GENERAL CONCLUSIONS AND RECOMMENDATIONS OF AN IPCS INTERNATIONAL WORKSHOP ON SKIN SENSITIZATION IN CHEMICAL RISK ASSESSMENT

17-18 October 2006, Berlin, Germany

Preamble

WHO/IPCS, in conjunction with the German Federal Institute for Risk Assessment, convened an international workshop on skin sensitization in chemical risk assessment in Berlin, Germany from 17-18 October 2006. The workshop focused on skin sensitization arising from exposure to chemicals. It aimed to evaluate experimental techniques for both hazard identification and hazard characterization, with the ultimate goal to evaluate their ability to produce data to inform risk assessment, including provision of dose-response information and information relating to sensitive sub-populations. The workshop focused on whether it is possible to distinguish between chemicals with a high potency to elicit allergic skin reactions and those with a low potency. Emerging approaches, such as Structure Activity Relationships (SAR) were explored. The meeting also explored whether experimental approaches used in identifying skin sensitization could inform approaches to identify chemicals with the potential for respiratory tract sensitization. The full report of this workshop will be published. The list of participants appears at Annex 1.

Conclusions

The relative ability of a chemical to induce sensitization is an intrinsic property of the chemical, and is determined by the amount of chemical per unit area required for the acquisition of skin sensitization in a previously naïve individual.

---

1 This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.

© World Health Organization, 2007
The Local Lymph Node Assay (LLNA) is the preferred test method for assessing skin sensitization ability of chemicals in view of animal welfare considerations. It has been validated for the purpose of hazard identification. However, presently there is still a need for guinea-pig tests. Guinea-pig tests may still have a place for the testing of aqueous solutions, extracts, fabrics, mixtures and preparations. When conducting guinea-pig assays the Buehler assay is preferred over the Guinea-pig Maximization Test (GPMT) from an animal welfare point of view. However, the GPMT is generally considered to be more sensitive than the Buehler Assay, for which reason some regulatory authorities prefer the GPMT.

(Quantitative)SARs and expert systems for identification of sensitizing capacity have not been validated to date, but may be used as part of a weight of evidence approach for identifying the sensitizing capacity of chemicals. There are certain local (Q)SARs that can be used for a small range of chemicals. However, these are currently insufficient to cover the full range of chemicals.

No in vitro assay systems for identification of sensitizing capacity have been validated to date. Some of these systems may be useful in a weight of evidence approach or as a preliminary screen.

Any test of skin sensitizing capability that includes dose-response assessment can be used to assess potency. Currently the LLNA is the most appropriate assay for single chemical substances, as it is the only test for which guidelines indicate to include dose-response assessment. Guinea-pig data may also be used to categorize a chemical according to its skin sensitizing potency. It is acknowledged that categorization of skin sensitizing potency is associated with a degree of uncertainty. Neither the approach using the LLNA, nor the approach using guinea-pig data have been validated for the purpose of assessment of potency.

Elicitation responses depend on several factors, among which are potency of the allergen and exposure conditions. Even though potency cannot be directly derived from human elicitation data, a low elicitation threshold is suggestive of a high potency. Where possible, attempts should be made to use clinical data for quantitative risk assessment.

The suitability of test methods for mixtures and preparations, including assessment of skin sensitization induction potency, is not established for any sensitization assay.

Elicitation thresholds cannot be determined on the basis of skin sensitizing potency.

Although respiratory allergens tested so far were positive in current tests evaluating skin sensitization potential, skin sensitization potency data available from current test methods do not predict respiratory sensitization potency.
Recommendations

There is a need for a standardized system of classifying and determining limits according to potency.

The use of the LLNA for potency categorization of induction of skin sensitization needs to be validated. An abbreviated test validation approach may be appropriate to assess the validity of potency assessment based on the LLNA and its appropriateness for predicting sensitizing induction potency in humans.

It is recommended to derive dose-response curves from patch testing and/or open testing in individuals diagnosed with contact allergy, and thereby establish a threshold which can be used to derive a point of departure/risk assessment.

Existing human data on variability in individual thresholds should be evaluated to derive adjustment factors for risk assessment.

It is recommended that further studies are carried out regarding potency ranking of chemicals according their potency to elicit allergic responses in individuals diagnosed with contact allergy.

Comparison of information on responses after occluded versus non-occluded exposures, and single versus repeated exposures, should be done to inform adjustment factors for risk assessment that may account for specific exposure conditions.

Methodology to assess skin penetration, deposition and metabolism needs to be further advanced.

The LLNA needs to be further developed with a view to testing of aqueous solutions, preparations and complex mixtures.

The effects of irritant activity in the LLNA should be further explored.

It is recommended that non-radioactive active forms of the LLNA, or LLNA-type assays that use reduced amounts of radioactivity get more attention.

It is recommended that QSAR models need to be further developed, and the applicability domain of each model needs to be established.

