Novel Methods for Integrated Risk Assessment of Cumulative Stressors in the Environment

NOMIRACLE

Integrated Project to Call FP6-2003-Global-2

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Topic VII.1.1.a ('Development of risk assessment methodologies')

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Science & technology objectives

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5. To quantify, characterise and reduce uncertainty in current risk assessment methodologies, e.g. by improvement of the scientific basis for setting safety factors
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7. To improve the provisions for the application of the precautionary principle and to promote its operational integration with evidence-based assessment methodologies

State of the art

The assessment of risks from chemicals to humans and the environment in the European Union has resulted in a number of comprehensive regulatory frameworks for various classes of compounds. For pesticides the European Community has developed Directive 91/414/EEC (EC 1991), defining strict rules for authorising the use and application. The Directive requires extensive risk assessments for effects on health and the environment to be carried out, before a product can be placed on the market and used. For biocides, Directive 98/8/EC (EC 1998) on the placing on the market of biocidal products was adopted in 1998 where the regulation for pesticides served as a model; for pharmaceuticals a Directive is under development. In parallel, a new Directive is being developed for industrial and other new and existing chemicals. The proposed new EU chemicals strategy and the REACH (Registration, Evaluation and Authorization of CHemicals) system will unify and amend these pieces of legislation (CEC 2001, 2003a).The Technical Guidance Documents (TGD) for risk assessment in these contexts have been recently updated (EC, 2003) and represent a pragmatic support tool for regulatory purposes. Recently, the European Environment and Health Strategy (SCALE) addressed the shortcomings of the current methods (CEC 2003a).

Many acute environment and health related problems have been solved, but much remains to be done, in particular with respect to the health implication of chronic exposures, as reported by organisations such as the European Environmental Agency, WHO and a number of national organisations. They indicate that the interaction between environment and health is far more complex than is commonly understood. In particular, little attention has been paid to the interaction of different pollutants in the human body as well as in the environment. Even low level exposure over a period of time to a complex cocktail of pollutants in air, water, food and consumer products is likely to contribute significantly to the health status of European citizens. It is estimated that around 25-33% of the burden of disease in industrialised countries can be attributed to environmental factors, with the bulk of this affecting children and vulnerable groups (Smith et al. 1999). The majority of Europeans also perceives the magnitude of the problem: in a recent survey, some 89% are worried about the potential impact of the environment on their health (Eurobarometer 2002). Furthermore, new technologies, changing lifestyles, work and life patterns, present new and sometimes unexpected impacts on the environment and its influence on health. Within this project we will improve both human and environmental risk assessment procedures by addressing a series of major shortcomings that exist within the current approaches, namely that:

i) they are based on direct effects of single compounds or products
ii) they apply uncertainty factors which are not strictly based on scientific principles
iii) they do not account for multiple stressors and indirect effects in a dynamic and heterogeneous environment
iv) they typically do not account for cumulative (integrated over time, space, substances) effects, and
v) they do not allow for site specific and other spatially detailed evaluations

Although it is generally acknowledged that chemical, biological, radiological, and other physical and even psychological stressors can cause a variety of human health or ecological health effects, assessing the risks associated with them is considerably more complex methodologically and computationally than current risk assessment practices. Given these lacunas there is an urgent need for ”cumulative risk assessment” which can be defined as “an analysis, characterisation, and possible quantification of the combined risks to health or the environment from multiple agents or stressors” (US-EPA 2003). Development of a framework for such complex risk assessments will greatly improve understanding of the effects of cumulative exposures occurring under the variety of field conditions within Europe and will provide a better scientific basis for forecasting risks and associated uncertainties. The understanding of the complexity of cumulative risks is a prerequisite for development of more efficient guidelines to provide data for future regulation of chemicals, on one hand taking into account the proportionality of different risks, and on the other hand meet the need for improving environment and human health.

In the integration of human and environmental risk assessment, a powerful and promising strategy is to follow the line of a bioinformatics approach to ecological systems, where the high degree of internal complexity is accepted as an inherent property, and consequently the state of the system must be analysed in terms of possibly several thousand measurable variables. The current project advocates such an approach based on a robust and computational reliable framework that answers the call for cumulative risk assessment and for reducing uncertainty. To formulate this framework, it is essential that the underlying processes and mechanisms are understood, as it is only by knowledge of how chemicals interact with the abiotic environment and within organisms that models to describe such effects can be developed and applied. By adopting this approach, NOMIRACLE will place Europe as the world leader in considering the complexity of interactions between populations inhabiting the real world.

In the following, the state of the art concerning each science & technology objective is presented together with the expected improvements provided by the NOMIRACLE project.

Ad 1 To develop new methods for assessing the cumulative risks from combined exposures to several stressors including mixtures of chemical and physical/biological agents

State of the art:
The shift from a single-compound to a cumulative approach has radical consequences for the assessment of exposure, effects and risks. In exposure assessment, current procedures tend to focus on the fate of chemicals in relatively homogeneous environments (e.g., in EUSES) and simple rules are applied to estimate the amount of chemicals that reaches the receptor (McKone & Ryan 1989). However, in a truly cumulative approach it is realised that human or ecological receptors are not exposed to individual substances in a relatively homogeneous environment, but to toxic mixtures and other natural stress factors (e.g., severe drought or extreme temperatures) in a heterogeneous environment. These factors have not been accounted for in current risk assessment procedures (Heugens *et al*. 2001). Also, space and time play a crucial role because the spatial and temporal patterns of the stressors and the receptors determine the ultimate effect.

