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WORKSHOP ON INTEGRATED APPROACHES TO TESTING AND ASSESSMENT

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

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No. 62, *Final OECD Report of the Initial Work Towards the Validation of the Rat Hershberger Assay: Phase-1, Androgenic Response to Testosterone Propionate, and Anti-Androgenic Effects of Flutamide (2006)*

No. 63, *Guidance Document on the Definition of Residue (2006)*

No. 64, *Guidance Document on Overview of Residue Chemistry Studies (2006)*

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No. 83, *Summary Report of the Peer Review Panel on the Stably Transfected Transcriptional Activation Assay for Detecting Estrogenic Activity of Chemicals, and Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-up of this Report (2007)*

No. 84, *Report on the Workshop on the Application of the GHS Classification Criteria to HPV Chemicals, 5-6 July Bern Switzerland (2007)*

No. 85, *Report of the Validation Peer Review for the Hershberger Bioassay, and Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-up of this Report (2007)*

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The Environment, Health and Safety Division publishes free-of-charge documents in ten different series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring**; **Pesticides and Biocides**; **Risk Management**; **Harmonisation of Regulatory Oversight in Biotechnology**; **Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; and the Safety of Manufactured Nanomaterials.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (http://www.oecd.org/ehs/).

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The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The participating organisations are FAO, ILO, OECD, UNEP, UNIDO, UNITAR and WHO. The World Bank and UNDP are observers. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

FOREWORD

The OECD Workshop on Integrated Approaches to Testing and Assessment was held in Washington D.C. (United States) on 11-13 December 2007. The Workshop was a joint activity of the Task Force on Existing Chemicals, the Task Force on New Chemicals, the Task Force on Biocides, and the Working Group on Pesticides. It was prepared by a Steering Group including the members of the bureaus of the Task Forces and Working Group.

This document is published on the responsibility of the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology.

WORKSHOP ON INTEGRATED APPROACHES TO TESTING AND ASSESSMENT

11-13 December 2007, Washington- United States

REPORT

TABLE OF CONTENTS

WORKSHOP ON INTEGRATED APPROACHES TO TESTING AND ASSESSMENT

11-13 December 2007, Washington - United States

INTRODUCTION

1. In February 2006, the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology held a focus session on Integrated Approaches to Testing and Assessment. Case examples were presented by member countries, stakeholder groups and the secretariat. The Joint Meeting encouraged member countries to continue exchanging information and understanding views on applying the various building blocks – *in vivo* and *in vitro* testing, (Q)SAR models, toxicogenomics, category and read-across assessment methodologies, weight of evidence, exposure considerations, etc. – to different kinds of chemicals and in different regulatory frameworks. The Joint Meeting also asked that a workshop be organised to consider and evaluate in a practical manner new and existing tools based on sound science, which can be applied in decision-making processes that maintain public confidence in the context of national/regional legislation.

Workshop objectives

2. The objective of the workshop was to share experience on integrated approaches to fulfil information requirements by reviewing case studies for six regulatory hazard endpoints (acute and chronic aquatic toxicity, dermal irritation, dermal sensitization, carcinogenicity, reproductive and developmental toxicity). The workshop was expected to review:

- case studies using currently available tools and methods to fulfil the requirements for the endpoint [e.g., testing (*in vivo* and *in vitro*), (Q)SARs, analogue read-across, chemical categories];
- how these tools and methods are used in different regulatory frameworks (new and existing industrial chemicals, biocides, pesticides);
- how these tools and methods can be used in an integrated approach to fulfil the regulatory endpoint, independent of current legislative requirements;
- how the results gathered using these tools and methods can be transparently documented; and
- how the degree of confidence of using them can be communicated throughout the decision making process.

Preparatory exercise for the workshop

3. An exercise of fulfilling information requirements for case examples was organised in advance of the workshop, by means of an OECD-dedicated Electronic Discussion Group. About 60 experts, experienced in human health hazard assessment, environmental fate and hazard assessment, and risk management were nominated by the heads of delegations to the Joint Meeting to participate in this exercise.

4. Three different groups of chemicals were proposed as case studies: a conazole fungicide (triadimefon); a pesticide inert ingredient group of chemicals (the sulfosuccinates); and a HPV chemical category (the ethylene glycols). In selecting these case studies, an attempt was made to identify chemicals that have data representing as many different levels of toxicity information (e.g., read-across, QSAR, *in vitro* models, genomics, animal tests) as possible. For example, triadimefon was chosen because it is a data-rich chemical that has, in addition to conventional toxicity studies, omics data available. For both the sulfosuccinates and ethylene glycols, a category approach (including read-across and use of [Q]SAR) has been used for examining the data, however, the regulatory context for each (pesticide inert ingredients for sulfosuccinate vs. industrial chemicals HPV for ethylene glycols) is different. Although the sulfosuccinates and the ethylene glycols were not as data-rich as the pesticide active ingredient, there was sufficient data available on them for this exercise. For these three cases, dossiers were prepared in which some of the key studies had been erased and provided to reviewers in a step wise manner. Initially, only data on physical-chemical properties were made available to participants for review to fill out a questionnaire (see below and Annex II). In successive steps, more data were provided on the endpoints of interest as more fully described below. ,

5. The data packages were uploaded onto the electronic discussion group for this exercise in a stepwise fashion over a four month period (identified as Phases I and II in the consolidated sample questionnaire in Annex II) . There were three workgroups (one for each case study). Each workgroup included at least one non-governmental stakeholder and representatives of several member countries. The experts were asked to fill out the questionnaire for each of the six endpoints of interest after reviewing the information provided after each Phase. Phases I and II were completed prior to the workshop and Phase III was completed at the workshop. The following options were offered for consideration for filling the data gap, as an alternative to testing according to an OECD Test Guideline:

- testing according to an alternative *in vitro* or other test method;
- no testing, based on other existing test results;
- no testing, based on (Q)SAR results;
- no testing, based on results from analogues or a chemical category;
- a combination of the above (weight of evidence).

6. The volunteers were also asked to perform the above exercise for different purposes (see questionnaire in Annex II) i.e.:

- Priority setting [identifying those chemicals within a large group of substances which would be candidates for further work];
- Classification and labelling;
- Risk Assessment for regulatory purpose (i.e., a quantitative analysis with dose/response information).

7. For each of the options above, volunteers were asked to apply their expertise as hazard assessors, i.e. their scientific opinion as to application of such a method independent of the regulatory context under which they operate (i.e. whether they could scientifically accept such a method). The exercise started five months in advance of the workshop and was finalised at the workshop. A summary report on the outcome of the exercise has been drafted as part of the report from the workshop (see Annex IIIA-C)

WORKSHOP PROGRESSION

8. The workshop was held on 11-13 December 2007 in Washington, DC, hosted by the United States. The workshop was chaired by Jack Moore (United States). The workshop was attended by approximately 70 participants (see Annex I for the list of participants).

9. Following the introduction, several presentations were given on the activities underway in member countries and OECD on integrated approaches to testing and assessment. The title and authors of the presentations are reported below:

- Intelligent Integration of Information in REACH
  Juan Riego-Sintes (European Commission)

- Tools and Approaches for the prioritization and Assessment of Existing Substances under the Canadian Environmental protection Act
  Kathy Hughes (Canada)

- A New Toxicology Testing and Assessment Paradigm: Meeting Common Needs
  J. Jones (United States)

- OECD (Q)SAR Application Toolbox
  Bob Diderich (OECD)/Mark Cronin (United Kingdom)

- Tox Testing in the 21st Century: A Vision and Strategy
  Mel Andersen (United States)

10. Team leaders of each case study presented conclusions (see Annexes IIIa, IIIb and IIIc) from the preparatory exercise that had taken place on the electronic discussion group. A consultant, Mike Comber, had helped sorting out responses to questionnaires for each phase of the exercise.

11. For the second day of the workshop, participants were in three break-out groups: *i)* the HPV chemical group, *ii)* the food inert ingredient group, and *iii)* the pesticide active ingredient group.

12. In the HPV chemical group, no additional information was provided but team leaders had prepared a list of general questions to stimulate discussion and recommendations for further work:

- How helpful was the provided modelled data in making a decision for priority setting, classification and labelling, and risk assessment? What was missing from the modelled data?
- How helpful was the provided analogue data in making a decision for priority setting, classification and labelling, and risk assessment? What was missing from the analogue data?
- Is the use of analogues, and the formation of categories, a viable option when making a decision for priority setting, classification and labelling, and risk assessment? What was missing from the analogue data?
- Do adequate animal data provide enough information for making a decision for priority setting, classification and labelling, and risk assessment?

13. In the food inert group, modelled and/or experimental data from two additional analogues to the chemical of interest were supplied, and the group addressed questions from the questionnaire (see Annex II) to see if their previous decisions for priority setting, classification and labelling, and risk assessment would change or not, based on the experimental data. The same questions as in the HPV chemical group were also raised to stimulate discussion and recommendations for further work.

14. In the pesticide group, experimental data for all endpoints of interest were supplied for the chemical of interest. The group went through the questionnaire again (see Annex II) to see if their previous decisions for priority setting, classification and labelling, and risk assessment would change or not, based on the experimental data.

15. During the morning of the third day, team leaders reported on the outcome of their break-out session. In the ensuing plenary session, the workshop reached agreement on the conclusions and recommendations.

OUTCOME OF THE WORKSHOP

Conclusions

16. The outcome of the preparatory exercise on the three case studies was the basis for deriving a number of conclusions relevant to the use of integrated approaches to testing and assessment, as outlined below:

- There is limited acceptability for use of structural alerts to identify effects. Acceptability can be improved by confirming the mode of action (e.g. *in vitro* testing, *in vivo* information from an analogue or category).

- There is a higher acceptability for positive (Q)SAR results compared to negative (Q)SAR results (except for aquatic toxicity).

- The communication on how the decision to accept or reject a (Q)SAR result can be based on the applicability domain of a (Q)SAR model and/or the lack of transparency of the (Q)SAR model.

- The acceptability of a (Q)SAR result can be improved by confirming the mechanism/mode of action of a chemical and using a (Q)SAR model applicable for that specific mechanism/mode of action.

- Read-across from analogues can be used for priority setting, classification & labelling and risk assessment.

- The combination of analogue information and (Q)SAR results for both target chemical and analogue can be used for classification & labelling and risk assessment for acute aquatic toxicity if the target chemical and the analogue share the same mode of action and if the target chemical and analogue are in the applicability domain of the QSAR.

- Confidence in read-across from a single analogue improves if it can be demonstrated that the analogue is likely to be more toxic than the target chemical or if it can be demonstrated that the target chemical and the analogue have similar metabolisation pathways.

- Confidence in read-across improves if experimental data is available on structural analogues "bracketing" the target substance. The confidence is increased with an increased number of "good" analogues that provide concordant data.

- Lower quality data on a target chemical can be used for classification & labelling and risk assessment if it confirms an overall trend over analogues and target.

- Confidence is reduced in cases where robust study summaries for analogues are incomplete or inadequate.

- It is difficult to judge analogues with missing functional groups compared to the target; good analogues have no functional group compared to the target and when choosing analogues, other information on similarity than functional groups is requested.

Recommendations

17. Following the discussions on the case-studies, the workshop agreed on 21 recommendations on future work to support member countries in using integrated approaches to fulfil information requirements for testing and assessment, as outlined below:

Overall recommendations

1. Stimulate the development and application of practical tools from research projects to help with data-gap filling.

2. Advance the ability to translate alternative data (*in silico* and/or *in vitro*) to adverse functional or behavioural effects used for regulatory decision making. This may involve a step-wise, iterative approach to elucidate various toxicity pathways.

3. Develop approaches to integrate possible testing and assessment methodologies for regulatory decision making (e.g., by applying Decision Analysis tools); the approaches need to be transparent, consistent, structured and hypothesis driven.

4. Continuously improve the availability of documentation, according to the OECD guidance documents, on possible testing and assessment methodologies:

   - An understanding of the performance of these methodologies and a description of uncertainty around the outcome is needed;

   - Communication of this understanding (above) is needed as well;

   - Availability of documentation on applicability domain of these methodologies needs to be improved;

   - Tools to determine applicability domains of these methodologies need to be developed.

5. Develop (or improve) guidance on the conduct of weight of evidence evaluations that encompass traditional and alternative data, including assessment and communication of associated uncertainties.

6. Improve the availability of training material and foster the continued exchange of expertise on alternative methods to facilitate acceptance of integrated approaches to testing and assessment.

Recommendations on the use of (Q)SARs in regulatory information gathering and assessment

7. Improve the availability of information on structural fragments to estimate the properties of chemicals (qualitative and quantitative).

8. Encourage the further development of quantitative predictors for various endpoints used for regulatory decision making (e.g., skin irritation). "Fit for purpose" model development is encouraged (e.g., classification and labelling of skin irritation under GHS and/or risk assessment).

9. Encourage the development of methods to confirm mechanisms/modes of action for well-defined endpoints and improve the dissemination of the results.

10. Encourage the development of mechanistically based models (i.e., *in silico* and/or *in vitro*).

11. Encourage the continual production of empirical data to support development of new and refinement of existing models (i.e. *in silico* and/or *in vitro*).

12. Improve the availability of documentation on (Q)SAR models according to the OECD guidance document on validation of (Q)SAR models:

- An understanding of the performance of the model and a description of uncertainty around the prediction is needed (e.g., algorithms as well as the training set should be available for further understanding of the model and the outputs);

- Means to communicate this understanding (above) also need to be developed (e.g., evaluate more models against the OECD validation principles).

- The availability of documentation on the applicability domain of (Q)SARs and the tools to determine applicability domains need to be improved.

Recommendations on grouping of chemicals for assessment

13. Expand the OECD Guidance on Grouping of Chemicals to include experience from assessment of e.g. pesticides, biocides, fragrances and flavouring substances.

