Workshop

Combined Exposure to Chemicals

11-12 July 2011, Berlin

European Centre for
Ecotoxicology and Toxicology
of Chemicals

WORKSHOP: COMBINED EXPOSURE TO CHEMICALS

Organised by

ECETOC - European Centre for Ecotoxicology and Toxicology of Chemicals

11-12 July 2011, The Westin Grand Hotel, Berlin

WELCOME

Thank you for participating in the workshop "Combined Exposure to Chemicals". Enclosed you will find the workshop programme and other essential information.

CONTENTS

VENUE

The meeting will be held in the Westin Grand Hotel, Berlin.

The plenary sessions will take place in Salon Unter den Linden.

The breakout sessions will be held in

I. Salon Friedrichstadt,

II. Club Diana

III. Salon Meissen.

PROGRAMME

BACKGROUND

Human and environmental chemical risk assessment is predominantly carried out on individual substances, and this is also reflected in most chemical-related legislation. In reality though, humans, fauna and flora are exposed to a variety of substances concurrently. The toxicology of chemical mixtures has been usually addressed through the concepts of concentration or dose addition and independent action, with synergism being acknowledged as only a rare occurrence. Today there is widespread interest in examining the question of whether current risk assessment procedures are adequate for dealing with combined exposure to multiple chemicals. Development of data and methodology for approaching this issue in a scientific fashion is recognised as very important.

AIMS OF THE WORKSHOP

This Workshop will review a number of key scientific areas which are relevant in the assessment of the health and environmental impact of combined exposures to chemicals. It will focus on the state of the science and on technical aspects of co-exposure. Further, it will discuss reliable and pragmatic approaches to risk assessment of combined exposures to chemicals.

(Publication of the outcome will be in form of an ECETOC workshop report, and possibly a follow-up paper in the open literature).

WORKSHOP STRUCTURE

The Workshop will be an active event with a limited number of invited participants. The aim is to have an adequate participation representing academia, industry and regulators. The Workshop will begin with presentations on the state of the science, followed by breakout group discussions on specific questions on where the science may need further developing.

ORGANISING COMMITTEE

Dr Carlos Rodriguez, P&G
Dr Christa Hennes, ECETOC
Dr Malyka Galay Burgos, ECETOC
Dr Mick Hamer, Syngenta
Dr Mark Pemberton, Lucite
Dr Kim Travis, Syngenta

PROGRAMME DAY 1, MORNING

08.30 – 09.00	Registration	
09.00 – 09.10	**Welcome and introduction**	**Neil Carmichael ECETOC**
	Chair: Christa Hennes, ECETOC	
09.10 – 09.30	**Overview on activities on the risk assessment of combined exposures to chemicals**	**Carlos Rodriguez P&G**
	HAZARD EVALUATION	
09.30 – 10.00	**Effects of low and high doses of combinations of chemicals on human health**	**Kim Travis Syngenta**
10.00 – 10.30	**Effects of combinations of chemicals in the aquatic environment**	**Mick Hamer Syngenta**
10.30 – 10.45	**Questions**	
10.45 – 11.25	Coffee break	
	EXPOSURE EVALUATION	
11.15 – 11.45	**Exposure to humans**	**Jacqueline van Engelen RIVM**
11.45 – 12.15	**Exposure in the aquatic environment**	**Chris Holmes Waterborne Environmental**
12.15 – 12.30	**Questions**	
12.30 – 13.30	Lunch	

PROGRAMME DAY 1, AFTERNOON

IMPACT AND RISK ASSESSMENT

13.30 – 14.00	**Conventional approaches to risk assessment of mixtures**	**John Lipscomb US EPA**
14.00 – 14.30	**WHO/IPCS Framework on risk assessment of combined exposure to multiple chemicals**	**Bette Meek University of Ottawa**
14.30 – 15.00	**Review of the evidence for the magnitude of low-dose synergy by ILSI/HESI**	**Alan Boobis Imperial College London**
15.00 – 15.15	**Questions**	
15.15 – 15.45	Coffee break	
15.45 – 16.15	**Cumulative risk assessment and MCR approach**	**Paul Price Dow Chemicals**
16.15 – 16.45	**Evaluating impacts of chemicals in the environment**	**Scott Dyer P&G**
16.45 – 17.15	**Toxicity and the assessment of mixtures of chemicals (Opinion of DG SANCO SCs)**	**Helmut Greim SCHER**
19.00 – 22.00	Dinner at “Altes Zollhaus” Restaurant	

