Risiken erkennen – Gesundheit schüt

Symposium
20th Anniversary of ZEBET at BfR
and 50 Years of the *3Rs* Principle
October 26-27, 2009
Federal Institute for Risk Assessment (BfR), Berlin,

International Pre-validation and Validation Studies

Horst Spielmann
Professor for Regulatory Toxicology
FU Berlin und BfR, Berlin

ZEBET's contribution to the concept of experimental validation

1989 no validation concept existed

1990 CAAT/ ERGATT AMDEN (CH) validation workshop

1990 ERGATT Vouliagmeni (GR) workshop on regulatory acceptance

1992 ECHO eye irritation study ➔not successful

1993-98 EU/ECVAM/COLIPA/ZEBET validation of in vitro phototoxicity tests➔ successful

1994 Amden II ECVAM workshop on practical aspects of validation

1995 Prevalidation concept (ECVAM, IIVS & ZEBET)

1996 Solna OECD validation WS & OECD acceptance

1997-2000 ECVAM validation of prediction models ➔ proof of principle successful

1997-2000 ECVAM catch-up validation➔proof of principle successful

1998- 2002 ECVAM validation of 3 in vitro embryotoxicity tests ➔successful

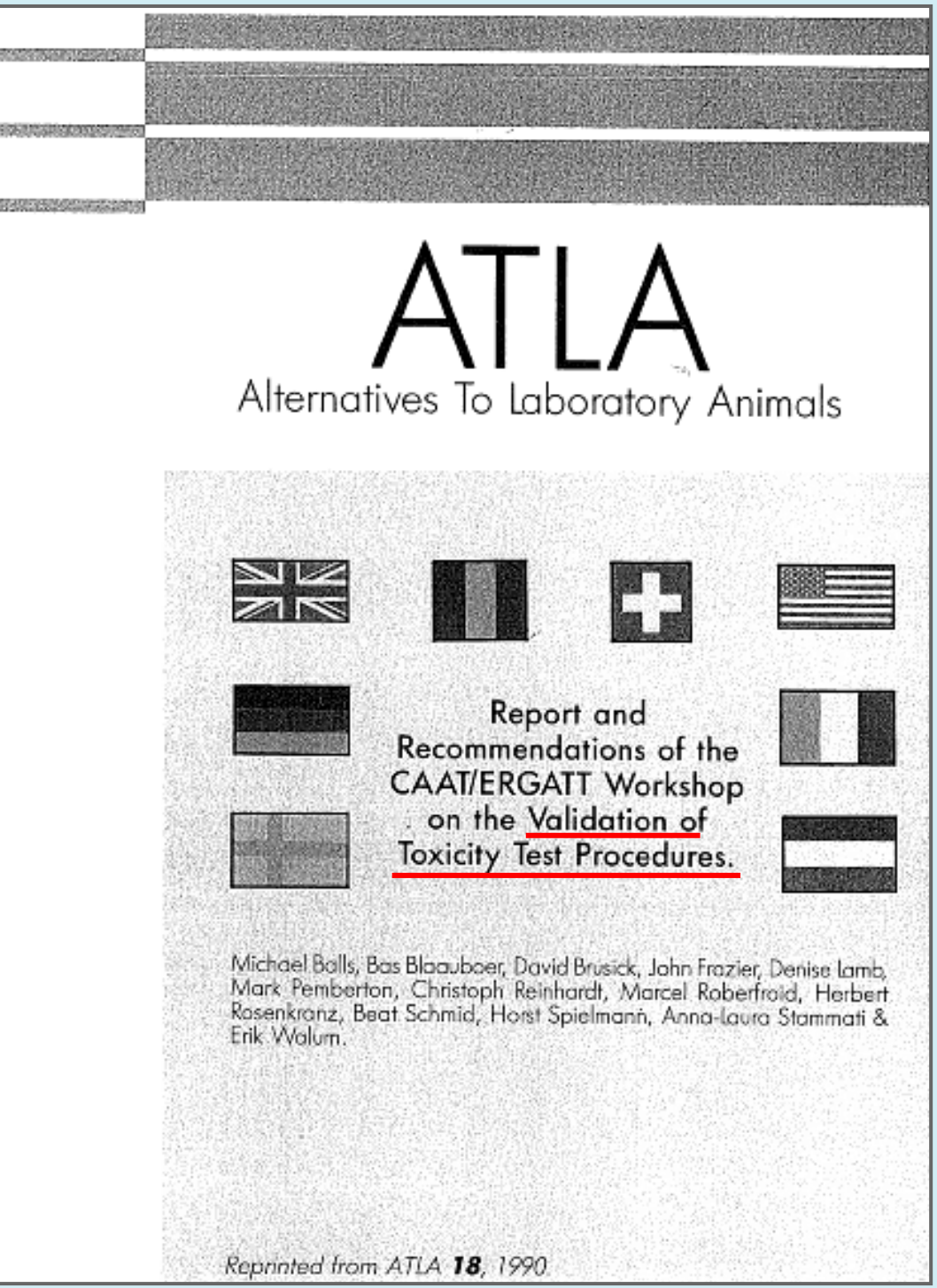
2003 ECVAM proposes "modular approach to validation"

2004 ECVAM WS on "Weight of Evidence (WoE) validation"

2005 OECD GD 34 on the "validation of new an updated methods for hazard assessment"

2004-2007 ECVAM validation study on in vitro tests for skin irritation ➔successful