14. Improve the OECD guidance for derivation of numerical values for quantitative endpoints based on read-across and for determining uncertainty.

15. Develop guidance on using ADME (absorption, distribution, metabolism, and excretion) and environmental transformation results for improving the robustness of read-across.

16. Improve the availability of tools to judge the adequacy of analogues and guidance for the use of these tools, taking into account structural similarity, biological activity profiles, mechanism, ADME and environmental transformation.

Other recommendations

17. Develop practical guidance on how to use screening information (including non-test data) to determine the most relevant endpoints for risk assessment, also taking into account exposure pathways (including environmental fate and transport).

18. Investigate why acceptance in a weight of evidence approach is different when no effect is identified compared to when an effect is identified in alternative test models (e.g. *in silico*, *in vitro* and non-standard tests).

19. Investigate the use of modelled ADME data (with robust metabolism information) for use in priority setting, classification & labelling, and risk assessment.

20. Develop *in vitro* assays and *in silico* methods that predict non-genotoxic mediated carcinogenicity that could identify chemicals that are not detected via currently available tests.

21. Encourage the use of existing data from non-traditional animal assays or accidental exposure to help inform priority setting, classification & labelling and risk assessment.

Follow-up activities

13. All recommendations emanating from the workshop will be submitted to the Joint Meeting for endorsement. The Secretariat will develop proposals for the implementation of recommendations and submit these proposals to the Joint Meeting.

ANNEX I- Participants list

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ANNEX II- Questionnaire for the preparatory exercise

(Questionnaire developed for the preparatory exercise, meant to be filled for each individual endpoint)

Questions to Workshop Participants

<table>
<tr><td colspan="2">Phase I – Human Health (Limited to cancer, reproductive/developmental, and dermal irritation/sensitization effects) and Ecological Effects (acute and chronic fish)</td></tr>
<tr><td rowspan="2">Ia-What physical-chemical properties, structures or sub-structures concern you in terms of potential human health and/or ecological hazard? Please indicate what SAR/QSAR methods you would use to substantiate your decision.</td><td>☐ Have a concern ☐ Do not have a concern</td></tr>
<tr><td>Rationale:</td></tr>
<tr><td colspan="2">Is the information adequate for:

Priority Setting? ☐ Yes ☐ No

Classification/Labeling? ☐ Yes ☐ No

Risk Assessment? ☐ Yes ☐ No

If you answered “no” to any of the above, what new information or approaches for the perceived endpoints of concern would you suggest to get a “yes”? For example, use of surrogate data from one or more (“read across”) similar chemicals; alternative testing data such as in vitro assays, ‘omics data, etc.</td></tr>
<tr><td>Ib – Given the additional data provided (analogue structure, p/chem. properties and some alternative data on the analogue), would your answers to Question Ia change for either human health or ecological hazard? Please indicate the main reasons for your decision to change your answer.</td><td>☐ Yes ☐ No</td></tr>
<tr><td colspan="2">Is the information adequate for:

Priority Setting? ☐ Yes ☐ No

Classification/Labeling? ☐ Yes ☐ No

Risk Assessment? ☐ Yes ☐ No</td></tr>
</table>

If you answered "no" to any of the above, what new information or approaches for the perceived endpoints of concern would you suggest to get a "yes"?

Phase II – Human Health (Limited to cancer, reproductive/developmental, and dermal irritation/sensitization effects) **and Ecological Effects** (acute and chronic fish)	
1Ia- Given the additional data provided, would your answers in Phase I change for either human health or ecological hazard? Please indicate the main reasons for your decision to change your answer.	☐ Yes ☐ No Rationale:
Is the information adequate for: Priority Setting? ☐ Yes ☐ No Classification/Labeling? ☐ Yes ☐ No Risk Assessment? ☐ Yes ☐ No If you answered "no" to any of the above, what new information or approaches for the perceived endpoints of concern would you suggest to get a "yes"?	
IIb – Given the additional data provided would your answers to Phase IIa change for either human health or ecological hazard?? Please indicate the main reasons for your decision to change your answer.	☐ Yes ☐ No Rationale:
Is the information adequate for: Priority Setting? ☐ Yes ☐ No Classification/Labelling? ☐ Yes ☐ No Risk Assessment? ☐ Yes ☐ No	
If you answered "no" to any of the above, what new information or approaches (except traditional animal/human studies) would you suggest to get a "yes"?	
IIc- Given the additional data provided would your answers in Phase IIb change for either human health or ecological hazard? Please indicate the main reasons for your decision to change your answer.	☐ Yes ☐ No Rationale:
Is the information adequate for: Priority Setting? ☐ Yes ☐ No Classification/Labeling? ☐ Yes ☐ No Risk Assessment? ☐ Yes ☐ No	

<table>
<tr><td colspan="2">If you answered “no” to any of the above, what new information or approaches for the perceived endpoints of concern would you suggest to get a “yes”?</td></tr>
<tr><td rowspan="2">Phase III – Given all the available data, would your answers to Phase II change for either human health or ecological hazard? Please indicate the main reasons for your decision to change your answer.</td><td>☐ Yes ☐ No</td></tr>
<tr><td>Rationale:</td></tr>
<tr><td colspan="2">Is the information adequate for:

Priority Setting? ☐ Yes ☐ No

Classification/Labeling? ☐ Yes ☐ No

Risk Assessment? ☐ Yes ☐ No</td></tr>
<tr><td colspan="2">If you answered “no” to any of the above, what new information or approaches would you suggest to get a “yes”?</td></tr>
</table>

ANNEX III

Preamble

Annexes IIIa, IIIb, IIIc present summaries of the questionnaire responses submitted as part of the OECD IATA Workshop exercise. The first few pages present the results using tables to answer several simple questions. This is followed by an annex which attempts to capture all responses submitted for this case study.

The summaries are based on the responses that were supplied in submitted questionnaires. It should be noted that a single questionnaire may represent the contribution or opinion of one or more individuals. The actual responses varied greatly from one questionnaire to another. Some responses indicated adequacy of information for the regulatory endpoints (or not) but with no justification. The source and number of submitted questionnaires varied from one phase to another, which means that changes occur from one phase to another, not for reasons of a change in the information available, but because different people have replied. Consequently, it is sometimes difficult to be definitive about the level of information that tripped a change in a group for a particular endpoint of legislative purpose.

Not withstanding these comments, an attempt to answer some over-arching questions has been made.

For each of the case studies, an overall summary of questionnaire responses is given and then is followed by a detailed presentation of all responses received.

Contents

ANNEX IIIA- Summary of the preparatory work on the HPV chemical case study

HPV PHASE I AND II SUMMARY

$HO(CH_2CH_2O)_3H$

Preamble : This document presents a report summarizing the questionnaire responses submitted as part of the OECD IATA Workshop exercise. The first few pages present the results using tables to answer several simple questions. This is followed by an annex which attempts to capture all responses submitted for this case study.

OVERALL SUMMARY PRESENTED IN A QUESTION-AND-ANSWER FORMAT:

- **How did the adequacy/confidence of a decision change with regulatory context? With successive information? By endpoint?**

The following table shows at which stage in the process, against the supplied information, the respondents were able to make a decision. The change from green to yellow and back to green for the assessment of the chronic fish endpoint for priority setting (phase IIa, b,c) is due to the reduced response at phase IIb (from 6, for phases IIa/c to 5 for phase IIb). The same reason is also the cause for the other changes, chronic fish (classification)

Table 1 : Overview of data available at different stages and when decisions were made

		Phase Ia	Phase Ib	Phase IIa	Phase IIb	Phase IIc
Decisions	**Priority setting**	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish
	Classification and labeling	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer Dev/Repro Acute fish Chronic fish	Irritation Sensitization Cancer Dev/Repro Acute fish Chronic fish
	Risk assessment	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish
HPV	**Basic data**	Structure Phys/chem properties				
	In-silico		QSAR results for HPV			
	Alternative data			Env end-points "Alternative data" available for HPV		
	Test data					Environmental endpoints- available data for the chemical of interest (HPV) Human Health Endpoints- ADME and available data for chemical of interest (HPV)

		Phase Ia	Phase Ib	Phase IIa	Phase IIb	Phase IIc
Analogue	**Basic data**		One analogue structure and physical/chemical properties			
	In-silico		QSAR results for analogue			
	In-vitro		Plus for Human Health endpoints some data on the analogue	Human Health endpoints - ADME data (absorption, distribution, metabolism, excretion) for analogue		
	Alternative data			Env end-points -"Alternative data" available for analogue	Human Health Endpoints- "Alternative data" available for analogue	
	Test data				Environmental endpoints - available data for one or more analogue(s)	

GREEN HIGHLIGHTS INDICATE A MAJORITY OF RESPONDENTS WERE ABLE TO MAKE THE DECISION INDICATED. THE ACTUAL NUMBERS CAN BE SEEN IN TABLES 3, 4 AND 5.

YELLOW HIGHLIGHTS INDICATE THAT THE RESPONDENTS WERE SPLIT, ALTHOUGH THERE MAY HAVE BEEN A MAJORITY ON ONE SIDE OF THE DECISION THE DIFFERENCE WAS NOT CONSIDERED SUFFICIENT TO WARRANT SAYING THAT THERE WAS CONSENSUS.

RED HIGHLIGHTS ARE WHERE A CLEAR MAJORITY WERE AGAINST MAKING A DECISION.

At phase Ia, in the exercise, respondents were asked whether they had a concern for the endpoint being assessed. The responses to this question are given in the summaries of the phases (see below). Subsequently the question asked was "Have you changed your mind?" This has been answered in a number of ways. For example, it might mean;

- that the respondents were moving from concern to no concern (or vice versa)
- a move from insufficient information for priority setting (or other legislative end-point) with respect to a hazard end-point to sufficiency of information for prority setting for that end-point
- that the change of mind related to a change in the level of confidence to making a specific decision, e.g. from low to high.

Comparing table 1 to table 2, it can been seen that at Phase Ib and IIb a number of decisions were amended, which does coincide with a significant number of changed minds.

Table 2 – Change of minds with succeeding phases

	No of submissions	**No of submissions**	**No of submissions**	**No of submissions**
	Phase Ib	Phase IIa	Phase IIb	**Phase IIc**
Irritation	8 1 changed mind	11 1 changed mind	6 4 changed minds	**4** **1 changed mind**
Sensitization	8 1 changed mind	11 1 changed mind	6 4 changed minds	**5** **1 changed mind**
Cancer	9 4 changed minds	9 1 changed mind	6 4 changed minds	**5** **3 changed minds**
Dev/Repro	6 0 changed mind	10 2 changed minds	6 5 changed minds	**5** **4 changed minds**
Acute Fish	5 4 changed minds	6 4 changed minds	5 2 changed minds	**5** **0 changed minds**
Chronic Fish	**6** **3 changed minds**	**6** **2 changed minds**	**5** **2 changed minds**	**6** **1 changed minds**

The following three tables show the actual numbers of respondents that felt that a decision could be made, at each phase and for each end-point. The data in parenthesis also highlight the confidence at which these decisions were being made

Table3 – Sufficiency of information by regulatory endpoint – Priority Setting

	Phase Ia		**Phase Ib**		**Phase IIa**		**Phase IIb**		**Phase IIc**	
	YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	3 (3L)	5 (3H, 2M)	8 (3M, 5L)	0	10 (2H,3M, 5L)	1 (H)	5 (4M, 1L)	1 (H)	4 (H, 2M, L)	0
Sensitization	3 (3L)	5 (3H, 2M)	8 (3M, 5L)	0	10 (2H,3M, 5L)	1 (H)	5 (H, 3M, 1L)	1 (H)	4 (H, 2M, L)	0
Cancer	4 (L & M)	4	7 (H, 2M, 4L)	2 (H, L)	7 (4M, 3L)	2 (H, M)	5 (3M, 2L)	1 (H)	5 (2H, 2M, L)	0
Dev/Repro	3 (M)	6 (L, M, H)	1 (M)	5 (H, M)	3 (H, 2M)	7 (5H, 2M)	6 (4H, 2M)	0	5 (4H, M)	0
Acute Fish	4 (L & M)	1	5 (4M & L)	0	5 (3H, 2M)	1 (H)	5 (3H, 2M)	0	5 (3H, 2M)	0
Chronic Fish	**0**	**5 (M & H)**	**4 (all M)**	**2 (M & H)**	**4 (H, 3M)**	**2 (M & H)**	**3 (H, 2M)**	**2 (H/L)**	**4 (3H, M)**	**2 (both L)**

Table 4 – Sufficiency of information by regulatory endpoint – Classification and Labeling

	Phase Ia		**Phase Ib**		**Phase IIa**		**Phase IIb**		**Phase IIc**	
	YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	0	8 (7H, 1L)	0	8 (6H, 2M)	1 (M)	10 (8H, 2M)	3 (all L)	3 (2H, L)	2 (M/L)	2 **(2H)**
Sensitization	0	8 (7H, 1L)	0	8 (6H, 2M)	1 (M)	10 (8H, 2M)	3 (all L)	3 (2H, M)	2 (M/L)	2 **(2H)**
Cancer	0	8 (7H, 1L)	0	9 (7H, 2M)	2 (H, L)	7 (4H, 2M, L)	0	6 (4H, 2L)	3 (2H, L)	2 **(H/L)**
Dev/Repro	0	9 (8H, 1L)	0	6 (6H)	0	10 (all H)	4 (H, 2M, L)	2 (all M)	4 (all H)	1 **(M)**
Acute Fish	0	5 (H)	3 (H,M,L)	2 (H,M)	5 (H,3M,L)	1 (H)	4 (3H,L)	1 (H)	5 (4H, L)	0
Chronic Fish	0	5 **(H)**	2 **(M, L)**	4 **(H)**	4 **(H, 2M, L)**	2 **(2H)**	2 **(M, L)**	3 **(3H)**	4 **(3H, L)**	2 **(2H)**

Table 5 – Sufficiency of information by regulatory endpoint – Risk Assessment

	Phase Ia		**Phase Ib**		**Phase IIa**		**Phase IIb**		**Phase IIc**	
	YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	**0**	**8** (7H, 1L)	**1** (M)	**7** (7H)	**1** (M)	**10** (9H, 1L)	**1** (M)	**5** (2H, M, 2L)	**1** (M)	**3** **(2H, L)**
Sensitization	**0**	**8** (7H, 1L)	**1** (M)	**7** (7H)	**1** (M)	**10** (9H, 1L)	**1** (M)	**5** (2H, 2M, L)	**1** (M)	**3** **(2H, L)**
Cancer	**0**	**8** (7H, 1L)	**1** (L)	**8** (8H)	**2** (2L)	**7** (6H, M)	**1** (M)	**5** (3H, 2L)	3 (2H, M)	**2** **(H/L)**
Dev/Repro	**0**	**9** (8H, 1L)	**0**	**6** (6H)	**1** (M)	**9** (9H)	**2** (H, M)	**4** (H, 3M)	4 (3H, M)	**2+** **(M)**
Acute Fish	**0**	**5** (H)	**0**	**5** (H)	**2** (2M)	**4** (2H, M, L)	2 (M, L)	3 (3H)	3 (3H)	**2** **(2H)**
Chronic Fish	**0**	**5** **(H)**	**0**	**6** **(4H, 2M)**	**1** **(H)**	**5** **(2H, M, L)**	**1** **(M)**	**4** **(4H)**	**3** **(all H)**	**3** **(H, M)**

GREEN HIGHLIGHTS INDICATE A MAJORITY OF RESPONDENTS WERE ABLE TO MAKE THE DECISION INDICATED.

