FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR

Risiken erkennen – Gesundheit schützen

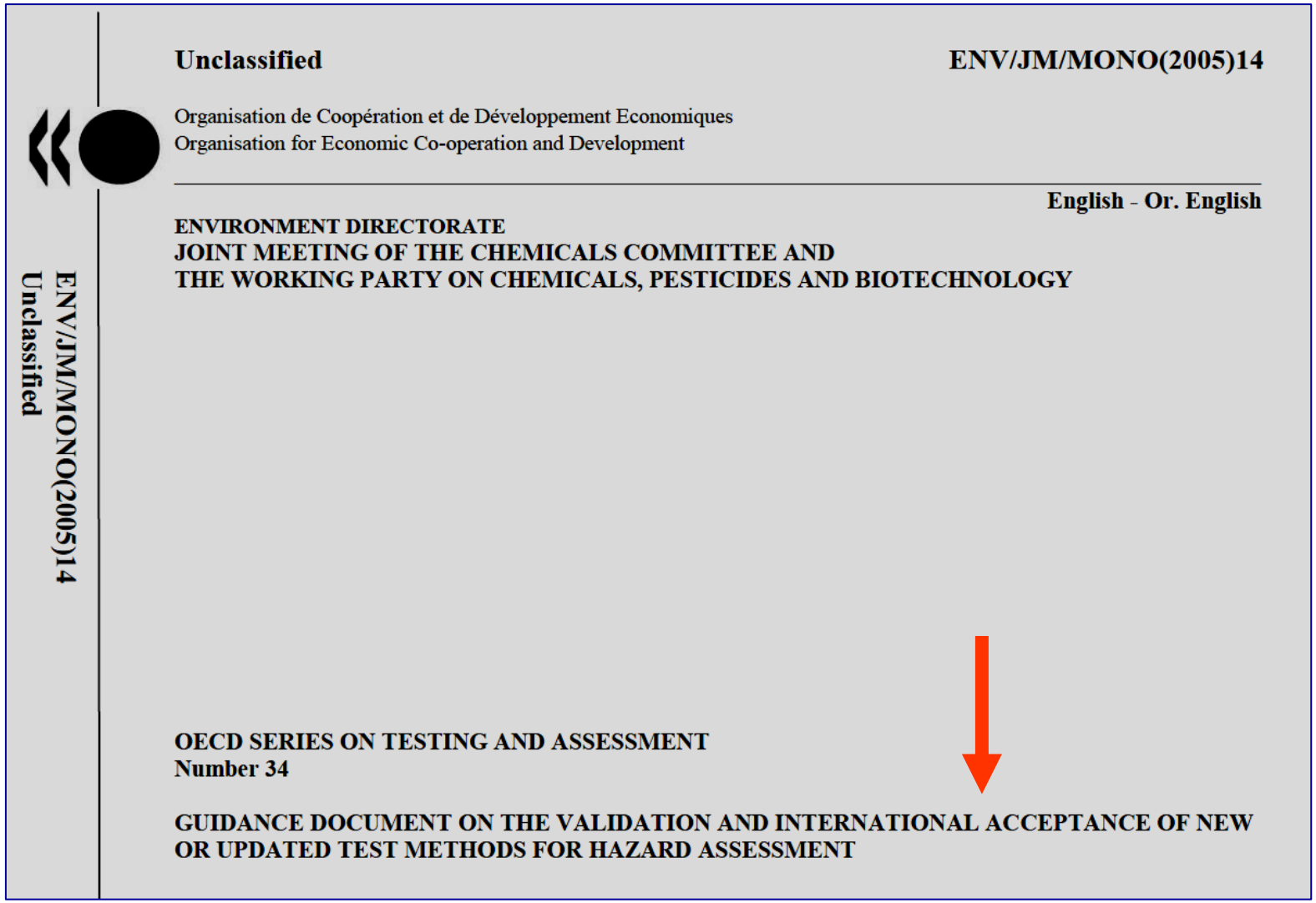
Towards the International Acceptance of alternative Methods!

