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Test Guidelines Programme

**FINAL REPORT OF THE OECD WORKSHOP ON HARMONIZATION OF
VALIDATION AND ACCEPTANCE CRITERIA FOR ALTERNATIVE TOXICOLOGICAL TEST
METHODS**

**Seventh Meeting of the National Co-ordinators of the Test Guidelines Programme, 18th-19th
September 1996 to be held at the Château de la Muette, Paris beginning at 09:30 a.m. on 18th
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OECD Environment, Health and Safety Publications

**FINAL REPORT OF THE OECD WORKSHOP ON HARMONIZATION OF
VALIDATION AND ACCEPTANCE CRITERIA FOR ALTERNATIVE
TOXICOLOGICAL TEST METHODS**

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

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

**Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris 2009**

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This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

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

This document is the final report of the OECD Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods, which was held on 22-24 January 1996 in Solna (Sweden). It is published on the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.

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INTRODUCTION

1. In October 1994, the 5th Meeting of the National Co-ordinators of the OECD Test Guidelines Programme agreed that an attempt should be made to internationally harmonize the various published and advocated concepts for the validation of alternative test methods. Considering the international debate on the issue, it was considered timely for the OECD to step in and provide a platform for all parties involved through which it might be possible to reach international consensus on validation and acceptance criteria. The National Co-ordinators emphasized that existing proposals should be used as the basis for an internationally acceptable approach, rather than to develop yet another concept. In this respect, the work of centers such as CAAT in the US (the Johns Hopkins University Center for Alternatives to Animal Testing), ECVAM (European Centre for the Validation of Alternative Methods) in the European Union, ERGATT (European Research Group for Alternatives to Animal Testing) and various national centers and committees such as the Fund for the Replacement of Animals in Medical Experiments (FRAME) in the UK, the Inter Regulatory Advisory Group (IRAG) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in the US, the National Centre for Alternatives (NCA) in the Netherlands, the Swiss Institute for Alternatives to Animal Testing (SIAT) in Switzerland and the Center for Documentation and Validation of Alternatives to Animal Experiments (ZEBET) in Germany was well-recognised.

2. The National Co-ordinators agreed that an OECD Workshop would be the best approach, since such a meeting would offer ample opportunity to all parties having an interest in the subject to discuss the issue and seek consensus. Further, it was considered of crucial importance that Member countries would include in their nominations individuals carrying responsibility in the regulatory area. Sweden offered to host the Workshop.

3. A Steering Committee was established in January 1995 in order to advise the Secretariat on the scope and structure of the Workshop and to assist in the development of its programme. Members of the Steering Committee were:

Bo Wahlström, KEMI, Solna, Sweden, **Chairman**
Michael Balls, ECVAM, Ispra, Italy
Mark Chamberlain, Unilever, Sharnbrook, UK
Alan Goldberg, CAAT, Baltimore, USA
Donald Grant, Pest Management Regulatory Agency, Ottawa, Canada
Richard Hill, US.EPA, Washington, USA
Nils-Gunnar Lindquist, KEMI, Solna, Sweden
Hiroshi Ono, Hatano Research Institute, Hadano, Japan
Horst Spielmann, ZEBET, Berlin, Germany
William Stokes, NIEHS, Research Triangle Park, USA
Erik Walum, Pharmacia AB, Stockholm, Sweden

4. The Steering Committee met once in Solna, Sweden on 15-16 February 1995 where they reached consensus on the objectives and scope of the Workshop. A second meeting of the Steering Committee, arranged as two telephone conference calls, was held on 11 and 13 October 1995. During this meeting the Steering Committee agreed on the final programme, speakers, co-chairs, rapporteurs, background documents to be used during the discussions of the three break-out Working Groups and on the list of centers, committees and organisations to be invited in addition to Member country nominations.

5. The Steering Committee selected more than twenty background documents for the Workshop. These documents were all existing publications from the scientific literature and meeting reports, together

representing all major international views on the issue of validation and acceptance of alternative tests. In addition, two OECD Environment Monographs (no. 36 and no. 76, respectively), OECD's original proposal for photoirritation testing together with a compilation of Member countries' comments on the proposal, and OECD options (submitted by the US and Germany) for dermal and eye irritation testing, were added to the package of background information. Most documents for the Workshop were distributed to Nominated Participants on 9 and 15 January 1996. Copies of all documents were available at the meeting.

SCOPE AND OBJECTIVES

6. The scope of the Workshop was limited to the area of risk assessment of chemicals and chemical products and included aspects of all Three Rs as defined by Russell and Burch in 1959: **R**eplacement, **R**eduction and **R**efinement of animal tests. In this context the substitution of testing in a species of a lower level in the phylogenetic hierarchy for species higher up in this hierarchy, though not the highest priority, was also considered. Defining the term 'alternative' was accepted as meaning the Three Rs.

7. The specific objectives of the Workshop were:

- to reach consensus on harmonized principles and criteria for the validation and acceptance of toxicological test methods with emphasis on alternative tests;
- to develop guidance for validation procedures including the purpose of the validation, selection procedures of tests to be validated, the review process, statistical data analysis, regulatory acceptance and further practical aspects;
- to discuss general principles concerning strategies and schemes for risk assessment which take into account alternative tests, and to reach consensus on testing strategies/schemes in specific areas such as dermal and eye irritation and phototoxicity

8. In order to facilitate the discussions, the Workshop was arranged as a series of meetings of three Working Groups, alternated with plenary sessions. The Workshop Programme and details of the three Working Groups including Working Group background documents are provided in Annex 1 to this report.

9. The Workshop was attended by fifty participants from OECD Member countries, the European Commission, Poland, UNEP, animal welfare organisations and international industry. A list of participants and their Working Group assignment is provided in Annex 2 to this report.

OPENING SESSION

10. The Workshop was chaired by Mr Bo Wahlström, Director International Activities, KEMI, Sweden.

11. The Workshop was officially opened by Mr Gunnar Bengtsson, Director General of the Swedish National Chemicals Inspectorate (KEMI). In his opening address, Mr Bengtsson emphasized the importance of ethical considerations in animal testing and the responsibility of animal experimentators in this respect. A copy of his opening address is attached to this report as Annex 3.

12. Mr Herman B.W.M.Koëter of the OECD Secretariat explained the objectives of the Workshop and reminded the meeting of the enormous amount of work done in Europe, Japan and North America on alternatives to animal testing and approaches for their acceptance. He again emphasized that the discussions should be based on these existing concepts, rather than developing new ones. Mr Koëter further explained that OECD's role would be to build upon national and regional achievements and agreements in order to reach international consensus on validation and acceptance criteria for new tests.

13. Keynote lectures were presented by Dr Erik Walum, Pharmacia AB, Sweden, Dr Mark Chamberlain, Programme Manager for Research, Unilever, UK, and Dr Bernard Schwetz, Director National Center for Toxicological Research (NCTR) and Associate Commissioner for Science FDA, USA, respectively. These leading scientists presented their views on the place of alternative tests in future risk assessment. The following fundamental questions which were to be further discussed during the various Working Group sessions were also addressed by these speakers: (1) why are alternatives needed? (2) why is validation of new tests needed? (3) why is harmonization of validation criteria of importance, and (4) should the same validation criteria apply for all new tests, animal or non-animal? A copy of Dr Schwetz' slides and a copy of the risk assessment paradigm as presented by Dr Chamberlain are attached to this report as Annex 4 (the slides of Drs Schwetz and Chamberlain could not be shown during the presentations because of a technical failure).

WORKING GROUPS AND PLENARY SESSIONS

14. Three Working Groups were established with the following missions:

Working Group 1: Principles and Criteria for the Validation and Acceptance of New or Modified Toxicological Tests

Working Group 1 was co-chaired by Dr Erik Walum (Sweden) and Dr Hiroshi Ono (Japan). Dr Robin Fielder (UK) and Dr Christoph Reinhardt (Switzerland) were rapporteurs. The Working Group mission was:

“To discuss and agree on criteria for the (scientific) justification of new and revised test methods in order to allow their use, and international acceptance, for the testing and assessment of chemicals and chemical products. The criteria should apply for all new tests, animal or non-animal. The Working Group should also consider whether the criteria should depend on factors such as: the application of the test, the chemical category for which it is used, and its place in testing schemes, or that the same criteria basically apply at all times.”

Working Group 2: Practical Approaches to Validation

Working Group 2 was co-chaired by Prof Michael Balls (ECVAM) and Prof Alan Goldberg (CAAT). Dr Leon Bruner (BIAC) and Prof Horst Spielmann (Germany) were rapporteurs. The Working Group mission was:

“To discuss practical validation approaches and to review various validation procedures used and discuss their adequacy. They should also consider the acceptability of adopting various approaches rather than one. Examples could be useful for the discussion. Aspects such as: study design, statistical considerations; candidate test selection, independent study review, study management, GLPs, data evaluation and practical matters should also be considered.”

Working Group 3: Testing Strategies/schemes to be Applied for the Testing and Assessment of Chemicals and Chemical Products

Working Group 3 was co-chaired by Dr Phil Botham (BIAC) and Dr Kathy Stitzel (US). Prof Nils Gunnar Lindquist (Sweden) and Dr Wolfgang Pape (Germany) were rapporteurs. The Working Group mission was:

“To discuss and agree on strategy concepts in general for the testing and assessment of chemicals and chemical products, which could be adopted as general principles and initial considerations in test guidelines and be integrated as part of data requirements. Further, specific strategies/testing schemes should be discussed and agreed for the testing and assessment of eye irritation/corrosion, skin irritation/corrosion and photoirritation/corrosion.”

15. All Working Groups met during three sessions which were alternated by plenary sessions. During each plenary session, the progress of the Working Group discussions were discussed and comments and suggestions made during plenary sessions were taken into account during the following session of the Working Group. During the final plenary session at the end of the Workshop all Working Group reports were extensively discussed.

DEFINITIONS

16. The Workshop agreed not to devote too much time on discussing definitions. However, it was considered essential to have a common understanding of some basic terms used by all three Working Groups. The Workshop agreed to adopt the following definitions, derived from the CAAT/ERGATT Workshop on the Validation of Toxicity test Procedures in 1990, to which is usually referred to as the first Amden Workshop (see documents used by Working Group 1 and 2):

Validation is the process by which the reliability and the relevance of a procedure are established for a particular purpose;

Regulatory Acceptance is the process by whereby a given test is considered suitable for risk assessment purposes aimed at the protection of human health and/or the environment;

Reliability is defined as the reproducibility of results from an assay within and between laboratories;

Relevance describes whether a test is meaningful and useful for a particular purpose.