In effect assessment, a substantial effort has been made to label the effect of mixtures as synergistic, antagonistic, or additive. Although these concepts can be communicated relatively easily, they have contributed fairly little to our understanding of joint toxic action. Part of the difficulty is that the underlying toxicological concepts are weakly defined and that the use of simplified mathematical characterisations of synergism and antagonism reveal either interaction or no-interaction and carry large uncertainties.

Currently, the division of the exposure estimate with an effect measure, as a proxy for dose-response relationship (e.g. PEC/PNEC-ratio), results in a characterisation of risk (Van Leeuwen 1995). This procedure can only be followed in cumulative risk assessment when the effects of the stressors can be expressed in comparable endpoints, either in biological terms or in terms of valuation.

This project adopts a unique spatial- and receptor-oriented approach for assessing the integrated exposure to multiple stressors. Using promising research directions, such as toxicokinetic and toxicogenomic studies, we will develop biologically based models of joint toxicity to replace current interaction labels for mixture risk assessment procedures (Groten *et al*. 2001, Hertzberg & MacDonell 2002). By doing so it will be possible to assess the overall effect of combined exposure to mixtures and (a) biotic stressors, and subsequently to develop integrated assessment methods, such as advocated by Van Straalen (2003). Mixture toxicity studies in combination with biotic and abiotic stressors will be based on a statistically robust framework for assessing combined effects which was developed, e.g. within the EU funded MIXTOX project ENV4-CT97-0507 (Jonker *et al*. in press a,b,c).

Expected Improvements:

- Methods for assessing potential effects and for characterising cumulative risk will be developed taking into account the real characteristics of potentially exposed human and ecological receptors (sensitivity, vulnerability, value as natural resource, realistic probability of exposure, etc).
- A unique aspect of NOMIRACLE is the conjunction of toxicity studies with mechanistic research at the chemical, biochemical, and genomic level, which will give understanding of the underlying mechanisms of combinatorial effects as, e.g., advocated by Van Straalen (2003).
- Development of integrative endpoints that can be used for characterisation of cumulative risks.
- Novel spatial- and receptor-oriented approaches for assessing the integrated exposure to multiple stressors.

Ad 2 To achieve more effective integration of the risk analysis of environmental and human health effects

State of the art:
A key dimension in integration of risk assessment is that between human and non-human receptors (WHO 2001). This is a central element in the evolving EU Environmental Health Strategy focused on chemicals (CEC 2003); it is also part of the new EU Chemicals Policy and the REACH system (CEC 2003). The development of science toward cross-cutting theories and methods has aided such integration e.g. through molecular biology and genetics. In environmental science, a reflection of this strive is the ecosystem health concept (e.g. Rapport et al. 1998). In exposure assessment better interaction of chemical fate data and models for the various receptors is needed. In toxicological risk assessment the traditional area of integration is extrapolation from animal models to humans. A key here is comparative tissue dosimetry utilising biokinetic and toxicodynamic models and data (Welsch et al. 1995, Anderson & Dennison 2001, Walton et al. 2001). In ecotoxicology the focus

has been on species sensitivity distributions (Forbes et al. 2001, Pennington 2003) but human-nonhuman integration will require also other inputs from comparative and evolutionary toxicology. Relatively little research has been made in human-nonhuman integration for substances with specific sites (Kalberlah et al. 2002) or modes of action (Barton & Clewell 2000, Bogdanffy et al. 2001), except for drugs. Mixture effects complicate this; options to address them include modelling of interactions (Frederick et al 2000) and integrative biomarkers (e.g. Gibson & Starr 1988). Some of the limitations to integration of human and nonhuman assessment are fundamental, some technical; some are related to differing ecology and exposure, some to physiology and metabolism (e.g. Kalberlah et al 2002). It is often stressed that human health unlike ecological assessments target individual level risks. Regardless of differences in receptor significance or in exposure and effects mechanisms, advanced methods in the human health area e.g. to distinguish the contribution of risk factors in multi-stressor settings offer tools also for ecological risk assessment; and vice versa. A better understanding of the shared and specific biological and other processes in the various receptors is highly needed, and will be developed in the NOMIRACLE project at various levels from molecular to ecosystems.

