NoMiracle: Novel Methods for Integrated Risk Assessment of Cumulative Stressors in Europe

Society of Toxicology Teleseminar
13th June 2008

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Steve Stürzenbaum, Kings College, London, UK
Jan Baas – Vrije Universiteit, Amsterdam, The Netherlands
Outline of the presentation:

- Science and Technology Objectives
- Research Pillar on effects: Some results
  - Mixture toxicity modelling
  - Toxicogenomics and "mode of action"
  - Dynamic energy budget models

- NoMiracle events and information
Science & technology objectives

1. Refine methods for assessing the cumulative risks from combined exposures to mixtures of chemical and physical/biological agents.

2. Integration of the risk analysis of environmental and human health effects. – Open workshop Frankfurt 8/9 Sept 2008

3. To improve understanding of and develop adequate tools for effect assessment.

4. To develop a research framework for the description and interpretation of cumulative exposure and effect.
Science & technology objectives

5. Quantify, characterise and reduce uncertainty in current risk assessment methodologies, e.g. by improving scientific basis for safety factors.

6. To develop assessment methods which take into account geographical, ecological, social and cultural differences in risk concepts and risk perceptions across Europe.

7. To improve the provisions for the application of the precautionary principle and to promote its operational integration with evidence-based assessment methodologies.
The NoMiracle Consortium
Consortium overall structure
Research Pillar 3 structure

RP1: Data & Cases

RP2: Exposure information for relevant scenarios

WP3.1: Chemical mixture assessment

WP3.2: Chemicals and natural stressors

WP3.3: Toxicokinetics

WP3.4: Molecular mechanisms of mixture toxicity

RP4: Risk analysis based on available data

Ecotoxicology = 75%, Human health toxicology = 25%
Science & technology objective 1

Refine methods for assessing the cumulative risks from combined exposures to mixtures of chemical and physical/biological agents.

Statistical tools for identification of interactions in mixtures

Slides from Claus Svendsen
Models for non-interacting mixtures

• Similar action model: (concentration addition)

\[ M = \sum_{i=1}^{n} TU_i \]

\[ TU_i = \frac{[c_i]}{[ECx]} \]

• Dissimilar action model: (independent action)

\[ h(c_1, c_2, \ldots, c_n) = \prod_{i=1}^{n} h(c_i) \]
Extend the reference models by adding “deviation” parameters

Add parameter “a” Add parameter “b”

1) CA & IA  2) S/A  3A) DL or 3B) DR

The nesting allows statistical testing for best fit (using likelihood theory)

(Jonker et al ET&C 2005)
An example: Cd + diuron in *C. elegans*

Predict ECx values by IA and compare to data

**IA residuals**

**IA + S/A residuals**

**Model fits**

Building a database of binary mixture studies ~150 (collaboration with Nina Cedergreen University of Copenhagen)

Species from bacteria to (in vitro) mammalian systems

Define the distribution of maximum deviations e.g. EC$_{50}$ gives EC$_x$
So far binary – what about more complex?

Ternary mixture modelling - approach

- Build from binary mixtures knowledge
- Predict the level of deviation when mixing 3 chemicals with known binary interactions
- So far only CA and only synergism or antagonism (not dose level or dose ratio)
The Experimental design
Singles
The Experimental design
Singles – Binary
The Experimental design
Singles – Binary - Ternary

Z Data
X Data
Y Data
Data analysis procedure – 2 ways
1) **Isobols** & two step regression

CA (reference plain)
Data analysis procedure –
1) Isobols & two step regression

[Diagram showing data points and regression lines]
Data analysis procedure – 1) Isobol & two step regression
Visualisation of response surface

Antagonism
Results – *Lemna* antagonism for three herbicides

Data provided by Dr Nina Cedergreen University of Copenhagen, Denmark
Results - *Lemna* for three herbicides

Glyphosate – mecoprop - mesotrion

Binary interactions

\[ a_{1+3} = 0.78 \]

\[ a_{1+2} = 0.86 \]

\[ a_{2+3} = 1.95 \]
Results - *Lemna*

Glyphosate – mecoprop - mesotrion

Ternary interactions

\[
a_{1+2} = 0.86
\]

\[
a_{2+3} = 1.95
\]

\[
a_{1+3} = 0.78
\]

\[
A_{1+2+3} = 7.98
\]
Results - *Lemna*

**Glyphosate – mecoprop - mesotrion**

**Conclusion:**
The ternary mixture is more antagonistic than the combination of binary antagonisms predict.

**Question:**
How big is the under prediction and what is the deviation from CA??

![Graph showing Mesotrion EC₅₀ (µg L⁻¹) vs. Glyphosate EC₅₀ (µg L⁻¹) vs. Mecoprop EC₅₀ (µg L⁻¹)]