WORKSHOP CONSENSUS

17. All major issues as discussed by the various Working Groups were reported to the Plenary Meeting. During the various intermediate Plenary Sessions progress made by each of the Working Groups was discussed and suggestions and comments were considered. During the final Plenary Session the draft final reports of all three Working Groups were discussed extensively and consensus was reached on all reports and recommendations. The Workshop reached consensus on: (1) Principles and Criteria for Validation and Regulatory Acceptance, (2) the Validation Process, and (3) Principles of Testing Strategies and Testing Schemes for Skin and Eye Irritation Testing, as described below.

PRINCIPLES AND CRITERIA FOR THE VALIDATION AND ACCEPTANCE OF NEW OR MODIFIED TOXICOLOGICAL TESTS FOR PURPOSES OF RISK ASSESSMENT AND OTHER USES RELATING TO THE PROTECTION OF MAN AND THE ENVIRONMENT

Initial Considerations

18. A prerequisite for regulatory acceptance of every new test is validation according to the criteria given in paragraph 21. Separate criteria must be considered in order to achieve regulatory acceptance. These separate criteria need to be taken into account already in the planning and design stage of the validation study as outlined in the chapter on the Validation Process.

19. In certain OECD Member countries, there is either an understanding or even a legal obligation that, once an alternative test has been considered as sufficiently validated, it has to be adopted for use. In such cases the criteria listed for both validation and acceptance must be fulfilled.

20. The validation and regulatory acceptance criteria as presented below were largely taken from the following documents and merged and/or modified as appropriate:

- “Validation and Regulatory Acceptance of Toxicological Test Methods”, Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Draft Report; October 16, 1995. National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA.
- “Draft Report: National Toxicology Program Workshop on Validation and Regulatory Acceptance of Alternative Toxicological Test Methods”, January, 1996. National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA.
- OECD Environment Monograph No. 36: “Scientific Criteria for Validation of In Vitro Toxicity Tests”.
- OECD Environment Monograph No. 76: “Guidance Document for the Development of OECD Guidelines for the Testing of Chemicals”.
- ECVAM Workshop Report 5: “Practical Aspects of the Validation of Toxicity Test Procedures”, ATLA 23, 129-147, 1995.
- “Report and Recommendations of an International Workshop on Promotion of the Regulatory Acceptance of Validated Non-animal Toxicity Test Procedures” ATLA 18, 339-344, 1990.
- “Report and Recommendation of the CAAT/ERGATT Workshop on the Validation of Toxicity Test Procedures” ATLA 18, 313-336, 1990.
- ECVAM Prevalidation Task Force Report 1: “The Role of Prevalidation in the Development, Validation and Acceptance of Alternative Tests”, ATLA 23, 211-217, 1995.
- Balls, M and Karcher, W. “The Validation of Alternative Test Methods”. ATLA 23, 884-886, 1995.

Criteria For A Valid Test

21. For any new or revised test method (animal or non-animal) to be valid for use for the testing and assessment of chemicals, it must meet the following minimum criteria:

- a) A rationale for the test method should be available. This should include a clear statement of scientific need and regulatory purpose.
- b) The relationship of the endpoint(s) determined by the test method to the in vivo biological effect and to the toxicity of interest must be addressed. The limitations of a method must be described, eg., metabolic capability.
- c) A formal detailed protocol must be provided and should be readily available in the public domain. It should be sufficiently detailed to enable the user to adhere to it, and it should include data analysis and decision criteria. Test methods and results should be available preferably in an independent peer reviewed publication. In addition, the result of the test should have been subjected to independent scientific review.
- d) Intra-test variability, repeatability and reproducibility of the test method within and amongst laboratories should have been demonstrated. Data should be provided describing the level of inter- and intra- laboratory variability and how these vary with time.
- e) The test method's performance must have been demonstrated using a series of reference chemicals preferably coded to exclude bias.
- f) The performance of test methods should have been evaluated in relation to existing relevant toxicity data as well as information from the relevant target species.
- g) All data supporting the assessment of the validity of the test methods including the full data set collected in the validation study must be available for review.
- h) Normally, these data should have been obtained in accordance with the OECD Principles of Good Laboratory Practice (GLP).

Criteria For Regulatory Acceptance

22. Regulatory Acceptance is dependent on the outcome of scientific validation with consideration of the criteria given above. Acceptance will be greatly facilitated by the involvement of regulatory agencies as early as possible in the validation process and the design of the validation studies. In considering the regulatory acceptance of a new test method the following criteria are important:

- a) Application of the method provides data that adequately predicts the end-point of interest in that it demonstrates either a linkage between (i) the new test and an existing test method or (ii) the new test and effects in the target species.
- b) The method generates data for risk assessment purposes that are at least as useful as, and preferably better than, those obtained using existing methods. This will give a comparable or better level of protection for human health or the environment.

- c) There are adequate testing data for chemicals and products representative of the type of chemicals administered by the regulatory programme or agency (e.g. pesticides, cosmetics).
- d) The test must be robust and transferable and allow for standardisation. If highly specialised equipment, materials or expertise are required, efforts should be sought to facilitate transferability. This is an important criterion to be considered at an early stage of a validation study. *[Note added by the Secretariat: According to current OECD policy, the test should not require equipment or material from a unique source. This would prevent the acceptance of patented methods. The Workshop did not discuss the issue of patented tests but referred the issue to higher policy levels at OECD].*
- e) The test is cost effective and likely to be used.
- f) Justification (scientific, ethical, economic) should be provided for the new method with respect to any existing methods available. In this respect due consideration should be given to animal welfare consideration including the 3 Rs.

Other Considerations

Flexibility

23. The criteria for validation apply in all cases as do the general criteria for regulatory acceptance, but the level of necessary reassurance that is appropriate for a specific purpose varies and needs to be identified on a case-by-case basis. However, some general guidance can be given.

24. A lower level of reassurance for acceptance is appropriate in the following instances:

- a) When the seriousness of the health effects detected by the test is minor, e.g., palatability effects (On the other hand greater reassurance will be needed for the most severe effects e.g. developmental toxicity or carcinogenicity.)
- b) When the new test is a screening method that will form part of a hierarchical approach to screen out positive compounds (a positive compound that is not classified in the screening test should be detected in the full definitive test, and the approach is therefore 'fail-safe' from the regulatory point of view).
- c) When the new test is a revision of an existing and already accepted test and the revision consists of minor variations in the test protocol.

Battery Approach

25. Individual test methods within a proposed battery should be validated using the criteria agreed. However, justification for the acceptance of batteries should be primarily on the basis of recommendations from an expert peer review group after their review of the total battery. This may involve a recommendation for more data on specific compounds but not for a formal validation study of the battery.

Adjunct Tests

26. These are usually applied to refine the risk assessment of specific chemicals or groups of chemicals by improved understanding of mechanisms and relevance to humans. These are highly specialised tests and need to be considered on a case by case basis. Tests in this area are not considered for development as OECD Guidelines and thus, in this respect, the issue of validation does not arise.

Parallel Submissions

27. Parallel submission of data from existing and new methods is a means of facilitating regulatory acceptance of new methods and should be encouraged. However, this should be limited to promising methods for which an optimised protocol is available and for which full validation may take some time. In the meantime, the protocol should be made widely available. Industry is encouraged to provide parallel submissions on a voluntary basis.

Patents

28. The development of novel and innovative test methods that will provide for improved risk assessment should be encouraged. In some cases, the profit motive underlying innovation and investment in alternative methods has resulted in the protection of intellectual properties in the form of patents. The participation in the development and validation of such methods by Member countries should include provision for the method to be provided at a reasonable cost to the users.

[Note added by the Secretariat: The adoption of patented tests as OECD Test Guidelines or patented animals, materials/equipment as part of OECD Test Guidelines is a matter of considerable debate. Since OECD Test Guidelines are part of a Council Decision they carry legal weight, implying that a patented method could become part of (inter)national data requirements. This may lead to an unprecedented favouring of one private enterprise over another which is contrary to the independent position of the OECD. This issue will be discussed at higher policy levels in OECD.]

THE VALIDATION PROCESS**Initial Considerations**

29. The Guidance and recommendations with respect to the validation process were largely based on the following documents:

- Balls, M., and Karcher, W. "The Validation of Alternative Test Methods", ATLA 23, 884-886, 1995.
- Goldberg, A.M., Epstein, L.D. and Zurlo, J. (1996). "A Molecular Approach to Validation - A Work in Progress" (In Press).
- Goldberg, A.M., Frazier, J.M., Brusick, D., Dickens, M.S., Flint, O., Gettings, S.D., Hill, R.H., Lipnick, R.L., Renskers, K.J., Bradlaw, J.A., Scala, R.A., Veronesi, B., Green, S., Wilcox, N.L. and Curren, R.D. (1993). "Framework for Validation and Implementation of In Vitro Toxicity Tests: Report of the Validation and Technology Transfer Committee of the John Hopkins Center for Alternatives to Animal Testing" J. of the Am. Coll. of Tox. 12, 23-30.

- “Report and Recommendation of the CAAT/ERGATT Workshop on the Validation of Toxicity Test Procedures” ATLA 18, 313-336, 1990.
- ECVAM Prevalidation Task Force Report 1: “The Role of Prevalidation in the Development, Validation and Acceptance of Alternative Tests”, ATLA 23, 211-217, 1995.
- ECVAM Workshop Report 5: “Practical Aspects of the Validation of Toxicity Test Procedures”, ATLA 23, 129-147, 1995.
- “Validation and Regulatory Acceptance of Toxicological Test Methods”, Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Draft Report; October 16, 1995, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA.
- “Draft Report: National Toxicology Program Workshop on Validation and Regulatory Acceptance of Alternative Toxicological Test Methods”, January, 1996. National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA.

Additional papers which were considered relevant to the validation process are referenced in the text.

30. The overall process leading to the adoption of an alternative method by appropriate authorities requires completion of three major steps including test development, validation, and acceptance. The purpose of the validation process is to provide independent confirmation that an alternative method provides information that is needed for making risk assessment or other decisions. Accordingly, validation must be considered a confirmation process. The purpose of formal validation is not to develop or optimise alternative methods.