Manfred Liebsch

Federal Institute for Risk Assessment

Centre for Alternative Methods to Animal Experiments - ZEBET

“Bible” in the Process of Regulatory Acceptance



Unclassified ENV/JM/MONO(2005)14

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

English - Or. English

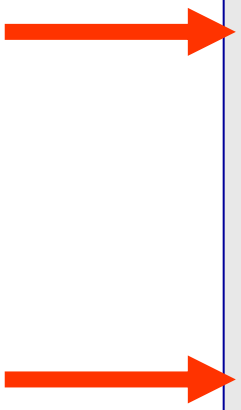
ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2005)14
Unclassified

OECD SERIES ON TESTING AND ASSESSMENT
Number 34

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

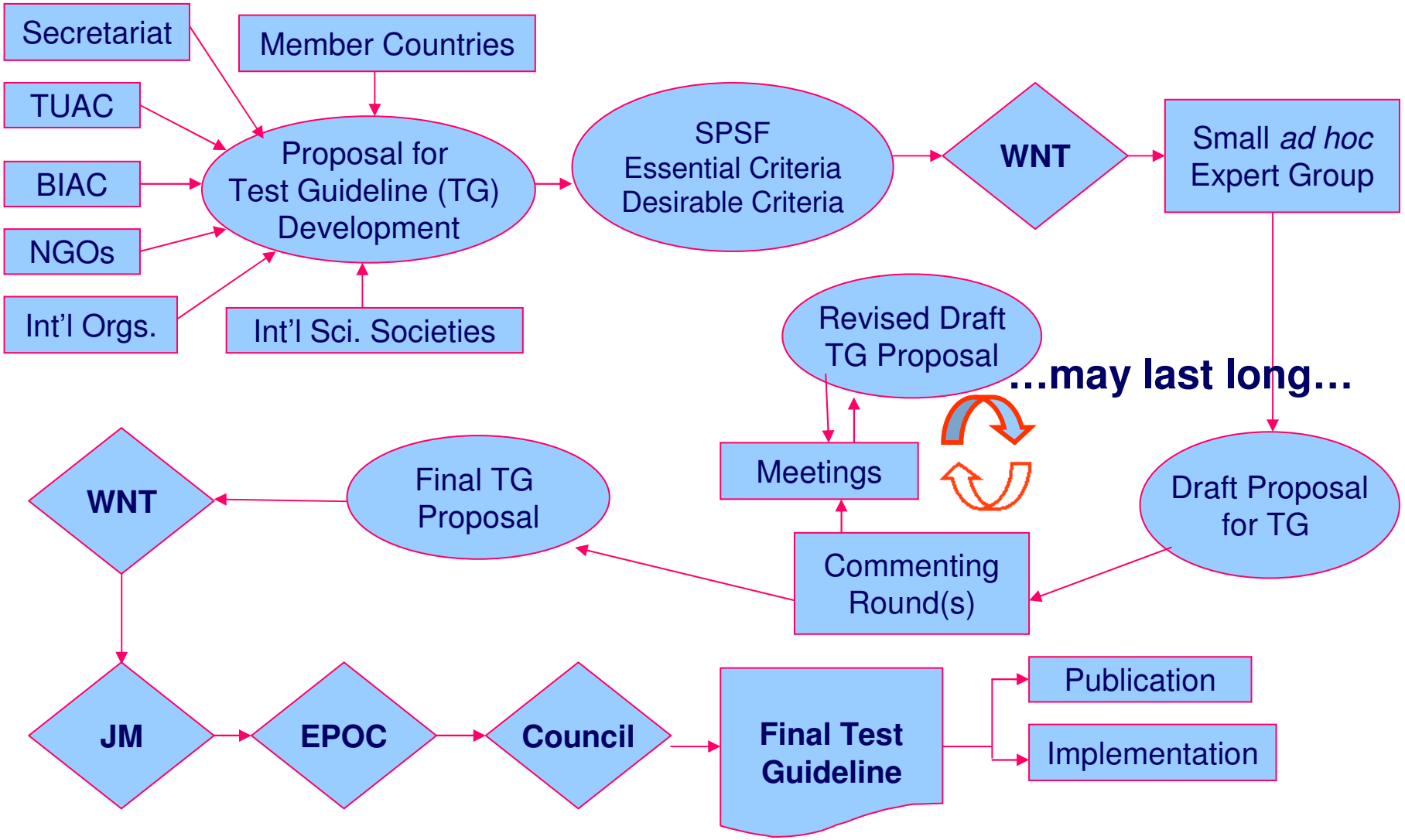
ZEBET Contributions to GD 34



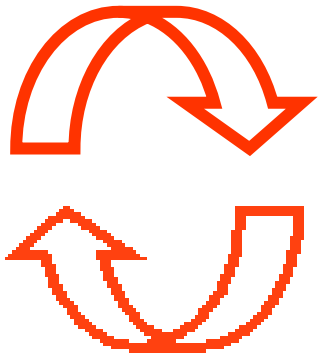
- Hans Ahr, Bayer AG, Wuppertal, Germany
- Michael Balls, EC/ECVAM, Ispra, Italy
- Robert Boethling, US-EPA, Washington, DC, USA
- Dorothy Canter, US-EPA, Washington, DC, USA
- Mark Chamberlain (BIAC) Unilever, UK
- Alan Goldberg, CAAT, Baltimore, MD, USA
- Petra Greiner, UBA, Germany
- Kailash Gupta, CPSC, Bethesda, MD, USA
- Karen Hamernik, US-EPA, Washington, DC, USA
- David Hattan, FDA, Bethesda, MD, USA
- Abigail Jacobs, FDA, Rockville, MD, USA
- Manfred Liebsch, ZEBET, Berlin, Germany