- $a_{1+3} = 0.78$
- $a_{1+2} = 0.86$
- $a_{2+3} = 1.95$
- $A_{1+2+3} = 7.98$
**Results – Summary for *Lemna* studies**

<table>
<thead>
<tr>
<th>Chemical 1</th>
<th>Chemical 2</th>
<th>Chemical 3</th>
<th>ΣTU at max. dev.</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>L*emna minor:</strong></td>
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<tr>
<td>Glyphosate</td>
<td>Mecoprop</td>
<td>Mesotrion</td>
<td>1.97 2.89 2.84</td>
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<tr>
<td>Glyphosate</td>
<td>Mecoprop</td>
<td>Mesotrion</td>
<td>1.63 1.63 2.03</td>
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<tr>
<td>Glyphosate</td>
<td>Mecoprop</td>
<td>Terbutylazine</td>
<td>1.41 1.41 1.45</td>
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<tr>
<td>Glyphosate</td>
<td>Mecoprop</td>
<td>Terbutylazine</td>
<td>1.64 1.64 2.04</td>
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<tr>
<td>Terbutylazine</td>
<td>Mesotrion</td>
<td>Mecoprop</td>
<td>2.19 2.19 2.19</td>
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<tr>
<td>Terbutylazine</td>
<td>Mesotrion</td>
<td>Mecoprop</td>
<td>1.25 1.25 1.78</td>
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<tr>
<td>Diquat</td>
<td>Acifluorfen</td>
<td>Mesotrion</td>
<td>2.22 2.22 2.19</td>
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<tr>
<td>Diquat</td>
<td>Acifluorfen</td>
<td>Mesotrion</td>
<td>1.66 1.87 1.74</td>
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</tbody>
</table>

**Lemna (Antagonism):** For ternary if:

1) CA SA > IA = antagonism in the ternary mixture
2) ΣTU CA SA < ΣTU CA SA+ = magnitude of maximum deviation in the ternary greater than predicted based on antagonisms from the binaries.

Some ternary deviations greater than predictions for antagonism (some less). Not yet found for synergism.
Science & technology objective 3

To improve understanding of and develop adequate tools for sound exposure assessment.

Toxicogenomic tools in model and non-model species
...the species...

*Lumbricus rubellus*
- Free-living in the soil
- Detritivorous
- Non-self-fertilizing, hermaphrodite

*Caenorhabditis elegans*
- Free-living nematode - lives in the soil
- Bacterivorous
- Self-fertilizing, hermaphrodite
Getting the bits of earthworm DNA - ESTs
Patterns of effect

*Cd*

*Fluoranthene*

*Atrazine*

*All exposed / controls*

Low dose = repro. $EC_{10}$ = different from no dose
Causes

Many unknowns

Some hypotheticals

Some other pathways e.g. protein degradation....

....but strong mitochondrial signature
Resource allocation - dynamic energy budget

- Food
- Faeces
- Reserves

1. Assimilation
2. Somatic maintenance
3. Growth costs
4. Reproduction costs
5. Hazard to embryo
Cadmium DEB effect - assimilation

**Nematodes**

![Graph showing the effect of cadmium concentration on volumetric length of nematodes.](image)

**Earthworms**

![Graph showing the effect of soil cadmium concentration on final attained weight of earthworms.](image)

