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

27-Nov-2007

English - Or. English

ENV/JM/MONO(2007)33
Unclassified

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

SERIES ON TESTING AND ASSESSMENT
Number 84

REPORT ON THE WORKSHOP ON THE APPLICATION OF THE GHS CLASSIFICATION CRITERIA TO HPV CHEMICALS, 5-6 JULY, BERN SWITZERLAND

JT03236863

English - Or. English

OECD Environment Health and Safety Publications

Series on Testing and Assessment

No. 84

REPORT ON THE WORKSHOP ON THE APPLICATION OF THE GHS CLASSIFICATION CRITERIA TO HPV CHEMICALS 5-6 JULY, BERN SWITZERLAND

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 2007

Also published in the Series on Testing and Assessment:

No. 1, *Guidance Document for the Development of OECD Guidelines for Testing of Chemicals (1993; reformatted 1995, revised 2006)*

No. 2, *Detailed Review Paper on Biodegradability Testing (1995)*

No. 3, *Guidance Document for Aquatic Effects Assessment (1995)*

No. 4, *Report of the OECD Workshop on Environmental Hazard/Risk Assessment (1995)*

No. 5, *Report of the SETAC/OECD Workshop on Avian Toxicity Testing (1996)*

No. 6, *Report of the Final Ring-test of the Daphnia magna Reproduction Test (1997)*

No. 7, *Guidance Document on Direct Phototransformation of Chemicals in Water (1997)*

No. 8, *Report of the OECD Workshop on Sharing Information about New Industrial Chemicals Assessment (1997)*

No. 9, *Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides during Agricultural Application (1997)*

No. 10, *Report of the OECD Workshop on Statistical Analysis of Aquatic Toxicity Data (1998)*

No. 11, *Detailed Review Paper on Aquatic Testing Methods for Pesticides and industrial Chemicals (1998)*

No. 12, *Detailed Review Document on Classification Systems for Germ Cell Mutagenicity in OECD Member Countries (1998)*

No. 13, *Detailed Review Document on Classification Systems for Sensitising Substances in OECD Member Countries 1998)*

No. 14, *Detailed Review Document on Classification Systems for Eye Irritation/Corrosion in OECD Member Countries (1998)*

No. 15, *Detailed Review Document on Classification Systems for Reproductive Toxicity in OECD Member Countries (1998)*

No. 16, *Detailed Review Document on Classification Systems for Skin Irritation/Corrosion in OECD Member Countries (1998)*

No. 17, *Environmental Exposure Assessment Strategies for Existing Industrial Chemicals in OECD Member Countries (1999)*

No. 18, *Report of the OECD Workshop on Improving the Use of Monitoring Data in the Exposure Assessment of Industrial Chemicals (2000)*

No. 19, *Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Humane Endpoints for Experimental Animals used in Safety Evaluation (1999)*

No. 20, *Revised Draft Guidance Document for Neurotoxicity Testing (2004)*

No. 21, *Detailed Review Paper: Appraisal of Test Methods for Sex Hormone Disrupting Chemicals (2000)*

No. 22, *Guidance Document for the Performance of Out-door Monolith Lysimeter Studies (2000)*

No. 23, *Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (2000)*

No. 24, *Guidance Document on Acute Oral Toxicity Testing (2001)*

No. 25, *Detailed Review Document on Hazard Classification Systems for Specifics Target Organ Systemic Toxicity Repeated Exposure in OECD Member Countries (2001)*

No. 26, *Revised Analysis of Responses Received from Member Countries to the Questionnaire on Regulatory Acute Toxicity Data Needs (2001)*

No 27, *Guidance Document on the Use of the Harmonised System for the Classification of Chemicals Which are Hazardous for the Aquatic Environment (2001)*

No 28, *Guidance Document for the Conduct of Skin Absorption Studies (2004)*

No 29, *Guidance Document on Transformation/Dissolution of Metals and Metal Compounds in Aqueous Media (2001)*

No 30, *Detailed Review Document on Hazard Classification Systems for Mixtures (2001)*

No 31, *Detailed Review Paper on Non-Genotoxic Carcinogens Detection: The Performance of In-Vitro Cell Transformation Assays (2007)*

No. 32, *Guidance Notes for Analysis and Evaluation of Repeat-Dose Toxicity Studies (2000)*

No. 33, *Harmonised Integrated Classification System for Human Health and Environmental Hazards of Chemical Substances and Mixtures (2001)*

No. 34, *Guidance Document on the Development, Validation and Regulatory Acceptance of New and Updated Internationally Acceptable Test Methods in Hazard Assessment (2005)*

No. 35, *Guidance notes for analysis and evaluation of chronic toxicity and carcinogenicity studies (2002)*

No. 36, *Report of the OECD/UNEP Workshop on the use of Multimedia Models for estimating overall Environmental Persistence and long range Transport in the context of PBTS/POPS Assessment (2002)*

No. 37, *Detailed Review Document on Classification Systems for Substances Which Pose an Aspiration Hazard (2002)*

No. 38, *Detailed Background Review of the Uterotrophic Assay Summary of the Available Literature in Support of the Project of the OECD Task Force on Endocrine Disrupters Testing and Assessment (EDTA) to Standardise and Validate the Uterotrophic Assay (2003)*

No. 39, *Guidance Document on Acute Inhalation Toxicity Testing (in preparation)*

No. 40, *Detailed Review Document on Classification in OECD Member Countries of Substances and Mixtures Which Cause Respiratory Tract Irritation and Corrosion (2003)*

No. 41, *Detailed Review Document on Classification in OECD Member Countries of Substances and Mixtures which in Contact with Water Release Toxic Gases (2003)*

No. 42, *Guidance Document on Reporting Summary Information on Environmental, Occupational and Consumer Exposure (2003)*

No. 43, *Draft Guidance Document on Reproductive Toxicity Testing and Assessment (in preparation)*

No. 44, *Description of Selected Key Generic Terms Used in Chemical Hazard/Risk Assessment (2003)*

No. 45, *Guidance Document on the Use of Multimedia Models for Estimating Overall Environmental Persistence and Long-range Transport (2004)*

No. 46, *Detailed Review Paper on Amphibian Metamorphosis Assay for the Detection of Thyroid Active Substances (2004)*

No. 47, *Detailed Review Paper on Fish Screening Assays for the Detection of Endocrine Active Substances (2004)*

No. 48, *New Chemical Assessment Comparisons and Implications for Work Sharing (2004)*

No. 49, *Report from the Expert Group on (Quantitative) Structure-Activity Relationships [(Q)SARs] on the Principles for the Validation of (Q)SARs (2004)*

No. 50, *Report of the OECD/IPCS Workshop on Toxicogenomics (2005)*

No. 51, *Approaches to Exposure Assessment in OECD Member Countries: Report from the Policy Dialogue on Exposure Assessment in June 2005 (2006)*

No. 52, *Comparison of emission estimation methods used in Pollutant Release and Transfer Registers (PRTRs) and Emission Scenario Documents (ESDs): Case study of pulp and paper and textile sectors (2006)*

No. 53, *Guidance Document on Simulated Freshwater Lentic Field Tests (Outdoor Microcosms and Mesocosms) (2006)*

No. 54, *Current Approaches in the Statistical Analysis of Ecotoxicity Data: A Guidance to Application (2006)*

No. 55, *Detailed Review Paper on Aquatic Arthropods in Life Cycle Toxicity Tests with an Emphasis on Developmental, Reproductive and Endocrine Disruptive Effects (2006)*

No. 56, *Guidance Document on the Breakdown of Organic Matter in Litter Bags (2006)*

No. 57, *Detailed Review Paper on Thyroid Hormone Disruption Assays (2006)*

No. 58, *Report on the Regulatory Uses and Applications in OECD Member Countries of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models in the Assessment of New and Existing Chemicals (2006)*

No. 59, *Report of the Validation of the Updated Test Guideline 407: Repeat Dose 28-Day Oral Toxicity Study in Laboratory Rats (2006)*