- Kimmo Louekari, Product Control Agency for Welfare and Health , Finland
- Yasuo Ohno, NIHS, Tokyo, Japan
- Willie Owens, (BIAC) Procter and Gamble, USA
- Richard Phillips, Exxon/Mobile, East Millstone, NJ, USA
- Amy Rispin, US-EPA, Washington, DC, USA
- Andrew Rowan, Humane Society of the US, Washington, DC, USA
- Len Schechtman, FDA, Rockville, MD, USA
- Jerry Smrchek, US-EPA, Washington, DC, USA
- Horst Spielmann, ZEBET, Berlin, Germany
- Martin Stephens (ICAPO), USA
- William Stokes, NIEHS, Research Triangle Park, NC, USA
- Gary Timm, US-EPA, Washington, DC, USA
- Leslie Touart, US-EPA, Washington, DC, USA
- Neil Wilcox, formerly of FDA, Rockville, MD, USA
- Marilyn Wind, CPSC, Bethesda, MD, USA
- Andrew Worth, JRC-EC, Italy
- Errol Zeiger, formerly of NIEHS, Research Triangle Park, NC, USA

Final consensus at the OECD: Bethesda 2004

OECD Test Guideline Development



…because CONSENSUS has to be reached !



…majority agreements are not sufficient !

Role of Regulators in Validation and Acceptance

Definition of information needs (suitable readouts / endpoints of the Alternative Method)

