IAEA EMRAS II
Biota Effects Group

Advances of the Multiple Stressor group

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SCK•CEN, Biosphere Impact Studies

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CENTRE D'ETUDE DE L'ENERGIE NUCLEAIRE

Overall goal

- perform a prospective analysis of the likely implications of taking into account the multi-stressor context on (evolving) radioprotection regulation and standards

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Objectives

- Review of approaches in ecotoxicology for risk assessment in multiple stressor scenarios (concentrating on EC-NoMiracle project)
- Evaluation of how these approaches can be applied in the context of environmental (radiation) protection
- Establishment of a multiple stressor effects literature database considering different exposure conditions, endpoints, ecosystems
- Tailored to the needs, experiments or studies in which benchmarks for chemicals and radiation exposure to non-human biota will be challenged in relevant experimental set ups (or ecotox tests) by the participating laboratories.
- Methods and guidance on approaches to study/assess multiple stressor impact

What did we promiss after the first meeting??

ULTIPLE STRESSOR	Persons	Timing	STATUS
iterature survey Look at UNSCEAR, Streffer, ERICA No rad/mix experiments in domain of oncology	Christina, Nele, Synove, Yoshida, Tamara, Karolina, Debby	Template: End feb Repartitioning of tasks: End feb Database: July 2009 Report: Dec 2009 **+ Publication**	We'll get there
ook what has been done for chemicals, concentrating on oMiracle *New methods for assessing cumulative risk assessment from combined exposures *To improve our understanding of complex exposure situations and develop adequate tools for exp assessment *To develop a research framework for description and interpretation of cumulative exposure and effect **Report: approach with chemicals and how it can be transferred to rad protection	Hildegarde, Tom, Tamara (field), David's colleague, Nele	Interim report : Dec 2009 Endreport: dec 2010 + extension with comments on results of exp data: July 2011	We might not get there under the form initially set
uidance on experimental set-up for mixed exposure	Hildegarde, Sinove, Tom, Nele, Tamara	End 2009!! Under condition	We might not get there under the form initially set
DDITIONAL: Multiple Stressor Course	**Nele, Nathalie, Hildegarde**	**Sept 2010**	**Success**
xperiments	Hildegarde, Nele, Yoshida, Karolia, Tom, Synove, Steve (Critical observer)	Identify and list of interested groups and test species used: July 2009 Decide on experimental approach and stressors: Jan 2010 Report of experiments: May 2011 + Publication	To be discussed

Multiple Stressor database

- Scope: multiple stressor exposure with one of stressors external radiation or uptake of radionuclides
- Aim: Get an overview of what has been done so far, how it has been done, generalities on outcome
  - Status of the research in this area

Following QA/QC: 38 out of 52 refs accepted

- **Terrestrial plants**
  - Before QC analysis: 6
  - After QC analysis: **5**
- **Aquatic plants**
  - Before QC analysis: 1
  - After QC analysis: **1**
- **Terrestrial animals**
  - Before QC analysis: 22
  - After QC analysis: **10**
- **Aquatic animals**
  - Before QC analysis: 4
  - After QC analysis: **4**
- **Freshwater microcosm**
  - Before QC analysis: 1
  - After QC analysis: **0**
- **Marine estuarine**
  - Before QC analysis: 19
  - After QC analysis: **13**

MS-paper

- 1. Introduction (NV and HV)
  - *Multiple stressor environment (HV)*
  - *Environmental standards and their requirements (HV)*
  - *Approaches to evaluate combined effects of stressors (NV)*
  - *Combined effect of substances (HV)*
    - ♣ Different exposure modes/diff modes of action/diff target organs
    - ♣ Interaction can occur at all levels – adsorption, metabolisation, decontamination mechanisms, damage repair mechanisms
- *2. Approach (Almudena)*
  - *Literature review, set up database, QA/QC*

MS-paper (2)