Expected Improvements:

- Statements about the validity of the systems for toxicity testing in human toxicology and ecotoxicology especially based on advances in the understanding of molecular and cellular mechanisms and biomarkers of toxicity, providing a better transferability between ecotoxicology and human toxicology
- Since this project is the first one that investigates ecotoxicological and human toxicological test principles simultaneously, a comparison will result in a better understanding of the outputs, which is expected to help interpret the results and transferability between both.
- Direct comparability between effects of chemicals (under different conditions) on the environment and the human health.
- The uncertainty analyses will help elucidate the relative share of the human and nonhuman components in overall uncertainty, and the options for integration across receptors and sectors

Ad 3 To improve our understanding of complex exposure situations and develop adequate tools for sound exposure assessment

State of the art:
Within the current regulatory framework of risk assessment (EC TGD 2003), the regional and continental exposure assessment of chemical substances is usually based on predictions from generic multimedia fate models such as EUSES (EC 1996, den Hollander et al. 2003). Whilst multimedia models are suitable instruments for exposure assessment, their application is currently hampered by serious shortcomings, particularly as regards modern bioactive agents such as biocides, pesticides and pharmaceuticals. Firstly, the release patterns and their variations in time and space depending on the uses of these agents are not well taken into account. Secondly, the model predictions are based on phase partitioning algorithms that work well only for non-polar and hydrophobic chemicals. Thirdly, the models lack a functionality to relate total compound concentrations to the matrix-specific effective concentrations that govern the resultant risk potential, as has been emphasised in recent publications (ECETOC 2002 and 2003). Quantifying available exposure is also a problem for soil-, sediment- and cell-based laboratory systems, and this problem affects exposure-concentration curves and the determination of endpoints for environmental and human toxicology accordingly. Fourthly, generic multimedia models do not account for indoor exposure that is of primary importance for humans, and do not address emissions from consumer products and confounding factors such as human time-activity patterns (e.g. ECETOC 2001). Fiftly, the

exposure predictions are frequently highly uncertain due to the paucity of reliable methods of predicting environmental degradation rates quantitatively (Sabljic & Peijnenburg 2001), and they usually do not address the fate of metabolites formed under natural conditions (Fenner et al. 2002). Sixthly, the models currently used to support risk assessment in the regulatory context are generic in nature and have not been parameterised to account properly for spatial and temporal variation across the European continent (Huijbregts et al. 2003).

Expected Improvements:

- Fate and exposure models that account properly for the compound-matrix interaction and resultant phase partitioning of modern bioactive agents
- Methodologies for quantifying the matrix-specific available exposure of xenobiotics that are relevant for toxic and ecotoxic effects, covering both the field and laboratory biotest systems
- Tools for improved prediction of degradation rates and pathways of organic chemicals
- Non-generic models that can be tailored to the complex exposure situations encountered in the European Union
- Indoor exposure patterns and assessment methods for homes, kindergartens and public building across Europe

Ad 4 To develop a research framework for the description and interpretation of combined exposure effects that leads to the identification of biomarkers of cumulative exposure and effect

State of the art:
It has been suggested that current reference models for mixture toxicity (concentration addition, independent action) could incorrectly predict combined effects in at least 25% of cases (Hertzberg and McDonell, 2002). Additionally, while the models are only descriptive it is impossible to address the uncertainty in when, how and why they may fail. This represents an unacceptable level of uncertainty in our ability to conduct predictive risk assessments for chemical mixtures. To create a robust and scientifically valid approach for risk assessment of complex exposures, there is a need to go beyond descriptive approaches and analyse the mechanisms and pathways that link cumulative exposures to eventual effects (Eggen *et al*. 2003, Hertzberg and McDonell, 2002, Van Straalen, 2003. Such mechanistic understanding should also enable risk assessment to include 1) the effects of environmental stressors which interact to change an organisms sensitivity to chemical exposure and 2) the effects of chemicals on the tolerance limits of the organism to natural stressors (e.g. Holmstrup *et al*. 2004; Heugen *et al*. 2003).

Adopting this mechanistic approach will require a coalescence of state of the art methods in toxicokinetics and the molecular biosciences. NOMIRACLE will use these approaches to investigate interaction mechanisms at the physiological level. Conducting this work in diverse species will highlight species specific and common biomarkers for used in ecological monitoring of cumulative exposure and resulting effect. These will be applicable as effects based monitoring tools for direct use in cases where the current state of knowledge leads to uncertainties in risk prediction. Further, as NOMIRACLE include mammalian cells and rodents among the systems investigated these indicators could be applicable to the epidemiological assessment of human population health.

Expected Improvements:

- Development of a biological-systems orientated approach to understanding the occurrence consequences of cumulative stress effects in the environment by linking molecular genetic and whole organism approaches.
- Understanding of the physiological mechanisms through which effects of combined exposures become manifest, allowing better estimates of when predictive models are reliable and when they may fail.
- Highlighting potential species specific and common biomarkers that can be used in monitoring of cumulative stress effects on environmental and human health.

Ad 5 To quantify, characterise and reduce uncertainty in current risk assessment methodologies, e.g. by improvement of the scientific basis for setting safety factors

State of the art:
In risk assessment, and particularly in cumulative risk assessment, levels of uncertainty are typically high, mainly due to the complexity of the problems involved and our limited knowledge of the underlying phenomena (Hellström 1996). This uncertainty often remains obscured by the use of arbitrary deterministic safety factors and default assumptions. The growing awareness that ignoring uncertainty can result in conservative or erroneous risk estimates (and consequently in a waste of resources) has resulted in a shift from deterministic towards probabilistic risk assessment (US-EPA 1997), also in EU e.g. for pesticides, but as yet in a rather rudimentary and non-integrated fashion. This shift requires novel concepts and techniques to characterise, quantify, reduce and deal with uncertainty in a risk management context. NOMIRACLE aims to develop PRA techniques that are scientifically sound and practicable for cumulative risk assessment.