No. 60, *Report of the Initial Work Towards the Validation of the 21-Day Fish Screening Assay for the Detection of Endocrine Active Substances (Phase 1A) (2006)*

No. 61, *Report of the Validation of the 21-Day Fish Screening Assay fort he Detection of Endocrine Active Substances (Phase 1B) (2006)*

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

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

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

No. 65, *OECD Report of the Initial Work Towards the Validation of the Rodent Utertrophic Assay - Phase 1 (2006)*

No. 66, *OECD Report of the Validation of the Rodent Uterotrophic Bioassay: Phase 2. Testing of Potent and Weak Oestrogen Agonists by Multiple Laboratories (2006)*

No. 67, *Additional data supporting the Test Guideline on the Uterotrophic Bioassay in rodents (2007)*

No. 68, *Summary Report of the Uterotrophic Bioassay Peer Review Panel, including Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the follow up of this report (2006)*

No. 69, *Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models (2007)*

No. 70, *Report on the Preparation of GHS Implementation by the OECD Countries (2007)*

No. 71, *Guidance Document on the Uterotrophic Bioassay - Procedure to Test for Antioestrogenicity (2007)*

No. 72, *Guidance Document on Pesticide Residue Analytical Methods (2007)*

No. 73, *Report of the Validation of the Rat Hershberger Assay: Phase 3: Coded Testing of Androgen Agonists, Androgen Antagonists and Negative Reference Chemicals by Multiple Laboratories. Surgical Castrate Model Protocol (2007)*

No. 74, *Detailed Review Paper for Avian Two-generation Toxicity Testing (2007)*

No. 75, *Guidance Document on the Honey Bee (Apis Mellifera L.) Brood test Under Semi-field Conditions (2007)*

No. 76, *Final Report of the Validation of the Amphibian Metamorphosis Assay for the Detection of Thyroid Active Substances: Phase 1 - Optimisation of the Test Protocol (2007)*

No. 77, *Final Report of the Validation of the Amphibian Metamorphosis Assay: Phase 2 - Multi-chemical Interlaboratory Study (2007)*

No. 78, *Final report of the Validation of the 21-day Fish Screening Assay for the Detection of Endocrine Active Substances. Phase 2: Testing Negative Substances (2007)*

No. 79, *Validation Report of the Full Life-cycle Test with the Harpacticoid Copepods Nitocra Spinipes and Amphiascus Tenuiremis and the Calanoid Copepod Acartia Tonsa - Phase 1 (2007)*

No. 80, *Guidance on Grouping of Chemicals (2007)*

No.81, *Summary Report of the Validation Peer Review for the Updated Test Guideline 407, and Agreement of the Working Group of National Coordinators of the Test Guidelines Programme on the follow-up of this report (2007)*

No.82, *Guidance Document on Amphibian Thyroid Histology (2007)*

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

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

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 30 industrialised countries in North America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

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

This publication was produced within the framework of the Inter-Organisation Programme for the Sound Management of Chemicals (IOMC).

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.

OECD Environment Directorate,
Environment, Health and Safety Division

2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org

FOREWORD

The OECD Workshop on the application of the GHS classification criteria to HPV chemicals was held in Bern (Switzerland) on 5-6 July 2007. The Workshop was a joint activity of the Task Force on Harmonization of Classification and Labelling and the Task Force on Existing Chemicals. It was prepared by a Steering Group including the members of the bureaus of the two Task Forces.

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

TABLE OF CONTENTS

WORKSHOP ON THE APPLICATION OF THE GHS CLASSIFICATION CRITERIA TO HPV CHEMICALS
5-6 July, Bern Switzerland

INTRODUCTION

1. In 2002, the World Summit on Sustainable Development encouraged countries to implement the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as soon as possible with a view to have the system fully operational by 2008. The GHS was adopted by the UN Economic and Social Council in 2003.

2. The Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology (Joint Meeting) recommended in February 2006 the organisation of a pilot exercise on the application of the GHS classification criteria to High Production Volume (HPV) Chemicals assessed within the OECD HPV Chemicals Programme. The exercise was on a voluntary basis. The objectives of the pilot exercise were to: 1) evaluate the suitability of the SIAR (SIDS[1] Initial Assessment Report) as a basis for the derivation of the classification, and 2) identify needs for further guidance in the application of the GHS criteria, either in the Manual for Investigation of HPV Chemicals, or at the level of the UN Sub-Committee of Experts on the GHS. The Joint Meeting agreed that the results of the pilot exercise should be presented at a Workshop. The pilot exercise enabled the application of GHS criteria to about 25 substances.

3. The GHS classifications prepared in the course of the pilot study will not be published, as they were prepared for the purpose of the Workshop only. The Workshop was a joint activity of the Task Force on Harmonization of Classification and Labeling (HCL) and the Task Force on Existing Chemicals. It was prepared by a Steering Group including the members of the bureaus of the two Task Forces.

Objective and scope of the Workshop

4. The objectives of the Workshop were to:

- Share national experience in the application of the GHS classification criteria,
- Evaluate the suitability of the SIAR (SIDS Initial Assessment Report) prepared for HPV Chemicals as a basis for the derivation of the classification,
- Identify the needs for further guidance in the application of the GHS criteria, and
- Identify the need for developing further guidance for the Manual for Investigation of HPV Chemicals.

[1] Screening Information Data Set

WORKSHOP PROGRESSION

5. . The Workshop was hosted by Switzerland in Bern, on 5-6 July 2007. It was chaired by Kim Headrick (Canada). Eighty participants from OECD countries, Brazil, the European Commission, UNECE, UNITAR, WHO/IPCS and BIAC participated in the workshop. The list of participants is available in Annex 1.

6. Georg Karlaganis, Head of Swiss Delegation to the Joint Meeting, welcomed participants to Bern and noted the large participation as a sign of major interest in such an event. The Chair and the Secretariat clarified the background, objectives and scope of the Workshop.

7. Several presentations followed to share experience gained at the national, regional or international level on the application of the GHS criteria. The title and authors of the presentations are reported below:

- Application of GHS criteria: Are there problems? Is there need for additional guidance?
  Thomas Gebel (Germany)

- Experience of GHS Classification in Japan
  Hiroshi Jonai (Japan)

- Implementation of GHS in New Zealand – approach and experiences
  Peter Dawson (New Zealand)

- Guidance developed by ICCVAM (US) to classify for eye irritation
  Amy Rispin (United States)

- The on-going implementation of the Globally Harmonized System of Classification and Labelling of dangerous substances and mixtures in the European Community
  Gunilla Ericsson, (European Commission)

- Experience of WHO in application of the GHS
  Lesley Onyon, (WHO/IPCS)

- Pilot on the GHS classification criteria for mixtures
  Maureen O'Donnell (United States)

- Experience of industry with the application of the GHS classification criteria
  Sue Hubbard (BIAC)

8. The outcome of the pilot study was presented by Andrew Fasey, consultant for the Secretariat. It was noted that the pilot exercise was almost limited to individual substances, and thus potential issues specific to mixtures were not identified. It was also mentioned that the exercise was limited to a few substances, not necessarily representative of all possible cases.

9. Problems identified in the course of the pilot exercise were supplemented with other issues identified by members of the Steering Group in similar exercises of application of the GHS classification criteria. The workshop participants had the opportunity to add other issues during the break out sessions.

10. Three breakout groups were formed to address:

1) hazard to human health (acute toxicity, skin and eye irritation/corrosion and sensitization (Chair: Thomas Gebel, Germany ; Rapporteur: Peter Howden, United Kingdom),

2) hazard to human health via long-term toxicity (Chair: Andrew Fasey ; Rapporteur: Amy Rispin, United States), and

3) hazard to the aquatic environment (Chair: Jonas Falck, Sweden; Rapporteur: Richard Goulet, Canada).

