		The Extended Advisory Group is invited to take note of the presentations.	
	6	**Work Process for Developing Adverse Outcome Pathways**	ENV/JM/TG(2013)37
	10:10-10:30	The Secretariat will propose a process for the development of AOPs at OECD. ***The Extended Advisory Group is invited to discuss the proposed process to develop an AOP and the proposals for the public website.***	
	Coffee Break		
	7	**Platform for Developing Adverse Outcome Pathways**	The proposal of Project 4.2 on Clearspace
	11:00-12:00	EC and the US will present a progress update and demonstration of the OECD AOP Knowledge Base (AOP-KB). ***The Extended Advisory Group is invited to discuss a platform for AOPD.***	
	Lunch Break		
	8	**Progress on the projects for AOP and other activities under the OECD Molecular Screening Project**	ENV/JM/TG(2013)38 Updates by developers available on Clearspace Room Document 1-2
	13:30-17:30	The leaders of Subgroups and AOP projects will present the current work status and present new project proposals. [about 15 minutes are given to each developer including questions and answers, and 30 minutes for some presentations.] ***The Extended Advisory Group is invited to comment on the progress reports and to agree on the workplan including new projects as appropriate.***	
	9	**Human toxome project**	
	17:30-18:00	Thomas Hartung (Johns Hopkins University) will present the human toxome project. ***The Extended Advisory Group is invited to take note of the presentation and comment on the presentation.***	
Day 2: Wednesday, 15 May 2013			
	8	**(continued from Day 1)** **Progress on the projects for AOP and other activities under the OECD Molecular Screening Project**	
	9:00-10:30	The co-chairs may make a brief summary of Day 1 and will open the floor on continued issues from Day 1.	

		The Extended Advisory Group is invited to comment on the progress reports and to approve the workplan including new projects as appropriate.
	10	**Future steps for developing AOPs**
	10:30-11:00	The participants will be requested to consider 1) any other remaining issues, 2) issues to be considered by the EAGMST in future as well as 3) the next steps/commitments/timelines for supporting the work on AOPs, and the timing of the next conference call and meeting.
	Coffee Break	
	11	**How to enable mutual understanding of the high-throughput-screening assay results in a regulatory context (e.g. for priority setting)**
	11:30-13:00	The US will present an update of the US Tox21 and ToxCast™ Phase 2. The Secretariat will present a proposal of the work on enhancing understanding of the HTS results in a regulatory context. ***The Extended Advisory Group is invited to provide comments on the presentations and advise on next steps.***
	Lunch Break	
	12	**Other relevant activities by member countries/organisations on AOPs / Molecular Screening/ Toxicogenomics/ future approaches for chemical assessment**
	14:30-16:30	There will be presentations of relevant activities on AOPs, molecular screening, toxicogenomics and future approaches for chemical testing and assessment. [about 15 minutes are given to each presenter including questions and answers.] - ASAT Knowledge Base concept, the Netherlands - Percellome Toxicogenomics application to Sick House Syndrome-level inhalation toxicity, Japan - The ChemScreen in vitro test battery for detecting reproductive toxicants, Bart van der Burg, the Netherlands. - MoA activities, WHO/IPCS ***The Extended Advisory Group is invited to take note of the report.***
	13	**Any Other Business and Conclusions by the Chairs**
		Meeting adjourns

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Agenda for the Expert meeting on skin sensitization, Meeting on the draft TGs for DPRA and Keratinosens assays

For Official Use **ENV/JM/TG/A(2014)1**

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

30-Jan-2014

English - Or. English

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

ENV/JM/TG/A(2014)1
For Official Use

Test Guidelines Programme

Draft Agenda for Expert Meeting on Skin Sensitisation

13-14 February 2014, OECD Conference Centre, Paris (France)

Ms. Julija FILIPOVSKA
Tel.:+33 1 45 24 16 76; E-mail: Julija.Filipovska@oecd.org

JT03351690

English - Or. English

Expert Meeting on Skin Sensitisation

Meeting on the draft TGs for DPRA and Keratinosens assays

Paris, France, 13-14 February 2014

The two TG address key events of the adverse outcome pathway for skin sensitisation therefore the first day will mainly cover common aspects of the TGs. Day 2 will cover specific aspects of the individual TG.

Meeting will start at 9 am on 13 February and on 8:30 am on 14 February.

Meeting will close at 6:30 pm on 13 February and on 5pm on 14 February

Day 1: 13 February 2014	
Item 1	**Opening of the Meeting** **Adoption of the Draft Agenda** **Background information** The meeting will be chaired by the Secretariat. Participants will be invited to introduce themselves. ***The expert group is invited to approve the draft agenda, revised as appropriate.***
Item 2	**Overview of the activities related to development of the GD of the IATA for Skin Sensitisation** The secretariat will update the group on the activates of the Expert Group developing a Guidance Document on Evaluation and Application of Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation ***The expert group is invited to take note of the activities.***
Item 3	**Presentation of the DPRA assay -scientific basis and development** The DPRA assay will be presented by the test developer ***The expert group is invited to take note of the presentation.***
Item 4	**Presentation of the Keratinosens assay -scientific basis and development** The Keratinosens assay and the validation study will be presented by the test developer. ***The expert group is invited to take note of the presentation.***
Item 5	**EURL ECVAM evaluation of the DPRA and Keratinosesns assays for TG development** ECVAM will present the evaluation of the assays, including validation, and the TG development.