YELLOW HIGHLIGHTS INDICATE THAT THE RESPONDENTS WERE SPLIT, ALTHOUGH THERE MAY HAVE BEEN A MAJORITY ON ONE SIDE OF THE DECISION THE DIFFERENCE WAS NOT CONSIDERED SUFFICIENT TO WARRANT SAYING THAT THERE WAS CONSENSUS.

RED HIGHLIGHTS ARE WHERE A CLEAR MAJORITY WERE AGAINST MAKING A DECISION.

- **What was the turning point (in terms of amount and type of information) that resulted in a majority opinion for a given decision?**

By endpoint this has been summarised above, it can be seen that generally, by regulatory endpoint

- Priority setting was agreed by the end of Phase Ib with the exception of developmental reprotoxicity, which required phase IIb.
- Classification and labelling for the human health endpoints never reached a consensus except for developmental reprotoxicity at Phase IIb. For the environmental endpoints generally agreement was reached at Phase IIa.
- Risk assessment also never reached a consensus for the human health endpoints, again with the exception of reprotoxicity, this time at phase IIc. Neither of the environmental endpoints reached a consensus.

- **When participants were not able to make a decision, were the suggested information/approaches identified as missing similar across endpoints?**

Some of the requests were similar, but these were very broad, e.g. suggestions for (Q)SARs, other analogueues, use of the OECD Toolbox. Other than experimental in-vivo testing specific information relating to the endpoint was normally targeted, e.g. in-vitro tests, LLNA. Other data was more general but then confined either to the Human Health endpoints (ADME information, metabolism information) or the environmental endpoints (biodegradation).

The following table highlights the type of data requests made at different points in the exercise by endpoint and regulatory need.

Table 6 - Type of data requested by Phase, endpoint and regulatory need

		Phase Ia	**Phase Ib**	**Phase IIa**	**Phase IIb**	**Phase IIc**
Irritation	PS	(Q)SAR/ ED[1]	Categorisation, (Q)SAR	Categorisation, (Q)SAR		
	C&L	(Q)SAR, in-vitro, ED, analogue, ADME	Categorisation,(Q)SAR Bioavailability Metabolism	Categorisation, (Q)SAR Bioavailability Metabolism	(Q)SAR	(Q)SAR
	RA	(Q)SAR, ED, in-vitro, analogue, MoA[2]	Categorisation, (Q)SAR Bioavailability Metabolism, ED - NOEL	Categorisation, (Q)SAR Bioavailability Metabolism ED - NOEL	(Q)SAR ED- NOEL	(Q)SAR ED- NOEL
Sensitisation	PS	(Q)SAR/ ED[1]	Categorisation, (Q)SAR	Categorisation, (Q)SAR		
	C&L	(Q)SAR, in-vitro, ED, analogue, ADME	Categorisation, (Q)SAR Bioavailability Metabolism	Categorisation, (Q)SAR Bioavailability Metabolism	(Q)SAR Metabolism Protein binding	(Q)SAR Metabolism Protein binding
	RA	(Q)SAR, ED, in-vitro, analogue, MoA[2]	Categorisation, (Q)SAR Bioavailability Metabolism ED - NOEL	Categorisation, (Q)SAR Bioavailability Metabolism ED - NOEL	(Q)SAR Metabolism Protein binding ED- NOEL	(Q)SAR Metabolism Protein binding ED- NOEL
Cancer	PS	(QSAR, Alerts, analogue, ED, mechanistic	(Q)SAR, alerts, analogue			
	C&L	ED, in-vitro, Alerts, WoE[3]	ED, *In vitro* genotoxicity (Q)SAR Analogueues Bioavailability, LogP, Metabolism	ED, *In vitro* genotoxicity (Q)SAR Analogueues Bioavailability, LogP, Metabolism	WoE In-vitro Categorisation Metabolism Adsorption	ED
	RA	DNEL plus all the	ED, *In vitro* genotoxicity	ED, *In vitro* genotoxicity	WoE, In-vitro	ED

		Phase Ia	Phase Ib	Phase IIa	Phase IIb	Phase IIc
		above	(Q)SAR Analogueues Bioavailability, LogP, Metabolism	(Q)SAR Analogueues Bioavailability, LogP, Metabolism	Categorisation Metabolism Adsorption TD - DNEL	
Dev/Repro	PS	(Q)SAR, ADME, ED, analogue	(Q)SAR, analogue categorisation	(Q)SAR, analogue categorisation		
	C&L	(Q)SAR, ADME, ED, analogue, WoE, in-vitro, mechanistic	(Q)SAR, analogue Categorisation, ED	(Q)SAR, analogue Categorisation, ED	(Q)SAR, analogue Categorisation ED	In-vitro ED
	RA	(Q)SAR, ED, analogue Mechanistic, DNEL/NOAEL	(Q)SAR, analogue Categorisation ED - DNEL	(Q)SAR, analogue Categorisation ED - DNEL	(Q)SAR, analogue Categorisation ED - DNEL	In-vitro ED - DNEL
Acute fish	PS	(Q)SAR, analogue, ED				
	C&L	(Q)SAR, analogue, ED biodegradation	(Q)SAR ED on analogue Biodegradation	(Q)SAR ED on inverts and plants		
	RA	(Q)SAR, analogue, ED biodegradation	(Q)SAR ED on analogue Biodegradation	(Q)SAR ED on inverts and plants	ED on HPV	ED – chronic tox Biodegradation
Chronic fish	PS	(Q)SAR,, ED biodegradation	(Q)SAR ED on analogue Biodegradation MoA info	(Q)SAR ED on analogue Biodegradation MoA info	ED on HPV Biodegradation (Q)SAR	
	C&L	Solubility, logKow, BCF, (Q)SAR, analogue, ED	(Q)SAR, ED on analogue Biodegradation MoA info	(Q)SAR, ED on analogue Biodegradation MoA info	ED on HPV Biodegradation (Q)SAR	ED on HPV Biodegradation
	RA	Solubility, logKow, BCF, (Q)SAR, analogue, ED, PNEC	(Q)SAR, ED on analogue Biodegradation MoA info	(Q)SAR, ED on analogue Biodegradation MoA info	ED on HPV Biodegradation (Q)SAR	ED on HPV Biodegradation

1 : Experimental data

2 : Mode of action – OECD TG 404

3 : Weight of evidence approach

- **In terms of regulatory context (priority setting, class/label, risk assessment), how much information do you need to inform a decision?**

Unfortunately this is not possible to answer for C&L and risk assessment, for these endpoints the actual scheme being applied was different across many of the respondents, and in some schemes,

e.g., GHS and REACH specific data requirements were identified as being needed before a decision could be made. In some cases this meant that some respondents were not able to make a decision with out test data on the target chemical. For priority setting it would seem that once people have a structure, some phys-chem data, some predictions, analogueues (with data) and some limited experimental data on the target compound, there were reasonably comfortable making this decision.

DETAILED QUESTIONNAIRE RESPONSES BY PHASES

Phase Ia

Information provided :

- Structure
- Physical/chemical properties

Phase Ia Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	8 (6 concerned)	3 (3L)	5 (3H, 2M)	0	8 (7H, 1L)	0	**8 (7H, 1L)**
Sensitization	8 (6 concerned)	3 (3L)	5 (3H, 2M)	0	8 (7H, 1L)	0	**8 (7H, 1L)**
Cancer	8 (6 concerned)	4 (L & M)	4	0	8 (7H, 1L)	0	**8 (7H, 1L)**
Dev/Repro	9 (8 concerned)	3 (M)	6 (L, M, H)	0	9 (8H, 1L)	0	**9 (8H, 1L)**
Acute Fish	5 (2 concerned)	4 (L & M)	1	0	5 (H)	0	**5 (H)**
Chronic Fish	**5 (2 concerned)**	**0**	**5 (M & H)**	**0**	**5 (H)**	**0**	**5 (H)**

Notes (Based on the three main questions in the questionnaire)

Do you have a hazard concern:

- For dermal irritation and sensitization, concern was based primarily on the absence of information – default assumption.
- With respect to cancer and developmental reprotoxicity, the class of compounds was identified as presenting a concern.
- In the case of acute and chronic fish toxicity again the class of chemical was identified and discussed.

Do you have sufficient information:

There were mixed views with all end-points other than chronic fish, as to whether there sufficient information for priority setting, with the confidence tending to the lower end especially when responses were indicating sufficient data for priority setting. However, it is clear that where there are specific needs, e.g. for C&L or risk assessment respondents confidence was high when saying the information was insufficient.

What further information is required:

- The requirement for improving the decision making ranged from (Q)SAR information, analogueue data and experimental information.
- In every end-point, a PNEC or DNEL was suggested for risk assessment, a requirement which would normally only be met with experimental information on the chemical being assessed.
- For the environmental endpoints further phys-chem data were suggested and data relating to the potential fate of the substance and metabolites suggested.
- For the Human Health endpoints data pertaining to ADME, mode of action and in-vitro assays were also specifically requested.
- The OECD Toolbox was specifically mentioned to help with categorization (identification of other analogueues) and for assessing specific mechanisms of action.

Phase Ib

Information provided :

- One analogueue structure and physical/chemical properties
- QSAR results for HPV and analogueue
- Plus for Human Health endpoints some data on the analogueue

Phase Ib Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	8 1 changed mind	8 (3M, 5L)	0	0	8 (6H, 2M)	1 (M)	**7** **(7H)**
Sensitization	8 1 changed mind	8 (3M, 5L)	0	0	8 (6H, 2M)	1 (M)	**7** **(7H)**
Cancer	9 4 changed minds	7 (H, 2M, 4L)	2 (H, L)	0	9 (7H, 2M)	1 (L)	**8** **(8H)**
Dev/Repro	6 0 changed mind	1 (M)	5 (H, M)	0	6 (6H)	0	**6** **(6H)**
Acute Fish	5 4 changed minds	5 (4M & L)	0	3 (H,M,L)	2 (H,M)	0	**5** **(H)**
Chronic Fish	**6** **3 changed minds**	**4** **(all M)**	**2** **(M & H)**	**2** **(M, L)**	**4** **(H)**	**0**	**6** **(4H, 2M)**

Note of concern: There is no obvious evidence that this has changed at this stage. However, as phrased, the questionnaire does not ask this question. The question asked is "Have you changed your mind?" This is answered in many ways. In this case, despite 5 respondents moving from insufficient information for priority setting with respect to dermal irritation and sensitization, to all 8 thinking there is sufficient information, none of them responded that they had changed their minds. In other end-points where a change of mind was noted, the explanation usually related to the legal framework (e.g. risk assessment) and not to a change in concern, however, in some cases the change of mind related to a change in the level of confidence making a specific decision.

Do you have a hazard concern:

Cannot be answered very easily. Firstly the questionnaire does not ask this question, secondly the number/identity of respondents changed from phase to phase.

Do you have sufficient information:

Priority setting : All respondents agreed there was sufficient information for priority setting for dermal irritation and sensitization and a majority for carcinogenicity. For developmental reprotoxicity, however, the majority felt there was insufficient information, quoting the lack of data and the lack of reliable (Q)SAR information.

With respect to the two environmental endpoints, there was sufficient information now for priority setting, with respect to acute fish, but views were mixed for chronic toxicity, with some respondents requiring experimental information or better predictions.

C&L:

- Human Health endpoints - All agreed that the data needs for classification were not met and this decision was made at a high (occasionally medium) level of confidence.
- Environmental endpoints – opinion differed due to the expected level of ecotoxicity and whether or not predictions could be used.

Risk assessment:

- Dermal irritation – one respondent now considered that a risk assessment could be done, although not optimal.
- Cancer – again a single response was received suggesting that a risk assessment could be done. In this case the reason being that cancer was unlikely to be the critical endpoint for the risk assessment.
- Developmental reprotoxicity – All responses indicated insufficient information, high level of confidence.
- Acute/chronic fish toxicity – all agreed not – requiring experimental data (even if only on the analogue).