PROGRAMME DAY 2

09.00 – 09.15	**Introduction to breakout groups**	**Christa Hennes** **ECETOC**
09.15 – 09.30	**Project briefing**	**Dimitris Kotzias** **JRC**

Direct measurements of human exposure to priority air pollutants within the frame of a European project

09.30 – 12.30 **Breakout Group Discussions**

(**10.30 – 11.00** Coffee break)

Breakout Group I: Assessment of combined toxicity

Moderator: ***Thomas Backhaus*** *Rapporteur:* ***Alan Boobis***

Breakout Group II: Exposure and risk assessment – Human health

Moderator: ***Angelo Moretto*** *Rapporteur:* ***Martin Wilks***

Breakout Group III: Exposure and risk assessment – Environment

Moderator: ***Theo Brock*** *Rapporteur:* ***Tobias Frische***

12.30 – 13.30	Lunch	
13.30 – 14.45	**Report of the breakout groups and panel discussion**	Moderator: **Mark Pemberton** **Lucite**
14.45 – 15.00	**Conclusions**	**Jim Bridges** **University of Surrey**

Close of Workshop

BREAKOUT GROUP I:
"ASSESSMENT OF COMBINED TOXICITY"

Salon Friedrichstadt, 1st floor

- **When is it appropriate to apply the available models?**
- **How can the developing methodologies be used in the future, e.g. systems biology, adverse outcome pathways?**
- **Are there adequate criteria for grouping substances?**
- **How can the current paradigm for hazard assessment of substances be adapted to the assessment of combined hazard of mixtures, e.g. how to deal with data-poor situations?**

***Question to all groups*: Can these approaches be applied in a regulatory context?**

First Name	Name		Affiliation
Thomas	Backhaus	*(Moderator)*	University of Göteborg
Alan	Boobis	*(Rapporteur)*	Imperial College London
Herman	Autrup		University of Aarhus
Paola	Cassanelli		DEFRA
Catherine	Clapp		Unilever
Eric	Debruyne		Bayer CropScience
Klaas	den Haan		Concawe
Jean-Lou	Dorne		EFSA
Katherine	Flynn		Safe Consortium
Helmut	Greim		Technical University Munich
Christa	Hennes		ECETOC
Per	Johansson		KEMI, Swedish Chemical Agency
Marion	Junghans		Swiss Centre for Applied Ecotoxicology
Markus	Junker		BASF
Reinhard	Kreiling		Clariant
Reinhard	Laenge		Bayer HealthCare Pharma
Giuseppe	Malinverno		Solvay
Marie-Louise	Meisters		DuPont
Karina	Petersen		NIVA
Paul	Price		Dow Chemicals
Chantal	Smulders		Shell
Volker	Soballa		Evonik
Roland	Solecki		BfR
Henrik	Tyle		Danish EPA
Carolyn	Vickers		WHO-IPCS

BREAKOUT GROUP II:
"EXPOSURE AND RISK ASSESSMENT – HUMAN HEALTH"

Club Diana, 1st floor

- **Are the available methods / tools for assessing combined exposure to chemicals adequate and, if not, what is needed?**
- **How can exposure considerations inform on the need for conducting risk assessment of combined exposures?**
- **What type of data (quantity and quality) are required for each level of the assessment tiers for combined exposure, and how can uncertainty be accounted for?**
- **How are developing technologies going to be used in the future?**

Question to all groups: Can these approaches be applied in a regulatory context?