31. In order to establish the validity of an alternative method, whether it is a single test or a battery of tests used together, its reliability and relevance for a specifically defined purpose must be confirmed. The preferred approach for the validation of test batteries is described in paragraph 25. Reliability of an alternative method was defined as the reproducibility of results from an assay within and between laboratories. An alternative method must be reproducible in two ways. First it must be possible to demonstrate that the same results are obtained from individual test substances across multiple laboratories over time. Secondly, it must also be possible to demonstrate that the same predictions of toxicity are obtained from an alternative method across appropriately defined sets of test substances. Establishing the relevance requires that all of the information supporting the scientific basis of the method be reviewed, and that ultimately a judgement be rendered that the probability of obtaining correct information from the alternative method is sufficiently high to allow its adoption.

32. The important steps that must be considered prior to the entry of a method into the validation process are indicated in figure 1. The key stages in the validation process are shown in Figure 2. The important steps to consider in a validation programme include planning, the conduct of the study, assessment of the data and reporting of results. Once the data from a validation study are appropriately summarised, they may be submitted to the appropriate authorities. The important details that should be considered within these processes are reviewed below:

Test Development

Definition of a Test

33. The definition of a test involves a description of its basis (e.g., inhibition of the differentiation of embryonic stem cell lines or the measurement of damage to reconstituted human skin) and of its purpose (e.g., as a screen or as a definitive test for the identification of potential human carcinogens or of materials likely to be damaging to the eye or skin).

34. There should be an explanation of the need for the test, not only in relation to type and extent of toxic effect, but also the type of assessment (i.e. of toxic potential, potency, hazard or risk), the chemical spectrum to which it can be applied, and the need for it in relation to the availability of other tests.

35. A clear and comprehensive protocol, together with any necessary SOPs suitable for the preliminary evaluation of its interlaboratory transferability, should be produced. This should contain a clear indication of the experimental system, exposure conditions, endpoint(s), endpoint measurement, expression of results, data analysis, and use of the outcome of this test in relation to its stated purpose.

36. Data should be provided to indicate the reproducibility of the data provided by the test within and between experiments, the quality of the results produced in relation to its purpose, and, ideally, the interlaboratory transferability of this protocol.

Test Optimisation/Prevalidation

37. Experience has shown that a test optimisation/prevalidation step is needed between test development and the possible inclusion of a test in a large-scale, formal validation study. This should involve the participation of other laboratories and/or experts in the further optimisation and standardisation of the test protocol and SOPs, identification of suitable controls, and the clear definition of the prediction model (which defines how to use the results from an alternative method to predict an *in vivo* toxicity endpoint) to which the results of the test will be applied in any future validation study. Evidence should be provided on the interlaboratory transferability of the test, on the reproducibility of the data it provides, within and between laboratories and with time, and on the spectrum of materials to which it can be applied. Any limitations on the way the test can be used should be clearly specified.

38. One detailed scheme for the test optimisation/prevalidation stage has been put forward by Curren *et al.* (ATLA 23: 211-217, 1995) and the ECVAM Prevalidation Task Force (see paragraph 29); other approaches have been proposed by Goldberg *et al.* (see paragraph 29).

Peer Review

39. Once a test has been fully optimized independent review is necessary of the test development data, confirmation that the final protocol is adequate and appropriate and that the prediction model is appropriate. Peer reviews should include assessment if the conclusions are supported by the data. In most cases it is expected that the method will be published in a quality, independent peer-reviewed journal.

Assessment of Readiness for Validation

40. The management committee of the validation study must provide adequate justification to the participating laboratories and other interested parties that the proposed validation study is well-designed

and that test(s) to be validated are selected based on agreed criteria. Submission of all details of the validation study for review to an independent committee, prepared for this task, would provide such independent and objective justification. Questions that need to be answered include:

- Is the prediction model sufficiently well defined?
- Is there adequate evidence of transferability (reproducibility between laboratories)?
- Is there adequate evidence of reproducibility within laboratories?
- Has the protocol been optimized and is it available?
- Have the SOPs been optimized and are they available?
- If yes, then validation can begin.
- If no, explain why the validation study cannot proceed.

The Prediction Model

41. In order for an alternative method to be useful it must be possible to convert its results into predictions that may be used for a defined purpose. This process is usually accomplished through the use of models derived from validated experimental data. In order to ensure the reliability and reproducibility of the predictions certain information must be provided before the study starts. First, the specific reference test endpoint which the alternative method predicts must be defined. Secondly, all of the possible results that are obtained from an alternative method must be defined. Thirdly, the techniques employed to derive the models must be clearly defined. Fourth, an indication of the accuracy of the predictions, in terms of some confidence measurement, must be stated. Finally, there must be an indication of the limitations that may be associated with use of the method. Collectively, this grouping of information has been called a Prediction Model (Bruner, *et al*, ATLA 24, 139-142, 1995)(see also paragraphs 54-56 on statistical recommendations).

Validation (Figure 2)

Planning

42. At the beginning of the formal validation study the goal(s) of the study should be defined in a goal statement to which participants, managers and sponsors have to agree. A management committee which should include (a) biostatistician(s), will have to design the study according to the goals and develop a project plan in which the objectives to be met, the time frame and the management structure are described. Schemes summarizing the organisation and management structure of validation studies have been described by Goldberg *et al* (see para. 29) and Ohno *et al*. (In Vitro Tox. 7: 89-94, 1994). Based on the scheme from Ohno, ZEBET in Germany developed a somewhat revised version which was discussed and amended at the second Amden Workshop (ECVAM Workshop Report No 5, see para 29). The scheme shown in Figure 3 is essentially similar to the scheme of Ohno/Amden 2 and includes the issues discussed during the Workshop. A new element in the scheme presented in figure 3 is the submission of the validation study proposal to an independent center/committee for an objective review with a view to regulatory acceptance. Depending on the scope of the proposed validation study this could be a national center or committee such as ICCVAM in the US or ZEBET in Germany, an international center focussing on a region such as ECVAM in the European Union or the OECD for wider international coverage.

43. The project plan will have to be updated and should contain essential information about participating laboratories and their duties. The management committee can delegate essential tasks to subcommittees/task forces, as e.g. selection of tests to be validated, selection of test chemicals, selection of laboratories including an experienced lead laboratory for each test and of a biostatistic group.

Agreement has to be reached during the design of the study about the levels of independence to be ensured for the selection of test chemicals and biostatistical analysis including data collection. The degree of blindness to be ensured for the distribution of coded chemicals has to be carefully evaluated since information on physicochemical properties and solvents to be used may help to improve proper handling during testing and because such information is usually available in routine testing.

44. Validation studies should be carried out according to GLP principles, which may be aided by standardised software programs for data collection. The selection of laboratories should be based upon competence which can be assessed by preliminary testing of a small number of coded chemicals.

45. The selection of test chemicals according to the goals of the study depends on the one hand on the availability of sufficient chemicals for which high quality *in vivo* or other relevant data are available and on the other hand upon the spectrum of chemical classes to be included in the study. Each laboratory should be fully trained on the test method and its SOP's reviewed before the study begins. For a large study, only a small portion of the study, for instance a subset of ten chemicals, are run first. Then a careful compliance check is done on each laboratory (including review of the complete data sets for these 10 chemicals). After this review is completed, a decision is made whether each laboratory should remain in the study and the remaining test compounds are released for evaluation to those laboratories who remain in the study. (see also paragraph 52).

46. Experience has shown that the number of chemicals meeting these quality criteria is often insufficient and may require additional testing *in vivo*. Sound human data of good quality in the relevant species, for instance human data when human toxicity is the endpoint, are preferred but in exceptional cases additional testing in animals cannot be avoided. Such animal testing needs to be strongly and scientifically justified in the study plan of the validation study.*

47. Biostatisticians have to collaborate with the lead laboratories and managers for each test to establish appropriate procedure for record keeping, data collection and for a standardised data submission format according to principles of GLP. Consideration should have been given at the beginning of the study to the degree of variability and agreement likely to be considered consistent with a valid test. (see also paragraph 57).

48. A process for the release of individual data has to be agreed upon since individual data will be needed at different levels of the reviewing process by the biostatisticians and study directors as well as for peer review and regulatory acceptance.

49. The management committee has to establish emergency procedures to avoid exposure to hazardous chemicals during transportation, storage and testing of coded chemicals as well as for their disposal at the end of the study. Chemical safety data sheets must be kept with an occupational safety officer within each testing laboratory.

Conduct of testing

50. The substances to be tested are independently coded and packaged in a manner that will not reveal their identities, if possible. The codes and chemical identities are stored by the individuals/organizations responsible for the decoding of the samples, and the identities are maintained so

* Three participants of the Workshop have expressed disagreement with this paragraph of the Workshop Report. Letters explaining their concern are attached to the Report as Annex 5.

as to be quickly available to the testing laboratory in the event of a chemical exposure or laboratory contamination (Brantom *et al*, ATLA 23: 348-351, 1995).

51. After receipt and logging-in of the coded samples, the laboratory initiates testing according to the optimized test protocol.

52. Compliance checks of each laboratory should be performed on behalf of the management committee early in the conduct of the testing, and at interim times during the course of the testing. These checks are designed to determine whether the laboratory is following the agreed-upon test protocol and record keeping procedures. A typical compliance check would include the review of complete data sets for a limited number of test samples as made available by the laboratory. The data and records are evaluated for compliance with the test protocol and data-recording methods. Additionally, the quality of the laboratory's work e.g., levels of contamination of samples; performance errors; high variability of data points; etc. is assessed. The results are compared against the expected results. Any deviations from the test protocol or recordkeeping procedure, or evidence of poor laboratory practices, should be identified and documented, and testing stopped in that laboratory. At this time, a decision must be made whether to correct the problems and continue the testing (rejecting the inadequately-tested samples) or to eliminate the laboratory and its data from the validation exercise.

53. At the conclusion of the testing, or at agreed-upon intervals, the full data records on completed samples shall be submitted to the data analyst using the appropriate format.

Specific Statistical Recommendations

54. A statistical advisor (biostatistician) should be a member of the management committee and thus be involved in all phases of the development, validation and acceptance of alternative methods. The statistical advisor should acquire knowledge of the biological basis and the practical limitations of the method and of the reference test (test to be replaced) or endpoint in the relevant species. This knowledge will aid in the selection of appropriate statistical methods, and communicating the results of the study.