11. Each breakout group also addressed generic issues. The recommendations on these generic issues developed in the breakout sessions were reviewed in plenary in order to reach agreement. The recommendations on specific issues were presented in plenary but not discussed further. It was agreed that the outcome of each breakout group would be included in the report without modification (Annex 2) and that the steering group and Chairs/Rapporteurs would finalize the Workshop report.

12. The Chairperson and the Secretariat thanked the hosts for their large support and contribution towards the success of the meeting.

WORKSHOP RECOMMENDATIONS

13. Annex 2 presents the outcome of each breakout session, as agreed in Bern. For many issues, the breakout groups considered that no further work was needed. The Chair's conclusion was that generally, the application of the classification criteria in the pilot exercises worked well. The Breakout groups identified the need for further guidance or clarification on some issues. They often highlighted the need for training, for getting experience with the application of the criteria, for sharing data and for relying on expert judgment. The identified issues and corresponding recommendations for further work that are presented below have been slightly revised by the Steering Group to increase consistency and clarity. Note that all references to the GHS document refer to the first revised edition of the GHS (2005).

Generic issue and recommendation

- **Issue 1**: The workshop recognized that guidance material is available on various topics (such as the grouping of chemicals, read across) that may be applied to GHS classification criteria, depending on Competent Authority requirements.

Recommendation 1: Explore mechanisms to share information and guidance available in other programs.

Problems identified and recommendations on issues related to hazard to human health in relation to acute toxicity, eye irritation, skin corrosion/irritation

- **Issue 2**: For Acute Toxicity [GHS Chapter 3.1], the use of the bridging principle "dilution" (GHS 3.1.3.5.2) leads to a different classification of the mixture than the use of the Acute Toxicity Estimate (ATE) formula [GHS 3.1.3.6.1].

Recommendation 2: Figure 3.1.1 presents a tiered approach for using the bridging principle before the ATE formula, but section 3.1.3.5.2 seems to allow either to be used. Some additional guidance may be useful.

- **Issue 3**: For Skin Corrosion/Irritation [GHS Chapter 3.2], which are the criteria when the additivity principle for corrosivity applies/does not apply?

Recommendation 3: Further guidance would be useful as there seems to be some conflict in section 3.2.3.3.3 and 3.2.3.3.4.

- **Issue 4**: For Eye Irritation [GHS Chapter 3.3], based on individual animal scores, classification was sometimes ambiguous, depending on the endpoint outcomes for certain cases; eye irritation criteria are provided in GHS in terms of a 3-animal test. GHS does not specify how to classify for existing data based on tests with 4, 5, or 6 animals.

Recommendation 4: This is an issue of toxicology assessment. The problem is not related to insufficient GHS criteria. There is a relatively urgent need for additional guidance. This could either be inserted into the purple book or be developed as external guidance.[2]

- **Issue 5**: For Skin Corrosion/Irritation and Serious Eye Damage/Eye Irritation[GHS Chapter 3.2], the flow chart 3.2.1 (and also 3.3.1) provides a mixture of test and classification strategy and is thus confusing for the self-classifier, e.g., there is no possibility to go for non-classification with a negative *in vitro* test.

Recommendation 5: The purpose of the flowcharts should be clarified i.e. not a combined testing/classification strategy, rather a guide on how to use available data. Negative validated *in vitro* test for corrosivity/irritation might be taken to propose no classification, although this may not hold true for all competent authorities.

Problems identified and recommendations on hazard to human health in relation with long-term toxicity

- **Issue 6**: For Specific Target Organ Toxicity (STOT) [GHS Chapter 3.9], it is not clear how to classify substances made of isomers having different toxicities: e.g. what if the substance contains three isomers, one of which is present at 4-5% and shows clear neurotoxic effects, should the substance be classified as Cat. 2 or not?

Recommendation 6: Considering whether guidance is appropriate to show how to deal with multi-component substances of reliable composition, if for a multi-component substance, data are available for a specific endpoint only on the individual components, should the mixtures rules apply? This recommendation is more general than for STOT and could apply to any endpoint.

- **Issue 7**: For Reproductive Toxicity, lactation [Chapter 3.7], given that a substance has the potential to be in breast milk, how can we judge that it will be at toxic levels? This is a current issue and not unique to GHS. Currently classification is occurring due to presence of a chemical alone and without regard to its potential toxicity.

[2] A presentation, made by Amy Rispin before the Breakout Group sessions, called for additional guidance in the GHS for experimental results based on tests with 4, 5, or 6 animals.

Recommendation 7: It appears to be a problem of how classifiers are applying the criteria that are in the GHS. It is not clear that current science and regulatory experience could support development of additional guidance. It is recommended to share information about specific experiences in performing actual classifications. In future, there may be a concrete process to develop additional guidance.

Problems identified and recommendations on hazard to the aquatic environment (GHS Chapter 4.1, Guidance given for classification of substances in GHS, Annex 9)

- **Issue 8**: Classification of substances which are mixtures of chemicals or isomers. Five substances of this type were included in the exercise:

a) When to use a Water Accommodated Fraction (WAF) for classification?

Recommendation 8a: Few words of guidance are provided in A9.3.5.10 of the GHS guidance but it lacks clarity. It would be useful to provide a clear formulation that said that the WAF/loading concept for classification can be used as a last possibility (i.e. because the loading concept generally leads to effects above the solubility of the substance). What are the caveats related to the use of the WAF/loading concept approach? Ideally, the measured concentration concept should be used as frequently as possible. It would also be advisable to provide concrete example of when and when not to use the WAF or in which situation it has been used in the past.

b) How to assess the bioaccumulation potential? [GHS, Annex 9, Section 5 deals with bioaccumulation of substances only]

Recommendation 8b: It is possible to assess bioaccumulation of a mixture but it is not clearly indicated in the GHS guidance. Some updating of the guidance might be advisable after exploring what is being developed.

- **Issue 9**: Derivation of a multiplying factor (M factor):

Recommendation 9: A few words on the philosophy and use of the M factor should be added to Annex 9.

- **Issue 10**: Application of guidance on the weight of evidence:

Recommendation 10: There is general guidance in Annex 9.3.4 and page 20, section 1.3.2.4.9 that provides general wording on weight of evidence. For more than 4 data, a geometric mean approach is presently recommended in GHS guidance. For data rich substances, the weight of evidence chapter of the GHS does not address the use of Species Sensitivity Distribution (SSD) and guidance might be needed.

ANNEX 1 : PARTICIPANTS LIST

Australia	Andrew WAGNER Assistant Secretary Standards and International Branch Office of the Australian Safety and Compensation Council Department of Employment and Workplace Relations GPO Box 9879 2601 Canberra Australia	Tel: +61 2 6121 9134 Fax: +61 2 6275 3619
Austria	Edmund PLATTNER Director Biocide Products, Quality Assurance Federal Ministry for Agriculture, Forestry, Environment and Water Management V/3 Stubenbastei 5 A-1010 Vienna Austria	Tel: +43 1 51522 2346 Fax: +43 1 5131 679 1480
Belgium	Thaly LAKHANISKY Head of Division Toxicology Scientific Institute of Public Health J. Wytsman 14 B 1050 Brussels Belgium	Tel: +32 2 642 5104 Fax: +32 2 642 5224
Canada	Kim HEADRICK International Harmonization Officer Policy & Programme Services Product Safety Programme Healthy Environments and Consumer Safety Branch Health Canada 123 Slater Street 3508D1 K1A OK9 Ottawa Canada	Tel: +1(613) 952-9597 Fax: +1(613) 946-1100