- *3. Presentation and discussion of literature data*
  - *3.1. Terrestrial and aquatic plants (Nathalie)*
  - *3.2. Terrestrial animals* (Almudena)
  - *3.3. Freshwater & marine animals* (Karolina/Clare)
- *4. Conclusions and recommendations for future research (all)*
- *Finalise draft by End Oct 2010*
- *→will become end of February 2011.*

Workshop on Mixture Toxicity

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Workshop on Mixture toxicity

September 22-24, 2010

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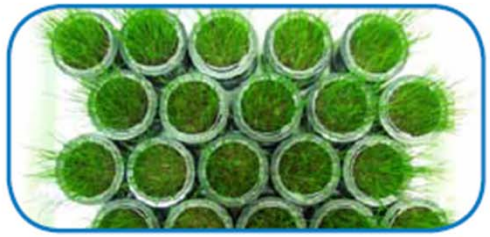
Venue

SCK•CEN, Mol, Belgium

Belgian Nuclear Research Centre, SCK•CEN
Club-House, Boeretang 201, 2400 Mol, Belgium



Objectives

Contaminants never occur in isolation, yet legislation is still largely based on effects of single compounds. In addition, more and more data are becoming available that suggest that compounds can exert effects in organisms when present in mixtures in concentration ranges at which the single contaminants do not induce effects.

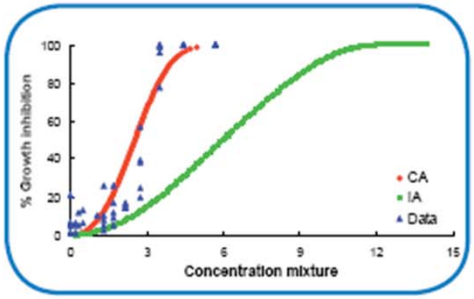
The examination of combined exposures, which corresponds much more realistically to exposure conditions in the environment than the analysis of single substances, entails major methodological difficulties in the experimentation and evaluation procedure.

This workshop intends to introduce you to some of the approaches and methodologies used in studying and predicting mixture toxicity effects. The workshop will be a mixture of lectures, exercises and open discussions.

More information
www.sckcen.be/en/Events/MIXTOX

Target audience

This workshop intends to attract PhD students and scientific researchers. As the general concepts discussed in this workshop apply to different fields of research, participants of all fields of (eco) toxicology are welcome.



Organisation

This workshop is organized by the unit Biosphere Impact Studies (BIS) from the Belgian Nuclear Research Centre (SCK•CEN).
It is organized in the framework of the IUR-IAEA Practical Arrangements for the exchange and dissemination of information within the EMRAS II project, Working Group 6 on Biota dose effects modelling - Multiple Stressors.

IUR International Union of Radioecology
IAEA International Atomic Energy Agency
Atoms for Peace

Programme

Registration

Registration fee before September 10th 2010 will be 250 euro (150 euro for students).

The registration fee is only to be paid by bank transfer or by VISA and includes welcome bag, course material, lunch, coffee breaks, welcoming reception on Wednesday and walking dinner on Thursday. More information can be found on the website.

Lecturers

Experts with international recognition within the field of mixture toxicity and biostatics have been invited.

- Thomas Backhaus, University of Göteborg, Sweden
- Claus Svendsen, Centre for Hydrology and Ecology, UK
- Tjalling Jager, Free University of Amsterdam, Netherlands
- Stefan Van Dongen, University of Antwerp, Belgium

Language

The workshop will be held in English.

Not to forget!

To be able to participate in the calculus sessions you will need a laptop with Excel installed. The statistical methods will be shown using the statistical program "R" which is as freeware available on the internet. If you can't bring a laptop, please inform us on your registration form.