1990 the first workshops on validation & acceptance



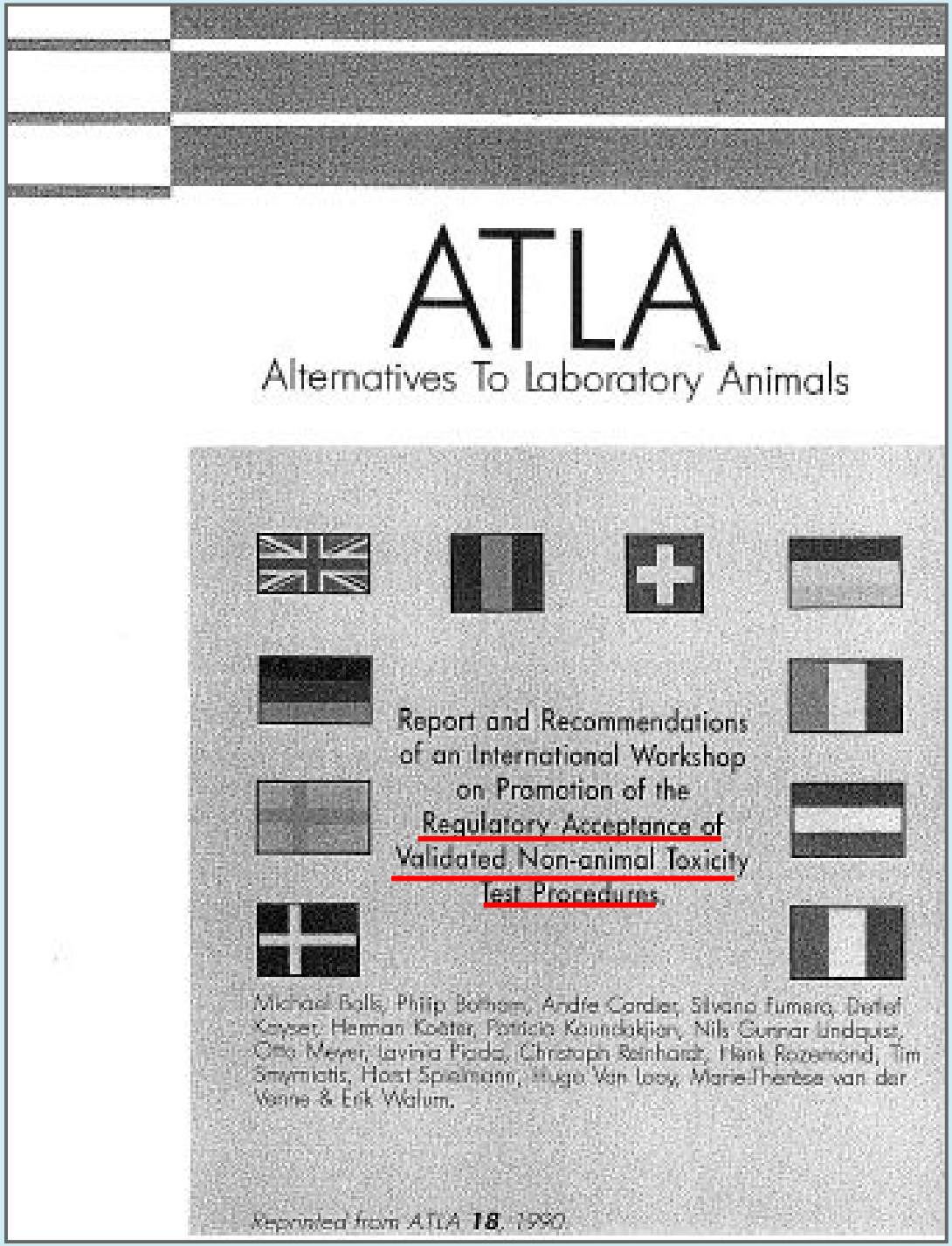
ATLA

Alternatives To Laboratory Animals

Report and Recommendations of the CAAT/ERGATT Workshop on the Validation of Toxicity Test Procedures.

Michael Balls, Bas Blaauboer, David Brusick, John Frazier, Denise Lamb, Mark Pemberton, Christoph Reinhardt, Marcel Roberfroid, Herbert Rosenkranz, Beat Schmid, Horst Spielmann, Anna-Laura Stammati & Erik Walum.

Reprinted from ATLA **18**, 1990



ATLA

Alternatives To Laboratory Animals

Report and Recommendations of an International Workshop on Promotion of the Regulatory Acceptance of Validated Non-animal Toxicity Test Procedures

Michael Balls, Philip Botham, André Cardier, Silvana Fumero, Detlef Keyser, Herman Koëter, Patricia Kouroukjian, Nils Gunnar Lindquist, Otto Meyer, Lavinia Prada, Christoph Reinhardt, Henk Rozemond, Tim Smyrniotis, Horst Spielmann, Hugo Van Looy, Marie-Thérèse van der Venne & Erik Walum.

Reprinted from ATLA **18**, 1990

Amden 1990

The Concept of Experimental Validation

Developed at the CAAT/ERGATT validation workshop in AMDEN (CH) 1990 (ATLA 18, 313-337, 1990)

DEFINITION

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

Experimental procedure

TEST-DEVELOPMENT

---

(1) intra-laboratory evaluation

↓

(2) inter-laboratory evaluation

↓

(3) data base development

↓

(4) Independen evaluation (peer review)

} VALIDATION

REGULATORY ACCEPTENCE

Amden II - 1994

ECVAM

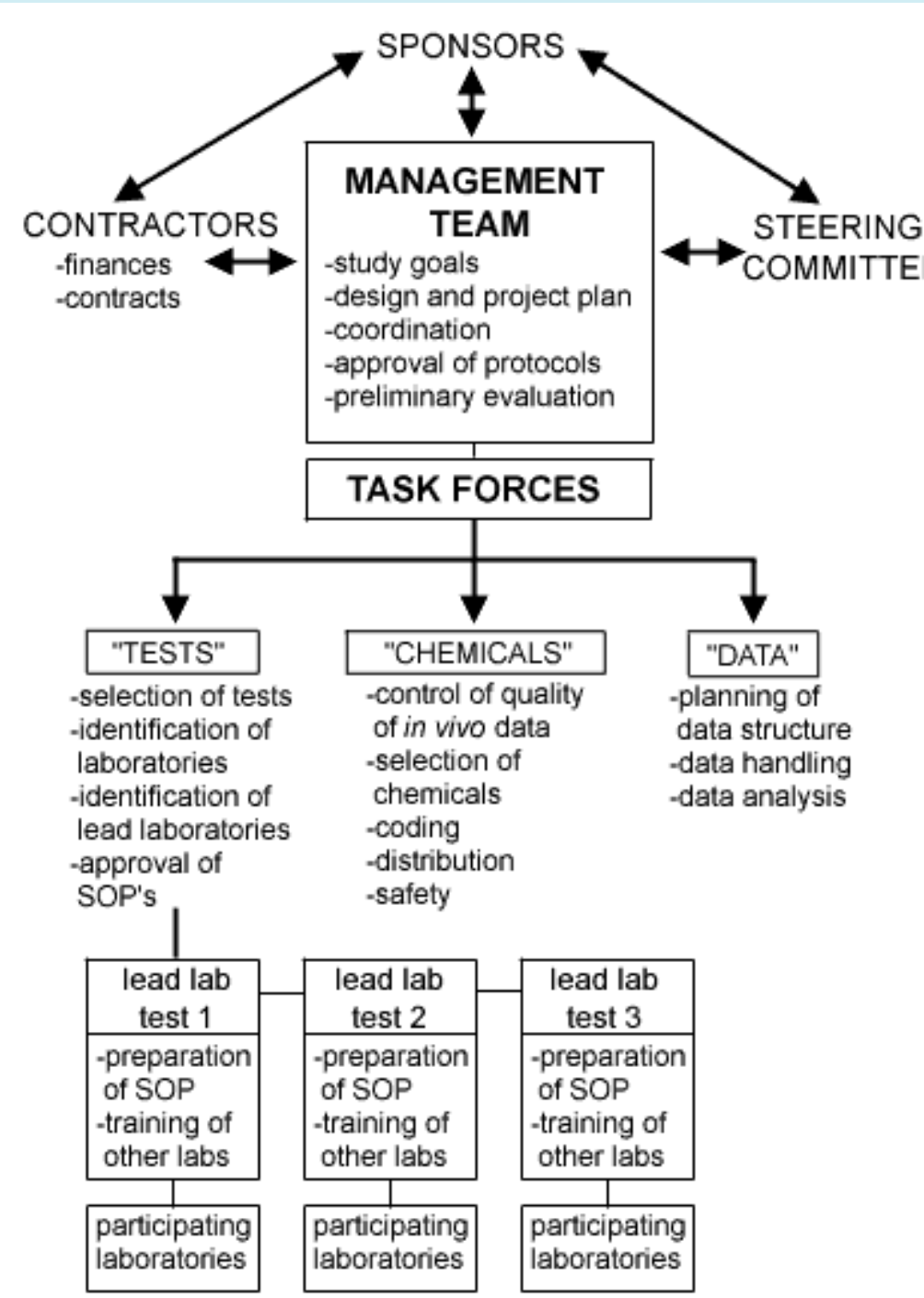
ATLA 23, 129–147, 1995

Practical Aspects of the Validation of Toxicity Test Procedures

The Report and Recommendations of ECVAM Workshop 5[1,2]