55. There is a wide range of standard statistical methods which can be applied to the analysis of data relating to alternative methods. However, it is important to recognise that these methods may not always be appropriate for use in the development and validation of alternative methods.

56. Research on the development of statistical methods that adequately address special features of data from validation studies (for instance, variability in both the *in vitro* and *in vivo* data, data with non-standard distributions, small sample sizes etc.) should be encouraged.

Assessment

57. The statistical methods to be used should be defined before the beginning of the study and be justified. The statistical analysis should involve consideration of the reproducibility of the study by assessing variability both within and between laboratories. An assessment should be made how well results from the alternative test agree with the reference data from the prediction model.

58. In a final consideration the management committee should reach a conclusion taking all factors into account to see whether the original goals of the study have been met.

Reporting

59. The result of the study should be discussed with all participants and others with an interest in the study and final conclusions developed.
60. The manuscript describing and discussing the validation study and the results obtained should be prepared for publication in a peer-reviewed journal and submitted for review. Results should also be submitted to appropriate authorities and sponsors of the study.
61. At the completion of the study all raw data should be archived and appropriate data sets should be made available in an easy retrievable format for independent reassessment.

PRINCIPLES OF TESTING STRATEGIES AND TESTING SCHEMES FOR SKIN AND EYE IRRITATION TESTING

Introduction

62. During the discussions on testing strategies, the documents listed below were used extensively. The proposed testing strategies for eye and skin irritation are derived from the US and German proposal.

- “Options for a Testing Strategy for the Testing of Skin and Eye Irritancy”. OECD discussion document, prepared for the Workshop, comprising the US proposal for a tier scheme for eye irritation testing and the German proposal for a skin and eye testing strategy.
- ECVAM Workshop Report No. 8: “The Intergrated Use of Alternative Approaches for Predicting Toxic Hazard” ATLA 23, 410-429, 1995.
- ECVAM Workshop Report No. 13: “Methods for Assessing Percutaneous Absorption” ATLA 24, 81-106, 1996.
- Basketter, D.A., et al. (1994). “Identification of Irritation and Corrosion Hazards to Skin: An Alternative Strategy to Animal Testing”. *Fd. Chem Tox.* 32: 539-542.
- Lovell, W.W. (1994). “Assessing Phototoxicity by *In Vitro* Methods: A Review”. In: *In Vitro Skin Toxicology*, Eds. A Rougier, A.M. Godberg, H. I. Maibach. Mary Ann Liebert Inc.
- G. Langley and C. Fisher (1995). “New Perspectives in Cosmetics Toxicology. Non-Animal Tier-Testing Strategies”. Ideal Publications, London.
- ECVAM Workshop Report No. 2: “*In Vitro* Phototoxicity Testing”, ATLA 22, 314-348, 1994.
- Initial OECD Proposal for Draft Test Guidelines on Acute Dermal Photoirritation Test, together with a compilation of comments received on the Proposal from Member countries. OECD Discussion document prepared for the Workshop.

Principles

63. Testing strategies should be organised to:

- provide a reasoned flow of studies
- maximise use of existing knowledge
- minimise use and suffering of animals
- optimise use of resources
- achieve appropriate and relevant risk assessments
- ensure that data are internally consistent and mutually supportive

64. Strategies should be developed with risk assessment and regulatory needs in mind. The use of testing strategies in chemical classification systems should be advocated and considered as an important element in the process of harmonization of classification systems

65. The validity of a testing strategy should be supported by validation of the component tests and by peer-review of the total process.

66. Wherever possible, strategies should make use of tests based on a known and relevant mechanism of action.

67. When deemed to be redundant, existing OECD Test Guidelines should be considered for deletion.

Recommendations for the Achievement of the Principles

68. Structure-activity-relationships (SAR's), structure-property-relationships (SPR's), databases, knowledge-based system, data mining and existing test data (including toxicokinetics) should be used whenever possible.

69. Preference should be given to the components of a strategy which relate specifically to measures in humans including use of human tissue for *in vitro* tests.

70. Where ethically possible, use of humans should be encouraged at an appropriate point in a strategy. All human testing should be approved in advance by a neutral ethical review body such as an Independent Review Body or Ethical Panel and abide by the Helsinki Agreement. Consideration should also be given to the current OECD Test Guidelines Programme's activity on human testing.

71. The sequence of tests in a test strategy should permit the prediction of adverse effects. In addition, dose-response information may be derived that would support quantitative risk assessment.

72. Consideration should be given to multiple use of test data within testing strategies. Less stressful procedures and those using fewer animals, and validated alternatives to animals should be given preference in testing strategies.

73. Experimental validation of a testing strategy itself is not considered necessary. The strategy should be peer-reviewed and this review could include a non-experimental animal simulation exercise to validate the strategy. Validation of the component tests includes an understanding of the types of chemicals to which the tests apply. Sufficient evidence must be provided to demonstrate that the test is applied only to chemicals within its established scope.

74. The use of empirical tests is not excluded, especially as screens.

Testing Strategies

75. After extensive discussions Working Group 3 agreed on detailed proposals for testing strategies for eye irritation/corrosion and skin irritation/corrosion. Subsequently, these proposals (which were basically a compromise between the US proposal for a tier scheme for eye irritation testing and the German proposal for a skin and eye testing strategy) were discussed in plenary. After some modifications the Workshop reached full consensus on the concept of both strategies. The Workshop further agreed that at each stage of the testing strategy a weight of evidence approach should be used that incorporates all available information at that stage. Flow charts, together with explanatory notes are presented in Figure 4 and 5.

76. Working Group 3 also discussed a testing strategy for local phototoxicity assessment. Agreement was reached on the basic elements of a testing strategy (see Figure 6). However, the Working Group considered that more time was needed to fully assess the validity of existing *in vitro* tests. It was recognized that work was under way conducted by ECVAM and COLIPA, in collaboration with DG XI/E/2 of the Commission, ZEBET and various companies in Europe and in the US. Due to lack of time, the issue was only briefly discussed in plenary. The Workshop agreed, however, that the discussion of the current OECD proposal for a testing strategy including options for two *in vivo* tests should be delayed until validated and accepted *in vitro* tests would become available.

WORKSHOP RECOMMENDATIONS

77. The Workshop recommended that the consensus reached on the principles and criteria for validation and regulatory acceptance and on the validation process should be the subject of a comprehensive OECD Guidance Document in the special series on Test Guidelines. In this document the concise description of the agreed principles and criteria as provided in the Workshop Report could be further elucidated and the validation process could be described in more detail.

78. The Workshop further recommended that the testing schemes for skin and eye irritation/corrosion testing be integrated in the the appropriate OECD Test Guidelines and that revision of these Guidelines to include these schemes should start without delay. The Workshop recommended that the schemes should be incorporated in the respective Test Guidelines in such a way that the test path described would be mandatory rather than be considered as an option. However, the decision as to whether to accept the outcome of a test at any of the steps or to progress to the next stage would be that of the product sponsor.

79. The Workshop also recommended that follow-up work on the current OECD proposal for photoirritation testing should be delayed until validated and accepted *in vitro* tests would become available.

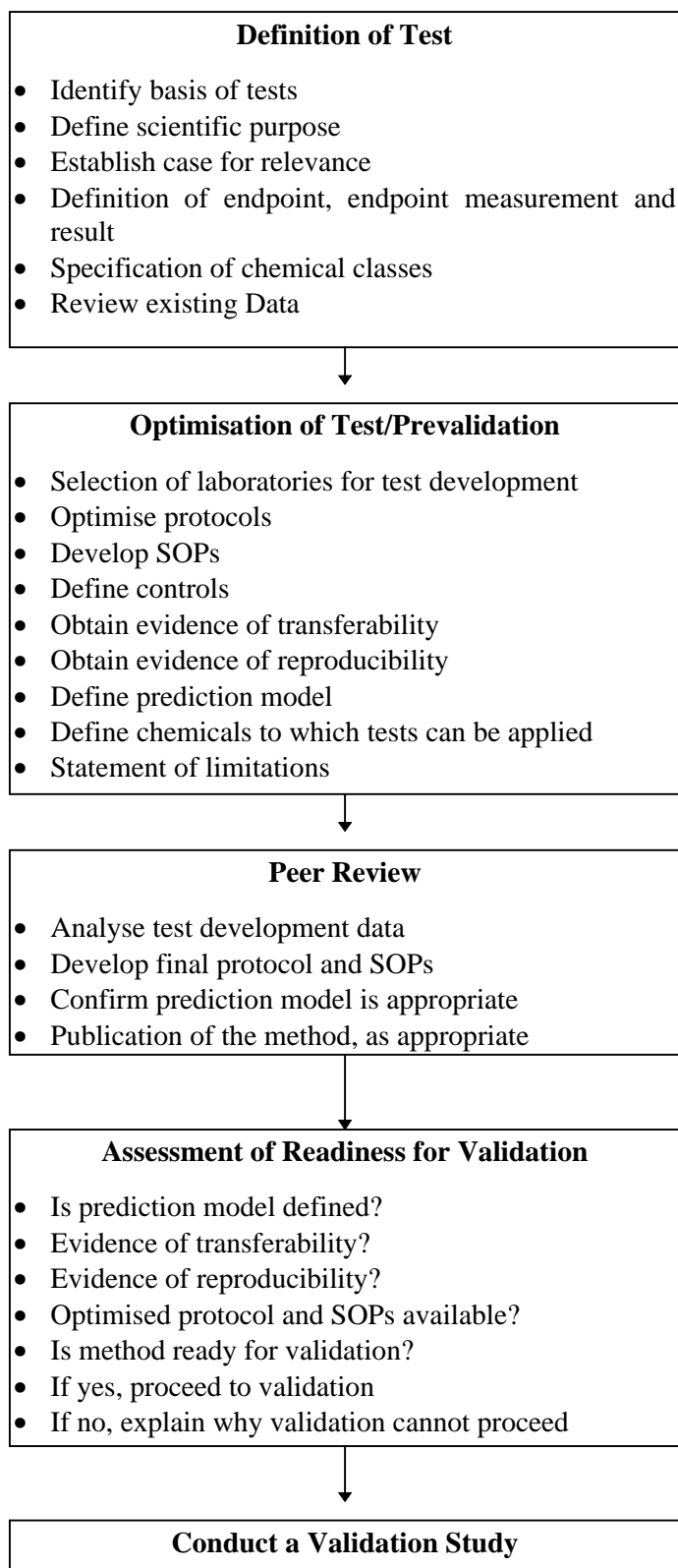
Figure 1: TEST DEVELOPMENT AND OPTIMISATION/PREVALIDATION PROCESS

