on OECD guidelines or non-guidelines studies.			3 (?)/ 1	4
Summaries of assessment of adequacy of available non-testing information including uncertainty of the predictions		1	3 (?)/ 4	

Comment: Input to the work or output? (input data. Needs to be reliable and adequate; Output was meant. Distinguish between "summaries" on tools and on chemicals (related to guidance documents). Important: Transparency about the selection of tools and the adequacy of information about chemicals.

Key Topic 2: Tools and instruments for testing strategies of OSIRIS

Existing tools in OSIRIS: What building blocks should be developed preferentially for inclusion in ITS?

Building blocks of ITS	1 = hightest priority 9 = lowest priority
Animal data generated according to accepted guidelines	3,1/ 2,1/ 4,9/ 1,7: difference: a) it is needed in general b) it is not the focus of Osiris c) generating primary data is not purpose of Osiris
Non-guideline animal data	3,2/ 2,2/ 4,7/ 1,5
In vitro methods generated according to validated methodologies	3,4/ 2,7/ 4,6/ 1,4
In vitro methods generated according to 'suitable' methodologies	3,4/ 2,8/ 4,5/ 1,3 depending on endpoints, if suitable, it is very important
Hazard data from structurally related chemicals (read-across)	3,3/ 2,3/ 4,1/ 1,1: if high quality data is there then high priority for all groups
(Q)SARs	3,6/ 2,6/ 4,2/ 1,1: again contingent on high quality data
Threshold of Toxicological Concern	3,7/ 2,5/ 4,4/ 1,2: contingent on high quality data and perspective on Osiris contribution
Human data	3,8/ 2,9/ 4,8/ 1,6: low in the context of Osiris; yet generally, of course, very important
Tool to estimate low level exposure	3,5/ 2,4/ 4,3/ 1,2: contingent on the ability to develop acceptable concepts for low exposure: if so, then important

Comment: yes (4) on the condition of having high quality data, dissent is disappearing Two dimensions: (1) high priority in general (2) priority for specific Osiris contribution Inclusion of a "environmental threshold of no concern" level

Note: First number indicates group, second number indicates priority, for example 3,1 means that group number 3 gave first priority to the ITS building block.

Two questions:

1) How much emphasis should Osiris place on getting high quality data?

a) High emphasis on best data because it adds an increase in precision

b) Quality data is not necessarily connected with known databases

b) However, if that data is not available this should not a reason for abandon the respective activity

2) How should Osiris deal with knowledge gaps?

a) REACH explicitly asks to include all relevant information even if they are of lower quality

b) One of the objectives is to develop methods to process lower quality data (need to characterize uncertainty and variability)

c) Degree of accuracy of data needed depends on purpose, context and application (for example labelling)

New tools: Should new tools be developed for the REACH process? And if so which ones do you have in mind?

Tools: Exposure assessment tools including exposure scenarios with updated default values; TTC for non-food chemicals and for non-oral routes. (2)

Comments: No need for new building blocks. Weight of evidence approach/ decision theory should be further developed. Guidance is rather needed than mandatory decision theory. Intelligent databases/ knowledge bases (for example: hyperlinks, data mining, intelligent routing, relational datasets, etc.). (4)

Key Topic 3: Databases of Chemicals

Which databases will be more important in the future for (eco)toxicity and exposure assessment than today?

Kind of databases	**1 = highest priority 7 = lowest priority**
Exposure and exposure categories	3,2/ 2,1/ 4,1
Descriptions of categories of chemicals related to mode of toxic action	3,1/ 2,3/ 4,2/ 1,2
Physicochemical properties	3,5/ 2,4/ 4,3
Toxicity data	3,6/ 2,6/ 4,6
Ecotoxicity data	3,7/ 2,6/ 4,5
Information of modes of toxic action (e.g. chemical reactivity)	3,3/ 2,2/ 1,2
Estimates of fate and (eco)toxicity data including an estimate of their uncertainty	3,4/ 2,6/ 4,4/ 1,1
Comment: yes (4), yes (1). Comment: Uncertainty and Variability are very important, last item has two different targets (ecotoxicity) and uncertainty Comment: if we have uncertainty characterisation there is no priority	

Which ongoing international efforts should be considered by OSIRIS?

