

Member State Committee and Committee for Risk Assessment Joint Workshop (11-12 October 2018, Helsinki)

Final Report

Introduction

In Helsinki on 11 and 12 October 2018, ECHA held for the first time a joint workshop with the members of the Member State Committee (MSC) and of the Committee for Risk Assessment (RAC). The main aim of this workshop was to raise awareness regarding the possibilities and limitations each of the two committees is faced with while executing their statutory tasks and, where possible, to align views on to topical issues.

The following topics of interest were identified for this workshop:

- Germ Cell Mutagenicity – testing and strategic issues;
- Dose selection in systemic toxicology tests and
- *In vitro* testing for skin sensitisation

Members of the two committees, stakeholders from industry and representing civil society, and representatives from observer organisations took part in the workshop, i.e. the Commission (namely DG Environment and DG Grow) the European Food Safety Authority (EFSA), the Joint Research Centre (JRC), the Organisation for Economic Co-Operation and Development (OECD).

Workshop structure

The workshop was held over two half days with and it included, a first open plenary session dedicated to the introduction of the committees and of the topics, followed by two discussion sessions on the topics of interest on October 11th. On October 12th, a second open plenary session for the analysis of the outcome of the breakout groups closed the meeting.

The Chairmen of the MSC and RAC, Watze de Wolf and Tim Bowmer respectively reminded the workshop participants of the structure and function of the two committees. Selected members from both Committees, assisted by ECHA's scientific experts, had developed the presentations on the three topics of interest and presented them during the first plenary session of the workshop:

- Dr Andrew Smith, from the UK Health and Safety Executive and member of the RAC, and Dr Katarzyna Malkiewicz, from the Swedish Chemical Agency and alternate member of the MSC, had prepared the material for the topic of Germ Cell Mutagenicity;
- Dr Betty Hakkert and Dr Marjolijn Woutersen, from the National Institute for Public Health and the Environment (RIVM) in the Netherlands, the former a RAC member, had developed the Dose Selection topic.
- Dr Christine Bjorge, from the Norwegian Environment Agency and RAC member, and Mr Henrik Tyle, from the Danish Environment Protection Agency and member of the MSC, had worked on the topic of *in vitro* testing for skin sensitisation.

Both the background documents and the presentation material included sets of questions aimed at structuring the discussion. Background material had been provided to the participants in

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advance of the workshop in order to prepare for the discussion; the background documents are now available on the ECHA website alongside the agenda of the meeting.

The breakout groups were selected and requested to discuss each topic and once finished, were rotated in order to gain a second opinion on each topic. In this way, two separate views on each topic were achieved.

Outcome of the discussion

On Friday October 12th, each of the six ECHA rapporteurs shortly presented the outcome for their respective breakout group in open plenary session, and the participants had the chance to share comments and inputs, allowing further development of the different views expressed in the discussion groups, and aiming to reach a more common set of conclusions.

1. Germ cell mutagenicity-testing and strategic issues

The aim of the workshop was to discuss on the type of studies able to provide data suitable for distinction of classification as Muta 2 or 1B under CLP¹, and the additional testing strategies necessary to overcome possible limitations of these studies.

For a substance already meeting the category 2 criteria for classification as germ cell mutagen, other data besides germ cell mutagenicity tests, if available and robust, can always be used in a weight of evidence approach to support a category 1B classification. Notably, REACH² substances may be considered data-poor in comparison to data rich substances such as PPPs and biocides. Where available, toxicokinetic (TK) information, reproductive toxicity, genotoxicity in gonadal tissue and carcinogenicity results can contribute to upgrade the classification from category 2 to 1B.

Although it may not be consistent with the criteria in the Globally Harmonised System of Classification and Labelling of Chemicals (GHS)³, or with past regulatory practice, one potential approach could be to consider germ cell as any other 'distant tissue' (e.g. bone marrow) – but this would assume (controversially) that all systemic somatic cell mutagens are also germ cell mutagens. An alternative approach could be based on the availability of data showing or indicating that the substance reaches gonads. Can/should a Muta 2 substance (i.e. mutagenic in somatic cells) that reaches gonads be upgraded to Muta 1B (germ cell mutagen)? Is there any evidence that DNA from germ cells are 'more protected' than somatic cells? It is incorrect to say that all stages of germ cell maturation are 'more condensed', and thus more protected.