Michael Balls[3], Bas J. Blaauboer[4], Julia H. Fentem[3], Leon Bruner[5], Robert D. Combes[6], Björn Ekwall[7], Robin J. Fielder[8], André Guillouzo[9], Richard W. Lewis[10], David P. Lovell[11], Christoph A. Reinhardt[12], Guillermo Repetto[13], Dariusz Sladowski[14], Horst Spielmann[15] and Flavia Zucco[16]

Management of validation studies



Prevalidation 1995

ATLA **23**, 211-217, 1995

The Role of Prevalidation in the Development, Validation and Acceptance of Alternative Methods

Rodger D. Curren[1], Jacqueline A. Southee[2], Horst Spielmann[3], Manfred Liebsch[3], Julia H Fentem[4] and Michael Balls[4]

Prevalidation scheme

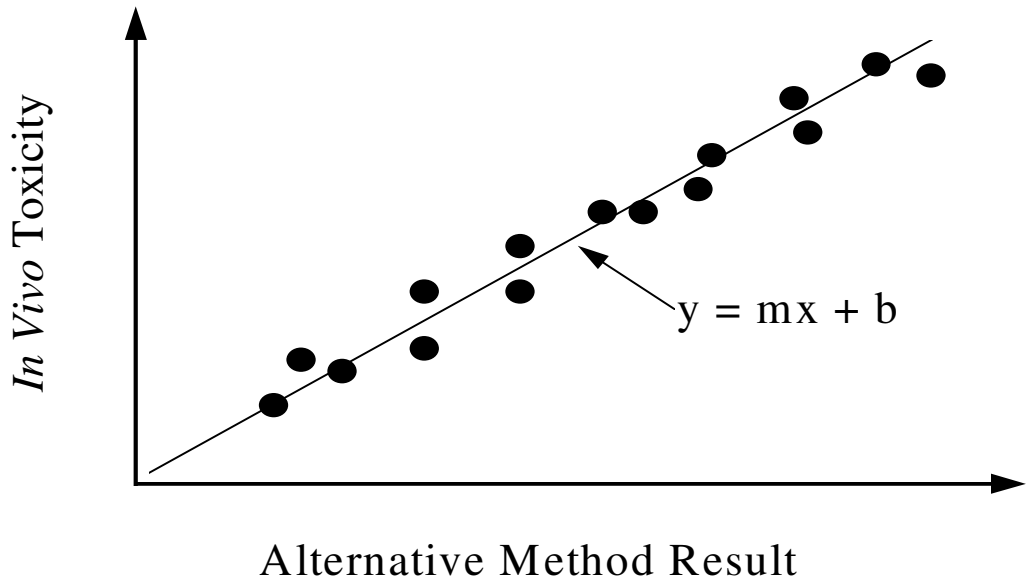
proposal for a prevalidation study (laboratory 1)

1. protocol refinement (laboratory 2)

2. protocol transfer (laboratory 3)

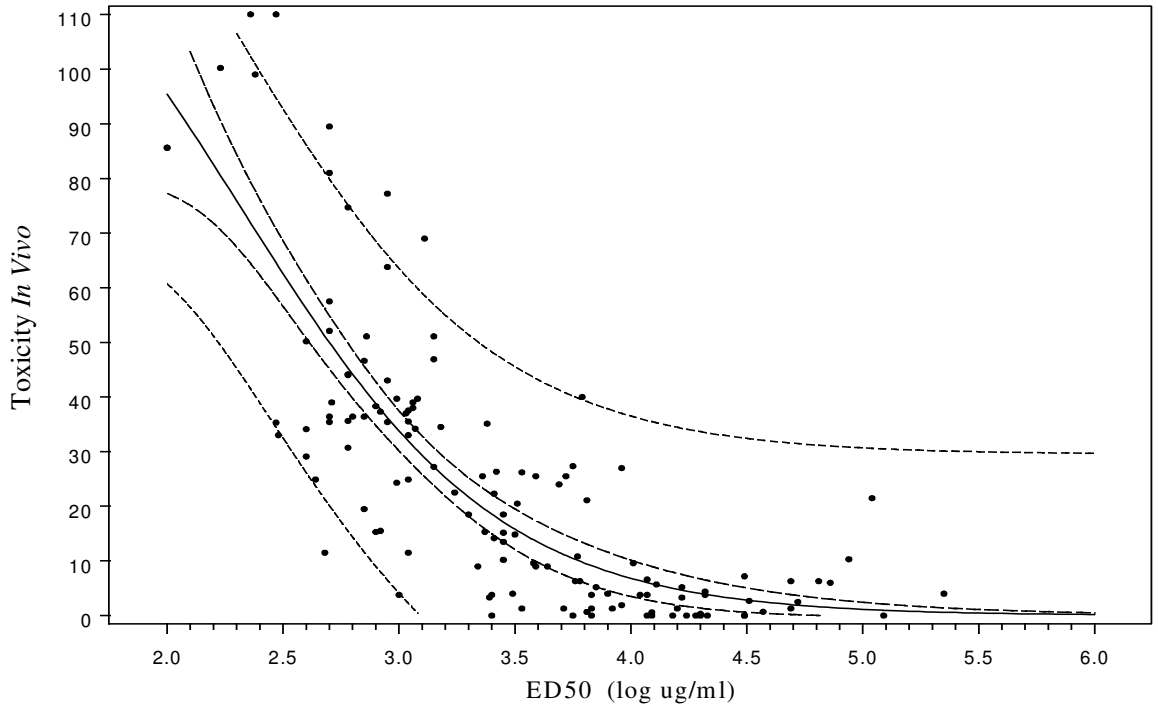
3. protocol performance. (laboratories 1-3)

Biostatistically based PREDICTION MODELS



in vitro/in vivo correlation

may be simple, e.g. linear



...or more complex

Harmonised OECD Validation Concept 1996 & ECVAM, ICCVAM (USA)

