Helsinki, 00.00.2014

MISSION REPORT

Name: [redacted]	**Unit: E1, E2, E3, D2, C3**
Place and Date: Seville, Spain. 03 September- 08 September 2016	**Mission Number: 15186**
Other participating ECHA staff: [redacted]	
Subject: Eurotox 2016	

Summary:

ECHA provided three speakers ([redacted]), one chair ([redacted]) and had proposed two continuing education sessions ([redacted]), which were both well attended. [redacted] presented a poster. ECHA participated actively in the scientific content of the meeting. ECHA presented a stand at the meeting. The stand was manned by all the ECHA attendees, and there was a steady stream of interest throughout the meeting.

Speciality Sections. [redacted] was elected as Chair of the Eurotox Risk Assessment Speciality Section, for a limited term, and will contribute to the scientific programme for 2018. [redacted] will continue as councillor in the Immunotoxicity speciality section (ITCASS).

Specific highlights were technical discussions on EOGRTS, inhalation toxicity and carcinogenicity studies (see below).

Main aspects of the mission:

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Speciality Sections. [redacted] was elected as Chair of the Eurotox Risk Assessment Speciality Section, for a limited term. The intention is to seek a replacement chair as soon as possible. [redacted] will contribute to the development of the scientific programme for 2018. [redacted] will continue as councilor in the Immunotoxicity speciality section (ITCASS).

CEC on "*Integrative Approaches to Testing and Assess-ment (IATA) for skin sensitization: from theory to practice*" was chaired by [redacted] and [redacted] (RIVM). The session contained five presentations 1) how to use non/animal testing approaches to fulfil REACH information requirements ([redacted]), 2) introduction to OECD IATA for skin sensitisation ([redacted], EURL ECVAM), 3) case studies illustrating different defined approaches for testing and assessment for skin sensitization ([redacted], RIVM), 4) Utility of integrated non-animal approaches for skin sensitisation for safety assessment of cosmetics ([redacted], representing cosmetics Europe), and 5) Computational tools and their role in integrative approaches ([redacted], University of Liverpool). The course was well

participanted by over 50 participants (mainly from industry). The course covered the recent developments of in vitro test methods and how they can be used, introduced the new IATA framework on reporting with representation of few case studies included in the OECD IATA GD. The approach of Cosmetics Europe was presented and what they are doing in tackling the animal testing ban for their products. The course was closed how to use computational models to support e.g. read-across approach and category building.

[redacted] gave a presentation "*Using EOGRTS under REACH, BPR and CLP*" in a workshop session on "*Design and interpretation of testing according to the extended one-generation reproductive toxicity study for regulatory use*". The session was chaired by [redacted] and contained the following other presentations: 1) "*The extended one-generation reproductive toxicity study: Expectations for the new guideline, opportunities, threats*" given by [redacted] (Frauenhofer institute for Toxicology and Experimental Medicine, Germany) replacing [redacted]; 2) "*First experiences from testing according to the EOGRTS*" by [redacted] (BASF SE); 3) "*Changes introduced with the new OECD 443 method and implications on the toxicological interpretation*" by [redacted]. During the session, the following challenges were highlighted: 1) There are still strong diverging views on the scientific value of the EOGRTS design in evaluating the effects on reproduction health compared to the two-generation reporoductive toxicity study and other study designs, such as ICH design (from pregnancy-to-pregnancy method) and NTP modified one-generation study; 2) When reviewing the OECD TG 433, experiences from these other methods should be considered; 3) EOGRTS is extremely challenging, especially if full-blown, from a laboratory point of view – additional investigations should be avoided (examples were 2 SEV cases); for pesticides, a risk-based approach was recommended by Ivana, meaning that the highest dose should be selected based on toxicokinetics reflecting "relevant" exposure levels and not based on toxicity. Questions releated to necessity of the toxicokinetics investigations (due to costs), an extensive range-finding study, and adequacy for classification and labelling purposes were raised.