Selection of Suitable Tests

Selection of Test Chemicals

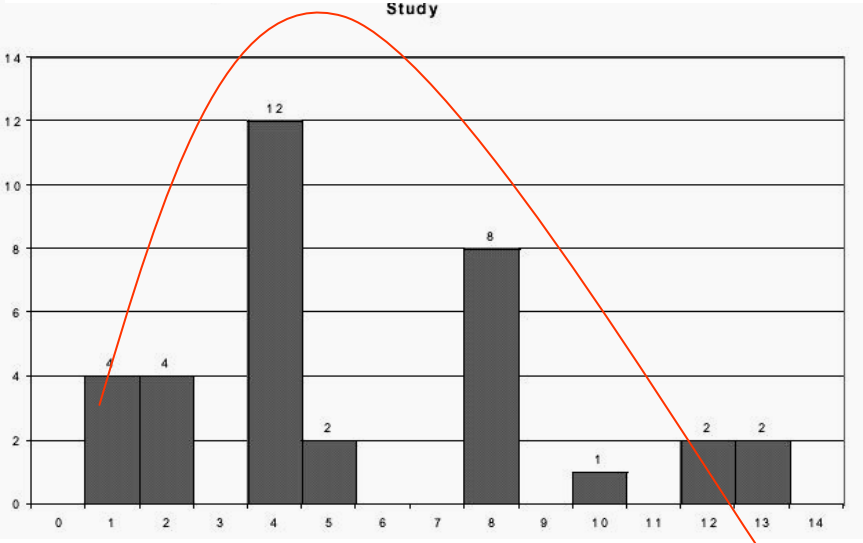
Participation in Method Peer Review

Participation in national and later international Consolidation Processes (e.g. OECD, ICH, ISO)

Participation in Definition of Performance Standards

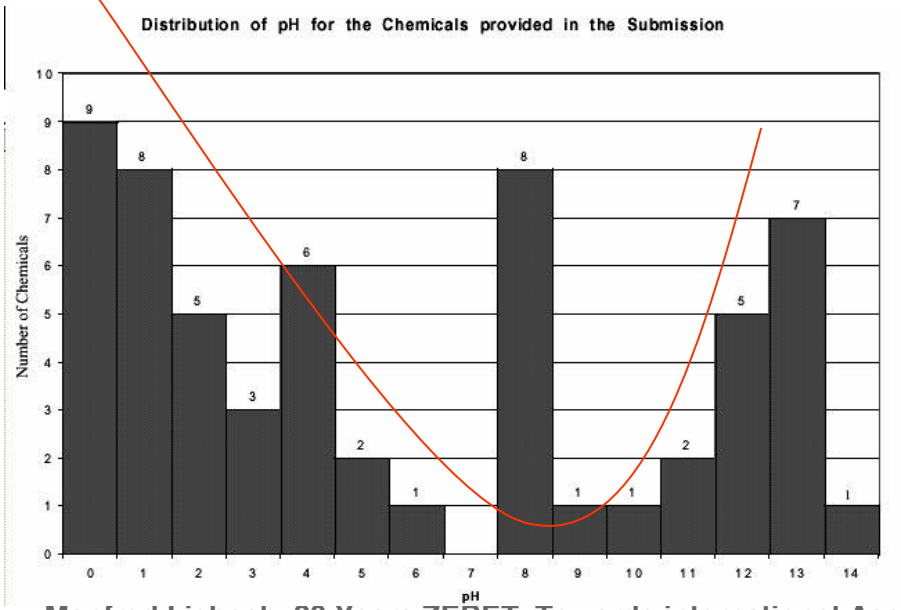
Definition of special studies to enlarge applicability domain (= enlarge regulatory acceptance in new areas than validated)

Selection of Test Chemicals



Regulator's
Chemical Selection

pH distribution
ECVAM SCVS



Test Producer's
Chemical Selection

pH distribution
ICCVAM Submission

WHY STANDARDS ?

COMPARABILITY

A while ago, we needed to study instruction manuals **to drive a new car without risk …**

WHY STANDARDS ?

COMPARABILITY

… today, when renting a modern car, we can use it within 15 minutes without risk …

… and without even reading the instruction manual

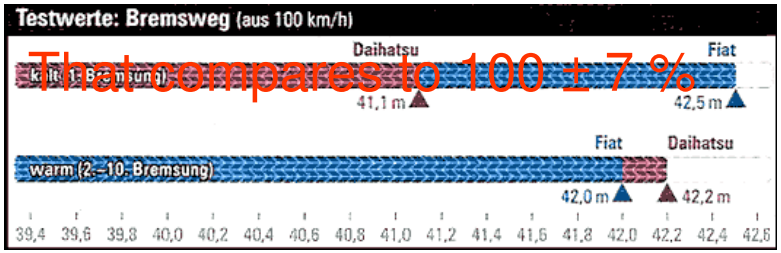
dashboards, switches, symbols, and instruments are standardised

WHY PERFORMANCE STANDARDS ?