An area of risk assessment where the role of uncertainty is particularly profound is the application of default safety factors to extrapolate laboratory toxicity date to human and ecological endpoints. The default factors currently used lack a sound scientific base and ignore uncertainty (Dourson & Stara 1983; Chapman *et al*. 1998). The processes covered by the default safety factors (e.g., inter-individual and inter-species differences in toxic effects) are rapidly being unraveled by molecular and genetic studies in (eco)toxicology (Renwick *et al.* 2000, Wild *et al*. 2002, Clewell *et al*. 2002, Snell *et al*. 2003). It is becoming increasingly clear that toxicological processes are governed by a limited number of mechanistic descriptors such as molecular characteristics, genetic predisposition and the toxic mode of action. The NOMIRACLE project aims to incorporate these new scientific insights to derive scientifically sound safety factors for human and ecological risk assessment that explicitly account for the uncertainties involved in the extrapolation process.

Expected improvement:

- Development of new concepts and techniques to characterise, quantify, reduce and deal with uncertainty that are scientifically sound and practicable for cumulative risk assessment
- Improved safety factors for human and ecological risk assessment based on new scientific insights in the underlying toxicological processes that explicitly account for uncertainty

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

State of the art:
One of the main problems for the site-specific application of predictive models for exposure assessment is the variability of environmental and land use characteristics. The implementation of a variety of models for exposure and effect prediction in conjunction with Geographical Information

Systems (GIS) would allow to handle spatial and temporal variability and to make reliable predictions at different scales. Most of the model implementation to date has been done at a regional scale using simple index approaches or models that neglect site-specific factors and their variability. Within the project, scenarios and models for release, fate and exposure assessment at different scales will be adapted and linked. The NOMIRACLE project will provide guidance to help identify what resolution and data are appropriate and when they are needed. The objective is to refine and integrate the techniques for more realistic PEC calculations for different European regions and land uses (FOCUS, 2002).
As for effect assessment, a PNEC is calculated from data obtained on simplified trophic chains (e.g. algae, *Daphnia* and fish) that do not represent natural biological communities. This approach does not fulfil the requirements of the Water Framework Directive (WFD) for an assessment of the bio-ecological quality of water bodies. A procedure capable to take into account ecological differences in aquatic and terrestrial ecosystems could be based on the Species Sensitivity Distribution (SSD) concept (Posthuma et al., 2002) combining this with mechanisms and ecogeography for spatial resolution and realism in assessment. Moreover, the impact on natural populations and communities should take into account resilience and recovery capability but also the possibility for their breakdown or decline (e.g. lagged).
Finally, in order to provide information suitable to assess the social and economic impacts of multiple environmental stresses, there is the need to describe (and, as far as possible, to quantify) the relevance and value of the potentially endangered system (strategic natural resources, protected areas, etc.)

Expected Improvements:

- The methods developed for assessing exposure and for characterising risk will be integrated in a comprehensive methodology with the development of suitable models and software for assessing location-specific risk, for integrating it into a GIS and for producing (eco)toxicological risk maps.

- The methodology will allow the production of maps of predicted exposures (PECs) and estimates of other validated metrics better reflecting actual exposure, of ecosystem characteristics and vulnerability and of (eco)toxicological risk at different scales (from the local scale, i.e. specific terrestrial and aquatic ecosystems, to the regional scale, i.e. different typical Ecoregions). The method should take into account different European environmental and land use characteristics and, therefore, should be valid across the European Union.

Ad 7 To improve the provisions for the application of the precautionary principle and to promote its operational integration with evidence-based assessment methodologies

State of the art:
The debate on how to evaluate and manage risks focuses on three major strategies (Stirling 1999): (a) evidence-based approaches, including numerical thresholds (e.g. NOEL), (b) reduction activities derived from the application of the precautionary principle (e.g. ALARA, BACT, containment, or constant monitoring), and (c) standards derived from discursive processes such as roundtables, deliberative rule-making, mediation or citizen panels. This project will particularly deal with strategy b). A precautious approach to risk management is required as a paradigmatic change in responding to environmental and health risks caused by both chemicals and other stressors (Harremoes et al. 2001). With the communication on precaution in the 2000, the EU has taken the lead in precautionary approaches to risk (e.g., Tickner & Raffensberger 2001). However, it is still unclear how to implement the principle in various cases of chemicals management, and what its relationships are with evidence-based risk assessment, both current and novel. This will be a particular challenge in developing assessment approaches for multi-dimensional and uncertain risks