Reliable TK data in testis or ovary, combined with demonstration of in vivo mutagenicity in somatic cells, could lead to category 1B classification; however, when only systemic TK data are available this outcome cannot be assumed. Availability of data indicating other (non-genotoxic) adverse effects e.g. in gonads can help in making TK data more relevant. It was discussed that a practical interpretation of the wording "interaction with germ cells", introduced with the CLP regulation in 2008, may be preferred instead of the work intensive process of updating GHS. The former text, which reads "reaching germ cells", was changed in order to avoid misinterpretation and over-classification. This aspect of the criteria was introduced following

¹ Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32008R1272>)

² Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L:2006:396:TOC>)

³ Rev. 2017: https://www.unece.org/trans/danger/publi/ghs/ghs_rev07/07files_e.html#c61353

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advice from respected academic specialists (including the UK Committee on Mutagenicity). It was not intended to make a Category 1B classification possible only when a substance's molecular interaction with germ cell DNA has been shown explicitly. Indirect information of a likely interaction (e.g. TK data and other data in Weight of Evidence arguments) may be considered sufficient to justify a Category 1B classification on a case-by-case basis.

It was mentioned that for data poor substances, shown already to be somatic cell mutagens, a pragmatic approach may be to perform germ cell testing rather than trying to build an argument on limited supportive data.

If the intention is to use data from reproductive toxicity studies to show that germ cells are a valid sensitive target, hormonal effects are to be excluded. Mode of action is important and metabolites are to be considered. This seems possible to use but is not straightforward. Information from the comet assay on gonadal tissue could be used for classification in 1B, but (time and resources allowing) RAC could be presented with cases to gain more experience with their assessment, specifically for data poor substances.

The workshop discussed proposals to request appropriate *in vivo* germ cell tests in the follow-up evaluation to *in vivo* somatic studies under REACH dossier evaluation: compliance check (CCH) and testing proposals examination (TPE) (see Table 1). It was considered that requests for germ cell testing should be triggered when there are positive genotoxicity results on somatic cells combined with either an absence of toxicokinetic information (or other relevant results), or when such data does not allow conclusion for classification category 1B (e.g. the results are negative or inconclusive).

The rodent dominant lethal test (OECD TG 478⁴) should not be requested except when there is the need to follow up on positive *in vitro* results of numerical aberration. If gene mutation is the concern, then ECHA guidance indicates that a suitable follow-up test is the transgenic rodent assay (TGR, OECD TG 488⁵) or comet assay (OECD TG 489⁶).

For practical, economic and ethical reasons, a maximum of one *in vivo* test should ideally be performed to test for mutagenic potential in both somatic and germ cells. This is currently possible for the TGR. The current ECHA approach when requesting a TGR in a REACH compliance check decision is that the:

- collection of germ cells is required at the same time as the other tissues (liver, glandular stomach and duodenum);
- storage of germ cells (frozen at or below -70°C) up to 5 years. This duration is sufficient to allow to decide on the need to analyse germ cells;
- analysis of germ cells should be considered in case of a positive result obtained in somatic cells (liver, glandular stomach, or duodenum).

The workshop participants suggested to modify the current approach and to request TGR in somatic and germ cells with a requirement (instead of a recommendation) to analyse germ cells under the following conditions:

- i) positive results obtained in the somatic cells and
- ii) no clear conclusion about germ cell genotoxicity is possible based on existing information.

Furthermore, a note could be included in the ECHA decisions that the registrants may consider the possibility to perform the TGR with an updated protocol (28d+28d) for sampling of both somatic and germ cells in the same study (Marchetti et al. 2018⁷). It is expected that an OECD

⁴ OECD Test Guidelines No. 478: Rodent Dominant Lethal Test (https://www.oecd-ilibrary.org/environment/test-no-478-rodent-dominant-lethal-test_9789264264823-en)

⁵ OECD Test Guidelines No. 488: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay (https://www.oecd-ilibrary.org/environment/test-no-488-transgenic-rodent-somatic-and-germ-cell-gene-mutation-assays_9789264203907-en)

⁶ OECD Test Guidelines No. 489: In Vivo Mammalian Alkaline Comet Assay (https://www.oecd-ilibrary.org/environment/test-no-489-in-vivo-mammalian-alkaline-comet-assay_9789264264885-en)

⁷ <https://doi.org/10.1016/j.mrgentox.2018.05.021>

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Expert Group on mutagenicity will discuss such a modification of the TG 488 for TGR within the near future.