Test Development

- basis
- need
- protocol
- prediction model

Scheme for Prevalidation

- optimisation protocol
- interlaboratory transferability
- optimisation

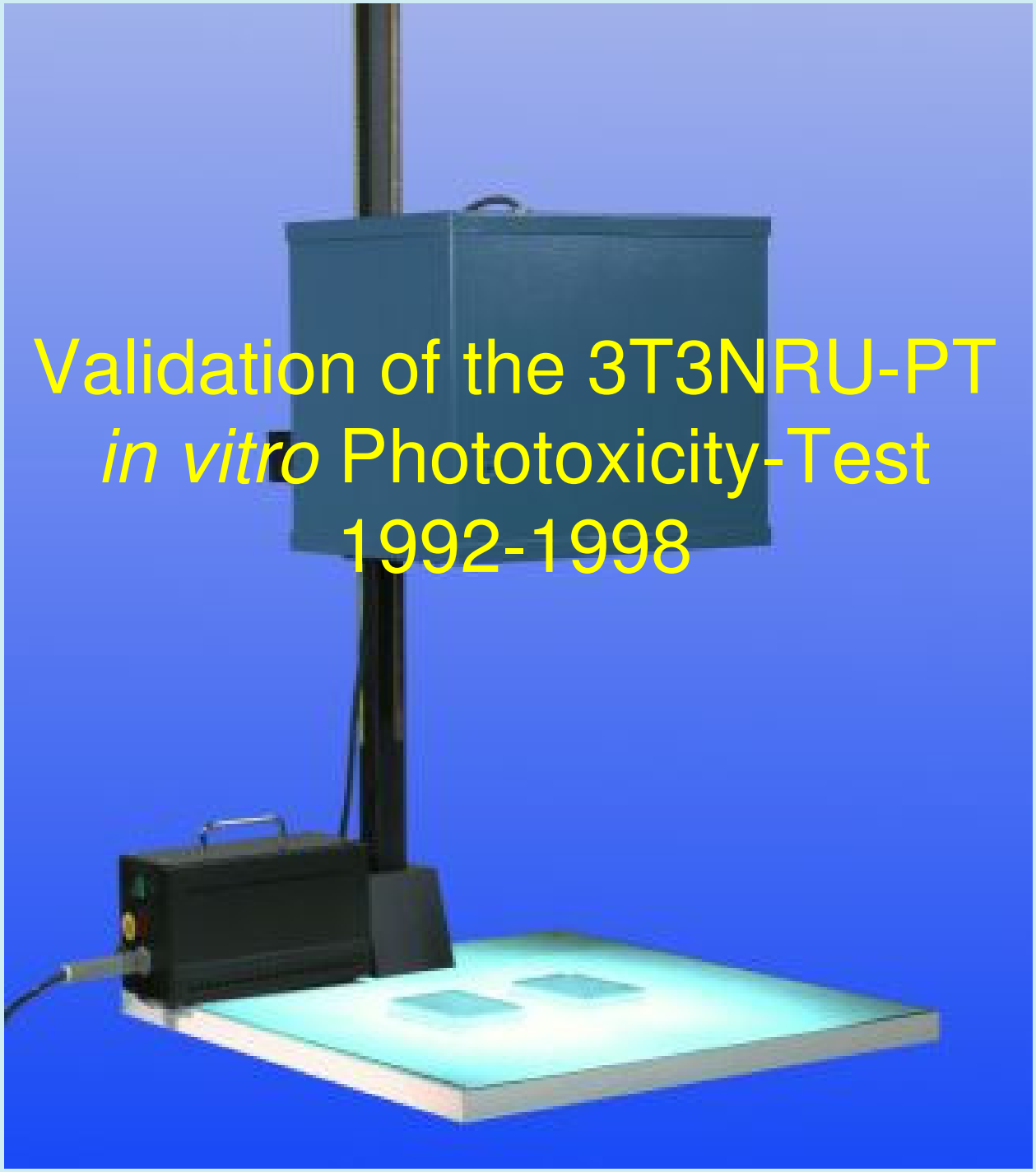
Validation

- blind trial
- relevance

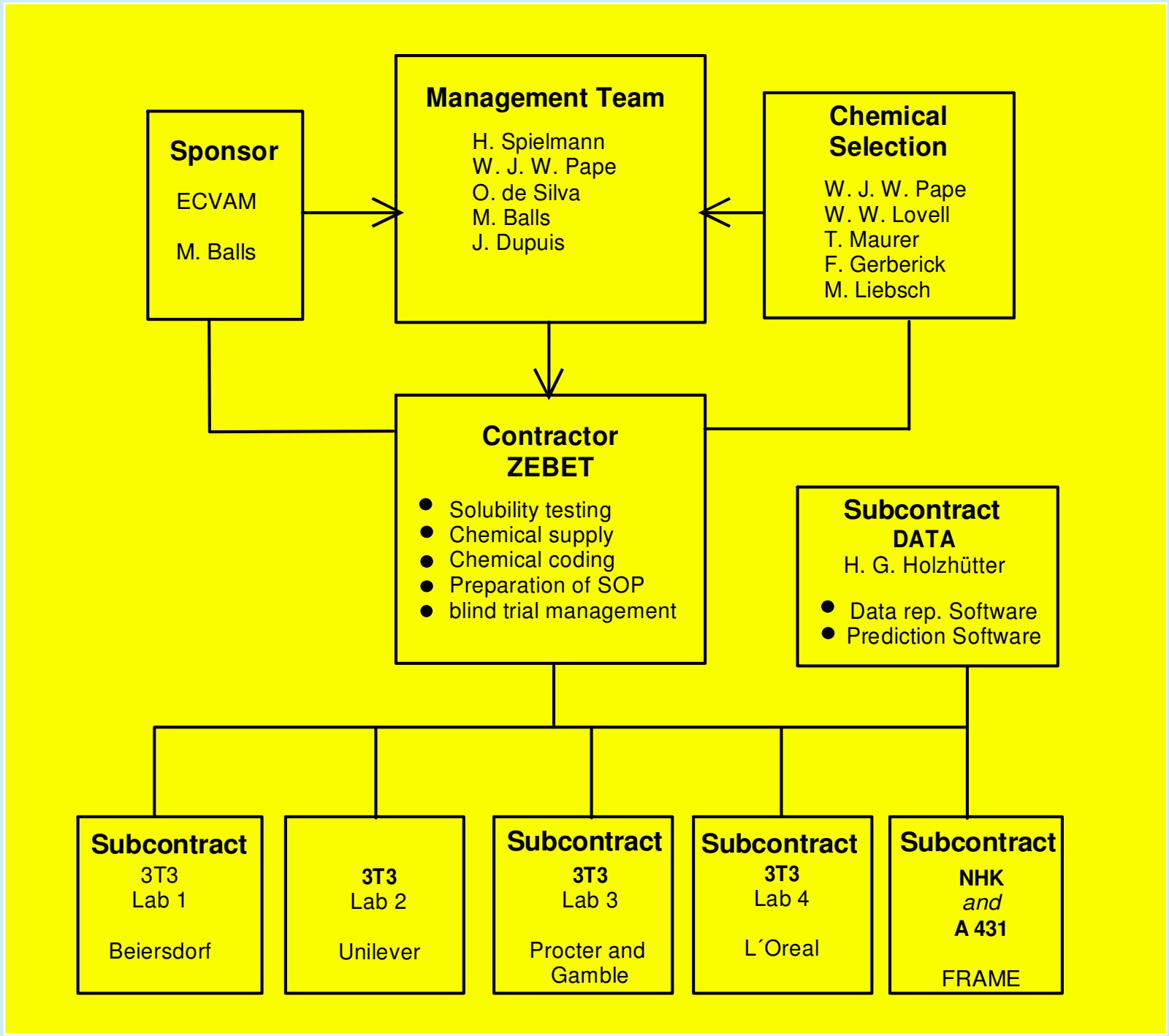
Independent Evaluation

Regulatory Acceptance

In vitro phototoxicity



Management of the UV Filter Study



The ECVAM International Validation Study of three in vitro embryotoxicity tests

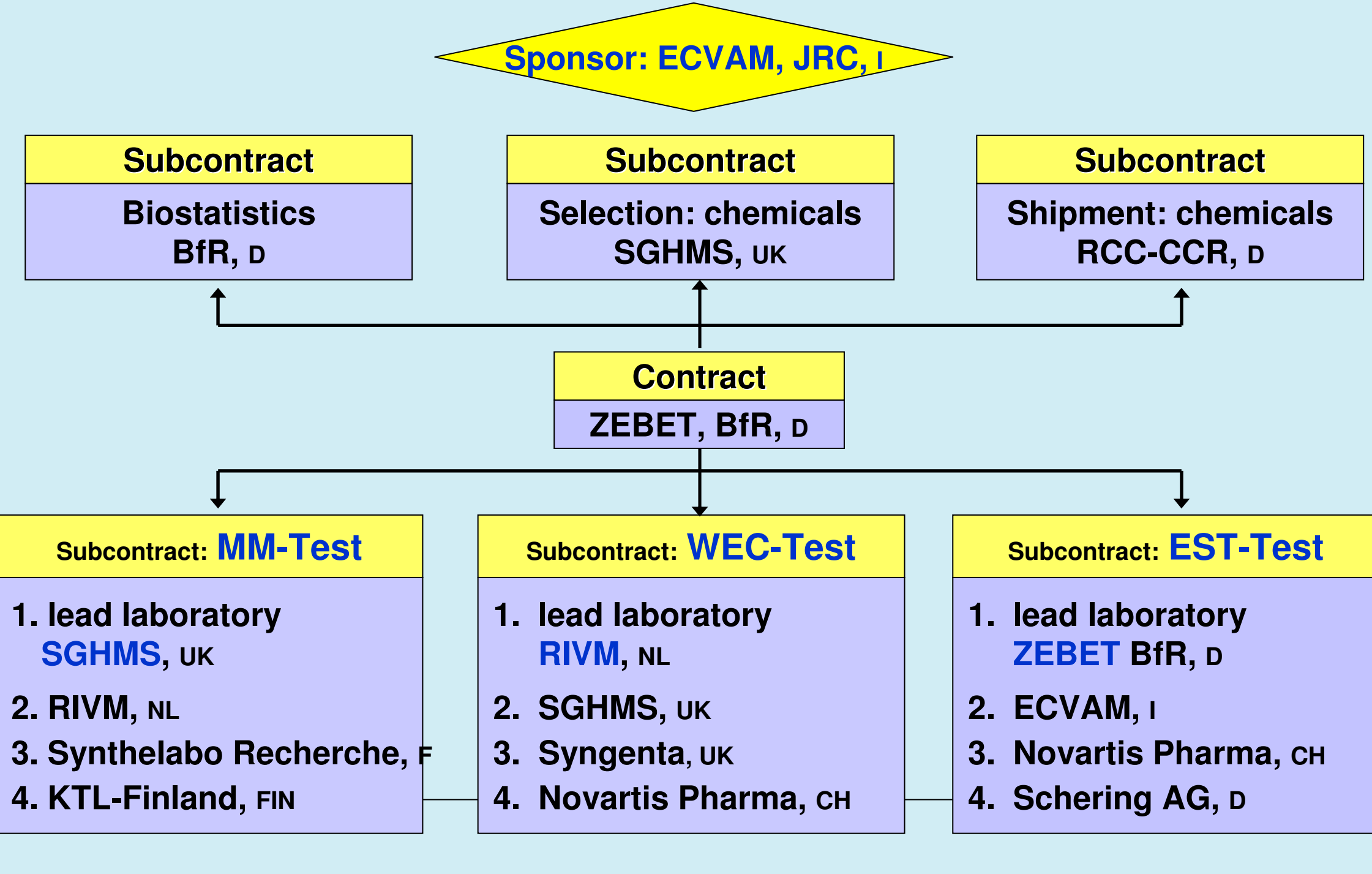
1998-2002

Embryonic Stem Cell Test (EST) (mouse = mEST)

Micromass (MM) Test (rat)

Whole Embryo Culture (WEC) Test (rat)

Management and Organisation of the ECVAM Embryotoxicity Validation Study 1998-2002



ECVAM Validation Study of Three in vitro Embryotoxicity Tests

CONCLUSIONS FROM THE STUDY

The ECVAM Scientific Advisory Committee ESAC concluded at the meeting in June of 2002 - published in ATLA - that the

- ➔ **the the 3 in vitro embryotoxicity tests WEC, MM and EST have successfully been validated according to the ECVAM validation criteria.**
- ➔ **Early in 2003 an ECVAM WORKSHOP will evaluate how the 3 in vitro embryotoxicity tests may be used by the industry and/or for regulatory purposes !**