	Brenda EVERSON Policy Advisor Product Safety Programme Health Canada 123 Slater Street K1A OK9 Ottawa Canada	Tel : +1 613 941 6273 Fax : +1 613 946 1100
	Richard GOULET Head Risk Unit Existing Substances Division Environment Canada 20th floor, Place Vincent Massey 351 St.Joseph Boulevard K1A 0H3 Gatineau Canada	Tel: 819-994-9556 Fax: 819-953-4936
Denmark	Henning CLAUSEN Ecotoxicologist M.Sc. Danish Environmental Agency Strandgade 29 DK- 14012 Copenhagen Denmark	Tel: +45 72 544 138
	Lena HÖGLUND Toxicologist M.Sc. Danish Environmental Protection Agency Strandgade 29 DK-1401 Copenhagen Denmark	Tel: +45 32 66 05 30
France	Matthieu LASSUS INERIS - DRC/ECOT Parc Technologique Alata 60550 Verneuil en Halatte France	Tel: +33 3 44 55 63 46 Fax: +33 3 44 55 67 67
	Elodie PASQUIER Bureau d'Evaluation des Risques des Produits et agents Chimiques (BERPC) 60-62, rue d'Hauteville 75010 Paris France	

France	Sylvie TISSOT Toxicologist Direction des risques chroniques / DRC-ETSC INERIS Parc ALATA -BP2 60550 Verneuil-en-Halatte France	Tel: +33 (0)3 44 55 64 31 Fax: +33 (0)3 44 55 68 00 Email: sylvie.tissot@ineris.fr
Germany	Joachim HEUER Director and Professor Federal Institute of Risk Assessment (BfR) Thielallee 88 14191 Berlin Germany	Tel: +49-30-8412-3615 Fax: +49-30-8412-3003
	Thomas GEBEL Federal Institute for Occupational Safety and Health (BAUA) Friedrich-Henkel-Weg 1-25 44149 Dortmund Germany	Tel: +49-231-9071-2563 Fax: +49-231-9071-2611
	Juliane KOCH National and International Chemical Safety Federal Environmental Agency (UBA) Wörlitzer Platz 1 06844 Dessau Germany	Tel: +49-340-2103-2424 Fax: +49-340-2104-2424
Greece	Maria MELANITOU Chemist General Chemical State Laboratory, Division Of Environment- Section B Ministry Of Economy & Finance 16, An Tsoha Str 11521 Athens Greece	Tel: +30 210 6479451 Fax: +30 210 6466917
Italy	Paola DI PROSPERO FANGHELLA Istituto Superiore di Sanita Viale Regina Elena, 299 00161 Rome Italy	Tel: +39 06 4990 2423 Fax: +39 06 4938 2423
Japan	Hiroshi JONAI Professor Nihon University Tokyo 1018302 Japan	

	Muneyuki MIYAGAWA Senior Researcher Health Effects Research Group Japan National Institute of Occupational Safety and Health (JNIOSH) 21-1, Nagao 6-chome Tama-ku 214-8585 Kawasaki Japan	Tel: +81(44) 865-6111 Fax: +81(44) 865-6124
	Takeshi MORITA Senior Researcher Division of Safety Information on Drug, Food and Chemicals National Institute of Health Sciences 1-18-1 Kamiyoga, Setagaya-ku, 158-8501, Tokyo Japan	Tel: +81(3) 3700-1141 Fax: +81(3) 2700-1483
	Nobuhiro YAMAMOTO Hygiene Specialist Office of Chemical Safety, Evaluation and Licensing Division Ministry of Health, Labour and Welfare 1-2-2, Kasumigaseki, Chiyoda-ku 100-8916 Tokyo Japan	Tel: +81 3 3595 2298 Fax: +81 3 3593 8913 Email: yamamoto-
Korea	Sam Rae CHO Chief Management Office Korea Chemicals Management Association 3F. Uil B/D 1623-2, Seocho-dong Seocho-gu 137-070 Seoul Korea	Tel: + 82.2.384.8092-6 Fax: + 82.2.384.9441-2
	Je Bong LEE Toxicologist Pesticide Safety Division National Institute of Agricultural Science & Techonology Korea	Tel: +82 31 290 0585 Fax: +82 31 290 0508
	ChangHo SEONG Senior Program Officer Chemicals Resistration & Evaluation Division National Institute of Environmental Research Korea	Tel: +82-32-560-7227

Mexico	Mario YARTO Director Research on Chemicals and Ecotoxicological Risks National Institute of Ecology - SEMARNAT Periférico 5000Col. Insurgentes CuicuilcoDelegación Coyoacán 04530 Mexico City Mexico	Tel: +52 55 54 24 64 25 Fax: +52 55 54 24 54 04
	Alberto ROSALES CASTILLO Manager Risk Prioritation Office Federal Commission for the Protection against Sanitary Risks Monterrey 33Colonia RomaDelegación Cuauhtémoc 06700 Mexico City Mexico	Tel: +52(55)508 05457
	Raúl HUESCA CADENA Deputy Director Foster and Regulations Ministry of Environment and Natural Resources Periférico Sur 4029 410 Piso Jardines en la Montaña 14210 Mexico City Mexico	
The Netherlands	Leo Perdon Senior Policy Advisor Ministry of Transport, Public Works and Water Management Plesmanweg 1 – 6 The Hague The Netherlands	
	Jean-Paul RILA Risk Assessor RIVM/SEC A.Van Leeuwenhoeklaan 9 Bilthoven The Netherlands	Tel: +31 30 274 2504
	Henk ROELFZEMA The Netherlands Ministry of Health,Welfare and Sport Parnassusplein 5 P.O.Box 20350 NL-2500 EJ Den Hague The Netherlands	Tel: +31 70 340 6965 Fax: +31 70 340 5554

New Zealand	Peter DAWSON Principal Scientist Hazardous Substances Group Environmental Risk Management Authority BP House (Level 1), 20 Customhouse Quay PO Box 131 Wellington New Zealand	Tel: +64 (4) 918 4833 Fax: +64 (4) 914 0433
Norway	Christine BJØRGE Senior Advisor Norwegian Pollution Control Authority Strømsveien 96 Postboks 8100 Dep 0032 Oslo Norway	Tel: +4722 573489
	Solvår HARDENG Senior Advisor Norwegian Pollution Control Authority PO Box 8100 Dep N-0032 Oslo Norway	Tel: +47 22 57 34 64 Fax: +47 22 67 67 06
Poland	Mariusz GODALA Bureau for Chemical Substances and Preparation Ut. Sv. Tercsy 8 91-348 Lodz Poland	Tel: +48 42 631 4679
	Monika WASIAK-GROMEK Bureau for Chemical Substances and Preparation Ut. Sv. Tercsy 8 91-348 Lodz Poland	Tel: +48 42 631 4679
Slovak Republic	Jan CEPCEK Centre for Chemical Substances and Preparations Mierova 19 Bratislava Slovak Republic	Tel: +421 2 4854 4504 Fax: +421 2 4854 4555
Spain	Elena MANEIRO FRANCO Département de l'Environnement.INIA Ministère de l'Education et de la Science Ctra. La Coruña. Km.7 28040 MADRID Spain	Tel: +34913471469 Fax: +34913474008

Sweden	Lennart DOCK Ph. D. Senior Scientific Officer Risk Assessment/International Secretariat Swedish Chemicals Agency (SEKI) P.O. Box 2 SE-172 13 Sundbyberg Sweden	Tel: +46 8 519 41 268 Fax: +46 8 735 76 98
	Jonas FALCK Ecotoxicology /Biology, Senior Scientific Officer Swedish Chemicals Agency (KEMI) P.O. Box 2 SE-172 13 Sundbyberg Sweden	Tel: +46 8 519 41 167 Fax: +46 8 735 76 98
	Gregory MOORE Head of Unit, Classification and Labelling Swedish Chemicals Agency (KEMI) P.O. Box 2 SE-172 13 Sundbyberg Sweden	Tel: +46 8 519 412 37 Fax: +46 8 735 76 98
Switzerland	Georg KARLAGANIS Swiss Federal Office for the Environment Worblentalstrasse 68 CH-3003 Berne Switzerland	Tel: +41 79 415 99 62 Fax: +41 31 324 79 78
	Peter BORMANN Knowledge Manager Chemical Product Division Swiss Federal Office of Public Health CH-3003 Bern Switzerland	Tel: 0041 31 323 86 66 Fax: 0041 31 324 90 34
	Josef TREMP Industrial Chemicals Section Swiss Federal Office for the Environment FOEN Substances, Soil, Biotechnology Division CH-3003 Berne Switzerland	Tel: 0041 31 324 46 18 Fax: 0041 31 324 79 78