The comet is approximately five times cheaper than the TGR (~30k€ vs. ~150 k€). However, OECD TG 489 for comet assay does not recommend to freeze germ cells (while freezing is possible for TGR), nor to perform the comet on matured germ cell. The OECD TG 489 does say that comet in gonadal cells can be tested and that a positive result would demonstrate that the substance reached gonads. To avoid the need for freezing (in order to wait for the results of comet assay on somatic cells), one option in ECHA decisions could be to

- request the comet assay with collection of somatic + gonadal cells;
- request the analysis of somatic tissues, and
- request the preparation (and storage of) slides for gonadal cells

It is noted that the comet assay showed good sensitivity to predict rodent carcinogens. An important caveat regarding the analysis of comet assay results is that the impact of cytotoxicity should be well monitored in order to avoid false positive results.

Table 1: Proposal to request appropriate *in vivo* germ cell tests in the follow-up evaluation to *in vivo* somatic studies

Mechanism / MoA identified <i>in vitro</i>	<i>In vivo</i> somatic test with positive results	Relevant follow-up <i>in vivo</i> germ cell test
Gene mutations	<ul style="list-style-type: none"> • Transgenic rodent (TGR) somatic cell gene mutation assays (OECD: 488) or • <i>In vivo</i> mammalian alkaline comet assay (OECD: 489) • Unscheduled DNA synthesis (UDS) test with mammalian liver cells <i>in vivo</i> (EU: B.39, OECD: 486)⁸ 	<ul style="list-style-type: none"> • Transgenic rodent (TGR) germ cell gene mutation assays (OECD: 488)
Cytogenetic (structural aberration)	<ul style="list-style-type: none"> • <i>In vivo</i> mammalian erythrocyte micronucleus test (EU: B.12, OECD: 474)⁹ or • <i>In vivo</i> mammalian bone marrow chromosome aberration test (OECD: 475)¹⁰ or • <i>In vivo</i> mammalian alkaline comet assay (OECD: 489) 	<ul style="list-style-type: none"> • Mammalian spermatogonial chromosome aberration test (OECD: 483)¹¹ or
Cytogenetic (numerical aberrations)	<ul style="list-style-type: none"> • <i>In vivo</i> mammalian erythrocyte micronucleus test (EU: B.12, OECD: 474) including FISH staining showing numerical chromosomal aberrations 	<ul style="list-style-type: none"> • Rodent dominant lethal test (OECD: 478)

In summary, the workshop agreed that it may be possible to further refine the MSC approach

⁸ https://www.oecd-ilibrary.org/environment/test-no-486-unscheduled-dna-synthesis-uds-test-with-mammalian-liver-cells-in-vivo_9789264071520-en

⁹ https://www.oecd-ilibrary.org/environment/test-no-474-mammalian-erythrocyte-micronucleus-test_9789264264762-en

¹⁰ https://www.oecd-ilibrary.org/environment/test-no-475-mammalian-bone-marrow-chromosomal-aberration-test_9789264264786-en

¹¹ https://www.oecd-ilibrary.org/environment/test-no-483-mammalian-spermatogonial-chromosome-aberration-test_9789264071469-en

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when considering how to follow-up testing of somatic cell mutagens. A number of options were identified from the experience of RAC in classifying for germ cell mutagenicity, and from other substances that were included in the harmonised list before RAC was established. It was also agreed, as RAC has had limited numbers of cases to test all the possible options, analysis of further CLH cases would be beneficial.

II. Dose selection in systemic toxicology tests

The aim of this section was to promote a constructive dialogue about toxicity testing and dose level selection for regulatory purposes. The committees discussed on the resulting consequences of particularly low top dose selection in terms of human health protection, threshold derivation (DNEL, ADI, etc.), identification of target organ(s), ED assessment, triggering of tailor made higher tier studies and fulfilment of the CLP regulation.

Several regulatory frameworks such as REACH, BPR¹² and PPR regulate on basis of hazard and risk assessment including classification and labelling (C&L) and endocrine disruptor (ED) assessment. The regulatory use and consequent requirements of toxicological data generated under these legal frameworks should be adequate to serve these purposes. Toxicological studies should be able to detect adverse effects in test animals and, preferably, be able to establish dose responses and provide information on "primary" and "secondary" effects. Therefore, the selection of appropriate dose levels in such studies is an essential requirement.

