In the near future, nature reserves in the Netherlands will total more than a half million hectares. The government is converting farmland and river forelands into natural habitat. This sounds like music to conservationists’ ears, but there is a catch. New nature reserves are burdened with a hidden environmental legacy. “We often find heavy metals, pesticides and veterinary medicines in former agricultural areas,” says Jack Faber, project leader at the research institute Alterra, part of Wageningen UR. “In river forelands, we find PAHs, heavy metals, PCBs, and a list that reads like a chemical company’s catalogue. A tremendous number of contaminants are circulating in the environment, and more are being introduced every day.”

In addition, not much is known about the risk these components pose to the environment, not to mention whether the risks are great enough to require measures. As a result, managers of new nature reserves do not know when they should take measures. Faber and his co-workers have developed a new model that should help these managers establish priorities.
Harmful effects
The research is part of NoMiracle, an integrated EU project involving 38 European partners. NoMiracle stands for ‘Novel Methods for Integrated Risk Assessment of Cumulative stressors in Europe’. All participating projects in NoMiracle revolve around the same problem, which toxicologists, ecologists and public health experts in practice run into time and again: how dangerous are harmful chemicals in the environment in reality? Toxicology often does not know the answer. “Toxicologists test different doses of a single chemical on a laboratory animal, often a mouse or a Japanese quail,” says Faber. “Then they study the effects. But in nature, you are dealing with other organisms. We don’t know whether, for example, badgers and godwits react the same as laboratory animals under controlled conditions. We can’t experimentally expose rare species. They are protected.” “The gap in knowledge represents an international problem in nature conservation,” says Faber. In his project, Faber is researching why one species reacts more severely to a contaminant than another species. “It’s not so much the laboratory determined toxicological sensitivity that predicts the sensitivity of an individual species, but rather the overall ecological vulnerability,” says Faber. “Once you know which frog species is the most vulnerable, then you also know which frog species you should protect first.”

Food choice
Faber has therefore developed a model that says something about the vulnerability of species to harmful chemicals. The project leader and his team have built a database based on the work of biologists who have recorded data on species in the wild. “We restricted ourselves to six common chemicals.” The analysis published in the report Ecological Vulnerability in Wildlife shows, for example, that the common tern (front page) is relatively vulnerable to cadmium. This is because this species sits high up in the food chain, has a long life and produces relatively few young. Consequently, cadmium, a poisonous metal that accumulates easily in aquatic food chains, has the opportunity to accumulate in the common tern, affecting the bird’s reproduction later in life. Other species that consume lots of energy, and therefore require lots of food, are also vulnerable to cadmium, according to the model.

Stress factors
Faber and his colleagues are not the only researchers at Wageningen UR participating in the European megaproject NoMiracle. Jan Kammenga and his colleagues at Wageningen University’s Laboratory of Nematology are working on research that should bring ecology and toxicology closer together. Kammenga studies the effects of combinations of stress factors in nematodes at the genetic level. In Kammenga’s experimental setup, a contaminant is considered to be one of these stress factors. “We would like to know if harmful chemicals are always harmful to the same degree,” he says. “Whether a compound is more or less harmful to soil life can depend on the humidity or the temperature. That’s why we expose nematodes to a contaminant, but at the same time other stress factors as well. We then measure how the genes react using DNA chips.” Wageningen nematologists are quickly closing gaps in basic science with this research. “Conditions are continually changing in the environment. We often don’t know what effect varying temperatures and humidities have on organisms at a molecular level. Only when we know more, can we say something about the interaction with harmful compounds.”

Health risks
“NoMiracle is intended to translate toxicological knowledge into the complex reality. Not only that it is important to protect nature, but also to gain a better insight into the health risks people are exposed to”, says Hans Løkke, coordinator of NoMiracle. There is a large amount of uncertainty in current models. Not only is little known about the role of ecology and the interaction with other stressors, but the knowledge about the toxicology of chemical mixtures is also in its infancy. Løkke hopes that these knowledge gaps will be filled by NoMiracle within the five year the project is running. “The NoMiracle approach is working,” he says. This sort of complex questions can only be solved by large-scale efforts.

Information:
Dr Jack Faber, jack.faber@wur.nl
Dr Jan Kammenga, jan.kammenga@wur.nl
3. Exposure & Fate Assessment – Man and Environment, April 1-2, 2008

The 3rd Open NoMiracle workshop, entitled “Exposure & fate Assessment – Man and Environment”, will be held in Leipzig on April 1-2, 2008. Risk assessment depends critically on how to assess the effect-relevant exposure of contaminants. In the EU project NOMIRACLE, novel methods have been developed to characterize the matrix-specific concentration and bioavailability of contaminants, to predict compound partitioning and degradation under natural conditions, and to simulate the multimedia fate of contaminants with explicit consideration of spatial and temporal variation. The new experimental and theoretical methods are expected to improve exposure assessment and through that risk assessment significantly. The workshop will serve as platform to inform industry, governmental authorities and academia about the novel methods and procedures developed, and about their scope in the context of EU-wide regulations concerning the human and environmental hazard and risk associated with chemical substances in the environment such as REACH, the Water Framework Directive, and Directives concerning biocides and pesticides.