	Markus HOFMANN Chemical Products Division Swiss Federal Office for Public Health CH-3003 Berne Switzerland	Tel: +41 31 32 50398 Fax: +41 31 32 49034
	Eva REINHARD Chemical Products Division Swiss Federal Office for Public Health CH-3003 Berne Switzerland	
	Dominique SCHENK Chemical Products Division Swiss Federal Office of Public Health CH-3003 Bern Switzerland	Tel: +41 (31) 324 46 18 Fax: +41 (31) 324 79 78
	Dr. Beat SCHMITTER Swiss Federal Office for Agricultre Mattenhofstr.5 3003 Bern Switzerland	Tel: +41 31 323 1517 Fax: +41 31 322 2634
	Sylvia KAZADI Swiss Federal Office for the Environment Worblentalstrasse 68 CH-3003 Berne Switzerland	Tel:+41 (31)322 93 49 Fax:+41 (31) 324 79 78
	Paul VESEL SGCI Chemie Pharma Schweiz Nordstrasse 15 CH-8035 Berne Switzerland	Tel: +41 44 368 17 34 Fax: +41 44 368 17 35
United Kingdom	Peter HOWDEN Chemical Assessment Schemes Unit Health and Safety Executive 2.3 Redgrave Court Merton Road L20 7HS Bootle United Kingdom	Tel: +44 151 9513594 Fax: +44 151 951 3308
United States	Tala HENRY US Environmental Protection Agency Office of Pollution Prevention and Toxic Substances 1200 Pennsylvania Ave., NW 20460 Washington United States	Tel: +1 202 564 2959

	Mary Frances LOWE OPPTS Office of Pesticide Program Field and External Affairs Division Environmental Protection Agency Ariel Rios Buildg 1200 Pennsylvania Ave. 20460 Washingtonm DC United States	Tel: +1 703 305 5689 Fax: +1 703 308 1850
	Maureen O'DONNELL Dir. of Standards and Guidance Department of Labor OSHA 200 Constitution Ave, NW 20210 Washington, DC United States	Tel: +1 202 693-2146
	Amy RISPIN OPPTS/Office of Pesticide Programs US Environmental Protection Agency Field & External Affairs Division Ariel Rios Building 1200 Pennsylvania Avenue 20460 Washington, DC United States	Tel: +1 703 305 5989 Fax: +1 703 308 1850
EC	Gunilla ERICSSON European Chemicals Bureau JRC TP 582 I-21020 Ispra Italy	Tel: +39 0332 786 446 Fax: +39 0332 789 963
	Anja KLAUK DG Enterprise European Commission BREY 12/223 B-1049 Brussels	Tel: +32 2 29 92937
	Kerstin NORDENHALL European Chemicals Bureau TP 582 I-21020 ISPRA Italy	Tel: +39 (0) 332 789593 Fax: +39 (0) 332 789963
UNECE	Rosa Garcia COUTO Secretary of the UNSCEGHS Palais des Nations Room 412-3 Geneva-10 CH-111 Switzerland	Tel: +41 22 917 2435

UNITAR	Dr. Burkhard WAGNER Senior Special Fellow Chemicals - Waste and Environmental Governance UNITAR Am Hirschsprung 37a 14195 Berlin Germany	Tel: +49-30-832 7728
Brazil	Rogerio DE OLIVEIRA CORRÊA Brazilian National Institute of Metrology, Standardization and Industrial Quality - INMETRO Brazilian TBT/WTO Enquiry Point Rua Santa Alexandrina, 416 - 5º andar 20261-232 Rio Comprido - RJ Brazil	Tel: +55-21-2563-2765 (2824) Fax: +55-21-2502-6542
	Mr. Andre FENNER Enviromental Health and Labour Health Depart;ent Setor Comercial Sul Ed. Principal Quadra 04 Conjuto A 6º Ander 70304-000 Brasilia - DF Brazil	Tel : +55 61 3213 8490 Mobil : +5561 815 59105 Fax: +55 61 3213 8484
Slovenia	Ms. Tatiana HARMAR-JURIC Senior Advisor Senior Advisor Ministry of Health Mali trg 6 SI-1000 Ljubjana Slovenia	
Business and Industry Advisory Committee (BIAC)	Johan BREUKELAAR Director, International chemicals Policy CEFIC Avenue E. Van Nieuwenhuyse, 4-B 1 1160 Bruxelles Belgium	Tel: +32 2 676 72 77 Fax: +32 2 676 73 32
	Leo HEEZEN Global Chemicals Manager European Chemical Industry Council (CEFIC) Av. E. Van Nieuwenhuyse 4Box 1 B-1160 Brussels Belgium	Tel: +32 2 676 73 33 Fax: +32 2 676 73 32

	Sue HUBBARD Principal Advisor Rio Tinto HSE 6 St Jame's Square London SW1Y 4LD United Kingdom	Tel: +44 20 7753 2234 Fax: +44 20 7753 2413
	Sylvia JACOBI Health and Environment Ablemarle Europe Parc Scientifique Einstein Rue du Bosquet, 9 1348 Louvain-la-Neuve Belgium	Tel: +32 (0) 10 481768 Fax: +32 (0) 10 481739
	Marie-Louise MEISTERS Corporate Affairs -Regulatory Toxicology DuPont de Nemours (Belgium) Antoon Spinoystraat 6-Vespel Building 2800 Mechelen Belgium	Tel: +32 2 6635952 Fax: +32 2 6755300
	KARIN MERKL Merck KGaA Frankfurter Strasse 250 64293 Darmstadt Germany	Tel: +49 6151 727897 Fax: +49 6151 917897
	Mme Marie-Pierre RABAUD Regulatory Affairs Adviser-Europe ExxonMobil Chemical France 2 rue des Martinets - BP 270 92505 Rueil-Malmaison Cedex France	Tel: +33 1 47 10 50 16 Fax: +33 1 47 10 51 78
	Hans-Gerhard ROHE Environment & Sustainability (BAG-E&S) Bayer AG Corporate CenterBuilding K 9 D-51368 Leverkusen Germany	Tel: +49 214 30 72485 Fax: +49 214 30 53407
	Mr. Roland ROSSBACHER BASF Aktiengesellschaft GUP/CB - Z 470 D-67056 Ludwigshafen Germany	Tel: +49 621 60 55673 Fax: +49 621 60 51734
	Dr. Klaus ROTHENBACHER Science Porgramme Manager BSEF 118, Av. de Cortenbergh 1000 Brussels Belgium	Tel: +32 2 743 66 19 Fax: +32 2 735 60 63

	Heinz-Guenter SCHAFER VCI- Verband der Chemischen Industie e.V Mainzer Landstr., 3c55 D-60329 Frankfurt/Main Germany	Tel: 49 69 255 61 1536 Fax: 49 69 255 61 1607
	Richard SEDLAK Senior Vice President Technical and International Affairs The Soap and Detergent Association 1500 K Street, NW Suite 300 Washington DC 20005 United States	Tel: +1 202 662 2523 Fax: +1 202 347 4110
	Chantal SMULDERS Toxicologist Shell International B.V. 2596 The Hague Netherlands	Tel: +31 70 377 2176
	Phil TODD HSE Classification Advisor HSE Operations Syngenta Swarzwaldalle 215 Postfach CH-4002 Basel Switzerland	Tel: +41 61 323 5102 Fax: +41 61 323 2212
	Jan WILMER EH&S/Toxicology Department Dow Europe GmbH Bachtobelstrasse 3CH-8810 Horgen Switzerland	Tel: +41-1 728 2996 Fax: +41-1 728 2965
OECD	Andrew FASEY Wearside Roe Downs Road Medstead United Kingdom	Tel: +(44 0)1420 560653
	Anne GOURMELON Administrator, Test Guidelines ENV/EHS OECD Annexe Maillot 5029 2 rue André-Pascal 75016 Paris France	Tel: +(33-1) 45 24 98 49 Fax: +33 1 44 30 61 80