from multiple stressors and to multiple receptors and generally in developing more detailed and yet more inclusive responses to risk. The precautionary principle essentially involves proactive risk management based on weak evidence e.g. on dose-response-relationships and action mechanisms but strong indices on either hazard criteria or widespread exposure. The typical characteristics that trigger precautionary actions, ubiquity, persistence, bioaccumulation, irreversibility of effect and intensive psychosomatic impacts (Renn and Klinke 2002), have not been systematically assessed or integrated in a predictable and consistent framework of risk management. Applying the principle across-the-board implies the danger of impeding necessary innovations since there is always a chance for unforeseen negative impacts. Suggestions for making prudent use of the precautionary principle include investigating the magnitudes and qualities of risks and associating uncertainties (Finkel 1995) and exploring risk reduction opportunities and their consequences. A precautionary approach also allows for the inclusion of social, psychological and cultural aspects of risk experience. If society responses to risk situations are included in the analysis, health-related, environmental and socio-cultural criteria can be combined for the risk evaluation process (Stirling 1999; Klinke and Renn 2001). This is pointed out by the analyses of the impacts of REACH (DG Enterprise 2003a,b,c; JRC 2003a,b; RPA 2003) but needs to be studied for specific classes of chemicals as well (e.g. Römbke et al. 2001).

Expected improvements:

- The project will improve the knowledge base and methodologies for efficient implementation of the precautionary principle in managing risks from chemicals and other stressors through multi-disciplinary studies of the key cognitive, knowledge-related and social issues in risk assessment.

- These studies will elucidate ways to integrate the precautionary principle with detailed scientific risk assessments, depending on the decision situation (e.g. the chemical product, receptor and region). The work will focus on the use of scientific information in integrated assessment to provide policy-relevant advice and on related processes of inference and deliberation.

- This R&D is expected to have significant value for the development and implementation of integrated risk assessment and for risk management, be it predominantly science-based or precautionary, in a variety of contexts, primarily in the project domains but also more generally.

- The R&D in this area will, by elucidating risk views and knowledge and inference in assessment, also serve to integrate the project.

B.2 Relevance to the objectives of the Sub-Priority "Global Change and Ecosystems"

The programme of activity offered by the Sub-Priority "Global Change and Ecosystems" will strengthen the necessary scientific knowledge for the future orientation of the ST strategy and the 6th Environmental Action programme; it will also provide the socio-economic tools and assessments and the overall management practises. Furthermore it will ensure their implementation at the enlarged EU level and, when relevant, at the world level. Risk assessment of chemicals is a central issue within this framework. Despite the implementation of a series of measures, chemicals still cause pressure on natural environmental resources and environmental health. Further, chemicals are a major factor in a general disaffection with technology and science that potentially threatens economic and social development in both the Member and Accession Countries, and at the world level. The NOMIRACLE Consortium will conduct a comprehensive and coherent research programme providing the scientific basis for a coming shift in paradigm for risk assessment of

chemicals taking into account realistic exposure and the cumulative risk following exposure to several stressors.

Contribution to the general objectives of area VII "Complementary research"
NOMIRACLE will focus on the development of advanced methodologies for risk assessment of chemicals aiming at integration of methods for assessment of environmental and human health. The project will develop new tools for risk assessment aiming at a general improvement of the environmental quality in Europe. A part of the activities will be pre-normative research on improving the current state of measurements and testing, e.g. for exposure assessment, for testing of combined stressors, and for indicators for monitoring of populations of humans (indoor and outdoor) and species in the environment.

Contribution to the topic VII.1 "Development of advanced methodologies for risk assessment"
NOMIRACLE will contribute to the overall aim to strengthen and advance risk assessment knowledge and practises with particular emphasis on cumulative risk assessment, taking into account recent trends in science. The Consortium combines 38 partners from 17 countries, including 11 EU and 4 NAS countries as well as Switzerland. The topic VII.1 will be addressed in 4 Research Pillars on respectively "Risk Scenarios", "Sound Exposure", "Effect Assessment", and "Risk Assessment". All pillars integrate human health and environmental quality, and knowledge for integrated risk assessment will effectively be transferred between the experts of the pillars. For the assessment of human health both indoor and outdoor exposure will be dealt with. The research will produce the base for establishment of an integrated risk assessment scheme based on geographic information that takes into account the diverse geographical, ecological, social and cultural differences in Europe. By integrating socio-economic studies, NOMIRACLE will analyse the use of the precautionary principle in relation to the findings, and address the question of risk communication with relation to risk assessment practise.

Contribution to topic VII.1.a "Development of risk assessment methodologies"
NOMIRACLE will focus on a conceptual change in risk assessment with emphasis of assessment of the effects of combined exposures by developing new models and test systems, integrated for environmental and human health, however based on existing methods and models whenever possible. The stressors will include chemical mixtures, pathogens, climatic stressors, and other environmental stressors such as anoxia and acidification. New developments are needed for realistic exposure and for measurement of combined exposures. The project will address the aim "to develop methodologies for assessing the risk of substances and molecules designed for provoking specific interactions with biological structures". The work will include pesticides, biocides and pharmaceuticals, and seek to provide for a future scientific basis for general harmonisation of protocols for all types of chemicals. NOMIRACLE will cover the aquatic and terrestrial environment (but not marine environments) and deal with exposure through water and air, including indoor exposure for humans. In dealing with chemical mixtures, the development of methodologies for assessing the risk of exposure to chemicals in products will have a high priority.