**Dose effect**
Cd changes on gene expression - nematodes

Condition tree

**Significant pathways**

<table>
<thead>
<tr>
<th>Biological process</th>
<th>Genes in Category</th>
<th>Genes in List in Category</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO:31323: regulation of cellular metabolism</td>
<td>620</td>
<td>58</td>
<td>0.00211</td>
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<tr>
<td>GO:19222: regulation of metabolism</td>
<td>625</td>
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<td>GO:51244: regulation of cellular physiological process</td>
<td>641</td>
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<td>GO:30794: regulation of cellular process</td>
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<td>GO:50791: regulation of physiological process</td>
<td>642</td>
<td>59</td>
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<tr>
<td>GO:19219: regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism</td>
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<td>GO:6350: transcription</td>
<td>635</td>
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<td>GO:45449: regulation of transcription</td>
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<td>GO:6629: lipid metabolism</td>
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<td>GO:44238: primary metabolism</td>
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<td>GO:8643: carbohydrate transport</td>
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<td>GO:6355: regulation of transcription, DNA-dependent</td>
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<td>GO:6139: nucleobase, nucleoside, nucleotide and nucleic acid metabolism</td>
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<td>GO:7155: cell adhesion</td>
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<td>GO:50789: regulation of biological process</td>
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<td>GO:50875: cellular physiological process</td>
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<td>GO:8152: metabolism</td>
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<td>GO:7582: physiological process</td>
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<td>GO:6470: protein amino acid dephosphorylation</td>
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<td>GO:44257: cellular protein catabolism</td>
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<td>GO:51603: proteolysis during cellular protein catabolism</td>
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<td>GO:19941: modification-dependent protein catabolism</td>
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<td>0.049</td>
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<td>GO:6511: ubiquitin-dependent protein catabolism</td>
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<tr>
<td>GO:6631: fatty acid metabolism</td>
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<tr>
<td>GO:16311: dephosphorylation</td>
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</tbody>
</table>
**Cd changes on gene expression - earthworms**

- Lots of metabolic genes represented on array
- Many change expression
Fluoranthene DEB effect - somatic and maturity maintenance

Nematodes

Earthworms

Dose effect
Fluoranthene changes on gene expression

Condition tree  
Significant pathways

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<tbody>
<tr>
<td>GO:9309: amine biosynthesis</td>
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<td>GO:44271: nitrogen compound biosynthesis</td>
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<td>GO:6629: lipid metabolism</td>
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<td>GO:6082: organic acid metabolism</td>
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<td>GO:19752: carboxylic acid metabolism</td>
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<tr>
<td>GO:16071: mRNA metabolism</td>
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<td>7</td>
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<td>GO:6519: amino acid and derivative metabolism</td>
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<td>GO:6520: amino acid metabolism</td>
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<td>GO:6118: electron transport</td>
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<td>GO:9308: amine metabolism</td>
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<td>GO:16070: RNA metabolism</td>
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</tbody>
</table>
Effect on body size? - Atrazine

Nematodes

Earthworms

Dose effect

Atrazine DEB effect - assimilation

Dose effect
Atrazine changes on gene expression

Condition tree

Significant pathways

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<td>GO:7275: development</td>
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<td>GO:9792: embryonic development (sensu Metazoa)</td>
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<td>GO:9790: embryonic development</td>
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<td>GO:2164: larval development</td>
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<td>GO:2119: larval development (sensu Nematoda)</td>
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<td>GO:3: reproduction</td>
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<td>GO:44249: cellular biosynthesis</td>
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</table>
Conclusions

- Common effect on expression of metabolic genes (in the mitochondria)

- Toxicity through resource allocation (AKA the energy budget)

- Can use a combination of ecological models and transcript analysis to define exact link between toxicological and physiological “modes of action” for chemicals.
Science & technology objective 4

To develop a research framework for the description and interpretation of cumulative exposure and effect.

Dynamic energy budget toxicity (DEBtox) models for mixtures.

Slides from Jan Baas
**LC$_{50}$, NOEC, LOEC**

No Observed Effect (NOEC) Concentration is a result from a statistical test not an indication of no effect.

High variation in the control means: NOEC > EC$_{50}$

LC$_{50}$, NOEC, LOEC all depend on the exposure time.

If no effect is desired why not focus on real no effect??
Alternatives to single time point empirical approaches

Consider toxicity as a process in time using biological process based modeling to predict (no) effects
Biological based models

Effect depends on combination of internal concentration and hazard rate based on that internal concentration

Toxicokinetic model

Hazard model

Process model (DEBtox)
Example for dieldrin survival

Poecilia reticulata

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<th>5.6</th>
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</table>

concentration *dieldrin* (µg l⁻¹)
Example for dieldrin survival

Poecilia reticulata

Elimination rate $0.73 \text{ d}^{-1}$
Blank hazard rate $0.0064 \text{ d}^{-1}$
NEC $2.8 (2.1-3.1) \text{ µg/L}$
Killing rate $0.031 \text{ L/(µg d)}$
Applying process models for mixtures