[redacted] presented a poster (PDF available here: Eurotox2016_poster_TK_final_version) about the use of mammalian toxicokinetic data in bioaccumulation assessment, which triggers interest by very many congress participants (the >50 poster leaflets were all taken by the end of the session). The poster presented the overall aims, strategy and first set of results (i.e. data collection and initial statistical analysis) of an ECHA cross-directorate project which is being conducted from 2015 on request from the PBT Expert Group by ECHA units D2, E and C3, in collaboration with the Norwegian Environment Agency and Norwegian Institute of Public Health (data compilation). The poster explained the current gap in the regulatory assessment of "B" for air-breathing organisms and the potential use of toxicokinetic (TK) parameters, particularly elimination half-life, to possibly determine benchmarks or numeric cut-off values, thus systemitise the employ of TK in the "B" assessment.

[redacted] gave a presenation on "*How to improve the quality of exposure information needed for REACH processes*" ([redacted]) in a workshop session "*Improving chemicals risk assessment with refined exposure characterisation*". The session was chaired by [redacted] and sponsored by ECETOC. It included the following other presenation: 1) Improving chemicals risk assessment through tiered and targeted application of exposure assessment (by [redacted], RIVM) – a presenation on the basic principles of risk assessment. 2) Experience from ECETOC TRA tool 2004-2016 (by [redacted], Cynara Consulting) – emphasing the TRA as a tool to enable high troughput Tier 1 exposure assessment feeding into exposure scenarios under REACH. 3) Refining exposure data acquisition and application of higher Tier consumer exposure assessment (by [redacted], ETH Zurich) –

explaning a probalaistic methode to determine co-exposure of consumer to substances from different consumer products. 4) Modelling aggregate exposure to chemicals from multiple sources (by [redacted], Procter&Gamble) – providing practical examples for simultaneous exposure to substances in cosmetic products. All the spreakers gave (in the one or the other way) one common message: Without better communication within industry (up and down the supply chain) about use patterns of substances, use condition of products and frame formulations, it will very difficult (if not impossible) to improve exposure charcaterisation for risk assessment.
Eurotox 2016 also featured a Glyphosate Task Force (GTF) Symposium, attended by [redacted]. It was chaired by Exponent (UK) expert [redacted] and featured speeches by [redacted] (Technical University of Munich), [redacted] (Harvard School of Public Health) and [redacted] (Exponent, USA). In his talk about the genotoxicity of glyphosate, [redacted] pointed to the IARC 2015 conclusion as "inconsistent" with the conclusions by other authorities [including, among others, EFSA, 2015, the joint FAO/WHO meeting on pesticide residues (JMPR, 2016), the Food Safety Commission of Japan (2016) and the Australian APVMA (2013)] and its assessment lacking several genetic toxicology studies published in Kier and Kirkland (2013). On the other hand, [redacted] (author of the 2015 peer-reviewed publication of glyphosate carcinogenicity studies, cf. http://www.ncbi.nlm.nih.gov/pubmed/25716480) pointed out the basic difference between the evaluation of IARC (hazard identification only) and the >20 regulatory authorities, scientific bodies and third-party esperts (which evaluate risk at human exposure, and concluded that glyphosate poses no cancer risk to humans). However, no IARC representatives were (seemingly) present at this event.

