Workshop on the State of the Art Report on Mixture Toxicity

Brussels 21/22 June 2010.

Summary overview of the different sessions and the chair's summary of the main messages.

NB: 1) Written statements received from a number of organisations in the context of the internet consultation on the State of the Art Report are also available on web-site.

2) Copies of the power-point presentations made by the contractors at the start of the different workshop sessions are also available on the web-site.

Summary Overview of the different sessions.

Introduction

The chair explained the background to the workshop

- Commission's wish to review the latest information on mixture toxicity and to understand the possible implications for chemicals' assessment.
- Contract based on an open call for tender launched in 2007 awarded to Andreas Kortenkamp of the School of Pharmacy, London University, Thomas Backhaus of Goteborg University and Michael Faust of Faust and Backhaus Environmental Consulting.
- Final report uploaded on the DG ENV website in January 2010 with an invitation for comments with deadline of end April.
- Commission request for an opinion on mixture toxicity/combination effects submitted to the Scientific Committee on Health and Environmental Risks, the Scientific Committee on Emerging and Newly Identified Risks and the Scientific Committee on Consumer Products. In preparing and finalising their consolidated opinion the Committees will consult widely. The opinion has been requested by March 2011.
- Environment Council in December 2009, called upon the Commission to assess how and whether relevant existing Community legislation adequately addresses risks from exposure to multiple chemicals from different sources and pathways, and on this basis to consider appropriate modifications, guidelines and assessment methods, and to report back to the Council by early 2012 at the latest.
- The purpose of the workshop was to discuss the State of the Art Report on Mixture Toxicity and to provide feedback to the Commission on what could/should be done at the level of the EU to address mixture toxicity.
Session I The Evidence Base for Combination Effects

Professor Andreas Kortenkamp presented a summary of the findings from the State of the Art report concerning the scientific evidence on mixture effects.

Participants generally acknowledged that there is a strong experimental evidence base for mixture toxicity. While it was recognised that we need to improve our understanding of how these experimental findings relate to the impacts of mixtures on human health and environment outside of the laboratory, it was accepted that mixture toxicity should be addressed in the context of chemicals' risk assessment in the EU. The challenge is to identify those cases when it is necessary/appropriate to assess mixture effects as well as the methods that should be used for carrying out such assessments.

Session II- Low Dose Effects

Dr. Michael Faust presented the contractors' findings in relation to the low dose effects. There was a large body of experimental evidence demonstrating that mixtures of three or more chemicals where each of the chemicals was present at concentrations below the nominal effective dose still exerted a toxic effect. In many cases the observed toxicity of the mixture was consistent with conceptual models such as dose/concentration addition or independent action.

Participants in general accepted the experimental evidence base for the low-dose effects, although some participants suggested additional scientific publications that should have been included in the review and which in their opinion were less clear cut with regard to clear, low-dose effects. The contractor explained the criteria that had been applied when deciding whether publications were, or were not, included in the State of the Art report. Some participants also raised the question of the "real world" significance of the observed low-dose effects.

Sessions III and IV Are existing assessment methods sufficient for addressing combination effects and finding the right framework.

Professor Thomas Backhaus presented the contractor's views concerning current assessment methods and how they might need to be adapted to address mixture toxicity. As part of this presentation he described how it might be possible to apply Mixture Assessment Factors in the same way that assessment factors were currently applied when setting "safe levels" for single chemicals based on toxicity tests.

Professor Backhaus also made a presentation on the dose addition and independent action models and how they might be applied in a regulatory setting. He concluded, that in many cases the dose addition model was effective in explaining/predicting the toxicity of a defined mixture and that as a default option, it was precautionary without being overly conservative. Professor Backhaus presented data to suggest that if the dose addition approach was applied in a situation where in fact the independent action model was the more appropriate, the dose addition model would over estimate the effective concentration by a factor of no-higher than 5.
Concerning the possible use of Mixture Assessment Factors, the participants recognized that such tools might form part of future approaches to the assessment of mixtures. With regard to the use of the dose addition model, or the independent action model, participants were generally of the view that the choice of the most appropriate assessment tools would need to be decided on a case by case basis. In some situations, for example for mixtures of substances with reliable data indicating clearly different modes of action, the independent action model may be the best approach. In other cases with data poor chemicals and little information about mode of action, the dose addition model was seen as a reliable and conservative default option at least at the stage of initial screening.