Requirements for experiments for process modelling:

- Design that allows measurements at intermediate times
- Design experimental setup that can find interactions

- Experiment with *Folsomia candida* held on compacted soil.
- Exposure to 6 binary mixtures of Cd, Cu, Zn and Pb
- 6 concentrations of each metal (36 combinations) in a factorial design
### Results using single time point models

Results for the mixture of Copper and Cadmium

<table>
<thead>
<tr>
<th>Time point (days)</th>
<th>CA</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 3</td>
<td>No interaction</td>
<td>Synergism</td>
</tr>
<tr>
<td>4 – 5</td>
<td>Synergism</td>
<td>Synergism</td>
</tr>
<tr>
<td>6</td>
<td>Synergism</td>
<td>DL Synergism</td>
</tr>
<tr>
<td>7 – 9</td>
<td>DL Synergism</td>
<td>DL Synergism</td>
</tr>
<tr>
<td>10 – 15</td>
<td>No interaction</td>
<td>DL Synergism</td>
</tr>
<tr>
<td>16</td>
<td>DR Interaction</td>
<td>DL Synergism</td>
</tr>
<tr>
<td>17</td>
<td>No interaction</td>
<td>DR Synergism</td>
</tr>
<tr>
<td>18 – 21</td>
<td>Syn ld Antag hd</td>
<td>DL Synergism</td>
</tr>
</tbody>
</table>

Comparison to Concentration Addition/Independent Action using analysis model of Jonker et al ET&C 2005
Survival for the Cu/Cd mixture

Actually no interaction in this mixture.

Apparent interactions due to different kinetics
DEB for complex mixture

Developing relations between parameters

Narcotics hazard model predicts relation between $K_{ow}$ and DEBtox parameters:

\[
\begin{align*}
\log \text{NEC} & = -\log K_{ow} + \text{constant} \\
\log b \text{ (kill rate)} & = +\log K_{ow} + \text{constant} \\
\log \text{Ke (elimination rate)} & = -0.5 \log K_{ow} + \text{constant}
\end{align*}
\]

All this seems to check out pretty much OK

Based on Pymephalus promelas data from Center for Lake Superior Environmental Studies 1985–1990
Experimental validation

- Experiment with fully grown *Folsomia candida*
- Test with phenanthrene only
- Test with mixture of phenanthrene, fluoranthene and pyrene
- Measured survival over 28 days including intermediate times

Predicted mixture effect, based on measurements for phenanthrene only (line) and use of DEBtox parameter QSARs to predict measured mixture effect (x).
Conclusions DEBtox models

- Process based models such as DEBtox can describe the progression of toxicity in time
- DEBtox can be applied to mixtures and can explain why in some cases interactions are seen for particular timepoints
- For narcotic compounds they can be combined with QSAR to allow predictions of the long-term effects of complex mixtures.
Communicating Chemical Risks
The role of risk perception and communication for characterizing and managing cumulative stresses

Meeting the Challenge of Communicating Chemical Risks
2nd NoMiracle Open Workshop, Stuttgart, April 2007

The workshop invited an audience of stakeholders from companies, NGOs, regulators, RE regulatory, academic, government, and private sector disciplines and projects similar to its topics. Participants from these diverse groups learned about the various ways in which the communication of chemical risks can be improved. Discussions took place on how to communicate risks and uncertainties in a clear and effective manner. The workshop aimed to address the need for improving risk communication and decision-making in a complex world.

In this issue:
1. Communicating Chemical Risks
2. NoMiracle Second Open Workshop on "Communicating Chemical Risks"
3. REI Governance Framework
4. Lessons for Good Risk Communication
5. Validation and Meaning of Input Data for Multiples Risks and Uncertainties
6. Insights from NoMiracle Work
7. Use and Value of Risk Information - The Significance of Information Dissemination in Integrated Risk Assessment and Management
8. Past Decisions: Addressing the Challenge
9. Future Directions
Open workshops and conferences

- Workshop: ”Integrated Assessment of Environmental and Human Health”, Frankfurt: Cambridge, September 2008

- 5th NoMiracle Workshop: ”Cumulative Risk Assessment”, the Netherlands, spring 2009

- Final NoMiracle Workshop: September 2009, Aarhus, Denmark
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