	The expert group is invited to take note of the presentation and comment as appropriate.
Item 6	**Overview of the general issues common to both TGs identified in the first WNT commenting round November 2014-January 2014** The comments received during the 1st WNT commenting round of the draft DPRA and Keratinosens Test Guideline were included in a table and will be presented jointly by ECVAM and the representative of the lead country developing the TG for Keratinosesns (Switzerland). This table also indicates how the lead developers of the TGs addressed these concerns and highlights issues that would be needed to be further addressed during the meeting. ***The expert group is invited to take note of the table and discuss the highlighted issues:*** • General terminology (including definition of Skin Sensitisation & IATA) • Accuracy (LLNA vs human, IATA context, negative results) • Sub-categorisation and potency • Applicability domain (weak/moderate, annex 2) • Performance standards • Proficiency chemicals
Item 7	**Overview of the issues specific to the TG for DPRA identified in the first WNT commenting round.** The DPRA specific issues identified in the 1st DPRA commenting round will be presented by ECVAM for the lead country developing the TG (EC) together with proposals for addressing them. • Applicability domain and clarification on the limitations • Utility of reactivity classes and quantification of reactivity • Cut-off values in the prediction model. How to deal with borderline substances with depletion values in particular around the lowest cut-off of 6.38% • Procedure description ***The expert group is invited to discuss the proposals and agree on a way forward to revise the TG as appropriate.***
Day 2: 14 February 2014	
Item 8	**Summary of outcomes of the day 1 meeting.**
Item 9	**Overview of the issues specific to the TG for DPRA identified in the first WNT commenting round (*continued*)**

Item 10	**Overview of the issues specific to the TGs for KeratinoSens identified in the first WNT commenting round.** The KeratinoSens specific issues identified in the 1st KeratinoSens commenting round will be presented by the representative of the lead country developing the TG (Switzerland) together with proposals for addressing them. • Format of the TG (PBTG or TG) • Proprietary aspects of the assay • Level of information to add to the TG (metabolism considerations, oxidative stress) • Procedures description (general, p. 21, title p. 38, data evaluation and acceptance criteria) • Test report • Performance standards ***The expert group is invited to discuss the proposals and agree on a way forward to revise the TG as appropriate.***
Item 10	**Conclusions, next steps, timeframes and closure of the meeting**

Coffee breaks and lunch will be at the most appropriate time.

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Agenda for the Meeting of the "Case Study" subgroup of the Expert group on IATA for skin sensitization

Meeting of the "Case Study" subgroup of the Expert group on IATA for Skin Sensitisation
OECD, Paris 12 February 2014, 13:30h-18:00h

The meeting is organised back-to back with the meeting of the Expert Group on alternative methods for skin sensitisation that is held at the OECD on 13-14 February where many but not all of the IATA Expert group members participate.
The aim of the meeting is to:

a. identify the individual information to be used within the IATA and
b. get a common understanding of how to report such information
c. identify candidate case-studies to be annexed to the IATA

Agenda

Item 1	Introductions: – Participants – Scope of the exercise in general – Aim of the meeting	JRC, Secretariat
Item 2	General framework for the skin sensitisation AOP-based IATA – Working definitions – Parts/modules/type of individual information constituting the IATA – Template for reporting the individual information sources within the IATA	JRC presentation (~10 min) followed by a discussion on each point to develop an proposal for the entire IATA group and continue the work on the GD)
Item 3	Presentation by the experts on case studies followed by discussion to identify candidate case-studies to be annexed to the IATA	Janine Ezendam Takao Ashikaga Masaaki Miyazawa Nathalie Alepee Gavin Maxwell Grace Petlewitz Joanna Javorska? All
Item 4	Outline steps and framework for the development of the GD on IATA for Skin Sensitisation	

Practical info: The meeting will be held in the Marshal Building (not the congress centre which is across at 2, rue André Pascal - 75775 Paris Cedex 16). To come to this room you will need to first go to the reception of the congress centre state that you are going to the Meeting of the IATA for Skin Sensitisation Sub-group and to contact Sanela Bajrovic at +(33-1) 45 24 **16 74** or Julija Filipovska **at** +(33-1) 45 24 **1676** they will have to come and pick you up. It would be nice if you can arrive between 13-13:30 h so that we can collect you as group.