First Name	Name		Affiliation
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Martin	Wilks	(Rapporteur)	Swiss Centre for Applied Human Toxicology
Karine	Angeli		ANSES
Jim	Bridges		University of Surrey
Neil	Carmichael		ECETOC
Ellen	Dhein		Bayer MaterialScience
Jacques	de Gerlache		Solvay
Claudia	Drucker		VCI
Alexius	Freyberger		Bayer
Vladimir	Garkov		EC, DG SANCO
Anne	Gourmelon		OECD
Hans	Ketelslegers		ExxonMobil
Dimitris	Kotzias		EC, JRC
Barry	Maycock		UK Food Standards Agency
Bette	Meek		University of Ottawa
Britta	Michalski		BfR
Pierre	Nord		KEMI, Swedish Chemical Agency
Mark	Pemberton		Lucite
Carlos	Rodriguez		P&G
Erik	Tielemans		TNO
Jacqueline	van Engelen		RIVM
Frederike	Wiebel		Henkel

BREAKOUT GROUP III:
"EXPOSURE AND RISK ASSESSMENT – ENVIRONMENT"

Salon Meissen, 5th floor

- **What tools are available for the assessment of environmental exposure to mixtures, are they fit for purpose, and if not, how would they need to be improved?**
- **Is environmental risk assessment a useful method to address combined exposure to chemicals, e.g. does an exceeding of EQS values indicate environmental degradation?**
- **How can the knowledge of mixture toxicity be used to maintain or improve environmental quality?**
- **How are developing technologies going to be used in the future?**

***Question to all groups*: Can these approaches be applied in a regulatory context?**

First Name	Name		Affiliation
Theo	Brock	(Moderator)	University of Wageningen
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Axel	Dinter		DuPont
Scott	Dyer		P&G
Frédéric	Frère		Harlan
Malyka	Galay Burgos		ECETOC
Mick	Hamer		Syngenta
Chris	Holmes		Waterborne Environmental
John	Lipscomb		US EPA
Giovanna	Meregalli		Dow Chemicals
Maximilian	Muehe		Lysoform Dr. Rosemann GmbH
Louise	Pope		Unilever
Johannes	Tolls		Henkel
Kim	Travis		Syngenta
Erik	Van Miert		Solvay
Marco	Vighi		University of Milan
Corinna	Weinz		Bayer
Paul	Whitehouse		UK Environment Agency

ABSTRACT

Overview on activities on the risk assessment of combined exposures to chemicals

Carlos Rodriguez
Procter & Gamble
Strombeek-Bever, Belgium

Humans and the environment are continuously being exposed to multiple combinations of substances both from a natural and synthetic origin. Toxicologists have traditionally mostly focused on studying the toxicology of single substances but have not ignored the need of accounting for combinations of substances (mixtures). The field of Toxicology of mixtures is well established but remained mainly of academic and specialised areas' interest until recently. Most regulations on the risk assessment of substances are based on the assessment of individual substances. Broad stakeholder's (regulators, industry, NGOs, media) attention to the need for assessing the risks of combined exposure to multiple substances started to mount in the last decade and has continued to develop with increasing intensity ever since. In the last five or six years a variety of regulatory agencies (including E.F.S.A., US EPA, UK IGHRC, and others) have issued or updated documents proposing guidance for addressing one or more aspects of the assessment of combined exposure to substances. In 2007 the WHO IPCS held an international workshop on the subject whose main outcome was the establishment of an experts group to develop a framework for risk assessment of combined exposures to multiple chemicals. This WHO framework was completed last year and was presented at an OECD/WHO/ILSI-HESI workshop last February. In 2007 the EU DG Environment commissioned a review on the "State of the Art Report on Mixtures Toxicity" which was completed and published by Kortenkamp *et al.* in December 2009. Also in December 2009, the EU Council asked the EU Commission to advise on the adequacy of current legislation for addressing the toxicology of mixtures and to propose appropriate guidance. The EU non-food Scientific Committees took on the scientific task and have just issued their opinion in June 2011. Numerous additional activities in the field have been triggered as a consequence of this keen regulatory interest. ECETOC recently formed two task forces, one to review evidence of toxicological effects as a result of low dose interaction of chemicals and the other to develop guidance for assessing the impact of mixtures of chemicals in the aquatic environment. Both ECETOC task forces have just completed their work. Last year CEFIC established a "mixtures team" (MIAT) that had proposed a decision tree for helping address the assessment of mixtures. The CEFIC decision tree is based on the WHO framework and uses the MCR (Maximum Cumulative Ratio) concept developed by Paul Price. A few years ago ILSI-HESI started a "mixtures group" and they have very recently completed a review of the evidence for the magnitude of low-dose synergy and are evaluating the use of TTC as a screening assessment tool. In February this year, SETAC held a special "Science Symposium on Prospective and Retrospective Environmental Risk Assessment of Mixtures". These are some important, recent activities in the field. All of them will be discussed in this workshop whose participants include some of their key representatives.