Approaches to evaluate respiratory sensitization induction potency need to be developed.
Annex 1: List of Participants

Dr Kristiina Alanko
Finnish Institute of Occupational Health
Topeliuksenkatu 41 aA
00250 Helsinki
Finland

Professor Klaus Ejner Andersen
Department of Dermatology
Odense University Hospital
DK-5000 Odense
Denmark

Dr Anne Marie Api*
Vice President
Human Health Sciences
Research Institute for Fragrance Materials, Inc.
50 Tice Boulevard
Woodcliff Lake, New Jersey 07677
USA

Dr Josje H.E. Arts
TNO Quality of Life
Dept Toxicology and Applied Pharmacology
P.O. Box 360
3700 AJ Zeist
The Netherlands

Dr Jonathan Chen
Antimicrobials Division, Office of Pesticide programs
United States Environmental Protection Agency, Washington DC 20460
USA

Ms Amanda Cockshott
Health & Safety Executive
2.3 Redgrave Court
Merton Road, Bootle
Merseyside L20 7HS
United Kingdom

Dr Wim H. De Jong
Laboratory for Toxicology
Pathology and Genetics National Institute for Public Health and the Environment
P.O. Box 1 3720 BA Bilthoven
The Netherlands

Dr Jeanne Duus Johansen
National Allergy Research Centre
Gentofte Hospital
University of Copenhagen
2900 Hellerup
Denmark

Dr Tom Gebel
Federal Institute for Occupational Safety and Health Friedrich-Henkel-Weg 1-25
D-44149 Dortmund
Germany

Professor An Goossens
Department of Dermatology
Contact Allergy Unit
U.Z. K.U. Leuven
Kapucijnenvoer 33
B-3000 Leuven
Belgium

Dr Peter Griem*
Clariant Produkte (Deutschland) GmbH
Corporate Product Safety
65840 Sulzbach
Germany

* Participants employed by a commercial entity with an interest in the workshop topic. These participants did not act as meeting Chairs or Rapporteurs and were invited as observers for the final plenary session of the workshop on "Agreement of workshop conclusions and recommendations".
Professor Ursula Gundert-Remy  
(Workshop Chair)  
Bundesinstitut für Risikobewertung  
Institue for Risk Assessment  
Thielallee 88-92  
D-14195 Berlin  
Germany

Mr Paul Harvey  
National Industrial Chemicals  
Notification and Assessment Scheme  
GPO Box 58,  
Sydney NSW 2001  
Australia

Dr Abigail Jacobs  
Assoc. Dir. Pharm/Tox  
ONDIO/CDER/FDA  
FDA,10903 New Hampshire Ave  
Bldg #22 Room #6484  
Silver Spring, MD 20993-0002  
USA

Professor Carola Lidén  
Stockholm Centre for Public Health  
and Karolinska Institutet  
Norrbacka, SE-171 76  
Stockholm,  
Sweden

Dr Joanna M. Matheson  
Toxicologist  
U.S. Consumer Product Safety Commission  
Health Sciences Division  
4330 East West Highway  
Bethesda, MD  20814  
USA

Dr Tim McMahon  
Senior Toxicologist  
Antimicrobials Division, Office of Pesticide Programs  
U.S. Environmental Protection Agency  
USA

Dr Erwin L. Roggen*  
Department of Pharma Protein Development  
Novozymes AS  
Smoermosevej 11  
DK-2880 Bagsvaerd  
Denmark

Ms Cindy Ryan*  
Procter & Gamble Company  
Miami Valley Innovation Centre  
P.O. Box 538707  
Cincinnati, OH  45253-8707  
USA

Dr MaryJane Selgrade  
Chief, Immunotoxicology Branch  
MD-B143-01, US EPA,  
Research Triangle Park, NC  27711  
USA

Dr Masahiro Takeyoshi  
Health Effect Research Section  
Chemicals Assessment Center  
Chemicals Evaluation and Research Institute (CERI-Japan)  
1600, Shimotakano, Sugito-machi, Kitakatsushika-gun  
Saitama 345-0045  
Japan

Professor dr Henk Van Loveren  
(Workshop Rapporteur)  
National Institute of Public Health and the Environment  
PO Box 1 3720 BA Bilthoven  
The Netherlands

Professor Dr Hans-Werner Vohr*  
Senior Expert in Immunotoxicology  
Bayer HealthCare AG  
PH-PD-P-T-TMST  
Aprather Weg  
D-42096 Wuppertal-Elberfeld  
Germany
Representatives of Organizations

Note: representatives of organizations did not act as meeting chairs or Rapporteurs and were invited as observers for the final plenary session of the workshop on "Agreement of workshop conclusions and recommendations"

**OEC**D: Ms Laurence Musset
OECD Environment Directorate
2 rue André Pascal
75775 Paris Cedex 16
France

**ECETOC**: Dr David Basketter
Safety and Environmental Assurance Centre
Unilever Colworth
Sharnbrook Beds.
MK44 1LQ

**ILSI**: Dr Michael P. Holsapple
Executive Director
ILSI Health and Environmental Sciences Institute
One Thomas Circle, NW, 9th Floor
Washington, DC 20005-5802
USA

**EC/JRC**: Ms Grace Patlewicz
European Chemicals Bureau (ECB),
Institute for Health and Consumer Protection (IHCP)
Joint Research Centre
European Commission
Via E.Fermi 1
21020 Ispra (VA)
Italy

**COLIPA**: Dr Pauline McNamee
Representing the European Cosmetics Trade Association Colipa from the Procter & Gamble Company
Whitehall Lane
Egham TW20 9NW
Surrey
United Kingdom

**WHO Secretariat**

Ms Carolyn Vickers
Harmonization Project Lead
International Programme on Chemical Safety
World Health Organization
20 Avenue Appia
1211 Geneva
Switzerland

Dr Helen McGarry
Industrial Chemicals Unit (CHSD1)
Health and Safety Executive
Redgrave Court 2.3
Merton Road, Bootle
Merseyside L20 7HS
United Kindgom

Mrs Christine Jolly
Secretary
International Programme on Chemical Safety
World Health Organization
20 Avenue Appia
1211 Geneva
Switzerland