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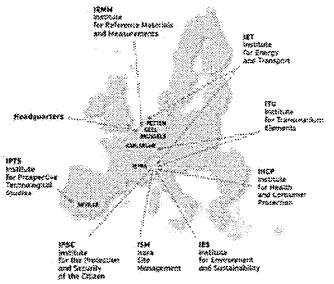
Agenda for the ECVAM SCIENTIFIC ADVISORY COMMITTEE (ESAC) 39th Meeting of the ESAC

European Commission



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ECVAM SCIENTIFIC ADVISORY COMMITTEE
(ESAC)
39th Meeting of the ESAC

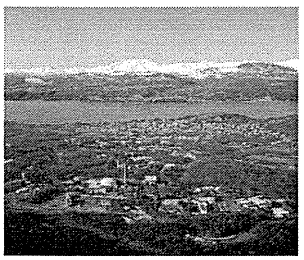
DRAFT AGENDA

11-12 March 2014

JRC, Ispra (VA), Italy
Meeting room 009, Bldg. 58

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

ECVAM SCIENTIFIC ADVISORY COMMITTEE (ESAC)
39th Meeting of the ESAC
11-12 March 2014



On the evening of 10 March at 20:00 there will be a social get together business dinner at Hotel Ristorante Dance Azzurra.

Tuesday 11 March 2014

08:30	Transfer from hotel to JRC campus
09:00 - 9:15	Welcome, adoption of the agenda
09:15 -10:00	Presentation of h-CLAT Working Group Report and draft ESAC opinion *(E. Roggen)*
10:00 - 10:30	*Coffee break*
10:30 - 13:00	Discussion/amendment/adoption of WG report & ESAC opinion.
13:00 - 14:00	*Lunch break*
14:00 - 14:30	Presentation of EURL ECVAM evaluation of the epiCS study *(M. Schaeffer)* & ESAC Request *(C. Griesinger)*
14:30 - 15:00	Initial observations of the rapporteurs on the epiCS PS-based validation study *(J. Richmond / R. Kraetke)*
15:00 - 15:40	Presentation of the CYP validation study, focus main results & conclusions *(C. Bernasconi)*
15:40 - 16:00	Presentation of ESAC Request CYP validation study *(C. Griesinger)*
16:00 - 16.30	*Coffee break*
16:30 - 17:30	Discussion / endorsement of ESAC Request CYP validation study
17:30 - 18:00	Wrap up of the meeting
18:10	Transfer to the hotels
20:00	Business dinner, Ristorante Belvedere

Wednesday 12 March 2014

08:30	Transfer from the hotel to JRC
09:00 - 9:40	Presentation of the eye irritation validation study (mainly EpiOcular), focus on main results & conclusions *(J. Barroso)*
09:40 - 10:00	Presentation of ESAC Request eye irritation validation study *(C. Griesinger)*
10:00 - 10:30	Coffee break
10:30 - 11:00	Discussion / endorsement of ESAC Request eye irritation validation study
11:00 - 11:40	Update by the OECD test guidelines programme *(A. Gourmelon via TC)*
11:40 – 12:40	Presentation of the GreenScreen assay for genotoxicity testing *(F. Madia)*
12:40 – 14:15	Lunch break
14:15 - 14:45	AOB, wrap up of the meeting
15:20	Transfer to airport or hotel

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SUMMARY REPORT OF THE 6th MEETING OF THE EXTENDED ADVISORY GROUP ON molecular screening and TOXICOGENOMICS

SUMMARY REPORT OF THE 6TH MEETING OF THE EXTENDED ADVISORY GROUP ON MOLECULAR SCREENING AND TOXICOGENOMICS

OECD conference centre in Paris

14-15 May 2013

1. The sixth meeting of the extended Advisory Group on Molecular Screening and Toxicogenomics (EAG) was opened by Bob Kavlock (United States) and Maurice Whelan (EC), co-Chairs of the EAG. The meeting was attended by forty one participants as listed in Annex 1 (*to be attached later*).

2. The main objectives of the meeting were to: i) review progress with projects on the development of Adverse Outcome Pathways included in the workplan and approve new project proposals, ii) discuss the process for the development of AOPs, including the IT platform, iii) discuss opportunities to increase the mutual understanding of high throughput screening assays and their results.

Draft Agenda

3. The meeting participants approved the draft agenda of the meeting [ENV/JM/TG/A(2013)3] without change.

Report from Secretariat

4. Hiro Aizawa (OECD Secretariat) presented the progress on relevant OECD activities following the last meeting in June 2012, such as i) discussions at the Joint Meeting in November 2012, ii) discussions at the Working Group of National Coordinators of the Test Guidelines Programme (WNT) at its meeting held in April 2013, and iii) major progress of OECD AOPs activities. The EAG took note of the presentation.

Draft Guidance and Template for the development of AOPs

5. Joop de Knecht (OECD Secretariat) presented an update of "Guidance and Template" document which was published in April 2013 [ENV/JM/MONO(2013)6]. Based on recent experience from AOP developers, the guidance part of the document received general support; the template part of the document might need a few adjustments to avoid redundancy in future. Similarly, AOP developers indicated that a user's manual would be beneficial. This is detailed further under paragraph 19..

Short report from AOP relevant workshops

6. Maurice Whelan (EC) provided updates of three SEURAT-1 workshops on Liver AOPs in October 2013), Data-mining for AOPs in November 2012 and Neurotoxicity AOPs in March 2013.

7. Gilly Stoddart (ICAPO) provided an update of the workshop on Inhalation Toxicity: Pathways to Better Methods. She informed that ICAPO planned to submit a proposal for the new project.