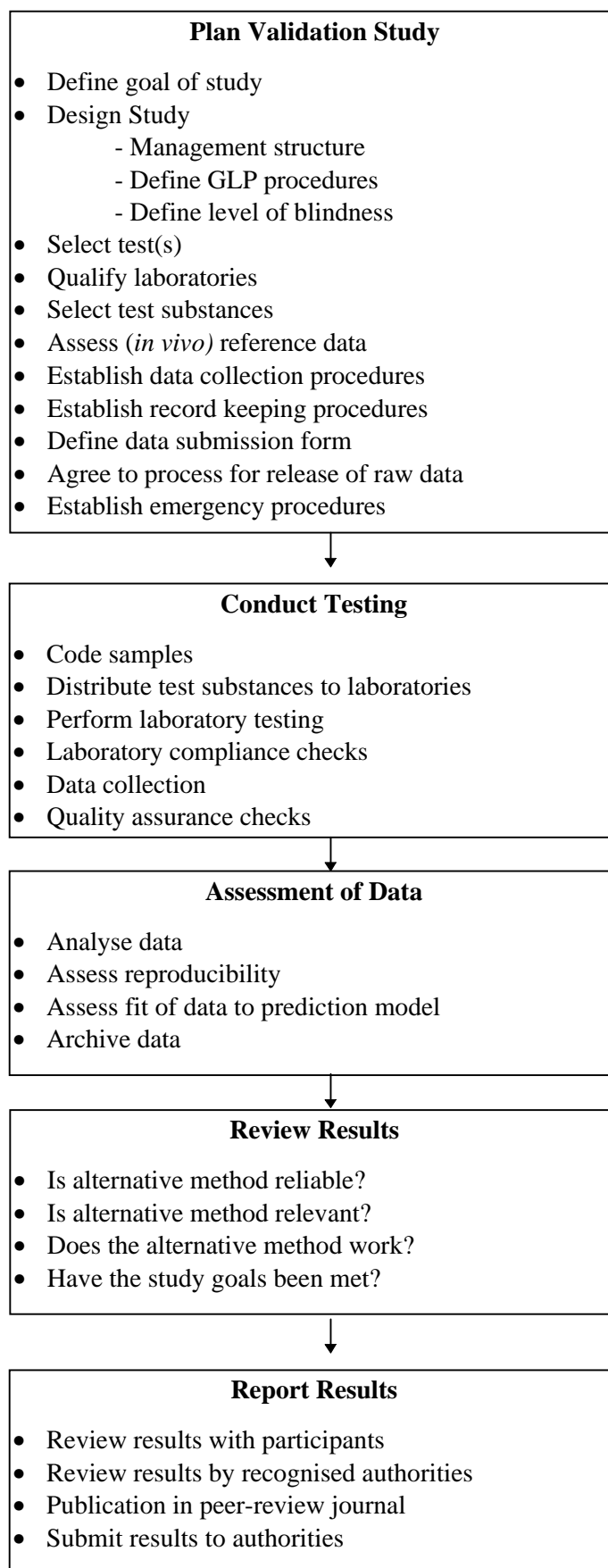
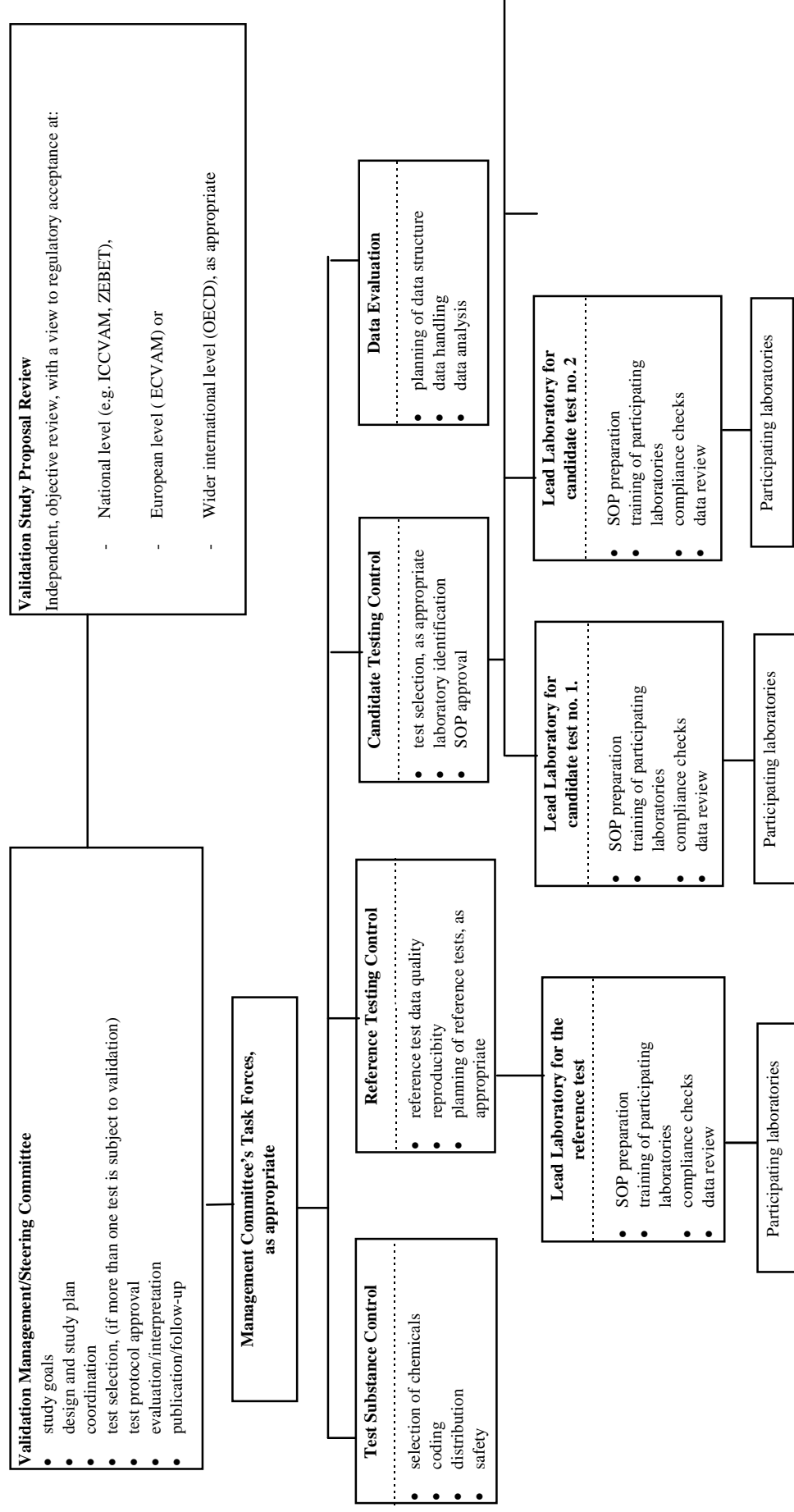
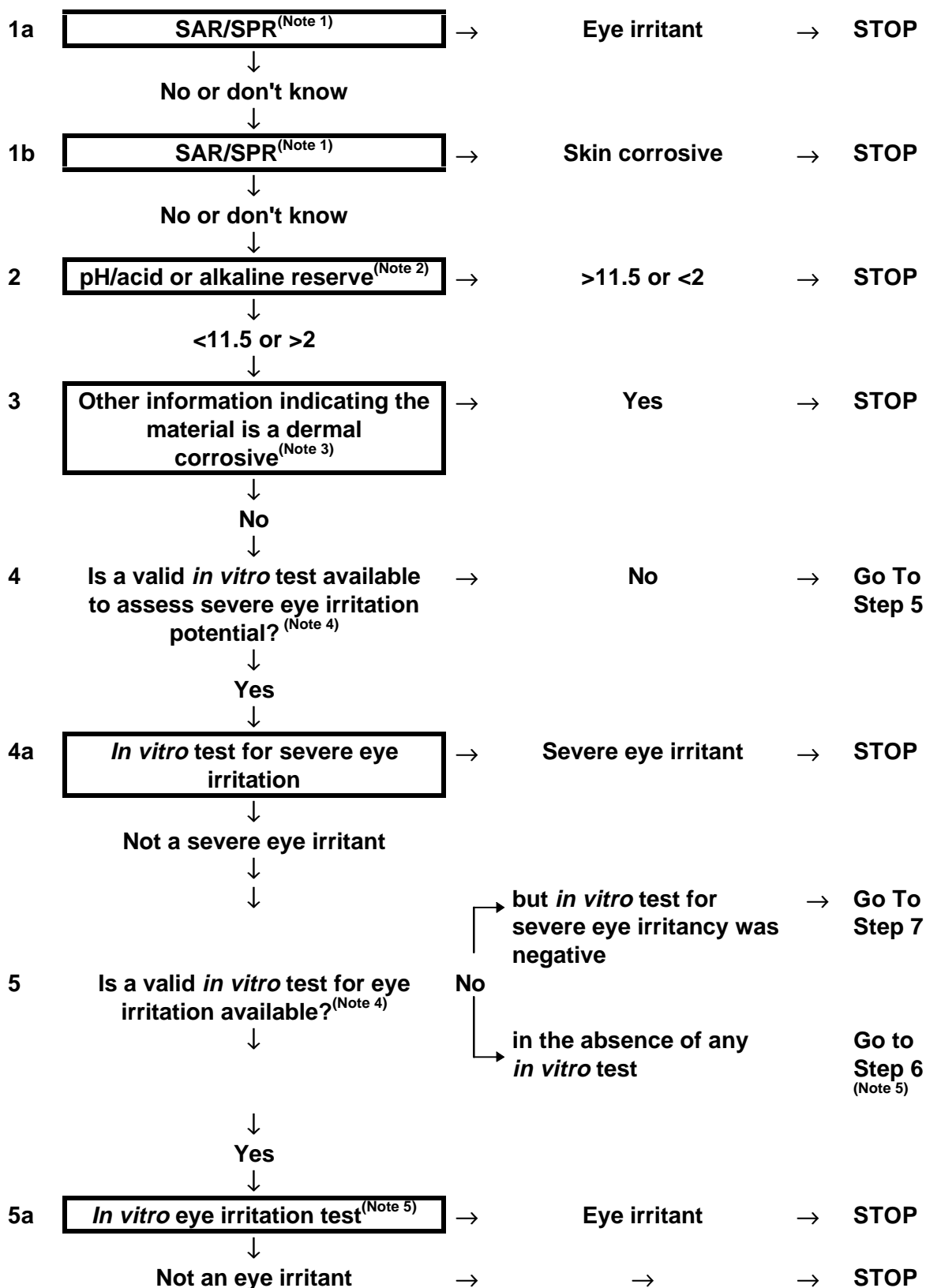
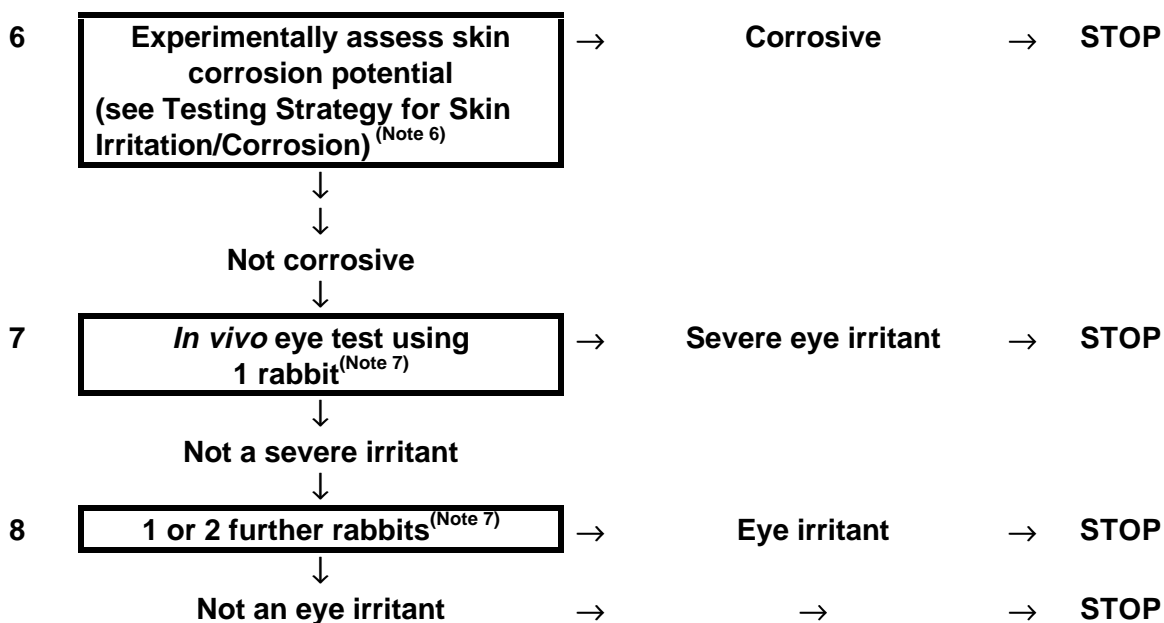
Figure 2: KEY STAGES OF THE VALIDATION PROCESS