B.3 Potential Impact

In Europe, health effects are related to environmental factors, such as respiratory diseases, asthma and allergies that are associated with pollution. Additionally, environmental pollution continues to stress ecosystems in spite of existing regulations. Stress on human health and ecosystems is increasingly related to complex chemical mixtures from multiple, dispersed sources. NOMIRACLE will mobilise expertise and resources on a sufficient scale to give Europe a leading scientific position in relation to addressing such issues.

Working with the JRC and other Directorate Generals, NOMIRACLE will provide inputs to the European Environmental and Health Strategy (the SCALE initiative) recently launched by the

Commission. NOMIRACLE will help fill the knowledge gap on the link between environment and health, in a first phase focusing on molecules designed for provoking specific interactions with biological structures.

This IP will provide increased knowledge and improvements to existing tools in relation to the transfer of pollutants between different environmental compartments and on the impact of cumulative stressors, including combinations of chemicals as well as different physical stressors. In particular, while fitting into the sustainable development framework of European policy, the findings of NOMIRACLE will contribute to improved methodologies in support of future revisions of, for example, the Plant Protection Directive (91/414/EEC), the Biocide Directive (98/8/EEC), the directive for pharmaceuticals that is underway, as well as revisions to the Sewage sludge disposal Directive.

In direct collaboration with partners from the Commission's JRC, NOMIRACLE will help support the Commission's thematic Strategy on the Sustainable Use of Pesticides, Strategy for Soil Protection, and Strategy for Waste Reduction and Recycling, by providing novel insights related to the fate of pollutants, species exposure, and cumulative effects attributable to multiple stressors.

The NOMIRACLE Consortium is highly competent in relevant areas, counting leading scientists within human toxicology and epidemiology, aquatic and terrestrial ecotoxicology, chemistry, biochemistry, toxicogenomics, physics, mathematical modelling, geographic informatics, and socio-economic science, as well as in the broader context of life cycle assessment and risk assessment.

To ensure efficient dissemination of the results and worldwide co-ordination, a close co-operation will be established with an independent Advisory Board of Stakeholders from, for example, government, industry, and non-governmental organisations. These stakeholders are key players in the development of improving risk assessment approaches for environmental and human health protection.

The Advisory Group and all interested stakeholders will be invited to the events planned by the research Consortium such as workshops, seminars and conferences. NOMIRACLE will establish a homepage, and a dissemination plan will be prepared to commit the partners to disseminate the results of NOMIRACLE to national, local, and regional authorities, the public, industry, academia (scientific publications), as well as international and non-governmental organisations. Consortium partners within the Commission's JRC are expected to play a vital role in this context, in addition to interactively developing methods in support of EU-level policy.

NOMIRACLE will build on the current state of knowledge as obtained by preceding EU projects such as MIXTOX (ENV4-CT97-0507) and will co-ordinate the work on pharmaceuticals with the consortium ERAPharm, dedicated to the work programme of topic VII.1.1b of this FP6 subprogramme. The project will be co-ordinated with the FP6 IP ALARM (Assessing Large-scale environmental Risks with tested Methods), sharing geographical and other data, which can find use in both projects.

NOMIRACLE will enhance the scientific and applied competitiveness of all partners involved. In particular, knowledge will be transferred between research institutions and SMEs, and between experts in the domains of human health and environmental quality. Partners from different regions of Europe will be able to directly share in improving the state of the art as produced in the project. The Consortium will employ at least 40 PhD students, who will receive supervision and training from leading scientists within the scope of NOMIRACLE and from collaborations amongst the partners.

Socio-economic impact assessment

The socio-economic impact assessment issue is approached from two complementary angles:

- The impacts of the project on socio-economic processes and factors
- The studies and assessments of socio-economic impacts of chemicals policy and related policies and procedures

The socio-economic impacts of the project itself are manifold, corresponding to the variety of the functions of dissemination and exploitation (cf. the plan on these). Some impacts will be realized immediately, e.g. through the empirical and theoretical methods produced, the assessment tools developed, and the dialogues initiated about assessment policies, while other results will have a more gradual and indirect impact on society that still may be of paramount long-term importance. This is true especially of the scientific results providing improved understanding and concepts.

The better grasp of how to integrate precautionary approaches with science-based assessment and management, expected to emerge from the project e.g. through the studies in the policy aspects of risk assessment, will be important from both economic points of view, e.g. by clarifying the necessary but not excessive requirements for assessment and reasonable conditions for innovation, and from a policy and social points of view by elucidating the processes and factors in building trust in the chemical risk management area.

For the important issue of testing strategies, including the objective of reducing animal testing, the project has, generally speaking, a two-fold contribution. First, new approaches to and methods for toxicity testing are expected to be identified and developed, capturing more extensively, efficiently and accurately crucial effects of the chemicals and stressors studied when *in vivo* testing is needed, as is the case for many endpoints that are difficult to predict or ascertain based only on theory, QSARs and *in vitro* tests. Secondly, the integrative uncertainty analyses including consideration of the information needs in a risk management decision context will aid to define the levels and kinds of toxicity test data needed; some of it may e.g. be diminished when a more precautionary approach can be shown to be feasible and justified. Both within the project itself and in a broader evaluation based on its results, improved testing strategies will thus be devised that fulfil both the ethical requirements (cf. B.9) and the need for realistic information for risk assessment and management.