8. Ed Perkins (US) provided an update of planned workshop on Integration of Ecological and Human Toxicology in Adverse Outcome Pathways for Chemical Hazard Assessment in 2014. The members were invited to contribute to the workshop.

Work Process for Developing Adverse Outcome Pathways

9. Anne Gourmelon (OECD Secretariat) presented the proposed work process for AOP development, as well as a proposal for contents of OECD webpage on AOPs [ENV/JM/TG(2013)37]. After development of the AOP on the IT platform (discussed in further details in paragraphs 12-16), the proposal is that, after EAG's review and agreement, the WNT and the Task Force on Hazard Assessment (TFHA) will review and endorse the AOP prior to its declassification by the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides & Biotechnology (JM). The proposal will also be circulated for review by the Task Force on Hazard Assessment and the Working Group of the National Coordinators of the Test Guidelines Programme, and a revised version will be presented at the next EAG teleconference and then at the WNT meeting in April 2014.

10. The EAG agreed to present information on AOPs, including on each AOP project on OECD public website. The AOP proposal submission form, flow diagram of process, information of ongoing projects (title, summary and contact) and OECD EHS generic account for questions. It was also clarified that the publication of an AOP as an OECD document does not prevent developers from publishing papers in the scientific peer-reviewed literature.

11. Members provided comments on the work process as below:

- Careful use of wording such as "approval"/ "acceptance" in the context of an OECD programme,
- Clear periodic review process,
- Needs for further elaboration of review criteria for the evaluation of AOPs, and
- Clarification on the use of the Knowledge-Base platform for the development of AOPs.

Platform for Developing Adverse Outcome Pathways

12. Clemens Wittwehr (EC), Stephen Edwards and Ed Perkins (US) presented a progress report and demonstration of the OECD AOP knowledge base (AOP-KB). It contains a wiki type platform linked with external resources. Users can use four types of entities to develop an AOP: AOP, key event (including Molecular Initiating Event), adverse outcome and chemical initiator. Users can find entities for their AOP from the list. A summary table of key events is available and users can create links between key events and document weight-of-evidence for the link.

13. Bob Diderich (OECD Secretariat) presented an overview of a tool that will be developed for quantitative AOPs for hazard assessment. It could complement and populate the QSAR toolbox and the AOP-KB. The OECD will send an elaborated proposal to members when financial resource becomes available for this project.

14. The EAG agreed to give access to the AOP-KB to all members of EAG and developers of AOPs included in the work plan for enabling feedback on the wiki part of the AOP-KB, and have discussion on the AOP-KB at the next teleconference.

15. The EAG focused on functions related to AOPs development, recognising the needs to define and discuss the reviewing process. The EAG were also reminded that all projects in the work plan will have to be implemented at some stage on the platform after its development. The EAG noted that the AOP-KB platform will also be discussed by the WHO/IPCS MoA steering group.

16. Members provided comments on the function of the AOP-KB for further development as below:

- Importance of harmonised terminology to develop an AOP,
- Needs for guidance or manual to use the AOP-KB,
- Track changes of AOPs and list of reviewers' comments and decisions taken on comments,
- Labelling of OECD project or non-OECD project, status in the work plan,
- Function to freeze an AOP for review, and
- Alert system for participants to be informed on what's new.

Progress on the projects for AOP and other activities under the OECD Molecular Screening Project

17. The EAG noted the presentations made by AOP developers on their projects (all presentations were made available to participants on Clearspace), and agreed on the inclusion of new projects into the work plan as listed below;

Section 1 (development of an adverse outcome pathway)

1.1: The Adverse Outcome Pathways for Skin Sensitisation Initiated by Covalent Binding to Proteins.

No presentation was made because the project has been completed.

1.2: The Adverse Outcome Pathways for Nonpolar Narcosis.

No presentation was made.

1.3: The Adverse Outcome Pathways for Acetylcholinesterase Inhibition.

It was informed that the slides to provide an update are available on clearspace.

1.4: Adverse Outcome Pathways for Five Cell Signalling Pathways Associated with Cell Proliferation and Differentiation that are Conserved Across Species.

Julija Filipovska (OECD Secretariat) presented an update and invited any contributor to join the project. The EAG agreed on the possible usefulness of this AOP for the QSAR toolbox as a profiler, but recognised that the adverse outcome is not currently identified.

1.5: Two Adverse Outcome Pathways for Mitochondrial Toxicity.

Julija Filipovska (OECD Secretariat) presented an update and invited any contributor to join the project. The EAG agreed on the possible usefulness of this AOP for the QSAR toolbox as a profiler, but recognised that the adverse outcome is not currently identified.

1.6: The Adverse Outcome Pathways for Embryonic Vascular Disruption and Developmental Defects.

Thomas B. Knudsen (US) presented an update. The EAG agreed to include this project in the work plan.

1.7: The Adverse Outcome Pathways for Sustained Activation of the Aryl Hydrocarbon Receptor:

Kennedy Sean (Canada) presented an update, then Bob Budinsky (BIAC) presented an update.