ABSTRACT

Effects of low and high doses of combinations of chemicals on human health

Kim Travis
Syngenta
Bracknell, UK

There is no doubt that the public is exposed each day to complex combinations of chemicals, whether natural or synthetic. In the case of chemicals subject to regulatory approval, tests on single chemicals and of products or preparations containing multiple chemicals form the basis by which society seeks to ensure the protection of human health. However, this does not explicitly address concerns about combinations of chemicals in the environment to which the public is exposed. For this reason, the topic of mixture toxicology has been active for many years, with thousands of studies being conducted and hundreds of reviews of the field. This presentation seeks to distil some lessons from this large body of work.

Much work on mixtures has been done at doses where individual chemicals in the mixture would already cause an effect if dosed alone. In these circumstances all manner of interactions may be seen. Dose addition and independent action are common, though synergy and antagonism also occur. However, if the public is exposed to any regulated chemical at an effect level when dosed alone, this represents a frank failure of existing regulation or exposure controls. Safety or assessment factors should prevent exposures to single chemicals from approaching effect levels. For this reason, the main focus of a discussion about the protection of human health in the context of chemical mixtures needs to be on lower doses, specifically on the effects of combinations of chemicals where each chemical is below a threshold of toxicity (e.g. NOEL).

An ECETOC Task Force has been reviewing the evidence for the effects of combinations of chemicals when each component is at a dose which would not by itself produce an effect. A thorough literature review has been conducted, with an emphasis on the identification of primary data sources, and with strict criteria for papers to be accepted as relevant for the review. Three classes of relevant studies were identified:

- Studies where combinations of chemicals were only tested at doses close to (but below) the NOEL of individual components.
- Studies where combinations of chemicals were tested at doses well below the NOEL of every individual component.
- Studies where animals are exposed to real or simulated environmental mixtures.

Based on this review, the Task Force will summarise the evidence, and will use it to address the following points in its remit.

- To evaluate whether the evidence on interactions at low doses demonstrates toxicologically relevant effects and determine whether there are any associations with specific modes of action.
- To look at the evidence of chemical interactions and comment on the likelihood of those being important in the context of environmental exposures.
- To evaluate the adequacy of current human safety risk assessment practice in light of the conclusions of the above.

This work and the preliminary conclusions will be presented.

ABSTRACT

Effects of combinations of chemicals in the aquatic environment

Mick Hamer
Syngenta
Bracknell, UK

The potential risk of combinations of chemicals, rather than single chemicals is increasingly becoming a concern. These combinations of chemicals or mixtures fall into different categories.

- Multi-constituent substances such as petroleum oils, natural dyes and essential oils.
- Chemical formulations and preparations prepared by blending different substances in specific proportions such as plant protection products, biocides, pharmaceuticals and other consumer products.
- Mixtures of chemicals due to co-concurrent release such as effluents, PPP tank mixes.
- Complex mixtures in the environment of unknown composition, consisting of anthropogenic discharges together with natural sources of chemicals mixtures.

