Research Pillar 3 - Effect Assessment (Sub-coordinator: David Spurgeon, NERC)

WP 3.1

Acronym	UFZ	NERC	VU	NERI	DSTA	WU	DBUA
Personmonths	60	36	18	12	6	12	18
Acronym	EKUT	NIPH	USALZ	RWTHA	LemTec	WRcNSF	LIMCO
Personmonths	20	36	36	12	12	30	30

WP 3.2

Acronym	NERI	UFZ	WU	DBUA	UJAG	EKUT	LIMCO
Personmonths	60	40	12	30	48	18	18
Acronym	USALZ						
Personmonths	12						

WP 3.3

Acronym	VU	NERC	DSTA	UJAG	UA	LMC	WRcNSF
Personmonths	48	24	12	36	12	36	18
Acronym	UFZ						
Personmonths	12						

WP 3.4

Acronym	DSTA	NERC	UFZ	WU	UWC	UCAM	EKUT
Personmonths	30	36	30	24	36	36	22
Acronym	UA						
Personmonths	36						

Aims and rationale

In natural ecosystems, organisms are frequently exposed to mixtures of chemicals/metabolites and non-chemical stressors (US EPA, 2003, Heugens et al. 2001). Recognising this, a central challenge in delivering the objectives of NOMIRACLE is estimating the interactive effects of single and combined chemical and non-chemical stressors. As this applies both to human health and ecological assessment, RP 3 will aim to integrate environmental and human health effect assessment for mixtures. This will be done by adopting a mechanistic-based approach to identify conserved cause and effect relationships in environmental species and human model systems. To achieve such integration, partners in RP 3 will undertake a set of mechanistic and experimental studies, with the results compiled in a single relational data store. This will be used in RP 4 to generate rules for risk assessment of combined effects. By working with researchers in RP 2, the role of chemical properties in defining the nature of interactions will be elucidated. These rules can then be used in cumulative risk assessments conducted for exposure scenarios relevant to Europe.

Background, the state of the art and the NOMIRACLE approach

Because of the potential importance of chemical mixture effects in biological systems, (eco)toxicologists have developed a number of approaches to mixture toxicity assessment. Among these approaches, one paradigm that is based on two underpinning concepts has found wide acceptance (Eggen *et al*. 2004, Cassee *et al*. 1998). First, if chemicals have the same mode of action, their combined toxicities can be described by the concentration addition model; second, if they have different modes of action, their combined effects can be described by the independent action model. The broad applicability of these two reference models for (eco)toxicological assessment of simple and complex mixtures has been demonstrated for both similarly acting (Altenburger *et al*. 2000, Deneer *et al*. 1998, Faust *et al*. 2001, Hermans, *et al*. 1985) and independently acting compounds (Backhaus *et al*. 2000, Deneer *et* al. 1988, Faust *et al*. 2003) in a range of species.

Although the concentration addition and independent action reference models have the potential to describe the combined toxicity of many chemical combinations, there are cases in which these approaches have been found to fail. These include not only where the well known, but comparatively rare, conditions of synergism (Johnson et al., 1994, Meled et al. 1998, Forget et al. 1999) and antagonism (Van Gestel and Hensbergen, 1997, Posthuma et al. 1997) occur, but also where there are more subtle conditions such as dose level deviations in which combined effects differ from predicted as dose level varies (e.g. synergism at low dose, antagonism at higher dose) (Gennings et al, 2002, Jonker, 2003) and dose ratio dependent deviations (e.g. extent of synergism or antagonism depends on which chemical is dominant) (Van Den Hurk et al., 1998, Jonker et al. 2004, in press, Carter and Gennings, 1994). To date the two reference models have been validated only for chemicals acting by precisely the same mechanism (e.g. 15 oxidative uncouplers), or for sets of chemicals acting by strictly different mechanisms. The challenge that will be tackeled in NOMIRACLE is assess multifunctional compounds, where interaction could occur synergistically or antagonistically for different dose levels and dose ratios.

In current risk assessment mixture effects are at best taken into account using the two existing reference models (additive, independent) and at worst merely by including a simple safety factors for single compounds. Recognising a more scientific approach to mixture toxicity analysis was needed, the EU funded MIXTOX project (ENV4-CT97-0507), co-ordinated by NOMIRACLE partner WU, developed and validated a framework for the detection and statistical interpretation of the full range of possible chemical mixture interactions. The approach uses an experimental design which, by testing individual compounds and mixtures of different dose levels and dose ratios simultaneously, provides maximum statistical certainty in identifying the shape of toxicity response surfaces (Jonker, 2003, Jonker *et al*. 2004, in press). The analysis framework can be applied both in cases where mode of action is known and importantly also where such information is not available, or where the known primary mode of action is not relevant to the species under study (e.g. herbicide effects on animals). Using this approach, four biologically relevant deviation patterns from both reference models can be identified by means of likelihood analysis: no deviation, absolute deviation (synergism/antagonism), dose level and dose ratio dependent deviations (see above for description).

As well as exposure to combinations of toxic chemicals, populations living in the real world are also subject to non-chemical stressors. These can interact either directly with chemicals through changing bioavailability or indirectly through changing organism biology (e.g. Friis, et al, 2004, Herbarth et al. 2002, Heugen et al, 2003, Malcolm et al. 2003). While there is some information on the mechanisms behind the interactions within chemicals mixtures taken from pharmacology (Yang, 1994) little is known about how chemical and non-chemical stressors may interact. For example, non-chemical stressors may cause significant changes in the physiology of organisms that may or may not reveal themselves as effects at the individual level, depending on the plasticity of the species regulatory mechanisms (Parker *et al*. 1999). The growing acceptance that (eco)toxicology is merely a branch of the wider field of stress biology (Van Straalen, 2003) offers the potential to unify approaches for mixture toxicity (multiple chemical) and multiple stressor (chemical/non-chemical) effect assessment. In NOMIRACLE multiple stressor analysis will be developed in line with the novel approach for mixture toxicity developed in MIXTOX (Jonker, 2003, Jonker et al., 2004). As NOMIRACLE proceeds, use of this quantitative approach will enable predictions regarding the combined effects of an ever increasing number of stressors. As complexity builds, a scientific basis for forecasting risks to organisms of cumulative exposures occurring under the variety of field conditions within Europe will be formulated. At this point work will move into a final field validation phase that will involve a coalescence of partners from all pillars and the final definition of a unified approach.