What further information is required:

- The requirement for improving the decision making ranged from (Q)SAR information, analogue data and experimental information.
- In every end-point, a PNEC or DNEL was suggested for risk assessment, a requirement which would normally only be met with experimental information on the chemical being assessed.
- For the environmental endpoints further phys-chem data were suggested and data relating to the potential fate of the substance and metabolites suggested.
- For the Human Health endpoints data pertaining to ADME, mode of action and in-vitro assays were also specifically requested. In at least on case, e.g. developmental reprotoxicity a 2 generation study was requested.
- The OECD Toolbox was specifically mentioned to help with categorization (identification of other analogueues) and for assessing specific mechanisms of action.

Was the analogue(ues) OK?

In nearly every case the analogueues were seen as being relevant and were generally identified as being in the same category as the target chemical. However, a number of responses requested extra information, e.g. Tamimoto index of similarity.

Phase IIa

Information provided :
Environmental endpoints - -"Alternative data" available for analogue and HPV

Human Health Endpoints- ADME data (absorption, distribution, metabolism, excretion) for analogue

Phase IIa Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	NO	YES	NO	YES	**NO**
Irritation	11 1 changed mind	10 (2H,3M, 5L)	1 (H)	1 (M)	10 (8H, 2M)	1 (M)	**10** **(9H, 1L)**
Sensitization	11 1 changed mind	10 (2H,3M, 5L)	1 (H)	1 (M)	10 (8H, 2M)	1 (M)	**10** **(9H, 1L)**
Cancer	9 1 changed mind	7 (4M, 3L)	2 (H, M)	2 (H, L)	7 (4H, 2M, L)	2 (2L)	**7** **(6H, M)**
Dev/Repro	10 2 changed minds	3 (H, 2M)	7 (5H, 2M)	0	10 (all H)	1 (M)	**9** **(9H)**
Acute Fish	6 4 changed minds	5 (3H, 2M)	1 (H)	5 (H,3M,L)	1 (H)	2 (2M)	**4** **(2H, M, L)**
Chronic Fish	**6** **2 changed minds**	**4** **(H, 3M)**	**2** **(M & H)**	**4** **(H, 2M, L)**	**2** **(2H)**	**1** **(H)**	**5** **(2H, M, L)**

Do you have sufficient information:

Priority setting : All but one respondents agreed there was sufficient information for priority setting for dermal irritation and sensitization. The one dissident was concerned about the slight irritation seen in a patch test and the lack of information relating to sensitization. For cancer, a majority were able to make a decision on priority setting. For developmental reprotoxicity, however, the majority felt there was insufficient information, quoting lack of data, evidence of adsorption from the toxicokinetic study, and the lack of reliable (Q)SAR information.

With respect to the two environmental endpoints, there was sufficient information now for priority setting, with respect to acute fish and for a majority with respect to chronic fish. The main sticking points with respect to some respondents on this end-point were now information on degradation and the formation of potential metabolites.

C&L:

- Human Health endpoints – General agreement that the data needs for classification were not met and this decision was made at a high (occasionally medium) level of confidence. Occasional differences were observed due to the very low level of activity observed.
- Environmental endpoints – a majority now felt that C&L (at acute and chronic) could be conducted, saying that the toxicity was very low.

Risk assessment:

- Dermal irritation – one respondent still an outlier, and considered that a risk assessment could be done.
- Cancer – 2 responses received suggesting that a risk assessment could be done. In one case the reason being that cancer was unlikely to be the critical endpoint for the risk assessment.
- Developmental reprotoxicity – Majority of responses indicated insufficient information, high level of confidence. The one outlier suggested that the ADME data could be used to indicate a hazard to reproductive organs/fetus.
- Acute and chronic fish toxicity – opinion was split, with a majority still suggesting that quantitative information was still lacking also information on degradation was requested.

What further information is required?

- The requirement for improving the decision making ranged from (Q)SAR information, analogue data and experimental information.
- In every end-point, a PNEC or DNEL was suggested for risk assessment, a requirement which would normally only be met with experimental information on the chemical being assessed.
- For the environmental endpoints – at the acute level, information needs now extended to experimental information on plants and invertebrates or experimental data on the target chemical.
- For the Human Health endpoints data pertaining to ADME, mode of action and in-vitro assays were also specifically requested. In at least on case, e.g. developmental reprotoxicity a 2 generation study was requested.
- The OECD Toolbox was specifically mentioned to help with categorization (identification of other analogueues) and for assessing specific mechanisms of action.

Phase IIb

Information provided :
Environmental endpoints - available data for one or more analogue(s)

Human Health Endpoints- "Alternative data" available for analogue

Phase IIb Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	NO	YES	NO	YES	**NO**
Irritation	6 4 changed minds	5 (4M, 1L)	1 (H)	3 (all L)	3 (2H, L)	1 (M)	**5** **(2H, M, 2L)**
Sensitization	6 4 changed minds	5 (H, 3M, 1L)	1 (H)	3 (all L)	3 (2H, M)	1 (M)	**5** **(2H, 2M, L)**
Cancer	6 4 changed minds	5 (3M, 2L)	1 (H)	0	6 (4H, 2L)	1 (M)	**5** **(3H, 2L)**
Dev/Repro	6 5 changed minds	6 (4H, 2M)	0	4 (H, 2M, L)	2 (all M)	2 (H, M)	**4** **(H, 3M)**
Acute Fish	5 2 changed minds	5 (3H, 2M)	0	4 (3H,L)	1 (H)	2 (M, L)	**3** **(3H)**
Chronic Fish	**5** **2 changed minds**	**3** **(H, 2M)**	**2** **(H/L)**	**2** **(M, L)**	**3** **(3H)**	**1** **(M)**	**4** **(4H)**

Do you have sufficient information:

Priority setting : All but one respondents agreed there was sufficient information for priority setting for dermal irritation and sensitization. The one who held out stated that analogueue A was not suitable, but then said that the endpoint could be predicted using the other analogue. For cancer and developmental toxicity a majority were able to make a decision on priority setting, the no responses (for cancer) were concerned with the analogues.

With respect to the two environmental endpoints, there was sufficient information now for priority setting, with respect to acute fish and for a majority with respect to chronic fish. The main sticking points with respect to some respondents on this end-point were now information on degradation and the formation of potential metabolites and the quality of the data available on the analogueues or the quality of the analogueues themselves

C&L:

- Human Health endpoints
    - For irritation and sensitization, respondents were now split as to whether the information was sufficient. The difference seems to be due to the extent to which different schemes allow for data or interpretation and that some respondents would classify because of a presumption to being positive.
    - Cancer – all respondents agreed that C&L could not be done. The data was insufficiently clear.
    - Developmental toxicity – a majority now felt that a decision on C&L could be made (although with a wide range of confidence).
- Environmental endpoints – a majority now felt that C&L (at acute) could be conducted, saying that the toxicity was very low. However, one respondent suggested that information on degradation was still required for the classification.
- For chronic toxicity a majority (2-3) were not able to make a decision requiring data on the test chemical in at least one case.

Risk assessment:

- Dermal irritation – still insufficient data especially relating to quantitative information needed for a risk assessment
- Cancer – 1 response received suggesting that a risk assessment could be done, although on its own it was not considered sufficient information.
- Developmental reprotoxicity – Majority of responses indicated the information did not address key concerns relating to developmental toxicity of the target chemical and the very limited experimental data. Two respondents were confident that the read across information was sufficient.
- Acute and chronic fish toxicity – opinion was split, with a majority suggesting that supporting information was still lacking (degradation, purity) and the extent to which the obviously low toxicity could be handled for a risk assessment, e.g. what assessment factors could be sued.

What further information is required:

- Human Health endpoints –
    - The requirement for improving the decision making indicated a preference for experimental information.

    - A DNEL was suggested for risk assessment, a requirement which would normally only be met with experimental information on the chemical being assessed.
- For acute fish endpoint, few extra requests made except for measured data on the target chemical (to raise level of confidence) and information relating to the degradation.
- For the chronic endpoint one respondent wanted an sac fry test, others suggested degradation information and metabolite formation.
- Weight of evidence approaches were still described, and the use of the OECD toolbox.

Was the analogue(ues) OK?

The analogueues were generally seen as helpful, with the following exceptions:

- Analogue A did not have an ether group – so the extent to which it could be sued for reading across for toxicological information was questioned.
- Analogue D was generally considered a poor choice as it was a mixture. Hence the extent for read across was limited.

Phase IIc

Information provided :
Environmental endpoints- available data for the chemical of interest (HPV)

Human Health Endpoints- ADME and available data for chemical of interest (HPV)

Phase IIc Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	4 1 changed mind	4 (H, 2M, L)	0	2 (M/L)	2 (2H)	1 (M)	**3** **(2H, L)**
Sensitization	5* 1 changed mind	4 (H, 2M, L)	0	2 (M/L)	2 (2H)	1 (M)	**3** **(2H, L)**
Cancer	5 3 changed minds	5 (2H, 2M, L)	0	3 (2H, L)	2 (H/L)	3 (2H, M)	**2** **(H/L)**
Dev/Repro	5 4 changed minds	5 (4H, M)	0	4 (all H)	1 (M)	4 (3H, M)	**2+** **(M)**
Acute Fish	5 0 changed minds	5 (3H, 2M)	0	5 (4H, L)	0	3 (3H)	**2** **(2H)**
Chronic Fish	**6** **1 changed minds**	**4** **(3H, M)**	**2** **(both L)**	**4** **(3H, L)**	**2** **(2H)**	**3** **(all H)**	**3** **(H, M)**

* : One respondent gave no opinion on the legislative endpoints

+ : One respondent said Y on risk assessment for devtox, but N for reprotox.

Do you have sufficient information:

Priority setting : All respondents agreed there was sufficient information for priority setting for dermal irritation and sensitization. For cancer and developmental toxicity a majority were able to make a decision on priority setting, with respect to the two environmental endpoints, there was sufficient information now for priority setting, with respect to acute fish (very low toxicity) and for a majority with respect to chronic fish. The main sticking points continued to be with respect to the need, by some respondents on this end-point for information on degradation and the formation of potential metabolites and the quality of the data available on the analogueues or the quality of the analogueues themselves

C&L:

- Human Health endpoints
    - For irritation and sensitization, respondents were split 50:50 disagreeing on the extent to which the data was sufficient
    - Cancer – the majority (3:2) of respondents now felt that C&L could be done. The differences related to the interpretation of the data as the quality was uncertain.
    - Developmental toxicity – a majority now felt that a decision on C&L could be made with a high level of confidence in the study on the HPC chemical.
- Environmental endpoints – all responses for acute toxicity to fish now felt that C&L could be conducted, saying that the toxicity was very low.
- For chronic toxicity a majority (4-2) were now able to make a decision. Although the quality of the data and its interpretation still caused problems.

Risk assessment:

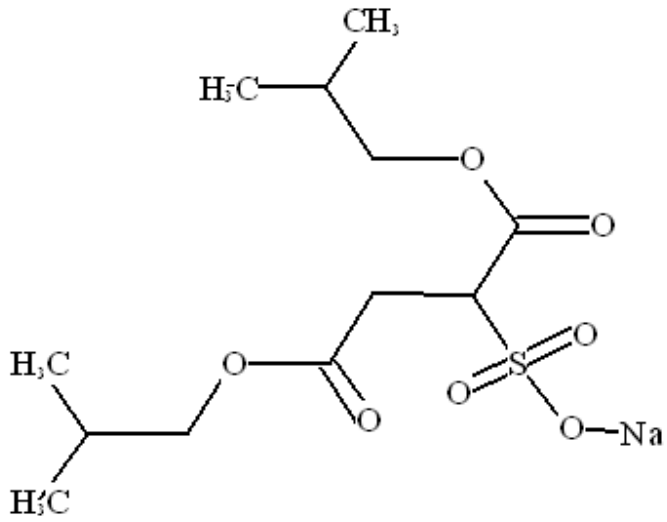
- Dermal irritation – still insufficient data especially relating to quantitative information needed for a risk assessment
- Cancer – Again a 3:2 in favour of risk assessment. The quality and the inconclusive nature were areas of dispute.
- Developmental reprotoxicity – Majority of responses were confident that the experimental data was sufficient. Concern was expressed about the information from the analogueues hence the split between reprotoxicity and developmental toxicity.
- Acute and chronic fish toxicity – opinion was split, but with a majority suggesting that supporting information was sufficient (at acute level) and exactly 50:50 at the chronic level. Again this was due to the interpretation of the data and how it could be used for risk assessment.

What further information is required:

- Human Health endpoints –
    - The requirement for improving the decision making indicated a preference for experimental information.
    - A DNEL was suggested for risk assessment, a requirement which would normally only be met with experimental information on the chemical being assessed.
- For acute fish endpoint, requests were made for biodegradation data on the target chemical and even chronic fish data.
- For the chronic endpoint one respondent wanted a sac fry test, others suggested degradation information and metabolite formation.

<u>ANNEX IIIB</u> - Summary of the preparatory work on the Inert Ingredient case study

$C_{12}H_{21}O_7SNA$



Preamble : This document presents a report summarizing the questionnaire responses submitted as part of the OECD IATA Workshop exercise. The first few pages present the results using tables to answer several simple questions. This is followed by an annex which attempts to capture all responses submitted for this case study.

OVERALL SUMMARY PRESENTED IN A QUESTION-AND-ANSWER FORMAT:

- **How did the adequacy/confidence of a decision change with regulatory context? With successive information? By endpoint?**

The following table shows at which stage in the process, against the supplied information, the respondents were able to make a decision. One of the problems with interpretation of the data can be seen with the irritation and sensitization endpoints, where initially there was a full consensus that priority setting could be done at Phase Ib, which was reduced to non-consensus at the subsequent phases. It is not very clear why this occurred, except there were fewer respondents (5 down to 3) and one respondent changed their mind – not saying why.