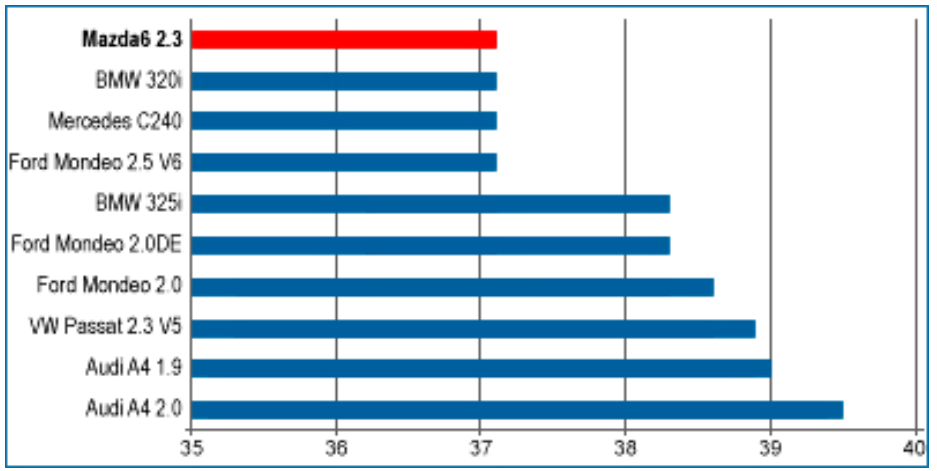
CAR SAFETY (1)

… today, we can rely on a similar performance of brakes in all cars**, regardless of their price and size:**

The braking distance (100 – 0 km/h) of all cars in the world falls in the range 37.5 -42.5 m