The selection of the correct dose levels in toxicological studies for hazard identification has been a topic of discussion in recent RAC and MSC meetings. RAC members have identified animal toxicity studies conducted with biocide or pesticide active substances with top dose levels not provoking clear toxicity in the test animals. In some cases, this resulted in an inconclusive outcome on classification and labelling under the CLP Regulation for the specific endpoints. During the discussion, it was also pointed out that pesticides have been regulated for decades and many studies reviewed by RAC can be 10, 20 or even 30 years old as well as conducted to satisfy various regulatory standards across Europe, the USA, Asia and elsewhere. All studies considered by RAC have generally been accepted and deemed adequate and compliant with OECD guidelines.

In dossier evaluation for industrial chemicals registered under REACH, ECHA evaluates experimental studies also with regard to the selection of the appropriate dose levels, but can only respond to studies showing low dosing, i.e. not being in accordance with the OECD test guideline (TG), by requesting new data. It is considered too early to conclude whether a general trend on low dose level selection in toxicity tests can be observed in this process or whether there is merely an increasing awareness of this as a problem. However, it was generally acknowledged that low dose levels in tests could hamper the regulatory use of a key study under for instance REACH or CLP. Additionally, the recently developed EU ED criteria are also based on intrinsic properties of the substance and the occurrence of adverse effects in test animals, for which selection of appropriate dose levels is essential.

In the workshop, various views were expressed on the possible reasons behind low dose level selection in animal studies. One reason could be that the available study may not have been conducted for regulatory purposes and thus its design may miss out the regulatory needs e.g. DNELS setting, OELs, risk assessment (e.g. BMD) or hazard assessment for C&L and ED-assessment. The regulatory framework (e.g. PPP vs industrial chemicals) and overall data richness under some regulations (PPR, BPR) may allow a weight of evidence approach, which may allow to occasionally accept low dose studies. Therefore, better understanding of the scientific and toxicological complexity of e.g. the concept of maximum tolerated dose (MTD), the

¹² Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32012R0528>)

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issue of maternal toxicity, the adequacy of the use of toxicokinetic (TK) information for dose selection is needed. Additionally, animal welfare considerations can influence the conduct of studies, including use of larger animal groups in order to detect a lower signal. Therefore, it is important to balance animal welfare considerations against the generation of sufficient, relevant toxicological information also taking into account the eventual need to repeat studies in case dosing is too low and appropriate toxicological assessment is not achievable

It is generally agreed that an optimum top dose should be at or around the level where clear signs of toxicity are observed while avoiding unnecessary animal suffering. In certain test guidelines the concept of the MTD is used, but it is acknowledged that the term is used inconsistently. Some consider the MTD to be reached when severe effects are seen, whereas others indicate that marginal changes in body weight gain are already sufficient to be considered as a MTD. In the workshop, it was agreed that further clarity on this concept is urgently needed.

In view of the fact that for various regulatory assessments, a dose response curve is deemed as important for identifying the intrinsic properties of a substance, the optimum mid-dose should also provide some toxicological effects. Ideally, the mid dose should be chosen just at or above the point where the effects of concern become significant. For this reason, also spacing between low, mid and top doses has to be considered carefully.

It was concluded that the dose selection rationale has to be clearly and thoroughly indicated in the study report, as requested in the OECD TGs and that justification for the dose level selection should subsequently be provided in the CLH and REACH dossiers. For an optimal (hazard identification) assessment, the results of dose range-finding studies are always needed.

In view of the criteria used for classification and labelling and ED assessment it is essential that the data generated for the various regulatory frameworks are adequate to serve that purpose. Information exchange between those who are in charge of conducting the studies and ECHA staff during dossier evaluation (DEv) or evaluating Member States (eMS) during substance evaluation (SEv) or evaluations of biocide and pesticide active substances might be helpful.

To assess the magnitude of inadequate dose level selection for regulatory purposes, a watching brief to carefully review the rationale for dose level selection and the effects observed in the study is needed. Actors could be dossier submitters preparing CLH proposals, ECHA & eMS when evaluating REACH registration dossiers (or biocide and pesticide active substance dossiers) and when following-up on evaluation decisions. As regards the latter aspect, it could also be reviewed if the dose levels of those studies conducted on request (testing proposals, CCH, and SEv) differ in dose level selections compared to studies performed before REACH or under different regulatory frameworks.