Table 1 : Overview of data available at different stages and when decisions were made

		Phase Ia	Phase Ib	Phase IIa	Phase IIb
Decisions	**Priority setting**	Irritation Sensitization Cancer DevRepro Acute and chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer Dev/Repro Acute fish Chronic fish
	Classification and labeling	Irritation Sensitization Cancer DevRepro Acute and chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer Dev/Repro Acute fish Chronic fish
	Risk assessment	Irritation Sensitization Cancer DevRepro Acute and chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer Dev Repro Acute fish Chronic fish
HPV	**Basic data**	Structure Phys/chem properties			
	In-silico		QSAR results for Inert		
	Alternative data			Human Health endpoints - ADME data (absorption, distribution, metabolism, excretion)	
	Test data				
Analogue	**Basic data**		One analogue structure and physical/chemical properties		
	In-silico		QSAR results for analogue		
	In-vitro		HH - Some data on the analogue (oral LD50?,		

		Phase Ia	Phase Ib	Phase IIa	Phase IIb
			mutagenicity?)		
	Alternative data			Env end-points - "Alternative data"	
	Test data				Environmental endpoints - acute fish toxicity study Human Health Endpoints- - available cancer and repro. data for analogue

GREEN HIGHLIGHTS INDICATE A MAJORITY OF RESPONDENTS WERE ABLE TO MAKE THE DECISION INDICATED. THE ACTUAL NUMBERS CAN BE SEEN IN TABLES 3, 4 AND 5.

YELLOW HIGHLIGHTS INDICATE THAT THE RESPONDENTS WERE SPLIT, ALTHOUGH THERE MAY HAVE BEEN A MAJORITY ON ONE SIDE OF THE DECISION THE DIFFERENCE WAS NOT CONSIDERED SUFFICIENT TO WARRANT SAYING THAT THERE WAS CONSENSUS.

RED HIGHLIGHTS ARE WHERE A CLEAR MAJORITY WERE AGAINST MAKING A DECISION.

At phase Ia, in the exercise, respondents were asked whether they had a concern for the endpoint being assessed. The responses to this question are given in the summaries of the phases (see below). Subsequently the question asked was "Have you changed your mind?" This has been answered in a number of ways. For example, it might mean;

- that the respondents were moving from concern to no concern (or vice versa)
- a move from insufficient information for priority setting (or other legislative end-point) with respect to a hazard end-point to sufficiency of information for prority setting for that end-point
- that the change of mind related to a change in the level of confidence to making a specific decision, e.g. from low to high.

Comparing table 1 to table 2, it can been seen that at Phase Ib a number of decisions were amended, which does coincide with a significant number of changed minds.

Table 2 - Change of minds with succeeding phases

	No of submissions	**No of submissions**	**No of submissions**
	Phase Ib	**Phase IIa**	**Phase IIb**
Irritation	5 (4 changed minds)	3 (0 changed minds)	**6 submissions** **(4 changed minds)**
Sensitization	5 (4 changed minds)	3 (0 changed minds)	**3** **(0 changed minds)**
Cancer	5 (4 changed minds)	5 (1 changed mind)	**5** **(0 changed minds)**
Dev/Repro	5 (no changed minds)	4 (0 chenged minds)	**4** **(2 changed minds)**
Acute Fish	3 (2 changed minds)	2 (1 changed mind)	**2** **(1 changed mind)**
Chronic Fish	**3** **(2 changed minds)**	**2** **(0 changed mind)**	**2** **(0 changed minds)**

The following three tables show the actual numbers of respondents that felt that a decision could be made, at each phase and for each end-point. The data in parenthesis also highlight the confidence at which these decisions were being made.

Table 3 – Sufficiency of information by regulatory endpoint – Priority Setting

	Phase Ia		**Phase Ib**		**Phase IIa**		**Phase IIb**	
	YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	0	4 (all H)	5 (2H, 3M)	0	2 (H, M)	1 (H)	2 (H, M)	**1 (H)**
Sensitization	0	4 (all H)	5 (2H, 3M)	0	2 (H, M)	1 (M)	1 (H)	**2 (H, M)**
Cancer	0	3 (all H)	5 (2H, 2M, L)	0	4 (H, 3M)	1 (H)	5 (2H, 3M)	**0**
Dev/Repro	0	4 (all H)	**1 (M)**	**4 (3H, M)**	**0**	**4 (3H, M)**	3 (2H, M)	**1 (H)**
Acute Fish	1 (M)	3 (1H and 2M)	3 (H, 2M)	0	2 (H, M)	0	2 (both H)	**0**
Chronic Fish	**1 (M)**	**3 (2H, M)**	**3 (H, M, L)**	**0**	**2 (H/L)**	**0**	**2 (H,L)**	**0**

Table 4 – Sufficiency of information by regulatory endpoint – Classification and Labeling

	Phase Ia		**Phase Ib**		**Phase IIa**		**Phase IIb**	
	YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	0	4 (all H)	2 (H,M)	3 (3H)	1 (H)	2 (2 H)	1 (H)	**2 (all H)**
Sensitization	0	4 (all H)	2 (H,M)	3 (3H)	1 (H)	2 (2 H)	1 (H)	**2 (all H)**
Cancer	0	3 (all H)	3 (all M)	2 (H, L)	3 (all M)	2 (H, M)	2 (2M)	**3 (2H, M)**
Dev/Repro	0	4 (all H)	**0**	**5 (4H, 1M)**	**1 (M)**	**3 (2H, M)**	3 (H, M, L)	**1 (H)**
Acute Fish	1 (M)	3 (1H and 2M)	1 (H)	2 (H, M)	2 (H, M)	0	2 (both H)	**0**
Chronic Fish	**1 (M)**	**3 (H, 2 M)**	**1 (H)**	**2 (H, M)**	**1 (H)**	**1 (H)**	**1 (H)**	**1 (H)**

Table 5 – Sufficiency of information by regulatory endpoint – Risk Assessment

	Phase Ia		**Phase Ib**		**Phase IIa**		**Phase IIb**	
	YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	0	4 (all H)	2 (H, M)	3 (3H)	1 (H)	2 (2 H)	1 (H)	**2 (all H)**
Sensitization	0	4 (all H)	2 (H, M)	3 (3H)	1 (H)	2 (2 H)	1 (H)	**2 (all H)**
Cancer	0	3 (all H)	2 (2M)	3 (2H, M)	2 (M, L)	3 (all H)	3 (H, M, L)	**2 (both H)**
Dev/Repro	0	4 (all H)	**0**	5 (4H, 1M)	**0**	4 (3H, M)	2 (H, M)	**2 (H, M)**
Acute Fish	1	3 (2H and M)	1 (H)	2 (2H)	1 (H)	1 (H)	2 (H, M)	**0**
Chronic Fish	**1 (M)**	**3 (3H)**	**1 (H)**	**2 (2H)**	**1 (H)**	**1 (H)**	**1 (H)**	**1 (H)**

GREEN HIGHLIGHTS INDICATE A MAJORITY OF RESPONDENTS WERE ABLE TO MAKE THE DECISION INDICATED.

YELLOW HIGHLIGHTS INDICATE THAT THE RESPONDENTS WERE SPLIT, ALTHOUGH THERE MAY HAVE BEEN A MAJORITY ON ONE SIDE OF THE DECISION THE DIFFERENCE WAS NOT CONSIDERED SUFFICIENT TO WARRANT SAYING THAT THERE WAS CONSENSUS.

RED HIGHLIGHTS ARE WHERE A CLEAR MAJORITY WERE AGAINST MAKING A DECISION.

- **What was the turning point (in terms of amount and type of information) that resulted in a majority opinion for a given decision?**

By endpoint this has been summarised above, it can be seen that generally, by regulatory endpoint

- priority setting was agreed by the end of Phase Ib with the exception of developmental reprotoxicity, which required phase IIb.
- classification and labelling for the human health endpoints never reached a consensus except for acute fish at phase IIa and developmental reprotoxicity at Phase IIb.
- risk assessment never reached a consensus for any of the endpoints except for acute toxicity to fish.

- **When participants were not able to make a decision, were the suggested information/approaches identified as missing similar across endpoints?**

Some of the requests were similar, but these were very broad, e.g. suggestions for (Q)SARs, other analogueues, use of the OECD Toolbox. Other than experimental in-vivo testing specific information relating to the endpoint was normally targeted, e.g. in-vitro tests, LLNA. Other data was more general but then confined either to the Human Health endpoints (ADME information, metabolism information) or the environmental endpoints (biodegradation).

The following table highlights the type of data requests made at different points in the exercise by endpoint and regulatory need.

Table 6 - Type of data requested by Phase, endpoint and regulatory need

		Phase Ia	**Phase Ib**	**Phase IIa**	**Phase IIb**
Irritation	PS	pH, (Q)SAR, in-vitro, analogue	(Q)SAR, analogue info	Analogue, (Q)SAR,	Analogue, (Q)SAR,
	C&L	pH, (Q)SAR, in-vitro, analogue	(Q)SAR, analogue info	Analogue, (Q)SAR, TD	Analogue, (Q)SAR, defatting info, TD
	RA	pH, (Q)SAR, in-vitro, analogue, exposure info	(Q)SAR, analogue info	Analogue, (Q)SAR, TD	Analogue, (Q)SAR, TD
Sensitisation	PS	pH, (Q)SAR, in-vitro, analogue	(Q)SAR, analogue info	Analogue , (Q)SAR, TD, in-vitro, LLNA	
	C&L	pH, (Q)SAR, in-vitro, analogue	(Q)SAR, analogue info	Analogue , (Q)SAR, OECD toolbox, metabollism, protein binding, TD, in-vitro,	Analogue , (Q)SAR, OECD toolbox, metabollism, protein binding, TD, in-vitro,
	RA	pH, (Q)SAR, in-vitro, analogue, exposure info	(Q)SAR, analogue info	Analogue , (Q)SAR, OECD toolbox, metabollism, protein binding, TD, in-vitro, LLNA-DNEL	Analogue , (Q)SAR, OECD toolbox, metabollism, protein binding, TD, in-vitro, LLNA-DNEL
Cancer	PS	SAR, genotox, analogue, chronic	(Q)SAR, analogue info		

		Phase Ia	Phase Ib	Phase IIa	Phase IIb
		toxicity, steric, electronic parameters			
	C&L	SAR, genotox, analogue, chronic toxicity, steric, electronic parameters	(Q)SAR, analogue info, TD for genotoxicity or carcinogenicity	(Q)SAR, analogue info, TD for genotoxicity or carcinogenicity	TD for genotoxicity or carcinogenicity + ADME
	RA	Above plus dose-response, exposure info	(Q)SAR, analogue info, 2y cancer bioassay	(Q)SAR, analogue info, 2 y cancer bioassay, ADME	, 2 y cancer bioassay, - 2 species + ADME
Dev/Repro	PS	(Q)SAR, in-vitro, analogue, metabolite info	(Q)SAR, analogue info	(Q)SAR, analogue Categorisation, TD	
	C&L	(Q)SAR, in-vitro, analogue, metabolite info	(Q)SAR, analogue info, ED, info on human fertility	(Q)SAR, analogue Categorisation, TD, info on human fertility,	TD – 2 species
	RA	(Q)SAR, in-vitro, analogue, metabolite info, exposure info	(Q)SAR, analogue info, ED, info on human fertility	(Q)SAR, analogue Categorisation, TD, info on human fertility, 2-gen study	TD – 2 species
Acute fish	PS	ECOSAr, ANALOGUE info, PBT profiler,TD[1]			
	C&L	ECOSAr, ANALOGUE info, PBT profiler,TD[1]	ED, phys-chem data		
	RA	ECOSAr, ANALOGUE info, PBT profiler,TD[1]	ED, phys-chem data	TD on chemical	
Chronic fish	PS	ECOSAr, ANALOGUE info, PBT profiler,TD[1]	PBT profiler, analogue info	PBT profiler, analogue info	
	C&L	ECOSAr, ANALOGUE info, PBT profiler,TD[1]	PBT profiler, analogue info	PBT profiler, analogue info	
	RA	ECOSAr, ANALOGUE info, PBT profiler,TD[1]	PBT profiler, analogue info, ED	PBT profiler, analogue info, ED	Chronic study + histopathology

1 : Experimental data; 2 : Mode of action – OECD TG 404; 3 : Weight of evidence approach

- **In terms of regulatory context (priority setting, class/label, risk assessment), how much information do you need to inform a decision?**

Unfortunately this is not possible to answer for C&L and risk assessment, for these endpoints the actual scheme being applied was different across many of the respondents, and in some schemes,

e.g. GHS and REACH specific data requirements were identified as being needed before a decision could be made. In some cases this meant that some respondents were not able to make a decision with out test data on the target chemical.. For priority setting it would seem that once people have a structure, some phys-chem data, some predictions, analogueues (with data) and some limited experimental data on the target compound, there were reasonably comfortable making this decision.

DETAILED QUESTIONNAIRE RESPONSES BY PHASES

Phase Ia

Information provided :

- Structure
- Physical/chemical properties

Phase Ia Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	4 2 with concern	0	4 (all H)	0	4 (all H)	0	**4** **(all H)**
Sensitization	4 2 with concern	0	4 (all H)	0	4 (all H)	0	**4** **(all H)**
Cancer	3 1 with concern	0	3 (all H)	0	3 (all H)	0	**3** **(all H)**
Dev/Repro	4 1 with concern	0	4 (all H)	0	4 (all H)	0	**4** **(all H)**
Acute Fish	4 2 with concern	1 (M)	3 (1H and 2M)	1 (M)	3 (1H and 2M)	1	**3** **(2H and M)**
Chronic Fish	**4** **2 with concern**	**1** **(M)**	**3** **(2H, M)**	**1** **(M)**	**3** **(H, 2 M)**	**1** **(M)**	**3** **(3H)**

Notes (Based on the three main questions in the questionnaire)

Do you have a hazard concern:

- For dermal irritation and sensitization, concern was based on the logKow and Mwt, both of which suggested that the chemical could penetrate the epidermis and as a default, due to lack of data.
- With respect to cancer and developmental reprotoxicity, the lack of obvious alerts made assessment difficult.
- For acute and chronic toxicity to fish, the solubility, limited volatility and lack of data were the reasons for concern. A further concern was the potential for surfactant activity.