An ECETOC Task Force has been looking at ways the impact of chemicals on aquatic environments can be assessed. Mixture toxicity has received much attention with numerous laboratory studies indicating that the effects of combinations of chemicals need to be considered, although these studies reinforced the position that the long-held concepts of concentration addition and independent action can explain the observed effects. It seems that mixture toxicity theory can be used to determine the potential for effects of mixtures of known composition. The testing of mixtures is another option, indeed it is a requirement for many chemical mixtures such as plant protection products. However, the ever changing nature of chemical mixtures in the environment due to the differing environmental fate parameters of the component parts, can lead to problems with estimating the risk in the environment. The potential for the impact of chemical mixtures in the environment is even harder to predict or evaluate when not all the components are known and this is where techniques such as whole effluent testing/direct toxicity assessment can be useful, followed by toxicity identification evaluation/effects directed analysis to characterise the chemical(s) driving the effects.

ABSTRACT

Exposure to humans

Jacqueline van Engelen / Marcel van Raaij
National Institute for Public Health and the Environment (RIVM)
Bilthoven, The Netherlands

The role of exposure assessment in risk assessment has long been underestimated.

Fortunately, the last decades it has been realised that refinement of exposure is a cheap, rapid, animal-friendly and effective tool to improve a risk assessment. It is important that exposure assessors work in cooperation with risk assessors, since the exposure assessment needs to be tailored to the specific goal of the risk assessment. It should be clear which question should be answered and in what time frame.

The level of detail of the exposure assessment, and consequently the data and/or model used, need to be decided on a case by case basis. If a low tier, conservative, estimate results in 'no concern', then there is no need for a sophisticated approach. On the other hand, when exposure via various routes and various sources needs to be assessed, this might require high tier models and high quality data. In the ideal case, the high tier exposure assessment results in exposure values that are close to realistic levels. Probabilistic approaches and preferably assessment of internal exposure values, by e.g. application of PBPK models in combination with biomonitoring are valuable tools.

For the various domains, like exposure assessment to contaminants in food or the exposure assessment for chemicals in non-food consumer products there is a large gap (difference) in available data. At the moment there are several initiatives in bridging the gap between these areas.

ABSTRACT

Exposure in the aquatic environment

Chris Holmes
Waterborne Environmental Inc.
Leesburg, VA, USA

Gaining a better understanding of the presence of chemical mixtures in the aquatic environment is critical to refined risk assessment. While many methods for estimating the presence and concentration of single-chemicals in surface water are available, few approaches attempt to quantify multiple-chemicals and/or multiple-stressors found in aquatic systems. This can be especially challenging when chemical co-occurrence in space and time is considered. However, it is possible to estimate the presence of multiple chemicals/stressors in spatially- and temporally-explicit assessments. This talk will present a number of chemical types and associated sources/routes of entry into surface water. Selected exposure models used to estimate presence or concentration of chemicals will be introduced. Of particular interest will be approaches which incorporate multiple chemicals, sources and/or stressors as part of the aggregate exposure to aquatic environments, specifically highlighting the spatial and temporal dimensions. Case studies from the US (Ohio and California) and the UK will be presented.

ABSTRACT

Conventional approaches to risk assessment of mixtures

John C. Lipscomb
U.S. Environmental Protection Agency
Cincinnati, OH, USA

Humans are never exposed to a single agent; human exposure patterns are dynamic and complex and they modulate the ensuing response(s) among the population. Cumulative risk assessment (CRA) approaches are employed to assess the risks to a given population from multiple agents emanating from multiple sources. Two key concepts in CRA are the suite of agents and the population of interest. In some instances, exposures can be reasonably well characterised, even if the nascent toxic properties of the individual agents cannot. The extent to which the agents have been toxicologically characterized is a major determinant of the choices that are made in a CRA. The initial phase of a CRA is based on the principles (and practice) of mixtures toxicology, where the major issue is characterising the degree to which the mode(s) of action of mixture components (agents) are similar or dissimilar. The concept of using similarity versus independence of MOA has traditionally been used as a means of judging the extent to which one agent is likely to add to the toxicity (response) elicited by a second agent. When both agents act through the same, or similar, MOA then the response anticipated is estimated as a function of the combined, individual doses of the agents, adjusted for potency. When two agents act through dissimilar or independent MOAs, then the combined response is predicted as the sum of the responses produced by the individuals, separately. While some CRA endeavours have limited the inclusion of chemicals to those acting through the same MOA (e.g., cholinesterase inhibition), CRA applications do not require similarity of MOA. There may be merit in also assessing the commonality among major effects, even when these effects are not key components of the MOA (e.g., enzyme induction). The second phase is to identify the population of interest and characterise the exposures. The response anticipated in individuals may vary among a population, and it is necessary to define the population of interest. CRA may be applied to small, well-defined populations, such as those living near a contaminated site, or to geographically-scattered and diverse populations such as those subjected to national-level regulations. In either case, it is important to define the toxicologically-relevant characteristics of the population and account for their variability in CRA. This presentation will provide an overview of CRA and its application, as well as lay out some issues for additional consideration.