Completion of the exposures and response modelling for mixture toxicity (WP 3.1) and multiple stressors (WP 3.2) will provide data that can be used to establish probabilistic rules that can forecast the magnitude of interactions between multiple stressors. To allow these rules to be used for predictions in general stress biology, detailed mechanistic understanding is needed (Hertzberg and McDonell, 2002). Such work should aim to identify generic traits, shared between

systems and taxa that define the nature and extent of interactions for mixtures of stressors. To achieve this improved understanding, as well as simply quantifying multiple stressor effects, NOMIRACLE will also directly investigate the controlling mechanisms in diverse species. This will include investigation of three levels of interaction (as adapted from Calamari and Alabaster, 1980 by Van Gestel and Hensbergen 1997 and Posthuma, *et al*. 1997) namely; those occurring in the exposure medium (environmental availability) in RP 2, those affecting the physiological processes of uptake (bioavailability) and elimination in WP 3.3 and excretion and finally those at receptor and target sites in WP 3.4. These analyses will concentrate on studies in animals, including mammalian cells and rodents, in order to increase the relevance of the data for human health.

WP 3.1 Interactive toxicological effects in diverse biological systems (Leader: Almut Gerhardt, LIMCO)

WP 3.1 will take a stepwise approach to mixture toxicity assessment. As detailed analysis of all mixtures combination is unfeasible, an initial analysis of the single compound and mixture toxicity scenarios identified in WP 1.2 will be made using rapid screening bioassays. This will allow us to select for detailed analysis 1) a set of single compounds with different modes of action causing varying effects in the different screening assays, 2) a set of chemical mixtures that show no deviation from the reference (additive, independent) models and 3) a set of mixture that show consistent deviations from the reference models. Detailed investigation of the most relevant scenarios identified in WP 1.2 will be undertaken using chronic exposures for the environmentally relevant species most likely to be affected. This data will then be used to define how conserved these response profiles are amongst species, life-stages and endpoints.

The rapid screening assays that will be used are:

- the *Vibrio fischeri* Microtox™ system (Doherty, 2001) (WRcNSF);
- a rapid benthic invertebrate exposure with *Tubifex* (Tichy et al. 2002) and/or Chironomidae (Gerhardt & Janssens de Bisthoven 1995, Gerhardt & Schmidt 2002) (NIPH, LIMCO);
- the early life stage fish test (OECD, 1992) (LIMCO);
- a single celled ciliate protozoan *Tetrahymena pyriformis* which act as a model for the effect of pollutants on cells of the human airway (Massolo et al. 2002, Muller and Herbarth, 1994, Netzeva et al. 2003) (UFZ);
- screens for human health effects based on existing and novel human cell lines (e.g. immune cells) (Bommel et al. 2000, 2003) (UFZ, USALZ).

The chronic exposures will be conducted for species that 1) fill significant positions in aquatic and terrestrial food webs, 2) come from different taxonomic groups and have different biological complexity and (3) have different habitats and requirements. Species selected are:

- aquatic algae and the higher plant Lemna (OECD, 2000a) (LemTec/RWTHA);
- *Daphnia magna* (Barata et al. 2002, OCED, 1995) (DBUA, UA);
- Chironomidae (OECD, 2001);
- the fish *Danio rerio* (Gerhardt et al., 2002, in press, Nagel and Isberner, 1998) (EKUT, UFZ, LIMCO);
- the marine mollusc *Mytilus galloprovincialis* (Panfoli et al. 2000) (DSTA)
- the terrestrial oligochaetes *Eisenia fetida* and *Lumbricus rubellus* (Kula & Larink 1997, Spurgeon et al. 2003); (NERC, NERI);
- the terrestrial collembolan *Folsomia candida* (ISO, 1999, Holmstrup and Krogh, 1996, Smit et al. 1997a,) (VU, NERI);

- the higher plants *Trifolium pratense*, *Lolium perenne* and *Sinapis alba* (OECD 2000b, Sverdrup et al. 2002) (NERI, NERC);
- the nematode *Caenorhabditis elegans* (Kammenga et al. 1997, Jonker et al, 2004) (WU); a terrestrial carabid (Lagisz et al. 2003, Laskowski, 1997) (UJAG);
- the slime mold *Dictyostelium discoideum* (Falugi et al. 2002)(DSTA) and finally;
- the mammalian models, mouse (Hahn et al., 2003, Grunewald et al. 2003) (Mus musculus) and rat (*Rattus norvegicus*) (Griffin et al. 2000) (NERC, USALZ).

Exposures will be conducted by experts skilled in the handling of the test organism/system ranging from bacteria to higher vertebrates according to routine in-house protocols and approved standards. SME partner Lemna-Tec will act as a technology platform provider to assist all partners to further optimise data collection from each test. During these exposures, a series of responses (e.g. gene and protein expression, metabolic dysfunction, immune dysfunction, cellular changes, weight change, proliferation, reproduction, behaviour, growth and viability) will be measured. Measurement of these endpoints will enable identification of biological dysfunction at all levels of organisation, encompassing not only acute, but also significant chronic effects (Calow and Forbes, 2003, Kammenga and Laskowski, 2000, Van Straalen, 2003). The mixture experiments will be undertaken and analysed using the novel framework developed during the MIXTOX project (Jonker, 2003, Jonker *et al*., 2004, in press) and outlined above. To allow this approach to be used in house by all partners, a guidance document will be written and a software version of the existing analysis program refined and distributed. Use of this framework will allow modelling of response surfaces for simple and later complex mixtures using an optimal design and minimum number of test animals, thus reducing the number of test organisms that need to be sacrificed. When deviations in combined toxicity from additive and independent effects are found, the mechanisms underpinning these will be elucidated by toxicodynamic (WP 3.3) and molecular (WP 3.4) approaches.

Completion of screening and detailed studies of simple chemical mixtures will provide us with the data required to develop a theoretical basis for predicting combined effects. This theoretical basis will then be extended to address complex mixtures. These predictions will be validated using experimental work that will study interactions for a progressively increasing number of compounds to ensure continued mechanistic understanding of the interactions. Analysis of complex mixtures has already been conducted in the MIXTOX project, and has demonstrated the ability of the data interpretation approach to identify interactions occurring between multiple chemicals (Jonker, 2003). To deliver this improved mechanistic understanding, in NOMIRACLE we will extend this approach to address the exposure, effect and resultant risk for organisms of cumulative chemicals. At this point work will move into a final field validation phase.