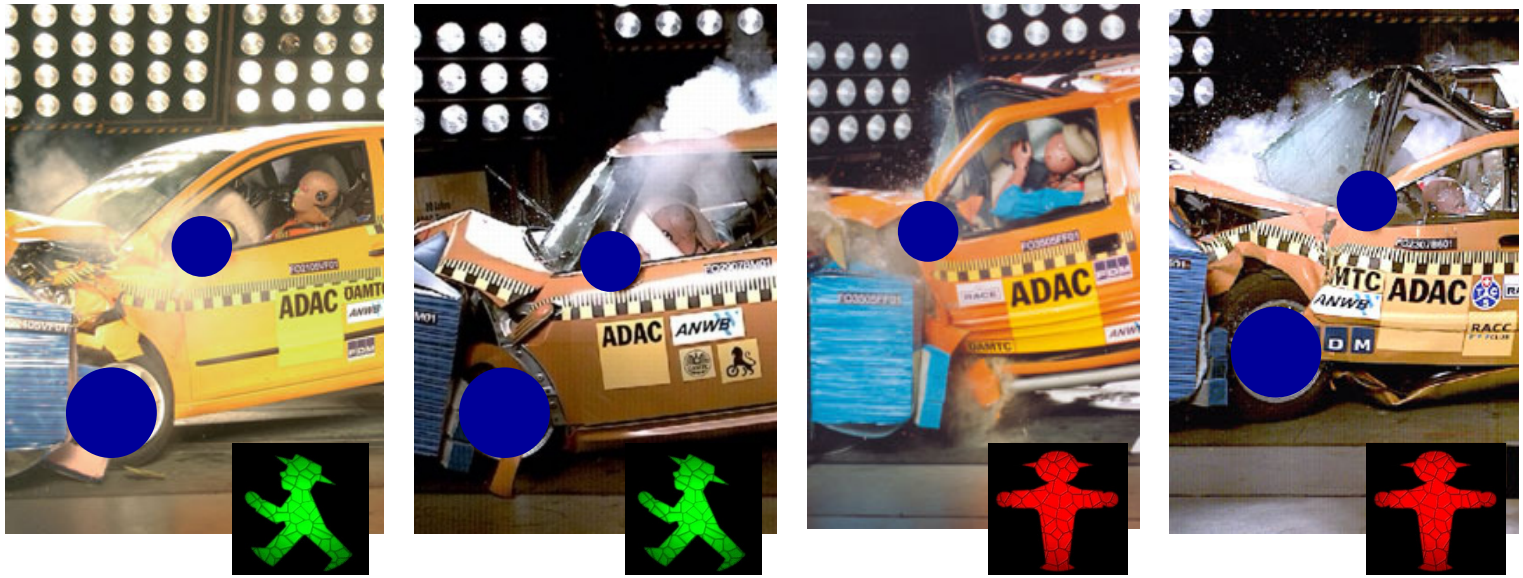


That compares to 100 ± 7 %



Braking distance (m) from 100 km/h to zero

WHY PERFORMANCE STANDARDS ?



CAR SAFETY (2)

However, in their performance to resist a crash, cars do still differ

Independent bodies are therefore defining minimum performance standards (crash test performance)

NASVA

EURO NCAP
www.euroncap.com

NHTSA
www.nhtsa.gov

ANCAP
Crash testing for safety
AUSTRALASIAN NEW CAR ASSESSMENT PROGRAM

“Father” of Performance Standards (PS)

ATLA 25, 483–484, 1997

Michael Balls, 1997

Editorial

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

The developers of new test procedures tend to want them to be tightly defined, so that they can gain their specific acceptance in the face of real or imagined competition, either for commercial reasons or to ensure that they gain the personal recognition they may deserve. However, it has become clear that this attitude is not in the interests of *in vitro* toxicology in general and may delay, or even prevent, the acceptance and application of scientifically relevant and reliable new approaches.

Three examples will illustrate the point. Firstly, Advanced Tissue Sciences withdrew their reconstituted human skin product, Skin^{2TM}, from the market, *after* it had been accepted by the US Department of Transport as a basis for classifying chemicals in terms of their skin corrosivity. Secondly, the withdrawal of Skin^2 and of EPISKIN^{TM}, a similar product made by Imedex, took place *during* a formal international study on *in vitro* tests for skin corrosivity, funded by ECVAM. Thirdly, Skin^2 was also in the process of being evaluated in the EU/

Catch up Validation

Available online at www.sciencedirect.com
SCIENCE DIRECT®

Toxicology in Vitro 20 (2006) 547–559

Toxicology in Vitro
www.elsevier.com/locate/toxinvit

Assessment of the human epidermis model SkinEthic RHE for in vitro skin corrosion testing of chemicals according to new OECD TG 431

Helena Kandárová [a,*], Manfred Liebsch [a], Horst Spielmann [a], Elke Genschow [a], Elisabeth Schmidt [a], Dieter Traue [a], Robert Guest [b], Andrew Whittingham [b], Neil Warren [b], Armin O. Gamer [c], Marina Remmele [c], Tanja Kaufmann [c], Elke Wittmer [c], Bart De Wever [d], Martin Rosdy [d]

[a] *ZEBET, Bundesinstitut für Risikobewertung, BfR, Diedersdorfer Weg 1, D-12277 Berlin, Germany*
[b] *Safepharm Laboratories, Derby, UK*
[c] *Experimental Toxicology and Ecology of BASF AG, Ludwigshafen, Germany*
[d] *SkinEthic Laboratories, Nice, France*

Received 2 June 2005; accepted 21 November 2005
Available online 7 February 2006

Important: General Performance Standards defined in OECD TG 431 !

ECVAM Accepted:

EUROPEAN COMMISSION
DIRECTORATE GENERAL JRC
JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection
European Centre for the Validation of Alternative Methods (ECVAM)

STATEMENT ON THE APPLICATION OF THE SKINETHIC™ HUMAN SKIN MODEL FOR SKIN CORROSIVITY TESTING

At its 25th Meeting, held on 16-17 November 2006 at the European Centre for the Validation of Alternative Methods (ECVAM), Ispra, Italy, the non-Commission members of the ECVAM Scientific Advisory Committee (ESAC)[1] unanimously endorsed the following statement:

On the basis of a peer review[2] of the results of an inter-laboratory study[3] with the SkinEthic™ reconstituted human epidermal (RHE) model, the Committee endorses the conclusion that the SkinEthic™ human skin model can be used for distinguishing between corrosive and non-corrosive chemicals within the context of the OECD test guideline, TG 431.