Differing views were expressed whether the wording of the OECD TG can be considered adequate and if there might be the need to give further guidance. However, there was consensus at the workshop that further discussion is needed on the issue of the MTD in dose selection. It was also noted that the OECD GD 116¹³ already gives the possibility for too low dose level selection due to the fact that 10% body weight (BW) gain change is considered as the MTD, whereas other experts stressed that such BW gain changes should be regarded in combination with other adverse effects. Additionally, it was noted that low-dose level selection has an impact on the power of the study, which depends on number of animals showing adverse effects. In this context, the limitations of using 3 dose levels was discussed.

It was mentioned during the discussion that ECHA in its draft decisions could also include a request for the rationale for dose level selection (which can be study-, endpoint- and regulatory

¹³ OECD Draft Guidance document No. 116 on the design and conduct of chronic toxicity and carcinogenicity studies, supporting TG 451,452,453 (<http://www.oecd.org/chemicalsafety/testing/46766792.pdf>)

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framework-dependent) and the submission of the results of dose-range finding studies. These could then be used to allow a more in-depth assessment of dose-level selection before or after the main study.

In summary, the topic of low dose level selection in animal toxicity studies successfully raised awareness and it was agreed that follow-up work may be needed. The workshop participants regarded the extent of the issue insufficiently clear to identify distinct priorities for follow-up actions. Currently, a watching brief for dossier evaluators (DEv and SEv) and submitters (CLH) is considered appropriate to better define the extent of the issue in the (near) future.

III. In vitro testing for skin sensitisation

The main aim of the workshop was to have the discussion on where we are now with the *in vitro* and/or *in silico* methods and Defined Approaches (Das) for skin sensitisation and how to prepare in the assessment and conclusion on the skin sensitisation endpoint based on such methods only. Important aspects were, for example, what type of information needs to be provided in a registration dossier to obtain confidence in the prediction of skin sensitisation potential and potency.

Workshop participants acknowledged the introduction of *in vitro* testing into the REACH Annexes as a significant contribution to the reduction of the number of animal tests required. The workshop served as a capacity building tool related to the concept of Defined Approaches (DA) that is currently under development within OECD. It was recognised that further work is needed to address uncertainties associated with the DAs e.g. false negative and positive predictions, potency determination, and applicability domain (AD) related issues. Because of these current uncertainties, it is difficult for the Committees to be actively engaged in the DA development before specific case examples have been presented to them.

Furthermore, it was acknowledged that, in general, when new OECD test guidelines are developed it is challenging to determine, when the right moment has come for the Committees apply these developments. However, regular updates of the Committees by ECHA and/or OECD on OECD TG developments are appreciated, and Committee members could more frequently interact with their OECD National Coordinators (for the OECD Test Guideline Program) on the foreseen regulatory relevance and application of new methods.

Assessment of the AD of each individual method in comparison with the AD of the DAs (based on two or more *in vitro* and/or *in silico* methods) is ongoing work for the OECD Expert Group on Defined Approaches for Skin Sensitisation where JRC, US NICEATM/EPA/CPSC and Health Canada are the leads of the project. The applicability domains will be described in the OECD TG on the DAs, and possibly more in detail by a specific Guidance Document. Overall, the OECD TG should be clear enough to allow appropriate selection of assays and DAs i.e. to avoid use of methods and DAs outside their AD, and they should adhere to the basic DA principles.

Many DAs may use the same or very similar information elements or methods but only differ in their decision logic (i.e. prediction model). To inform on regulatory application of DAs, it was considered that the OECD Expert Group could address overlap of false negatives and false positive predictions between different DAs employed on the same set of substances – and in addition on as many as possible (defined by available data). An analysis of the overlaps of different DAs in respect to overlaps of false positives and false negatives may help to assess situations where in individual cases a selection has been made to give a desired outcome (i.e. biased selection of a DA). Based on such analysis it may later be possible to establish some rules for selection of the most appropriate DA in certain cases e.g. in respect to relevant physical-chemical properties or functional groups of the substances under consideration.