WP 3.2 Combined effects of natural stressors and chemicals (Leader: Martin Holmstrup, NERI*)*

Given the likely importance of multiple stressor exposures, this area has not, to date, been a priority area of research (Calow and Forbes, 2003, Eggen *et al*. 2004, Holmstrup *et al*. 2000; Højer *et al*. 2001). To address this gap in understanding, work package 3.2 in NOMIRACLE will place classical (mixture) toxicity studies within the context of the diverse environmental conditions that exist across Europe. The environmental and population specific factors considered will be selected in the prioritisation and scooping process undertaken in RP 1. Examples already under investigation by partners include, diet quality (all partners as applicable), population vulnerability due to genetic erosion as a result of ecological bottlenecks or habitat fragmentation (Lopes et al. 2004, Van Straalen and Timmermans, 2002) (UJAG), prevalence of pathogens/allergens (Fritz and Herbarth, 2004, Rolle-Kampcyyk et al. 2002) (USALZ, UFZ, UJAG), UV exposure (Hatch and Blaustein, 2003) (DBUA, NERI), extreme temperatures (Heugen et al. 2003, Holmstrup et al. 1998) (all partners as applicable), acidification (Herrmann et al. 1993) (all partners as applicable), soil

moisture content (drought/water logging) (Friis et al. 2004) (NERI, UJAG, VU) and anoxia/eutropication (Ivora et al. 2002) (DBUA).

RP 1 will identify which cumulative stress combinations should be assessed for which types of test organism in order to maximise the relevance of the assessments. Thus, the influence of pathogens may be most relevant in humans/mammals, the influence of drought most relevant for soil organisms etc. The ultimate goal of WP 3.2 is to have a broad understanding of the effects of relevant cumulative stressor combinations (chemicals combined with environmental stress) on a wide range of organisms and human immuno-responses to cover most environments and human communities of the European continent.

The approach to identifying the interactive effects of the environmental stressor will mirror that used for contaminant mixtures in WP 3.1. For each factor, the response profile for each environmental stressor will first be described in the most environmentally relevant set of the organisms listed in WP 3.1. These responses will be collated, thereby providing spin-off information concerning the limits of the tolerance of diverse taxa to environmental variation and change. Once the stress response profiles for the single stressors have been established, this information will be used to design multiple stressor studies that can be analysed using the novel framework for chemical mixtures outlined above. Likelihood analysis will be applied in order to identify if there are deviations (absolute synergism/antagonism, stress level and stress ratio) from either reference model (additive, independent). Using both reference models will allow determination of which of these acts as the better predictor of each multiple stressor effect.

In the later stages of the project a set of field validation studies are planned to verify the interactions demonstrated in the laboratory-based studies. These will focus on different types of emission scenario including point-source/end of pipe, landscape, catchment, regional and national scales in combination with relevant multiple environmental stressor combinations identified in WP 1.2. These field studies will be a crosscutting issue encompassing the disciplines of all four research pillars. These field studies will also form an important part of the demonstration activities planned in the last phase of the NOMIRACLE project. In parallel with ecological based field studies, we will undertake work that enables us to understand the epidemiological significance of combined stressor interaction identified in human model systems. For this, the results of epidemiological studies that have been done or are ongoing will be sorted and used to provide information concerning the effects of the substances and environmental stress scenarios on the population at large. This data will be mined and used to confirm or renounce finding concerning the possible effects derived on the basis of laboratory studies. This process will provide essential validation of the potential of combined exposure as a risk factor for public health.

WP 3.3 Toxicokinetic modelling (Leader: C. Van Gestel, VU)

This work package is one of two within NOMIRACLE that will improve mechanistic understanding of how single chemicals, mixtures and multiple stressors affect species with different physiologies. In it the role of uptake and elimination in governing the effects of such exposures will be investigated. The approach uses chemical analysis to determine toxicokinetics under each exposure scenario. This work will directly address interactions affecting the physiological processes of uptake and elimination for which there are numerous examples concerning modulation of absorption, metabolism, localisation and excretion of one compound by another (Haddad *et al*. 2000, Van Den Hurk *et al*. 1998).

A suitable approach to evaluate the relationship between external exposure, organism or target tissue dose, and biological outcome is through toxicokinetic models. As these will need to describe each species in terms of their physiology, biochemistry and ecology, a range of approaches will be needed to encompass the taxonomic variety included in NOMIRACLE. Methods developed will range from simple one and two compartment models for aquatic (UA), soil dwelling (VU, NERC) and soil surface dwelling (UJAG) invertebrates; to complex models that describe the physiological processes of vertebrates (VU, NERC). Fortunately past work has identified potential

prototypes for all of these (Andersen 1995, Belfroid *et al*. 1994, Lien *et al*. 2001, Mackay & Fraser 2000, Widianarko *et al*. 2001). After an initial review of these methods, the best approaches will be developed into fully operational models (co-ordinated by VU in co-operation with WP 4.1). These models can then be used to assess the contribution of toxicokinetic modulation to the toxicity of species to mixtures and multiple stressors.

With suitable models in place for each species, toxicokinetic assessments will be made in relevant species. Colleagues involved in WP 2.2 will help identify suitable methods for the analysis of test chemicals in substrates and organisms and SME partner WRcNSF will provide advice and technical supervision to assist partners in further refining these methods. To ensure proper implementation of each analytical method, a series of research training visits will be initiated between the partners in WP 3.3 (particularly WRcNSF) and WP 2.2. Using existing and modified protocols, toxicokinetic assessments will first be made in all species for two compounds selected from the priority list. This data will be used to ensure optimisation of each toxicokinetic model (in collaboration with partners in WP 4.1). As will be the case throughout the project, data concerning these parameters for compounds (both singly and in combination) will be recorded and used in risk assessment models that consider bioaccumulation (in WP 4.1 and 4.2). Following this refinement step, assessments of toxicokinetic parameters in mixture experiments can begin. Work will start by first assessing toxicokinetic parameters in simple mixtures of chemicals with the same mode of action that show no deviations from concentration addition in all tested species. Next, mixtures with different mode of action that fit the independent model will be assessed, before moving on finally to investigate the role played by toxicokinetics in simple and complex mixtures that show consistent deviation from either of the two reference models. As the role of metabolism in prioritising chemicals will be important both in terms of kinetic parameters, the deactivation of some parent compound and the production of toxic metabolites for other this will also be modelled in detail. To predict metabolism and toxicity for compounds, the tissue metabolism simulator (TIMES) system will be applied to predict metabolic activation of chemicals (Mekenyan et al., 2004a, 2004b). The system uses a heuristic algorithm to generate plausible metabolic maps from a comprehensive library of biotransformations and abiotic reactions and estimates for system-specific transformation probabilities. To further the mechanistic understanding and prediction of hazardous effects on human health caused by indoor exposure, targeted QSAR investigations of the toxic effects of VOC chemicals on ciliates, immunocompetent and other human cells will be undertaken. This work will include effect profile analyses across non-human species, and aims at building a mechanistic mapping between epidemiological human health status and biotest system response patterns. Using the range of data collected and by working with QSAR developers in RP 2, a predictive approach that describes kinetic changes at different dose level and dose ratio combinations will be sought.