International activities	**1 = highest priority N = lowest priority**
Tools	
OECD QSAR toolbox	3,1/ 2,2/ 4,3
RIP's	3,2/ 2,1/ 4,1/ 1,1
Test guidelines OECD	3,6/ 2,4/ 4,7
EU CAESAR	3,4/ 2,3/ 4,5
Health Canada	3,3/ 2,5/ 4,4
Fobig/ECVAM data quality	3,5/ 2,7/ 4,6
US-PMN-Activities *It is wise for OSIRIS to use the existing data bases and this one is worth considering (Group 4): Response; this has been done already (1992); interesting to revisit this database after OSIRIS is completed; also check how much "real" data is available*	3,7/ 2,6/ 4,3
Data (distinction is not quite consistent)	
Predictomics: it lines up with the EU-FP: should mine them	Low (3) 2,3/ 4,2
EU-FP: reprotect, Acute-tox, Sensitiv…..	Low (3) 2,2/ 4,2
EPAA	Low (3) 2,4
Others: SIDS Data (2,1), yes (1)	

Should OSIRIS incorporate all existing tools and databases or should OSIRIS ensure simple communication with them (=full compatibility)?

3. Ensure simple communication, no full incorporation

1. same opinion

2. same opinion

4. same opinion (based more on feasibility, and cost-efficiency not desirability)

On what databases/endpoints should OSIRIS focus in order to reduce or replace vertebrate testing?

Databases needed	**1 = highest priority** **7 = lowest priority**
Local toxicity (skin, eye)	3,7/ 2,8/ 4,7
Reproductive toxicity	3,1/ 2,1/ 4,1/ 1,1
Carcinogenicity	3,5/ 2,5/ 4,2/ 1,5
Repeated dose toxicity	3,6/ 2,4/ 4,3/ 1,5
Sensitisation	3,3/ 2,2/ 4,6/ 1,3
Mutagenicity	3,2/ 2,6/ 4,4/ 1,2
Aquatic tox (BCF) longterm (3)	3,4/ 2,7/ 4,5/ 1,5
Others: Chronic aquatic toxicity (2,3) *Carcinogenicity: related on number of chemicals = low priority; related animals per chemical higher priority, if multiplied – medium to low priority*	

Key Topic 4: Quality of data

Risk assessors use scoring systems to assess the quality of the available information. Which aspect do you consider important with respect to a scoring system?

Quality aspect	Should be included	Should not be included	Relevant, but not integratable
Single studies			
Data uncertainty	3/ 2/ 4/ 1 (?)		
Model uncertainty	3/ 2/ 4/ 1 (?)		
Distinction between model uncertainty for non-testing data and data uncertainty for test data (Interspecies extrapolation not relevant in this context)			
Data sets			
Representativeness of results (generalisability)	2/ 4		1
Stochastic effects a) correlation versus causation b) is covered by outlayers (percentiles) c) emphasis on robust systems that are resilient against outlayers		2/ 1	(4)
Outlayers and surprises	4/ 1	2	(4)
……			
Comment: yes (4) Different meanings of generalisability: across chemical domains, space, populations, ecosystems, machine learning capability 1. Outlayers and surprises cannot be scored yet it may detect other endpoints 2. Oulayers and surprises depend on the limitations of the research framing 3. Leverage points (these are crucial points that exert influence in a regression): dominate the slope Identify surprises: (intelligent) speculation, trial and error,			

What kind of information on uncertainty needs to be communicated to the regulators?

Ask the regulators (1)

_____

_____

_____

Key Topic 6: Support for industry and regulation

How can we support industry and regulators in providing effective and efficient testing methods and procedures in a timely manner? Please be as specific as possible.