Some participants questioned the conclusion that the dose addition model was precautionary without being overly conservative. In particular it was questioned whether the evidence base was sufficiently conclusive to support the assertion that the dose addition model would overestimate toxicity by a factor of 5 as a maximum. The contractors defended their conclusions on this issue but accepted to look at any additional factual evidence that Industry wished to present.

Session 5 Where to Start—the possible number of chemical combinations is immense.

Professor Kortenkamp, presented ideas on how to identify those chemical mixtures that were priorities for assessment. Information from chemical monitoring in the environment, in the workplace, in the home may provide information on the chemical mixtures to which humans and the natural environment are really exposed. Chemicals that have a similar structure, similar modes of action, or which impact the same biological processes or target organs, may also be suitable candidates for more in-depth assessment. Professor Kortenkamp also presented information on the use of the Hazard Index which represents a systematic and endpoint neutral tool for identifying chemical mixtures of high concern.

Participants acknowledged the need to identify chemical mixtures that were of high(est) priority for further assessment and recognised that the Hazard Index was a potentially powerful tool to be used in the decision making process.

Session VI Recommendations from the Contractors to the Commission

Professor Kortenkamp presented 6 key recommendations from the contractors:

1. That the EU should develop integrated guidelines addressing both human health and environmental concerns on the assessment of chemical mixtures;
2. That the legal mandate for mixtures risk assessment in the European Union should be strengthened.
3. That in addition to a consideration of mixture toxicity in the context of product oriented legislation, environmental legislation such the Water Framework Directive, the Marine Strategy Directive and the IPPC Directive should also be included in the scope of any future initiative.
4. That at the level of the EU the concentration (dose) addition model should be applied as the default concept for mixture effects in the context of tiered assessment approaches.
5. That it should be ensured that the generation of toxicity data is made amenable to future mixture effect evaluations.
6. That more research be carried out to identify typical exposure scenarios with respect to chemical mixtures.

The presentation from Professor Kortenkamp also served as an introduction to the final session of the meeting where participants were requested by the chair to reflect on what type of action they would like to see taken at the EU level with regard to mixture toxicity. The chair also invited participants to take into account how to ensure an integrated/holistic approach to an assessment of mixture effects across different pieces of EU legislation and how to address the issue of liability/responsibility with regard to the assessment of mixture effects.

The presentation from Professor Kortenkamp together with the indications from the chair gave rise to a very far reaching discussion from which the chair drew the following conclusions regarding the main messages from the meeting.

**Chair's Conclusions**

1. It is necessary and appropriate to address the issue of mixture effects as part of chemicals' risk assessment in the EU.
2. The assessment of mixture toxicity should be undertaken both in product oriented chemicals' legislation and media oriented environmental legislation.
3. We have sufficient information to develop technical guidelines for the assessment of mixture toxicity which could be applied across the different pieces of EU legislation. The legal form of such guidelines (Commission decision, recommendation etc) is to be decided.
4. As and when existing pieces of EU legislation dealing with chemicals are reviewed and revised, language should be introduced that allows mixture effects to be assessed and acted upon.
5. The review of REACH foreseen to be completed by 2012 presents an excellent opportunity for ensuring that the assessment of mixture toxicity is properly addressed in this key piece of legislation. It was recognised that the question of responsibility/liability is an important issue that would need to be tackled.
6. To ensure an integrated and holistic approach to the assessment of chemical mixtures it was important that the relevant departments in the Commission as well as the relevant agencies co-ordinate their activities to ensure a "joined up" approach.
7. The identification of chemical combinations that are a priority for assessment is absolutely essential in order to ensure the effective and targeted use of limited resources.
8. More effective use of data collected in the context of product oriented chemicals' legislation and media oriented environmental legislation would allow priority chemical mixtures to be identified.
9. EU initiatives in relation to mixture toxicity should take into account international initiatives such as those being taken by WHO/IPCS and the OECD.
10. Further discussion of the mixture toxicity issue should continue in bodies such as CARCAL. Further dedicated meetings of stakeholders such as the present workshop
would be appropriate when the Commission can provide further insights as to how it will take this issue further.