WP 3.4 Molecular mechanisms of mixture toxicity (Leader: Aldo Viarengo, DSTA)

Even when interaction between chemicals at the levels of bioavailability (WP 2.1) and toxicokinetics (WP 3.3) are accounted for, there are still likely to be a set of unexplained deviations in combined effects from concentration addition and independent action due to interactions at the site of toxicity. To elucidate the conserved and distinct molecular changes that underpin the systemic response of species to chemical mixtures (WP 3.1) and multiple stressors (WP 3.2), WP 3.4 will use a dual approach that combines comprehensive and targeted methods. The comprehensive analyses will exploit global gene, protein and metabolite analysis technologies. At the genomic level, gene screening, discovery and mapping methods (UWC, UA)(Stürzenbaum *et al*. 1998; De Coen and Janssen 1997, Moens *et al*. 2003) will be used. Additionally, transcriptomic studies will be made using established commercial and custom printed microarrays. These include a 14,000 gene zebra fish cDNA array (UFZ), a 16,000 gene oligonucleotide nematode array (WU, UWC), an 8,000 gene earthworm cDNA array (Sturzenbaum *et al*., 2003) (UWC), a 2500 gene *Daphnia magna* cDNA array (Soetaert *et* al. 2003), a 2,000 gene cDNA mussel and a 2000 gene cDNA *Dictyostelium* arrays (DSTA). Proteomic analyses will investigate protein expression within targeted sub-proteome and in limited cases also for global profiles (Pennington & Dunn 2001;

Hogstrand *et al*. 2002, Vido *et al*. 2001). Both 2-D electrophoresis and chromatography based separations (UA, NERC, DSTA) will be used with mass spectroscopy for protein identification (DSTA, UA, UCAM, NERC). To investigate the metabolic consequences of changes in gene expression and resulting functional protein complement, large-scale analysis of metabolites will be conducted using ^{1}H nuclear magnetic resonance spectroscopy (NMR), GC-MS and LC-MS based metabolomics (UCAM, NERC) (Bundy *et al*. 2002; Nicholson *et al*. 2002; Griffin *et al*. 2001).

To supplement the use of post-genomic screening techniques, detailed biochemical and molecular genetic analyses will also be used to further investigate interaction mechanisms. These will include measurements for cholinesterase (DelOmo *et al*. 1996, Amaroli *et al*. 2003) (DSTA, NERC), cytochrome P450 (Viarengo *et al*. 1997) (NERC, DSTA), glutathione-s-transferases (Saint-Denis *et al*. 1998) (NERC), stress proteins (Kohler *et al*. 1998, 2001, Triebskorn *et al*. 2002) (EKUT), antioxidant enzymes (Regoli *et al*. 1998) (DSTA), metabolic enzymes (Long *et al*. 2003, De Coen and Janssen, 1997) (NERC, UA) and energy budgets via cellular energy allocation (UA) (De Coen and Janssen, 2003a) and organ pathology (EKUT) (Hinton and Lauren, 1990, Triebskorn *et al*, 2002). These approaches (e.g. cellular energy allocation) offer the possibility to link short term biomarkers with population level responses through the DEBtox model (De Coen and Janssen, 2003b, Kooijman, 1993). On completion of analyses, pattern recognition techniques (UCAM, NERC) (Lindon *et al*. 2001; Raamsdonk *et al*. 2001) can be used to overlay species responses profiles to identify if modes of action and interactions are unique to species or common between taxa. This approach has the potential to highlight potential species specific and common biomarkers that can be used in ecological monitoring of cumulative stress effects. Further because analyses are concentrated into a series of animal phyla, including mammalian cells and rodents these indicators could be applicable to the epidemiological assessment of human population health. Such biomarkers will be validated in the field studies conducted as a cross cutting initiative in NOMIRACLE, thereby providing a set of indicators of chemical mixture and multiple stressor exposure for broad application in environmental and human health monitoring.

Research Pillar 4 –Risk Assessment (Sub-coordinator: Ad Ragas, DESUN)

WP 4.1

Acronym	VU	DESUN	RIVM	USOUTH	EPFL
Personmonths	48	52	4	36	18

WP 4.2

Acronym	DESUN	URV	UFZ	ALTERRA
Personmonths	46	42	49	22

WP 4.3

Acronym	SYKE	DIA	JRC
Personmonths	54	21	18

WP 4.4

Acronym	ALTERRA	UFZ	URV	UNIMIB	NERI	JRC	DESUN
Personmonths	8	7.5	6	4	4	3	2

Aims and rationale

The main aim of RP 4 is to develop novel methods for integrated risk assessment that make optimum use of available data and models, ensuring an efficient use of valuable resources. This aim will be accomplished by the integration of the results of RP 1, RP 2 and RP 3 within a probabilistic

and spatially explicit modelling framework that is tailored to support risk management decisions. The new concepts and techniques developed in RP 4 will be applied to produce probabilistic estimates and characterisations of risk for the scenarios identified in RP 1.

For a selected number of critical environmental functions, endpoints and agents (RP 1), emission and environmental data gathered in RP 1 will be used to produce probabilistic (cumulative) exposure estimates (RP 2 and RP 4). Comparison of these estimates with the effect data on mixture toxicity and multiple stressors gathered in RP 3 will result in refined probabilistic estimates of cumulative risk including evaluations of qualitative dimensions of risk and indices of significance. The dependencies between management and assessment approaches will be identified, and options outlined to deal with these risk estimates in a multi stakeholder setting, i.e., relating to risk perception, risk communication and a prudent application of the precautionary principle.
The activities in RP 4 are organised in four work packages. WP 4.1 aims at developing novel concepts and techniques to quantify uncertainty in different stages of the integrated risk assessment process (exposure assessment, effects assessment, risk characterisation and risk management). Starting point of WP 4.1 is the notion that uncertainty is a measure of information quality that plays an important role in risk management decisions. WP 4.2 addresses modelling techniques that can integrate exposure and risk over space and time. Contrary to traditional risk assessment practices that tend to concentrate on the stressor, the approach taken here focuses on the receptor as the main target of the modelling effort, as the receptor integrates (the effects of) stressors as it moves through space and time. WP 4.3 aims to analyse cognitive, social and contextual aspects of integrated risk assessment in order to improve the overall knowledge base for dealing with multiple and complex risks, uncertainty and ambiguity. Finally, the presentation and visualisation of the cumulative risks that have been quantified in WP 1.2 (assessment of potential cumulative risks) and WP 4.2 (refined cumulative risk assessment) will be the subject of WP 4.4.