The regional dimension in risks and in assessing and managing them are among the key socio-economic aspects. This entails both the consideration of the natural (including human demographic) variations between regions of Europe, as well as the policy-related issues and implications of how risks from chemicals and accompanying stressors are perceived and responded to across Europe and how this interacts with cultural differences. The project will make contributions in both areas, in the first by a significantly improved spatial resolution, analysis and presentation of risks that incorporates the variability in environmental conditions and processes, and in the second by studies of risk views particularly in case regions and of the general policy issues within integration in risk assessment across geographic scales and across related levels or regimes of administration.

Socio-economic aspects of chemicals policies will be studied in relation to risk perception, risk knowledge, policy links of assessment, and risk communication. However, within this project it is neither possible nor meaningful to attempt e.g. a follow-up or expansion of the analyses by the Commission (DG-Enterprise 2003a,b,c, DG-Environment 2003) and elsewhere (JRC 2003a,b, RPA 2003) of the socio-economic consequences of REACH. Instead, the studies in this area will target issues directly related to risk assessment and to the production and use of scientific information, particularly in the areas of integration (multiple stressors, receptors and regions) and for the classes of stressors subject to closest study. The project will herein address the socio-economic dimension by a decision, policy and communication analytical approach emphasising risk views and uncertainty management instead of e.g. risk-benefit economics, apart from value-of-information analyses.

All in all, it is expected that the project will have a significant impact on the socio-economic area, and will contribute to a comprehensive, balanced and broadly acceptable approach to risks that is protective and supportive of both environmental quality and human health as well as social and economic values in a long-term sustainable perspective. Finally, it should be pointed out that an

important contribution to this goal will be made already by identifying and explicating the issues, conditions and constraints, including controversies and impediments, in science and technology and in other areas that are relevant for its fulfilment, even if not attempting to solve them, as this is the domain of policy and decision makers, not researchers (even decision or policy scientists).

B.3.1 Contributions to standards/policies/regulations

As indicated in the description of the overall strategic and socio-economic impacts and in more detail in the work descriptions, the project will offer many contributions, direct and indirect, to the development and implementation of EU policies and regulations within its scientific scope. It will help resolve how best to refine the risk assessment procedures based on the present and already proposed regulations (especially under REACH but also other relevant areas). Still more importantly, the project will provide knowledge and methods for assessment of agents, cofactors and risks that are intractable by present methods; this is expected to be crucial for the future dynamic development of EU risk management policies and regulations. In connection with this, the linkages between policy and these novel needs, factors and concepts in risk assessment will be illuminated.

In terms of collaboration and co-ordination between branches of administration (both at the Community level and at national levels), the integrated treatment of ecosystem and human health will make an important contribution; in addition, in addressing the context and conduct of risk assessment, also other branches, particularly that within enterprise, will be included, due also to the developing role of industry in risk assessment. As to chemicals regulations, the focus on mixture effects assessment will by definition help unify the presently separate areas of policies and regulations (such as between different categories of chemicals) especially in areas of greatest gaps and needs.

No unequivocal and detailed standards can be produced for risk assessment, due to the inherent complexity and multi-dimensionality of risks and to the dependence of assessment on its context and purpose. Likewise, harmonisation of risk assessment is only possible to a limited degree, to retain and promote the attention of variation e.g. based on particular sector, regional or other reasons. However, at a more general level, commonly applicable frameworks can and will be produced, and integrated and harmonised information useful for the varied assessments will be provided. This will serve a sensible level of harmonisation that allows e.g. both common EU policies and the necessary subsidiarity in identifying and responding to risks.

B.4 Outline implementation plan

Description of science and technology approach and ways to achieve the NOMIRACLE objectives - General approach

The risk assessment models and methods for chemicals currently in use within the European Union (e.g. European Communities, 2003; Annex VI of Directive 91/414/EEC) are based on a series of default assumptions and deterministic assessment factors which tend to result in relatively conservative predictions of risk. It is a major challenge to introduce more detail into these risk assessment procedures so that better informed management decisions become possible. Dealing with mixture toxicity and multiple stress is one of the areas where risk assessment of chemicals can and should be considerably improved. Other important areas include spatial differentiation, temporal variation, inter-individual variability (in exposure, toxicokinetics and dynamics), uncertainty and theoretical issues such as the quantification of critical stress levels in situations where cumulative stressors act in combination.

The research of NOMIRACLE will in particular focus on pesticides, biocides and pharmaceuticals and their effects in conjunction with other important natural or anthropogenic stressors such as industrial chemicals. The assessment scheme that will be developed will be equally applicable to each of these types of substances. The scheme for industrial chemicals will differ, however also the applicability in assessment of industrial chemicals of the new methods to be developed will be considered. Realistic exposure scenarios will be evaluated with respect to chemical mixtures and cumulative stressor combinations likely to occur.