Programme

Wednesday September 22, 2010

08:30 Opening and registration
09:00 Introduction
Frank Hardeman, SCK•CEN, Belgian Nuclear Research Centre, Belgium
09:30 Mixture toxicity concepts and Risk assessment
Thomas Backhaus, University of Göteborg, Sweden
11:00 Break
11:15 Mixture toxicity concepts and Risk assessment
Thomas Backhaus
13:00 Lunch
14:00 Mixture toxicity concepts and Risk assessment
Thomas Backhaus
15:00 Break
15:15 Calculus session
Nele Horemans and Nathalie Vanhoudt, Biosphere Impact Studies, SCK•CEN, Belgium
18:30 Welcome reception

Thursday September 23, 2010

09:00 Deviations from Concentration Addition and Independent Action
Claus Svendsen, Centre for Hydrology and Ecology, UK
11:00 Break
11:15 Deviations from Concentration Addition and Independent Action
Claus Svendsen
13:00 Lunch
14:00 Biology-based approaches for mixture ecotoxicology
Tjalling Jager, Free University of Amsterdam, Netherlands
16:00 Break
16:15 Biology-based approaches for mixture ecotoxicology
Tjalling Jager
18:00 Round-up and open discussion on day 1-2
18:30 Walking dinner

Friday September 24, 2010

09:00 Linear and generalized linear models in R
Stefan Van Dongen, University of Antwerp, Belgium
11:00 Break
11:15 Linear and generalized linear models in R
Stefan Van Dongen
13:00 Lunch
14:00 Round up on day 3 and closing remarks

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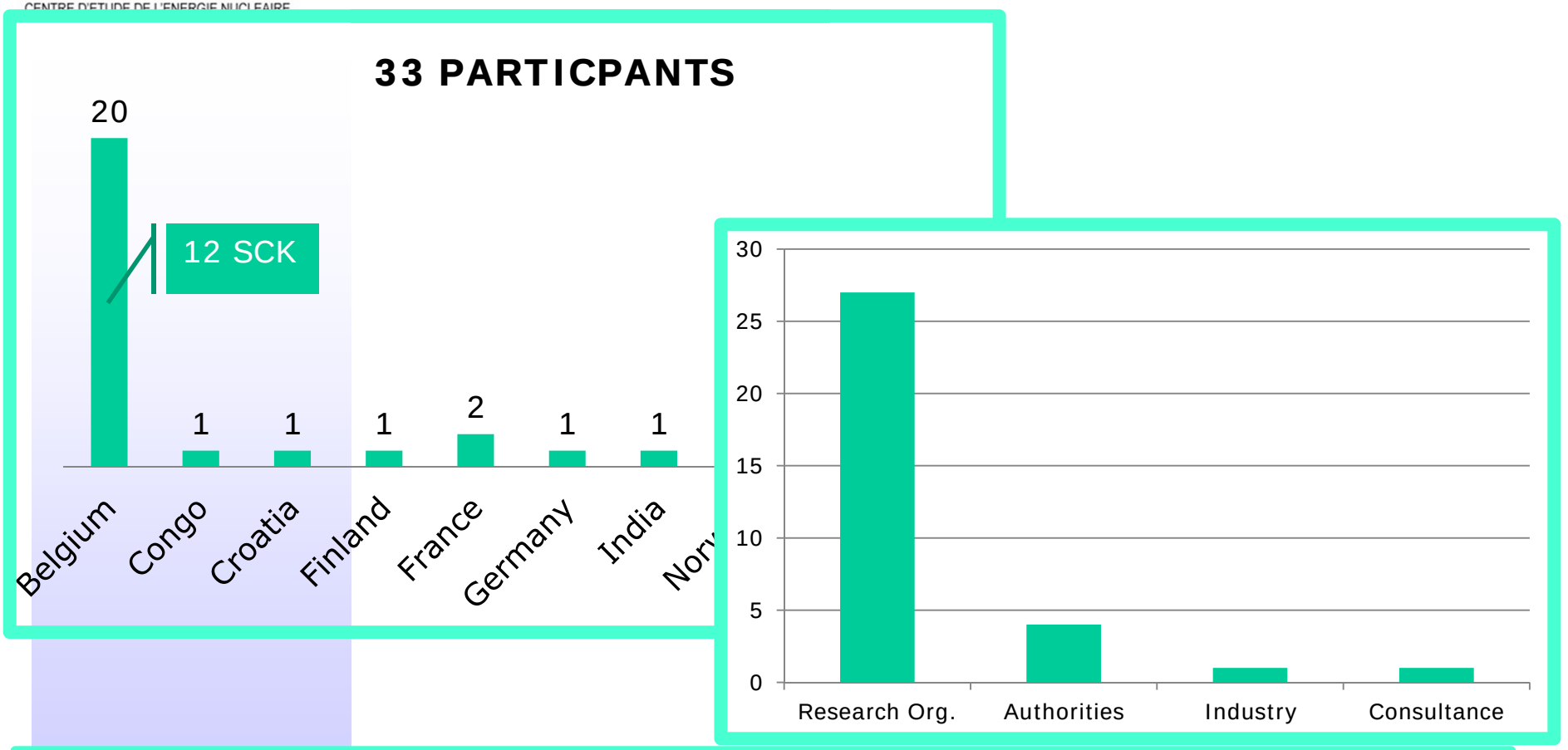
BE-2400 MOL