WP 4.1 New concepts and techniques for probabilistic risk assessment (Leader: Ad Ragas, DESUN)

The growing awareness that deterministic risk assessment procedures can result in conservative or erroneous risk estimates (and consequently in a waste of resources) has resulted in a shift towards probabilistic risk assessment (PRA; Ragas 2000). However, most techniques currently used in PRA have considerable shortcomings from a scientific as well as a management perspective. Examples are a lack of differentiation between various types of output variance (i.e., true uncertainty and interindividual, spatial and temporal variability), the considerable amount of subjectivity involved in the choice of the probability distributions, the sub-optimal use of existing data, and the complex interpretation of the probabilistic output. WP 4.1 aims to develop new concepts and PRA techniques that are scientifically sound and practicable for management purposes. Examples are nested and Markov Chain-based Monte Carlo simulation (Cullen & Frey 1999, Johansson & Jonsson 2002), Bayesian methods including dynamic Bayesian belief networks and nonparametric hierarchical Bayesian analysis (Bates *et al*. 2003, Varis & Kuikka 1999, Arjas & Andreev 2000), distribution-free techniques (Ferson *et al*. 1998) and techniques to quantify the added value of new information (Hammitt & Shlyakhter 1999).

Some concepts and techniques that will be developed in WP 4.1 are restricted to a certain phase of the risk assessment process (e.g., derivation of a probabilistic NEC for mixtures), whereas others are more generally applicable. Two general techniques explored in WP 4.1 are (1) the separation of uncertainty and variability by means of nested Monte Carlo simulation, and (2) quantification of the added value of new information (VOI) for risk management decisions (Dakins 1999) (DESUN). The former technique will initially be applied to an integrated human exposure model that describes the uptake of contaminants from relevant environmental exposure pathways (i.e., air, drinking water, swimming water, food, soil and dust). In a later stage of the project, this technique will be used in ecological risk assessment, i.e., to separate the influence of intraspecies and interspecies variability from true uncertainty in estimation of the NEC_{eco}. The VOI technique will initially be applied to quantify the reduction in uncertainty that can be realised by performing

extra toxicity tests before deriving a NEC_{eco}. The costs of an extra ecotoxicity test will be weighed against the possible benefits of a less stringent NEC_{eco} due to reduced uncertainty. In a later stage of the project, this VOI technique will also be used in other areas of the risk assessment process.
In the area of effect assessment, a new method will be developed to derive a probabilistic NEC for simple and complex mixtures based on the Dynamic Energy Budget theory of Kooijman (2001) (VU). This theory quantifies the effects of compounds by influencing the resource allocation within organisms to various endpoints, i.e., feeding, maintenance, development, growth, reproduction and aging processes. Co-limitation by food and other factors that modulate toxic effects are included in the model. ISO and OECD have recently accepted the current model for the analysis of data from standardised ecotoxicity tests (Kooijman *et al*. 2004). In the NOMIRACLE project, the method will be extended for the assessment of simple and complex mixtures. Profile likelihood and Monte Carlo methods will be used to study the confidence intervals of the NEC-estimates.

Another important activity in WP 4.1 is the derivation of new probabilistic assessment or uncertainty factors (UFs) for the extrapolation of laboratory toxicity data to relevant human and ecological endpoints (Amler *et al*. 2003, Pelekis *et al*. 2003, Roelofs *et al*. 2003). This will be achieved by meta-analysis of toxicity data, i.e., those gathered in RP 3 and those stored in existing human and ecotoxicological databases. The UFs currently used in human and ecological effect assessment have evolved along comparable, but separate lines. Although there are some clear differences between human and ecological effect assessment, the awareness is growing that the underlying toxicological principles are to a large extent comparable and governed by a limited number of mechanistic descriptors, e.g., substance parameters, the genetic predisposition of receptors and the toxicological mode of action. In WP 4.1, new probabilistic UFs will be derived separately for human and ecological endpoints, but the underlying analytical framework used for the meta-analyses will be harmonised to the extent possible as regards the relevant mechanistic descriptors. Furthermore, there will be an exchange and evaluation of toxicological data that describe comparable phenomena (e.g., data on interspecies differences are relevant for extrapolation from test animals to humans and for deriving the NEC_{eco} from a limited number of single species tests).

Derivation of UFs for human risk assessment (USOUTH) will concentrate on the quantification of human variability in pharmacokinetics and pharmacodynamics for individual compounds and chemical mixtures that are handled by major polymorphic pathways (CYP2C9, CYP2C19, CYP2D6, NAT, glutathione-S-transferases, sulphation) (Dorne *et al*. 2002, 2003ab, 2004ab). Meta-analyses and quantification of interspecies differences will also be performed as a comparison of pharmacokinetic and pharmacodynamic differences between humans and test species (rat, mouse, rabbit, dog including neonatal animals) (Walton *et al*. 2001ab, 2004).

For ecological risk assessment, probabilistic UFs will be derived for extrapolation of (1) acute to chronic endpoints and (2) the median value of a species sensitivity distribution to the NEC_{eco} (Roelofs *et al*. 2003, Pennington *et al*. 2003c). The database used for these analyses (Wintersen *et al*. 2002) already contains extensive data on pesticides and will be supplemented with data on pharmaceuticals and other substances, partly gathered in RP 3. The dose response surfaces on mixture toxicity and multiple stress situations provided by RP 3 will be analyzed to identify adherence and deviation from concentration and effect addition mixture models. Based on these analyses, UFs will be derived to describe the possibility and magnitude of particular deviations when chemicals have similar and dissimilar modes of action (DESUN, RIVM).

Finally, probabilistic indicators will be developed that enable comparative risk assessment (CRA) due to different stressors, e.g., toxic stress, eutrophication and acidification (EPFL). CRA is based on the premise that not all environmental problems pose the same degree of risk to human and ecosystem health, and that all environmental problems cannot be addressed fully at the same time. In this study, methods developed in Life Cycle Assessment (LCA; Goedkoop & Spriensma 1999, Jolliet *et al*. 2003, Pennington *et al*. 2003ab) and in the EU FP5 OMNITOX project (Payet *et al*. 2003; Larsen *et al*. 2003) will be extended to integrated risk assessment of mixtures and multiple stressors.

WP 4.2 Explicit modelling of exposure and risk in space and time (Leader: Uwe Schlink, UFZ)

It is common practice in risk assessment of chemicals to use a spatial and temporal average of the measured concentration(s) to estimate exposure and risk. This approach eliminates all information about spatial and temporal patterns of the contamination and of the exposed receptor. It is therefore a rather crude method that may result in over- or underestimation of the actual risk. The main aim of WP 4.2 is to develop new methods and models that explicitly address the temporal and spatial dimensions of cumulative risks, both for human and ecological receptors. The structure of WP 4.2 is illustrated in Figure B.4-3.