	Laurence MUSSET Principal Administrator ENV/EHS OECD Annexe Maillot 5047 2 rue André-Pascal 75016 Paris France	Tel: +(33-1) 45 24 16 76 Fax: +33 1 44 30 61 80
	Amanda SUDIC Assistant ENV/EHS OECD Annexe Maillot 5036 2 rue André-Pascal 75016 Paris France	Tel: +(33-1) 45 24 17 37 Fax: +33 1 44 30 61 80

ANNEX 2: OUTCOME OF THE BREAK OUT SESSIONS

PROBLEMS IDENTIFIED AND RECOMMENDATION ON GENERIC ISSUES, AGREED BY THE PLENARY

Generic issues identified	Recommendation to the UN Sub-Committee	Recommendation to the HPVC Programme
Individual substances forming parts of a group of chemicals assessed together (i.e. chemical category) sometimes miss data for a particular endpoint. Extrapolation from one substance with data to another with data missing was made, based on similar solubility range.	No action is needed; it is up to competent authority discretion whether grouping is allowed for what purpose.	There is already a guidance document on the grouping of substances.
It is possible that higher or lower specific concentration limits may be set for each GHS endpoints under the prerequisite that specific additional information is available supporting to do this.	No action needed.	No action needed.
Recognize that there is guidance material available on various topics in relation to classification that may be applied to GHS Classification, depending on Competent Authority requirements.	Explore mechanisms to share that information.	-
A substance or mixture need not be classified under GHS when it can be shown by conclusive experimental data from internationally acceptable test methods that the substance or mixture is not biologically available (See1.3.2.4.5). However, it is not clarified which methods are internationally acceptable for which endpoint.	There is currently no consensus on whether this is really an issue or not, it needs further discussion.	-

PROBLEMS IDENTIFIED AND RECOMMENDATION ON ISSUES RELATED TO HAZARD TO HUMAN HEALTH FOR ACUTE TOXICITY, SKIN AND EYE IRRITATION/CORROSION, SENSITIZATION

Generic issues identified	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPVC Programme**
Taking into account the physical form (i.e. supplied or used in a form that is not bioavailable): should classification be based on intrinsic properties (e.g., viscous substance made into an aerosol for testing pruposes)	Not a specific problem with GHS 'a generic issue. GHS classifies on intrinsic hazard properties (GHS section 1.1.2.6.2) But, sometimes hazard properties may depend on the physical form for instance inhalation tests may not always directly be related to classification. Might be worth further consideration (not a consensus view). Clear identification of problem needed.	

Specific issues identified: **hazard to human health for acute toxicity**	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**

Specific issues identified: **hazard to human health for acute toxicity**	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
The different GHS category cut-offs for the different exposure routes do not always match to values obtained after toxicological route-to-route extrapolation.	No further guidance needed.	
How to classify in case of multiple LD50/LC50?	GHS provides some direction i.e. to use the most appropriate value using expert judgment (section 3.1.2.3). Decision requires expert judgment and should be very transparent on why a value is chosen. No further guidance needed.	
In a GHS annex for a substance forming part of a group, no data for acute inhalation toxicity for that substance is available. Considering the acute oral toxicity of the substance of interest, the potential for absorption via the respiratory tract and observed lethality of another soluble substance of the group in a 16-days inhalational study, additional classification for acute inhalational toxicity is considered to be justified. The classification category reflects the same level of concern as that for oral toxicity. In the absence of directly relevant data, the classification is based on expert evaluation of all available data.	Not a priority for GHS. GHS needs to leave open option to predict hazard on the basis of read across. Expert judgment required, guidance is available from OECD (HPV Chemicals). No change to criteria required.	

Specific issues identified: hazard to human health for acute toxicity	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
The GHS criteria Section 3.1.3.6 *Classification of mixtures based on ingredients of the mixture (Additivity formula)* of the GHS criteria explicitly allows for extrapolation between oral, dermal and inhalation acute toxicity estimates where data is lacking. However, this extrapolation is not included in the actual criteria for substance evaluation.		
In the case of a substance with low toxicity, there was some difficulty in dealing with the classification. There was hesitation between "Not classified", "Category 5", "Not applicable", based on a limited test in rats the value of LD50 is >2000 mg/kg bw.It is of course important to state that Category 5 is not a default and that reliable data is needed for classification.	Section 3.1.2.5 and footnote f(ii) to table 3.1.1, gives guidance on when category 5 is appropriate. This issue seems to be covered adequately.	
Use of the bridging principle 'dilution' (GHS 3.1.3.5.2) leads to a different classification of the mixture than use of the ATE formula (GHS 3.1.3.6.1).	Fig.3.1.1 presents a tiered approach for using bridging principle before ATE formula, but section 3.1.3.5.2 seems to allow either to be used. Some additional guidance may be useful.	

Specific issues identified: hazard to human health for acute toxicity	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
Eye irritation: Problem identified: In a GHS annex the substance was classified as eye irritant Category 1 (irreversible effects on the eye), as the effects observed indicated irreversible effects on the eye even though observation time was much shorter than indicated in table 3.3.1 of the GHS. In addition the irritation scores were not reported in SIAR or IUCLID.	No guidance required. Not a specific problem with GHS, an issue of insufficient data. Classification should be based on data available reversibility within a period of "normally" 21 days.	
Clearer guidance is needed in 3.2.3.3.4 and table 3.2.4 to indicate which are the criteria when the additivity principle for corrosivity applies / does not apply.	Further guidance would be useful some conflict in section 3.2.3.3.3 and 3.2.3.3.4 on how to do it.	
Based on individual animal scores, classification was sometimes ambiguous, depending on the endpoint outcomes for certain cases	Issue of toxicology assessment. The problem not related to insufficient GHS criteria. Additional guidance is needed; relatively urgent need. Not sure if it would be in purple book or in other guidance.	
Flow chart 3.2.1 (and also 3.3.1) are a mixture of test and classification strategy and thus confusing for the self-classifier. E.g. there is no possibility to go for non-classification with a negative in vitro test.	The purpose of the flowcharts should be clarified ' i.e. not a testing strategy rather a guide on how to use the data available. Negative validated in vitro test for	

Specific issues identified: hazard to human health for acute toxicity	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
	corrosivity/irritation might be taken to propose no classification, although this may not hold true for all competent authorities.	
Respiratory sensitization: Classification as respiratory sensitizer based on evidence a closely related substance is a respiratory sensitizer in humans. The GHS criteria (section 3.4.2.1.2.3) includes a reference to: "a chemical structure related to substances known to cause respiratory hypersensitivity" as supportive evidence to "clinical history and data from appropriate lung function tests related to exposure to the substance, …". However, as the respiratory sensitisation is associated with the metallic ion, other substances containing the ion should be regarded as a respiratory sensitizer.	Not a priority for GHS. GHS needs to leave open option to predict hazard on the basis of read across. Expert judgement required, Guidance is available from OECD (HPV). No change to criteria required.	
Skin sensitizer: The wording of the GHS criteria in section 3.4.2.2.2.3 is complex. In the absence of specific data "the substance need not be classified as a contact sensitizer. However, a combination of two or more indicators of contact sensitization as listed below may alter the decision. This shall be considered on a case-by-case basis. (a) Isolated episodes of allergic contact dermatitis; (b) Epidemiological studies of limited power, e.g. where chance, bias or confounders have not been ruled out fully with reasonable confidence;	Not a priority for GHS. GHS needs to leave open option to predict hazard on the basis of read across. Expert judgement required, Guidance is available from OECD (HPV). No change to criteria required.	

Specific issues identified: **hazard to human health for acute toxicity**	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
(c) Data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in paragraph 3.4.2.2.4.1 of this chapter, but which are sufficiently close to the limit to be considered significant; (d) Positive data from non-standard methods; (e) Positive results from close structural analogues." As the metallic ion is considered exclusively responsible for the immunological effects of nickel the classification of nickel carbonate is in accordance with the criteria of GHS.		