Figure 3: MANAGEMENT AND ORGANISATION OF VALIDATION STUDIES¹

¹The management and organisation scheme is designed to cover for multitest validation studies and therefore includes options for special Task Forces. As a consequence, the scheme may appear rather complex and heavily hierarchical. However, since it is unlikely that task forces are needed in the case of single, straight-forward test validation and, moreover, the need for task forces should be decided on a case-by-case basis, in practice the management and organisation scheme will often be considerably more simple.

Figure 4: PROPOSED TESTING STRATEGY FOR EYE IRRITATION/CORROSION

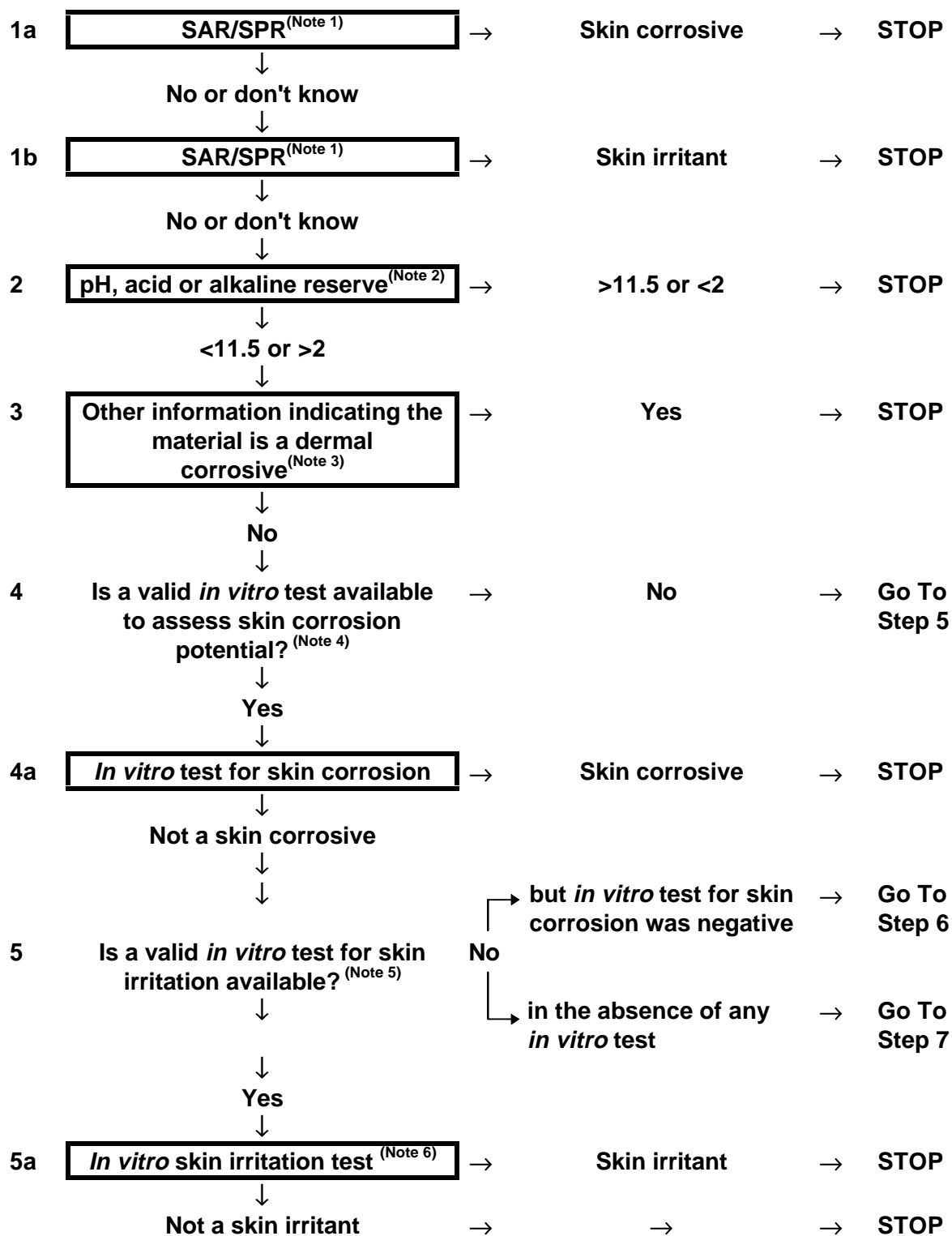


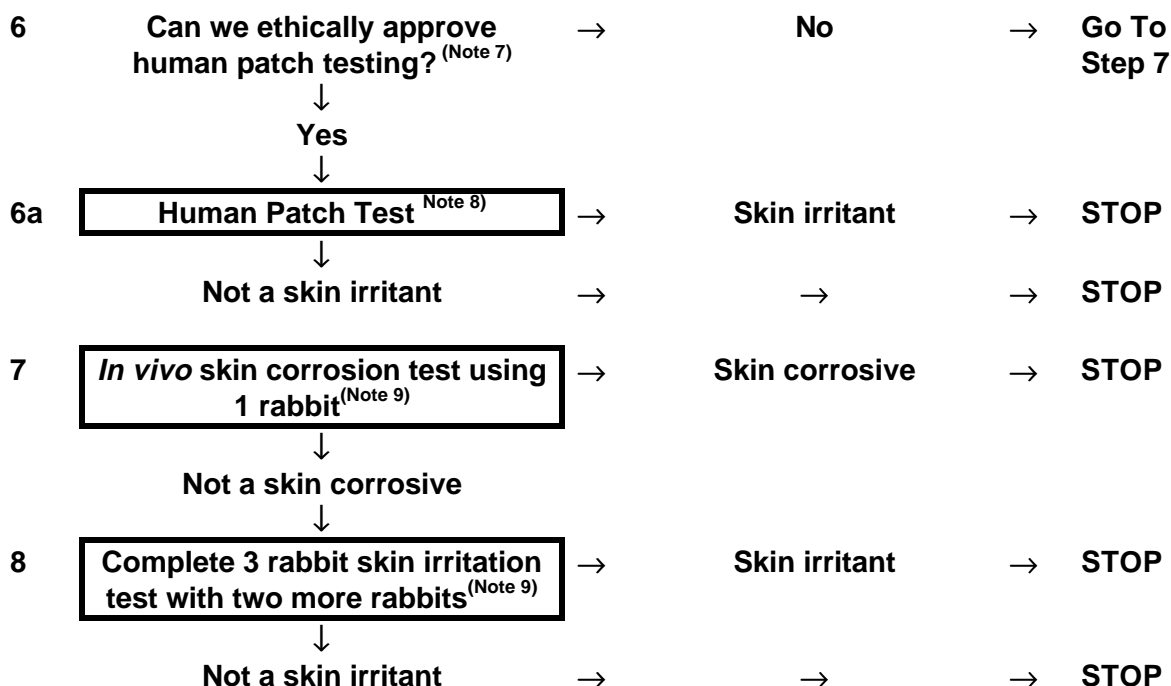


Notes to the Proposed Testing Strategy for Eye Irritation/Corrosion

- Note 1: Structure-Activity-Relationships (SAR)/Structure-Property-Relationships (SPR) for eye irritation and skin corrosion are shown separately but in reality would probably be done in parallel. This stage should be completed using validated and accepted SAR/SPR approaches.
- Note 2: Although measurement of pH alone may be adequate, assessment of acid or alkali reserve is likely to be more useful.
- Note 3: This information should be restricted to that which pre-exists. No laboratory or animal work need be conducted at this stage.
- Note 4: These must be alternative methods which have been validated and accepted as per the criteria established by the Workshop.
- Note 5: In the event that the *in vitro* eye irritation test will be performed in the absence of any *in vitro* data on severe eye irritation (coming from step 4, No), severe eye irritation cannot be precluded, irrespective of the outcome of the test. However, considering that it is highly unlikely that *in vitro* eye irritation tests will become available before *in vitro* tests for severe eye irritants, this situation is considered mainly as a theoretical one.
- Note 6: In the absence of any other information on skin corrosion, it is essential to obtain this via a rabbit skin corrosion/irritation test before proceeding to a rabbit eye irritation test. This must be conducted in a staged manner. If possible, this should be achieved using a validated, accepted *in vitro* skin corrosivity assay. If this is not available then the assessment should be completed using animal tests (see the skin irritation/corrosion strategy).
- Note 7: Staged assessment of eye irritation *in vivo*. Further analysis of existing data is required to determine whether 2 or 3 rabbits in total are required.

Figure 5: PROPOSED TESTING STRATEGY FOR SKIN IRRITATION/CORROSION





Notes to the Proposed Testing Strategy for Skin Corrosion/Irritation

- Note 1: Structure-Activity-Relationships (SAR)/Structure-Property-Relationships (SPR) for skin corrosion and skin irritation are shown separately but in reality would probably be done in parallel. This stage should be completed using validated and accepted SAR/SPR approaches.
- Note 2: Although measurement of pH alone may be adequate, assessment of acid or alkali reserve is likely to be more useful.
- Note 3: This information should be restricted to that which pre-exists. No laboratory or animal work need be conducted at this stage.
- Note 4: At present there are no validated and accepted alternative methods for assessment of skin corrosivity. A “pre-validation” study using three methods has been completed (Botham et al, 1995) and an ECVAM validation study is currently being planned. The current strategy therefore requires progression from stage 3 to 5.
- Note 5: At present there are no validated and accepted alternative methods for assessment of skin irritation. In absence of such method(s), options for progress are stage 6 or 7.
- Note 6: In the event that the *in vitro* skin irritation test will be performed in the absence of any data on *in vitro* corrosivity (coming from step 4, No), skin corrosivity cannot be precluded irrespective of the outcome of the test. However, considering that it is highly unlikely that *in vitro* skin irritation tests will become available before *in vitro* skin corrosion tests, this situation is considered mainly as a theoretical one.

Note 7: It is accepted that scientific, ethical and cultural issues are raised and that a human test may not be possible for any of these reasons:

Science

It is incumbent on the investigators to ensure that they have complete knowledge of prior work in order to identify where data/information/knowledge on the toxicity or potential toxicity already exists and where it does not. Specific toxicity, e.g. skin sensitization, genotoxicity, carcinogenicity, neurotoxicity or other systemic toxicity, may be taken as “gross negatives” indicating that a human patch test may not be possible.

Ethical