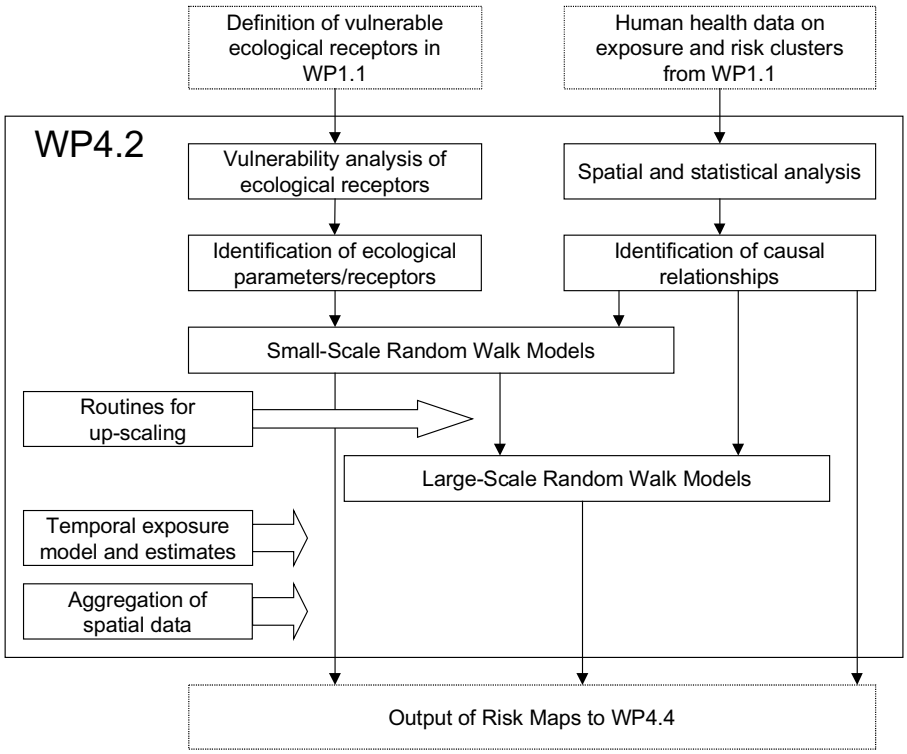

Figure B.4-3: Flow chart representing the structure of Work Package 4.2.

The temporal dimension of exposure and risk is addressed in a modelling study that focuses on the temporal variation of human risks for selected inhalative chemical compartments in indoor air based on data gathered in WP 2.2 (UFZ). For that purpose, principal vector analysis (PVA; Bright *et al*. 1999, Johnson *et al*. 2002) will be applied. This will result in the identification of characteristic exposure spectra in indoor air as a risk for human health. Combining the exposure with activity patterns of the inhabitants (e.g., renovation and ventilation; Rehwagen *et al*. 2003, Schlink *et al*. 2003) a model will be developed for the prediction of long-term risks based on short-term measurements.

The spatial dimension of exposure and risk is addressed by developing geo-referenced random walk models for human and ecological receptors (DESUN). These models will include critical pathways that are representative for selected stressors and vulnerable environmental functions identified in WP 1.2. In these models, an individual receptor (human or mobile organism) is represented by a set of algorithms that describe the processes relevant for exposure and risk assessment, i.e., movement, dietary composition, food consumption rate, inhalation, migratory behavior and interactions with other individuals, species and pathogens. The movement algorithm allows the receptor to move over a GIS map, encountering and accumulating different contaminants and stressors over space and time (Hope 2000, Linkov *et al*. 2002, Topping & Odderskaer 2004, Rafoss 2003, Woodbury 2003). The receptor thus becomes a spatial and temporal integrator of stressors. Human and ecological random walk models will be developed along similar lines with an emphasis on ecological models during the first phase of WP 4.2 and on human models during the second phase.

Selection of critical ecological pathways and parameters to be included in the random walk models will be based on the ecological receptors (identified in WP 1.1 and prioritised by scenario ranking in WP 1.2) on the basis of a vulnerability analysis using multi-criteria analysis (MCA; Faber *et al*. 2003). This will be in line with recent innovative pilot studies and relevant critical limits will be derived (De Bruin *et al*. 1999). The analysis will be further developed to facilitate probabilistic use of species data in spatial modelling or the development of "virtual species" representing critical target species for modelling on the basis of underlying variability of ecological traits in real species (ALTERRA). Further development of MCA techniques for this purpose will be undertaken in cooperation with the experts of RP 1.

The ecological random walk models will describe exposure and risks at the scale of the habitat or home range of organisms, and will focus on incorporating spatial variations of contaminants in soils and relate these to the habitat use by organisms. Knowledge gathered in the EU INTERREG BERISP project (conditionally approved; development of a decision support system for spatially explicit risk analysis for ecological receptors) will support the development and validation of ecological random walk models in WP 4.2 (ALTERRA).

For the development of human random walk models it is crucial to identify the most important causal parameters that determine human exposure and risk. This is no easy task, since human health is affected by a variety of environmental factors including genetics, diet, activity patterns, and environment-dependent factors such as proximity to hazardous waste sites, air and water quality, etc. The identification of causal parameters is a research effort in its own right that will not only support model development, but will also aid in the development of a non-biased method for identifying at-risk populations and potential hotspots. The methodology will enable evaluation of the effect of spatial scales on observing clusters of risk, cancer mortality or exposure (at predefined ranges). This approach should also provide a framework for developing regional surveillance systems.

Analysis of spatial patterns and cause-effect relationships will encompass the use of correlations, regressions, cluster analysis, and artificial neural networks (ANN). ANN have been used successfully, e.g., to develop predictor variables in the diagnosis of myocardial infarction, for toxicities of complex mixtures and for modelling and predicting exposure (Tu 1996, Buscema 1997, Gagne *et al*. 1997, Schlink *et al*. 2003). This technique is still relatively unexplored in risk analysis and the identification of risk patterns in space and time. Kohonen's self-organizing maps (Kohonen 1982) will be used to facilitate a visual identification of relationships among data and identify potential exposure and risk hotspots. Fuzzy ARTMAP neural networks will be used to analyze noisy and incomplete data sets (Espinoza 2001).