ABSTRACT

WHO IPCS Framework on risk assessment of combined exposures to multiple chemicals

Bette Meek
McLaughlin Centre for Population Health Risk Assessment
University of Ottawa, Canada

More efficient methodology for assessing the impact of combined exposures to multiple chemicals has been considered in a project of the World Health Organization (WHO) International Programme on Chemical Safety (IPCS).

Following an initial international workshop to review advances in this area, a draft framework for assessment of combined exposures was developed which includes problem formulation, followed by stepwise consideration of both exposure and hazard in several tiers of increasingly data-informed analyses. These analyses build on recent developments in assessment in a range of programs internationally, incorporating predictive approaches in early tiers and increasingly refined, more data-informed and probabilistic analyses in later tiers.

The framework, authored by M.E.(Bette) Meek, Alan R. Boobis, Kevin M. Crofton, Gerhard Heinemeyer, Marcel Van Raaij and Carolyn Vickers is illustrated by a number of case studies which provide examples of assessments in different tiers. The framework and case studies were considered recently in a second international workshop for which proposed follow-up includes international coordination in the development of a broader range of more encompassing case studies.

Recommendations regarding terminology and the status of development of the framework, its content, review and application will be described. Evolving experience in its application will be illustrated by example with special emphasis on the critical content of problem formulation, the role of predictive tools in grouping of chemicals for consideration and the importance of explicit delineation of relative uncertainty and sensitivity for tiered exposure assessment.

ABSTRACT

Review of the evidence for the magnitude of low-dose synergy by ILSI/HESI

Alan R Boobis
Imperial College
London, UK

Exposure to chemicals almost never occurs in isolation; rather there is co-exposure to several chemicals. As it is not feasible to test all potential combinations, default assumptions are used in the risk assessment of relevant assessment groups. The most common such assumptions are dose or response addition, as appropriate, depending on available information on the mode of action of the mixture components. The ILSI Health and Environmental Sciences Institute convened a tripartite working group comprising scientists from academia, government and industry, to explore the development of a screening level risk assessment as part of a tiered approach in the risk assessment of co-exposures to chemicals. Specifically, the threshold of toxicological concern (TTC) was investigated for this purpose. In such a screening approach, chemicals that could conceivably share a mode of action would be assumed to exhibit dose addition, as this would be more conservative than assuming response addition. However, before applying such an approach, it was necessary to take into account any synergistic interactions that might occur at low, environmentally relevant exposure levels.

A systematic literature review on the occurrence and magnitude of synergy in mammalian test systems was therefore performed. The emphasis was on studies undertaken at doses close to the points of departure (PODs) for the mixture components. The search identified 90 studies on mixture additivity. However, few of the papers included a quantitative estimate of the magnitude of any synergy at low doses. Only 11 papers included such information. The methodology used varied amongst the studies, including the null hypothesis tested, the POD used to investigate synergy and whether or not the slope of the dose-response curve was considered. The method used for calculating the magnitude of the synergistic interaction also varied amongst the studies. Based on the findings of this review, it was concluded that consistent approaches should be applied for quantification of synergy, including: Defining synergy in terms of departure from dose addition; development of harmonised procedures for assessing synergy at low exposure levels; and standardisation of the POD used when calculating synergy.