Effort	Very important	Important	Partly important	Not important at all
Demo version of the OSIRIS webtool to get feedback and enhance implementation	3/ 2	4/ 1		
Training	3/ 2/ 4/ 1			
Guidance documents	3/ 2	4/ 1		
Case examples	3	2/ 4/ 1		
……..				
Comment: yes (1): 4: Two-way communication rather than just training; case examples could be part of the demo 1: Beta version should be out to get feedback and acceptance; to be in accordance with REACH time lines (aggressive time line: so a real challenge; needs to have it ready in 2010-2011)				

How should the results of OSIRIS be evaluated after the project is completed?

Criteria for success will be if the tool will be used by industry and regulators! (3)

Have a test case early on: Start early as possible with one. (1)

What is the goal: how many replacements? How many accepted? How many used?

Usual evaluation processes are included (publication, peer review).

Consistent and reproducible outcome.

International harmonisation on a global scale (starting with the EU).

Three goals: adequacy, acceptance and global implementation.

BE REALISTIC!! AND HELP US TO MAKE THE GOALS BECOME TRUE!

Section 4: Concluding remarks

The Delphi exercise demonstrated the importance of structured discussion about terms and categories as the individual responses indicated a degree of consensus that did not reflect the true representation of the respondents' views. The process of small group judgment and plenary justification for explaining group differences lead to a more precise wording of the issues and topics and helped the OSIRIS research team to gain a better view of the priorities that the participants assigned to the different tasks and activities. Furthermore new topics were introduced in the group discussions that added more depth to the analysis.

The results of the Group Delphi will have an impact on the protocol and agenda of Pillar 4. Since the respondents made clear choices with respect to priorities, the research team can concentrate on those tasks that all respondents felt of having high importance to the OSIRIS overall objectives. In addition, the team has gained a better understanding of the preferences of the respondents and are better informed about their needs. Finally, the respondents approved of the main tasks and planned activities of Pillar 4 which represents a powerful message to the team that they are on the right track.

Annex 1: Additional comments

***PD Dr. Jan Ahlers, Federal Environmental Agency, Dessau, Germany,* member of the OSIRIS Advisory Board**

- The target of OSIRIS was defined in "substitution of **vertebrate** testing", which in my understanding is far too narrow.

Although definitely substitution of vertebrate tests is - beside protection of man and the environment - an important issue of REACH, I interpret the objectives of OSIRIS

- "OSIRIS will undertake distinct research ……, and their *integration in a decision theory framework*" or
- "The OSIRIS project will develop ITS ….to significantly increase the use of non-testing information for *regulatory decision making*", (flyer of the workshop)
- …."minimizing the need for new testing in *risk assessment procedures*" (Objective Pillar 4)

in a broader way. At least two additional items are rather important:

1. substitution of non-vertebrate testing (e.g. tests for soil and sediment organisms) will help to save time and costs and even more important integrating alternative information enables us to perform a more comprehensive and faster assessment of these compartments and thus will certainly be an important contribution to environmental protection.
2. The information obtained from alternative methods should not only be used for testing strategies, but should also be introduced in risk assessment. It can contribute considerably in reducing uncertainty in regulatory decision making.

Dr. Monika Nendza, Analytical Laboratory Luhnstedt, Germany

As agreed, I comment on the QSAR principles:

1. I agree with the OECD criteria for QSARs, I only have same reservations about their practical use.
2. 'Unambiguous algorithm' is a good idea with regard to transparency, but may not be realizable (i) with modern statistics, e.g., multivariate procedures with continuous update of databases or (ii) in case of proprietary models (with independent external validation).
3. 'Defined applicability domain' is currently often restricted to chemical domain and as such may be misleading: It may pretend confidence in a model but that is not substantiated because other (more) important aspects of similarity / dissimilarity are neglected (e.g. toxicological domain, mode of (inter)action).

