IDEA-JRC Joint Strategy Meeting on the
Inclusion of animal testing alternatives into QRA for skin sensitisation

June 28th, 2017 from 09:00 to 12:00

JRC
Ispra, Italy

Participants:

IDEA: Hans Bender (HB, IDEA Management Team), Martina Bianchini (MB, IDEA Management Team), Jim Bridges (JB, IDEA Supervisory Group Chair), Cécile Gonzalez (CG, IDEA Management Team), Helmut Greim (HG, IDEA Supervisory Group) , Amaia Irizar (AI, IDEA Consultant), Charles Laroche (CL, IDEA Management Team), Matthias Vey (MV, IDEA Management Team).

JRC: Stephanie Bopp (SB), Silvia Casati (SC), Raffaella Corvi (RC), Andrew Worth (AW).

Final minutes

1. Opening of the meeting

SC opened the meeting and welcomed the participants. A short tour de table was organized introducing roles and responsabilities of the participants.

MB briefly explained the role and activities of the International Fragrance Association (IFRA) including its voluntary regulatory program and its role in IDEA (International Dialogue for the Evaluation of Allergens).

AW provided a short summary of the structure and functionning of JRC. The role of JRC, as a Directorate-General of the European Commission, is to provide advice for the European Commission and the major agencies, and the focus is on methodologies rather than on the evaluation of chemicals. The JRC is under the responsibility of Tibor Navracsics, Commissioner for Education, Culture, Youth & Sport. JRC has 5 sites around Europe and the headquarter is in Brussels.

2. Summary of IDEA activities

MV provided a short background of the collaboration between IDEA and JRC so far, which started when the JRC reviewed the QRA2 dossier in 2014. As a result, questions were raised by the JRC on different aspects of the methodology. These questions were answered by IDEA for the second submission of the dossier, which was shared with DG Grow in October 2016. The SCCS has meanwhile received the mandate to

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evaluate the methodology for its suitability to prevent induction of skin sensitization to fragrance ingredients for the majority of the population. IDEA had the opportunity to provide additional insight and answer some questions from SCCS members as per their request.

The IDEA Management Team will share the mandate from the SCCS with the JRC participants.

ACTION: IDEA Management Team to share the mandate of the SCCS with the JRC participants.

IDEA is now looking into the challenge of how to demonstrate the effectiveness of the QRA2 as a risk assessment tool enabling appropriate risk management interventions. The issue of 'other uncontrolled uses' was shortly discussed as the IFRA Standards are a voluntary initiative and in the best case cover a large segment of the consumer product market, but not all potential applications of fragrance ingredients. Aromatherapy was mentioned as a problematic area. AW explained that JRC has a unit that is working on the harmonization of data collection for disease studies, but skin allergy is not (currently) one of them.

MV explained that from this first exchange with the JRC, two recommendations were made for further work by IDEA where JRC expressed interest in:

- Pre- and pro haptens:
  On pre- and pro- haptens, a framework that will become an addendum to the QRA2 dossier is currently being prepared by IDEA WG participants. It may be the case that for the majority of pre- and pro- haptens, they are adequately considered by the QRA2 methodology. However, for slow oxidizing materials which may form peroxides, IDEA has focused on improving the exposure data by developing a method to detect and quantify the main hydroperoxides of Linalool and Limonene (serving as key examples). In addition a market surveillance study will be conducted in which new and used consumer products will be analyzed to quantify their Linalool and Limonene hydroperoxides content. This information will be used to better understand the factors affecting generation of the hydroperoxides to aid interpret of the clinical data.

- The replacement of LLNA in QRA2, which led to the development of the IDEA AAT outreach plan and will be the centre of discussion of the meeting (see item 3 and following).

JRC was very appreciative of the use of an aggregate exposure model. JB pointed out that a simplified aggregate exposure model is needed and will be worked on in that context. AI agreed to send Creme model related publications for information to SB, who is working on exposure to mixtures in JRC.