- ➔ **Today the EST is established in several laboratories of the international drug industry.**

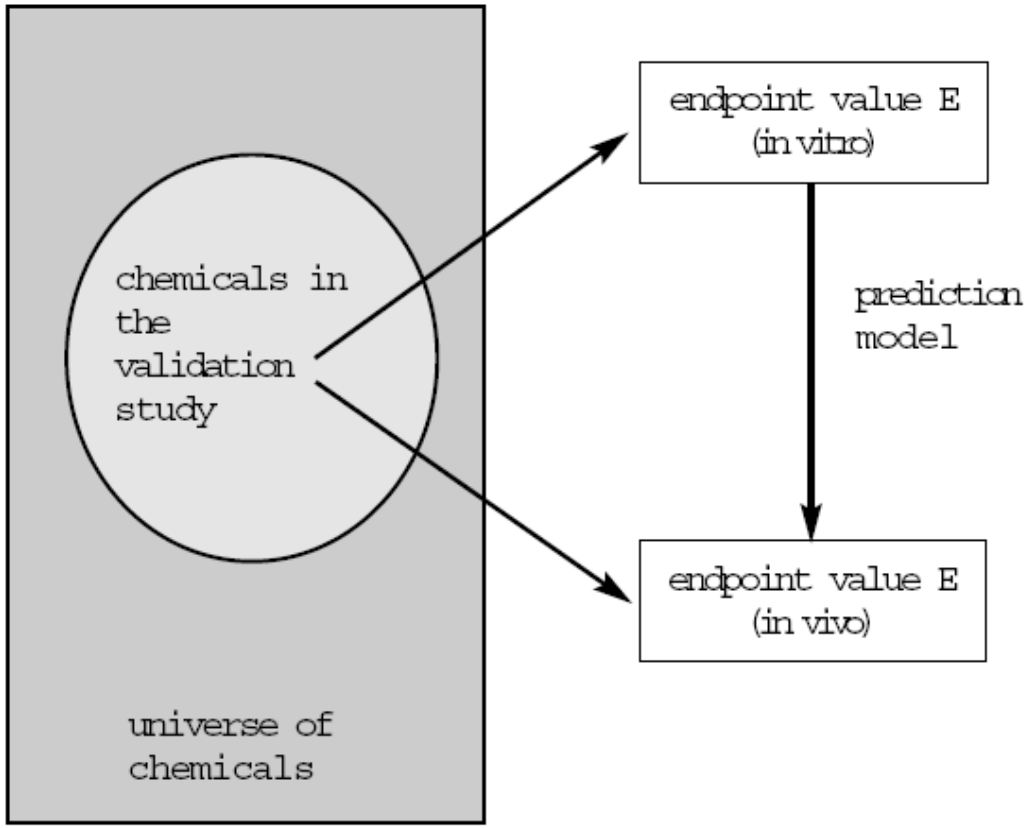
ATLA **25**, 505–516, 1997

The Validation of Toxicological Prediction Models

Graeme Archer,[1] Michael Balls,[1] Leon H. Bruner,[2] Rodger D. Curren,[3] Julia H. Fentem,[1] Hermann-Georg Holzhütter,[4] Manfred Liebsch,[5] David P. Lovell[6] and Jacqueline A. Southee[7]

[1]ECVAM, JRC Environment Institute, 21020 Ispra (VA), Italy; [2]The Procter & Gamble Company, Health and Beauty Care Europe, Egham, Surrey TW20 9NW, UK; [3]Institute for In Vitro Sciences Inc., Suite 220, 21 Firstfield Road, Gaithersburg, MD 20878, USA; [4]Humboldt-Universität zu Berlin, Bereich Medizin (Charité), Institut für Biochemie, Mon Bijou Strasse 2a, 10117 Berlin, Germany; [5]ZEBET, Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (BgVV), Diedersdorfer Weg 1, 12277 Berlin, Germany; [6]BIBRA International, Woodmansterne Road, Carshalton, Surrey SM5 4DS, UK; [7]Microbiological Associates Ltd, Stirling University Innovation Park, Stirling FK9 4NF, UK