Do you have sufficient information:

Sensitisation/irritancy/CancerDevelopmental/acut fish/chronic fish toxicity – insufficient data.

What further information is required:

- The requirement for improving the decision making ranged from (Q)SAR information, analogue data, pH (skin endpoints) and experimental information

Phase Ib

Information provided :

- One analogue structure and physl/chem properties
- QSAR results for Inert and analogue

HH - Some data on the analogue (oral LD50?, mutagenicity?)

Phase Ib Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	5 (4 changed minds)	5 (2H, 3M)	0	2 (H,M)	3 (3H)	2 (H, M)	**3** **(3H)**
Sensitization	5 (4 changed minds)	5 (2H, 3M)	0	2 (H,M)	3 (3H)	2 (H, M)	**3** **(3H)**
Cancer	5 (4 changed minds)	5 (2H, 2M, L)	0	3 (all M)	2 (H, L)	2 (2M)	**3** **(2H, M)**
Dev/Repro	5 (no changed minds)	1 (M)	4 (3H, M)	0	5 (4H, 1M)	0	**5** **(4H, 1M)**
Acute Fish	3 (2 changed minds)	3 (H, 2M)	0	1 (H)	2 (H, M)	1 (H)	**2** **(2H)**
Chronic Fish	**3** **(2 changed minds)**	**3** **(H, M, L)**	**0**	**1** **(H)**	**2** **(H, M)**	**1** **(H)**	**2** **(2H)**

Note re concern; There is no obvious evidence that this has changed at this stage. However, as phrased, the questionnaire does not ask this question. The question asked is "Have you changed your mind?" This is answered in many ways. In this case, despite 5 respondents moving from insufficient information for priority setting with respect to dermal irritation and sensitization, to all 8 thinking there is sufficient information, none of them responded that they had changed their minds. In other end-points where a change of mind was noted, the explanation usually related to the legal framework (e.g. risk assessment) and not to a change in concern, however, in some cases the change of mind related to a change in the level of confidence making a specific decision.

Do you have a hazard concern:

Cannot be answered very easily. Firstly the questionnaire does not ask this question, secondly the number/identity of respondents changed from phase to phase.

Do you have sufficient information:

Priority setting :

- All respondents agreed there was sufficient information for priority setting for dermal irritation and sensitization (although the data was noted as being less certain).
- All agreed this was also possible for carcinogenicity. The level of confidence was variable caused be differing weights being given to the analogue data and the degree of interpretation made.
- For developmental reprotoxicity, however, the majority felt there was insufficient information, quoting the lack of data.
- With respect to the two environmental endpoints, there was sufficient information now for priority setting for both endpoints, confidence varied, especially for the chronic endpoint, due to the discrepancy between the target and analogue..

C&L:

- Human Health endpoints
    - Irritation and sensitization – split opinion. It was clear the substance was an irritant, but the level of information would be insufficient for a tiered classification system. For sensitization the data was equivocal.
    - Cancer – a slight majority (3:2) felt that classification was possible. Again caused by the extent to which respondents felt they wanted to read-across and interpret the data on the analogue.
    - Developmental reprotoxicity – no decision possible – insufficient data
- Environmental endpoints
    - Acute/chronic toxicity – 1 for classification 2 against – this primarily reflects the difference between classification systems

Risk assessment:

- Dermal irritation – 2 out of 5 were able to agree that risk assessment was possible (at least for irritancy).
- Cancer – now a slight majority against risk assessment (2:3). Those for argued that genotoxicity was unlikely, those against were arguing for more extensive data (e.g. a 2y study).
- Developmental reprotoxicity – All responses indicated insufficient information, high level of confidence.
- Acute/chronic fish – difference primarily reflects the extent of data with which some will conduct a tiered risk assessment.

What further information is required:

- The requirement for improving the decision making ranged from (Q)SAR information, analogue data and experimental information.
- A PNEC (quantitative data) was suggested for risk assessment, a requirement which would normally only be met with experimental information on the chemical being assessed.
- For the environmental endpoints further phys-chem data were suggested as well as exposure data.
- In-vitro assays were specifically requested. In at least on case, e.g. a 2 year cancer bioassay was requested.

Was the analogue(ues) OK?

In nearly every case the analogueue was seen as being relevant and identified as being in the same category as the target chemical and similar functional groups. The fact that the analogue had a longer fatty acid chain was a concern in the environmental endpoints (possibly higher toxicity). A number of responses requested extra information, e.g. Tanamoto index of similarity.

Phase IIa

Information provided :

Environmental endpoints - - "Alternative" test data (acute aquatic invertebrate) on analogue

Human Health Endpoints- ADME data (absorption, distribution, metabolism, excretion) for Inert

Phase IIa Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	NO	YES	NO	YES	**NO**
Irritation	3	2	1	1	2	1	**2**
	(0 changed minds)	(H, M)	(H)	(H)	(2 H)	(H)	**(2 H)**
Sensitization	3	2	1	1	2	1	**2**
	(0 changed minds)	(H, M)	(M)	(H)	(2 H)	(H)	**(2 H)**
Cancer	5	4	1	3	2	2	**3**

	(1 changed mind)	(H, 3M)	(H)	(all M)	(H, M)	(M, L)	**(all H)**
Dev/Repro	4	0	4	1	3	0	**4**
	(0 chenged minds)		(3H, M)	(M)	(2H, M)		**(3H, M)**
Acute Fish	2	2	0	2	0	1	**1**
	(1 changed mind)	(H, M)		(H, M)		(H)	**(H)**
Chronic Fish	**2**	**2**	**0**	**1**	**1**	**1**	**1**
	(0 changed mind)	**(H/L)**		**(H)**	**(H)**	**(H)**	**(H)**

Do you have sufficient information:

Priority setting : The opinion was split 50:50 about whether there was sufficient information for priority setting for dermal irritation and sensitization. The data provided did not seem to have provided much extra information. For cancer a majority were able to make a decision on priority setting. For developmental reprotoxicity, all respondents agreed that there was insufficient data.

With respect to the two environmental endpoints, there was sufficient information now for priority setting, with respect to acute and chronic fish.

C&L:

- Human Health endpoints –
    - Sensitization/Irritation – mixed opinions, conflicting opinions on interpretation and extent to which the data was sufficient for a tiered classification scheme.
    - Cancer – again differing views about the analogue and validity/sufficiency of the read-across.
    - DevReprotox – a majority in favour of insufficient data – one respondent was able to make a decision using the rapid metabolisation and clearance data.
- Environmental endpoints – the data was sufficient for acute toxicity to fish. For chronic toxicity, however, the opinion was split with one respondent requiring further additional phys-chem and explosivity data.

Risk assessment:

- Dermal irritation/sensitization - insufficient information
- Cancer – differing interpretations of the data and relevancy for risk assessment.
- Developmental reprotoxicity – all agreed that the data was insufficient.
- Acute fish – the two respondents disagreed about the ability to interpret the data and with the no respondent not being able to compute a PNEC and there being no exposure data
- For chronic fish toxicity – opinion was split, with the no respondent not being able to compute a PNEC and there being no exposure data

What further information is required:

- Sensitization – in-vitro data, good human data analogue data
- Irritation – in-vitro or analogue data
- Cancer – in-vivo data for C&L and RA, including a suggestion of a 2y cancer bioassay. More analogues and more data on the analogues were also mentioned.
- For the developmental reprotoxicity more (Q)SAR, analogue and experimental data were requested, including a 2y gen study.
- For the environmental endpoints – at the acute level, information needs extended to experimental information on the product
- For the chronic toxicity to fish endpoint data from the PBT profiler and in-vivo bioassays was requested.

Phase IIb

Information provided :
Environmental endpoints - - acute fish toxicity study on analogue

Human Health Endpoints- - available cancer and repro. data for analogue

Phase IIb Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	NO	YES	NO	YES	**NO**
Irritation	6 submissions (4 changed minds)	2 (H, M)	1 (H)	1 (H)	2 (all H)	1 (H)	**2 (all H)**
Sensitization	3 (0 changed minds)	1 (H)	2 (H, M)	1 (H)	2 (all H)	1 (H)	**2 (all H)**
Cancer	5 (0 changed minds)	5 (2H, 3M)	0	2 (2M)	3 (2H, M)	3 (H, M, L)	**2 (both H)**
Dev/Repro	4 (2 changed minds)	3 (2H, M)	1 (H)	3 (H, M, L)	1 (H)	2 (H, M)	**2 (H, M)**
Acute Fish	2 (1 changed mind)	2 (both H)	0	2 (both H)	0	2 (H, M)	**0**
Chronic Fish	**2 (0 changed minds)**	**2 (H,L)**	**0**	**1 (H)**	**1 (H)**	**1 (H)**	**1 (H)**

Do you have sufficient information:

Priority setting : Disagreement about the interpretation of the data (irritancy) and sufficiency (sensitization). For cancer all respondents felt that there was sufficient data for making a decision and developmental toxicity a majority were able to make a decision on priority setting.

With respect to the two environmental endpoints, there was sufficient information now for priority setting, with respect to acute and chronic toxicity to fish.

C&L:

- Human Health endpoints
    - For irritation and sensitization, respondents were split as to whether the information was sufficient.
    - Cancer – The respondents were split, those against making a decision wanted more data, expressing a preference for in-vivo data.
    - Developmental toxicity – a majority now felt that a decision on C&L could be made (although with a wide range of confidence).
- Environmental endpoints – both responses felt that C&L (at acute) could be conducted, saying that the toxicity was known reasonable well.
- For chronic toxicity the two respondents disagreed, but this is mainly due to two different classification systems being addressed

Risk assessment:

- Dermal irritation – still insufficient data especially relating to quantitative information needed for a risk assessment e.g. a dose-response.
- Cancer – Again a split decision, with a difference of opinion of the validity and usefulness of the data provided..
- Developmental reprotoxicity – 50:50 split over the decision – differing views about the utility of the data and the extent it covered the risk assessment endpoint.
- Acute fish toxicity – possible, data across predictions and analogue consistent and application factor can be applied.
- chronic fish toxicity – again opinion was split, with different ways of addressing the information available, one saying there was no dose response the other using the available acute LC50.

What further information is required:

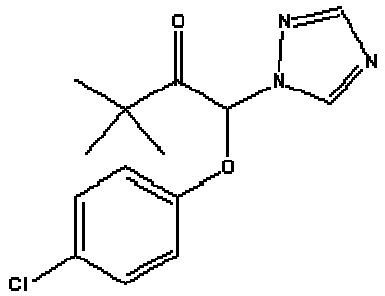
- Human Health endpoints
    - Sensitization/irritancy - The requirement for improving the decision making indicated a preference for experimental information, although in-vitro data was also requested.
    - Cancer – preference for in-vivo cancer bioassays.
    - DevTox – A developmental toxicity study on either analogue or the inert (in one case a request for 2 studies on different species was made).
- For acute fish endpoint no extra data requested
- For the chronic endpoint one respondent wanted a chronic test.

Was the analogue(ues) OK?

The analogueues were generally seen as helpfu

<u>ANNEX IIIC</u> - Summary of the preparatory work on the Pesticide Active Ingredient case study

$C_{14}H_{16}ClN_3O_2$



Preamble : This document presents a report summarizing the questionnaire responses submitted as part of the OECD IATA Workshop exercise. The first few pages present the results using tables to answer several simple questions. This is followed by an annex which attempts to capture all responses submitted for this case study.

OVERALL SUMMARY PRESENTED IN A QUESTION-AND-ANSWER FORMAT:

- **How did the adequacy/confidence of a decision change with regulatory context? With successive information? By endpoint?**

The following table shows at which stage in the process, against the supplied information, the respondents were able to make a decision

Table 1 : Overview of data available at different stages and when decisions were made

		Phase Ia	**Phase Ib**	**Phase IIa**	**Phase IIb**	**Phase IIc**
Decisions	**Priority setting**	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish
	Classification and labeling	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish
	Risk assessment	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish	Irritation Sensitization Cancer DevRepro Acute fish Chronic fish
Pesticide	**Basic data**	Structure & Physical/chemical properties				

		Phase Ia	Phase Ib	Phase IIa	Phase IIb	Phase IIc
	In-silico		QSAR results for a.i			
	In-vitro					in vitro and 'omics data
	Alternative data					
	Test data					acute invertebrate
Analogue	**Basic data**		One analogue structure and phys/chem properties			
	In-silico		QSAR results for analogue			
	In-vitro			ADME data (absorption, distribution, metabolism, excretion) for AI		
	Alternative data			" Alternative data" available for analogue (acute and chronic invertebrate, in vitro fish?)	"Alternative data" available for analogue	
	Test data		HH Some data on the analogue (oral LD50?, mutagenicity?) Environment acute fish toxicity study on analogue		available data for one or more analogue(s)	

GREEN HIGHLIGHTS INDICATE A MAJORITY OF RESPONDENTS WERE ABLE TO MAKE THE DECISION INDICATED. THE ACTUAL NUMBERS CAN BE SEEN IN TABLES 3, 4 AND 5.

YELLOW HIGHLIGHTS INDICATE THAT THE RESPONDENTS WERE SPLIT, ALTHOUGH THERE MAY HAVE BEEN A MAJORITY ON ONE SIDE OF THE DECISION THE DIFFERENCE WAS NOT CONSIDERED SUFFICIENT TO WARRANT SAYING THAT THERE WAS CONSENSUS.