QRA2 and the aggregate exposure model will be incorporated in the next Amendment at IFRA (49th Amendment). Every two years, IFRA issues its Amendment to the Code of Practice, containing a set of Standards restricting, prohibiting or specifying the use of a selection of fragrance ingredients. The 49th Amendment is expected to be published in Spring 2018. For this Amendment, all the Standards will be reviewed and reissued. As set of additional examples (other than Citral, as contained in the dossier) has been shared with the SCCS and the JRC representatives expressed interest to see those.

ACTION: IDEA Management Team to share with the JRC the 20 examples of QRA2 application that were shared with the SCCS.

The aggregate exposure model is owned by RIFM and Creme. Upon request from AW, MV offered to ask RIFM whether JRC could find out more about the model. It was agreed to proceed in a stepwise approach.

As a first step JRC would appreciate getting more insight into the application of the model and its functioning e.g. in form of a presentation or webinar.

ACTION: IDEA Management Team to set up a meeting/webinar for JRC members to get deeper insight into the RIFM-Creme Agregate Exposure model.

3. **Update on JRC's strategy for skin sensitization and future engagement.**

See presentation by SC (Att. 01).

There are 5 methods accepted by OECD. TG442 C, D, E cover KE1, KE2 and KE3 respectively but they cannot be used to conclude on the absence of skin sensitization potential of chemicals in isolation nor to assess skin sensitization potency. These methods should be used in the context of an IATA (OECD TG 255), in combination with complementary information. Test guidelines alone do not guarantee the use and acceptance of *in vitro* data. In the assessment flow within IATA there is always a need of expert judgement (e.g. WoE). As a consequence, due to the flexibility of IATA, these tools cannot be described under OECD guidelines. JRC has been looking to different approaches to combine and integrate *in vitro* data. Defined approaches have been proposed and consist of a fixed data interpretation procedure (DIP) as an input to the evaluation process within IATA (OECD GD 255 and 256).

Of twelve defined approaches proposed by industry and published in OECD TG 256, only a few claim to derive potency, some only potency categories. When comparing to human data, the results of these defined approaches were encouraging and showed improved accuracy for predicting LLNA responses compared to the individual methods. More importantly, they appeared to be more relevant in predicting human effects than the LLNA (see OECD TG 256 – Annex I).

So far, only the publication from David Basketter (2014) adresses in detail the human categorisation of sensitisers used to evaluate these defined approaches. AI mentioned that an updated manuscript with more examples of human categorisation of sensitisers has been prepared by David Basketter and she offered to check the status of the paper and share any information with the JRC participants.

ACTION: AI to provide feedback to the JRC participants on the status of the draft manuscript

After a meeting with the ICATM (International Cooperation on Alternative Test Methods), the JRC has recently submitted to OECD a project proposal for the development of a Performance-Based Test Guideline (PBTG) on defined approaches. The proposal has been endorsed and work will start in Q4 2017. The US and Canada will also be involved in the project. AI enquired whether the performance of defined approaches should be evaluated against the performance of current animal models used for regulatory purposes, as during the SOT Meeting 2017, this was stated as the conclusion of ICATM workshop participants. SC confirmed that this is the case but it is also important to compare it to human data. Both should be done.

The aim is to assess the 12 defined approaches according to the agreed framework:

- Systematic evaluation of the uncertainty of LLNA reference data (reproducibility and relevance to humans) to define performance thresholds for acceptance of defined approaches.
- Define an assessment framework (including acceptance criteria) for defined approaches in the light of the systematic review of LLNA reference data.
- Assess the 12 defined approaches (as per Annex I of TG256) according to an agreed framework.

- Defined approaches (and possibly individual test methods) meeting the acceptance criteria would be annexed to the PBTG.

After running these 4 steps, one should be able to derive a GHS classification by using the new defined approach proposal. AW added that under UNGHS there is a project to explore the introduction of non-animal data into the classification criteria based on, and they have started to reevaluate the criteria. They have started with skin irritation/corrosion and the JRC has suggested to consider eye irritation / serious eye damage and skin sensitization next.