1.8: The Adverse Outcome Pathways for Mutagenic Modes of Action for Cancer.

No presentation was made.

1.9: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals.

Kevin Crofton (US) presented an update. The EAG agreed to include this project in the work plan.

1.10: Xenobiotic Induced Inhibition of Thyroperoxidase and Depressed Thyroid Hormone Synthesis and Subsequent Adverse Neurodevelopmental Outcomes in Mammals.

It was indicated that the slides providing an update are available on clearspace.

1.11: The Adverse Outcome Pathways for Heritable Germ Cell-Derived Disease.

Carole Yauk (Canada) presented an update on progress with the development of the AOP and feedback on the application of the OECD guidance document.

1.12: The Adverse Outcome Pathways linking Aromatase Inhibition, Androgen Receptor Agonism, Estrogen Receptor Antagonism, or Steroidogenesis Inhibition, to Impaired Reproduction in Small Repeat-Spawning Fish Species.

Dan Villeneuve (US) presented an update on progress with the development of the AOP and feedback on the application of the OECD guidance document. The EAG agreed to include this project in the work plan.

1.13: Neurotoxicant-induced Neuroinflammation: a converging key event in an adverse outcome pathway:

No presentation was made.
Note from the Secretariat: the update of the SEURAT-1 related AOP-neurotox workshop on item 5 provided an update of this project.

1.14: The Adverse Outcome Pathways from protein alkylation to liver fibrosis.

Brigitte Landesmann (EC) presented an update. The EAG agreed to include this project in the work plan.

1.15: The Adverse Outcome Pathways for Neurotoxicity induced by GABAA receptor inhibition.

Ed Perkins (US) presented an update. The EAG agreed to include this project in the work plan.

1.16: The Adverse Outcome Pathway Describing Hematotoxicity due to Nitroaromatics and N-hydroxyl anilines.

Ed Perkins (US) presented an update. The EAG agreed to include this project in the work plan.

1.17: CAR and PPARa-mediated pathways to non-genotoxic rodent liver cancer.

Chris Corton and Imran Shah (US) presented an update. The EAG agreed to include this project in the work plan.

1.18: CAR and PXR-mediated pathways to rodent liver hyperplasia.

Chris Corton and Imran Shah (US) presented an update. The EAG agreed to include this project in the work plan.

Section 2 (development of an adverse outcome pathway case study)

2.1 Adverse Outcome Pathways – Case Studies Using Aquatic Organisms

No presentation was made. Tom Hutchinson (UK) had informed the Secretariat that he could not participate but would provide an update on another occasion.

2.2 AOP Hepatotoxicity due to 2,4,6-trinitrotoluene

Ed Perkins (US) presented an update. The EAG agreed to include this project in the work plan.

2.3 AOP on Energy Metabolism affected by 2,6-Dinitroluene

Ed Perkins (US) presented an update. The EAG agreed to include this project in the work plan.

Section 5 (others)

5.1 In vitro test method development strategy for the OECD Skin Sensitisation AOP.

Maurice Whelan (EC) presented an update.

Notes from the Secretariat: Section 3 (guidance document related to adverse outcome pathway development including its evaluation) was discussed on item 4 Guidance and Template for the development of AOPs. Section 4 (knowledge management tool) was discussed on item 7.

Human toxome project

18. Thomas Hartung (Johns Hopkins University) presented the human toxome project and expressed interest in possible future collaboration with the AOPs activities.

Future steps for developing AOPs

19. The EAG agreed summary of the discussion and proposed next steps by co-chairs as follows;

- The work plan will be updated periodically (i.e. twice a year) as a living document. A summary document will be developed to include abstract of each AOPs projects and contact information for the purpose of the OECD public website.
- Developers must comply with the AOPs template, and develop a draft AOP as a first milestone to substantiate the AOP.
- After the AOP-KB becomes available for use by developers, i.e. at the end of June, feedback of AOPs developers will be provided via AOP-KB.
- The EAG agreed to provide an access of the AOP-KB to EAG members and project developers of AOP on the work plan.
- The EAG agreed to develop supplemental guidance or manual for evaluation of AOPs. Grace Tier (BIAC) and Bette Meek will be co-leaders of the project. The members of the project are Brigitte Landesmann (EC), Kevin Crofton (US), Dan Villeneuve (US, TBC), Carole Yauk (Canada) and Julija Filipovska (OECD Secretariat).
- Further discussion is needed for good practice to support AOPs to provide evidence such as how to apply Bradford-Hill criteria.
- Work process should be revised and consolidated and the EAG will discuss it at the next teleconference.

- The EAG agreed to present information on AOPs, including on each project on the OECD public website. It should include the proposal submission form, the flow diagram describing the process, the information of ongoing projects (title, summary and contact) and the OECD EHS generic account for queries.
- After submission of a new project proposal, the Secretariat will provisionally include it in the work plan as appropriate. After the EAG's discussion, it will be included in the work plan if agreed.
- The AOP template will be revised in future, based on experience from AOP developers. The EAG requested the Secretariat to collect feedback.
- The EAG agreed to hold a teleconference in November/December 2013 and next face-to-face meeting in Paris or Japan around May 2014.