4. Integrated Assessment of Environmental and Human Health

(Planned September/October 2008)

The 4th Open Workshop, entitled “Integrated Assessment of Environmental and Human Health”, will be held in Prague/October 2008. The workshop will address two major issues, namely new developments in methods for assessing the effect of mixtures of chemicals and of combinations of chemicals and natural stressors, and how to achieve more effective integration of the risk analysis of environmental and human health effects. The topics of the workshop will include agents (chemical mixtures, multiple sources, chemicals and other agents), time scales (also intergenerational) and receptors (human and non-human, age groups), endpoints and consequences, and stages of activity (research or testing – assessment – management – monitoring). The topics include investigations on the uptake, elimination and metabolism kinetics of chemicals in test organisms, upon exposure in soil or water, and methods for pharmacokinetics analysis of chemical mixtures. The area of uncertainty analyses will be included, helping elucidate the relative share of the human and non-human components in the overall uncertainty, and the options for integration across receptors and sectors. Further, the development of new methods for comparative risk assessment by integration of mixture toxicity and multiple stressors (i.e., comparison of toxic stress and climate) will be addressed in the workshop, as well as pre-normative research on improving the current state of measurements and testing for testing of combined stressors, and for indicators for monitoring of populations of humans (indoor and outdoor) and species in the environment.

5. Receptor-oriented approaches in assessing cumulative exposure of humans and wildlife

(Planned spring 2009)

The 5th Open Workshop, entitled “Receptor-oriented approaches in assessing cumulative exposure of humans and wildlife”, will be held in the Netherlands in the spring of 2009.

The final main results from NoMiracle will be presented during a workshop held in September 2009 in Aarhus, Denmark.
Third year activities of NoMiracle

By Hans Løkke

During the third year of the NoMiracle Project the work on establishing the data background for scenario selection and on developing methods for risk scenario selection has been accomplished according to the work plan. A new procedure for identification of risk hot spots has been developed. It contributes to a clear and measurable determination of the appropriate level of precaution based on the uncertainty level on one side and the seriousness of the harmful effects on the other side. The new approach is also able to elucidate the level of uncertainty that takes into account the entire chain of assumptions governing risk assessment. This new NoMiracle methodology is general and thus applicable in many areas of regulation and policy, where identification of realistic worst case conditions for potential risk is needed. It will be especially valuable in complex problems where determining uncertainty requires more than just a variability check of parameter values. For the long term, the methods developed will be useful in the search for data gaps in understanding of risk levels and thus useful in design of future research and monitoring activities.

Exposure assessment

Major achievements were attained with regard to both algorithms and models addressing molecular-level processes, and regional-scale multimedia fate predictions. The work has been continued on processes and mechanisms that determine the effective exposure of chemical substances under realistic conditions in the environment. The focus has been on polar and bioactive compounds, which form a great challenge because of their complex potential for intermolecular interaction with environmental matrices.

There are now preliminary novel models and methods available

- to address partitioning into soil organic and biological matter in terms of fundamental interaction forces,
- to characterize well-defined availability aspects of the compound concentrations in different environmental media,
- to predict biodegradability patterns and simulate metabolic pathways, and
- to consider spatial variation for multimedia fate predictions.

In this way, the uncertainty of exposure assessment of contaminants can be reduced already, taking into account the partly preliminary status of the newly developed techniques.

Effects assessment

An extensive amount of data has been produced on single chemical and joint effects required to define a basis for estimating uncertainty and variability associated with predictions of the combined effects of chemicals. The measurement of a series of parameters in test organisms/cell systems ranging from bacteria to higher vertebrates enables the identification of dysfunction at all levels of organisation after multiple chemical exposure.

It has been shown that in environmental species, responses to combinations of natural stressors and chemicals can be described by models used for chemical mixtures if experiments are designed appropriately. Since this is a new research direction in environmental science it has taken considerable effort to develop such appropriate and environmentally relevant experimental designs.
The ongoing research on toxicokinetic modelling is developing new approaches, including time series assessment of uptake and effect in different species using resource allocation concepts. An integrated effort is made to elucidate molecular mechanisms of mixture toxicity using various transcriptomic platforms, protein analysis methods and nuclear magnetic spectrometry and gas chromatography-based metabolomics. This approach offers the potential to detect effects occurring at the biochemical level. Such effects may be detrimental to the health of an organism without manifesting obvious outward signs.