PROBLEMS IDENTIFIED AND RECOMMENDATIONS ON HAZARD TO HUMAN HEALTH IN RELATION WITH LONG-TERM TOXICITY

Specific issues identified: hazard to human health in relation with long-term toxicity	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
STOT Repeated exposure: Problem identified: Problem to classify substances made of isomers having different toxicities: the blend contains three isomers, one of which is present at 4-5% and shows clear neurotoxic effects, should the blend be classified as Cat. 2 or not?). Extract from the SIAR: "Rats given the substance developed the same symptoms (decreased body weight, blue discoloration of the skin and urine, weakness of hind limbs, paralysis) as those described for the mixed isomers. (…) A time-dependent decrease in motor conduction velocity (MCV), sensory conduction velocity (SCV), amplitude of the sensory action potential (ASAP) was observed in animals dosed with 1,2-isomer but not with 1,3-isomer or 1,4-isomer." Issue of how to treat a blend of isomers where the blend comes out of the industrial synthesis. Should the mixtures rules be applied to the isomeric blend? Are there cases where the mixtures rules should not apply??	UN should consider whether guidance is appropriate to show how to deal with isomeric blends of reliable composition. On the assumption that the isomeric blend is a substance, and we have data for a specific endpoint only on the individual components, should the mixtures rules apply? (Note that read across is not necessary in this case) Consider whether guidance is needed for this situation. More general than STOT but could apply to any endpoint.	HPV has guidance on assessment of multi-component substances. Consider whether it applies to this situation.
STOT Repeated exposure: Problem identified: A substance was difficult to classify given that data available are from studies using therapeutic dose in humans. SIAR shows that no effect was seen in animals. But the clinical studies showed effects in humans, even at therapeutic doses. The	No additional guidance needed. The GHS already specifies that human data takes precedence, as long as the therapeutic studies normally provide reliable and good quality human data. Expert judgment is specified in the GHS to be used for evaluating such human data.	

Specific issues identified: hazard to human health in relation with long-term toxicity	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
Germ cell mutagenicity: Problem identified: The substance of interest shows positive results from in vivo somatic cells genotoxicity tests in non-mammalian species (Drosophila), supported by the positive results from the in vitro gene mutations and chromosome aberration tests, therefore there was no difficulty with classification. However, it should be noted, that Drosophila melanogaster tests are not mentioned in GHS. We suggest adding short comment on what to do with these studies.	No additional guidance needed on non mammalian tests.	HPV program only gets a limited amount of data – which might not be sufficient for classification of a substance as a mutagen. Note in criteria allows use of other information. No additional guidance needed for HPV program.
Germ cell mutagenicity Problem identified: This case illustrates the generic issue on classification of chemicals from a chemical category. In the present case the data on both in vitro and in vivo genotoxicity of one substance in the group of substances are very limited. The two available in vivo studies showed single DNA strand breaks in lung and kidney nuclei. There is no evidence concerning possible hereditable effects on germ cells. Overall, there is some evidence indicating that the substance of interest is genotoxic in vitro and in vivo and the substance of interest is thus regarded as being genotoxic in somatic cells in vivo; hence the possibility that the germ cells are affected cannot be excluded. An expert judgement evaluation of the data for the substance of interest concluded that there is insufficient evidence of in vivo genotoxicity for the substance alone to justify classification. This would lead to a "Classification not possible due to lack of data". However, based on the conclusion for the related soluble substances in the group, the possibility that the germ cells are affected cannot be excluded. The chemical was classified Category 2 (Chemicals which cause concern for humans owing to the possibility that they may induce inheritable mutations in the germ	No additional guidance needed	This would be dealt with by the grouping guidance for use by certain regulatory authorities.

Specific issues identified: hazard to human health in relation with long-term toxicity	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
cells of humans). (e.g. nickel compounds)		
Carcinogenicity: Problem identified: This case illustrates the generic issue on classification of chemicals from a chemical category. A chemical from a chemical category was classified as Category 1A (known to have carcinogenic potential for humans; the placing of a chemical is largely based on human evidence) "May cause cancer by inhalation". Since there is epidemiological evidence that both water soluble metallic compounds and insoluble inorganic metal compounds are considered as human carcinogens consequently also the substance of interest (sparsely soluble metallic compound) is considered to be a human carcinogen. The substance of interest is not considered to be carcinogenic following dermal or oral administration.	*Is additional guidance warranted for grouping?* At this time, no action needed for UN for grouping. May be too soon to revisit criteria in GHS, but note that other groups (IPCS etc) that are looking at more specific guidance.	*Issue: solubility, etc. of chemicals in the Ni group. To what extent do we need data on the various Ni compounds?* May not be possible to go much further in guidance for the group in particular. *Is this case by case? Political decision to group Ni compounds.* But this group might not typify all groups. *How to achieve global consistency in cancer classification? Would this occur at the expense of optimum weighing of the evidence?* OECD- EU is working on generic grouping guidance for various types of chermical groups. Category approaches being done elsewhere for use by various regulatory sectors.
Reproductive toxicity: In the SIAP, sub-divide the section on reproductive toxicity into toxicity to fertility and developmental toxicity	The GHS calls for a single hazard classification for repro effects. Although is is possible to use labelling to label separately if specific information is available – See Table 3.7.2 No additional action required..	Issue: Can- should repro endpoint be subdivided? GHS specifies that they be combined – also IPCS combines the endpoint. Note that labelling could be used to specify the different effects. (T 3.7.2) No additional action needed.
Lactation- Given that a substance has the potential to be in breast	Appears to be a problem of how classifiers are applying the criteria	No additional guidance at this time

Specific issues identified: hazard to human health in relation with long-term toxicity	Recommendation to the UN Sub-Committee	Recommendation to the HPV Chemicals Programme
milk, how can we judge that it will be at toxic levels? This is a current issue and not unique to GHS. Currently classification is occurring due to presence alone and without regard to potential toxicity.	that are in the GHS. Should we consider whether additional guidance can be developed to further guide weight of evidence judgment? Consideration could be given to assessing whether there is sufficient science now to provide additional guidance. Share information about specific experiences in performing actual classifications. In future, there may be a concrete process to develop additional guidance.	
Maternal Toxicity in assessing reproductive effects. GHS has language providing description of evidence that should be weighed to. Can guidance in addition to that in the GHS be developed for greater certainty- consistency in classification?? Issue: in the absence of maternal toxicity, what is a significant enough effect? Expert judgement is called for. Section 3.7.2.3.3 describes specific effects that can be excluded as significant, even if these effects occur in the absence of maternal toxicity. Do we need more guidance? Issue: How can an effect be shown to be related to maternal toxicity and not a primary reproductive effect. Issue: Delayed ossification occurring in absence of maternal toxicity.	No additional guidance for UN or HPV for this issue.	No additional guidance for UN or HPV for this issue.

Specific issues identified: hazard to human health in relation with long-term toxicity	Recommendation to the UN Sub-Committee	Recommendation to the HPV Chemicals Programme
Issue: Pilot experiences for GHS showed inconsistency in classification outcomes for the repro endpoint. Do the GHS criteria need reevaluation ? Issue: Jonai's example potentially an issue regarding maternal toxicity.	At this time, it is not possible to develop additional guidance The GHS caveats this as far as possible in light of current science. This issue could be revisited in future. GHS gives room to use expert judgment to classify of not. No additional guidance needed for UN or HPV The criteria are in fact reflecting the current state of the art. Perhaps training for consistency should be considered. Note that this endpoint calls for use of real expertise and use of expert judgement. Guidance is constantly being developed elsewhere such as IPCS . Need more practical experience in applying the GHS criteria. Need to look carefully at future experience in applying the criteria and then reevaluate the situation. Authorities should also consider training classifiers to achieve greater consistency.. No additional guidance for HPV or UN at this time.	