Session on Nanosafety: Present and Future (attended by [redacted]). The session covered topics for predicting toxicity-, immunotoxic and pulmonary effects- as well as developmental toxicity of engineered nanomaterials. It also contained a talk covering dose metric for the prediction of toxicity of nanomaterials. Finally, a presentation on innovation and model organisms for the environmental hazard assessment of engineered nanomaterials was included in this session. From the presentations it became clear that the current assessment of hazards of engineered nanomaterials material by material is not any more viable because of the large number of nanomaterials, the slow testing, and uncertainties of the reliability of results. New predictive methods for the assessment of nanomaterial hazards and risks need to be developed. It was also highlighted that even though no definite solutions so far appears to be available, the current attempts focus on the generation of validated in vitro methods with the potential for long-term hazard assessment of well characterized and carefully grouped engineered nanomaterials in which organ-on-a-chip and in vitro models validated by using in vivo models, and consequent use of in silico methods are crucial according to the presenters. Regarding events leading to pulmonary inflammation, no unifying dose metric was identified to describe pulmonary inflammation for all nanomaterials, although surface reactivity might be a useful measure. For the environmental hazard assessment the key practical challenges include: (i) developing screening methods to manage the large number of potential engineered nanomaterials; (ii) providing new endpoints that can inform on the relationship between engineered nanomaterials physico-chemistry and ecotoxicity; (iii) identifying ecologically sensitive organisms; and (iv) facilitating predictive toxicology for future innovations.

Session on *in vitro* and alternative methods for developmental toxicity (attended by [redacted]). The session described the currently available *in vitro* methods with focus on rat whole embryos, ZETA fish method, chicken egg method and pathway specific assays related to angiogenesis and vascular genesis. Concerning the methods described, they have the general problems that *in vitro* cultures have e.g. lack or limited metabolisms, lack of

maternal exposure. The outcome of these test may be useful for screening purposes (potential hazard identification), however the results on their own may not be useful to fulfil regulatory requirements as one does not get a NOAEL and the results may not be useful for making proper classification and labelling decision.

A similar type of session on "*A multidisciplinary approach for novel developmentl neurotoxicity risk assessmen contributing to the AOP consept*" (attended by [redacted]) described the systematic review based on an EFSA report, 3D models and omisc approaches, species specific analysis, an example case, and an application of an AOP concept. It is clear that the methods are applicable for screening, prioirtisation and mechanistic investigations, but it was highlighted that "*the whole is greater than the sum of its parts*" and more research is needed. The AOP concept has been developed for regulatory purposes, however, challenges for DNT AOP include 1) lack of understanding of MIE, diverse pathophysiology, compensatory/defence processes, lack of quantitative data and complexity of the nervous system. To try to develop an AOP-informed IATA was proposed.

Session on Toxcast and AOPs (attended by [redacted]) discussed on developing predictive toxicological testing for various regulatory frameworks. This requires understanding of complex biological pathways e.g. AOPs, early biomarkers in order to predict toxicological effects in humans. Under the Toxcast program few case studies will be assessed and the potential problems were discussed e.g. what is needed for risk assessment purposes. A website was just launched for the project and the progress of the work on-going can be followed from there (www.eu-toxrisk.eu).

Discussion with the speakers responsible for the reproductive and developmental toxicity part of the EU-ToxRisk revealed that classification and categorisation aspects have not been considered. The focus is on developmental toxicity but some reprotox endpoints are planned to be included.

Session on Chemical Specific Adjustment factors and interspecies variability (attended by [redacted]) where the original WHO guidance published in 2005 on uncertainty was presented and the work that they are performing for the upcoming update of the guidance document. It was presented how e.g. information obtained from kinetics and dynamic could help in modifying the assessment factor by decreasing or increasing them to obtain more reliable values. The biggest challenges for the regulatory uptake would be in their opinion is to improve the common understanding of the content, alignment of terminology, rules of thumb, reporting templates and increasing reliance on *in vitro* data. For our regulatory perspectives, the data sources that were mentioned in the general presentations and case studies is not something that we could request under REACH, therefore the usability for REACH specific purposes is uncertain.

Session on Integrating epidemiology and experimental toxicology to improve pesticide risk assessment (attended by [redacted]). In this session the advantages and disadvantages of using epidemiological studies and their importance for risk assessment was discussed. It was highlighted that an integrated approach of in vivo, in vitro and in silico data, together with well-designed epidemiological studies will improve hazard and exposure assessments of pesticides and provide a strong basis for regulatory decisions. This 'adverse outcome pathway framework' (omics and computational systems biology) will potentially in the future facilitate development of integrated testing strategies for human and environmental risk assessment of chemicals.