To isolate potential predictors (stressors and other relevant causal factors), database information collected in WP 1.1 will be utilised and converted, as necessary, to GIS compatible databases (including census tract information). The GIS environment will be used to analyze scale-related associations between various environmental, social, demographic factors and risk data. Variables such as toxic releases, air quality, demographics, watershed quality, industry

distributions, education, income, health coverage, hazardous waste sites, various exposure measures, individual activity patterns and other pertinent databases will be analyzed at various scale levels. Formal statistical tests will be used to assess where exposures and risks are significantly higher than average and to examine the strength of variable relationships with the impact measures. Another important issue addressed in WP 4.2 is the aggregation of spatial data in relation to the accuracy and interpretation of the final spatial output (Haining 1981). Application of Bayesian models (UFZ) with conditional autoregressive terms (CAR) will result in interpolated, smoothed, and aggregated risk data (Besag and Kooperberg 1995; Sun *et al*. 1998). Particular problems that will be addressed in WP 4.2 are the specification of the smoothing parameter (Clayton *et al*. 1993) and the effect of risk attenuation that occurs at aggregated data of a heterogeneous population (Schlink 2002). Besides individual chemical compounds and mixtures, an adjustment will be made for risks due to further stressors, such as socio-economic factors and climate (Schlink *et al*. 2002). This activity will be co-ordinated with the studies on mixture toxicity and other stressors in RP 3.

A final issue addressed in WP 4.2 is the consideration of risks at different spatial scales. Data analyses at different scales can determine the relationship between risk clusters and facilitate its geographical identification (Fayyad 1996). For example, in ecological risk assessment, the habitat of the receptor naturally provides a typical length that can serve as a separator defining small and large spatial scales (Landis 2003). Properties of ecological risks at different scales will be described and analyzed in order to identify relevant processes that govern risks at different spatial scales and to develop routines for up-scaling (ALTERRA). Also, the analysis of human exposure and risk clusters will be conducted at different spatial scales to determine the relationship between cluster size and its potential identification relative to geographical scale and the identifying factors. The use of different scales will demonstrate the relative limitations of using large-area scales to identify impact clusters. In this way, the homogeneity of associations across various geographic scales will be analyzed.

WP 4.3 Dealing with multiple and complex risks in a management context (Leader: Timo Assmuth, SYKE)

Risk assessment and management involves the integration of factual assessments and value judgments. These overlap and interact causing subjective reasoning also in so-called scientific facts and claims, and challenging the traditional separations between science, 'scientific' assessment and management (see Putnam 2002). Especially when there is uncertainty and ambiguity involved, estimates of cumulative risk become blurred or fuzzy, and the value-fact borderline becomes vague. Examples are scientists that make subjective assumptions about model structures and parameters, and stakeholders that take advantage of uncertainties for their own interests. Communication needs to be improved not only between various stakeholder groups, but also between scientists and assessors of various backgrounds. This requires systematic study of risk perception and cognition, of knowledge-related processes and factors in responses to risks and uncertainties, of views of the qualities and significance of risks, of the multi-actor and multi-level communication in assessment and management contexts, and of the relationships between science, assessment and management policy. Such studies are important for the development of new assessment and management strategies involving e.g. balanced combinations between detailed and simplified approaches, notably those based on the precautionary principle (Pidgeon 1998). In this WP a coherent set of mental and social aspects of risk will be studied as dictated by the particular contexts and overall foci and approaches of the project.

The overall aim of this WP 4.3 is to improve the knowledge base for dealing with multiple and complex risks, uncertainties and ambiguities by studying cognitive and knowledge-related, social and contextual aspects of integrated risk assessment, and by providing new interdisciplinary, reflexive and pluralistic approaches to addressing these aspects. Emphasis will be placed on risks associated with specific multi-stressor activities and on the uses and limits of knowledge in integration of the precautionary principle with in-depth evidence-based assessments. The WP will in particular address epistemological and policy issues in steering, conducting, developing and

evaluating integrated risk assessments in the relevant key areas of EU chemicals policy. Integration and its relations with differentiation will be investigated along several dimensions, including agents (chemical mixtures, multiple sources, chemicals and other agents), time scales (also intergenerational) and spatial scales (mainly EU, national and regional level, in interaction with WP 4.2), receptors (human and non-human, age groups), endpoints and consequences, other risk attributes (e.g. associated benefits), stages of risk formation (exposure and effect), stages of activity (research or testing – assessment – management – monitoring), management sectors, and actors (experts, regulators, regulated). Given the many dimensions of integration, selected combinations will be treated more closely in cases.

The key operational objectives and work areas are (1) to study risk perception and cognition and particularly their patterns and influences in integrative risk assessment, (2) to examine strategic issues in the assessment-management interfaces including precautionary approaches and production and uses of knowledge to manage associated uncertainties, (3) to analyze expert and stakeholder communication about multiple risks and uncertainties, (4) within all these areas, to develop methodologies for multi-dimensional analysis of risks in a management context, and (5) to analyze and support the dissemination and exploitation of results. These objectives involve both scientific and applied activities. The focus will be on knowledge and its opposites uncertainty, ambiguity and ignorance in various domains of activity (research, assessment, policy decisions); this focus will serve to tie the work together internally and, for broad external utility, to direct these activities to the most meaningful and decisive questions in the various settings given.

Risk perception and cognition related to integrated assessment will be studied among key actors at European level (SYKE, with partners), based on earlier work (Renn 1998a, Assmuth & Hildén 2002, cf. Carthy *et al*. 2002). The key general topics include dimensions of risk, roles and kinds of knowledge, modes of thinking and plurality of views (e.g., Funtowicz & Ravetz 1992). Expressed views of risk comparisons will be analyzed, emphasizing multiple stressors and receptors and taking into account the implications of the above other dimensions and of uncertainty for risk comparisons (Finkel 1992, 1995). This will be aided by meta-analyses of documented studies and surveys. The cognitive aspects in the representations and processing of risks will be examined by theoretical models of risks as socially amplified constructs (e.g., Pidgeon *et al*. 2003), and empirically by soliciting expert and stakeholder opinions among the consortium and affiliated experts and stakeholders including the Competent Authorities and industry responsible for assessment (SYKE). Knowledge about risks and uncertainties will be evaluated in connection with framing issues, extending the value-of-information analyses in WP 4.1 to account for qualitative and procedural aspects and multidimensionality of risks and for higher-level uncertainties (JRC). The work will be tied to the other WPs to devise conceptual models of risks and inference in assessment, especially to risk and scenario identification and multi-criteria analyses in RP 1.