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Use of DAs for classification and potency assessment might be difficult without further updated classification criteria for *in vitro* methods (i.e. no specific criteria for use of the DA method outcomes), without additional supporting data, e.g. relevant information on potency from similar substance(s) (i.e. read across /Structure Activity Relationships) and an agreed CLP Guidance on the assessment of various DAs. However, already now any relevant and reliable data can be used in a Weight of Evidence assessment using expert judgement for classification also for skin sensitisation. For the committees, OECD TGs and agreed guidance may be sufficient to enable assessment of skin sensitisation potency, but revision of the legal text may be needed to ensure correct self-classification. Revision of the skin sensitisation criteria regarding non-animal testing methods is in the pipeline for GHS update. The CLP Regulation/ CLP Guidance may have to put the new DA-containing OECD TGs into context and also reflect the experiences of using such data and approaches by ECHA and its Committees (i.e. RAC in charge of for example classification and labelling, granting authorizations and setting conditions for restrictions of chemicals; MSC in respect to evaluation cases, including requesting more information on skin sensitisation). It may also be needed to develop criteria related to use of multiple DAs already in the near future, because DAs are distinct from IATAs in that expert judgment and Weight of Evidence assessment is not needed.

It was considered that the OECD TGs for DAs should be able to provide information on potency determination according to CLP and UN GHS. Some DAs are only for hazard identification, while others are stated to include potency assessment. The OECD Experts group aims to bring the first 3 proposed DA in a TG for skin sensitisation to the meeting of Working Group on New Test Guidelines (WNT) in April 2020. Two of the DAs are for hazard identification of skin sensitizers whereas the third is also predicting hazard potency according to GHS category 1 A and 1 B. Publication of the draft TG on 3 DAs was imminent at the time of the workshop and OECD invited comments from all parties.

If sub-categorisation of skin sensitisation potency according to GHS is not possible with a DA and there is a residual concern on this endpoint in the REACH dossier, it is the Registrant(s) responsibility to perform an *in vivo* skin sensitisation test i.e. the local lymph-node assay (LLNA). If the Registrant(s) have not taken this responsibility or authorities have a diverging view, ECHA can open a compliance check on a registration dossier and request an LLNA.

Development of training or of examples on the use and assessment of the results from *in vitro* methods (and/or *in silico* and/or read-across) and DAs for skin sensitisation hazard classification was not seen as a high priority for the Committees already at this point. When DAs are adopted by OECD, the test guidelines that include the DAs should be clear enough to allow assessment of the delivered results. "Training by doing" through case specific evaluations discussions in MSC or of the assessment of CLH proposals in RAC was proposed to be a first approach to more capacity building of the Committees. In this context, it was suggested that ECHA should, if considered necessary by the Committees, prepare training cases, since there are representative data in the dossiers.

WS participants also called for ECHA Guidance (REACH and CLP) on the regulatory use of the DAs. In case of conflicting data, i.e. DA outcomes and other available data, one would always need to assess all the data via Weight of Evidence and expert judgment, as for any other hazard class. Especially when negative DA results are obtained, additional investigations may need to be performed whether such negative results can be further rationalized, e.g. some supposed negative results might be due to lack of metabolic activation in the *in vitro* test systems, or application of methods of the DA outside their applicability domain etc.

Before Partner Expert Group (PEG) work and consultation on ECHA CLP Guidance development can be initiated suitable CLP criteria and adopted OECD Test Guidelines need to be available. Uncertainties not already addressed in the OECD TGs, should be addressed in the CLP Guidance.

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Development or revision of UN GHS criteria for the use of *in vitro* methods for the assessment and hazard classification of skin sensitisation (hazard identification, potency categorization) would be helpful, but may take many years. Alternatively, it should be analysed whether such additional criteria can be incorporated / added into CLP (Regulation and / or Guidance) without revision of the GHS criteria, if the latter are legally interpreted to be flexible enough. This should be considered at least at the time of the possible adoption of the first proposed DA for skin sensitisation as OECD TGs (or not long time thereafter).

General conclusions

The workshop achieved the overall objectives: it managed to raise inter-Committee awareness regarding the structure and function of both Committees, and possibilities and hurdles encountered in the Committees on the three topical issues. Different levels of knowledge and different expectations on the three topics were revealed and the joint search for solutions and future ways of operating proved to be beneficial. Additional perspectives from OECD, EFSA and JRC representatives were very useful in this context.