Figure 1: A schematic representation of the role of the prediction model in an alternative method

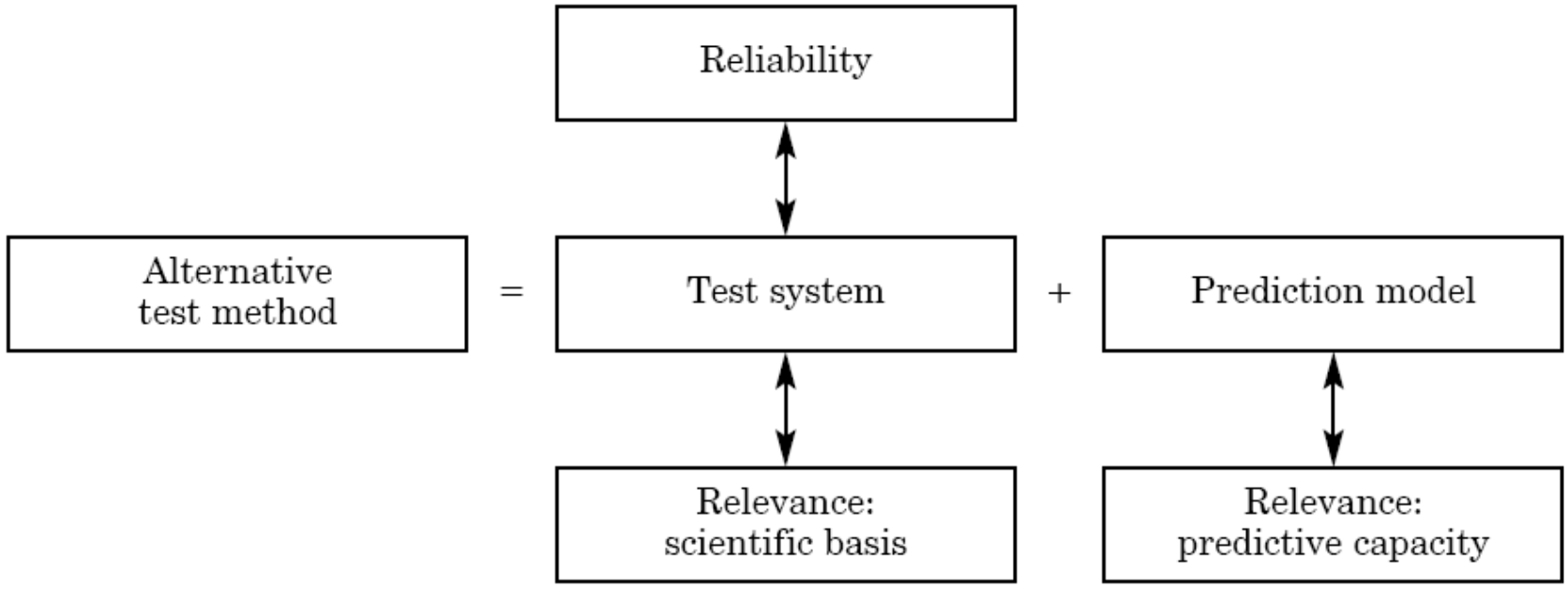


ATLA **29**, 135–143, 2001

The Importance of the Prediction Model in the Validation of Alternative Tests

Andrew P. Worth and Michael Balls

Figure 1: A schematic representation of an alternative test and its performance properties



Catch-up validation concept 1997

ATLA **25**, 483–484, 1997

Editorial

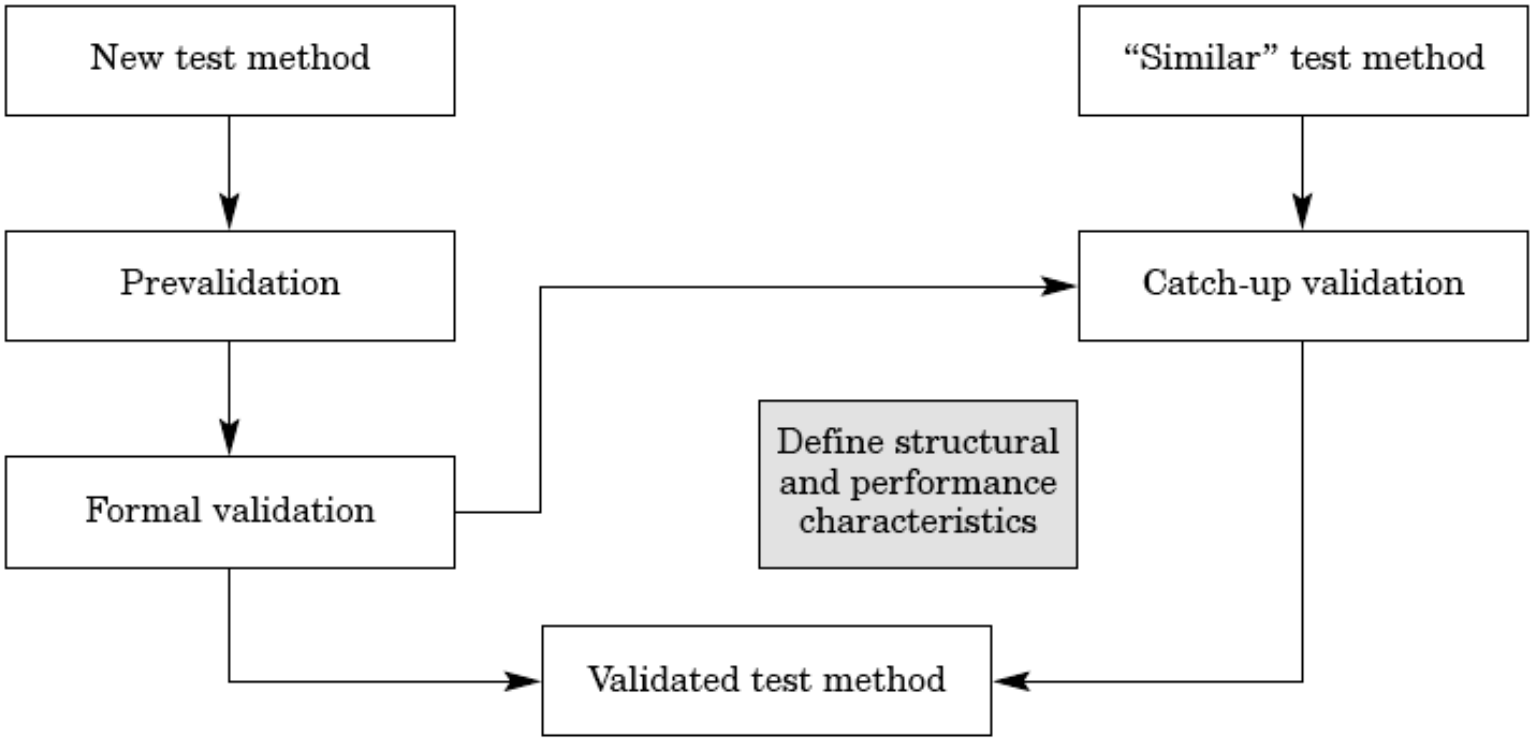
Michael Balls

Defined Structural and Performance Criteria would Facilitate the Validation and Acceptance of Alternative Test Procedures

It is for this reason that ECVAM and ZEBET are supporting studies on the applicability for *in vitro* corrosivity and photoirritancy testing of another human reconstituted human skin equivalent, EpiDerm™, made by MatTek, which, happily, promises to survive longer than its competitors. We are using our experience with Skin[2] and EPISKIN to speed up the acceptance of EpiDerm, not because we have any particular interest in MatTek or its products, but because we do not want much valuable experience to be wasted or the undoubted promise of this kind of test system to be lost.