Only six studies provided useful, quantitative estimates of synergy. The magnitude of synergy at low doses, but exceeding the PODs of the mixture components, observed in these studies ranged from 1.5 to 3.5 fold, i.e. the effects observed were not more than 3.5-fold those predicted by dose addition. Such information suggests that it should be possible to use the threshold of toxicological concern for screening and prioritisation of co-exposures to chemicals, as part of a broader, tiered approach for mixture toxicology.

Acknowledgement: The work described reflects the efforts of the ILSI HESI Risk Assessment Methodology working group on Mixtures.

ABSTRACT

Cumulative risk assessment and MCR approach

Paul Price
Dow Chemicals
Midland, MI, USA

Human and environmental receptors are exposed to multiple chemicals from multiple sources. Despite widespread discussion of the need to consider cumulative exposures when determining chemical safety, there has been little investigation into how much greater the cumulative toxicity would be than the toxicity from individual chemicals. Because of the considerable level of resources required by cumulative assessments, it is useful to determine when this difference is large and cumulative assessments are needed and when it is sufficiently small that a chemical-by-chemical approach is adequate.

In this talk we describe the use of a simple tool, the Maximum Cumulative Ratio (MCR) that provides a quantitative measure of the magnitude of the toxicity that is "missed" by not performing a cumulative risk assessment. The MCR can be applied whenever there are sufficient data to use either a TEQ-based approach or Hazard Index/Hazard Quotient approach for the evaluation of cumulative toxicity of individuals in a population. By calculating the MCR for individuals with known cumulative exposures, the tool can determine if there is value in performing cumulative risk assessments for similar populations or if certain groups of chemicals have larger or smaller needs for a cumulative risk assessment. This information can be used to guide future collections of data and risk management decisions.

A case study is presented of the application MCR to human exposures to mixtures of pesticides in surface waters. In this study we show how the MCR can be used within the WHO/IPCS tiered approach for assessing the toxicities of mixtures (Meek et al. 2011). Specifically, the example examines how MCR values from exposures to mixtures of pesticides change as the mixtures are assessed under simple assumptions of additivity (Tier 1), when mechanism of action is considered (Tier 2), and when probabilistic models of non cancer toxicity are used (Tier 3).

ABSTRACT

Evaluating impacts of chemicals in the environment

Scott D. Dyer
Procter & Gamble
Cincinnati, OH, USA

Logical frameworks by which measured biological impacts can be attributed to chemical mixtures have been developed. The foundation from which these frameworks depend is the definition of impact. For environmental risk assessment, impact is typically defined as a measured deviance from reference conditions. Reference conditions typically refer to sites in which biological communities are minimally affected by human influences. Large deviances from reference are indicative of large impacts. For example, if the impact is spatially and temporally related to a point source (e.g., waste water treatment plant discharge), then use of biologically directed tests to determine the potential chemical causes can be employed. However, if these tests (acute to chronic toxicity) do not indicate a single component or suite of components related to toxicity, then the next step is to consider chemical mixtures and other potential stressors as potentially responsible for the impairment. These eco-epidemiologically-based assessment methods include the use of prospective mixture and stressor modelling to derive statistically relevant relationships with observed impacts. That is, it must be recognized that the impairments may be a symptom of physical, chemical as well as biological (i.e., invasive species) factors. Several methods have been investigated that relate these diverse factors to biological impairments for single sites as well as large regional areas. Comparisons of similar relationships found elsewhere add strength to the weights of evidence in which decision-makers depend before management actions are often enacted. Case studies within different landuse categories (urban, agriculture, forest) will be provided that illustrate where best to investigate the potential impacts of mixtures and where to avoid based on the types of mixtures of interest.

LIST OF PARTICIPANTS

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VENUE AND WORKSHOP HOTEL

- **The Westin Grand Berlin**
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  www.westingrandberlin.com

  U-bahn (Metro): Unter den Linden or Französische Strasse

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  U-bahn (Metro): Hallesches Tor
  Meeting time: 19.00 (7.00 pm)
  Date: July 11
  http://www.bvg.de/index.php/de/3713/name/Liniennetz.html (To access Berlin's metro map)

  Take the **U-bahn (line U6 direction Alt-Mariendorf) from Französische Strasse and exit at Hallesches Tor.**

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