www.sckcen.be/en/Events/MIXTOX

More than 20 participants from outside SCK



IUR - 3000 EUR; MEZ – 2000 EUR

SCK•CEN: ~14000 EUR

Guidelines for experimental set-up

- It was the intention to use the material presented at the course as a basis for producing these guidelines
- However
  - Different views (Backhaus vs Svendson)
  - Different approaches (CA-IA vs SfN)
  - Different filosophies (CA/IA vs DEB)
- Even NoMiracle did not produce clear guidelines for experiments though this was intended
  - Claus wrote a draft for MIXTOX (an extract of this was presented at an earlier meeting)

Setting up multiple stressor experiments

- If sufficient interest and resources, collaborate on a common, multi-stressor, radiological experiment:
  - Realistic?
  - Something from nothing?
    - Did some initial screening for
      - P-industry
      - U mining
      - Geological disposal
      - NPP
- Sept 2010 meeting – no fingers raised

Look what was done for chemicals concentrating on NoMiracle

- Extract from NoMiracle Science & Technology objectives
  - New methods for assessing cumulative risk assessment from combined exposures
  - To improve our understanding of complex exposure situations and develop adequate tools for experimental assessment
  - To develop a research framework for description and interpretation of cumulative exposure and effect
- Report: Evaluate approaches used for chemicals and how these can be transferred to radiation protection
- Timing: Look at suitable reports from NoMiracle and their availability (March 2009); Interim report: Dec 2009; End report: Dec 2010
- Contributors: Tom, Tamara, Nele, Carmel, a colleague of David, Hildegarde

NoMiracle: “65” deliverables Few directly interesting reports for MS. Hardly any reports available

- D2.2.4. Lab and field data of compound exposure, and assessment of availability parameters
  - describes examples of how availability parameters and measurement approaches can be applied.
    - Chemical activity, Accessibility, Diffusive conductivity, Diffusive flux
- D3.1.4. Final report on the outcomes of chronic toxicity studies with four chemicals and three mixtures focusing on inter-species sensitive for each compound and the fit of mixture data-sets to the reference models for concentration addition and independent action (Confidential)
- D3.2.2. Initial experiments to validate applicability of the chemical mixture assessment model (Confidential)
- D3.4.3.Comparison of the effects of two compounds on biochemical responses in cell lines and animal models (Confidential)
- D3.1.7. Preliminary data-base resource holding summary results of all single chemical and mixture toxicity data collected in the effect assessment phases of NoMiracle (Password)
- D3.3.4. Final report relating the toxicity of two selected chemicals and their mixtures to the uptake, elimination and metabolism kinetics in test organisms (not available)
- D3.3.6. Report on the uptake, elimination and metabolism of a second set of selected chemicals and their mixtures in test organisms (no access)