How to enable mutual understanding of the high-throughput-screening assay results in a regulatory context

20. Kevin Crofton (US) made a presentation on computational toxicology update: chemical screening, model development and Dashboards. It pointed that 1) significant progress has been made on using HTS methods to generate screening data for thousands of chemicals by ToxCast and Tox21, 2) predictive toxicology and systems models are being derived using combination of biology, chemistry and statistics (i.e. AOPs), 3) and informatics models are being developed for data use and visualization.

21. Anne Gourmelon (OECD Secretariat) made a presentation on a proposal to enhance understanding of the HTS results in a regulatory context. It was clarified that the proposal is to enhancing understanding of the HTs results and not to develop or validate a Test Guideline on HTS. Japan expressed concern to develop a Test Guideline by the VMG due to the low number of experts on HTS in that group.

22. The EAG agreed to establish a drafting group to discuss possible guiding principles to enhance understanding of the HTS results in a regulatory context. Grace Tier Patlewicz (BIAC), George Fotakis (EC), Brigitte Landesmann (EC), Natalia Reyero (US), Kevin Crofton (US), Bart Van Der Burg (Netherlands) and Anamaria Colacci (Italy) expressed interest to be members of the group. There was suggestion that the OECD harmonised template, OHT201, can provide a good starting point to discuss this. Canada agreed on the needs of the guiding principles.

Other relevant activities by member countries/organisations on Molecular Screening/ Toxicogenomics/ future approaches for chemical assessment

23. Rob Stierum (Netherlands) made a presentation on Assuring Safety without Animal Testing (ASAT) Knowledge Base concept. Two projects have been completed: risk assessment of liver toxicity without animal data, and data integration and mining towards risk assessment apply for skin sensitization. It will develop data infrastructure for human risk assessment. It could also contribute to the development of an adverse outcome pathway for cholestasis and tie in into AOP Knowledge Base.

24. Jun Kanno (Japan) presented the framework and an update of the Japanese Percellome Project. Percellome Inhalation Project aims to identify the molecular mechanism of the "indefinite or unidentified complaints" in Sick-House/Building-Syndrome level exposure. He also presented an update of related tools such as Gene Network Drawing and International Publication, and Garuda.

25. Bart van der Burg (Netherlands) made a presentation on ChemScreen: in vitro test battery for detecting reproductive toxicants. The focus of activities to establish exposure modules, toxicity screening tool, in vivo reprotoxicity databases, Bayesian network approach and automated analysis tool. The progress was made on extension of reprotox (rodent, environment) databases, chemical selection, new

assay development (CALUX panel, steroid metabolism), set-up of HTS screening, screening 150 chemicals, assay validation, QSAR analysis of 75,000 chemicals, integrative software tools, ITS setup, high throughput PBPK, feasibility studies and AOP design. He also illustrated working model AOP androgen/estrogen-dependent sex organ development and difficulty in designing AOPs.

26. Bette Meek (WHO/IPCS) presented an update of WHO International Steering Group on Mode of Action. The objectives of the WHO framework update are to clarify terminology, to reflect evolving experience in application, to extend utility to emerging areas in toxicity and non-toxicity testing. The modified MoA Framework addresses modified Bradford-Hill considerations, and weighting evidence.

27. Romualdo Benigni (Italy) made a presentation of molecular screening and toxicogenomics: experience at the ISS. It includes the Istituto Superiore di Sanita' (ISS) experience in genomics and metabolomics, and suggestions to develop AOPs. The suggestions are the genome works as a connected system and not as a set of independent agents, difference of genes' involvement between patients and controls, and the possible difference of AOPs between patients and controls.

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SUMMARY RECORD, MEETING OF THE OECD EXPERT GROUP ON SKIN SENSITISATION

MEETING OF THE OECD EXPERT GROUP ON SKIN SENSITISATION
13-14 February 2014
OECD, Paris

SUMMARY RECORD

Item 1: Opening of the meeting and adoption of the draft agenda

1. The meeting was chaired by the OECD Secretariat. Participants from France, Italy, Spain, Netherlands, Japan, Switzerland, United Kingdom, European Chemicals Agency, European Commission (JRC), industry, ICAPO and the OECD Secretariat attended the meeting. The list of participants is available to government representatives (Annex 1). The Chair introduced the draft agenda, indicating that the main objective was to address comments received from the WNT on the draft test guidelines for DPRA and KeratinoSens™ received in the period November 2013-January2014.

2. The Secretariat also informed the group that late comments were received from Japan the day before the meeting and that they will also be addressed by the lead countries to the extent possible.

3. The draft agenda was adopted (Annex 2) with the change of the order of presentation of Item 3 and Item 4, Item 4 was presented first. The draft test guidelines with the changes (in track) agreed at the meeting are presented in Annex 3.