Specific issues identified: hazard to human health in relation with long-term toxicity	Recommendation to the UN Sub-Committee	Recommendation to the HPV Chemicals Programme
	Need to see if the example raises a problem with the criteria..	
STOT: Is the GHS guidance sufficient to identify a serious effect or to eliminate effects not warranting classification? The GHS has examples to illustrate the criteria. Are the criteria actually being consistently applied? The criteria and examples appear to be sufficient.	In future, review application of the criteria in practice to determine if they are being consistently apllied or to determine if trainig, etc might be in order.	No guidance needed.

Additional generic issues identified for which no recommendation has been formulated, due to lack of time:

A number of potential issues related to data quality, interpretation and expert judgment were raised. The GHS includes guidance on a number of these issues in hazard class-specific chapters as well as introductory chapters.

- Both positive and negative data of different qualities. Conflicting results. Guidance in GHS.
- Expert judgment in conflict with GHS criteria. Examples not clear.
- Orientation of new classifiers. Manual of decisions what is a significant effect?) Training and records of decisions possible useful tools during implementation but not related to GHS criteria.
- Chemical characterization – (identity). Issue not clear, not discussed.
- Lack of expertise in classifying in any system as well as GHS. Implementation issue.
- Isomers with different properties. Data for only some of the isomers. Apply mixtures approach to the mix if sufficient data.
- Use of data from therapeutic testing in humans. Note, likely to have animal data available as well.
- Use of incidence data. Note there is guidance in GHS on this in both specific and general terms.
- Guidance on testing difficult substances, e.g. substances that hydrolyze rapidly in the environment. Also for inhalation or some other types of human exposure. Not discussed.
- models, computer simulation of human health effects.

PROBLEMS IDENTIFIED AND RECOMMENDATIONS ON HAZARD TO THE AQUATIC ENVIRONMENT

Specific issues identified: hazard to the aquatic environment	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
Classification for chronic aquatic hazard, use of calculated values for biodegradation - absence of data from a ready biodegradation test for the blend of isomers – a single isomer present at 30% shows no ready biodegradability in an OECD TG 301 - a calculated value (ECQ/BIOWIN) is available for inherent biodegradability of the blend indicating that the blend would likely meet the criteria for inherent biodegradability under aerobic conditions *Despite the fact that the simulated data apply to inherent and not to ready biodegradation in this case, could one envisage to use (Q)SAR data for ready biodegradation for the classification on chronic aquatic toxicity?*	Already have guidance on these issues (Inherent degradation, QSARs).	
Classification of substances which are mixtures of substances or isomers. Five substances of this type were included in the exercise. Toxicity testing, when to use WAF, this method was applied in toxicity testing of two substances	Few words of guidance are provided in A9.3.5.10 of the GHS guidance but it lacks clarity. It would be wise to get a clear formulation that said that WAF as a loading concept for classification can be used as a last possibility (i.e. because the loading concept generally leads to effects above the solubility of the substance). What are the caveats related to the use of	Same.

Specific issues identified: hazard to the aquatic environment	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
	the WAF loading concept approach? Ideally, the measured concentration concept should be used as frequently as possible. It would also be advisable to provide concrete example of when and when not to use the WAF or in which situation it has been used in the past.	
Classification of substances which are mixtures of substances or isomers. Five substances of this type were included in the exercise. How to assess the bioaccumulation potential?	Section 4.1.3.5.5 of the GHS Is it possible to estimate the bioaccumulation potential of a mixture of isomers. It is possible to assess bioaccumulation of a mixture but it is not clearly indicated in the GHS guidance. Some updating guidance would be advisable after exploring what is currently developing. For instance, a predicted log Kow estimate for petroleum chemicals, lead to an estimation of bioaccumulation potential of each individual chemical in the mixture.	
Assessment of bioaccumulation potential of difficult substances: poorly water soluble substances (use of models, experimental estimation of BCF, interpretation of data) ionic substances	There is some guidance in Chapter 5 of Annex 9. There is a need to update guidance on how to correctly apply predicted	

Specific issues identified: hazard to the aquatic environment	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
	log Kow for assessing bioaccumulation for difficult substances. As an example, there can be some problems in using predicted log Kow to assess bioaccumulation of difficult substances. For instance, for pigments and dyes that have low water AND octanol solubility, the predicted log Kow might provide high bioaccumulation estimates even though there are not expected to bioaccumulate. For substances that have acid dissociation constants in the range of environmentally relevant pH, there is a further need to update guidance.	
Derivation of M factor	A few words on the philosophy and use of the M factor should be added to Annex 9.	
Classification of metals	The GHS guidance has been developed in chapter 7 of annex 9 and in annex 10. However, the test method is going through a validation step. There might be a need to provide sufficient training.	
Application of guidance on weight of evidence	There is general guidance in Annex	

Specific issues identified: hazard to the aquatic environment	**Recommendation to the UN Sub-Committee**	**Recommendation to the HPV Chemicals Programme**
	9.3.4 and page 20, section 1.3.2.4.9 that provides general wording on weight of evidence. For more than 4 data, a geometric mean approach is presently recommended in GHS guidance. For data rich substances, the weight of evidence chapter of the GHS does not address the use of Species Sensitivity Distribution (SSD).	
Data quality	Annex 9.3.4 (and page 20 1.3.2.4.9 general wording on weight of evidence). Do we need to get into quantitative weight of evidence?	

Other issues related to aquatic hazards for which no recommendation was formulated, due to lack of time:

- Guidance on validation of QSAR and building of the QSAR toolbox. Chapter 6 of Annex 9 needs to be updated based on the recent work explained earlier
- General use of QSARs for classification purpose
- Bioaccumulation Factor derived from QSAR
- Data quality, something in the GHS guidance and refer to OECD RRS?
- Problems in the application on chronic category 4, safety net
- There is much training needed to apply the GHS classification\criteria. Provide good case studies that will support the training of people destined to apply the GHS criteria.
- How about substances that partition mainly into air (gases)?
- Application of chronic category 4 (safety net)
- Problem identified: Substances that partition into air (gases)

EXTRACTS FROM THE PURPLE BOOK RELEVANT TO THE HAZARD TO THE AQUATIC ENVIRONMENT

CHAPTER 4.1

HAZARDOUS TO THE AQUATIC ENVIRONMENT

"In developing the set of criteria for identifying substances hazardous to the aquatic environment, it was agreed that the detail needed to properly define the hazard to the environment resulted in a complex system for which some suitable guidance would be necessary."

(A9.1.1)

"Two Guidance Documents (see Annexes 9 and 10) have been prepared to cover issues such as data interpretation and the application of the criteria…

…Considering the complexity of this endpoint and the breadth of the application of the system, the Guidance Documents are considered an important element in the operation of the harmonized scheme."

(4.1.1.7.3)

ANNEX 9

GUIDANCE ON HAZARDS TO THE AQUATIC ENVIRONMENT

"…the purpose of this document is twofold:

(a) to provide a description of and guidance to how the system will work;

(b) to provide a guidance to the interpretation of data for use in applying the classification criteria."(A9.1.1)

CONTENTS

Appendix I	**Determination of degradability of organic substances**
Appendix II	**Factors influencing degradability in the aquatic environment**
Appendix III	**Basic principles of the experimental and estimation methods for determination of BCF and K_{ow} of organic substances**
Appendix IV	**Influence of external and internal factors on the bioconcentration potential of organic substances**
Appendix V	**Test guidelines**
Appendix VI	**References**

Guidance and Training (outcome of the break out session discussion)

Substances

Annex 9 (and 10) – Developed seven years ago. Certain parts could be updated.

Mixtures

Not covered – There is a need to develop guidance on ingredient in mixtures. Case studies need to be developed in order to develop guidance.

Labelling

Not covered – Rules of precedence of hazard statement should be provided and how to combine them in the GHS.

Training

Having good criteria does not necessarily equate to good classification. Training of people (e.g. including case studies on substances and **especially mixtures**) is crucial in order to get consistent classification.