The foundation of ethical consideration is the Helsinki Agreement (World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964; and amended by the 29th World Medical Assembly, October 1975; the 35th World Medical Assembly, October 1983 and the 41st World Medical Assembly, September 1989) but clearly account has to be taken of other relevant international and national laws. In addition, national and local procedures for ethical review (e.g. by ethical committees or Institutional review boards) must be adhered to. A key input to the ethical review are the scientific considerations (see above).

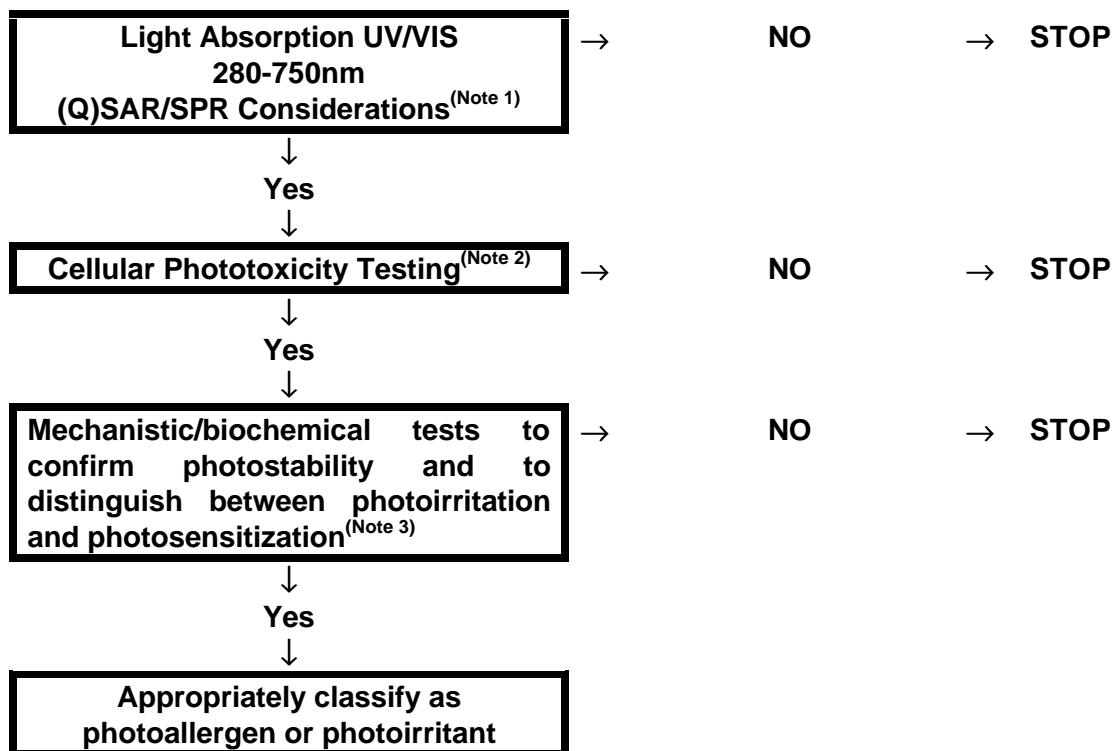
Cultural

It is recognised that use of humans (or human tissue) may not be acceptable in certain countries whereas it is in others.

Note 8: A protocol for an ethically approved four-hour human patch test is currently being drafted and will be considered for development as OECD Guideline.

Note 9: The skin corrosive potentially initially should be assessed using one animal. A positive response conforming to local regulatory criteria would result in classification. In the case of negative or equivocal results two further animals should be tested to complete the assessment of skin corrosion/irritation.

Figure 6: OUTLINE OF A TESTING STRATEGY FOR LOCAL PHOTOTOXICITY ASSESSMENT



Notes to the Proposed Outline of a Testing Strategy for Local Phototoxicity Assessment

- Note 1: Measurement of light absorption in the range between 280-750 nm and (quantitative) Structure-Activity-Relationships (SAR)/Structure-Property-Relationships (SPR) considerations give evidence for a phototoxic potential of a substance.
- Note 2: Apply the substance to validated cellular phototoxicity tests. For validation of such methods which is ongoing at present there is need for more acceptable *in vivo* data than those which are available at present in the public domain (scientific literature).
- Note 3: Mechanistically based photochemical tests should be applied to confirm whether a strong photobinding to proteins makes a photoallergic potential likely or relevant generation of photooxides gives evidence for a photirritant chemical.

ANNEX 1

OECD WORKSHOP ON HARMONIZATION OF VALIDATION AND ACCEPTANCE CRITERIA FOR ALTERNATIVE TOXICOLOGICAL TEST METHODS Solna, Sweden, 22nd-24th January 1996

WORKSHOP PROGRAMME

MONDAY 22 JANUARY 1996

MORNING SESSION

Plenary Session 1:

- | | |
|-------------|---|
| 9:00- 9:10 | Official Opening of the Workshop
Swedish Official, name to be confirmed |
| 9:10- 9:20 | Introduction of OECD, Workshop Objectives and Introduction of the Workshop Chair
Herman B.W.M. Koëter, Principal Administrator, OECD |
| 9:20- 9:25 | Introduction of the Speakers of Session 1 and Housekeeping Matters
Bo Wahlström, Director International Activities, KEMI and Chairman of the Workshop |
| 9:25- 9:45 | “Rationale of the Workshop: some fundamental questions”.
Erik Walum, Pharmacia AB, Sweden |
| 9:45- 10:05 | “A Risk Assessment Paradigm”
Mark Chamberlain, Programme Manager for Research, Unilever, U.K. |
| 10:05-10:25 | “Alternative Tests and Regulatory Risk Assessment”
Bernard Schwetz, Associate Commissioner for Science, US FDA (not yet formally confirmed) |
| 10:25-10:45 | COFFEE/TEA BREAK |
| 10:45-12:30 | <u>Session 1 of the three Working Groups:</u> <ul style="list-style-type: none"> • Introduction of the Working Group participants; • Introduction of the background documents and list of questions/issues to be considered; • defining the scope of the discussions • addressing the questions/issues; • discussion of the background documents; • considering the possibilities of reaching consensus |
| 12:30-14:00 | LUNCH |

AFTERNOON SESSION

- 14:00-17:00 Session 1 of the three Working Groups continues
- 15:30-15:45 **COFFEE/TEA BREAK**
- 17:00-18:00 Plenary Session 2:
- Working Group chairs/rapporteurs to report progress to the plenary meeting;
 - feedback from the other Working Groups;
 - adjustment of the scope/focus of Working Groups, as appropriate
- 18:00 **Meeting adjourns for the day**

Evening DINNER in Stockholm Town Hall

TUESDAY 23 JANUARY

MORNING SESSION

- 8:30-12:30 Session 2 of the three Working Groups:
- to consider the comments and suggestions of Plenary Session 2;
 - to further discuss and reach consensus on all questions/issues;
 - to agree on proposals, conclusions and recommendations.
 - to agree on the provisional report summarizing the major discussion items, proposals and recommendations of the Working Group
- 10:00-10:15 **COFFEE/TEA BREAK**
- 12:30-14:00 **LUNCH**

AFTERNOON SESSION

- 14:00-16:00 Session 2 of the three Working Groups continues
- 16:00-16:15 **COFFEE/TEA BREAK**
- 16:15-18:00 Plenary Session 3:
- discussion of all 3 provisional Working Group Reports;
 - suggestions for changes, as appropriate;
 - identification of gaps, not yet sufficiently discussed;
 - working towards Workshop consensus on issues.