RED HIGHLIGHTS ARE WHERE A CLEAR MAJORITY WERE AGAINST MAKING A DECISION.

At phase Ia, in the exercise, respondents were asked whether they had a concern for the endpoint being assessed. The responses to this question are given in the summaries of the phases (see below). Subsequently the question asked was "Have you changed your mind?" This has been answered in a number of ways. For example, it might mean;

- that the respondents were moving from concern to no concern (or vice versa)
- a move from insufficient information for priority setting (or other legislative end-point) with respect to a hazard end-point to sufficiency of information for prority setting for that end-point
- that the change of mind related to a change in the level of confidence to making a specific decision, e.g. from low to high.

Comparing table 1 to table 2, it can been seen that at Phase Ib and IIb a number of decisions were amended, which does coincide with a significant number of changed minds in the table below.

Table 2 – Change of minds with succeeding phases

	No of submissions	**No of submissions**	**No of submissions**	**No of submissions**
	Phase Ib	Phase IIa	Phase IIb	**Phase IIc**
Irritation	7 (6 changed minds)	4 (no changed minds)	5 (4 changed minds)	**4** **(0 changed minds)**
Sensitization	7 (1 changed mind)	4 (no changed minds)	5 (4 changed minds)	
Cancer	6 (3 changed minds)	4 (1 changed mind)	4 (1 changed mind)	**2** **(1 changed mind)**
Dev/Repro	5 (1 changed mind)	4 (2 changed minds)	3 (2 changed minds)	**3** **(1 changed mind)**
Acute Fish	4 (1 changed mind)	3 (0 changed minds)	2 (1 changed mind)	**3** **(0 changed minds)**
Chronic Fish	**3** **(2 changed minds)**	**2** **(0 changed minds)**	**1**	**1** **(did not change minds)**

The following three tables show the actual numbers of respondents that felt that a decision could be made, at each phase and for each end-point. The data in parenthesis also highlight the confidence at which these decisions were being made.

Table 3 – Sufficiency of information by regulatory endpoint – Priority Setting

	Phase Ia		**Phase Ib**		**Phase IIa**		**Phase IIb**		**Phase IIc**	
	YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	2 (M,L)	4 (4H)	4 (H, 2M, L)	3 (H, 2M)	3 (H, M, L)	1 (H)	4 (2H, L)	1 (L)	2 (H, L)	**1 (L)**
Sensitization	1	5	4 (H, 2M, L)	3 (H, 2M)	2 (H, M)	2 (H, M)	4 (2H, M)	1 (L)	2 (H, M)	**1 (L)**
Cancer	1 (L)	3 (all H)	4 (H, 2M, L)	2 (H, L)	2 (H, M)	2 (H, L)	2 (H, M)	0	1 (H)	**0**
Dev/Repro	2 (H, L)	2 (both H)	3 (H, M, L)	2 (M,L)	4 (2H, M, L)	0	3 (2H, L)	0	2 (H, L)	**1 (M)**
Acute Fish	6	1	3 (H, 2M)	1 (H)	3 (2H, M)	0	2 (both H)	0	2 (H, ?)	**0**
Chronic Fish	**6**	**0**	**2 (H, M)**	**1 (L)**	**2 (H, M)**	**0**	**1 (H)**	**0**	**1 (H)**	**0**

Table 4 – Sufficiency of information by regulatory endpoint – Classification and Labeling

	Phase Ia		**Phase Ib**		**Phase IIa**		**Phase IIb**		**Phase IIc**	
	YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	0	6 (4H, M, L)	0	7 (4H, 3M)	0	4 (2H, 2M)	2 (H, L)	2 (H, M)	1 (H)	**2 (H, M)**
Sensitization			0	7 (4H, 3M)	0	4 (2H, 2M)	1 (H)	3 (2H, M)	2 (H, L)	**1 (M)**

Cancer	0	5 (3 H, 2 L)	1 (M)	5 (4H, L)	1 (M)	3 (2H, L)	1 (L)	0	1 (H)	0
Dev/Repro	0	5 (3H, 2L)	0	5 (2H, M, 2L)	1 (M)	3 (2H, L)	1 (H)	2 (H, L)	1 (H)	**2 (H, M)**
Acute Fish	0	7	1 (M)	3 (H)	1 (H)	2 (both H)	1 (H)	1 (H)	1 (H)	**1 (?)**
Chronic Fish	**0**	**6**	**0**	**3 (2H, M)**	**0**	**2 (all H)**	**0**	**1 (H)**	**0**	**1 (H)**

Table 5 – Sufficiency of information by regulatory endpoint – Risk Assessment

	Phase Ia		**Phase Ib**		**Phase IIa**		**Phase IIb**		**Phase IIc**	
	YES	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	0	6 (4H, M, L)	0	7 (6H, M)	0	4 (3H, M)	2 (all H)	2 (H, M)	0	**3 (2H, M)**
Sensitization			0	7 (6H, M)	0	4 (3H, M)	2 (all H)	2 (H, M)	0	**3 (3H)**
Cancer	0	5 (3 H, 2 L)	0	6 (5H, L)	0	4 (3H, L)	2 (M, L)	0	1 (M)	**0**
Dev/Repro	1	4 (3H, L)	1 (M)	4 (3H, L)	0	4 (3H, M)	2 (2M)	1 (H)	1 (M)	**2 (all H)**
Acute Fish	2	5	0	4 (all H)	1 (M)	2 (both H)	1 (H)	1 (H)	1 (H)	**1 (?)**
Chronic Fish	2	4	0	**3 (2H, M)**	0	**2 (all H)**	0	**1 (H)**	0	**1 (H)**

GREEN HIGHLIGHTS INDICATE A MAJORITY OF RESPONDENTS WERE ABLE TO MAKE THE DECISION INDICATED.

YELLOW HIGHLIGHTS INDICATE THAT THE RESPONDENTS WERE SPLIT, ALTHOUGH THERE MAY HAVE BEEN A MAJORITY ON ONE SIDE OF THE DECISION THE DIFFERENCE WAS NOT CONSIDERED SUFFICIENT TO WARRANT SAYING THAT THERE WAS CONSENSUS.

RED HIGHLIGHTS ARE WHERE A CLEAR MAJORITY WERE AGAINST MAKING A DECISION.

What was the turning point (in terms of amount and type of information) that resulted in a majority opinion for a given decision?

By endpoint this has been summarised above, it can be seen that generally, by regulatory endpoint

- Priority setting was agreed by the end of Phase Ia for fish acute (and chronic???) toxicity, phase IIa for Developmental toxicity and irritation, and Phase IIb for cancer and sensitisation.
- Classification and labelling for all endpoints never reached a consensus except for cancer at Phase IIb.
- Risk assessment also never reached a consensus for any of the endpoints, again with the exception of cancer, again at phase IIb.

❖ **When participants were not able to make a decision, were the suggested information/approaches identified as missing similar across endpoints?**

Some of the requests were similar, but these were very broad, e.g. suggestions for (Q)SARs, other analogueues, use of the OECD Toolbox. Other than experimental in-vivo testing specific information relating to the endpoint was normally targeted, e.g. in-vitro tests, LLNA. Other data was more general but then confined either to the Human Health endpoints (ADME information, metabolism information) or the environmental endpoints (biodegradation).

The following table highlights the type of data requests made at different points in the exercise by endpoint and regulatory need.

Table 6 - Type of data requested by Phase, endpoint and regulatory need

Endpoint	Reg. Need	Phase Ia	Phase Ib	Phase IIa	Phase IIb	Phase IIc
Irritation	PS	pH, in-vitro, analogue (Q)SAR	(Q)SAR, glutathione and patch tests, analogue	(Q)SAR, WoE, in-vitro, analogue		
	C&L	pH, in-vitro, analogue (Q)SAR	(Q)SAR, glutathione and patch tests, analogue	(Q)SAR, WoE, in-vitro, analogue, ED	WoE : (Q)SAR, in-vitro, analogue, pH	WoE : (Q)SAR, in-vitro, analogue, pH
	RA	(Q)SAR, ED[1], in-vitro, analogue	(Q)SAR, glutathione and patch tests, analogue	(Q)SAR, WoE, in-vitro, analogue, ED	WoE : (Q)SAR, in-vitro, analogue, ED	WoE : (Q)SAR, in-vitro, analogue, ED
Sensitization	PS	in-vitro, analogue (Q)SAR	(Q)SAR, analogue, reactivity information	WoE : (Q)SAR, in-vitro, analogue	LLNA	LLNA
	C&L	pH, in-vitro, analogue (Q)SAR	(Q)SAR, analogue, reactivity information	(Q)SAR, WoE, in-vitro, analogue, ED	LLNA, analogue	LLNA, analogue
	RA	(Q)SAR, ED[1], in-vitro, analogue	(Q)SAR, analogue, reactivity information	(Q)SAR, WoE, in-vitro, analogue, ED	LLNA, ED	LLNA, ED
Cancer	PS	(Q)SAR, read-across, in-vitro and ED	WoE[3], Genotox battery, analogues, metabolite info, genomics and proteonomics	WoE[3], Genotox battery, analogues, metabolite info, genomics and proteonomics		
	C&L	Read-across, ED, genomics, proteonomics, metabolite data (including ED)	WoE[3], Genotox battery, analogues, metabolite info, genomics and proteonomics	WoE[3], Genotox battery, analogues, metabolite info, genomics and proteonomics, ADME	ED (2 species)	In-vitro, ED-especially mechanistic data
	RA	DNEL/NOAEL plus all the above	Above plus life-time bioassay, NOAEL/LOAEL	Above plus life-time bioassay, NOAEL/LOAEL	ED (2 species)	In-vitro, ED-especially mechanistic data
Dev/Repro	PS	(Q)SAR ED, analogue, genomics, proteonomics	(Q)SAR ED, analogue, genomics, proteonomics	: (Q)SAR, analogue,		
	C&L	(Q)SAR ED, analogue,	(Q)SAR ED, analogue,	WoE : (Q)SAR, analogue,	WoE : (Q)SAR,	WoE : (Q)SAR,

Endpoint	Reg. Need	Phase Ia	Phase Ib	Phase IIa	Phase IIb	Phase IIc
		genomics, proteonomics	genomics, proteonomics	genomics, proteonomics, ADME	analogue, genomics, proteonomics, ADME	analogue, genomics, proteonomics, ADME
	RA	(Q)SAR ED, analogue, genomics, proteonomics	(Q)SAR ED, analogue, genomics, proteonomics, NOAEL/LOAEL	WoE : (Q)SAR, analogue, genomics, proteonomics, ADME , Use pattern, ED	WoE : (Q)SAR, analogue, genomics, proteonomics, ADME , Use pattern, ED, NOAEL	WoE : (Q)SAR, analogue, genomics, proteonomics, ADME , Use pattern, ED, NOAEL
Acute fish	PS	MoA and reactivity, (Q)SAR, read-across/analogue, OECD toolbox				
	C&L	MoA and reactivity, (Q)SAR, read-across/analogue, OECD toolbox, ED	Phys-chem data (explosivity etc), MoA, ED	Phys-chem data (explosivity etc), MoA, ED, fate	Phys-chem data (explosivity etc), MoA, ED, fate	
	RA	MoA and reactivity, (Q)SAR, read-across/analogue, OECD toolbox, ED, fate info	Phys-chem data (explosivity etc), MoA, ED, PNEC	Phys-chem data (explosivity etc), MoA, ED, fate	Data on aq plants/algae and the AI	Mechanism data
Chronic fish	PS	MoA and reactivity, (Q)SAR, read-across/analogue, OECD toolbox				
	C&L	MoA and reactivity, (Q)SAR, read-across/analogue, OECD toolbox, ED	Phys-chem data (explosivity etc), MoA, ED	Phys-chem data (explosivity etc), MoA, ED, fate	Phys-chem data (explosivity etc), MoA, ED, fate	Phys-chem data (explosivity etc), MoA, ED, fate
	RA	MoA and reactivity, (Q)SAR, read-across/analogue, OECD toolbox, ED, fate info	Phys-chem data (explosivity etc), MoA, ED, fate info	Phys-chem data (explosivity etc), MoA, ED, fate	Data on aq plants/algae and the AI	

1 : Experimental data, 2 : Mode of action – OECD TG 404, 3 : Weight of evidence approach

- **In terms of regulatory context (priority setting, class/label, risk assessment), how much information do you need to inform a decision?**

Unfortunately this is not possible to answer for C&L and risk assessment, for these endpoints the actual scheme being applied was different across many of the respondents, and in some schemes, e.g. GHS and REACH specific data requirements were identified as being needed before a decision could be made. In some cases this meant that some respondents were not able to make a decision with out test data on the target chemical. For priority setting it would seem that once people have a structure, some phys-chem data, some predictions, analogueues (with data) and some limited experimental data on the target compound, there were reasonably comfortable making this decision.

DETAILED QUESTIONNAIRE RESPONSES BY PHASES

Phase Ia

Information provided :

- Structure
- Physical/chemical properties

Phase Ia Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	6 (4 concerned)	2 (M,L)	4 (4H)	0	6 (4H, M, L)	0	**6 (4H, M, L)**
Sensitization	6 (2 concerned)	1	5				
Cancer	4 (all concerned)	1 (L)	3 (all H)	0	5 (3 H, 2 L)	0	**5 (3 H, 2 L)**
Dev/Repro	5 (all concerned)	2 (H, L)	2 (both H)	0	5 (3H, 2L)	1	**4 (3H, L)**
Acute Fish	7 (6 concerned)	6	1	0	7	2	**5**
Chronic Fish	**6 (5 concerned)**	**6**	**0**	**0**	**6**	**2**	**4**

Notes(Based on the three main questions in the questionnaire)

Do you have a hazard concern:

- For dermal irritation and sensitization, concern was based primarily on the absence of information – default assumption.
- With respect to cancer and developmental reprotoxicity, the class of chemicals and potential structural alerts were all mentioned.
- In the case of acute and chronic fish toxicity again the class of chemical was identified and discussed.