NoMiracle: Few directly interesting reports for MS. Hardly any reports available

- D4.1.2. Paper on the model formulation for effects of a mixture of 2 compounds (outline of paper projects)
- D4.1.4. Report describing a method for quantification of impacts of different stressors on aquatic freshwater ecosystems
  - define a framework for the development of Comparative Risk Assessment method for freshwater ecosystems
- D.4.1.8 Report on the impact of an additional ecotoxicity test when deriving environmental quality standards
  - This report focuses on the derivation of EQSs, and specifically considers the impact of additional ecotoxicity data on both the level of the EQSs themselves, as well as the consequences for environmental management of that.
- D4.1.12. Report on the experimental validation of the many compound mixture model for survival – just 3 pages
- D4.2.6. Report on ecological vulnerability
  - a new method is developed which incorporates ecological characteristics of wildlife species in ecological risk assessment

NoMiracle not so directly useful as initially thought

There are for sure other sources

NoMiracle output might become more usefull towards future

- Appeared in 2010; not on NoMiracle website

Science of the Total Environment 408 (2010) 3746–3762

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

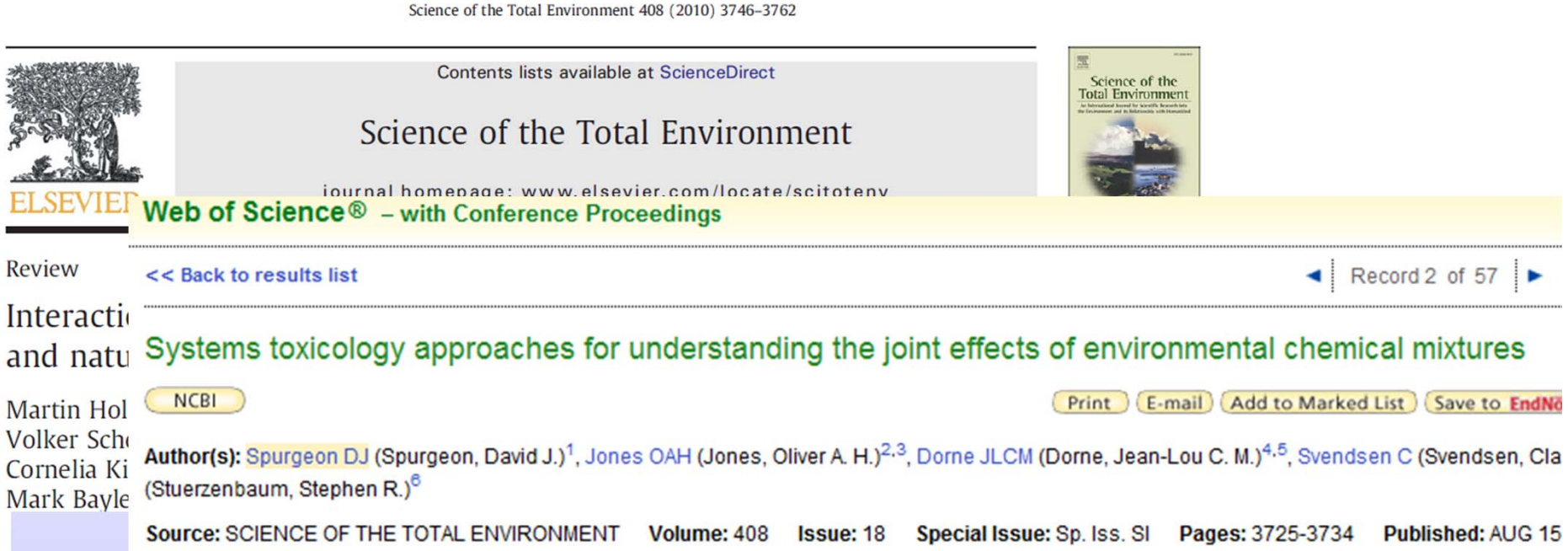
Review

Interactions between effects of environmental chemicals and natural stressors: A review