The discussion on the mutagenicity topic uncovered the possibility for further refinement of the MSC approach when requesting more tests, and the necessity for RAC to be presented with further case studies in order to test out the interpretation of the criteria. On the low-dose topic, the workshop participants considered that the full extent of the issue is insufficiently clear to assess what its overall priority should be for follow-up actions. Currently a watching brief for dossier evaluators (DEv and SEv) and submitters (CLH) is thought to be appropriate to better define the extent of the issue in the (near) future. On the sensitisation topic, workshop participants acknowledged the contribution of *in vitro* testing to a reduction of the number of animal tests. The workshop also served as a capacity building on the new concept of Defined Approaches. It was recognised that it is still an ongoing process and that further development is needed to address uncertainties associated with false negatives and potency determination. This makes it difficult for the Committees to be actively engaged before specific case examples are presented to them.

The feedback received was decisively positive: the participants believe to have gained knowledge and information that will be useful in their work and that both committees would benefit from more events of this kind. From ECHA's side, the workshop has been the ideal platform for awareness raising regarding some issues of high interest for the Agency, and for the members to familiarise with upcoming possible scientific and regulatory developments relating to the three topics of the workshop.

- [Annex I – Agenda of the meeting](#)
- [Annex II – List of abbreviations](#)

Annex I – Agenda of the meeting

MSC-RAC/001/2018 Provisional Draft agenda

Draft Agenda **Member State Committee & Committee for Risk Assessment** **Joint Workshop**

Fine tuning the testing requirements and evaluation of selected human health endpoints under REACH and CLP

11-12 October 2018
ECHA Conference Centre
Annankatu 18, in Helsinki, Finland

11 October: starts at 1 pm
12 October: ends at 1 pm

Item 1 – Welcome

Item 2 – Practicalities

Item 3 – Introduction of the Member State Committee and the Committee for Risk Assessment

Presentation of the two committees' functions, regulatory processes and main areas of work, with special focus on the possible circumstances of further interaction.

Item 4 – Examples of interaction

Short introductory presentations will be given on each of the topics below by members of MSC and RAC:

- **Mutagenicity**
Discussion on the ability of newer test methods (e.g. comet assay; genotoxicity test *in vivo*) to produce results that are suitable for classification, labelling and risk assessment.
- **Dose selection in systemic toxicology tests**
Discussion on possible reasons and suitability of the results of low dose toxicity testing for classification, labelling and risk assessment.
- ***In vitro* testing for skin sensitisation**
Discussion on the future role and interpretation of *in vitro* skin sensitization testing.

These will be followed by discussion of key questions in breakout groups.

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Item 5 – Conclusions

- Conclusions with a short discussion on the developments in OECD and on their impact on the work of the two committees.
- Proposals for future cooperation between the two committees.

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Annex II - List of abbreviations

AD – Applicability Domain
ADI – Acceptable Daily Intake
BPR – Biocidal products Regulation
BW – Body Weight
CCH – Compliance Check
CLH – Harmonised classification and labelling of chemical substances and mixtures
CLP – Classification, labelling and packaging regulation
C&L – Classification and labelling of chemical substances and mixtures
DA – Defined Approach
DEv – Dossier Evaluation
DG – Directorate general
DNEL – Derived no-effect level
ED – Endocrine Disruptor
EFSA – European Food Safety Authority
eMS – evaluating Member State
EOGRTs – Extended one-generation reproduction toxicity study
FISH – Fluorescence in situ hybridization
FN – False Negative
FP – False Positive
GHS – Globally Harmonised System of classification and labelling of chemicals
JRC – Joint Research Centre
LLNA – Local Lymph Node Assay
MSC- Member State Committee
MTD – Maximum Tolerable Dose
NGO – Non-Governmental Organisation
OECD – Organisation for Economic Co-Operation and Development
OELs – Occupational Exposure Limits
PEG – Partner Expert Group
RAC – Committee for Risk Assessment
REACH – Registration, Evaluation, Authorisation and Restriction of Chemicals regulation
SEv – Substance Evaluation
TG – Test Guidelines
TGR – transgenic rodent
TK - Toxicokinetic
TPE – Testing Proposal Evaluation
UDS - Unscheduled DNA synthesis
US CPSC – United States Consumer Product Safety Commission
US EPA – United States Environment Protection Agency
US NICEATM – United States National Toxicology Program Centre for the Evaluation of Alternative Toxicological Methods
WNT – OECD Working Group of National Coordinators of the Test Guidelines Programme
WoE – Weight of Evidence