Do you have sufficient information:

- Dermal irritation – Insufficient data
- Dermal sensitization - Insufficient data
- Cancer – Insufficient data
- Dev Tox – For Priority Setting there was a split decision, however, for the Classification and Risk Assessment the data was insufficient
- Acute toxicity – Priority Setting – yes sufficient to prioritise for further testing. For Classification and Risk Assessment there was a majority clearly indicating a need for further data

What further information is required:

- The requirement for irritation included pH info.
- Other requests were for in-vitro, analogue and (Q)SAR data and experimental information.
- For the environmental endpoints mechanistic information was requested, QSAR, more phys-chem data, and persistence
- For the Human Health endpoints data pertaining to ADME, mode of action and in-vitro assays were also specifically requested as were proteomincs and genomic information specifically for cancer and dev tox

Phase Ib

Information provided :

- One analogue structure and physl/chem properties
- QSAR results for a.i. and analogue
- Some data on the analogue (oral LD50?, mutagenicity?)
- acute fish toxicity study on analogue

Phase Ib Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	7 (6 changed minds)	4 (H, 2M, L)	3 (H, 2M)	0	7 (4H, 3M)	0	**7 (6H, M)**
Sensitization	7 (1 changed mind)	4 (H, 2M, L)	3 (H, 2M)	0	7 (4H, 3M)	0	**7 (6H, M)**
Cancer	6 (3 changed minds)	4 (H, 2M, L)	2 (H, L)	1 (M)	5 (4H, L)	0	**6 (5H, L)**
Dev/Repro	5 (1 changed mind)	3 (H, M, L)	2 (M,L)	0	5 (2H, M, 2L)	1 (M)	**4 (3H, L)**
Acute Fish	4 (1 changed mind)	3 (H, 2M)	1 (H)	1 (M)	3 (H)	0	**4 (all H)**
Chronic Fish	**3 (2 changed minds)**	**2 (H, M)**	**1 (L)**	**0**	**3 (2H, M)**	**0**	**3 (2H, M)**

Note re concern ; There is no obvious evidence that this has changed at this stage. However, as phrased, the questionnaire does not ask this question. The question asked is "Have you changed your mind?" This is answered in many ways. In this case, despite 5 respondents moving from insufficient information for priority setting with respect to dermal irritation and sensitization, to all 8 thinking there is sufficient information, none of them responded that they had changed their minds. In other end-points where a change of mind was noted, the explanation usually related

to the legal framework (e.g. risk assessment) and not to a change in concern, however, in some cases the change of mind related to a change in the level of confidence making a specific decision.

Do you have a hazard concern:

Cannot be answered very easily. Firstly the questionnaire does not ask this question, secondly the number/identity of respondents changed from phase to phase.

Do you have sufficient information:

Priority setting :

- Dermal irritation and sensitization – the respondents were split over the data and the extent to which it was sufficiently consistent.
- Cancer – insufficient data – those who said yes indicated the presence of structural alerts, other data, all of which could be used for priority setting
- A majority for developmental reprotoxicity were able to make a decision on Priority Setting – but the confidence was mixed.
- Acute/chronic fish – a majority could now make a decision on Priority Setting.

C&L:

- Irritation and sensitization – the data (analogue and QSAR) was conflicting and/or insufficient.
- Cancer : Insufficient data for the majority of respondents
- Dev Tox : Insufficient data
- With acute/chronic fish toxicity a majority were still of the opinion that the data was insufficient.

Risk assessment:

- Irritation and sensitization – the data (analogue and QSAR) was conflicting and/or insufficient.
- Cancer – insufficient data
- Developmental reprotoxicity – All responses indicated insufficient information, high level of confidence.
- Acute/chronic fish toxicity – all agreed not – requiring experimental data (even if only on the analogue), phys-chem data, etc.

What further information is required:

- Irritation and sensitization – better (Q)SAR data, in-vitro data or data on the analogueue
- Cancer – analogue experimental data, (Q)SAR, in-vitro assays. Genomics and proteomics were also mentioned (for classification) and a NOAEL for risk assessment.
- For Dev Tox read-across, (Q)SAR, genomics and proteomics were all mentioned as extra data needs. For risk assessment a DNEL was suggested.
- For the environmental endpoints further phys-chem data were suggested and data relating to the potential fate of the substance and metabolites suggested. Information on the mode of action was also requested.

Was the analogue(ues) OK?

In nearly every case the analogueues were seen as being relevant and were generally identified as being in the same category as the target chemical. However, some responses requested extra information, e.g. Tanamoto index of similarity. In the environmental endpoints one respondent wanted an analogue from the triazole class.

Phase IIa

Information provided :
Environmental endpoints -" Alternative data" available for analogue (acute and chronic invertebrate, in vitro fish?)

Human Health Endpoints- ADME data (absorption, distribution, metabolism, excretion) for AI

Phase IIa Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	NO	YES	NO	YES	**NO**
Irritation	4 (no changed minds)	3 (H, M, L)	1 (H)	0	4 (2H, 2M)	0	**4 (3H, M)**
Sensitization	4 (no changed minds)	2 (H, M)	2 (H, M)	0	4 (2H, 2M)	0	**4 (3H, M)**
Cancer	4 (1 changed mind)	2 (H, M)	2 (H, L)	1 (M)	3 (2H, L)	0	**4 (3H, L)**
Dev/Repro	4 (2 changed minds)	4 (2H, M, L)	0	1 (M)	3 (2H, L)	0	**4 (3H, M)**
Acute Fish	3 (0 changed minds)	3 (2H, M)	0	1 (H)	2 (both H)	1 (M)	**2 (both H)**
Chronic Fish	**2 (0 changed minds)**	**2 (H, M)**	**0**	**0**	**2 (all H)**	**0**	**2 (all H)**

Do you have sufficient information:

Priority setting :

- For irritancy a slight majority agreed there was sufficient information for priority setting, but for sensitization this was split 50:50.
- For cancer, a decision on priority setting was split 50:50.
- For developmental reprotoxicity, all respondents were able to make a decision.
- With respect to the two environmental endpoints, there was sufficient information now for priority setting, with respect to acute and chronic toxicity to fish

C&L:

- Irritation and sensitization – the data (analogue and QSAR) was conflicting and/or insufficient.
- Cancer : Insufficient data for the majority of respondents. One respondent felt that there was enough data to classify the AI but more data would help.
- Dev Tox : Insufficient data
- With acute fish toxicity a majority were of the opinion that the data was insufficient especially given the proximity of the daphnia study to the 1 mg/l lower toxicity band.
- Chronic toxicity to fish – no-one could make a decision – the data was insufficient

Risk assessment:

- Irritation and sensitization – the data (analogue and QSAR) was conflicting and/or insufficient.
- Cancer – insufficient data
- Developmental reprotoxicity – All responses indicated insufficient information, high level of confidence.
- Acute fish toxicity – split opinions – one could (conservatively) the rest not requiring experimental data (even if only on the analogue) on other species
- Chronic fish toxicity – insufficient data – no NOEC

What further information is required:

- Irritation and sensitization – better (Q)SAR data, in-vitro data or data on the analogueue – trans-species data was also suggested and a weight of evidence approach identified by one respondent.
- Cancer – analogue experimental data, (Q)SAR, in-vitro assays. Gene activation and metabonomics were also mentioned. Other tests included ADME, a genotox battery, genomics, proteomics and metabolite characterisation. For risk assessment a bioassay was also suggested.
- For Dev Tox read-across, (Q)SAR, genomics and proteomics were all mentioned as extra data needs. Experimental data that addressed the endpoint were requested, Other tests included ADME, a genotox battery, genomics, proteomics and metabolite characterisation. For risk assessment a bioassay was also suggested.
- For the environmental endpoints further phys-chem data were suggested and data relating to the potential fate of the substance and metabolites suggested. Information on the mode of action was also requested. More experimental data and studies on the AI.

Phase IIb

Information provided :
Environmental endpoints - available data for one or more analogue(s)

Human Health Endpoints- "Alternative data" available for analogue

Phase IIb Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	NO	YES	NO	YES	**NO**
Irritation	5 (4 changed minds)	4 (2H, L)	1 (L)	2 (H, L)	2 (H, M)	2 (all H)	**2** **(H, M)**
Sensitization	5 (4 changed minds)	4 (2H, M)	1 (L)	1 (H)	3 (2H, M)	2 (all H)	**2** **(H, M)**
Cancer*	4 (1 changed mind)	2 (H, M)	0	1 (L)	0	2 (M, L)	**0**
Dev/Repro	3 (2 changed minds)	3 (2H, L)	0	1 (H)	2 (H, L)	2 (2M)	**1** **(H)**
Acute Fish	2 (1 changed mind)	2 (both H)	0	1 (H)	1 (H)	1 (H)	**1** **(H)**
Chronic Fish	**1**	**1** **(H)**	**0**	**0**	**1** **(H)**	**0**	**1** **(H)**

** : Not all respondents answered the questions – very brief questionnaires returned.*

Do you have sufficient information:

Priority setting :

- For both irritancy and sensitization a majority agreed there was sufficient information for priority setting
- Cancer - those that responded were of the opinion that the data was sufficient.
- For developmental reprotoxicity, all respondents were able to make a decision.
- With respect to the two environmental endpoints, there was sufficient information now for priority setting, with respect to acute. Only 1 response for chronic toxicity received.

C&L:

- Human Health endpoints
    - For irritation and sensitization, respondents were split as to whether the information was sufficient. The difference seems to be due to the extent to which different schemes allow for data or interpretation and that some respondents would classify with less data than others..
    - Cancer – only one response – this one was able to make a classification decision.
    - Developmental toxicity – a majority felt a a decision on C&L could not be made requiring more data
- Environmental endpoints – for the acute endpoint the two respondents disagreed as to whether the data was sufficient. However, they were both from very different classification schemes.
- For chronic toxicity the one respondent did not want to make a decision.

Risk assessment:

- Dermal irritation and sensitization – still insufficient data especially relating to quantitative information needed for a risk assessment
- Cancer – 2 responses received suggesting that a risk assessment could be done.
- Developmental reprotoxicity – Majority of responses indicated the information did not address key concerns relating to developmental toxicity of the target chemical and the very limited experimental data.
- Acute fish toxicity – opinion was split, the difference being the extent to which one respondent would use the available data to "screen" a risk assessment while the other wanted more experimental data on more species.
- For chronic toxicity the one respondent did not want to make a decision.

What further information is required:

- Human Health endpoints –
    - Weight of evidence was mentioned
    - In-vitro data and (Q)SAR information
    - The requirement for improving the decision making indicated a preference for experimental information.
    - A DNEL was suggested for risk assessment, a requirement which would normally only be met with experimental information on the chemical being assessed.
- For acute fish endpoint for C&L other phys-chem and explosivity data was requested. For risk assessment more experimental data was requested.

Was the analogue(ues) OK?

- The analogueues were generally seen as helpful, although the anolog selection approach was n ot described.

Phase IIc

Information provided :
Environmental endpoints- acute invertebrate with a.i.

Human Health Endpoints- - in vitro and 'omics data for chemical of interest (ai)

Phase IIc Participant Response

	No of submissions	**Priority Setting**		**Classification & Labeling**		**Risk Assessment**	
		YES	**NO**	**YES**	**NO**	**YES**	**NO**
Irritation	4 (0 changed minds)	2 (H, L)	1 (L)	1 (H)	2 (H, M)	0	**3** **(2H, M)**
Sensitization		2 (H, M)	1 (L)	2 (H, L)	1 (M)	0	**3** **(3H)**
Cancer	2 (1 changed mind)	1 (H)	0	1 (H)	0	1 (M)	**0**
Dev/Repro	3 (1 changed mind)	2 (H, L)	1 (M)	1 (H)	2 (H, M)	1 (M)	**2** **(all H)**
Acute Fish	3 (0 changed minds)	2 (H, ?)	0	1 (H)	1 (?)	1 (H)	**1** **(?)**
Chronic Fish	**1** **(did not change minds)**	**1** **(H)**	**0**	**0**	**1** **(H)**	**0**	**1** **(H)**

Do you have sufficient information:

Priority setting :

- for priority setting for dermal irritation and sensitization the respondents were split as to the relevancy of the supplied information
- For cancer the one respondent who answered considered there was enough data for PS
- Developmental toxicity a majority were able to make a decision on priority setting,
- With respect to the two environmental endpoints, there was sufficient information now for priority setting, with respect to acute fish
- The one respondent for chronic toxicity felt the information was sufficient.

C&L:

- Human Health endpoints
    - For irritation and sensitization, respondents were split disagreeing on the extent to which the data was sufficient
    - Cancer – "It is possible to classify on this data"
    - Developmental toxicity – the respondents were split over whether the data was sufficient and allowed for a decision on the toxicity of the chemical.
- Environmental endpoints – acute toxicity to fish – split response between sufficient data and the need for more species.
- For chronic toxicity the respondent pointed out there was other data available that should be considered than that provided in this phase (public literature data)

Risk assessment:

- Dermal irritation – still insufficient or conflicting data especially relating to quantitative information needed for a risk assessment
- Cancer – The data is sufficient.
- Developmental reprotoxicity – majority were not able to make this decision saying the data was insufficient.
- Acute fish toxicity – opinion was split, exactly 50:50 at the acute toxicity endpoint, due to the interpretation of the data and how it could be used for risk assessment.
- Chronic endpoint - the respondent pointed out there was other data available that should be considered than that provided in this phase (public literature data)

What further information is required:

- Human Health endpoints –
    - The requirement for improving the decision making indicated a preference for experimental information.
    - A DNEL was suggested for risk assessment, a requirement which would normally only be met with experimental information on the chemical being assessed.
    - Exposure information for risk assessment also recommended