Martin Holmstrup [a,*], Anne-Mette Bindesbøl [a], Gertie Janneke Oostingh [b], Albert Duschl [b], Volker Scheil [c], Heinz-R. Köhler [c], Susana Loureiro [d], Amadeu M.V.M. Soares [d], Abel L.G. Ferreira [d], Cornelia Kienle [c,e], Almut Gerhardt [e], Ryszard Laskowski [f], Paulina E. Kramarz [f], Mark Bayley [g], Claus Svendsen [h], David J. Spurgeon [h]

NoMiracle output might become more usefull towards future

- Appeared in 2010; not on NoMiracle website



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Review

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Martin Hol
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Cornelia Ki
Mark Bayle

<< Back to results list

Record 2 of 57

Systems toxicology approaches for understanding the joint effects of environmental chemical mixtures

NCBI

Print E-mail Add to Marked List Save to EndNo

Author(s): Spurgeon DJ (Spurgeon, David J.)[1], Jones OAH (Jones, Oliver A. H.)[2,3], Dorne JLCM (Dorne, Jean-Lou C. M.)[4,5], Svendsen C (Svendsen, Cla
(Stuerzenbaum, Stephen R.)[6]

Source: SCIENCE OF THE TOTAL ENVIRONMENT Volume: 408 Issue: 18 Special Issue: Sp. Iss. SI Pages: 3725-3734 Published: AUG 15

NoMiracle output might become more usefull towards future

- Appeared in 2010; not on NoMiracle website

Science of the Total Environment 408 (2010) 3746–3762

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Cornelia Ki
Mark Bayle

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Systems

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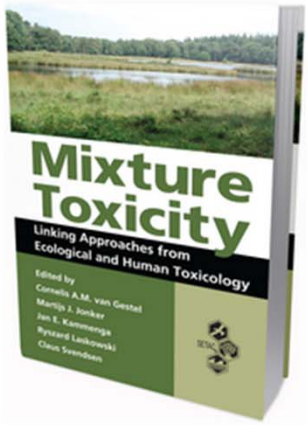
Author(s): Sp
(Stuerzenbau

Source: SCIE

Mixture Toxicity: Linking Approaches from Ecological and Human Toxicology

Editor(s): Cornelis A. M. van Gestel, *Vrije Universiteit, Amsterdam, The Netherlands*; Martijs Jonker, *University of Amsterdam, Amsterdam, The Netherlands*; E. Kammenga; Ryszard Laskowski; Claus Svendsen, *Centre for Ecology and Hydrology, UK*



Price: $119.95
Cat. #: K11470
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Publication Date: November 01, 2010
Number of Pages: 320
Availability: In Stock
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Description | Table of Contents

Features

- Takes an unusual approach to exposure to and risk assessment by exploring the perspectives of ecotoxicologists, human health specialists, and risk assessors
- Includes a broad and detailed review of problems related to realistic exposure to pollutants, with special

Related Titles

- Organic Pollutants: An Ecotoxicologi
  Second Edition
  C. H. Walker, *Devon, UK*
  Publication Date: November 18, 2
  Price: $97.95
- Fundamentals of Ecotoxicology, Thir
  Michael C. Newman, *College of Willi*
  Gloucester Point, Virginia, USA
  Publication Date: September 28,
  Price: $92.95
- Ecotoxicology: A Comprehensive Tr
  Michael C. Newman, *College of Willi*
  Gloucester Point, Virginia, USA; Willi
  H. Clements, *Colorado State Univers*
  USA
  Publication Date: December 13, 2
  Price: $157.95

Achievements vs Future
What additional to STAR?
Extract from Sept Meeting

- Review literature for multiple stressor data in which radiation was among the mix
- Query ecotoxicologists from the chemical industry to see what their most recent conclusions are relative to the need for multiple stressor analyses
  - **Mixture toxicity workshop**
  - Screen NoMiracle and provide limited synthesis ←→STAR
- Report on "Evaluation of approaches used for chemicals and how transferrable to radiation protection" ←→STAR
  - Report to the IAEA on whether this should be a topic requiring further exploration in the future
- MS-experiment
  - Guidelines for experimental set-up:
    - Intended after Mixture Toxicity Course
    - Feasible/realistic? ←→STAR
  - Experiments seem unrealistic

TIME !!!