Thomas Hartung
Head of Unit
ECVAM
Institute for Health & Consumer Protection
Joint Research Centre
European Commission
Ispra

17 November 2006

Support of Acceptance by Background Doc's

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Institute for Health and Consumer Protection
In-vitro Toxicology Unit
European Centre for the Validation of Alternative Methods (ECVAM)

Skin Irritation Testing based on Reconstructed Human Epidermis (RhE): Explanatory background document for the OECD draft Test Guideline

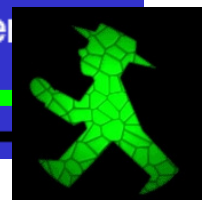
1. Test Method Performance under UN-GHS;
2. Update of Performance Standards;
3. Comprehensive Data Compilation pursuant to the Validation Process and preceding Optimisation Studies

Claudius Griesinger[1], João Barroso[1], Valérie Zuang[1], Thomas Cole[1], Elke Genschow Manfred Liebsch[2],

1) European Commission, Joint Research Centre, Institute for Health and Consumer Protection, In vitro methods Unit, European Centre for the Validation of Alternative Methods (ECVAM), Ispra, Italy
2) Federal Institute for Risk Assessment, Centre for Alternative Methods to Animal Experiments (ZEBET), Berlin, Germany.

Upon Regulator's Request (SCCNFP): Enlargment of Applicability Domain

Activity	Stage	Experts
selection of tests	prevalidation	COLIPA
selection of chemicals		COLIPA
assessment of outcome		ECVAM Workshop 2
selection of tests	validation	ECVAM Workshop 2
selection of chemicals		ECVAM Workshop 2
biostatistics		Humboldt University Berlin
assessment of outcome		ESAC, SCC
request of special study	special study on UV filter chemicals	SCC
selection of chemicals		SCC, COLIPA expert group
biostatistics		Humboldt University Ber
assessment of outcome		ESAC, SCCNFP



SCCNFP and EMEA involved before Method was submitted to EC Annex V & OECD

A perfect Rergulator – Industry co-operation

EUROPEAN COMMISSION
DIRECTORATE GENERAL JRC
JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection
European Centre for the Validation of Alternative Methods (ECVAM)

STATEMENT ON DOG TOXICITY STUDIES

At its 25th Meeting, held on 16-17 November 2006 at the European Centre for the Validation of Alternative Methods (ECVAM), Ispra, Italy, the non-Commission members of the ECVAM Scientific Advisory Committee (ESAC)[1] unanimously endorsed the following statement:

Extension of a dog toxicity study beyond a 13-week duration does not provide additional essential information and reliance on the chronic rodent and 13-week dog studies would provide and adequate basis for chronic RfD derivation in pesticide risk assessment.

There is no further need to require a one year dog study for the evaluation of repeated dose toxicity of pesticides. The short-term oral toxicity of the active substance to non rodents must always be reported only in a 90-day study, usually in dogs.

Make scientific use of regulatory data !!

Do „Valitators“ need CA‘s ?

YES

At a minimum, for:

- **Defining need for the test**
- **Selection of reference chemicals that challenge the tests**
- **Checking the applicability domain for their specific regulation**

Do CA‘s need us “validators“ ?

Evaluation of skin irritation of chemical using (Q)SAR models

BfR-rules

Integrated Testing Strategy

Structural alerts

In general YES, but sometimes NO:

this prediction tool has been developed by three CA‘s, validated by the ECB, and is used …

Only by early involvement of CA‘s we will be able to short-cut the long road to Acceptance

FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR

Risiken erkennen – Gesundheit schützen

Thanks for your attention !

Manfred Liebsch

BfR Unit 37: Centre for Alternative Methods to Animal Experiments – ZEBET

Berlin

manfred.liebsch@bfr.bund.de