Item 2: Overview of the activities related to development of the GD of the IATA for Skin Sensitisation

4. The secretariat updated the Expert Group on the activities of the Task Force for hazard Assessment nominated Expert Group for developing a Guidance Document on Evaluation and Application of Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation. The group shares a number of experts with the Test Guidelines Expert Group for Skin Sensitisation. The IATA for skin sensitisation expert group is working jointly with the task force organising a workshop on development and assessment of IATAs on developing relevant definitions and a general outline of the guidance document. The group has had two webex meetings and a face to face meeting of a case study subgroup on 12/2/2014. Some of the case studies discussed at the meeting included DPRA and KeratinoSens™. Draft working definitions for IATA, ITS and other relevant terms, are still being discussed.

5. The expert group for test guidelines for skin sensitisation took a note of the activities of the IATA expert group for skin sensitisation and emphasised that it is important that relevant outcomes of the work of each of the groups is shared timely.

Items 3 (Item 4 in the agenda): Presentation of the KeratinoSens™ assay

6. Andreas Natsch (test developer from Givaudan, representing Switzerland at this meeting) presented the scientific basis, development and the validation study for the KeratinoSens™ assay. The assay is proposed to address the activation of the Nrf2 protein dependent oxidative stress response pathway in keratinocytes, a biological mechanism covered by key event 2 of the skin sensitization AOP, by

measuring activation of Luciferase gene expression driven by a Nrf2 responsive ARE promoter element. The validation study for this assay was coordinated by Givaudan and five laboratories were involved. Data were reviewed by the EURL ECVAM and peer reviewed by the EURL ECVAM Scientific Advisory Committee (ESAC) (discussed more under agenda item 5).

7. The Expert Group took a note of the presentation. UK indicated that flavonoids could interfere with the Luciferase assay, an issue considered in other Luciferase based TGs (e.g. TG 455 and TG457). The developer of the assay and the group took note of the information and undertook to look at how similar concerns were addressed in Luciferase based TGs.

Items 4 (Item 3 in the agenda): Presentation of the Direct Peptide Reactivity Assay (DPRA)

8. Frank Gerberick (test developer from P&G representing EC at this meeting) presented the scientific basis and development of the DPRA assay. The assay is proposed to address the molecular initiating event of the skin sensitization AOP by quantifying/measuring the reactivity of chemicals towards model synthetic peptides containing either lysine or cysteine. The validation study for this assay was coordinated by EURL ECVAM and three laboratories were involved.

9. The group addressed questions related to the choice of solvents for the assay, solubility of the chemicals tested (see paragraph 15 below, fourth bullet point) and the ability of the assay to discriminate the different potency categories based on the reactivity observed. It was agreed that the choice of solvent is based on what is appropriate for the assay and the particular chemical tested and that this has been the case for all assays including LLNA. Moreover, the EURL ECVAM validation study demonstrated that there is almost no impact of solvent choice on the results obtained as long as the solvent does not impact on the percent peptide depletion (as monitored with the relevant reference control). For the sub-categorisation purposes (potency among sensitizers) it was clarified that the assay and the current TG could only provide useful supporting information in the context of an IATA and should not be used directly for determining subcategories of sensitizers. It was also agreed to emphasise this point during the revision of the TG (agenda item 6).

Items 5: EURL ECVAM evaluation of the DPRA and KeratinoSens™ assays for TG development

10. Silvia Casati from the EURL ECVAM made a presentation on the process of the validation, evaluation and peer review for the two assays and the development of the TGs. Validation studies, ESAC review report and EURL ECVAM recommendations for the assays were made available to the WNT and the expert group during the first commenting round of the test guidelines (closed on 14 January 2014).

11. On the basis of the results generated in the validation studies the ESAC peer-review working group concluded that: i) WLR and BLR are acceptable for both assays (for DPRA the BLR exceeded the target value set at the onset of the validation study by excluding from the calculation the two metals for which the test method is not applicable); and ii) assays are transferable to laboratories sufficiently experienced with the main components of the method (HPLC for DPRA and cell culture for KeratinoSens™); iii) the predictive capacity for skin sensitisation for both assays was found to be consistent with published information. Also it was recommended that future evaluation of the predictive capacity should be performed in the context of integrated approaches.

12. The group appreciated the well outlined presentation of the validation and evaluation process coordinated by EURL ECVAM.

Items 6: General issues common to both TGs identified in the first WNT commenting round November 2013-January 2014

13. The secretariat introduced the agenda item and the main common issues identified in the first WNT commenting round, one of which concerned the terminology including the definition of Skin Sensitisation & IATA. The Secretariat informed the group that the definition for skin sensitisation used is consistent with the UN GHS and the definition used in other TGs related to skin sensitisation. In terms of reference to IATA for skin sensitisation in the TGs discussed at the expert meeting, the Secretariat referred the group to the discussion for agenda item 2.

14. In addition the group was informed that the use of the general terms substance/chemical/test chemical was reviewed by the Secretariat to be consistent with the decisions of the Joint Meeting and the WNT and with the UN GHS definitions. The Secretariat explained that the decision of the WNT in 2013 was to use the term "test chemical" to designate what is tested, without implication for what it is exactly (this being left to the applicability of individual methods). Any further general terminology issues relevant to these or other TGs would be discussed at the WNT level. The expert group acknowledged the information without further comment.