**Risk assessment**

Based on the results from testing of selected mixtures of chemicals with the array of NoMiracle species and test systems, modelling has shown that the Independent Action model is frequently not the most suitable model to describe the mixture toxicity of chemicals with different modes of action. In these cases, NoMiracle has introduced the dynamic energy budget (DEB) model as a better tool to describe mixture toxicity and at the same time as a tool to integrate toxicological, toxicodynamic and molecular data. A very elaborate database on single component survival data was used to show that it is possible to estimate toxicity measured survival (beams) and DEBtox modelled survival (net like structure) of Folsomia Candida on compacted soil for a mixture of copper and cadmium, measured in a full factorial design at day 2, 4, 8, 12, 16 and 20. No mixture interaction was shown in contrast to inconsistent results at fixed time points as found with existing models.
parameters from the physical and chemical properties of narcotic compounds. The derived model can predict the effect of a mixture of any number of components, for instance PAHs or chlorinated benzenes, on survival for any point in time, when limited experimental data on the components in the mixture are available. With this approach it is possible to greatly diminish the experimental effort that is needed to describe mixture effects. In addition, a start was made with the experimental setup that is needed for a model to describe endpoints other than survival for binary mixtures. This modelling work aims to develop an easy interpretation of a safe mixture concentration in the form of one parameter: the No Effect Concentration for a mixture. In the short term the models will give a better understanding of the effects of mixtures in terms of underlying biological mechanisms. In the long(er) term the research will help in the understanding of the effects of mixtures in the field situation and contribute to optimising laboratory tests.

The work on individual-based and spatially explicit risk assessment of cumulative stressors has been presented at an internal workshop, and will comprise several initial experiments regarding an algorithm for human and wildlife mobility. The task is of high relevance for the integrated consideration of ecological and human exposure models within NoMiracle. While work is still ongoing, the results to date may have strong implications for the future structure of ecological and human random walk models.

The work dealing with uncertainty and ambiguity in risk management was initiated by successfully completing the survey of risk experts across Europe and beyond. The survey, which itself employed novel representational and data-collecting methods using the internet, achieved such high response quality that it was possible to produce a peer reviewed published report, a scientific contribution and several shorter contributions as well as oral presentations.

The proceedings from the Second Open Workshop at Stuttgart (“Communicating Chemical Risks: The role of risk perception and communication for characterising and managing cumulative stressors”, April 2007) give an overview of the area. The workshop assembled experts from NoMiracle, industry, regulation and from projects dealing with related themes to discuss key issues concerning risk communication.

Activities in the coming two years

The work on new methods for assessing the exposure of chemicals in matrices at different scales will continue with focus on polar and multifunctional compounds, which form a great challenge because of their complex potential for intermolecular interaction with environmental matrices. The very promising results on mixture toxicity and modelling will continue with more elaborate experiments. More work will be dedicated to develop more efficient protocols for testing mixtures with the possibility to reduce testing needs and use of animals for experimental purposes. Based on the experiences of the first years, 2 scenarios are under preparation for testing of models and methods developed in the project. The topics are

- Cumulative assessment of agricultural pesticide application
- Chemical driven effects on children in urban areas

About NoMiracle

Thirty-eight institutions from 17 countries involving 200 persons work together for 5 years (2004-2009) on the development of better methods to analyse, characterise and quantify the combined risks to health or the environment from multiple stressors. Examples of such cumulative stressors are mixtures of chemicals alone or in combination with biological or physical environmental factors such as pathogens and climatic conditions.
NoMiracle’s main science & technology objectives are:

1. To develop new methods for assessing the cumulative risks from combined exposures to several stressors including mixtures of chemical and physical/biological agents
2. To achieve more effective integration of the risk analysis of environmental and human health effects
3. To improve our understanding of complex exposure situations and develop adequate tools for exposure assessment
4. To develop a research framework for the description and interpretation of cumulative exposure and effect
5. To quantify, characterise and reduce uncertainty in current risk assessment methodologies, e.g. by improvement of the scientific basis for setting 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

NoMiracle Scientific Articles published the first three years of NoMiracle*

Morten Strandberg, NoMiracle Secretariat


* The list will soon be available on the NoMiracle web page (http://nomiracle.jrc.it)


NoMiracle Newsletter No. 10

NOvel Methods for Integrated Risk Assessment of Cumulative stressors in Europe

NoMiracle co-ordination

Visit NoMiracle and subscribe to the Newsletter at: http://nomiracle.jrc.it

For further information contact

NoMiracle Secretariat
E-mail: nomiracle@dmu.dk

• Project co-ordinator and Editor responsible under the press law*:
  Dr. Hans Løkke
  National Environmental Research Institute,
  University of Aarhus
  Vejlsevej 25, P.O. Box 314,
  DK-8600 Silkeborg, Denmark
  Phone +45 8920 1482
  Fax +45 8920 1414
  E-mail: hlo@dmu.dk

• Databases and selection of scenarios:
  Dr. Hanne Bach
  National Environmental Research Institute,
  University of Aarhus, Denmark
  E-mail: hba@dmu.dk

• Exposure assessment:
  Professor Gerrit Schüürmann
  UFZ, Umweltforschungszentrum Leipzig,
  Germany
  E-mail: gerrit.schuermann@ufz.de

• Effects assessment:
  Dr. Dave Spurgeon
  NERC, Centre for Ecology and Hydrology,
  United Kingdom
  E-mail: dasp@ceh.ac.uk

• Risk Assessment:
  Dr. Ad Ragas
  Radboud Universiteit Nijmegen,
  The Netherlands.
  E-mail: A.Ragas@science.ru.nl

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EC Scientific Officer for the project:
Dr. Georges Deschamps

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