18:00 **Meeting adjourn for the day**

(Working Group Chairs and Rapporteurs may need time in the evening to make revisions of the respective Working Group reports)

WEDNESDAY 24 JANUARY 1996

MORNING SESSION

8:30-11:30 Session 3 of the three Working Groups:

- to discuss the consequences of the outcome of Plenary Session 3 for the provisional Working Groups Reports and to reach consensus of the Working Group participants on all final recommendations, proposals and conclusions of the Group.

10:00-10:15 **COFFEE/TEA BREAK**

11:30-12:30 Plenary Session 4:

- Final discussion of the recommendations, proposals and conclusions of the three Working Groups.
- discussion of the Workshop proposals, recommendations and conclusions;
- agreement on the format and content of the Workshop Report (including Working Group conclusions etc.);
- discussion of the Workshop follow-up;

12:30-14:00 **LUNCH**

AFTERNOON SESSION

14:00-16:40 Plenary Session 4 continues

16:40-17:00 Summing-up and Conclusions of the Workshop
Bo Wahlström, Workshop Chairman

17:00 **Workshop adjourns**

WORKING GROUP 1: PRINCIPLES AND CRITERIA FOR THE VALIDATION AND ACCEPTANCE OF NEW OR MODIFIED TOXICOLOGICAL TESTS

Co-Chairs:	Rapporteurs:
Erik Walum	Robin Fielder
Hiroshi Ono	Angela Auletta

Working Group Mission:

To discuss and agree on criteria for the (scientific) justification of new and revised test methods in order to allow their use, and international acceptance, for the testing and assessment of chemicals and chemical products. The criteria should apply for all new tests, animal or non-animal. The Working Group should also consider whether the criteria should depend on factors such as: the application of the test, the chemical category for which it is used, and its place in testing schemes, or that the same criteria basically apply at all times.

Background documents:

- Draft ICCVAM report on Validation and Regulatory Acceptance of Toxicological Test Methods.
- Report of the NTP/ICCVAM Workshop on the Validation and Regulatory Acceptance of Alternative Toxicological Test Methods.
- OECD Environment Monograph No. 36: “Scientific Criteria for Validation of In Vitro Toxicity Tests”.
- OECD Environment Monograph No. 76: “Guidance Document for the Development of OECD Guidelines for the Testing of Chemicals”.
- ECVAM Workshop Report 5: “Practical Aspects of the Validation of Toxicity Test Procedures”, ATLA 23, 129-147, 1995.
- “Report and Recommendations of an International Workshop on Promotion of the Regulatory Acceptance of Validated Non-animal Toxicity Test Procedures” (ATLA 18, 339-344, 1990).
- “Report and Recommendation of the CAAT/ERGATT Workshop on the Validation of Toxicity Test Procedures” ATLA 18, 313-336, 1990.
- ECVAM Prevalidation Task Force Report 1: “The Role of Prevalidation in the Development, Validation and Acceptance of Alternative Tests”, ATLA 23, 211-217, 1995.
- Balls, M. and Karcher, W., (1995). “The Validation of Alternative Test Methods”, ATLA 23, 884-889.

- Compilation of Additional Documents, submitted to the OECD Secretariat prior to the Workshop:
 - Balls, M. (1995). "The Harmonisation of Validation Criteria for Replacement Alternative and Animal Test Methods", ATLA 23, 179-181.
 - Balls, M. (1995). "Scientific Validation: A Crucial and Unavoidable Prerequisite to the Acceptability of New Tests and Testing Strategies", ATLA 23, 474-479.
 - Balls, M., Fentem, J.H. "Progress Toward the Validation of Alternative Tests". ECVAM. (no publication information).
 - Goldberg, A.M., Frazier, J.M., Brusick, D., Dickens, M.S., Flint, O., Gettings, S.D., Hill, R.H., Lipnick, R.L., Renskers, K.J., Bradlaw, J.A., Scala, R.A., Veronesi, B., Green, S., Wilcox, N.L. and Curren, R.D. (1993). "Framework for Validation and Implementation of In Vitro Toxicity Tests: Report of the Validation and Technology Transfer Committee of the John Hopkins Center for Alternatives to Animal Testing" J. of the Am. Coll. of Tox. 12, 23-30.
 - Koëter, H.B.W.M. (1994). "Principles for a Pragmatic Approach to the Regulatory Acceptance of Alternative Test", Toxic. *In Vitro* 8, 925-930.
 - Koëter, H.B.W.M. (1995). "Validation: A Highly Charged Concept", Toxic. *In Vitro* 9, 851-856.
 - Walum, E. Clemenson, C. Ekwall, B. (1994). "Principles for the Validation of *In Vitro* Toxicology Test Methods". Toxic *in Vitro*. 8, 807-812.

WORKING GROUP 2: PRACTICAL APPROACHES TO VALIDATION

Co-Chairs:	Rapporteurs:
Alan Goldberg	Leon Bruner
Michael Balls	Horst Spielmann

Working Group Mission:

To discuss practical validation approaches and to review various validation procedures used and discuss their adequacy. They should also consider the acceptability of adopting various approaches rather than one. Examples could be useful for the discussion. Aspects such as: study design, statistical considerations; candidate test selection, independent study review, study management, GLPs, data evaluation and practical matters should also be considered.

Background documents:

- Goldberg, A.M., Epstein, L.D. and Zurlo, J. (1996). "A Molecular Approach to Validation - A Work in Progress". (In Press).
- Goldberg, A.M., Frazier, J.M., Brusick, D., Dickens, M.S., Flint, O., Gettings, S.D., Hill, R.H., Lipnick, R.L., Renskers, K.J., Bradlaw, J.A., Scala, R.A., Veronesi, B., Green, S., Wilcox, N.L. and Curren, R.D. (1993). "Framework for Validation and Implementation of In Vitro Toxicity Tests: Report of the Validation and Technology Transfer Committee of the John Hopkins Center for Alternatives to Animal Testing". J. of the Am. Coll. of Tox. 12, 23-30.
- "Report and Recommendation of the CAAT/ERGATT Workshop on the Validation of Toxicity Test Procedures" ATLA 18, 313-336, 1990.
- ECVAM Prevalidation Task Force Report 1: "The Role of Prevalidation in the Development, Validation and Acceptance of Alternative Tests", ATLA 23, 211-217, 1995.
- ECVAM Workshop Report 5: "Practical Aspects of the Validation of Toxicity Test Procedures", ATLA 23, 129-147, 1995.
- Current Activities on Validation of New Test Methods in Japan (a revised version of the document presented at the 1st Steering Committee meeting).
- Draft ICCVAM report on Validation and Regulatory Acceptance of Alternative Toxicological test Methods.
- Report of the NTP/ICCVAM Workshop on the Validation and regulatory Acceptance of Alternative Toxicological Test Methods.

- Compilation of relevant literature, submitted to the OECD Secretariat prior to the Workshop:
 - Balls, M. and Karcher, W. (1995). "The Validation of Alternative Test Methods". ATLA 23, 884-889.
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 - York, M. Basketter, D.A., Cuthbert, J.A. and Neilson, L. (1995). "Skin irritation testing in Man for Hazard Assessment - Evaluation of Four Patch Systems". Human & Experimental Toxicology 14, 729-734.
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WORKING GROUP 3: TESTING STRATEGIES/SCHEMES TO BE APPLIED FOR THE TESTING AND ASSESSMENT OF CHEMICALS AND CHEMICAL PRODUCTS

Co-chairs:	Rapporteurs:
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Kathy Stitzel	Wolfgang Pape (to be confirmed)

Working Group Mission:

To discuss and agree on strategy concepts in general for the testing and assessment of chemicals and chemical products, which could be adopted as general principles and initial considerations in test guidelines and be integrated as part of data requirements. Further, specific strategies/testing schemes should be discussed and agreed for the testing and assessment of eye irritation/corrosion, skin irritation/corrosion and photoirritation/corrosion.

Background documents:

- ECVAM Workshop Report 2: “*In Vitro* Phototoxicity Testing”. ATLA 22, 314-348, 1994.
- Initial OECD proposals for photoirritation testing, together with a compilation of comments from Member countries.
- Balls, M. Botham, P.A. Bruner, L.H. and Spielmann, H. (1995). “The EC/HO International Validation Study on Alternatives to the Draize Eye Irritation Test”. Toxicol. *In Vitro* 9, 871-929.
- Options for a Testing Strategy for the Testing of Skin and Eye Irritancy. OECD discussion document, prepared for the Workshop, comprising the US proposal for a tier scheme for eye irritation testing and the German proposal for a skin and eye testing strategy.
- Compilation of relevant literature, submitted to the OECD Secretariat prior to the Workshop:
 - Basketter, D.A. Scholes, E.W. Chamberlain, M. Barratt, M.D. (1995). “An Alternative Strategy to the Use of Guinea Pigs for the Identification of Skin Sensitization Hazard”. Fd. Chem. Toxic. 33, 1051-1056.
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 - Lovell, W.W. (1994). “Assessing Phototoxicity by *In Vitro* Methods: A Review”. In: Rougier, M., A. Goldberg A.M., Maibach (eds) *In Vitro* Skin Toxicology. Mary Ann Liebert, Inc., Publishers, NY, USA; 195-202.

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ANNEX 2

**OECD WORKSHOP ON HARMONIZATION OF VALIDATION AND ACCEPTANCE
CRITERIA FOR ALTERNATIVE TOXICOLOGICAL TEST METHODS**

22nd-24th January 1996
Solna, Sweden

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ANNEX 3

Opening Address by G. Bengtsson

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ANNEX 4

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ANNEX 5

**Letters of Three Workshop Participants Concerning their Disagreement with Paragraph 46
of the Report**

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