Annex 2: Agenda

Wednesday, 28th of November 2007

13.00	On-site Registration
14.00	**Welcome and Introduction** *Dr. J.J. M. (Han) van de Sandt, TNO Quality of Life, Zeist, the Netherlands* *Prof. Dr. Ortwin Renn, DIALOGIK & University of Stuttgart, Germany*
14.15	**OSIRIS Pillar 4: Envisioned products and procedure** *State of the art; focus and output of OSIRIS* *Dr. Han van de Sandt, TNO Quality of Life, Zeist, the Netherlands* *Questionnaire topics 2-6* *Dr. Dinant Kroese, TNO Quality of Life, the Netherlands* *Results of the questionnaire* *Prof. Dr. C. J. (Kees) van Leeuwen, TNO Quality of Life, the Netherlands*
15.15	**Delphi method: aim and procedure** *Introduction to method* *Prof. Dr. Ortwin Renn, DIALOGIK & University of Stuttgart, Germany*
15.30	**First Round: Group Experts Delphi: break out in smaller groups**
17.00	Coffee break
17.30	**Plenary discussion: Justification of Group Results**
19.00	Adjourn, invitation for a joined dinner

Thursday, 29th of November 2007

9.15	**Feedback from day 1** **Second Round: Group Experts Delphi: break out in smaller groups**
10.45	Coffee break
11.15	**Plenary Discussion: Justification of Group Results**
12.30	Lunch
13.30	**Third Round: Group Experts Delphi: break out in smaller groups**
14.30	Coffee break
15.00	**Plenary Discussion: Justification of Group Results**
15.30	**Concluding Session: General Feedback**
16.00	End of the workshop

Annex 3: Participants of the Workshop

Nr.	Titel	Name Email	Institution
1.	Prof. Dr.	Tom Aldenberg	*RIVM, National Institute for Public Health and the Environment (RIVM), the Netherlands*
2.	PD Dr.	Jan Ahlers	*Federal Environment Agency (UBA), Germany*
3.	Dr.	Jochen Dettke	*DEKRA, Germany*
4.	Dr.	Steve Enoch	*Liverpool John Moores University, UK*
5.	Dr.	Robert Finking	*BASF Ludwigshafen, Germany*
6.	Dr.	Anne Gourmelon	*Organisation for Economic Co-operation and Development (OECD), France*
7.	Dr.	Betty Hakkert	*National Institute for Public Health and the Environment (RIVM), the Netherlands*
8.	Dr.	Joachim Haselbach	*ATC GmbH - Angewandte Tox-Consult, Germany*
9.		Christian Hofmaier	*DIALOGIK, Germany*
10.	Dr.	Ralph Kühne	*Centre for Environmental Research (UFZ) Leipzig, Germany*
11.	Dr.	Dinant Kroese	*TNO Quality of Life, the Netherlands*
12.	Prof. Dr.	C. J. (Kees) van Leeuwen	*TNO Quality of Life, the Netherlands*
13.	Dr.	Monika Nendza	*Analytical Laboratory Luhnstedt, Germany*

Participants of the Workshop (continued)

14.	Prof. Dr.	Ortwin Renn	*DIALOGIK & University of Stuttgart, Germany*
15.	Dr.	Andrea Richarz	*Centre for Environmental Research (UFZ) Leipzig, Germany*
16.	M.A.	Michael Ruddat	*DIALOGIK, Germany*
17.	Dr.	Han van de Sandt	*TNO Quality of Life, the Netherlands*
18.	Dr.	Sandra Schäfer	*Chemical Safety (ESM-CS) Environment, Safety, Management Systems, Industriepark Wolfgang GmbH, Germany*
19.	Dr.	Julia Scheel	*Henkel KGaA, VTS-Corporate SHE and Product Safety, VTS-Human Safety Assessment, Germany*
20.	Dr.	Hans-Christian Stolzenberg	*Ecotoxicological Assessment of Substances Federal Environmental Agency (UBA), Germany*
21.	Dr.	Sebastian Strempel	*Institute for Chemical and Bioengineering, HCI ETHZ Hönggerberg Zürich, Switzerland*
22.	Dr.	Theo Vermeire	*National Institute for Public Health and the Environment (RIVM), the Netherlands*
23.	Dr.	Richard Vogel	*Federal Institute for Risk Assessment (BfR), Centre for Alternative Methods to Animal Experiments - ZEBET, Germany*
24.	Dr.	Watze de Wolf	*Du Pont, Health & Environmental Sciences - Europe, Belgium*