Risk management strategies that focus on methods for dealing with uncertainty and ambiguity (routine, risk-based, precautionary, discourse-based, preventive) will be studied, including analysis of regulatory frameworks and management performance (DIA). Policy issues will be studied in integration across stressors, receptors, regions and actors (e.g., Renn 2001). Interactions of management and assessment will be analyzed in regulatory procedures for case chemicals (cf. Assmuth *et al*. 2000), in connection with quantitative environmental risk criteria and goals, and in environmental health (e.g., Jalonen, accepted) (SYKE). In particular, strategic aspects in integrating evidence-based and precautionary assessment for case chemical categories will be studied, including inputs from and back to research, testing and monitoring; this policy-level analysis will link with and complement the VOI analyses in WP 4.1. The strategic issues in risk and uncertainty analysis under the REACH system will be an important case (all partners). These studies will also address options for risk prevention e.g. through alternative products and their pros and cons such as counter-veiling risks of alternatives but account also for indirect and process impacts such as benefits from learning, participation and trust-building. Multi-objective approaches will be used as traditional risk-benefit analyses are not well suited to deal with multidimensionality and ambiguity of risks and with multiple goals (e.g., Voulvoulis *et al*. 2002). Methods and guidance

will be developed for addressing multiple risks and uncertainties (JRC), particularly within scientific advice for integrative chemical policies (cf. Funtowicz *et al*. 1999, Craye 2003). Risk communication will be studied on a multi-actor and multi-dimensional communication paradigm in relation to discourses of concepts and approaches in integrative assessment (SYKE with partners), focusing on inter-disciplinary and expert-stakeholder communication under uncertainty and controversy (cf. Dreyer 1997) and examining links with assessment models (Renn 1998b). Communication within risk assessment under EU's new Chemicals Policy and the REACH system, related key specific regulations such as the Biocide Directive, and the EU Environmental Health Strategy development and implementation will be used as cases. Options and obstacles for cross-disciplinary and interactive communication will be identified (cf. Breakwell 2000), including language and sector barriers. Frameworks for new approaches to communication of risk assessment will then be developed (cf. Assmuth 2003) and tested in cases using e.g. dialogue techniques and visualizations to frame and identify issues (DIA). The latter methodologies will be explored in collaboration with the work on presentation of risks in WP 4.4, complementing this with analyses of and methods for communication of the social and controversial aspects of risk that will be done in close collaboration with the applied dissemination and exploitation activities in WP 5.4.

The WP will provide results for dissemination and exploitation processes also by studying them and the assessment-management links; efficient exploitation will thus be ensured. The WP will involve researcher and expert training, and also contribute to training in other ways, e.g., by focusing on cognition, communication and assessment as learning processes.

WP 4.4 Risk presentation and visualisation (Leader: Joost Lahr, ALTERRA)

In NOMIRACLE, risk estimates are produced during different phases of the project (i.e., in WP 1.2, WP 4.1 and WP 4.2). These risk estimates relate to different endpoints (humans, ecosystems, specific species), different spatial scale levels (EU, regional, local), different levels of detail ('potential cumulative risks' in WP 1.2 and 'refined cumulative' risks in WP 4.2), and different levels of accuracy. It will be necessary to integrate and visualise these risks in Geographic Information Systems (GIS) before they can be presented and communicated to the scientific community, policy makers, stakeholders and the general public. The main objective of WP 4.4 therefore is to develop and demonstrate the most appropriate and/or novel techniques for presentation and visualization of cumulative risks and of environmental and human health risks combined. The work in WP 4.4 will provide tools to make risk assessment results accessible for further dissemination (see WP 5.4). Where WP 4.4 concentrates on the presentation techniques that may help to increase the perception of cumulative risks by the end-users, WP 5.4 concentrates on the most efficient ways (e.g., brochures, internet, workshops, etc.) to communicate these results. WP 4.4 has a highly integrative character throughout the NOMIRACLE project and strongly depends on the availability and suitability of data and output produced by the consortium members in other RPs and work packages. The participants in WP 4.4 are all represented in WP 1.1 (data background) as well.

The work will be divided into two stages. The first stage is to establish ways to produce 'potential cumulative risk maps', among others for chemical mixtures, based on the type of data gathered in WP 1.1 and the scenario ranking procedure of WP 1.2 (ALTERRA, NERI, UFZ, UNIMIB, URV, JRC). The methods must be suitable to construct GIS-based risk maps for the EU and selected regions (depending on data availability in WP 1.1) that integrate the cumulative risks of exposure to chemicals with a specific mode of action (e.g., pesticides, pharmaceuticals and biocides) in combination with other relevant stressors (identified in WP 1.2). These initial presentation and visualization methods will in turn be used as input for WP 4.3, i.e., the examples (maps etc.) produced are evaluated with respect to their suitability to inform key actors and stakeholders and it will be investigated in WP 4.3 in what type of cumulative risks/parameters these groups are most interested.

During the second stage of WP 4.4, the 'potential cumulative risk maps' and other visualization products will be updated with information and new scientific insights from the other

research pillars and work packages (ALTERRA, NERI, JRC, UFZ, UNIMIB, URV, DESUN). For example, the results of WP 2.4 (sound exposure modelling) will be used to update the predictions of exposure through various environmental media involved. The results of RP 3 (advanced effect assessment) and WP 4.1 (uncertainty factors) will be applied to update effects of cumulative stressors predicted during the initial stage. Uncertainties in the updated risk estimates can be quantified and made visible at the basis of the PRA techniques developed in WP 4.1. Scaling routines for risks and aggregation methods developed in WP 4.2 can be employed to aggregate spatial data and describe risks at different spatial scale levels. These work packages contribute to more scientifically sound and accurate predictions of the risks of cumulative stressors. Importantly, the results of the risk perception and communication studies under WP 4.3 will be used to finalise the presentation and visualization methods that were developed during the first stage of WP 4.4 in such a way that cumulative risks are made readily perceivable for end-users and decision making is facilitated. WP 4.4 will also be constantly in touch with WP 5.4 to ensure user-friendly communication of results with end-users and other interested parties. The examples of risk maps produced during this second stage of WP 4.4 will include actual cumulative risks and risks for a limited number of future scenarios, e.g., dealing with the effects of climate change.

Management - Pillar 5 (Project co-ordinator: Hans Løkke, NERI)

The management activities are organised in a cross-cutting pillar consisting of four work packages as depicted in Figure B.4-1.

WP 5.1

Acronym	NERI	UFZ	NERC	DESUN
Person months	31.5	1.5	1.5	1.5

WP 5.2

Acronym	JRC	NERI
Person months	14	1

WP 5.3

Acronym	APINI	DBUA	DESUN	All university partners contribute with at least 0.5 month training activity
Person months	8	1	0.5	
Acronym	DIA	ENVI	JRC	
Person months	0.5	2.5	2	
Acronym	NERI	SYKE	UFZ	
Person months	3	1.5	1	

WP 5.4

Acronym	SYMLOG	NERI	All other partners participate in this activity with input for scientific and popular dissemination
Person months	7.5	3	

WP 5.1 General Project Management (Leader: Hans Løkke, NERI)

This activity is described in detail in section B.6. The WP 5.1 includes information on the activities of the Project Co-ordinator, the Management Board, the Project Secretariat, the Advisory Board, the management at Research Pillar and at WP level, and the General Assembly. It contains a plan for management of knowledge, of intellectual property and of other innovation-related activities arising in the project.