Session on Risk assessment of metals via inhalation: Challenges and new developments

(attended by [redacted]). The session started with three general presentations on pulmonary immunology, immune system vs. immune function and lung overload of inert insoluble dust followed by two presentations with results from studies on metals (cobalt and nickel). The key outcome of the presentations were: an in depth understanding of the physico-chemical and aero dynamical behaviour as well as an understanding the chemical properties (and ion toxicity) of the metals is important. In addition it was highlighted that it would be more relevant to focus on studies on lung function alterations, histopathology and clinical chemistry instead as in the standard studies focus on NOAEC derivation. Finally, it was emphasised that in case of inert insoluble particles special attention must be given to the occurrence of particle overload, a response which is considered typical for the rat. It was emphasized that a scientific debate on the predictability of the particle overload reaction for humans is ongoing. In the closing remarks of the session it was concluded that once all information on the hazard profile has been gathered the extrapolation from the animal model to the human situation must still be done. The use of a dosimetric model for the calculation of the Human Equivalent Concentration will help in the translation of the NOAEC to reliable limit values for human subjects.

Session on Rat carcinogenicity studies- Can they be replaced? This session reflected an initiative led by the EMA to replace carcinogenicity studies. EMA takes into account mode of action data for other substances, the toxicity database for the substance (including a 6 month study), and invites the registrant to place the substance into one of four groups. (1) will cause cancer in human (no rat study required) (2) unclear if it will cause cancer in human (rat study required) (3a) will cause cancer in rat, but not relevant for human (no study required) (3b) won't cause cancer in rat or human (no study required). Retrospective studies indicate this can be done successfully, and EMA are currently trialling this approach on a prospective basis now.

Selected Oral communications:

EpiAirway model (attended by [redacted]): interesting 3D tissue model to assess acute inhalation toxicity. Seems to be predictive for Cat 1 and Cat2 (and maybe Cat 3) acute inhalation toxic substances. As with other *in vitro* models, the suitability for classification and riks management is limited at this point of time as differentiation between CLP categories cannot be made at this point of time.

Keynote Lecture "Evolution of Computational Toxicology: From Primitive Beginnings to Sophisticated Application" by [redacted], US-EPA (attended by [redacted]): this was a fashinating lecture about how the diverse set of data streams from the structure-based QSAR analyses to the high-thoughtput screening (HTS) and the toxicokinetic (TK) models can be used to make better regulatory decisions. In particular, we learned how the ToxCAST/Tox21 assay results, interpreted in a MoA context, are being used by EPA for biological read-across to prioritise further testing, and how TK is proving a bridge between HTS and human exposure estimates by predicting tissue concentrations.

Conclusions, follow-up and implications for ECHA:

[redacted] and poster co-author [redacted] (Norwegian Institute of Public Health) met at the poster area and discussed the collaborative project. Interesting exchange of ideas also came from discussions with JRC staff visiting the poster.

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Regarding the discussion on glyphosate, it iwas very interesting to learn about the risk vs. hazard, i.e. the impact of the exposure component, to the evaluation of glyphosate cancer studies. However, the upcoming RAC discussion on the CLH proposal received by ECHA will be based exclusively on hazard.

Considerations should be given whether it is absolute necessary to include additional investigations into EOGRTS design (under SEV) as it is already very complex and full study and the study integrity may be jeopardised.

New learnings from non-animal approaches (e.g. IATAs and AOPs) will be included to the ANAA-report. ECHA should follow-up animal testing initiatives from EMA.

In the workshop on improving exposure characterisation all the spreakers gave one common message: Without better communication within industry (up and down the supply chain) about use patterns of substances, use condition of products and frame formulations, it will very difficult (if not impossible) to improve exposure charcaterisation for risk assessment. This confirms that ECHA is on the right track when promoting "*use-maps*" as an efficient way to organise such communication.

Name [redacted]

Signature

ENCLOSURES

cc: [redacted]