Availability

Deliverables in STAR

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D4.1	Review of methods in ecotoxicology for mixed exposure	3	4.00	R	PU	13
D4.2	Tools for assessing availability and exposure in a multiple contaminant context	4	6.00	R	PU	50
D4.3	Tools for mechanistic understanding of induced effects for mixed exposure	1	6.00	R	PU	50
D4.4	Critical Evaluation	3	3.00	R	PU	54

Milestones in STAR

MS41	Report of expert workshop to get acquainted with the state of the art of multiple stressor research	WP4	3	4
MS42	Review of approaches for exposure and effects assessment and draft proposal for research programme	WP4	3	11

So ....

- A big thanks for the pleasant contribution from a number of people
- Paper and MixTox course
  - → Nice outputs and achievements
- For remaining deliverables evaluate if
  - It makes sense to deliver them them given the constraints and STAR upcoming
  - If they need to be deliverd if they then can be delivered (in modified form) based on STAR-output
  - Critically evaluate and come on terms on
    - ♣Timing/Scope/Responsables
- Evaluate if this topic requires further exploration in the future in and IAEA context
  - May be “interesting” for “timing of delivery” aspect.

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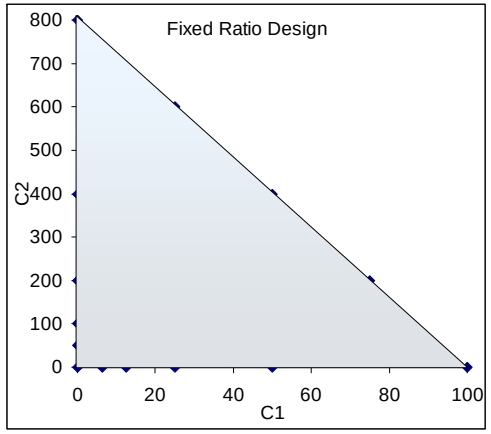
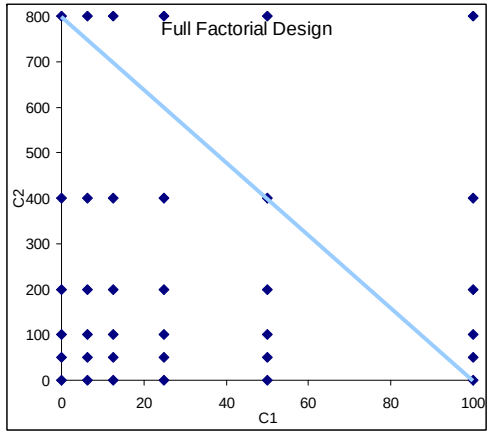
- Thanks for listening ☺

7 steps for mixture exposure experiments and modelling

- Define objective: testing for synergism and antagonism, or looking for dose-level or dose-ratio effects
- Chose analysis tool
- Decide what kind of set up to run (e.g. fixed ratio, factorial design).





- Get an idea of the variability of biological endpoint (CV)
- Decide how big an experiment you can handle in the lab (i.e. how many experimental units)
  - Always run single dose stressor levels with mixtures
  - Always have as many dose (or stressor) levels as you can manage, and cover the whole response range (worry less about replication)
- Decide how big a deviation (e.g. 1.1 [i.e 10%], 1.5 or 2 fold) from the additivity you want to be able to detect at 5% significance
- Look up table for # experimental units
  - 40- >75

Participants vs contributors

Name	IUR/IAEA	Organisation
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Stanislav GERAS'KIN	IUR	Russia
Rodolphe GILBIN	IUR/IAEA	IRSN (France)
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Nathalie Vanhoudt