4. Prioritisation of potential roles of IDEA AAT to help identify and enable broad acceptance of an approach to skin sensitization QRA in the absence of animal data for fragrance ingredients

The aim for IDEA is to obtain the point of departure (NESIL or EC3) from non-animal data. SC said that within JRC, so far they do not have a clear view of how the PBTG project can be implemented and they are currently evaluating activities, resources needs, etc. JRC understands IDEA's needs and having this planning done would help to define activities of common interest and potential collaborations. IDEA proposed to bring to the JRC expertise to interpret in vivo data, notably human data, which the JRC indicated that they would benefit from. IDEA can provide such expertise, through the creation of a multistakeholder working group which would work on a case study (e.g. potency determination through one or two of the already defined approaches). Both parties agreed that developing a guideline for the application of QRA without animal data based on a defined approach would be helpful for the objective of IDEA and also complementary to the activities that the JRC is undertaking in this regard. It was emphasized that it is key that such a guideline should gain recognition from the scientific community. The JRC participants mentioned that CosEU is organizing a workshop in October where the companies will provide case studies for inclusion of animal testing alternatives for different endpoints.

This IDEA working group would need to evaluate the uncertainty of the point of departure and how it is incorporated into the QRA2. For this purpose, a comparison between animal (i.e. LLNA), human (e.g. HRIPT) and in vitro data should be performed for different compounds. AI mentioned that there are at least 100 fragrance materials for which there is animal, human and in vitro data. AW added that we should first understand what is being done by CosEU and what can IDEA additionally bring. He pointed out that uncertainty considerations will be an important element within the OECD PBTG project.

The SENS-IS is not included within the 12 defined approaches but evaluations perfomed so far suggest it might have the potential to qualify as a standalone test whilst fullfiling the conditions of the PBTG. However this still needs to be reviewed and resolved by OECD. So far, SENS-IS appears promising to determine potency. In this context, models that can translate the in vitro data to a safe dose on humans are missing and that could be another area where IDEA could work on. AI confirmed there is SENS-IS data for many fragrance materials that also have animal and human data, which is owned by the Research Institute for Fragrance Materials (RIFM). Another activity of interest would be to perform a comparison between LLNA and HRIPT data. In the eyes of JRC, for any project that JRC/IDEA will embark on, there is a need to gather as much data as possible, and IDEA could offer the platform where the data already available for fragrance ingredients tested through the CosEU project and the additional data obtained independently by RIFM could be gathered.

ACTION: Building on the OECD defined approaches with greatest possibility for potency, IDEA will work on developing a case study with the objective to share with OECD. The initial framework will be shared with JRC.

JRC suggested IFRA to be part of the OECD's skin sensitization task force, which is going to be reestructurated soon and will review its membership. A meeting of the OECD Working Group of the National Coordinators for the Test Guidelines Programme (WNT) will take place in December at Ispra to bring all the group to the same level of understanding regarding the PBTG project, and discuss the main issues related to the development of such PBTG for defined approaches. If IFRA's membership in the OECD skin sensitisation TF is not possible, JRC kindly offered to keep IFRA updated on progress. MB offered to contact OECD to get more information on how could IFRA join the OECD skin sensitization TF.

ACTION: MB to contact OECD on how IFRA could join the OECD skin sensitization working group.

5. Conclusion

The participants agreed that IDEA should focus on a case study. An ingredient will be selected at the next meeting of the IDEA Working Group on the inclusion of animal testing alternatives into QRA for skin sensitisation and then one or two of the 12 defined approaches, those with the greatest possibility for characterising potency (and if possible SENS-IS as well) will be applied. The IDEA Management Team will prepare a draft action plan and share it with the JRC participants. The JRC will not lead the discussions, as they should remain independent. CL asked whether a mandate from DG Grow could be given to the JRC to allow them to get actively involved in the discussions under IDEA. JRC indicated that the organisation should maintain an independent role and this request would eventually need to be discussed with JRC management and with DG Grow.

ACTION: IDEA Management Team to share a draft action plan with JRC.