Catch-up validation concept 1997

Figure 2: A schematic representation of the European Centre for the Validation of Alternative Methods (ECVAM) validation process



First successful Catch-up validation 2000

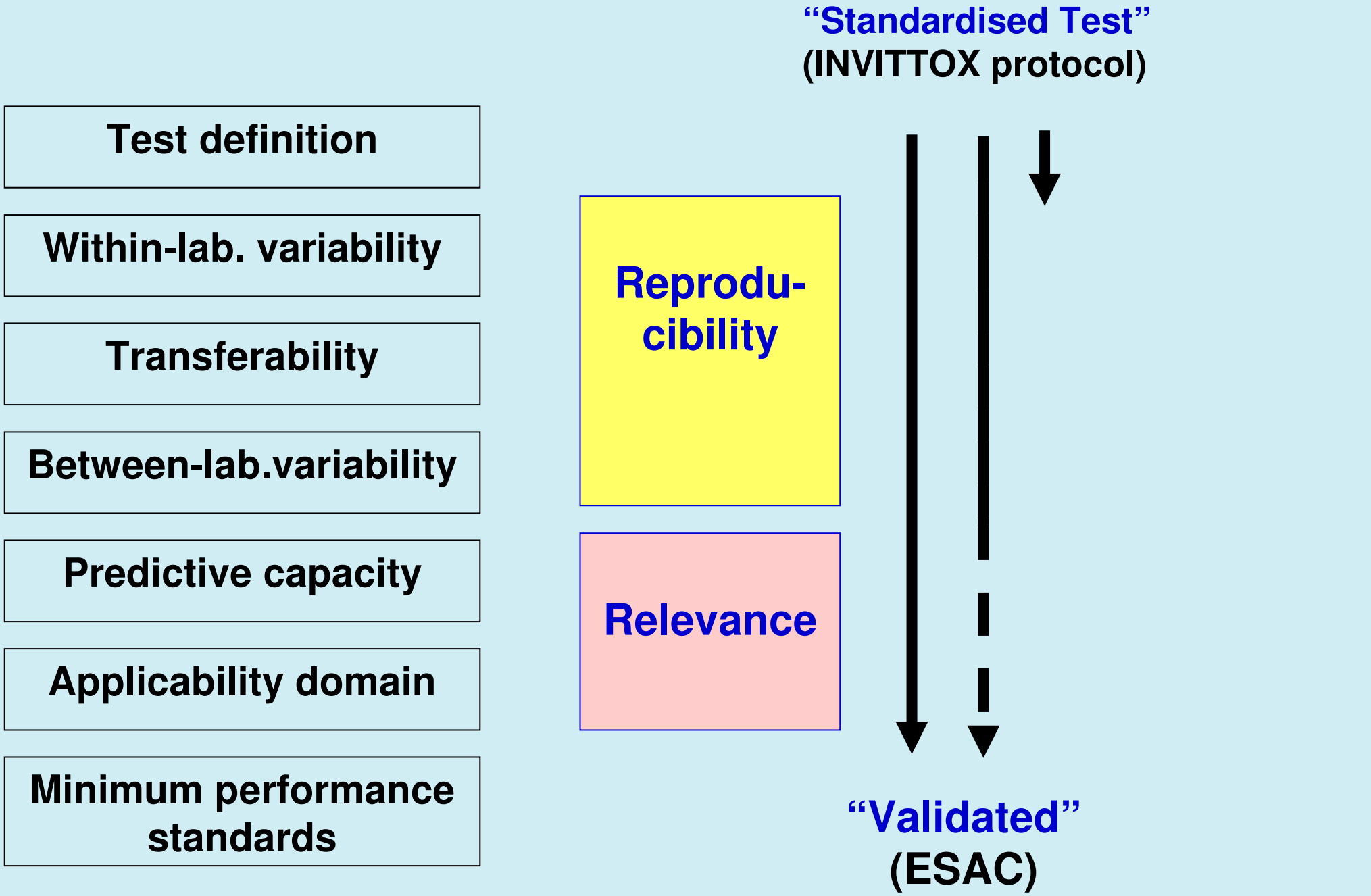
ATLA **28**, 371–401, 2000

The ECVAM Prevalidation Study on the Use of EpiDerm for Skin Corrosivity Testing

Manfred Liebsch,[1] Dieter Traue,[1] Christa Barrabas,[1] Horst Spielmann,[1] Patricia Uphill,[2] Susan Wilkins,[2] Janet P. McPherson,[2] Christiane Wiemann,[3] Tanja Kaufmann,[3] Martina Remmele[3] and Hermann-Georg Holzhütter[4]

[1]ZEBET, BgVV, Diedersdorfer Weg 1, 12277 Berlin, Germany; [2]Huntingdon Life Sciences, Huntingdon, Cambridgeshire PE18 6ES, UK; [3]BASF AG, Department of Product Safety, 67056 Ludwigshafen, Germany; [4]Institut für Biochemie, Humboldt-Universität zu Berlin, Monbijoustrasse 2a, 10117 Berlin, Germany

ECVAM's Modular Approach to Validation 2003



ECVAM's WoE Approach to Validation 2004

ATLA 34, 603–620, 2006

The Principles of Weight of Evidence Validation of Test Methods and Testing Strategies

The Report and Recommendations of ECVAM Workshop 58[a]

Michael Balls,[1] Patric Amcoff,[2] Susanne Bremer,[3] Silvia Casati,[3] Sandra Coecke,[3] Richard Clothier,[4] Robert Combes,[1] Raffaella Corvi,[3] Rodger Curren,[5] Chantra Eskes,[3] Julia Fentem,[6] Laura Gribaldo,[3] Marlies Halder,[3] Thomas Hartung,[3] Sebastian Hoffmann,[3] Leonard Schechtman,[7] Laurie Scott,[3,b] Horst Spielmann,[8] William Stokes,[9] Raymond Tice,[9] Drew Wagner[2,c] and Valérie Zuang[3]

[1]FRAME, Nottingham, UK; [2]Environment Directorate, OECD, Paris, France; [3]ECVAM, Institute for Health & Consumer Protection, EC Joint Research Centre, Ispra, Italy; [4]School of Biomedical Sciences, University of Nottingham, Nottingham, UK; [5]Institute for In Vitro Sciences, Gaithersburg, MD, USA; [6]SEAC, Unilever, Sharnbrook, Beds., UK; [7]National Center for Toxicological Research, Food and Drug Administration, Rockville, MD, USA; [8]ZEBET, Federal Institute for Risk Assessment (BfR), Berlin, Germany; [9]National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