It is clear that the number of combinations of stressors is practically infinite, and therefore it is not possible to cover this to the full extent. However, in this project a shortcut is suggested where focus is put on the most frequent chemical mixtures present in the regions of Europe, in combination with other major stresses such as extreme climate, acidification, eutrophication, particles etc. By this exercise it is ensured that relevance and realism is given high priority.

The project will develop methods focusing on the effects of long-term exposure, and will investigate the possibility to make regional risk assessment based on “stress maps” including these major background environmental factors acting on humans and the environment. In the end, e.g. regional safety factors will be assessed for individual chemicals based on sound exposure taking into account the real world exposure.

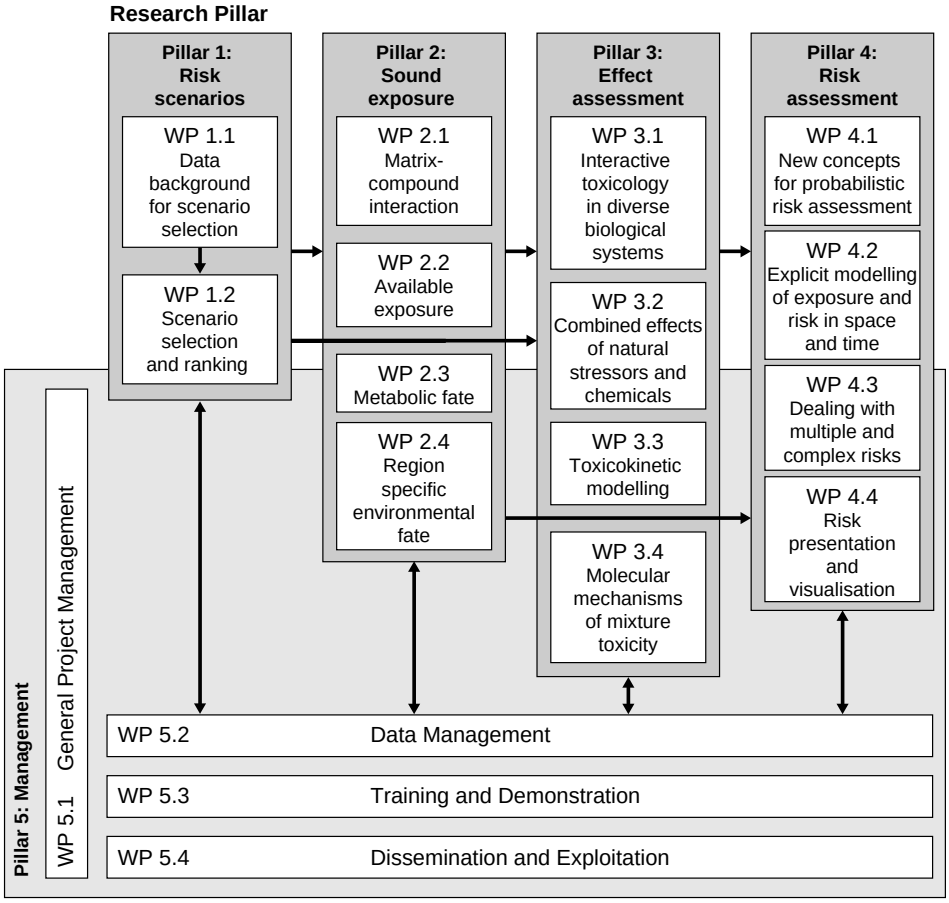

Figure B.4-1: NOMIRACLE activities and their components (Pert diagram).

The NOMIRACLE approach is summarised in Figure B.4-1 and consists of 4 main Research Pillars (RP) each containing a number of Work Packages (WP). Briefly, in RP 1 the most important and relevant stressors occurring across Europe and EU accession countries will be identified in order to find the most relevant scenarios of cumulative stressors to be studied. These "potential risk scenarios" will feed into RP 2, RP 3 and RP 4, and dictate which particular combinations of stressors and risk scenarios will be studied in detail.

RP 2 will address the European-wide fate of environmental contaminants and its dependence on compound properties as well as external factors such as emission sources, climate parameters, their matrix-specific availability, and in particular the human-specific exposure pattern.

The goal of RP 3 is to generate data to be used in development of generic rules for the assessment of combined exposure effects that are underpinned by mechanistic understanding. RP 3 will investigate interactive effects in species ranging from plants to bacteria to vertebrates to fish to humans. Comparative analysis will be used to identify the generic physiological changes that dictate the consequences of exposure to toxicant mixtures and combinations of chemicals with environmental/pathological stresses identified as important during RP 1.

The main aim of RP 4 is to develop novel methods for integrated risk assessment that enable the optimum use of available information in the decision-making processes, thus ensuring an efficient use of valuable resources. This aim will be realised by integration of the results of Research Pillars 1, 2 and 3 within a probabilistic and spatially explicit modelling framework.

The crosscutting management pillar (Pillar 5) will secure the overall co-ordination of the project via the work of the projects secretariat and a Management Board (described in section B6). A sound data management strategy will be developed in WP 5.2 securing that data generated during