15. Silvia Casati and Chantra Eskes presented the other common issues. The following issues were discussed:

- Reporting of accuracy of the test in the TGs – it was discussed whether reporting of accuracy relative to LLNA is ideal or should be reported also compared to human data or other animal tests. In addition the issue of accuracy of the test alone and in the context of IATA was discussed. Changes to the text of the TGs were agreed to clarify that accuracy is reported compared to LLNA as it is the test for which best quality data is available. In addition a sentence was added to both TGs that responses in the animal tests may not fully reflect the situation in humans and this would need to be considered when evaluating the performance of alternative assays. . It was also clarified that the accuracy for each test as reported in the TG is intended for information only since the test methods are not proposed as stand-alone methods and that the predictive capacity of both tests should be better considered in the context of an IATA where DPRA and KeratinoSens™ are used together with other information sources. However change to the text was added to allow for the possibility that positive results from both tests may be used on their own to classify a chemical into UN GHS category 1 based on the provisions of a particular regulatory framework.

- Sub-categorization of sensitizers and potency evaluation using the test – changes were introduced in both TGs to better explain that the tests cannot be used alone for sub-categorization of sensitizers into the GHS subcategories 1A or 1B but that they provide information that could potentially be useful for assessment of sensitising potency when used in integrated approaches such as IATA.

- In relation to the comments received including the proposal to add a statement in the KeratinoSens™ TG on its limited performance for predicting low to moderate sensitisers and the need to test additional weak sensitisers with the DPRA, the group discussed this should not be perceived as a specific limitation of the in chemico/in vitro methods since the in vivo methods are also prone to higher variability for chemicals giving a response close to the threshold used to discriminate between sensitisers and non-sensitisers. Joao Barroso and Silvia Casati (ECVAM)

informed the group that a preliminary analysis of the ICCVAM LLNA database showed that reproducibility of LLNA for weak sensitizers is 53% which implies that 47% of the weak sensitisers would be classified as negative in another LLNA study. It was therefore agreed not to consider the limited predictivity for borderline chemicals a specific limitations of the alternative methods. Changes introduced to indicate how the results should be analysed (i.e. in the context of IATA) should help in overcoming limitations of the different assays/results included within an IATA.

- Chemical Coverage/Applicability domain of the TGs – It was agreed that Annex 2 listing all functional groups found in the chemicals tested for the validation, is not helpful in defining the chemical structural space to which the TGs are applicable and should be deleted from both TGs. It was agreed that it is better to define limitation WHEN KNOWN rather than limiting the applicability of the method to only what was tested so far. The secretariat also clarified that in general TGs are considered applicable to nanomaterials and mixtures unless there is evidence showing that they are not applicable or need adaptations; a publication reviewing applicability of OECD TGs to nanomaterial testing has been issued in 2009 [ENV/JM/MONO(2009)21]. In relation to the comments received on the non-applicability of the DPRA to highly hydrophobic chemicals changes were introduced to paragraph 11 of the TG to clarify how to deal with chemicals that are not soluble up to the requested concentration.

- Proficiency chemicals – It was clarified that proficiency chemicals were selected to best cover the dynamic range of each test method and they are intended to be used to demonstrate that the assay is working properly in a new test facility or from time to time. It was agreed that the number of proficiency chemicals should be lowered to 10 for DPRA but still keeping a good balance of different physical states and dynamic range of the assy. It was also agreed that historical data of mean (and range) % depletion will be identified and added to the updated table in the next draft of the TG for DPRA. This will result in more consistent tables with proficiency chemicals in the two TGs. In addition a clarification was added in the TGs to indicate that for proficiency demonstration 8 out of the 10 need to match the historical results.

- Performance standards (PS) – The purpose of inclusion of performance standards only for Keratinsens, was clarified (due to presence of proprietary elements in the method) and that similar (me-too) methods should demonstrate similarity based on the performance standards but for MAD to apply, they will need to be reviewed and included in the TG by OECD. The group discussed the need for inclusion of PS in the DPRA TG. Even though the DPRA does not have proprietary elements and no potential new me-too assays have been identified, France (Nathalie Alépée) raised the issue that the use of different HPLC set-ups than the one used during the validation of the DPRA (e.g. use of a different HPLC column or different flow rates) may raise the need to evaluate such changes to the validated protocol. The expert group agreed to revise paragraph 22 of the DPRA TG to accommodate the possibility of changes to the HPLC set-up as long as its equivalence to the validated set-up is demonstrated (e.g. by testing the proficiency chemicals). Since it was not clear what kind of other changes than those already addressed in the revised TG may be under consideration, the group decided to form a working group to determine whether PS are necessary in the case of DPRA and if so to undertake on their development (including the identification of the Essential Test Method Components and Reference Chemicals and the establishment of Target Values for reproducibility and predictive capacity). The working group, in addition to the developers and EURL ECVAM includes Andres Natsch, Nathalie Alépée and Annette Mehling. The Secretariat also undertook to discuss with National Coordinators the circumstances that determine the need for PS at the WNT 26 in April 2014 and therefore suggested that the development of Performance Standards for the DPRA is undertaken in a EURL ECVAM-