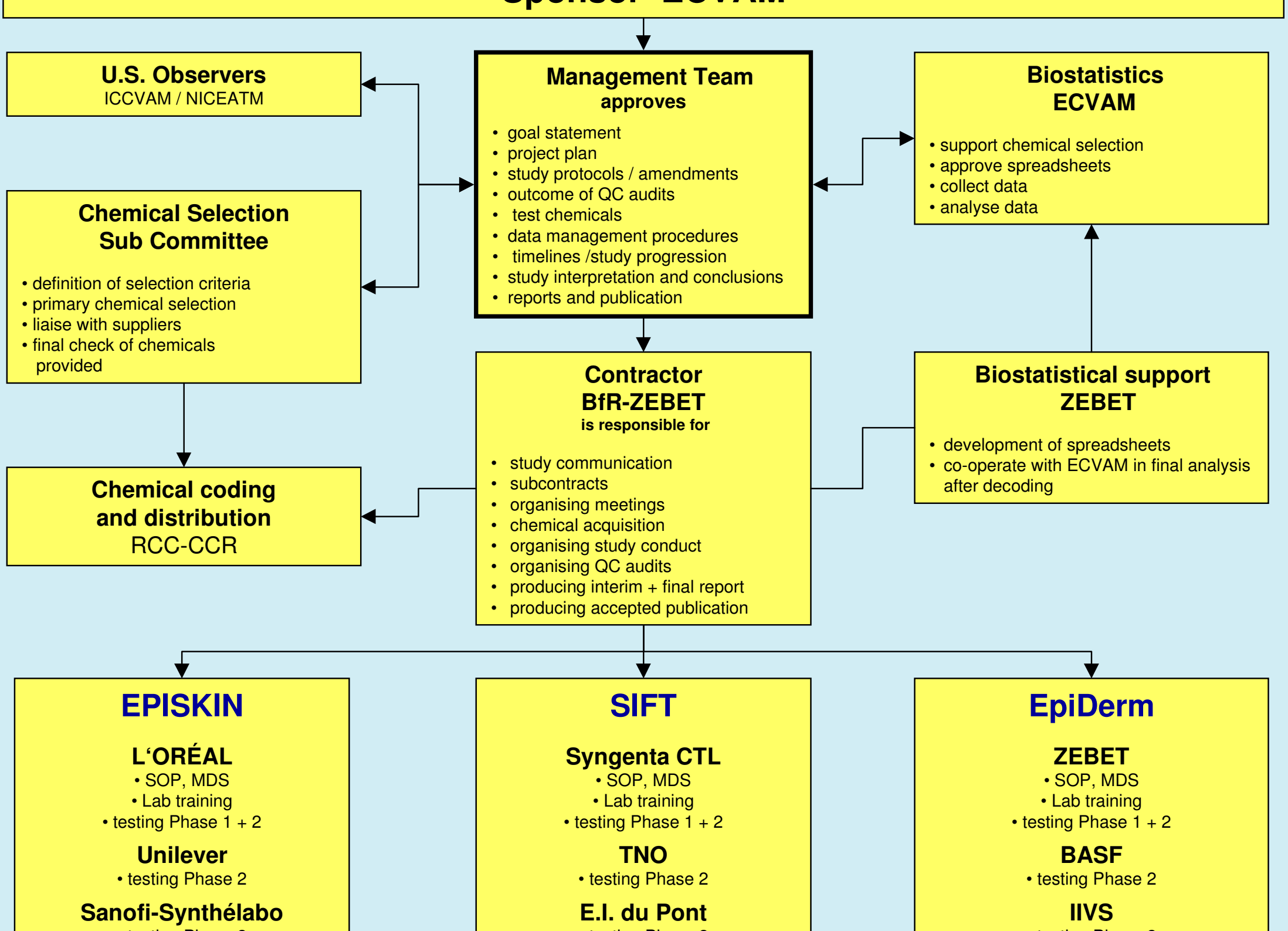
ECVAM in vitro Skin Irritation validation Study (2004 - 2007)

ATLA 35, 559–601, 2007

The ECVAM International Validation Study on *In Vitro* Tests for Acute Skin Irritation: Report on the Validity of the EPISKIN and EpiDerm Assays and on the Skin Integrity Function Test[a]

Horst Spielmann,[1] Sebastian Hoffmann,[2] Manfred Liebsch,[1] Phil Botham,[3] Julia H. Fentem,[4] Chantra Eskes,[2] Roland Roguet,[5] José Cotovio,[5] Thomas Cole,[6] Andrew Worth,[6] Jon Heylings,[3] Penny Jones,[4] Catherine Robles,[7] Helena Kandárová,[1] Armin Gamer,[8] Marina Remmele,[8] Rodger Curren,[9] Hans Raabe,[9] Amanda Cockshott,[10] Ingrid Gerner[11] and Valérie Zuang[2]

[1]National Centre for Alternative Methods (ZEBET), Berlin, Germany; [2]ECVAM, Institute for Health & Consumer Protection, European Commission Joint Research Centre, Ispra, Italy; [3]Syngenta, Macclesfield, UK; [4]Unilever, Sharnbrook, UK; [5]L'Oréal, Clichy, France; [6]ECB, Institute for Health & Consumer Protection, European Commission Joint Research Centre, Ispra, Italy; [7]Sanofi Aventis, Montpellier, France; [8]BASF, Ludwigshafen, German; [9]Institute for In Vitro Sciences, Gaithersburg, MD, USA; [10]Health and Safety Executive (HSE), Bootle, UK; [11]Federal Institute for Risk Assessment (BfR), Berlin, Germany


Sponsor: ECVAM
U.S. Observers
ICCVAM / NICEATM
Management Team
approves
• goal statement
• project plan
• study protocols / amendments
• outcome of QC audits
• test chemicals
• data management procedures
• timelines /study progression
• study interpretation and conclusions
• reports and publication
Biostatistics
ECVAM
• support chemical selection
• approve spreadsheets
• collect data
• analyse data
Chemical Selection
Sub Committee
• definition of selection criteria
• primary chemical selection
• liaise with suppliers
• final check of chemicals provided
Contractor
BfR-ZEBET
is responsible for
• study communication
• subcontracts
• organising meetings
• chemical acquisition
• organising study conduct
• organising QC audits
• producing interim + final report
• producing accepted publication
Biostatistical support
ZEBET
• development of spreadsheets
• co-operate with ECVAM in final analysis after decoding
Chemical coding
and distribution
RCC-CCR
EPISKIN
L'ORÉAL
• SOP, MDS
• Lab training
• testing Phase 1 + 2
Unilever
• testing Phase 2
Sanofi-Synthélabo
SIFT
Syngenta CTL
• SOP, MDS
• Lab training
• testing Phase 1 + 2
TNO
• testing Phase 2
E.I. du Pont
EpiDerm
ZEBET
• SOP, MDS
• Lab training
• testing Phase 1 + 2
BASF
• testing Phase 2
IIVS

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

DRAFT PROPOSAL FOR A NEW GUIDELINE

In Vitro Skin Irritation: Reconstructed Human *Epidermis* (RhE) Test Method

INTRODUCTION

1. Skin irritation refers to the production of reversible damage to the skin following the application of a test substance for up to 4 hours [as defined by the United Nations (UN) Globally Harmonized System of Classification and Labelling of Chemicals (GHS)](1). This Test Guideline provides an *in vitro* procedure that, depending on country requirements, may allow determining the skin irritancy of chemicals as a stand-alone replacement test, as a screen, or within a testing strategy in combination with, if appropriate, a weight of evidence approach.

TODAY

OECD Environment, Health and Safety Publications
Series on Testing and Assessment
No. 34

published 2005

GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT