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Exploring Environmental Quality and Human Health Relationships: a Risk-based Tool for Ranking Environmental Chemical Stressors at the Regional Scale

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SUMMARY

The European Environment and Health Strategy (2003) and the associated Action Plan 2004-2010 promote the improvement of the "environment and health" information chain and ask for the development of innovative methodologies and tools for health risk and impact assessment, able to address the complexity of environment-health causal pathways and to effectively support decision-makers in setting up appropriate health protection policies. In this context, there is the need for screening tools, suitable to identify the most critical scenarios and the most dangerous health stressors with the aim of addressing assessment efforts and resources towards the most critical situations. The identification in a regional context of the priority chemical contaminants to be further investigated according to the risk they pose to human health is indeed a challenging task. To this purpose, within the present PhD thesis, a "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors" has been developed, aimed at supporting decision-makers in the identification of priority environmental contaminants, as well as priority areas, to be further assessed. Different methodologies for ranking environmental contaminants are currently available, but most of them is based on the use of data on the intrinsic properties of chemicals (e.g. physico-chemical or toxicological parameters). Instead, the developed methodology make use of site-specific environment and health data, with the aim of exploiting monitoring datasets which are becoming available at the local, regional and European level. Specifically, the methodology is based on the integration of data from three "Lines-of-Evidence", namely concerning environmental contamination, human biomonitoring (exposure biomarkers) and health outcomes monitored in the region of interest. Weight-of-Evidence (WoE), as an approach aimed at synthesizing individual Lines of Evidence (LoEs) to derive a conclusion about the degree of impairment or risk of a certain situation, has been explored as framework for integrating different monitoring information from the environmental domain and the health domain. In particular, the need for structure, transparent, flexible and reproducible WoE methods has guided the methodological development towards the application of Multi-Criteria Decision Analysis (MCDA) for implementing a quantitative WoE. MCDA, indeed, offers flexible options for quantitatively integrating information from different sources with value-based assessment and expert judgement. Rankings of chemical stressors at the regional level as well as within each sub-area (e.g. counties, municipalities) are the main outputs of the proposed Tool. Moreover, the Tool allows the end-user to identify priority sub-areas within the region of interest, where environmental and health data suggest possible effects on population health and therefore more investigation efforts are required. The tool has been applied to a case-study in the Flemish region (Belgium), using soil contamination data and data on biomarkers of exposure and

effect measured in adolescents in the frame of the Flemish Biomonitoring Programme 2002-2006. The application allows to analyse the potentialities and possible drawbacks of the developed tool and demonstrates the utility of integrating different environment and health data for screening purposes. The issue of uncertainty incorporation and analysis in health risk assessment is tackled through different approaches, such as the application of Fuzzy membership function as MCDA normalization functions. Moreover a sensitivity analysis based on Monte Carlo approach permits to investigate in the developed methodology the role of LoEs' weights in influencing the final ranking of chemical stressors.

SOMMARIO

La Strategia Europea per l'Ambiente e la Salute (2003) ed il Piano d'Azione per l'Ambiente e la Salute 2004-2010 ad essa associato sollecitano l'approfondimento della conoscenza delle relazioni tra stressori ambientali e salute umana e promuovono lo sviluppo di metodologie e strumenti innovativi per la valutazione dei rischi e degli impatti sanitari, in grado di analizzare le complesse relazioni causali ambiente-salute e di supportare efficacemente le autorità competenti nella definizione di adeguate politiche di protezione della salute. In questo contesto, emerge la necessità di sviluppare strumenti di screening adatti a identificare gli stressori ambientali più pericolosi, al fine di indirizzare le attività e le risorse disponibili verso gli scenari caratterizzati da una maggiore criticità. L'identificazione a scala regionale dei contaminanti ambientali prioritari che devono divenire oggetto di analisi dettagliata può infatti costituire un processo complesso.

Per superare questa problematica, nell'ambito del presente lavoro di tesi è stato sviluppato uno strumento per la prioritizzazione degli stressori chimici a scala regionale sulla base del rischio per la salute umana, finalizzato a supportare l'identificazione di contaminanti chimici prioritari e di aree prioritarie da analizzare in dettaglio. Nel contesto internazionale sono attualmente disponibili numerose metodologie per la prioritizzazione di contaminanti chimici, ma la maggior parte di esse utilizza dati relativi alla proprietà intrinseche delle sostanze chimiche (quali le proprietà chimico-fisiche o tossicologiche). La metodologia sviluppata nella presente tesi si basa invece sull'uso di dati ambientali e sanitari sito-specifici derivati da monitoraggi effettuati nella regione oggetto di studio. Nello specifico, la metodologia si fonda sull'integrazione di dati relativi a tre "Linee di Evidenza", riguardanti rispettivamente la contaminazione ambientale, l'esposizione della popolazione determinata attraverso il biomonitoraggio e gli effetti sulla salute monitorati nella regione di interesse. Un approccio di tipo *Weight-of-Evidence* (*WoE*), in grado di sintetizzare i dati da multiple *Linee di Evidenza* per ottenere una valutazione sul grado di impatto o di rischio di una specifica situazione, è stato scelto per la sua capacità di offrire una struttura metodologica adatta ad integrare informazioni dal contesto ambientale e da quello sanitario. In particolare, l'importanza di utilizzare dei metodi *WoE* strutturati, trasparenti, flessibili e riproducibili ha guidato lo sviluppo metodologico verso l'applicazione dell'Analisi Decisionale Multi-Criteriale (MCDA) con l'obiettivo di implementare una metodologia *WoE* quantitativa. I metodi MCDA offrono infatti la possibilità di integrare secondo un approccio quantitativo informazioni provenienti da differenti fonti con il giudizio esperto.

I risultati principali dello strumento sviluppato consistono nella prioritizzazione degli stressori chimici a scala regionale e all'interno di singole sotto-aree (ad esempio province o comuni). Inoltre, lo strumento permette all'utente di identificare le sotto-aree prioritarie nella regione dove i dati

suggeriscono possibili effetti sulla salute della popolazione e potrebbero essere quindi necessarie ulteriori indagini.

Lo strumento sviluppato è stato applicato ad un caso di studio nella regione delle Fiandre (Belgio), utilizzando dati relativi alla contaminazione del suolo e a biomarkers di esposizione e di effetto monitorati in adolescenti nell'ambito del Programma Fiammingo di Biomonitoraggio 2002-2006. L'applicazione ha permesso di analizzare potenzialità e possibili debolezze dello strumento e ha dimostrato l'utilità di integrare dati ambientali e sanitari in uno strumento con finalità di screening.

La problematica dell'inclusione e analisi dell'incertezza nella valutazione del rischio sanitario è stata affrontata ricorrendo a diversi approcci, quali, ad esempio, l'utilizzo di funzioni basate sulla logica *Fuzzy* per la fase di normalizzazione della procedura MCDA. Inoltre un'analisi di sensitività basata sul metodo di Monte Carlo ha consentito di analizzare il ruolo che svolgono i pesi attribuiti dall'utente alle diverse *Linee di Evidenza* nell'influenzare la classificazione degli stressori ambientali prioritari a scala regionale.

LIST OF CONTRIBUTIONS

PUBLISHED PAPERS

Agostini P., Suter G.W. II, Gottardo S., **Giubilato E.,** 2009. Indicators and Endpoints for Risk-Based Decision Processes with Decision Support Systems. In: Marcomini A., Suter G.W. II, Critto A. (Eds). Decision Support Systems for Risk Based Management of Contaminated Sites, 2009, Springer Verlag, New York.

PAPERS IN PREPARATION

Giubilato E., Zabeo A., Giove S., Critto A., Marcomini A., Den Hond E., Koppen G., 2012. A Risk-based Tool for the Regional Ranking of Health Environmental Stressors.

Giubilato E., Zabeo A., Giove S., Critto A., Marcomini A., 2012. Sensitivity analysis of a MCDA risk-based model for the prioritization of environmental contaminants.

ABSTRACTS

Giubilato E., Critto A., Micheletti C., Marcomini A., Bois F., 2007. Assessment of Environmental Health Risk in Multi-causal Systems: the 2-FUN Project. Accepted as poster presentation at the 25th European SEGH Conference, 4-5 June 2007, Liverpool (UK).

Giubilato E., Critto A., Micheletti C., Marcomini A., Bois F., 2007. Full-chain and UNcertainty Approaches for Assessing Health Risks in FUture Environmental Scenarios: the 2-FUN project. Accepted as poster presentation at the INTARESE Annual Conference, 21 November 2007, Prague (Czech Republic).

Giubilato E., Critto A., Micheletti C., Marcomini A., Bois F., 2008. *Environmental Contamination and Human Health in Multi-causal Scenarios: the 2-FUN project*. Accepted as poster presentation at SETAC Europe Annual Conference – 25-29 May 2008, Warsaw (Poland).

Marcomini A., Critto A., **Giubilato E.**, Pizzol L., Gottardo S., Semenzin E., Agostini P., 2009. GIS-based Decision Support Systems for spatial-oriented assessment and communication of ecological and

human health risks. Accepted as platform presentation at NoMiracle Conference on "Multiple Stressors – Novel Methods for Integrated Risk Assessment", 28-30 September 2009, Aarhus (DK).

Giubilato E., Zabeo A., Giove S., Critto A., Marcomini A., 2011. A Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors. Accepted as poster presentation at the conference INTARESE / HEIMTSA / 2-FUN Final Conference, Bruxelles (Belgio), 20 Gennaio 2011.

Giubilato E., Zabeo A., Giove S., Critto A., Marcomini A., Den Hond E. Koppen G., Van Gestel G., 2011. *Risk-based Regional Ranking of Health Environmental Stressors.* Accepted as platform presentation at the conference GEOMED 2011- 4th International Conference on Medical Geology, 20-25 Settembre 2011, Bari (Italia).

Pizzol L., **Giubilato E.**, Critto A., Marcomini A., Bittens M., Bartke S., 2011. Development of an Expert System for optimizing the evaluation and selection of risk based approaches and technologies for brownfield rehabilitation: perspectives from TIMBRE project. Accepted as poster presentation at the conference GEOMED 2011- 4th International Conference on Medical Geology, 20-25 Settembre 2011, Bari (Italia).

EXTENDED ABSTRACTS

E. Giubilato, Zabeo A., Giove S., Critto A., Marcomini A., 2011. Analisi di rischio a scala regionale per la prioritizzazione di contaminanti chimici pericolosi per la salute umana. Accepted as platform presentation at the conference "Analisi di rischio: attualità e casi applicativi" in the frame of *REMTECH 2011 - 5° Salone sulle Bonifiche dei Siti Contaminati e sulla Riqualificazione del Territorio*, 28-30 Settembre 2011, Ferrara (Italia).

CHAPTER 1

INTRODUCTION

1.1 MOTIVATIONS AND OBJECTIVES

The relationships between environmental quality and human health is playing (and will keep playing) a central role in the policy agenda of the European Union, also as a consequence of the citizens' demand for their right to a safe life environment being pursued and guaranteed. Even if in the last decades environmental legislation was aimed at reducing the negative effects of chemical and physical stressors generated by anthropogenic pressures on ecosystems and human populations, there is still the need for identifying actual, emerging and potential health threats and to propose and implement adequate risk management actions.

To promote and enhance an effective plan for better understanding and adequately managing environmental health issues at the European scale, the European Commission developed in 2003 the "Environment and Health Strategy" (EC, 2003), followed by the "Environment and Health Action Plan 2004-2010" (EC, 2004). The Action Plan promotes the improvement of the "environment and health" information chain, the strengthening of research efforts for filling knowledge gaps and the setting up of adequate response policies for the protection of citizens' health. The Action Plan asks for the development of innovative methodologies and tools for health risk and impact assessment, able to address the complexity of environment-health causal pathways and to effectively support decision-makers in setting up appropriate health protection policies. In this context, emerges also the need for screening tools able to identify the most critical scenarios and the most dangerous hazards, in order to identify those situations where a detailed assessment of health risks is advisable. In complex system, indeed, where multiple stressors interact, many targets are contemporary involved and different health outcomes can be detected in the population, initial assessment efforts should be directed to the most relevant scenarios, with the aim of focusing the further risk assessment on the most critical situations (Menzie et al., 2007). This should be a "focusing exercise" aimed at guiding assessment efforts and resource towards those health stressors which could correspond to the greatest potential effects on human health.

Several methodologies for screening and ranking chemical substances are currently available at the international level, developed in particular by agencies and research institutes in the United States or in the European Union with the aim of estimating the level of concern to which a chemical should be

associated and identifying therefore “priority substances” to be further investigated (IEH, 2004a). Most of these methodologies commonly make use of data on intrinsic properties of substances (physico-chemical properties and toxicological/ecotoxicological properties) or estimates of potential population exposure to these substances (for example, calculated from production tonnages and potential applications/uses) and allow to screen chemicals considering generic exposure scenarios. Examples of such methodologies are EURAM – European Union Risk Ranking Method (Hansen et al., 1999), CHEMS - Chemicals Hazard Evaluation for Management Strategies developed by US EPA (Davis et al., 1994; Swanson et al., 1997), the Prioritisation Scheme developed by the MRC Institute for Environment and Health of the University of Leicester (IEH, 2004b).

It is more difficult, however, to find in the literature structured and quantitative ranking methodologies suitable for screening chemical substances in reference to a site-specific context, which could identify at the local or regional scale priority environmental chemical stressors on which focus further investigations and analyses.

In recent years consistent monitoring efforts have been accomplished within EU Member States, as results of regional, national or international projects and initiatives aimed at investigating the environmental and health status for verifying legislation compliance or for research purposes (Smolders and Schoeters, 2007). Therefore, different types of environment and health data may be available within a region as output of monitoring campaigns and surveys: there is hence the opportunity to collect these data from different sources and to exploit them with the aim of identifying priority contaminants within a selected region.

The main objective of the work presented in this PhD thesis (realized in the context of the European Project “2-FUN”, described in Paragraph 1.3) is to develop a methodology for ranking environmental chemical stressors at the regional scale, suitable to support decision-makers in the evaluation of environment and health data collected within a region of interest with the aim of identifying which pairs of “chemical-health outcome” should become the subject of a detailed assessment. One of leading criteria for the methodological development consists in the use of data on actual population exposure to environmental contaminants and on health outcomes measured in the population of interest, i.e. the exploitation of site-specific data rather than data about the intrinsic properties of chemical compounds and general exposure scenarios. The integration of data about environmental contamination, human exposure and health effects, if properly managed, could indeed support effectively the exploration of environment and health relationships (Mather et al., 2004; Smolders and Schoeters, 2007). Weight-of-Evidence (WoE), as an approach aimed at synthesizing individual Lines of Evidence (LoE) to derive a conclusion about the degree of impairment or risk of a certain situation (Linkov et al., 2009), has been explored as framework for integrating different monitoring information from the environmental domain and the health domain. In particular, the need for

structured, transparent, flexible and reproducible WoE methods (Weed, 2005) has guided the methodological development towards the application of Multi-Criteria Decision Analysis (MCDA) for implementing a quantitative WoE method. MCDA, indeed, offers flexible options for quantitatively integrating information from different sources with value-based assessment and expert judgement (Linkov et al., 2011).

Moreover, the work performed in the context of this PhD thesis is aimed at exploring some aspects related to the management of uncertainty in health risk assessment. Environmental epidemiologists and health risk and impact assessors grapple since long time with problems of uncertainty in data and their relationships, and this issue is becoming more challenging due to the increasing complexity of the environment and health systems under analysis (Briggs et al., 2008). Therefore, one of the objectives of this thesis consists in achieving an overview about how uncertainty is commonly classified, assessed and managed in environmental health risk and impact assessments. Some of the reviewed approaches have then been applied in the development and evaluation of the methodology for ranking environmental chemical stressors, also taking into account the particular characteristics of MCDA approach such as the incorporation of expert judgement that could represent a significant source of uncertainty in the assessment.

A case-study in the Flemish region (Belgium), concerning the relationships between soil contamination and health outcomes in adolescents, has been selected in order to translate the methodological developments into a concrete analysis of a real environmental health issue and to allow a testing application of the proposed methodology for ranking environmental chemical stressors with the aim of exploring its potentialities and weaknesses.

In conclusion, the specific objectives of the work presented in this PhD thesis are:

- to explore the applicability of MCDA-based quantitative WoE procedures for effectively integrating information from the environmental domain and the health domain;
- to develop a risk-based methodology for ranking environmental chemical stressors at the regional scale, allowing also the identification of priority areas within the region of interest, based on the integration of available environment and health monitoring data;
- to test the developed methodology on a real case-study, with the aim of analysing its potentialities and possible drawbacks;
- to identify current approaches for evaluating and incorporating uncertainty analysis in procedures for assessing human health risks;
- to analyse the uncertainty associated with the choice of input parameters in the developed MCDA model and its consequences on risk-based prioritization of chemicals.

1.2 THESIS STRUCTURE

The thesis is structured in seven chapters, presenting the theoretical backgrounds, the methodological developments and the applications of the developed methodology on a case-study.

The first chapters are aimed at depicting the policy context and the methodological backgrounds:

Chapter 2 – "Environment and health policies and research initiatives in Europe"

presents the main foundations of the EU approach to environment and health policies and offers a synthetic overview on EU-funded research on issues related to the "environment and health" topic;

Chapter 3 – "Environment and health assessment frameworks and tools"

illustrates how different approaches to the assessment of environmental health risks and impacts developed in the last decades and then gives an insight into available typologies of environment and health data and indicators; moreover, principles and characteristics of Weight-of-Evidence approaches and of Multi-Criteria Decision Analysis methods as useful tools for supporting health risk assessment are introduced;

Chapter 4 – "Dealing with uncertainty in health risk assessment"

offers a state-of-the-art taxonomy of uncertainty in health risk assessment and presents an overview of available probabilistic methods for incorporating and analysing in health risk assessment.

The results of the research activities are illustrated in the following chapters:

Chapter 5 – "Development of a tool for ranking environmental chemical stressors at the regional scale"

presents the conceptual approach and the methodological development of a risk-based methodology for ranking environmental contaminants at the level of sub-areas within a region, at the regional scale and for the prioritization of sub-areas within the region; moreover, the implementation of the methodology into a prototype software is described.

Chapter 6 – "Case-study: soil contamination and adolescents' health in Flanders (Belgium)"

illustrates the application of the developed tool to a cases-study in the Flemish region (Belgium), with the aim of exploring the potentialities and the possible drawbacks of the proposed methodology.

Chapter 7 – "Sensitivity analysis"

describes the sensitivity analysis performed for the developed methodology, in particular with reference to the effects of user's choice about input parameters of the MCDA-based model.

Chapter 8 – "Conclusions"

includes considerations and remarks about the main findings of the developed activities and highlight potentialities and criticalities as well as possible further improvements of the proposed methodology.

1.3 2-FUN PROJECT

The work presented in this thesis has been developed within the European Project "2-FUN" (www.2-fun.org), started in 2007 and closed at the beginning of 2011. The acronym 2-FUN stands for "*Full-chain and UNcertainty Approaches for Assessing Health Risks in Future ENvironmental Scenarios*". The project was funded by the European Commission (EC) within the 6th Framework Programme for Research and Technological Development (FP6), under the Thematic Priority "Global Change and Ecosystems". 2-FUN project involved 12 partners from 9 EU Countries and was coordinated by the French National Institute for Industrial Environment and Risks (Institut National de l'Environnement Industriel et des Risques - INERIS). 2-FUN belongs to a set of projects funded by the EC under the FP6 with the aim of developing innovative approaches and tools to support the estimate of risks and impacts on human health caused by environmental factors and to help decision-makers in defining their priorities in environmental health management.

2-FUN project focused in particular on the following primary objectives:

- to establish methods for constructing long-term environmental and socio-economic scenarios;
- to develop multi-media and QSAR (Quantitative Structure–Activity Relationship) modelling of indirect exposures;
- to perform toxicity assessment for mixtures of substances using Physiologically based pharmacokinetic (PBPK) models;
- to improve health risk assessment for children;
- to develop methods for uncertainty and sensitivity analyses in risk assessment.

The project was structured in 6 Work Packages:

- **WP1** aimed at developing innovative tools for the selection and building of realistic environmental health scenarios, including methods for downscaling climatic and socio-economic

data to construct regional and local scenarios, statistical methods for the treatment of small samples of strongly uncertainty data, methods for the prioritization of environmental chemical stressors to be further analysed;

- **WP2** aimed at developing a flexible, modular multi-media exposure model for estimating the transfer of chemical contaminants from different environmental media to human population, including indirect exposure pathways (e.g. diet);
- **WP3** aimed at building a general PBPK model, including children, women of all age and the foetus, to predict the absorption, distribution, metabolism and excretion of chemical compounds in the organism; moreover, WP3 had the objective of developing pathology models (dose-response models) for linking internal dose of toxic chemicals to health response, taking into account the interactions between different chemicals;
- **WP4** aimed at testing and demonstrating the effectiveness of the approaches and tools developed in the previous WPs in case-studies covering different environmental health scenarios and spatial scales in several European contexts (air contamination and thermal stress in the Lisbon region in Portugal; soil contamination and health effects in children in Upper Silesia region in Poland; freshwater contamination and potential health effects in the river Seine basin in France) ;
- **WP5** and **WP6** were devoted to the communication of results and training activities and to project management respectively.

The multi-media exposure model, the PBPK model and the dose-response models are linked together in a sequence (they constitute the so-called 2-FUN TOOLBOX), that allows to apply a full-chain approach to environmental health risk assessment, starting from the release of a chemical substance into the environment to the development of an adverse effect in a target organ.

As illustrated in Figure 1.1, the methods developed in WP1 are preliminary to the application of the predictive models included in the 2-FUN TOOLBOX, because they allow to selected the environmental contaminants of interest, to derive and statistically manage all the data needed for the health risk assessment (e.g. environmental data, socio-economic data, climatic data, etc.).

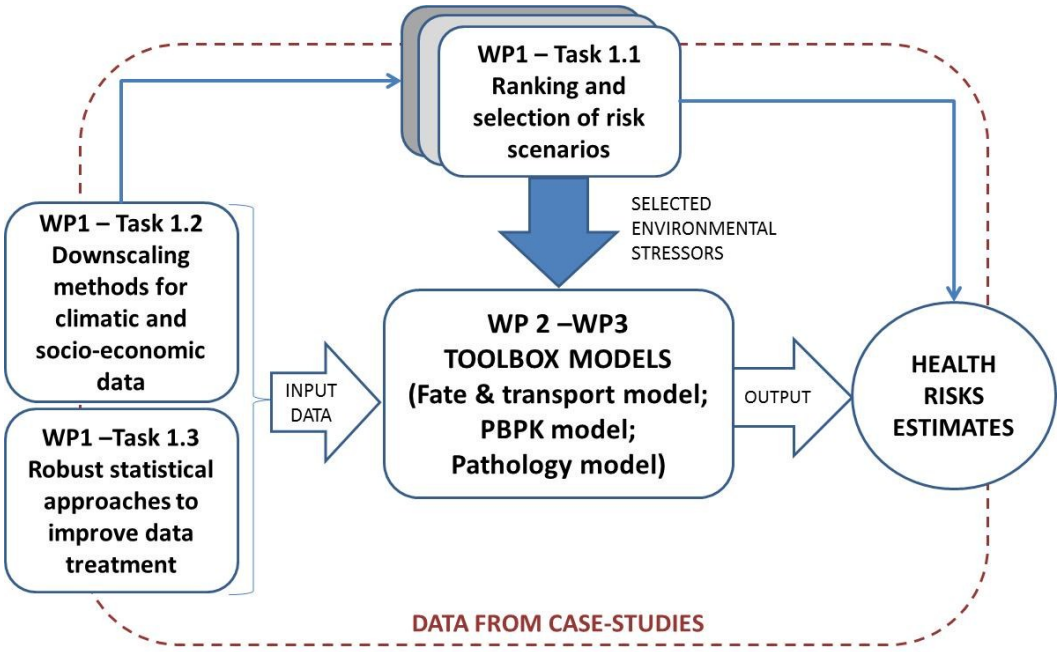


Figure 1.1 Overview of the structure of 2-FUN project

The methodological developments and outcomes merged within this thesis were partially developed within WP1 (coordinated by the University Ca' Foscari of Venice), and in particular are related to the activities of Task 1.1, aimed at the development of a methodology for the ranking and selection of environmental chemical stressors in order to select priority scenarios to be further investigated. The dataset needed for a testing application of the developed methodology was collected in collaboration with the Flemish Institute for Technological Research – VITO (one of the component of 2-FUN consortium), and are the results of previous environmental and biomonitoring campaigns realized in the Flemish region (Belgium).

1.4 REFERENCES

Briggs D.J., Sabel C.E., Kayoung L., 2008. Uncertainty in epidemiology and health risk and impact assessment. Environmental Geochemistry and Health 31: 189-203.

Davis G.A., Kincaid L.E., Swanson M., Schultz T., Bartmess J., Griffith B. & Jones S., 1994. Chemical Hazard Evaluation for Management Strategies: A Method for Ranking and Scoring Chemicals by Potential Human Health and Environmental Impacts. EPA/600/R-94/177. United States Environmental Protection Agency, Office of Research and Development, Washington DC.

EC, 2003. A European Environment and Health Strategy. Communication from the Commission to the Council, the European Parliament and the European Economic and Social Committee, COM (2003) 338 final, European Commission, Brussels, Belgium.

EC, 2004. Communication from the Commission on the "European Environmental and Health Action Plan 2004-2010", COM (2004) 416 final, European Commission, Brussels, Belgium.

Hansen B.G., van Haelst A.G., van Leeuwen K. and van der Zandt P., 1999. Priority Setting for Existing Chemicals: the European Union Risk rAnking Method. Environmental Toxicology and Chemistry 18: 772–779.

IEH, 2004a. A Review of Prioritisation Methodologies for Screening Chemicals with Potential Human Health Effects as a Result of Low-Level Exposure. IEH Web Report W13. MRC Institute for Environment and Health, Leicester, UK. Report available at http://www.le.ac.uk/ieh/.

IEH, 2004b. A Screening Method for Ranking Chemicals by their Fate and Behaviour in the Environment and Potential Toxic Effects in Humans Following Non-occupational Exposure. IEH Web Report W14. MRC Institute for Environment and Health, Leicester, UK. Report available at http://www.le.ac.uk/ieh/.

Linkov I, Loney D., Cormier S., Satterstrom F.K., Bridges T. 2009. Weight-of-evidence evaluation in environmental assessment: review of qualitative and quantitative approaches. Science of the Total Environment 407(19): 5199–205.

Linkov I.,Welle P., Loney D., Tkachuk A., Canis L., Kim J.B., Bridges T., 2011. Use of Multicriteria Decision Analysis to support Weight of Evidence evaluation. Risk Analysis 31(8): 1211-1225.

Mather F.J., White L.E., Langlois E.C., Shorter C.F., Swalm C.M., Shaffer J.G., Hartley W.R., 2004. Statistical methods for linking health, exposure and hazards. Environmental Health Perspectives 112 (14): 1440-1445.

Menzie C.A., MacDonell M.M., Mumtaz M., 2003. A phased approach for assessing combined effects from multiple stressors. Environmental Health Perspectives 115 (5): 807-816.

Smolders R. and Schoeters G., 2007. Identifying opportunities and gaps for establishing an integrated EDR-triad at the European level. International Journal of Hygiene and Environmental Health 210: 253-257.

Swanson M.B., Davis G.A., Kincaid L.E., Schultz T.W., Bartmess J.E., Jones S.L. and George E.L., 1997. A screening method for ranking and scoring chemicals by potential human health and environmental impacts. Environmental Toxicology and Chemistry 16: 372–383.

Weed D. L., 2005. Weight-of-Evidence: a review of concepts and methods. Risk Analysis, 25(6): 1545 1557

CHAPTER 2

ENVIRONMENT AND HEALTH POLICIES AND RESEARCH INITIATIVES IN EUROPE

2.1 ENVIRONMENT AND HEALTH POLICIES IN EUROPE

In the last decades an increasing awareness of the deep relationship between environmental quality and human health guided the European Union (EU) in the development of new policies and strategies aimed at protecting the health of citizens from environment-related hazards, moving towards more integrated approaches to environmental and health issues.

The EU Sixth Environment Action Programme (6EAP) recognized the relevance of the environment-health link and included among its main objectives to contribute to a *high level of quality of life and social well-being for citizens by providing an environment where the level of pollution* (and other health stressors) *does not give rise to harmful effects on human health and the environment* (EC, 2002). The topic "environment and health" is identified as one of the four priorities of the Environment Action Programme to be deal with since 2002 until 2012 and thus, at the beginning of the XXI century, this issue start playing a central role in the European policies.

Following the 6 EAP, the European Commission developed in 2003 the European Environment and Health Strategy (EC, 2003), aimed at reducing the burden of environment-related diseases in the EU, at identifying and reducing new health threats related to environmental determinants and at reinforcing the capability of EU to development adequate response policies. The Strategy was launched as the "SCALE initiative", where the acronym stands for:

- Science, since there is the need for achieving a more complete knowledge on environmental health thanks to the contributions of different actors;
- Children, who, as vulnerable individuals and future of the society, deserve a specific approach to be adequately protected;
- Awareness, as the starting point for each component of the society to start acting towards health protection;
- Legal Instruments, necessary to translate knowledge and decisions into proper actions at the international, national and local level;
- Evaluation, i.e. continuous monitoring of the effectiveness of the actions in terms of reduction of environmental-related problems.

The Environment and Health Strategy proposes an integrated approach to environmental health issues, which means an increased integration between the environment and health sectors in the monitoring and collection of data, in research activities, in developing response actions. The investigation and intervention efforts of each Member State should converge into a unique European Integrated Environment and Health Monitoring and Response System, constituting the base for a solid European knowledge on environmental population exposures and their health effects. Moreover, the Strategy promotes the involvement all stakeholders (international, national and local authorities, industry, academia, citizens, NGOs) which are asked to actively cooperate in the implementation of the aforementioned objectives.

The Strategy set out a long-term approach and is due to be implemented through several cycles. The Environment and Health Action Plan 2004-2010 (EC, 2004) constitutes the first cycle and was adopted by the Commission in 2004; it is designed to fit with already existing initiatives at regional, national and EU/international level, in particular the World Health Organization (WHO) pan-European Environment and Health process (ISS, 2006). The Action Plan 2004-2010 is aimed at improving and refine available knowledge of the significant causal links between environmental factors and diseases, and identifies four priority diseases to be considered first, namely respiratory diseases, neuro-developmental disorders, cancer and endocrine disrupting effects.

This first Action Plan identifies 13 concrete recommendations for action, structured in three main themes, i.e.:

1) *improve the information chain by developing integrated environment and health information*
2) *fill the knowledge gap by strengthening research on environment and health and identifying emerging issues*
3) *response: review policies and improve communication by developing awareness raising, risk communication, training and education.*

Under the first theme, the development of environmental health indicators is required, with the aim of enabling the collection of data comparable among the Member States. Moreover, adequate environmental monitoring systems should be set up to estimate the exposure of population to different environmental factors (chemical, physical, biological, life-style and socio-economic factors) which could be implicated in the aetiology of diseases. Also exposure through food has to be monitored and the communication between health, food and environment professionals should be strengthened. Moreover, the Action Plan 2004-2010 asks for the development of a coherent approach to biomonitoring in Europe, whereas the monitoring of human biomarkers (of exposure, effects, genetic susceptibility) represent a fundamental step in the elucidation of the exposure-disease causal chain. The coordination among Member States should improve data comparability

and support the integration of information through the exchange of experiences between teams and countries.

The second theme of the Action Plan focuses on the need to reinforce research activities on environment and health with the aim of filling knowledge gaps and promptly identifying emerging issues. In the "Background Papers to the EU SCALE process" (EEA, 2004), the Europena Environmental Agency highlights the need to adopt a multi-causal approach in investigating the development of diseases, through the exploration of the complex interconnections existing between environmental and socio-economic risk factors; it is recognized that this task poses significant challenges to traditional science and calls for a broader integration across different disciplines. The Action Plan therefore asks for the development of innovative methodologies and tools for risk assessment able to address the multi-causality of diseases, and also to improve the economic valuation and impact analysis of prevention strategies. Moreover, potential environmental hazards should be promptly identified, such as those related to global environmental changes (including climate change), and suitably addressed. To achieve these objectives, the Action Plan aims at strengthening and consolidate the integration between environment and health research sectors and at making full use of results from project, networks and clusters, also to enhance the transfer of know-how and information from research to policy development. In Paragraph 2.2 an overview of the research initiatives on environment and health funded by the European Commission will be provided.

Finally, under the third theme the Action Plan addresses the need for adequately communicate the results of risk assessment processes and for reviewing and refine risk reduction policies once more information on environmental health risks become available. The Action Plan highlights the relevance of raising the awareness about environmental health risks among EU citizens and of properly and effectively communicating information about the main risk factors and corresponding risk reduction measures and behaviours. The training of professionals in environmental health topics and the reinforcement of organisation dealing with these issues is identified as a crucial element in achieving an adequate and effective risk management. The increased understanding of environmental health dynamics should be the starting point for testing the effectiveness of existing policies and adapting them when necessary. The Commission is charged of implementing a number of risk reduction initiatives targeting first the four priority diseases and should ensure that the results of technical working groups are taken into account in the development of such initiatives.

One of the key component of the Strategy and the Action Plan 2004-2010 consists in the special attention paid to children. Children have indeed a unique vulnerability, because they go through several distinct developmental and learning phases (i.e. foetal, neonatal, school-age and pubertal phases) and at each stage they are exposed and vulnerable to different stressors, according to their

age-specific typical behaviours (e.g. hand-to-mouth behaviour) and changing in their bodies (e.g. development of reproductive system). Moreover, due to their life expectancy, they are likely to endure exposure to environmental stressors for a time longer than other components of the population. These considerations support the focus on children throughout the Strategy and guide the choice of the priority pollutants to be addressed (i.e. dioxins and PCBs, heavy metals and endocrine disrupters, selected also in view of the significant effects they can have on children's health).

The main actors asked to share the responsibility for the implementation of the Strategy and its Action Plan are:

a) *EU Member States*, who are responsible for implementing monitoring and risk management measures, for research, education and training, as well as for ensuring the exchange of information and practices across the national/EU level;
b) *Stakeholders groups* including industry and civil society, who are asked to actively participate in the environment and health debate, in supporting the collection of data, in adopting preventive actions and innovative responses to environmental hazards;
c) *the European Commission*, who has to coordinate all the main actors and promote the collaboration at the EU level, to liaise with relevant European agencies and bodies (e.g. EEA, EFSA), to implement monitoring, research and management actions through already existing initiatives and programmes (e.g. Framework Programmes for Research and Scientific Development, Public Health Programme), to consult relevant technical committees and working groups;
d) *International Organisations* (such as OECD, WHO, United Nations bodies), who can support the implementation thanks to their long experience in the field and are asked to support the integration of their initiatives with EU level programmes.

All these actors are invited to take part and contribute also to the initiatives organized by the WHO Regional Office for Europe (WHO, 2010a), that is one of the six WHO Regional Offices throughout the world. The WHO Environment and Health process is a not-legally binding initiatives, started in the '80s, and has in particular been marked by a series of Ministerial Conferences, participated by National Environment and Health Ministries together with many national and international NGOs: Frankfurt (1989), Helsinki (1994), London (1999), Budapest (2004) and Parma (2010).

During the Budapest conference, entitled "The future of Our Children", the focus was on the measures that the Governments can take to protect children's health: on this occasion, the "Children's Environment and Health Action Plan for Europe" (CEHAPE) (WHO, 2004) was adopted. It identifies four Priority Goals for the European region, namely:

1) to guarantee safe and affordable water and sanitation for all children;

2) to reduce health consequences from injuries and to assure adequate physical activity;
3) to guarantee safe indoor and outdoor air with the aim of reducing respiratory diseases;
4) to reduce the risk of disease arising from the exposure to chemical, physical and biological stressors and hazardous working environments during pregnancy, childhood and adolescence.

The last WHO Ministerial Conference was held in Parma in 2010 and its main output is the Parma Declaration on Environment and Health (WHO, 2010b). With this document, the Environment and Health Ministries of the European WHO Region recognize that population health effects are amplified by financial constraints, broader socio-economic and gender inequalities, and by a changing environment, characterized by more frequent extreme climate events. They confirm their commitment in carry out all actions necessary to achieve the Four Priority Goals of the CEHAPE set in Budapest, reasserting the central role that children's health should play in the environment and health agenda of all Countries. Moreover, climate change is identified as a significant source of potential threats to population health, and the need for integrating health issues in all climate change mitigation and adaptation measures, policies and strategies at all levels and in all sectors is strongly highlighted. Participating Countries commit themselves in setting up and reinforce early-warning and preparedness systems for extreme events and disease outbreaks and in supporting scientific research to improve the understanding of health vulnerabilities to climate change. They confirm their support to the establishment of a European Environment and Health Information System (ENHIS), to the creation of common tools and guidelines to evaluate the economic impacts of environmental risk factors to health, to the development of a coherent, shared approach to human biomonitoring tool to assist evidence-based public health policies. Finally, the signatory Countries recognize the essential role of multi-disciplinary research to face environmental health issues and secure their support in promoting the further development of existing tools and approaches.

All these aspects should guide the initiatives of the Countries until the next European Ministerial Conference on Environment and Health which will be held in 2016. In the meanwhile, it is also expected that the second Environment and Health Action Plan will be developed by the EC, according to the results and the knowledge/management gaps come up during the first Action Plan.

2.2 EU RESEARCH INITIATIVES ON ENVIRONMENT AND HEALTH

The European Framework Programmes for Research and Technological Development represent one of the main pillars of the European Research Area and are aimed at merging all research-related EU

initiatives together under a common frame, with a central role for reaching the goals of innovation, growth and employment in the EU.

Since the 5th Framework Programme (FP5; 1998-2002) a dedicated Key Action on *Environment and Health* was included within the *Quality of Life and Management of Living Resources* Theme and more than 90 trans-national interdisciplinary research projects were initiated.

The European Environment and Health Strategy and the associated Action Plan 2004-2010 have been some of the main drivers for environment and health research since the beginning of the 6th Framework Programme (FP6; 2002-2006), because they act as a catalyst to increase research funding at the EU level and provided inspiration and stimulus for FP6 research.

The FP6 funded more than 60 projects, increasing with respect to the past the overall EU contribution per year up to about 50 million € to this research field. Within FP6, a dedicated "Scientific Support to Policy" programme has been included, aimed at enhancing communications and cooperation between researchers and policy-makers and at enlarging the discussion about the effects and implications of research outcomes on new policies (EC, 2011a) . EU policy initiatives such as the Thematic Strategy on Air Pollution (2005), the Thematic Strategy on Urban Environment (2006) and the REACH regulation (Registration, Evaluation, Authorisation and Restriction of Chemicals) (2006) were supported by the results and policy recommendations provided by FP6 environment and health research projects.

Tarkowski (2007) revised through a bibliometric analysis the status of environmental health research in Europe and highlighted the need for more emphasis on investigation of issues such as exposure to multiple contaminants and their combined influence on health in different population groups, reinforcing the focus on complex relationships and multi-causality. This was exactly the aim of many Environment and Health FP6 projects, that tried to clear the way for gaining deeper insight in such issues. Some of the main results from FP6 include the establishment of large scale networks or coordination actions to face research fragmentation and to address relevant environment and health issues in an integrated way, such as in the fields of effects of endocrine disruptors, effects of indoor air pollution, aetiology of allergy and asthma. Emerging threats have also been tackled by FP6 projects, in particular the effect of global warming on distribution patterns of communicable diseases and the assessment of exposure and effects related to natural and engineered nanoparticles. Furthermore, relevant accomplishments concern the development of integrated environment and health risk assessment approaches and tools, including methodologies and tools for health impact assessment of policies. Significant results in this field have been achieved by a set of integrated projects including:

a) *INTARESE - Integrated assessment of health risks from environmental stressors in Europe*, within which the concept and framework of Integrated Environmental Health Impact Assessment has been developed (see Chapter 3);

b) *HEIMTSA - Health and environment integrated methodology and toolbox for scenario assessment,* that implemented a series of models and databases into a web-based modular toolbox aimed at performing health impact assessment of future policies across all Europe;

c) ENVIRISK - *Assessing the risks of environmental stressors: contribution to the development of integrating methodology,* that set up a conceptual and methodological framework to highlight the cumulative effect environmental risks have on the population health.

All these projects have been carried out contemporary to 2-FUN project (described in Chapter 1) and their developments have been followed during the thesis considering the deep interrelation and the complementarity among these projects.

With the first three calls for proposals of the 7th Framework Programme (FP7; 2007-2013) a total EU contribution of 265 million € have been assigned to 79 projects addressing environment and health research activities. The area of environment and health has become more integrated into environmental research as one of the main sub-activities of the theme "Environment (including climate change)". The identified priorities are:

1. health impacts of climate change;
2. health effects of environmental stressors other than climate change;
3. methods and decision-support tools for environmental health risk analysis and policy development.

A recent study by the EC investigates the contribution of the research initiatives launched under FP5, FP6 and FP7 in achieving the goals of the 13 specific actions of the Environment and Health Action Plan (EHAP; EC, 2004), through a desk-study and e-surveys and interviews with European experts (EC, 2011b). It results that most of the EHAP priorities have been covered by EU research, nonetheless there are still some coverage gaps in few research topics and in the method research outcomes are communicated and exploited in the research-policy dialogue. It is recognized that the EU-funded projects permitted the creation of a wide EU research platform with a high degree of legitimacy among the involved actors. The EU level is the most appropriate for environment and health research, since this topic involves common European problems which are not dependent on individual Member States' conditions. However, positive impacts of EU research on Member States' initiatives could be very relevant and should be monitored and reinforced in the future. The report also highlights a significant level of consensus among involved experts about emerging and re-emerging issues which deserve much attention in the future years, identified in: (1) development of common EU methodologies for health risk and impact assessment and harmonisation of

environment and health data monitoring; (2) assessment of combined exposure to (emerging) chemicals, also through biomonitoring tools; (3) assessment of the health effects of global change (including climate change). After the conclusion of the first Environment and Health Action Plan (2004-2010), EU research results achieved up to now trigger the preparation of a second Action Plan, able to enlarge the vision of the first one by covering activities which are not fully covered in policies and programmes so far and reinforcing the effectiveness of the research/decision-making dialogue (EC, 2011b).

2.3 REFERENCES

EC, 2002. Sixth Community Environment Action Programme. Decision No 1600/2002/EC of the European Parliament and of the Council of 22 July 2002, Brussels, Belgium.

EC, 2003. A European Environment and Health Strategy. Communication from the Commission to the Council, the European Parliament and the European Economic and Social Committee, COM (2003) 338 final, European Commission, Brussels, Belgium.

EC, 2004. Communication from the Commission on the "European Environmental and Health Action Plan 2004-2010", COM (2004) 416 final, European Commission, Brussels, Belgium.

EC, 2011a. European Research on Environment and Health funded by the Seventh Framework Programme. EUR 24641 EN. European Commission, Directorate-General for Research, Luxembourg Press Office.

EC, 2011b. Study on the longer-term impact of European Union funding of research in the field of Environment and Health. Directorate-General for Research and Innovation, Directorate I – Environment, Unit I.4 – Climate Change and Natural Hazards, Bruxelles.

EEA, 2004. Some EEA background papers to the EU SCALE process. Documents presented to the EEA/WHO/Collegium Ramazzini Workshop "Children in Their Environments: Vulnerable, Valuable and at Risk: The Need for Action", Budapest 22 June 2004.

EEA, 2005. Environment and Health. EEA Report n. 10/2005. European Environmental Agency, Copenhagen, Denmark.

EEA, 2007. Europe's Environment: the Fourth Assessment. European Environmental Agency, Copenhagen, Denmark.

ISS, 2006. International policies and instruments on environment and health: methodological suggestions for the Italian Action Plan. Liliana Cori, Loredana Musmeci (Eds,). Rapporti ISTISAN 06/26, Istituto Superiore di Sanità, Rome. (in Italian)

Tarkowski S.M., 2007. Environmental health research in Europe - bibliometric analysis. European Journal of Public Health 17(1): 14-18.

WHO, 2004. Children's Environment and Health Action Plan for Europe. EUR/04/5046267/7, adopted during the Fourth Ministerial Conference on Environment and Health, Budapest (Hungary), 22-24 June 2004.

WHO, 2010a. Parma Declaration on Environment and Health, Fifth Ministerial Conference on Environment and Health "Protecting children's health in a changing environment", EUR/55934/5.1 Rev. 2, 10–12 March 2010, Parma, Italy.

WHO, 2010b. The journey to Parma: a tale of 20 years of environment and health action in Europe. EUR/55934/BD/2, World Health Organization, Regional Office for Europe, Copenhagen, Denmark.

CHAPTER 3

ENVIRONMENTAL HEALTH ASSESSMENT FRAMEWORKS AND TOOLS

3.1 ENVIRONMENTAL HEALTH ASSESSMENT FRAMEWORKS

Environmental health issues are very complex and multi-faceted and the assessment and management of human health risks and impacts due to environmental stressors puts high demands on researchers and policy-makers. The effects of environmental contamination on population health concern and cross different spatial and administrative scales (e.g. local, regional, national, transnational) as well as various temporal scales (due to the latency period between actual exposure and appearance of effects).

The need of structuring the problems at hand and of implementing rational and coherent approaches to environmental health analysis lead in the last decades to the development of several methodological frameworks, differing in scope and structure for different forms of assessment.

In the context of health, the dominant paradigm has been that of Risk Assessment, initially developed in the 70's and then "crystalized" in the principles and procedures proposed in the "Red Book" by the National Research Council (NRC, 1983). Risk may be defined as *the combination of probability, or frequency, of occurrence of a defined hazard and the magnitude of the consequences of the occurrence* (NRC, 1983; Royal Society, 1992). Accordingly, risk assessment is the procedure aimed at estimating, either quantitatively or qualitatively, the risks posed by inherent hazards to a given target organism, system or population (in the case of human health risk assessment, the risks to human individuals and (sub)populations).

The human health risk assessment procedure proposed by NRC (1983) is a four-stage procedure (Figure 3.1), consisting in:

a) *Hazard Identification:* it is aimed at identifying the adverse effects that an agent has the inherent capacity to cause in an exposed organism;
b) *Effect Assessment (or dose-response assessment):* it consists in the estimation of the relationship between the magnitude of exposure and the incidence and severity of the effects in question;
c) *Exposure assessment:* it determines the extent of the exposure, by identifying sources, exposure pathways and amount and duration of the exposure;

d) *Risk Characterization*: it is aimed at the determination of the probability of occurrence of known and potential effects of the identified agent(s) in a given target, including the evaluation of attendant uncertainties.

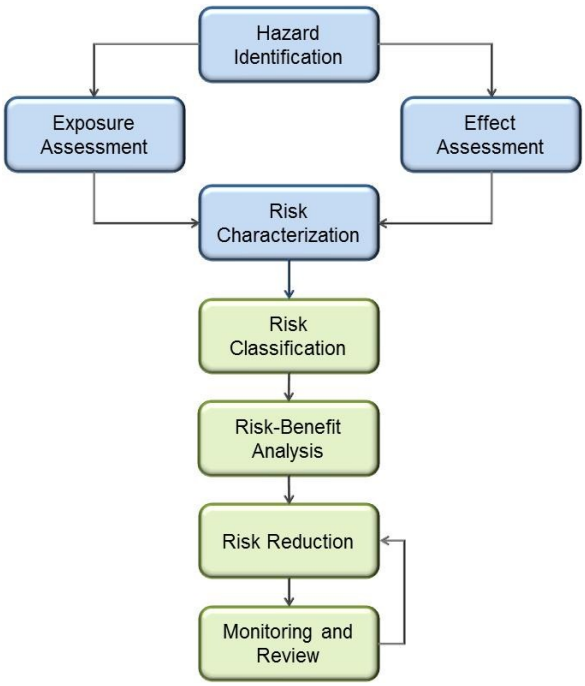


Figure 3.1 Steps in the Risk Assessment and Management process
(Van Leeuwen and Vermiere, 2007)

Once the risk characterization has been successfully completed, the attention turns to Risk Management (Figure 3.1). This is the decision-making process for identifying, evaluating, selecting and implementing regulatory and non-regulatory options to reduce and control risks and it involves consideration of political, social, economic and technical factors (IPCS, 2004). Risk management requires the valuation of risk by decision-makers with the aim of deciding if risk reduction is required (risk classification phase); this phase deals with risk acceptance, which may vary according to technical/scientific, ethical, legislative, socio-economic contexts (Van Leeuwen and Vermiere, 2007). Then, if necessary, options for risk reductions should be identified and submitted to a risk-benefit analysis, where the risks reduced by a certain intervention are compared to the net benefits and costs to society. Finally, the selected risk reduction measures should be implemented and a proper monitoring should verify, in an iterative process, if previously formulated standards are being met or corrective actions are needed.

The first formal human health risk assessment guidance manual was known as the Superfund Public Health Evaluation Manual (US EPA, 1986). After several years of Superfund program experience

conducting risk assessment at hazardous waste sites, US-EPA updated the Public Health Evaluation Manual with the Human Health Evaluation Manual (US EPA 1989). That guidance is currently used for the evaluation of hazardous waste and other sites in many states around the USA and internationally (CARACAS, 1999). Moreover, approaches based on the risk assessment paradigm have been and are widely applied in Europe to support the development and implementation of recent European policies concerning, for examples, the production and use of chemicals (such as the recent regulation REACH – Registration, Evaluation, Authorization and Restriction of chemicals), the remediation of contaminated sites, the management of surficial water and groundwater resources (Marcomini et al., 2009).

Health Impact Assessment (HIA) provides an alternative paradigm to the evaluation of potential or actual impacts (positive or negative) on human health and can be seen as a component of Environmental Impact Assessment (EIA) dealing specifically with effects on human health (Fehr, 1999). It has been defined as a *combination of procedures, methods, and tools by which a policy, program or project may be judge as to its potential effects on the health of a population, and the distribution of these effects among the population* (WHO, 1999b). HIA differs from risk assessment because it usually takes multiple exposures and health outcomes into account, many of which have to be dealt with only in a qualitatively manner and without the use of dose-response and exposure data which can lead to a quantitative risk estimate (Cole et al., 2005). HIA is concerned with reducing health inequalities and should estimate the differential distribution of health impacts across different population groups (European Observatory on Health Systems and Policies, 2007), paying a special attention to vulnerable groups (e.g. children, elderly people). HIA should be a transparent and democratic process, with the interests of community groups reflected through direct or indirect public involvement and participation (WHO, 1999b).

In HIA, first the scope of the assessment should be agreed (geographical scale, population, and topics), then information should be obtained from three sources: published scientific evidence (qualitative or quantitative), data from the local context, and the perspective of (potentially) affected people and all other stakeholders (Mindell and Joffe, 2003). Quantitative HIAs provide results generally expressed in terms of the attributable change in morbidity or mortality for each considered health endpoint (Briggs, 2008).

Many frameworks were developed to help practitioners in performing HIA (Mindell et al., 2008), however some basic common steps in the HIA process may be identified (Figure 3.2). The S*creening Phase* consists in the preliminary evaluation to determine whether a propose action (project, policy) is likely to pose any significant health question, and thus to decide if conduct a HIA or not; various tools and checklist have been developed for this purpose (European Observatory on Health Systems and Policies, 2007). The *Scoping Phase* has the aim of outlining the impacts, methodological

approach, expected challenges and resources needed to conduct the impact analysis (Cole et al., 2005); the input of key stakeholders and relevant health authorities is critical in this step. The core of HIA process consists in the *Appraisal of health impacts*, when the nature, magnitude, extent and likelihood of potential health impacts and their qualitative or quantitative ranking is determined, using a variety of kinds of information and methods (Mindell et al., 2008). The following phase consists in *Reporting on health impacts and policy options*: considering the ranked impacts and making explicit the trade-offs to be made in decision making, a health management plan is proposed, that establishes the revisions to the policy/project at hand and the actions needed to mitigate identified impacts and to promote health opportunities in the project (European Observatory on Health Systems and Policies, 2007; IFC, 2009). The last phase is that of *Evaluation and Monitoring*, when a process and impact evaluation of the HIA is performed, and the monitoring of health impacts is carried out to ensure that mitigation progress is satisfactory, with a system suitable to capture unanticipated effects occurring at the community level (IFC, 2009).

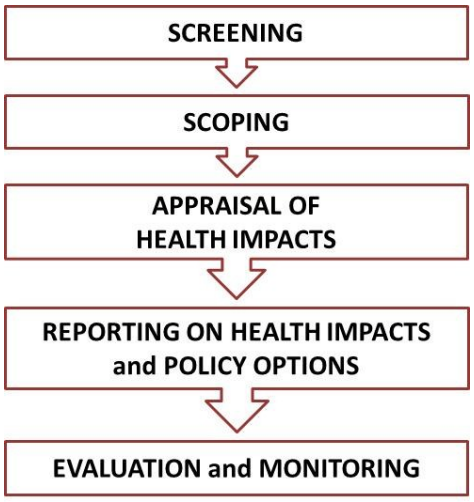


Figure 3.2 Schematic representation of the main phases of Health Impact Assessment process (modified from European Observatory on Health Systems and Policies, 2007)

In the last decade, the awareness of the complexity of many environmental health issues grew, together with the recognition of the need for more integrated approaches to the development of new policies. The concept of systemic risk has been formulated by Klinke and Renn (2006): *Systemic risks do not only raise primary consequences to human health and the environment, but their hazardousness rather trigger secondary and tertiary impacts, since they are embedded in a larger context of societal, economic and political risks and opportunities*. Four main aspects characterize systemic risks, namely (Klinke and Renn, 2006):

a) *complexity*: it concerns the difficulties in identifying and quantifying causal relationships between a variety of potential candidates and specific adverse effects;
b) *uncertainty:* in its various components, it reduces the confidence in the knowledge of the cause-effects chain;
c) *ambiguity*: it comes from discrepancies in interpreting the same model or data, due to differences in applying interpretation rules and criteria;
d) *ripple effects:* this term refers to the secondary and tertiary effects which may occur in time and space and in different contexts (environmental, political, socio-economical).

Risk assessment, health impact assessment and other kind of assessment approaches proposed for environmental health, such as comparative risk assessment (Murray et al., 2003; Ezzati et al., 2006) or integrated risk assessment (Suter et al., 2005), do not present the potentialities for suitably dealing with the assessment of the health effects of systemic risks and for supporting the development of proper policies (Knol et al., 2010).

To overcome the limitations of traditional approaches, the concept of Integrated Environmental Health Impact Assessment (IEHIA) has been developed (Briggs, 2008) as result of the work carried out within two recent FP6 Integrated Projects (INTARESE and HEIMTSA; see Chapter 2). IEHIA is defined as a *means of assessing health-related problems deriving from the environment, and health-related impacts of policies and other interventions that affect the environment, in ways that take account of the complexities, interdependencies and uncertainties of the real world* (Briggs, 2008). This definition implies a broad idea of both environment and health. The former covers not only environmental hazards but also all those components of the living environment which can have an effect, in a positive or negative way, on human health (e.g. through the use of environmental resources), while the latter is seen as the well-being of human populations, not only restricted to the concepts of morbidity or mortality.

The IEHIA framework incorporates other typologies of risk assessment (Figure 3.3) and it is characterized by a process of integration occurring at different dimensions: along the full chain from sources to health impacts; laterally across different sources, risk pathways and health effects; spatially, across different spatial scale; temporally considering both short- and long-term processes; sectorally, across different policy areas (Briggs, 2008).

The process of performing IEHIA is indeed very complex and needs to be adapted to the specific issues that the decision-makers are facing, often in a circular and reiterative way. The framework is partially based on a qualitative approach (for framing the issue and designing appropriate assessment methods) and partially on a quantitative approach (for carrying out integrated assessment of systemic problems).

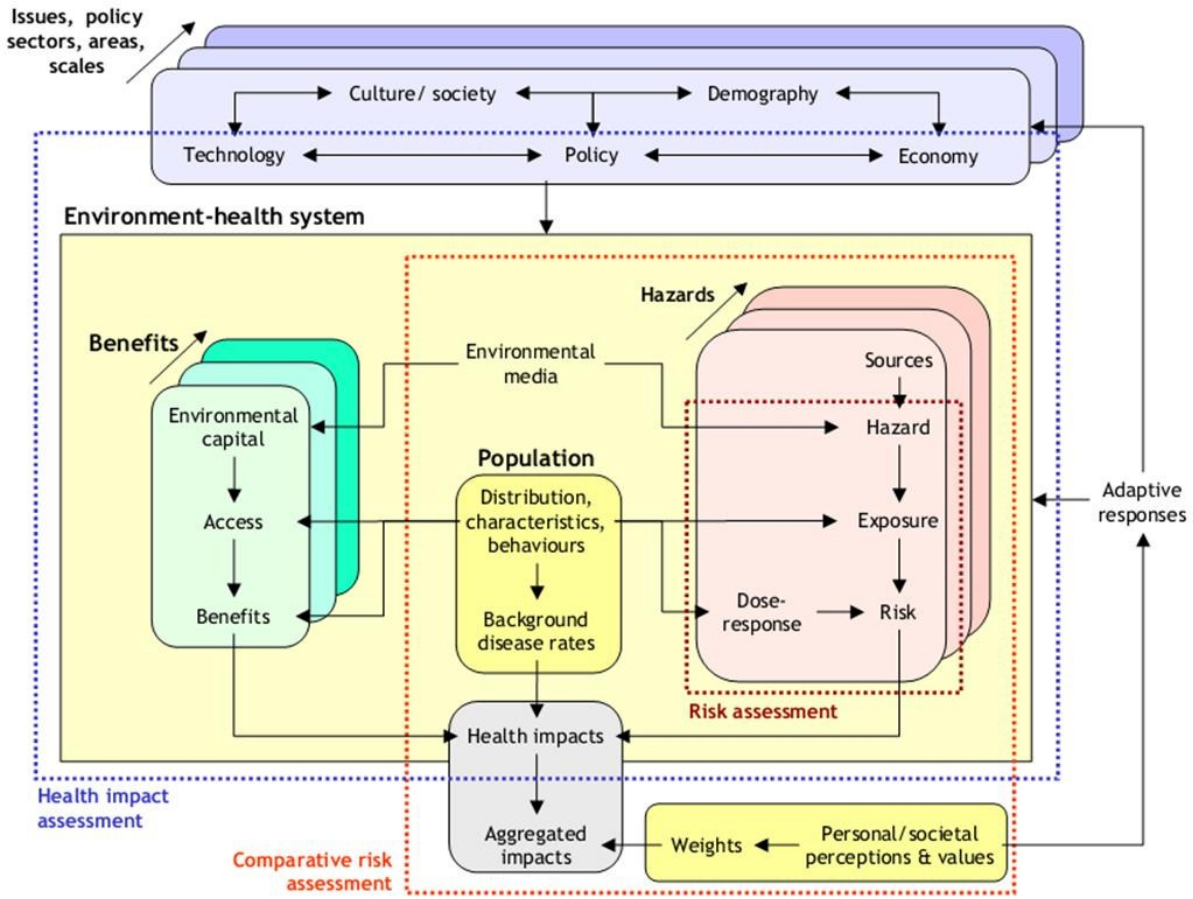


Figure 3.3 Integrated Environmental Health Impact Assessment in relation with other frameworks of risk and impact assessment (Briggs, 2008)

Four main steps have been identified in IEHIA procedure, as illustrated in Figure 3.4, i.e.:

a) issue framing
b) design
c) execution
d) appraisal.

The step of *Issue Framing* is aimed at developing the conceptual model of the issue to be addressed, which will guide then the whole assessment procedure. It requires to define the goal of the assessment, to set the boundaries of the problem, to select relevant elements and factors to be included in the assessment and to sketch out the policy scenario and the management options to be considered. The impact pathway, that is the causal chain linking sources of stressors to health outcomes, should be the guiding structure for completing these tasks. Different actors should play a role in this step: researchers/scientists, policy-makers and other stakeholders such as citizens and associations. The communication among groups and the development of a shared conceptual model

could be eased by the use of different techniques such as mind maps, system diagrams, causal diagrams.

The purpose of the step *Design* consists in specifying the methodological approach to be followed in the assessment process. To define this assessment protocol, it is necessary to identify key variables and their relationships, the directions of effect, significant confounding factors and metrics to be computed along the assessment. Moreover, since IEHIA is basically a comparative process, the terms of the comparison have to be set up (e.g., the current situation versus a no-risk factor scenario, current situation versus a specific "new-policy scenario"). An important task during the design step is screening, aimed at deciding whether and how the assessment should proceed. Issues and scenarios which merit a full integrated assessment have to be identified during this phase, excluding for example those scenarios not implying a relevant variation in health risks. Moreover, the most suitable assessment procedure (e.g., comparative risk assessment, focused health impact assessment) should be selected before moving to further steps.

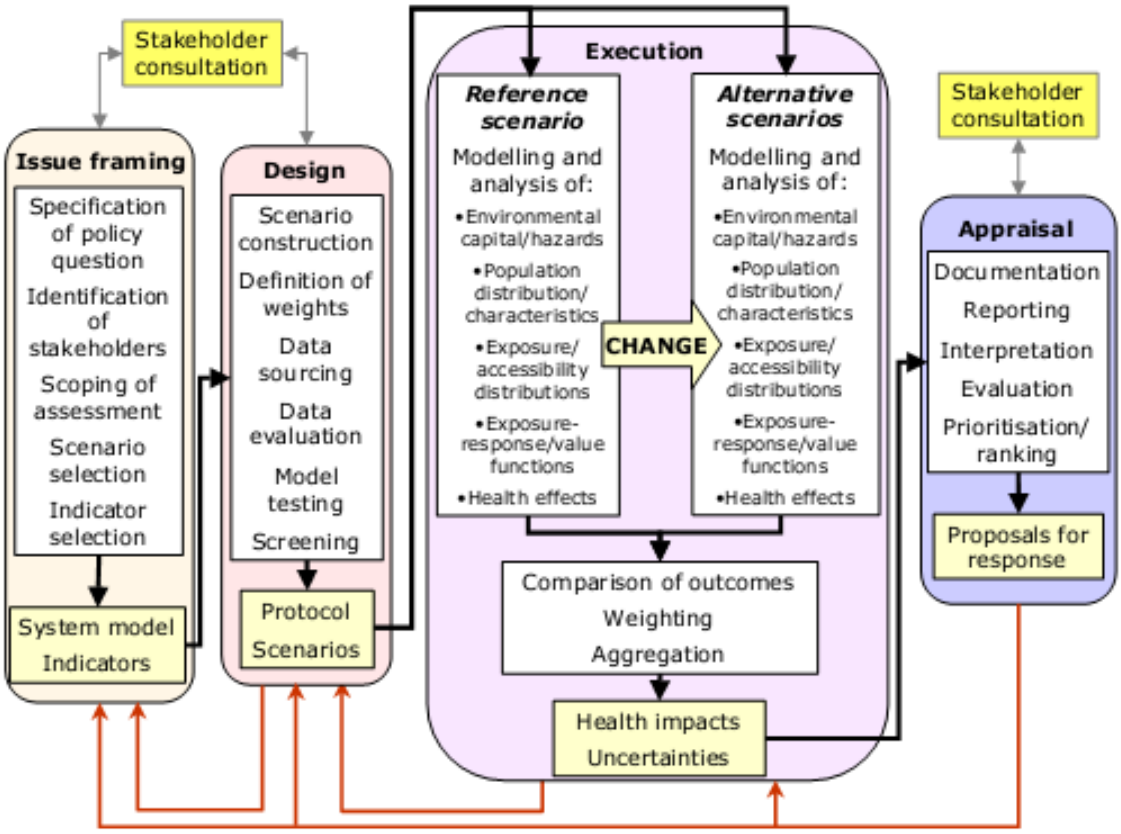


Figure 3.4 Operational framework for Integrated Environmental Health Impact Assessment as proposed by Briggs (2008).

The *Execution* step represents the core of IEHIA, where all relevant data are collected, integrated and analysed. It includes the phases of hazard identification, exposure assessment and risk characterization but it extends the boundaries of traditional risk assessment for quantifying health consequences, also from the economic point of view, and further combining impacts through aggregation indicators. This step relies on the application of different mathematical models (especially for exposure assessment but the application field is quite wide) with the aim of filling data gaps, for prediction future situations or to reconstruct past conditions. Information from toxicology and especially from epidemiological studies provided the basis for deriving exposure-response functions; when they are not available (such as, often, for combined exposure) more qualitative methods such as Delphi surveys or nominal group techniques must be used.

The results of the assessment are usually presented in terms of measures of health impact. Since mortality or morbidity data cannot be easily translated in the policy domain (for example, not all diseases are comparable due to different severity or duration), measures like years of life lost (YLL), disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs) can be used (Prüss-Üstün et al., 2003), while economic measures can also be proposed, as in cost-benefit analysis.

Finally in the last IEHIA step, the A*ppraisal*, the outcomes of the assessment are reviewed, interpreted and communicated. The results for each considered scenario are evaluated and the distinct policy options are ranked according to their acceptability and effectiveness or other criteria defined by the stakeholders. The appraisal should be, again, a participatory process where the different actors should be actively involved so that they can discuss their views on the assessment outcomes and the implications of the different policy options.

The procedure for IEHIA is not distant from the tasks included in other methods such as traditional risk assessment or health impact assessment, but the main difference lies in that it is aimed at being more inclusive and policy-driven (Knol et al., 2010). The application of such approach is surely challenging, especially due to issues related to multi-causality of health effects, non-linearity of systemic risks, complex changes and dynamic which distinguish environmental health systems (Briggs, 2008). In any case, IEHIA currently represents the more comprehensive approach to the assessment of environmental health risks for coherently supporting related decision-making and offers a rational and rigorous structure for framing and cope with the complexity of such risks. Following this framework may help to ensure that complex assessment are targeted at the right issue and follow strict scientific principle

The development of a methodology for supporting the ranking of environmental health stressors and therefore the identification of priority scenarios, as it is among the objectives of this thesis, can be instrumental to the goals of the Design Phase of the IEHIA framework, and should therefore been considered in this perspective.

3.2 ENVIRONMENTAL AND HEALTH DATA: TYPOLOGIES OF DATA, INDICATORS AND SOURCES

Investigating environmental health issues requires, by definition, the collection and analysis of data from different domains and sources. The seven-step framework proposed by Thacker and colleagues (1996) represents the process whereby an environmental stressor is distributed within environmental compartments (hazard), enters the human body (dose), and causes an adverse health effect on the organism (health outcome). This framework elucidates therefore the "hazard-dose-outcome" chain and can be used for supporting the collection, analysis and interpretation of environment and health data.

3.2.1 HAZARD DATA

Hazard data provide information about the emission, presence and quantity of different health stressors (chemical, physical or biological stressors) in environmental compartments (air, soil, water, sediment, food, etc.). This type of date is often collected in the frame of environmental monitoring activities implemented for regulatory purposes, such as periodical measurements of water or air pollutants for evaluating the compliance with national environmental standards or guidelines. Therefore, the typology of collected data, the spatial and temporal distribution of samples and the collection methods may be adapt for enforcement tasks, but may be far from the specific needs of health surveillance (McGeehin et al., 2004).

For some kinds of data, a substantial amount of information is beginning to be available at the European level through the implementation of dedicated networks and programmes (Smolders and Schoeter, 2007). For example, for air monitoring, information about emission sources and modelled concentration of pollutants in the atmosphere are made available by the European Monitoring and Evaluation Programme for Long-Range Transboundary Pollution (EMEP; http://www.emep.int/index.html) or by the European-wide Air Quality Monitoring Network (EUROAIRNET; http://acm.eionet.europa.eu/databases/airbase/index_html), the public air quality database of the European Environmental Agency. Moreover, data may be available at the local, regional or national level according to the different types of environmental monitoring networks implemented and routinely used in each area.

Hazard data depict conditions having the potential for harmful effects on human health but, if considered alone, are not representative of actual individual exposure (McGeehin et al., 2004).

Environmental standards are used to classify and evaluate the compliance of environmental data with regulations; they are usually available only for a selected set of substance for every

environmental medium, and are derived mainly from the evaluation of (eco)toxicological studies. Therefore, the exceedance of standards cannot be used to predict the appearance of specific health outcomes in the population (Mather et al., 2004).

3.2.2 DOSE DATA

Dose data represent the fundamental link between environmental hazard and health outcomes data and describe the actual "contact" of individuals, communities and population groups with an environmental contaminant or its metabolites. They are indicated by some authors as "exposure data" (e.g., McGeehin et al., 2004) since they show whether and to what extent chemical compounds are actually taken up from contaminated media (Angerer et al., 2007).

For chemical stressors, optimally dose data consists in human biomonitoring data, specifically data on biomarkers of exposure, i.e. measurement of parent compounds, metabolites, or DNA or protein adducts of parent compounds and/or metabolites measured in human biological specimens (blood, urine, breast milk, etc.) that indicate a direct exposure to the compound of interest (Ryan et al., 2007). The relation between environmental concentration and levels of contaminants in biological samples is not necessarily proportional and appears influenced by several factors (e.g. frequency and duration of the exposure, baseline health status, behavioural and genetic factors); moreover, the relationship between internal dose and health effects is often not completely known (Mather et al., 2004; Clewell et al., 2008). Nonetheless, human biomonitoring data may represent a significant component in the framework for linking environmental and health data (Smolders et al., 2008); they represent an *integration of exposure from all source and routes, which provides an important perspective on overall population exposure* (Albertini et al., 2006).

Basically, data on biomarkers of exposure can be originated from two types of studies. They can derive from small-scale research projects, usually covering a restricted geographic area and involving a small number of participants (Smolders et al., 2008). In this case, the monitoring is usually aimed at testing well-defined research questions (e.g. quantitative relationship between environmental exposure to a certain contaminant and the resulting human exposure). The other source of exposure biomarkers data consist in large scale survey programmes directed at achieving an overall view of the pollutant load among the general population. These biomonitoring programmes usually cover a relevant number of substances (and corresponding biomarkers) and often involve participants from different age classes and large geographic areas. In the last years, different EU Member States designed and implemented such kind of biomonitoring programmes. Examples are the German Environmental Survey (Schulz et al., 2007) routinely realized in Germany since the mid 1980's, the Environmental Health Monitoring System in the Czech Republic (Černa et al., 2007) or the Flemish

Human Biomonitoring Programme (Schroijen et al., 2008). In the United States, the National Health and Nutrition Examination Surveys is a continuous programme since the 1999 and its data are analysed and reported by the US Centre for Disease and Control (CDC, 2009). Several research initiatives have been funded in recent years by the European Commission with the aim of developing an holistic framework for the interpretation of biomonitoring data within health risk assessment, harmonising local and national on human biomonitoring to improve data comparability across Europe, validating new biomarkers (e.g., ESBIO – Expert team to Support BIOmonitoring in Europe; COPHES – Consortium to Perform Human Biomonitoring on a European Scale).

Different approaches can be used for the definition of benchmark values for the classification and interpretation of human biomonitoring data. Reference ranges can be defined, which are statistically derived from large scale population monitoring (e.g., 95^{th} percentile of the distribution of concentration of a compound in a matrix of a reference population) (NRC, 2006; Smolders et al., 2008). They can serve for identifying individuals with an increased level of exposure in comparison to the background level, but they cannot lead to any conclusion about risk potential (NRC, 2006). The setting of health-related criteria is more challenging. Such risk-based criteria can be defined by international agencies when enough toxicological and epidemiological information is available and there is adequate consensus on the occurrence of health effects at certain concentrations of the selected compound (Smolders et al., 2008). Recently, a modelling approach which include the use physiologically-based pharmacokinetic (PBPK) models (Bois et al., 2010) has been proposed by Hays et al. (2007) and which leads to the derivation of the so-called "Biomonitoring Equivalent" representing a biomonitoring threshold *consistent with an existing exposure guidance values such as Tolerable Daily Intake (TDI) or Reference Dose (RD)* (Hays and Aylward, 2009). Currently, risk-based values have been set by international bodies only for a restricted number of biomarkers (e.g. lead in blood, cadmium in urine), while much more efforts are still needed for setting the same values for other chemical compounds.

Due to confidentiality issues, it is difficult to obtain detailed publicly available information on geographically referenced biomonitoring data at the individual level (Smolders et al., 2008). Most of the time, these date are made available only in an aggregated form (e.g. mean values, percentiles, etc.), which is not the most suitable for further analysis.

3.2.3 HEALTH DATA

Data about health outcomes (response data) are aimed at describing the health status of a population and, in particular, at providing information about the distribution and/or the frequency of disease/deaths by means of morbidity and mortality data. These are the outcomes of interest in

efforts to understand the relationships between environmental contamination and exposure data on the one hand and effects in humans on the other.

Health outcomes may be expressed as individual-level data or may be aggregated for populations (often identified by administrative units) like those available from local, regional and national surveys. Aggregated data consists in measures of disease frequency and involve the occurrence of new cases or deaths (measure of incidence or mortality) or the presence of existing cases (measures of prevalence) (Morgenstern and Thomas, 1993). Individual and aggregated data are characterized by different advantages and limitations and this affects the specific use of each type of data (Mather et al., 2004). Sources of health outcomes data include local, regional and national health surveys, health events and reportable disease registries (e.g. cancer registries, birth defects registries), vital statistics data, administrative data systems (e.g. hospital discharge data, emergency room data), insurance health statistics (McGeehin et al., 2004).

Confidentiality issues notably restrict the quantity of health outcomes data which can be obtained through public sources, with some exceptions only for cancer data which are usually object of national or international projects and databases. At the European level, some databases exist presenting data on cancer incidence, prevalence and mortality (usually at the level of each Member State), such as the EUROCARE-3 (www.eurocare.it) or the GLOBOCAN-2008 (www.globocan.iarc.fr) (Smolders et al., 2008). It may be difficult to use these data for correlating and integrating environment and health information since the scale is usually too coarse. However, at the regional and local level data can be archived and are often available through cancer registries (such as the databases made available by AIRTUM – Italian Association of Cancer Registries, www.registri-tumori.it). Also for respiratory diseases there are some networks covering the whole European region, like ECRHS-II (EU Respiratory Health Survey, www.ecrhs.org) or the worldwide ISAAC project (International Study of Asthma and Allergies in Childhood; http://isaac.auckland.ac.nz/index.html). For other typologies of diseases it is much more difficult to find international or national databases including incidence, prevalence or mortality data, however, thanks to several initiatives funded by the EC within the 6th and the 7th Framework Programmes, it is expectable that in the next years a significant amount of health outcomes data will be available for scientific purposes.

The main potential limitations to be considered when dealing with health outcomes data consist in the possible incompleteness of data, the evolution and change in diagnostic criteria over time, relevant possibilities of misclassification, measurement and registration errors (Mather et al., 2004). Moreover, the information about many outcomes of concern may be incomplete because many disease and health conditions are not reportable and thus are not registered.

3.2.4 OTHER SUPPORTING DATA

Besides the described types of data, there is the need to collect data on other known or potential risk factors for the disease of concern. These relevant data, referred as covariates, may be relevant to the exposure effect in three ways: as confounders, as intermediate variable or as effect modifiers (Morgenstern and Thomas, 1993). These data may concern different kinds of health determinants, such as socio-economic status, age and race variables. These variables have to be considered, measured and controlled in the assessment according to the specific objectives. Some types of these data (e.g. socio-economic information) can be obtained from census data and other surveys (e.g. EUROSTAT, the statistical office of the European Union, provides statistics about several social and economic aspects, enabling the comparison across different Member States and regions).

That information is usually aggregated by administrative units (e.g. region, census tract) and can suffer the same limitations previously highlighted for health outcome data. Despite the problems concerning data completeness and updating, information about population characteristics is of basically importance for establishing denominator estimates (i.e. identify and quantify the number of individuals at risk of experiencing the health event in question) and properly investigating the relations between hazard/exposure data and health outcomes data (Mather et al., 2004).

3.2.5 ENVIRONMENTAL HEALTH INDICATORS

A significant quantity of environment and health data (of varying quality) is already and is becoming available at different spatial scales in Europe, as mentioned in the previous paragraphs. However, this information is not always in a form relevant to support decision-makers in setting appropriate policies and monitoring their effectiveness (Von Schirnding, 2002). Indicators can play an important role in turning data into relevant information, in a form which all those involved in the decisional process can appreciate and accept: in this sense, they constitute a fundamental link in the data-to-decision-making chain (WHO, 2000).

An indicator has been defined *as a parameter, or a value derived from parameters, which points to/provides information about/describes the state of a phenomenon/ environment/area with a significance extending beyond that directly associated with a parameter value* (OECD, 1993). Specifically, an environmental health indicator may be defined as *an expression of the link between the environment and human health, targeted at an issue of specific policy or management concern, and presented in a form which facilitates interpretation for effective decision-making* (Corvalàn et al., 1997). In this sense, environmental health indicators are more than either environmental indicators

or health indicators because they are chosen and used for the known or supposed causal relationship (the link) existing between environmental risk factors and health outcomes.

Environmental health indicators may be useful (WHO, 1999a):

- to monitor trends in environment and in health with the aim of identifying threats and guiding policy developments;
- to compare areas or countries in terms of their environmental health status;
- to support the investigation of potential environment-health links as basis for informing health intervention measures and development of targeted policies;
- to help raise awareness across different stakeholder groups.

A specific framework for analysing environmental health issues is the DPSEEA (Driving Force-Pressure-State-Exposure-Effect-Action) first proposed by Corvalan and colleagues (1996) and endorsed by WHO (1997). DPSEEA framework, whose structure is inspired by the DPSIR (Driving Forces–Pressures-State-Impacts-Responses) framework developed by the European Environmental Agency (EEA, 1999), links different components in order to represent how various driving forces generate pressures that affect the environment and finally human health, through the different exposure pathways by which people come into contact with environmental hazards (Figure 3.5). Indicators may be developed for any component of the DPSEEA so that they could effectively support the assessment, management and communication of environmental health issues.

Creating a sustainable environment and health information and knowledge system is a key priority of the European Environment and Health Strategy (EC, 2003), therefore the use of environmental health indicators gained much attention at the European level in the last two decades. At the Fourth Ministerial Conference on Environment and Health (held in Budapest in 2004) the EU Member States committed to join actions with WHO, the European Commission and other international organizations on methodological and technical developments for the pan-European implementation of an information system on environmental health main topics. Therefore, these actors established and runs *ENHIS – Environment and Health Information System*, a harmonized and evidence-based information system on environment and health to support public health and environmental policies in the European Region. It consists of a set of 22 indicators, concerning exposure, health effects, and policy actions, that were selected for their relevance towards environmental health issues at the EU level (WHO, 2005).

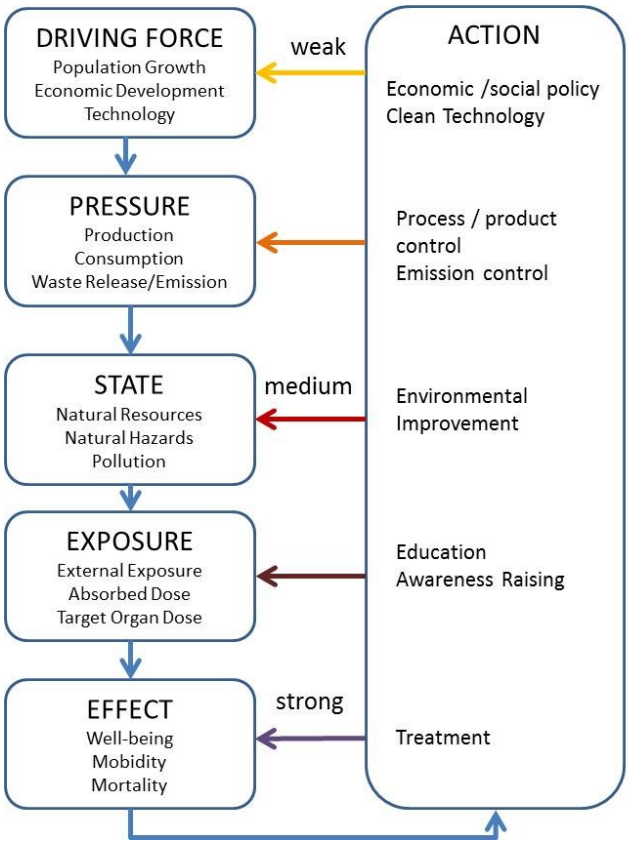


Figure 3.5 The Driving Force-Pressure-State-Exposure-Effect-Action (DPSEEA) framework shows how humans come to be affected by the environment and how management actions may address any step in the process (WHO, 1997).

The system is also aimed at feeding with appropriate information the Children's Environment and Health Action Plan for Europe (CEHAPE) (WHO, 2004). Moreover, since at the Fifth Ministerial Conference on Environment and Health (held in Parma in 2010), the relevance of children's health monitoring has been confirmed (WHO, 2010a), a set of 18 environmental health indicators to be integrated into ENHIS will measure progress towards the five time-bound commitments to reduce environmental health effects in children adopted in Parma (WHO, 2010b). The meeting also set schedules for the development of indicator methodologies, data collection protocols and implementation of these indicators in ENHIS, and specified communication mechanisms with the European Environment and Health Process. Such information system is therefore candidate to become in short time a relevant reference for environment and health data at the European level.

3.3 METHODOLOGICAL APPROACHES TO SUPPORT DATA INTEGRATION: WEIGHT-OF-EVIDENCE APPROACH AND MULTI-CRITERIA DECISION ANALYSIS

Integrating data from different sources, such as environment and health data, constitutes a great challenge and different methods have been proposed for supporting this task (e.g., epidemiological models). In this paragraph an overview on Weight-of-Evidence (WoE) approach and on Multi-Criteria Decision Analysis (as a tool to support the implementation of a quantitative WoE) is provided, because these approaches have been selected as valuable for integrating information with the aim of developing a ranking methodology for environmental chemical stressors.

3.3.1 WEIGHT-OF-EVIDENCE APPROACH

Human and ecological risk assessment procedures are used to summarize and synthesize evidence, sometimes conflicting, across several dimensions: small and large studies, new and old investigations, human and animal studies, researches involving different biological levels - from cells to human or ecological populations. Moreover, an additional challenges is constituted by the need to integrate scientific with extra-scientific values, which only sometimes are made explicit. In this context, there is the need for interpretative frameworks (Weed, 2005) supporting a consistent and transparent integration of information, which could be offered by Weight-of-Evidence approaches.

Weight of Evidence (WoE) has been defined as a *framework for synthesizing individual lines of evidence, using methods that are either qualitative (examining distinguishing attributes) or quantitative (measuring aspects in terms of magnitude) to develop conclusion regarding questions concerned with the degree of impairment or risks* (Linkov et al., 2009).

This framework allows to incorporate judgements concerning the quality, extent and congruence of the data contained in the different LoEs (Chapman et al., 2002). In this contest, LoEs are intended to be a set of information that pertains to an important aspect/domain of the environmental problem at hand (Smith et al., 2002).

The utility of combining different pieces of evidence when making inference is explicitly clarified by Suter and Cormier (2011), and motivations include the fact that each piece of evidence tell something different about the situation being assessed and that one type of evidence may compensate for the limitations of another evidence. A single LoE may be useful for a screening assessment but the possible conflicting results from combining different LoEs require a WoE assessment for final decision-making (Hall and Giddings, 2000).

This concept has been concretized in a number of applications and frameworks adopting different methods (varying from qualitative to quantitative) for the integration and evaluation of the different

LoEs. WoE has been proposed in human health risk assessment for assessing the impacts of chemicals substances, their carcinogenicity and mutagenicity in particular (e.g. USEPA 1986; 2005), as well as for evaluating the toxic mode-of-action (USEPA, 2005; 2007) according to the causality criteria proposed by Hill (1965).

Similarly, in the last decades WoE methodologies have been developed also for ecological risk assessment, where the integration of information from different domains (e.g. environmental monitoring data, toxicity data, biological field surveys, physiological biomarkers) is required (Suter, 2007). Probably the most well-known approach for combining multiple Lines of Evidence (LoEs) is the Sediment Quality Triad (SQT) proposed by Long and Chapman (1985) for assessing the risk associated to contaminated sediments and articulated on a standard combination of three LoEs (sediment chemistry, benthic community structure, sediment toxicity). Further applications concern a variety of fields, including contaminated sites assessment, management of watersheds and of other environmental resources.

A varied set of assessment methods could be counted in the category of WoE approaches, frequently developed for very specific purposes, and there is a considerable debate within the scientific community about the definition and the application of such approach. Weed (2005) reviewed WoE procedures used in human health risk assessment and found that there is no univocal definition of this approach and in current practice its applications are often based on qualitative methods which do not include rigorous application rules.

According to Suter and Cormier (2011), WoE should not be considered as a particular type of assessment, but *rather as a method for planning, analysing or synthesizing information* which can be applied to each type of environmental assessment.

After analysing recent WoE applications to human and ecological risk assessment and classification methods suggest by Weed (2005) and Chapman et al. (2002), Linkov and colleagues (2009) propose a taxonomy of WoE methods according to the increasing efforts they pose in structuring a coherent and sound quantitative assessment (though, the authors acknowledge that all WoE methods may make use of both qualitative and quantitative evaluations). This taxonomy, taken as reference for the present work, includes the following categories of methods: *Listing Evidence*, *Best Professional Judgement*, *Causal Criteria*, *Logic*, *Indexing*, *Scoring* and *Quantification*. When two methods occupy the same level in the classification frame, it means that they are characterized by a comparable quantitative rigor within the qualitative/quantitative continuum (Figure 3.6).

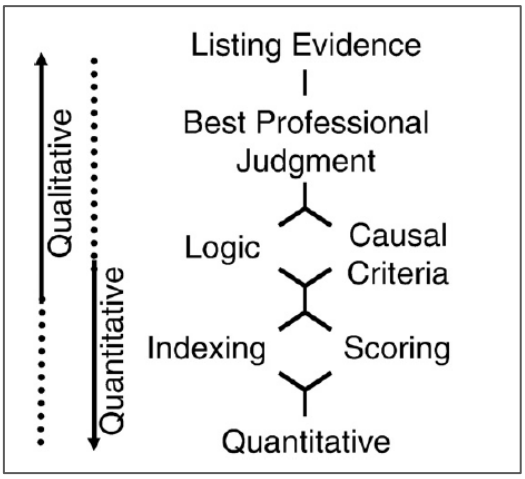


Figure 3.6 Classification of Weight-of-Evidence methods as proposed by Linkov et al. (2009)

Listing Evidence consists simply in the presentation of individual LoEs and it is the only method which does not include any attempt of integration.

Methods based on *Best Professional Judgement* (BPJ) try to integrate all LoE to draw a conclusion about the question at hand, and this is achieved mainly through a professional judgement (very peculiar to the specific situation).

Causal Criteria category encompasses all WoE methodologies based on the definition and verification of criteria (commonly based on Hill's criteria) for determining cause-effect relationships. *Logic* category includes methods based on a standardized evaluation of individual LoE based on qualitative logic models. An examples of such method is the USEPA framework for carcinogenicity evaluation (USEPA, 2005). The LoE integration process in Causal Criteria and Logic methods is more transparent but the information for one or more LoE can be qualitative and both methods rely on BJP to synthesize the information from different LoEs.

Scoring methods are based on a quantitative integration of multiple LoE using simple weighting or ranking, and weights are usually defined using BPJ according to rules such as consistency, specificity or strength of the association.

The category *Indexing* include methods relying on the integration of LoEs based on empirical models, where the weights can be specified both in numerical values attributed to the LoEs and the proportion of the final index value that each LoE comprises.

In neither *Scoring* or *Indexing* the judgement is quantified by application of formal decision analysis or probabilistic techniques, thus transparency, reproducibility and possibility to handle nonlinearity and correlation across the criteria are not guaranteed. These features characterize only WoE methods in the last category, i.e. *Quantification*: here quantitative procedures to weight the

evidence and quantitative procedures to weight the body of evidence are indeed used. These WoE methods permit a transparent and reproducible integration of scientific information with expert/decision-maker judgment and, moreover, allow comparison across multiple experts.

As highlighted by Linkov and colleagues (2009), Multi-Criteria Decision Analysis (MCDA) can be considered as a suitable mathematical approach for implementing WoE quantitative methods because it allows to maintain a rigorous quantitative assessment and at the same time to incorporate value-based assessment and expert judgment (Linkov et al., 2006). Moreover, MCDA represents an opportunity for building consensus in decisional processes where multiple experts or stakeholders are involved. Experts/stakeholders have the opportunity to debate about the selection of the numerical value to be assigned to each LoE and there is the opportunity to adjust the weight as necessary to reach consensus (Linkov et al., 2006). For these reasons, MCDA has been selected in this work for the implementation of a WoE approach for ranking environmental chemical stressors and some introductory notes on MCDA methods are thus provided in the next paragraph.

3.3.2 MULTI-CRITERIA DECISION ANALYSIS (MCDA)

Multi-criteria decision analysis (MCDA) methods may offer a meaningful approach to deal with complex environmental and health decisional process, since they offer the framework for integrating both qualitative and quantitative information in a structured and transparent manner. MCDA helps indeed decision-makers evaluate and choose among alternatives based on multiple criteria using systematic analysis that overcomes the limitations of unstructured individual or group decision-making (Linkov et al., 2006).

As highlighted by Linkov et al. (2011), MCDA methods are not aimed at removing expert judgment from the decisional process, but rather at distinguishing judgement calls from technical data and making all assumptions and value attribution visible and traceable. Therefore, the main advantage in using MCDA for implementing WoE quantitative procedures consists in its rigorous and reproducible approach to integrate different LoEs and in its ability to evaluate how sensitive are the results to changes in the specific input parameters or in the logic used to achieve the integration (Linkov et al., 2009).

MCDA includes a large number of methods for the evaluation and ranking or selection of alternatives that considers all the aspects of a decision problem involving many actors (Giove et al., 2009). Some techniques rank options, some identify a single optimal alternative, some provide an incomplete ranking and others differentiate between acceptable and unacceptable alternatives (Kiker et al., 2005).

A structural platform common to almost all the decision problems includes the following elements:

- the decision-maker (DM): a conceptual figure, a single person, a group of persons or an entity in charge of finding the best solution for the problem under assessment;
- a set A of alternatives, in the finite case: $A = \{a_1, \dots, a_m\}$, they represent the possible choices out of which the DM has to choose the "best" solution;
- a countable family of criteria or attributes or parameters, $K = \{k_1, \dots, k_n\}$. These are aspects of the problem that the DM considers crucial and they allow to measure the achievements of the alternatives. Criteria can be organized into a hierarchical structure, i.e. a decision tree where the root is the objective function whose leaves are the first-level criteria, each of them split again into second-level criteria (sub-criteria), and so on till the last level, whose terminal leaves are the indicators (or the last level sub-criteria) formed by the available information (data or judgments);
- an objective or target function (to be optimized) used to score, and in case to rank, the alternatives, usually an aggregation function;
- the decision maker's preferences for the different evaluation of the criteria;
- an algorithmic tool designed to optimize the objective function, considering all the above information.

All MCDA methods make the options in the decisional process and their evaluation against different criteria explicit, and all require the exercise of judgement. They differ however in how they consider and combine the data. MCDA methods can be categorized into 3 groups (Vinke, 1992): MAUT/MAVT (Multi-Attribute Utility/Value Theory), Outranking and Interactive methods. The methodology proposed in this thesis (illustrated in Chapter 5) is based on a Multi-Attribute Utility/Value Theory (MAUT/MAVT) approach. In MAUT/MAVT approach, criterion values are first normalized into a common numerical scale by means of a suitable transformation function (or Utility/Value Function). Then criteria are aggregated by a suitable aggregation operator, a function that satisfies a set of rationality axioms (Beinat, 1997).

Using a bottom up approach, this operation is repeated for all the nodes in the decision tree (if the problem is hierarchically structured) for all the alternatives. Each branch or level of the tree may be aggregated to its root by using different aggregation functions based on the criteria relations. At the tree root (the objective) a single numerical value is finally computed, which is the score of the proposed alternatives. The alternatives can then be rated and ranked, since MAUT/MAVT produces a total ordering, and so the most suitable one can be selected.

The assignment of value/utility functions (normalization functions) is subjective in the sense that they depends on the user's preference structure or perception about the impact and role of each criterion. Many methods exist to support the definition of value functions, such as direct rating,

bisection, curve selection (Beinat, 1997). The value functions convert the attribute values into a common closed numerical scale and these numerical values should then be aggregated.

Aggregation operators consist in mathematical objects that have the function of reducing a set of numbers into a unique representative (or meaningful) number. In MAUT/MAVT approaches, aggregation operators are needed to aggregate each option's performance across all criteria to achieve an overall evaluation of each option, on the basis of which the set of considered options (i.e., alternatives) can be compared (and ranked).

The aggregation operator needs to be carefully selected and, as discussed by Giove and colleagues (2006), the simplest and most widely used aggregation function in the MAUT context is the Weighted Averaging (WA) operator. Weighting of criteria in the aggregation phase is included in MCDA aggregation procedure when it is necessary to distinguish among criteria in order to reflect their relative importance or strength to the decision. WA approach is a compensative method and requires mutual independence of criteria; it means that the preference scores assigned to all options on one criterion are unaffected by the preference scores on the other criteria (Beinat, 1997).

In more general terms, aggregation operators can be classified, considering their characteristic behaviour, in three main classes: Minimum Operators, Mean Operators, and Maximum Operators (Calvo, 2002).

The class of Mean Operators includes, for example:

a) *Arithmetic mean*:

$$M(x_1, \dots, x_n) = \frac{1}{n}\sum_{i=1}^{n} x_i \qquad \text{(Eq. 3.1)}$$

b) *Weighted Mean*:

$$M(x_1, \dots, x_n) = \frac{1}{n}\sum_{i=1}^{n} w_i \cdot x_i \quad \text{where} \quad \sum_{1=1}^{n} w_i = 1 \qquad \text{(Eq. 3.2)}$$

As cited before, it allows to place different weights (w_i) on different arguments (i.e. normalized values).

c) *Median*:

It consists in ordering the arguments (normalized values) from the smallest to the biggest and then choosing the element in the middle.

The Minimum and the Maximum Operator are also basic operators: the former allows to choose the smallest element of a set, while the latter allows to select the greatest element.

All these operators are widely applied in MAVT/MAUT methods and can be useful in different decisional processes but are also affected by a certain poorness of expressivity, i.e. they do not allow to represent complex decision schemes. To face this issues, many other aggregation operators have been proposed, such as the Order Weighted Averaging (OWA) operator (Yager, 1988), which is a

generalization of the Weighted Mean and includes the Maximum and the Minimum as extreme cases. Aggregation operators can also be associated to Logical Operators (AND - conjunction, OR – disjunction, etc.), especially when dealing with Fuzzy sets and Fuzzy logic problem (Fuzzy logic approach will be introduced in Chapter 4). A detailed description of aggregation operators is out of the scope of this work and can be found in Beliakov et al. (2007). When developing a MCDA methodology, the choice of the most suitable aggregation operator depends on the relations existing among criteria and on the specific preference structure that should be reflected , according to the specific goals of the assessment.

3.4 REFERENCES

Albertini R., Bird R., Doerrer N., Needham L., Robinson S., Sheldon L., Zenick H., 2006. The use of biomonitoring data in exposure and human health risk assessment. Environmental Health Perspectives 114 (11): 1755-1762.

Angerer J., Ewers U., Wilhelm M., 2007. Human biomonitoring: state of the art. International Journal of Hygiene and Environmental Health, 210: 201-228.

Beinat E., 1997. Value functions for environmental management. Kluwer Academic Publisher, Dordrecht, The Netherlands.

Beliakov G., Pradera A., Calvo T., 2007. Aggregation functions: a guide for practioners. Series on Studies in Fuzziness and Soft Computing, Springer Verlag, Heidelberg, Germany, pp. 361.

Bois F.Y., Jamei M., Clewell H.J., 2010. PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. Toxicology, 278: 256–267.

Briggs D., 2003. Making a Difference: Indicators to Improve Children's Environmental Health. World Health Organization, Geneva.

Briggs D.J., 2008. A framework for integrated environmental health impact assessment of systemic risks. Environmental Health 7:61.

Calvo T., Mayor G., Mesiar R., 2002. Aggregation operators: new trends and applications. Series: Studies in Fuzziness and Soft Computing Vol. 97. Physica-Verlag, Heidelberg.

CARACAS, 1999. Risk Assessment for Contaminated Sites in Europe. Volume 2 – Policy Frameworks. LQM Press, Nottingham.

CDC, 2009. Fourth National Report on Human Exposure to Environmental Chemicals. Centers for Disease and Control Prevention, US Department of Health and Human Services, Atlanta, USA.

Černà M., Spevackova V., Batariova A., Smida J., Cejchanova M., Ocadlìkova D., Bavorova H., Benes B., Kubınova R., 2007. Human biomonitoring system in the Czech Republic. International Journal of Hygiene and Environmental Health, 210: 495-499.

Chapman M.P., McDonald B.G., Lawrence G.S., 2002. Weight of Evidence issues and framework for sediment quality (and other) assessment. Human and Ecological Risk assessment 8 (7): 1489-1515.

Clewell H.J., Tan Y.M., Campbell J.L., Andersen M.E., 2008. Quantitative interpretation of human biomonitoring data. Toxicology and Applied Pharmacology 231: 122-133.

Cole B.L., Shimkhada R., Fielding J.E., Kominski G., Morgernstern H., 2005. Methodologies for realizing the potential of health impact assessment. American Journal of Preventive Medicine, 28 (4): 382- 389.

Corvalàn C., Briggs D., Kjellstrom T. , 1996. Development of environmental health indicators. In: Briggs D., Corvalàn C., Nurminem M. (Eds), Linkage Methods for Environmental and Health Analysis. General Guidelines. World Health Organization, Geneva, pp. 19–53.

Corvalàn C., Kjellström T., Briggs D., 1997. Health and environmental indicators in relation to sustainable development. In: Moldan B., Billharz S. (Eds), Sustainable Indicators. Report on the Project on Indicators of Sustainable Development, Scientific Committee on Problems of the Environment (SCOPE), Wiley.

EC, 2003. A European Environment and Health Strategy. Communication from the Commission to the Council, the European Parliament and the European Economic and Social Committee, COM (2003) 338 final, European Commission, Brussels, Belgium.

EEA, 1999. Environmental Indicators: Typology and Overview. Technical Report n.25. European Environmental Agency, Copenhagen, Denmark.

European Observatory on Health Systems and Policies, 2007. The effectiveness of health impact assessment. Scope and limitations of supporting public health policies in Europe. Wismar M., Blau J., Ernst K., Figueras J. Editors, World Health Organization, Regional Office for Europe, Copenhagen.

Ezzati M., Hoorn S.V., Lopez A.D., Danei G., Rodgers A., Mathers C.D., Murray C.J.L., 2006. Comparative quantification of mortality and burden of disease attributable to selected risk factors. In: Lopez A.D., Mathers C.D., Ezzati M., Jamison D.T., Murray C.J.L. (Eds), Global burden of disease and risk factors. World Bank, Washington, 2006.

Fehr R., 1999. Environmental Health Impact Assessment, Evaluation of a Ten-Step Model. Epidemiology 10 (5): 618-625.

Giove S., Agostini P., Critto A., Semenzin E. and Marcomini A., 2006. Decision Support System for the management of contaminated sites: a multi criteria approach. In: Linkov I., Kiker G. A. and Wenning R. J. (Eds), Environmental Security in Harbors and Coastal Areas: Management Using Comparative Risk Assessment and Multi-Criteria Decision Analysis. Springer, Amsterdam, The Netherlands, pp. 267–273.

Giove S., Brancia A. Satterstrom F.K., Linkov I., Decision Support Systems and Environment: role of MCDA. In Marcomini A., Suter G.W. II, Critto A., (Eds). Decision Support Systems for Risk Based Management of Contaminated Sites. Springer Verlag (2009), New York.

Hall L. W. and Giddings J. M., 2000. The need for multiple lines of evidence for predicting site specific ecological effects. Human and Ecological Risk Assessment 7: 459-466.

Hays S.M. and Aylward L.L., 2009. Using Biomonitoring Equivalent to interpret human biomonitoring data in a public health risk context. Journal of Applied Toxicology, 29: 275-288.

Hays S.M., Becker R.A., Leung H.W., Aylward L.L., Pyatt D.W., 2007. Biomonitoring equivalents: A screening approach for interpreting biomonitoring results from a public health risk perspective. Regulatory Toxicology and Pharmacology 47: 96-109.

Hill A.B., 1965. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine, 58: 295-300.

IFC, 2009. Introduction to Health Impact Assessment. Environment and Social Develop Department, International Finance Corporation, World Bank Group, Washington DC.

IPCS, 2004. IPCS Risk Assessment Terminology. Harmonization Project Document n.1. International Programme on Chemical Safety, World Health Organization, Geneva.

Keeney R., Raiffa H., 1976. Decision with multiple objectives. Preferences and value trade-off. Wiley, New York, pp 589.

Kiker G.A., Bridges T.S., Varghese A., Seager T.P., Linkov I., 2005. Application of Multicriteria Decision Analysis in environmental decision making. Integrated Environmental Assessment and Management 1(2): 95–108.

Klinke A. and Renn O., 2006. Systemic risks as challenge for policy making in risk governance. Forum: Qualitative Social Research.

Knol A.B., Briggs D.J., Lebret E., 2010. Assessment of complex environmental health problems: framing the structures and structuring the frameworks. Science of the Total Environment 408(14):2785-94.

Linkov I, Loney D., Cormier S., Satterstrom F.K., Bridges T. 2009. Weight-of-evidence evaluation in environmental assessment: review of qualitative and quantitative approaches. Science of the Total Environment 407(19): 5199–205.

Linkov I., Satterstrom F.K., Kiker G., Batchelor C., Bridges T., Ferguson E., 2006. From comparative risk assessment to multi-criteria decision analysis and adaptive management: recent developments and applications. Environment International 32: 1072-1093.

Linkov I.,Welle P., Loney D., Tkachuk A., Canis L., Kim J.B., Bridges T., 2011. Use of Multicriteria Decision Analysis to support Weight of Evidence evaluation. Risk Analysis 31(8): 1211-1225.

Long E. R. and Chapman P.M., 1985. A sediment quality triad: measures of sediment contamination,toxicity and infaunal community composition in Puget Sound. Marine Pollution Bulletin 16: 405-415.

Marcomini A., Suter G.W., Critto A. (Eds.), 2009. Decision Support Systems for Risk-Based Management of Contaminated Sites. New York, Springer Verlag, 435 pp.

Mather F.J., White L.E., Langlois E.C., Shorter C.F., Swalm C.M., Shaffer J.G., Hartley W.R., 2004. Statistical methods for linking health, exposure and hazards. Environmental Health Perspectives 112 (14): 1440-1445.

McGeehin M.A., Qualters J.R., Niskar A.S., 2004. National Environmental Public Health Tracking Program: Bridging the Information Gap. Environmental Health Perspectives 112 (14): 1409-1413.

Mindell J. and M. Joffe, 2003. Health impact assessment in relation to other forms of impact assessment. Journal of Public Health Medicine 25 (2): 107-113.

Mindell J.S., Boltong A., Forde I., 2008. A review of health impact assessment frameworks. Public Health 122 (11): 1177-1187.

Morgenstern H. and Thomas D., 1993. Principles of study design in environmental epidemiology. *Environmental Health Perspectives Supplements 101 (S4).*

Murray C.J.L., Ezzati M., Lopez A.D., Rodgers A., Hoorn S.V., 2003.: Comparative quantification of health risks: conceptual framework and methodological issues. Population Health Metrics, 1(1): 1-20.

NRC, 1983. Risk assessment in the Federal Government: Managing the process. Committee on the Institutional Means for Assessment of Risks to Public Health, National Research Council, Washington D.C., National Academies Press, 191 pp.

NRC, 2006. Human biomonitoring for environmental chemicals. Committee on Human Biomonitoring for Environmental Toxicants, National Research Council, The National Academy Press, Washington D.C.

OECD, 1993. OECD Core Set of Indicators for Environmental Performance Reviews. Environmental Monograph 83. Organization for Economic Co-operation and Development, Paris, France.

Prüss-Üstün A., Mathers C., Corvalàn C., Woodward A., 2003. Introduction and methods: assessing the environmental burden of disease at national and local levels. WHO Environmental Burden of Disease Series, No. 1. World Health Organization, Geneva.

Royal Society, 1992. Risk Analysis, Perception and Management. The Royal Society, London.

Ryan P.B., Burke T.A., Cohen Hubal E.A., Cura J.J., McKone T.E., 2007. Using biomarker to inform cumulative risk assessment. Environmental Health Perspectives, 115(5): 833-840.

Schroijen C., W. Baeyens, G. Schoeters, E. Den Hond, G. Koppen, L. Bruckers, V. Nelen, E. Van DeMieroop, M. Bilau, A. Covaci, H. Keune, I. Loots, J. Kleinjans, W. Dhooge, N. Van Larebeke, 2008. Internal exposure to pollutants measured in blood and urine of Flemish adolescents in function of area of residence. Chemosphere, 71: 1317–1325

Schulz C., Conrad A., Becker K., Kolossa-Gehring M., Seiwert M., Seifert B., 2007. Twenty years of the German Environmental Survey (GerES): Human biomonitoring – Temporal and spatial (West Germany/East Germany) differences in population exposure. International Journal of Hygiene and Environmental Health, 210: 271-297.

Smith E.P., Lipkovich I., Ye K., 2002. Weight of Evidence: quantitative estimation of probability of impairment for individual and multiple Lines of Evidence. Human and Ecological Risk Assessment, 8 (7): 1585-1596.

Smolders R. and Schoeters G., 2007. Identifying opportunities and gaps for establishing an integrated EDR-triad at the European level. International Journal of Hygiene and Environmental Health 210: 253-257.

Smolders R., Koppen G., Schoeters G., 2008. Translating biomonitoring data into risk management and policy implementation options for a European Network on Human Biomonitoring. Environmental Health 7 (Suppl I): S2.

Suter G.W. II and Cormier S., 2011. Why and how to combine evidence in environmental assessments: Weighing evidence and building cases. Science of the Total Environment 409: 1406–1417.

Suter G.W. II, 2007. Ecological Risk Assessment. 2nd Edition, Boca Raton, CRC Press.

Suter G.W. II, Vermeire T., Munns W.R., Sekizawa J., 2005. An integrated framework for health and ecological risk assessment. Farmacology and Applied Toxicology, 207: S611-S616.

Thacker S.B., Stroup D.F., Parrish R.G., Anderson H.A., 1996. Surveillance in Environmental Public Health: Issues, Systems and Sources. American Journal of Public Health, 86 (5): 633-638.

US EPA, 1986. Superfund Public Health Evaluation Manual. EPA/540/1-86/060. United States Environmental Protection Agency, Office of Emergency and Remedial Response, Washington DC.

US EPA, 1989. Risk Assessment Guidance for Superfund (RAGS): Volume I – Human Health Evaluation Manual (HHEM). EPA/540/1-89/002. United States Environmental Protection Agency, Office of Emergency and Remedial Response, Washington DC.

USEPA, 1985. Guidelines for carcinogen risk assessment. EPA/630/R-00/004, United States Environmental Protection Agency, Washington DC, USA.

USEPA, 2005. Guidelines for carcinogen risk assessment. EPA/630/P-03/001F, United States Environmental Protection Agency, Washington DC, USA.

USEPA, 2007. Framework for determining a mutagenic mode of action for carcinogenicity. EPA/120/R-07/001, United States Environmental Protection Agency, Washington DC, USA.

Van Leuwen C.J. and Vermiere T.G. (Eds), 2007. Risk Assessment of Chemicals – An introduction. 2nd Edition, Springer, The Netherlands, 686 pp.

Veerman J. L., Barendregt J.J., Mackenbach J.P., 2002. Quantitative health impact assessment: current practice and future directions. Journal of Epidemiology and Community Health 59: 361-370.

Vincke P., 1992. Multicriteria Decision-Aid. Wiley & Sons, Chickester, UK.

Von Schirnding Y., 2002. Health in Sustainable Development Planning: the Role of Indicators. WHO/HDE/HID/02.11, World Health Organization, Geneva.

Weed D. L., 2005. Weight-of-Evidence: a review of concepts and methods. Risk Analysis, 25(6): 1545 1557.

WHO, 1997. Health and Environment in Sustainable Development. World Health Organization, Geneva.

WHO, 1999a. Environmental Health Indicators: Framework and Methodologies. Protection of the Human Environment - Occupational and Environmental Health Series, WHO/SDE/OEH/99.10. Sustainable Development and Healthy Environments, World Health Organization, Geneva.

WHO, 1999b. Health impact assessment: main concepts and suggested approach. Gothenburg consensus paper. WHO Regional Office for Europe.

WHO, 2000. Environmental Health Indicators: Development of a Methodology for the WHO European Region. Working Paper n. 19 of the Joint ECE/Eurostat Work Session on Methodological Issues of Environment Statistics, held in Ottawa (Canada), 1-4 October 2001. WHO-European Centre for Environment and Health, World Health Organization, Geneva.

WHO, 2004. Children's Environment and Health Action Plan for Europe. EUR/04/5046267/7, adopted during the Fourth Ministerial Conference on Environment and Health, Budapest (Hungary), 22-24 June 2004.

WHO, 2005. Implementing Environment and Health Information System In Europe – ENHIS. Final Technical Report. European Centre for Environment and Health, World Health Organization, Bonn, Germany.

WHO, 2010a. Parma Declaration on Environment and Health, Fifth Ministerial Conference on Environment and Health "Protecting children's health in a changing environment", EUR/55934/5.1 Rev. 2, 10–12 March 2010, Parma, Italy.

WHO, 2010b. Tools for the monitoring of Parma Conference commitments. Report of a meeting held in Bonn (Germany) on 25-26 November 2010. World Health Organization, Regional Office for Europe, Copenhagen, Denmark

World Health Organization (WHO), 2002. Health in Sustainable Development Planning: The Role of Indicators. World Health Organization, Geneva.

Yager R.R., 1988. On ordered weighted averaging aggregation operators in multicriteria decision-making. IEEE Trasactions on Sytems, Man and Cybernetics 18 (1): 183-190.

CHAPTER 4

DEALING WITH UNCERTAINTY IN HEALTH RISK ASSESSMENT

4.1 INTRODUCTION: A GLOSSARY ON UNCERTAINTY

Uncertainty is a key issue in the assessment of effects of environmental stressors on human health, independently from the specific type and framework of the assessment (e.g., risk assessment, epidemiological study, environmental health impact assessment, assessment of the environmental burden of disease). The issue of facing uncertain knowledge is actually serious in environmental health assessment because this discipline usually deals with very complex systems, it requires the use of large amounts of information from different sources (empirical data, model results, expert judgments) and it is usually based on multi- and inter-disciplinary processes, involving a strong collaboration between experts from different disciplines (e.g. chemistry, epidemiology, environmental sciences, toxicology, statistics, etc.). This chapter is aimed at reviewing available approaches for incorporating and managing uncertainty in health risk assessment, with the aim of identifying possible methods which could support the treatment of uncertainty issues in the development and application of a methodology for ranking environmental chemical stressors.

Walker et al. (2003) define uncertainty as *any departure from the unachievable ideal of complete determinism*. In recent decades, many authors tried to provide comprehensive classification scheme of uncertainty and proper definitions of the different types of uncertainty, but an agreement has not been achieved yet, due to the fact that uncertainty is a non-intuitive term (Ascough et al., 2008) which can receives different interpretations according to the discipline and the context where it is considered and the goal of the assessment.

The first, most common and simple distinction can be made between the concept of *uncertainty* and the concept of *variability*. Variability refers to true heterogeneity or diversity (US EPA, 2001) and it is an intrinsic characteristic of every natural system, i.e. is an attribute of reality (Rotmans and Van Asselt, 2001). Variability characterizes, for example, the spatial and temporal heterogeneity of chemical concentrations in environmental matrices, or the properties of environmental matrices themselves (e.g. soil porosity, water or air temperature). Variability is immediately evident when observing characteristics of human populations. Specifically, it is possible to distinguish between inter-individual variability, i.e. the differences in characteristics or behaviour among distinct

individuals, and intra-individual variability, i.e. the differences concerning the same individual in time (e.g., inhalation rate, excretion rate).

Uncertainty, on the other hand, occurs because of a lack of knowledge about the system (US EPA, 2001), and may be reduced by means of further investigations, for instance by increasing the number of sampling points in the study area or by improving the measurement instruments and thus lowering the detection limit. Uncertainty can lead *to inaccurate or biased estimates, whereas variability can affect the precision of the estimates and the degree to which they can be generalized* (US EPA, 1997).

Following the same distinction, Rotmans and Van Asselt (2001) distinguish between an *ontological dimension* of uncertainty (corresponding to variability) and an *epistemological dimension*, which concerns the human ability to know. Similarly, Daneshkah (2004) names the variability as *aleatory uncertainty*, whereas he calls *epistemic uncertainty* the impossibility to adequately know and describe the observed system.

In the context of human health risk assessment, US EPA (1992; 1997; 2001) proposes three broad categories for classifying uncertainty, described as follows.

- **Parameter uncertainty** corresponds to the uncertainty in the estimate of an input variable to the risk model. According to Moschandreas and Karuchit (2002), US EPA uses the term *parameter* to reflect two concepts: distribution parameter (i.e. the constants characterizing the probability distribution of a variable, such as μ or σ) and model variable (i.e. the variables included in the risk model, such as concentration or body weight). Parameter uncertainty may originate from measurement errors (imprecise or biased measurements), sampling errors, natural variability and use of surrogate data when site-specific data are not available.
- **Model uncertainty** refers to uncertainty about the structure of a model (e.g. exposure model equation) and its application in a specific context (i.e. application to situation beyond the scale used to calibrate the model). The simplification of reality inherent in the modelling process can lead to modelling errors, while errors in correlation among model variables result in relationship errors.
- **Scenario uncertainty** is defined as the uncertainty derived by missing or incomplete information necessary to fully characterise exposure and dose (US EPA, 1992; US EPA, 1997). Its sources include: descriptive errors (concerning the magnitude and extent of chemical exposure or toxicity), aggregation errors derived by approximations (homogeneous population, steady-state conditions, etc.), errors in professional judgement and incomplete analysis (e.g. missing exposure pathways).

Among several, sometimes overlapping, proposals for an uncertainty typology (a good overview can be found in Ascough et al., 2008), the conceptual framework structured by Walker and colleagues

(2003) pursues the goal of being exhaustive and comprehensive and is taken as reference by many authors (e.g. Refsgaard et al., 2007; Briggs et al., 2008). These authors focus on the wide context of *model-based decision making*, and recognize three dimensions of uncertainty, namely: location, nature, level.

The location of uncertainty concerns where it manifests itself within the model complex. The generic possible "locations" identified by the authors are the following ones:

- *context uncertainty*, associated to the definition of the boundaries of the system to be modelled and the evaluation of model completeness;
- *model uncertainty*, including the uncertainty associated to the form of the model and the uncertainty associated to its computer implementation;
- *uncertainty associated to model inputs*, depending on the data which describe the reference system and all the external driving forces having an influence on the system and its changes;
- *parameter uncertainty*, concerning the data and the approaches used to calibrate model parameters;
- *model outcomes uncertainty*, due to the propagation of all the aforementioned types of uncertainty and their manifestation in model outputs.

The nature of uncertainty concerns the form that the uncertainty can takes. Walker and colleagues (2003) identify *epistemic uncertainty* and *variability uncertainty* as two extremes, corresponding to the difference between the imperfection of human knowledge on phenomena and the inherent variability of real systems/processes already described before. The authors identify as sources of variability uncertainty the following ones: inherent randomness of nature, behavioural variability (differences in micro-level behaviour, at the level of individuals) and societal variability (due to the unpredictable nature of societal, i.e. macro-level, processes).

The level of uncertainty indicates the magnitude of the uncertainty. The authors present a complete spectrum of different possible levels of knowledge (Figure 4.1), starting from full deterministic understanding at one extreme of the scale and ending with the total ignorance at the other extreme.

Figure 4.1 The spectrum illustrating different levels of uncertainty (from Walker et al., 2003).

Statistical uncertainty, between the two extremes, is identified as what is usually referred to as "uncertainty" in natural science, that is, any form of uncertainty that can be properly described in statistical terms by traditional statistical tools (e.g. confidence intervals). The following level consists in *scenario uncertainty*, occurring when there is a range of possible outcomes, but it is impossible to determine the probability of any one particular outcome occurring and uncertainties are often described in terms of best- and worst-case estimates. Briggs et al. (2008) criticize the choice of the term "scenario uncertainty" because these uncertainties do not necessarily originate in the definition or modelling of the scenario. *Recognised ignorance* occurs when the analysts know the potential for an effect, but neither the direction nor the probability of this effect can be assessed because of a lack of knowledge about the mechanisms of the system.

Briggs et al. (2008) take the framework proposed by Walker et al. (2003) as reference for describing the uncertainties which affect epidemiology, health risk assessment and health impact assessment. They prefer to use the terms "intrinsic uncertainty" and "extrinsic uncertainty" for naming variability uncertainty and epistemic uncertainty respectively. They identify as sources of intrinsic uncertainty randomness: sparseness (especially important in relation to binary phenomena such as health outcome), nonlinearity (occurring due to self-regulating or self-amplifying nature of many biological processes, interaction among risk factors leading to effect modification, inelasticity in phenomena due to buffer capacity). They observe that intrinsic and extrinsic uncertainty cannot be considered completely independent: in highly regular systems, indeed, the underlying patterns may be detected even by imprecise measurements or small samples, while when intrinsic uncertainty is huge, imprecise or biased measurement/sampling may be even more difficult and prediction is problematic. They refer to well-known issues of epidemiologic study, such as the small-number problem or Modifiable Area Unit Problem (MAUP) to describe how study design and data treatment may affect the uncertainty associated to the results.

As far as location of uncertainty is concerned, Briggs and colleagues (2008) differentiate among *conceptual uncertainty* (affecting the initial phase of framing of the study), *analytical uncertainty* (which is the most considered), and *communicational uncertainty* (arising from the communication of study results to different stakeholders). The authors notice that, if many statistical methods have been developed or are under development for treating statistical uncertainty, there is however a strong needs for methods able to face conceptual and communicational uncertainty. Participatory approaches and more qualitative measures of uncertainty may offer support in this direction, and help in understanding and communicate the implication of the complete range of uncertainties affecting the assessment.

Proposed typologies of uncertainty provide the assessors with a sort of "checklist" for identifying before, during and at the end of the assessment all possible sources of uncertainty and support them

in selecting the most appropriate tool to deal with specific types of uncertainty. Often some types of uncertainty in the assessment may not be reduced, however it is fundamental to be aware of their occurring and provide the adequate information to stakeholders/risk managers when communicating assessment results.

In recent years guidelines on the selection of methods for uncertainty treatment have been proposed, which provide an extended range of different tools and include also methods for facing those type of uncertainty which are more difficultly quantified (e.g. model uncertainty associated to the selection of one model instead of another); additional details on these topics can be found in Van der Slujis et al. (2004).

The approaches and methods included in this review and summarized in the following paragraphs basically deals with statistical uncertainty associated with input and output data in a risk model (even if in some cases their use can be seen in a wider perspective) and have been included according to their potential for dealing with uncertainty in the development of a methodology for ranking environmental chemical stressors.

4.2 DETERMINISTIC VERSUS PROBABILISTIC APPROACHES

Traditionally, health risk assessment is based on a deterministic approach: point values are used as inputs to risk model, usually chosen on the basis of "worst case" hypothesis (US EPA, 2001; Spanjersberg et al., 2007). The worst-case approach is aimed at assuring that even the most sensitive component of the population would be protected under all exposure conditions. For this aim, common approaches may include the use of the 90^{th} percentile or the maximum of concentration data, the selection of worst-case consumption level, the use of safety factor for incorporating in the assessment the uncertainty due to extrapolations (Verdonck et al., 2006).

In US EPA (2001), two alternatives are proposed for estimating exposure under a conservative perspective. The first consists in the estimate of the *Reasonable Maximum Exposure* (RME), which correspond to the highest exposure which is supposed to occur at the contaminated site of interest. The second option consists in estimating a *Central Tendency Exposure* (CTE) which corresponds to an average exposure and in a sense may provide a more realistic evaluation.

However, all these kinds of assumptions might typically lead to overestimate the risk for the population of interest. The combination (multiplication) of several conservative values lead to consider an unnecessarily conservative and almost unlikely (or even unrealistic) scenario and therefore ends with an overestimated risk (EC, 2003). Another serious disadvantage is that actually

the magnitude of the potential impact is unknown because there is no information about the proportion of the population that might be at risk.

With the conservative approach, the risk assessor does not know where his risk estimate falls within the overall distribution of risk (Burmaster, 1995). If the estimated risk falls below a defined regulatory definition of Maximum Acceptable Risk, than the risk assessor and stakeholders can have confidence that the distribution of risk is truly acceptable. But, if the estimated risk falls above the regulatory limit, it is not possible to know if the distribution of risk is truly unacceptable.

The advantages of deterministic, "worst-case" assessment consist mainly in its simplicity and easiness of application (it does not require powerful computational tools). It can be useful in particular as a screening method, for evaluating the need for further investigations and analysis, and it is apparently easy to communicate to non-expert stakeholders (US EPA, 2001; Burmaster, 1995). However, this approach basically makes impossible to consider uncertainty and variability inherent to the problem and alternatives in this direction have been offered by probabilistic risk assessment (Burmaster, 1995; Jager, 2000; Sander and Ober, 2006; Verdonck et al., 2006).

Probabilistic approaches to human health risk assessment are based on the use of probability density function for characterizing uncertainty and variability in input data to the risk model (US EPA, 2001; EC, 2003). The several components and steps of risk assessment are connected by mathematical relationships and the variability and uncertainties in the input data at each step are propagated along the assessment up to the final output. Subsequently, output risk estimates will be represented by probability distributions as well, and from this output distribution the median and any percentiles results can be known (US EPA, 2001; IEH, 2000; EC, 2003). This can surely provide more complete information if compared to point estimates of risks. Probabilistic assessment allows indeed to obtain not only quantitative risk estimates, but express the uncertainty and variability associated with these estimates. Moreover, this approach attempts to consider information from a wide range of sources and to account for its relevance and quality (Cullen and Small, 2004). This provide risk assessors and stakeholders with more realistic and detailed output information which may constitute a solid basis for risk management decisions (US EPA, 2001; Sander and Oberg, 2006).

Drawbacks of probabilistic approaches to risk assessment have also been pointed out. Concepts and approaches used in probabilistic risk assessment may result tough for non-expert stakeholders and this aspect may create difficulties in communicating and discussing risk assessment (US EPA, 2001). Among the disadvantages of probabilistic risk assessment, computational difficulties and application costs may be included as well. Moreover, it is surely more time- and resources-consuming than deterministic risk assessment. However, these limitations should be evaluated in comparison to the improvements in the informative contents that a probabilistic approach can provide.

Probabilistic risk assessment may not be considered as the adequate option in all situations and the implementation of a probabilistic method should always be properly evaluated. For this purpose, tiered approaches are proposed for supporting the choice of the most adequate assessment approach to be used in different contexts and according to specific assessment goals (US EPA, 2001; Lunchick, 2001; ECHA, 2008). Commonly, tiered risk assessment approach include as first step a deterministic method, and as further steps the application of probabilistic assessment of increasing level of detail (e.g. Monte Carlo approach, such as in US EPA, 2001). Higher tiers correspond to an increased complexity of the assessment and to the need of detailed, site-specific data. Higher tiers also reflect an improved characterisation of variability and/or uncertainty in the risk estimates. At the end of each step, the results are evaluated and the compliance of information with risk management needs is appraised, in order to decide if the shift to a higher assessment step could provide significant benefits.

Probabilistic approaches can be essentially based on two distinct statistical paradigms: the *frequentist* or *classical paradigm*, that leads to the development and application of sampling-based methods, and the *Bayesian paradigm* (funded on a subjective definition of probability), that leads to the development of Bayesian methods such as Bayesian Networks. In the following paragraphs these two families of methods are presented.

4.3 PROBABILISTIC APPROACHES: SAMPLING-BASED METHODS

4.3.1 MONTE CARLO ANALYSIS

Sampling-based methods represent possibly the most widely used probabilistic modelling framework in human health and ecological risk assessment (Krupnick et al., 2006). Sampling-based methods allow to propagate uncertainty and variability from model inputs through to model outputs and among them Monte Carlo analysis is the most common and widely applied. Monte Carlo Analysis is a computer-based method developed in the 1940's in which statistical sampling techniques are used for obtaining a probabilistic approximation to the solution of a model (US EPA, 2001).

In Monte Carlo simulation, a deterministic model is run repeatedly using for each run a combination of values of input parameters randomly sampled from the probability distributions describing the input values. The procedure is repeated for a fixed number of times (typically between 500 and 1000) and through these iterations a distribution of output is generated. The set of simulations propagates defined uncertainties from model inputs through to model outputs. The output dataset can be analysed statistically, to estimate its descriptive parameters, such as the mean or the

variance, in order to define the probability distribution of the dependent variable of interest (e.g. risk). Figure 4.2 describes this process. Random samples are taken from the distributions of independent input variables x_1 and x_2, and the output z is calculated using the chosen relationship (i.e., the model) between the input variables.

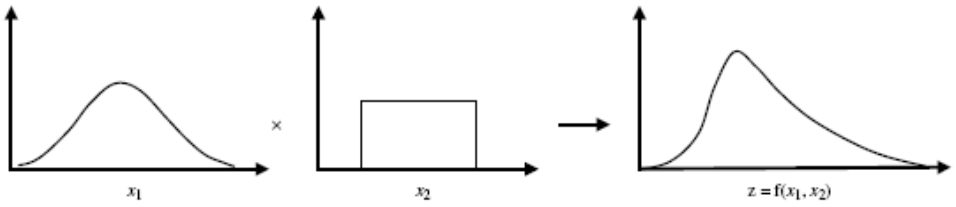


Figure 4.2 Simple Monte Carlo simulation based on random sampling (from Chowdhury et al., 2009).

It should be noticed that, if the generation of the values used in the model is a probabilistic process, the run of the model for each combination of input values is actually deterministic (Frey, 1992).

US EPA (1997) provided complete guidelines for the application of Monte Carlo analysis. The main steps for the application of a Monte Carlo analysis can be summarized as follows (US EPA, 1997; 2001):

1) selection of input data and selection of their probability distributions;
2) estimate of uncertainty and variability related to the assessment;
3) presentation of results.

In step 1, sensitivity analysis or numerical experiments may support the identification of exposure pathways that provide a significant contribution to the total risk estimate, in order to exclude the unimportant pathways from the probabilistic assessment or from further analysis altogether. For identified significant pathways, sensitivity analysis may identify those model variables giving the most significant contribution to overall uncertainty. The excluded variables may be represented in the assessment as a point estimates (US EPA, 2001), because Monte Carlo analysis can be applied to a mixed set of point estimates and distributions for the input variables.

The selection of the most appropriate probability distributions is an important and challenging phase of Monte Carlo analysis, which should be based on all the available information about the variables of interest. The selection of the probability distributions can be driven by the knowledge of the mechanism (physical, biological, etc.) underlying the process of interest for that variable. For example, a Poisson distribution may be chosen to describe the number of independent and randomly distributed events in a unit of time (or space) while lognormal distribution is usually selected for

describing chemical concentrations in environmental media (US EPA, 2001). In other cases, when real conditions deviate from theoretical models, instead of using parametric distributions, empirical distribution functions (EDFs) can be derived from the frequency distribution of observed values for the variable of interest. In this case, attention must be paid to the basic principles of sampling, and in particular to the quality of information at the tails of distributions (US EPA, 1999). Goodness-of-Fit tests may be used to test the fit of a theoretical distribution to a data set.

Expert elicitation techniques can also be used for supporting the selection of input distributions (USEPA, 1997; Cullen and Small, 2004). Distributions based primarily or exclusively on expert judgement may be subject to significant bias because they are the results of individual or group opinions. In any case the inclusion of expert judgement has to be clearly explicate in the communication of assessment results.

In this step, correlations between input variables should be investigated and described, because correlations may influence model results in a significant way, depending on the strength of the correlation and on the contribution of the correlated variables to the overall variance in the output (Cullen and Small, 2004).

Step 2 consists in the assessment of variability and uncertainty (i.e. epistemic uncertainty): these two aspects may be treated conjointly or separately within the assessment framework, and in the latter case the assessment gains transparency and reliability. A bi-dimensional Monte Carlo analysis (illustrated afterwards in this paragraph) permits to track them separately.

Step 3 consists in the communication of results of Monte Carlo analysis. In this phase, models and input data, assumptions, methodological choices, use of expert judgement have to be adequately described in order to provide the stakeholders with all necessary information for understanding and using the assessment results. Plots of selected input distributions and of output distributions should be provided, both as Probability Density Function (PDF) and as Cumulative Density Function (CDF) (Figure 4.3). The two curves display the same distribution, but PDF is most useful for showing the relative probability of values, the most likely values and the shape of the distribution (e.g. more or less skewed), while CDF can show percentiles, high-end risk range, confidence intervals for specific percentiles and stochastic dominance (Frey, 1993; US EPA, 2004).

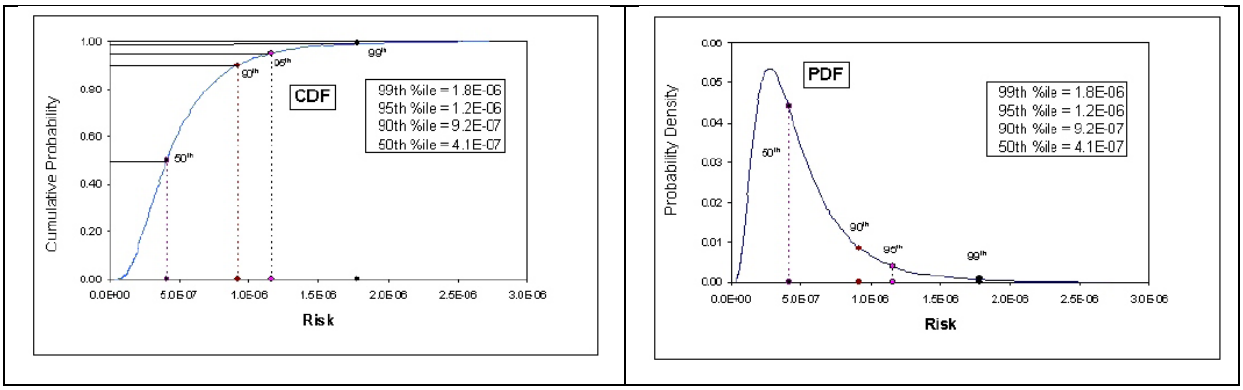


Figure 4.3 Examples of results of a Probabilistic Risk Assessment: a Probability Density Function (PDF) (left window) and a Cumulative Density Function (CDF) (right window). The CDF shows that the regulatory limit for acceptable risk (1E-06) falls between the 90th and 95th percentile of the risk distribution (US EPA, 2004).

Correlations between variable should be presented and discussed. The comparison of probabilistic assessment results to point estimates (e.g., by inserting the point estimate within the final output distribution) may turn out to be useful for a better communication of assessment results.

Several software are available for performing Monte Carlo analysis. The most widely used and commercialized are @Risk (by Palisade Corporation), Crystal Ball (by Oracle), and Analytica (by Lumina Decision System).

By applying a simple Monte Carlo analysis (mono-dimensional or 1-D Monte Carlo Analysis) the variance reported in the final outputs will include both components of uncertainty (i.e. epistemic uncertainty and variability), but this way limits interpretation (Krupnick et al., 2006). A possible solution is the use of a second-order Monte Carlo analysis (also called two-dimensional or 2-D Monte Carlo analysis) (Frey, 1992; US EPA, 2001; Verdonck, 2006). This approach allows to disaggregate and handle uncertainty and variability separately and to evaluate individually their consequences on the assessment results (Cullen and Small, 2004). The distinction of the separate contributions may be critically important within the scope of health risk assessment and may address further collection of data or other actions for improving the precision of the assessment.

All probability distribution that are used to describe variability in a probabilistic risk assessment have a certain degree of associated uncertainty. If a particular type of probability distribution (PDF) is selected to describe the variability of an input variable, this PDF can be in its turn be affected by uncertainty: it means that distribution parameters (e.g. μ and σ in a normal distribution) can be supposed to be random variables and that a probability distribution can be assign to each of them. Two PDFs may thus be defined for each distribution parameters, and these PDFs will be described by

their own parameters. A model variable that is characterized in this way is called a *second order random variable* (USEPA, 2001).

The second-order Monte Carlo analysis is based on the concept of performing separate samplings from distributions representing variability and distribution representing uncertainty. This is obtained by using nested computational loops, for each of M simulations in dimension X, N simulations are performed in dimension Y (Krupnick et al., 2006). The inner loop simulates variability by repeatedly sampling values for each variable from their probability distributions. The outer loop deals with uncertainty: for each circuit of the outer loop, new distribution parameters for each variable are chosen, and the sampling within the inner loop is replicated (USEPA, 2001). By this way, a set of inner loop simulations is obtained, one for each value of the distribution parameter selected. The process of a second-order Monte Carlo analysis is illustrated in Figure 4.5.

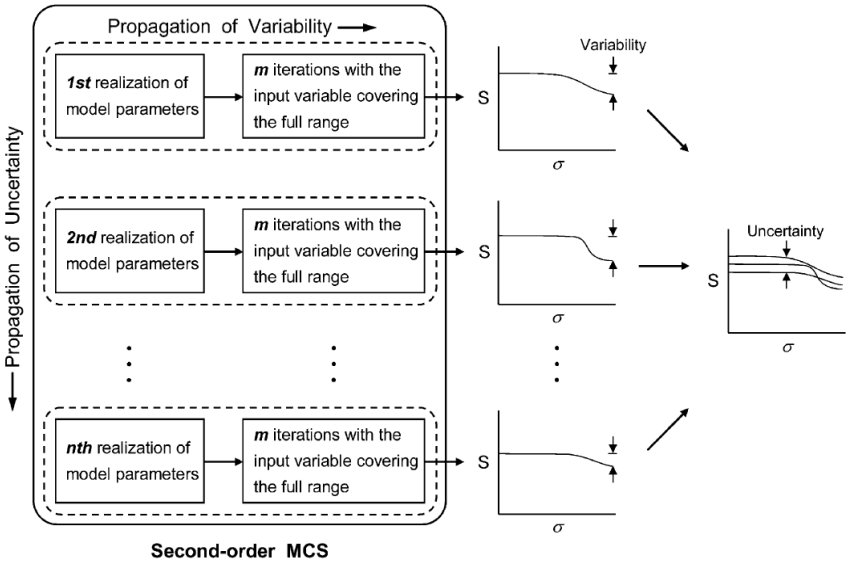


Figure 4.5 Procedure for the application of a 2-dimension Monte Carlo analysis. The inner loop consists in m iterations propagating system variability, while the outer loop consists in n iterations propagating uncertainty (Wu and Tsang, 2004).

The final result after propagation of uncertainty and variability through the model is a probability distribution (for example, a distribution of intake estimates or risk) with an uncertainty or confidence band. An example is reported in Figure 4.6, representing the exposure (total intake) of dioxin for a selected population.

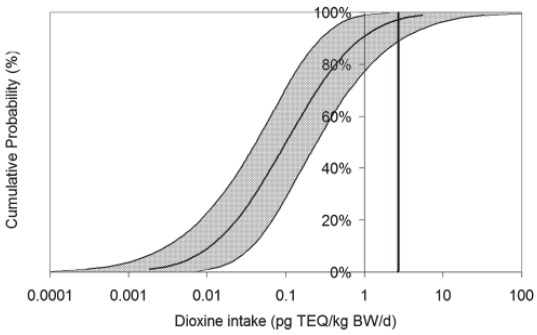


Figure 4.6 Probability distribution of exposure to dioxin (daily intake): central black line represents inherent variability, 90% grey confidence bands represent uncertainty (Verdonck et al., 2006).

Monte Carlo nested analysis is computationally more complex than one-dimensional simulations, and furthermore, it is often not easy to distinguish between uncertainty and variability in variable characterization. Because of these reasons, the application of a 2-D Monte Carlo analysis is not always the best choice, however it might be powerful if the assessment is aimed at identifying which uncertainties may be reduced by further analysis, or if extensive or exhaustive uncertainty analysis is required (Krupnick et al., 2006).

4.3.2 OTHER SAMPLING METHODS

Classical Monte Carlo analysis is based on random sampling, namely independent sampling with replacement. A problem of clustering may arise when a small number of iterations is performed, because they could be not enough for adequately capture and represent low probability outcomes (i.e. tail ends of skewed distributions). For assuring that also the tails of the cumulative distribution are properly included in the analysis, an alternative to purely random sampling used in Monte Carlo analysis is offered by stratified random sampling techniques, in which input distributions are divided into several strata which are sub-sampled (Cullen and Small, 2004). The most known method is Latin Hypercube Sampling (LHS). Stratification divides the cumulative curve into equally probable intervals and the sampling is then forced to take randomly values from each interval (or “stratification”) in order to adequately represent the input probability distribution (Figure 4.7). The number of sampling iterations in LHS is equal to the number of strata and the sampling is performed without replacement. The main advantages of LHS are that it allows to better characterize the variability and/or uncertainty distributions in case of smaller sample size and usually fewer simulations are required in comparison with Monte Carlo analysis.

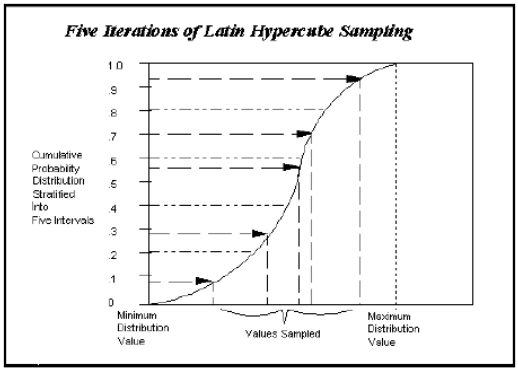


Figure 4.7 An example of Latin Hypercube Sampling: the cumulative curve is divided into 5 strata and a sample is drawn from each interval (Iman et al., 1980).

Another sampling method proposed in literature is the so-called Targeted Sampling (or Importance Sampling): the probability distribution is divided into strata but, differently from LHS, in this case some strata of the curve (e.g., the tail of the distribution) are sampling more often because they are considered to be associated with high risk conditions or result more relevant to risk management (Cullen and Small, 2004).

4.4 PROBABILISTIC APPROACHES: BAYESIAN APPROACHES

4.4.1 BAYESIAN PARADIGM

Bayesian approaches are becoming increasingly popular in human and ecological risk assessment. Bayesian approaches cannot be simply considered as a set of methods, but on the contrary represent a complete framework for modelling and statistical inference (Moe, 2010) and offer the researchers an alternative option to the classic (also called “frequentist”) statistical approach on which sampling-based approaches are based (Ascough II et al., 2008).

In the Bayesian statistical framework, probability is considered as a “degree of belief” or “degree of certainty” about an event, that is, how likely it is thought to be than an event will occur, based on available knowledge/data (IEH, 2000; Ricci, 2006). It must obey certain mathematical rules (for example, total probability is equal to one), but it is suitable to many more events if compared to frequentist probability, such as past events and non-repeatable events. Different events may be attributed different estimates of probability according to anyone’s information or experience.

Let X and Y be two random variables, with probability density functions (PDFs) $p_x(x)$ and $p_y(y)$, respectively; the basic version of Bayes' theorem (stated in 1763 by Reverend Thomas Bayes) for random variable is expressed as follows:

$$p_y(y \mid x) = \frac{\left[p_x(x \mid y)\, p_y(y)\right]}{p_x(x)} \qquad \text{(Eq. 4.1)}$$

where

$p_x(x|y)$ is the conditional PDF for X given Y= y

$p_y(y|x)$ is the conditional PDF for Y given X= x

If we rewrite the theorem for two events A and B, it results:

$$p(A \mid B) = \frac{\left[p(B \mid A)\, p(A)\right]}{p(B)} \qquad \text{(Eq. 4.2)}$$

Bayesian theorem combines a prior knowledge p(A) (represented by the probability distribution of the event A based on prior knowledge) with new evidences (represented by the probability distribution of the evidences, p(B)). The probability distribution of new evidence given the event A (p(B|A)) is called *likelihood function*. The final product is a posterior probability distribution, p(A|B), conditional on the evidence, which represents the updated probability of the hypothesis. Figure 4.8 provides a graphical representation of these concepts.

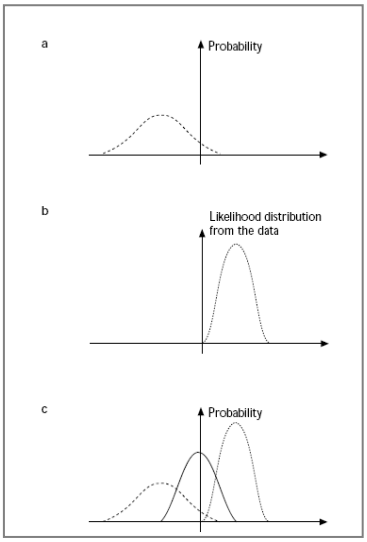


Figure 4.9 Graphical representation of Bayes' theorem. The joint posterior probability distribution (normalized to a total probability of one) is represented by the solid line in graph (c) (IEH, 2000).

The possibility to include in the model new information and data and thus to accumulate evidences along the assessment makes the Bayesian framework particularly flexible and appealing: combing data from more studies and add more data in a sequential study is almost straightforward within a Bayesian framework model (Dennis, 1996). Moreover, different types of information may be combined within the same assessment model, such as sampling data, model predictions or expert judgement (IEH, 2000): this aspect turns out to be particularly interesting in context with scarce empirical data, where the integration of all available types of knowledge may help in overcoming limitations. Another advantage of Bayesian probabilistic paradigm is that anything can be treated as a probability distribution, both the hypotheses (including the model parameters) and the evidence (empirical data or other kind of information) (Moe, 2010). Therefore it offers the possibility for uncertainty to be accounted for and integrated along all steps of the model.

At the same time, Bayesian approach has been criticized for excessive subjectivity and arbitrariness due to the inclusion of subjective opinion into a model (as prior probability distribution) (Dennis, 1996). Since there is no single "truly correct" prior distribution, all results obtained from posterior distribution can be debatable. However, such subjectivity is not in contrast with the way scientific data are usually gathered and used. Bayesian concepts do not depend on assumptions of infinite unbiased sampling and are not restricted to the comparison with a single null hypothesis as frequentist concepts are. Moreover, subjectivity in prior distribution selection may be limited by properly discussing, documenting and justifying it, and the effect that this choice has on the results can be verified by comparing different distributions (IEH, 2000), thus obtaining more transparent and traceable results than classical methods (Clark, 2005). Moreover, the more empirical data are collected, the less the prior distribution influences the posterior distribution if compared to the data (Bullard, 2001). Some computational limitations may affect Bayesian methods, and probably for this reason historically they have not been more exploited, however this issue is now faced by modern advances in mathematics and computer technology (IEH, 2000; Moe, 2010).

In conclusion, Bayesian approach turns out to be an interesting methodological option to be applied in environmental health risk/impact assessment to integrate probabilities for any type of available information together with on-going developments, with the aim of obtaining a revised probability of the occurrence of an event or of an hypothesis being true (IEH, 2000).

4.4.2 BAYESIAN NETWORKS

The Bayesian relationship between prior knowledge and new data represents the basic "building block" in Bayesian (Belief) Networks (IEH, 2000), which will be briefly illustrated in this paragraph

because of their relevance and potential further expansion in environmental and health risk assessment (Uusitalo, 2007). A Bayesian Network (BN) is a graphical model that represents a set of variables and their probabilistic relationships/dependencies (Heckermann, 1996). The graphical structure takes the form of a Directed Acyclic Graph (DAG), Acyclic because there are no feedback loops in the system (Ricci, 2006).

Bayesian Networks are a recently-developed modelling approach of artificial intelligence (AI) research which has the objective of providing a decision-support framework for facing problems characterized by complex relationships and uncertainty and involving probabilistic reasoning (Wooldridge, 2003). A Bayesian Network is a direct representation of a system/domain, and not of the reasoning process, i.e. the relationships represented in the graph are an expression of real connections among variables and not of the "reasoning flow" as in rule-based models (Pearl and Russel, 2000).

The elements composing a Bayesian Network are (Charniak, 1991; Wooldridge, 2003):

- a set of nodes, each one representing a random variable (discrete or continuous) of the domain of interest represented by a probability distribution; the nodes are typically defined by discrete intervals representing mutually exclusive states;
- a set of arcs/arrows, connecting the nodes and representing causal relationships between the nodes (the direction of the arrow indicates which node has an influence on the other node);
- a set of probabilities for each node, specifying the belief that a node will be in a particular state.

A "child node" (output node) descends from a "parent node"(input node) by an arrow exiting from the parent node and entering the child node. The "strength" of relationships between nodes (variables) is measured in terms of conditional probability and expressed by means of Conditional Probability Tables (CPTs). CPTs illustrates the probability that a child node is in a particular state given the states of the nodes that affect it. Probability distributions of the children nodes are estimated as the combined probabilities of all combinations of all their parent nodes. Nodes without parents are called root nodes and the probability distributions of their states is specified as Marginal Probability distribution. Marginal Probability Distributions and Conditional Probability Distributions can be derived from several kind of information, such as empirical data (e.g. monitoring data), expert judgement, estimates or predictions obtained from other models.

Bayesian Networks can also be developed into Influence Diagram. In Influence Diagram there are three types of nodes: besides uncertainty (or probability) nodes like in BNs, decision nodes and utility nodes are included. A decision node contains alternative decisions, such as "intervention" or "no intervention". Influence Diagrams can be used as decision-support tool to be used under uncertain conditions (Ricci, 2006) and in this sense provide an extension of the typical applicability of Bayesian Networks.

For building and understanding BNs, identifying the relationships of dependence and independence among the variables is a fundamental task. A basic concept to be clarify is that of *conditional independence,* which is a building concept for set up a BN as well as for understanding the transmission of evidence along the network. Two sets of variable A and B are said to be (conditionally) independent given a third set C if, when we know the values of the variables C, knowledge about the values of the variables B add no further information about the values of the variables A. It can be written as:

$$p(A|B, C) = p(A|C) \qquad \text{(Eq. 4.3)}$$

The consequence of conditional independence is that, in the case of variables A, B, and C, the knowledge about variables B is useless to predict A, thus the number of parent nodes necessary to estimate A may be reduced. This independence allow the assessor to factorise the BN, considering each node and its parents in isolation from the rest of the model (Wooldridge, 2003).

Once defined all probabilities in the BN, Bayesian rules may be used to up-date the system and to perform several analysis. It is possible to fix the state of some nodes and to analyse the impact on other nodes of the network (Moe, 2010). The verb "to instantiate" is used to say that to a random variable a specific value is assigned. The impact of changing any variable is transmitted along the whole network (propagation process) according to the relationships expressed in the Conditional Probability Tables (Fenton and Neil, 2007). More formally, we can say that as the BN *encodes a joint probability distribution over all the nodes,* when the state of any node is modified, the joint distribution is updated through the iterative application of Bayes' theorem (Cain, 2001). This potentiality of BN to investigate "what if" scenarios is not feasible with other types of reasoning and classical statistical analysis methods (Fenton and Neil, 2007).

As highlighted by Moe (2010), the interesting point in BNs is that not only parent nodes but also children nodes may be instantiated. The consequence is that any direction of investigation of the network can be used, and for example the model may be used to project scenarios "backwards".

Formally, Wooldridge (2003) identifies three basic types of inference that the BN may aimed at:

- *diagnostic inference*, in which evidences about an effect are used to make inference about the most probable causes that may have provoked it (a common goal in expert systems). This is a "bottom-up" approach, leading from consequences to causes;
- *causal inference*, in which starting from the knowledge about possible causes, we attempt to characterized the most probable effects. In this case we deal with a "top-down" approach;
- *inter-causal inference*, in which the assessors try to "explain away" potentially competitive causes of a shared effect.

After analysing their potentialities, Bayesian Networks result particularly interesting for making probabilistic inference about model domains characterized by inherent complexity and uncertainty, in which the uncertainty can be related to an uncompleted understanding of the domain, imprecise knowledge about the state of the system at the time of interest, the existence of random mechanisms governing the behaviour of the model (Wooldridge, 2003).

In addition to offering a rational framework to deal with complex systems, BNs present several advantages for the treatment of uncertainty and scarcity of data if compared to other modelling approaches. They are flexible in the sense that allow to merge in a mathematically coherent manner different types of data, either subjective (derived from expert judgement) or objective (measured or estimated data), and also measured at different accuracy level (Uusitalo, 2007). Moreover, BNs allow to incorporate new knowledge in the system as soon as it becomes available (Moe, 2010), whatever "form" takes this new piece of information. The updating of the system may even provoke an overturn of previous belief in the light of newly acquired knowledge (Fenton and Neil, 2007). Moreover, as previously explained, BNs offer the opportunity to perform bi-directional analysis, from causes to effects but also backwards.

BNs provide the assessors with a support for structuring their knowledge about the system understudy, and, as BNs allow them to incorporate also individual belief in the network, they permit to explicit these believes, to visualize them and by this way support a transparent treatment and revision of expert judgements (Wooldridge, 2003). In addition, BNs are not based on a black-box approach and that means that there are not hidden variables in the process.

Their modular structure facilitates the modelling of the system and permits the assessor to begin an analysis even if the whole system has not been understood yet, because deterministic relationships among interested variables do not need to be known at the beginning of the analysis. Moreover, the graphical visualization of the networks facilitates the analysis and communication of knowledge about linkages among key variables. Finally, BNs allow to make hypothesis about and model future scenarios, and in that are not so bound to data-driven processes as other techniques (like regression analysis as an example) are.

Some limitations of Bayesian Network have at the same time to be highlighted. First, they are potentially high-demanding from a computational point of view: if the estimate of the prior probabilities and the posterior probabilities may be relatively immediate in simple networks with few variables, performing the propagation in complex networks with a reasonable number of nodes is generally very difficult and time consuming. Actually because of this reason BNs, despite the known advantages over other techniques, did not find wide application until the 80's, when the algorithms published by Lauritzen and Spiegelhalter (1988) and Pearl (1986) allowed to perform the propagation more rapidly. The implementation of these algorithms into software tools, which also provide a

graphical support for the building of BNs, determine a rapidly extension of BNs' application and popularity in many fields and had permitted to use them widespread and successfully to solve real-world complex problems (Fenton and Neil, 2007; Wooldridge, 2003).

BNs can deal only in a limited way with continuous data, thus usually variables have to be discretized and the model is built over the discrete domain. However this task is often not straightforward, as the way data are discretize can determine a significant difference in the resulting model (Uusitalo, 2007). Other potential drawbacks of BNs lay in the possibility to give an excessive weight to expert opinion (Wooldridge, 2003), a risk that may be faced by properly evaluate the balance between empirical data and expert judgement and by favourite the comparison and integration of "believes" from different experts. Moreover, particular attention should be paid in maintaining the number of variables within a manageable number, because in very large networks the specification of conditional probabilities can result extremely difficult. Finally, BNs may behave rigidly to unforeseen events (BNs require that the influence relationships in the system are at least partially known and cannot provide information about unknown dependencies) and cannot account yet for temporal changes in the system under observation.

4.5 FUZZY APPROACHES

In addition to probabilistic approaches (i.e. sampling-based approaches and Bayesian approaches illustrated in the previous paragraphs), other non-stochastic approaches have been explored in recent years to face the issue of uncertainty in environmental and health risk assessment and management. Among these, approaches based on fuzzy set theory received attention due to their capability of handling linguistic vagueness and imprecision of everyday reasoning (Ascough et al., 2003). These approaches are included in the review due to the attention they attract in environmental assessment and decision-making and for their interesting application in Multi-Criteria Decision Analysis.

Fuzzy logic was first introduced by Lofti Zadeh in 1965 (Zadeh, 1965) with the aim of providing a means of processing data by extending classical set theory to handle *partial membership* (McKone and Deshpande, 2005). Fuzzy approaches have the power to deal with the concept of "partial truth" to quantify uncertainties associated to linguistic variables and allow indeed to translate qualitative and vague information (e.g. qualitative judgement) into numerical reasoning with the aim of incorporating it into a mathematical framework (Chowdury et al., 2009; Li et al., 2007).

McKone and Deshpande (2005) state that Fuzzy Logic is suitable to be applied in health and environmental fields because in these fields a lots of "fuzzy concepts" are commonly used, such as

"hazardous", "acceptable" or "safe; these authors notice that also concepts as "carcinogen" or "neurotoxin" define fuzzy sets, *whose members are identified by experts after reviewing and judging conflicting toxicological or epidemiological data*.

We may identify two contexts in which fuzzy sets arise (Cullen and Small, 2004). The first occurs when we would like to classify a condition which is inherently vague, for example "good/poor water quality" or "low/high risk". If the boundaries between categories are fuzzy, membership in any of them can be expressed as a measure which is a function of the observed or modelled "hard" variables. Fuzzy sets can thus be used as a means to bridge the gap between the quantitative output of risk assessment and the need to value this result in a more qualitative, judgemental way for supporting management. The second type of use of fuzzy sets occurs when the sets are "crisp" (with sharp boundaries) but uncertainty in membership is represented by a fuzzy measure that expresses "plausibility" or "possibility". In this sense fuzzy sets can be seen as competitive to more traditional probability methods, but anyway use a set of its own rules and calculus.

Confronting fuzzy concepts and use them in a real-world assessment process requires three skills: constructing fuzzy sets and then performing logical operations and mathematical operations on those sets (McKone and Deshpande, 2005).

Fuzzy Sets, in contrast to classical or crisp sets where an element is identified as being a member of a set or not, have a progressive transition from membership to non-membership in the set (Ascough et al., 2008). This partial membership is expressed by means of a membership function, which maps the domain of interest (e.g. concentration, temperature, etc.) onto the interval [0,1].

Figure 4.10 illustrate an example from of a membership function μ_A which expresses the degree of membership of elements *x* (temperature) in the set A (where A include the classes "cold", "mild" and "hot").

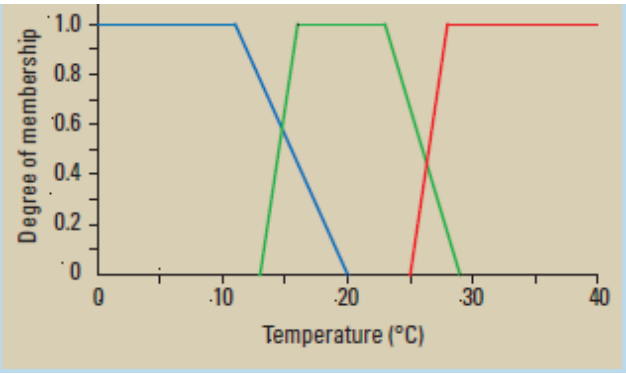


Figure 4.10 An example of membership function μ_A of elements x (temperature) to set A (McKone and Deshpande, 2005)

The membership function of the set A defined over a domain X takes the form:

$\mu_A : X \rightarrow [0,1]$ (Eq. 4.4)

The set A is defined in terms of its membership function by $A = \{\mu_A(x), x \in X\}$

The function μ_A is a set of ordered pairs: the first element of the pair is taken from the set x of temperature, while the second element is a real number on the interval [0,1] and represents the degree of membership in A (the degree to which a linguistic variable satisfies each term of a fuzzy set). The value 0 indicates that the element does not belong to the set and 1 indicates that the element completely belongs to the set, while all the values in between represent a partial degree of membership.

Triangular and trapezoidal fuzzy numbers are often used to represent imprecise parameter values for simplifying calculations (Chowdhury et al., 2009). In general, membership in a fuzzy set can be defined on the basis of observations (i.e. by using empirical data) or by expert/users elicitation.

At this stage, it might be important to highlight the difference between probabilistic approaches and fuzzy approach, because the rationale behind them for dealing with uncertainty is definitively different. Fuzzy membership function represents the possibility of an outcome rather than the likelihood of an outcome as in probabilistic approach. With fuzzy logic the uncertainty is modelled as the degree of membership in the set that defines an outcome, in contrast to frequentist approach where it is modelled as the relative frequency of occurrence of an event and Bayesian approach where it is modelled by expressing a belief that an event will occur or not (McKone and Deshpande, 2005). If we compared a Probability Density Function and a membership function (Figure 4.11), it should be noticed that if the total area under a Probability Density Function is 1 (meaning that the sum of all probabilities in the same space is 1), on the contrary the area under the membership function does not have any meaning and the total area may be smaller or greater than one (Li et al., 2007).

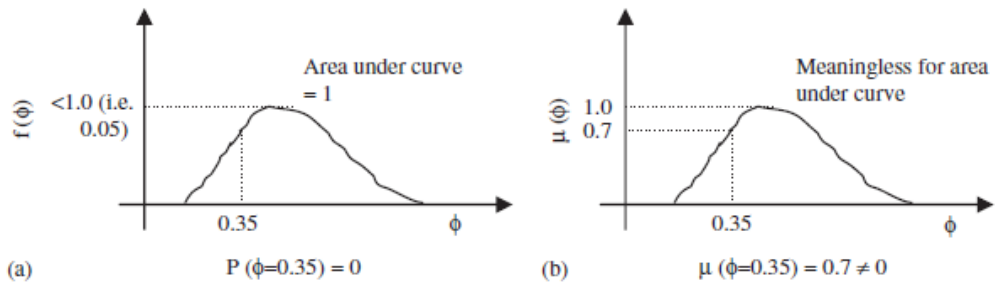


Figure 4.11 Comparison of probabilistic (a) and fuzzy (b) uncertainties (Li et al., 2007).

Rules for operating on fuzzy sets are provided by fuzzy logic, which is actually a generalization of standard Boolean logic (McKone and Deshpande, 2005). Fuzzy set can be operated on using operators generalizing operations of classical sets such as union and intersection. Moreover, there are fuzzy sets operators that have no counterparts in ordinary set theory, for example concentration, intensification or fuzzification. Intensification increases the degree of membership of all set elements that have a membership > 0.5 by a fixed factor and at the same time reduce the degree of those elements having a membership < 0.5: the overall result is that it makes the fuzzy set more defined (i.e., less fuzzy). Fuzzification operates in the opposite direction by making the set fuzzier (McKone and Deshpande, 2005). In addition to logical operations, interval arithmetic operations apply to fuzzy sets, such as addition, subtractions, multiplication, division and "degree of match". Finally, defuzzification is the process of combining several partial memberships to obtain a single numerical value: it is used to translate fuzzy results in outputs compatible with non-fuzzy contexts (Silvert, 2000).

Several applications of fuzzy approaches have been implement for facing issue of environmental decision-making, and some of these applications concerning the field of human health risk assessment, such as Chowdhury et al. (2009) and Fischer (2003). In these applications, the authors appreciate the possibility to use fuzzy approach in a context of scarce quantitative information and the degree of flexibility and robustness of this approach in terms of predictions using diverse and linguistic information.

Despite their power to address specific types of uncertainty in the decision process, fuzzy set theory presents some not negligible issues. The definition of membership functions from complex distributions of input data may considerably increase up to a wide number of gradations. For example, triangular membership function requires at least 3 rules and the trapezoidal function at least 4 rules, so the issue may became complicate with more complex function (Chowdhury et al., 2009). Ascough and colleagues (2008) highlight the need of new methods for generating reasonable membership functions, in particular of simple and intuitive methods and able to exploit input from decision-makers or historical resources.

McKone and Deshpande (2005) observe that for some researchers fuzzy approach is well suited to address uncertainty, however it has not been demonstrate a similar power in dealing with variability and fuzzy set may even fail to capture the range of values in complex data sets and the correlations among variables. Moreover, up to now validation and optimization problems resulted sometimes in non-reliable models. The use of hybrid approaches combining fuzzy rule-based models with probabilistic data-driven technique is suggested for overpass these problems (Ascough et al., 2008). An example of this method is provided by Kentel and Aral (2004), who used a combination of fuzzy approach and classical probabilistic approach for the assessment of health risk due to tap water

contamination. Some variables of the risk model (such as ingestion and inhalation rate, water use rate, exposure time) are treated using probability density functions, while contaminant concentration in water and cancer potency factors are treated as fuzzy variables, because the author consider it is more correct to treat them as uncertain parameters rather than highly variable parameters as the others. The authors notice the importance of exploring methods distinct from probabilistic ones and consider that the proposed approach is robust and may improve the treatment of uncertainty in health risk assessment. Integrated fuzzy-stochastic modelling approaches are proposed by Li et al. (2007) as well, concerning health risk due to groundwater contamination and air pollution respectively, and in both works is recognized that this combined approach may provide more realistic support for remediation and management processes.

4.6 FINAL REMARKS

The issue of facing uncertain knowledge is surely pivotal in environmental health risk assessment and many efforts have been and still are dedicated to the identification of a proper classification of different types of uncertainty (as illustrated in Paragraph 4.1) and to the development of exhaustive methods to treat uncertainty in the analysis and account for it in the communication of results to stakeholders. Probabilistic approaches to risk assessment have proven in several applications to represent a valid alternative to deterministic approaches for dealing with the different components of uncertainty in a more exhaustive and effective way and the performed literature review provides a synthetic overview of approaches and methods most commonly applied in probabilistic risk assessment. Some of the methods briefly illustrated in this chapter have been selected during the development of the methodology for ranking environmental health stressors. In particular, it has been decided to adopt such approaches for dealing with two specific issues: the setting of normalization functions in the MCDA procedure (when it is necessary to “classify” the available data, and it could be difficult to set clear boundaries between different classes/categories), and the evaluation of the decision-maker’s selection of weights to be assigned to the criteria against which alternatives are ranked. These aspects will be illustrated in detail in Chapter 5 and Chapter 7.

4.7 REFERENCES

Ascough II J.C., Maier H.R., Ravalico J.K., Strudley M.W., 2008. Future Research Challenges for Incorporation of Uncertainty in Environmental and Ecological Decision Making. Ecological Modelling 219: 383-399.

Briggs D.J., Sabel C.E., Kayoung L., 2008. Uncertainty in Epidemiology and Health Risk and Impact Assessment. Environmental Geochemistry and Health 31: 189-203.

Bullard F., 2001. A Brief Introduction to Bayesian Statistics. NCTM, National Council of Teachers at Mathematics.

Burmaster D.E., 1995. Benefits and Cost of Using Probabilistic Techniques in Human Health Risk Assessment, with an Emphasis on Site-Specific Risk Assessment. Commentary invited by Human and Ecological Risk assessment, Alceon Corporation, Cambridge MA.

Cain J., 2001. Planning improvements in natural resources management. Guidelines for using Bayesian Networks to support the planning and management of development programmes in the water sector and beyond. Centre for Ecology & Hydrology Crowmarsh Gifford, Wallingford, Oxon, UK.

Charniak E., 1991. Bayesian Networks without Tears. Artificial Intelligence magazine (Winter): 50-63, American Society of Artificial Intelligence.

Chowdhury S., Champagne P., McLellan P.J., 2009. Uncertainty Characterization Approaches for Risk Assessment of DBPs in Drinking Water: a Review. Environmental Management 90: 1680-1691.

Clark J.S., 2005. Why environmental statistics are becoming Bayesian? Ecology Letters 8: 2–14.

Cullen A.C. and M.S. Small. 2004. Uncertain Risk: The Role and Limits of Quantitative Assessment. In Risk Analysis and Society: An Interdisciplinary Characterization of the Field. In: McDaniels T. and Small M. (Eds), Cambridge University Press, Cambridge, UK.

Daneshkhah A.R., 2004. Uncertainty in probabilistic risk assessment: a review. Bayesian Elicitation of Experts' Probabilities (BEEP) Working Paper, University of Sheffield, 2004. http://www.shef.ac.uk/beep/publications.html.

Dennis B., 1996. Discussion: should ecologists become Bayesian?. Ecological applications 6(4): 1095-1103.

EC, 2003. Report on the Future of Risk Assessment in the European Union: Second Report on the Harmonisation of Risk Assessment Procedures, as adopted by the Scientific Steering Committee at its meeting on 10-11 April 2003. Health and Consumer Protection Directorate General, European Commission, Brussels.

ECHA, 2008. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.19: Uncertainty analysis. European Chemicals Agency, Helsinki.

Fenton N. and Neil M., 2007. Managing Risk in the Modern World. Applications of Bayesian Networks. A Knowledge Transfer Report from the London Mathematical Society and the Knowledge Transfer Network for Industrial Mathematics, London Mathematical Society, London, UK.

Fisher B., 2003. Fuzzy environmental decision-making: applications to air pollution. Atmospheric Environment 37: 1865–1877.

Frey H.C., 1992. Quantitative Analysis of Uncertainty and Variability in Environmental Policy Making. AAAS/EPA Environmental Science and Engineering Fellow.

Heckerman D., 1996. A Tutorial on Learning with Bayesian Networks. Technical Report, MSR-TR-95-06, Microsoft Research, Advanced Technology Division, Redmond.

IEH, 2000. Probabilistic Approaches to Food Risk Assessment. Report of a workshop held on 8–9 June 1998. MRC Institute for Environment and Health , Leicester, UK.

Iman R.L., Davenport J.M., and Zeigler D.K., 1980. Latin Hypercube Sampling (A Program Users Guide), Technical Report SAND79-1473, Sandia Laboratories, Albuquerque, USA.

Jager T., Vermiere T.G., Rikken M.G.J., van der Poel P. 2001. Opportunities for a probabilistic risk assessment of chemicals in the European Union. Chemosphere 43: 257-264.

Kentel E. and Aral M.M., 2004. Probabilistic-fuzzy health risk modelling. Stochastic Environment Research and Risk Assessment 18: 324–338.

Krupnick A., Morgenstern R., Batz M., Nelson P., Burtraw D., Shih J., McWilliams M., 2006. Not a Sure Thing: Making regulatory Choices under Uncertainty. Resources for the Future, Washington DC, February 2006.

Li A., Huang G.H., Zeng G., Maqsood I., Huang Y., 2007. An integrated fuzzy-stochastic modeling approach for risk assessment of groundwater contamination. Journal of Environmental Management 82: 173 – 188.

Lunchick, C., 2001. Probabilistic exposure assessment of operator and residential non-dietary exposure. Ann. Occup. Hyg. 45, 29–42.

McKone T.E. and Deshpande A.W., 2005. Can Fuzzy logic bring complex environmental problems into focus? Environmental Science and Technology 15: 42A-47A.

Moe S.J. 2010. Bayesian Models in Assessment and Management. In: Environmental Risk Assessment and Management from a Landscape Perspective. L. Kapustka, W.G. Landis, A. Johnson (Eds), John Wiley & Sons, 2010.

Moschandreas D.J. and Karuchit S., 2002. Scenario-model-parameter: a new method of cumulative risk uncertainty analysis. Environment International 28: 247-261.

Pearl J. and Russel S., 2000. Bayesian Networks, Technical Report, R-277, Handbook of Brain Theory and Neural Networks, MIT Press, November 2000.

Refsgaard J.C., van der Sluijs J.P., Højberg A.L., Vanrolleghem P.A., 2007. Uncertainty in the Environmental Modelling Process – A Framework and Guidance. Environmental Modelling and Software 22: 1543-1556.

Ricci, F. R., 2006. Environmental and Health Risk Assessment and Management. Principles and Practises. Springer. Volume 9.

Rotmans J., Van Asselt M.B.A., 2001. Uncertainty management in integrated assessment modelling: towards a pluralistic approach. Environmental Monitoring and Assessment 69 (2): 101-130.

Sander P., Oberg T., 2006. Comparing Deterministic and Probabilistic Risk Assessment. A case study at a closed steel mill in southern Sweden. J Soils & Sediments, 6 (1): 55-61.

Silvert W., 2000. Fuzzy indices of environmental conditions. Ecological Modelling 130: 111 – 119.

Spanjersberg, M.Q.I, Kruizinga, A.G., Rennen, M.A.J., Houben, G.F., 2007. Risk assessment and food allergy: the probabilistic model applied to allergens. Food and Chemical Toxicology, 45: 49–54.

US EPA, 1992. Guidelines for exposure assessment. EPA/600/Z-92/001. Office of Research and Development, Office of Health and Environmental Assessment Washington, DC.

US EPA, 1997. Guiding Principles for Monte Carlo Analysis. Risk Assessment forum, U.S. Environmental Protection Agency, Washington, DC 20460. EPA 630-R-97-001.

US EPA, 1999. Report of the Workshop on Selecting Input Distributions For Probabilistic Assessments. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, C 20460. EPA/630/R-98/004

US EPA, 2001. Risk Assessment Guidance for Superfund: Volume III – Part A, Process for Conducting Probabilistic Risk Assessment. Office of Emergency and Remedial Response, U.S. Environmental Protection Agency, Washington, DC 20460. EPA 540-R-02-002.

US EPA, 2004. Risk Assessment and Modelling: Air Toxics Risk Assessment Reference Library. Volume 1, Technical Resource Manual. US Environmental Protection Agency, Washington, DC 20460 EPA-453-K-04-001°.

Uusitalo L., 2007. Advantages and challenges of Bayesian Networks in environmental modelling. Ecological Modelling 203: 312-318.

Van der Sluijs J.P., Janssen P.H.M., Petersen A.C., Kloprogge P., Risbey J.S., Tuinstra W., Ravetz J.R., 2004. RIVM/MNP Guidance for Uncertainty Assessment and Communication: Tool Catalogue

for Uncertainty Assessment (RIVM/MNP Guidance for Uncertainty Assessment and Communication Series, Volume 4). Utrecht University & RIVM; Utrecht/Bilthoven. Report nr: NWS-E-2004-37.

Verdonck F.A.M., Sioen I., Baert K., Van Thuyne N., Bilau M., Matthys C., De Henauw S., De Meulenaer B., Devlieghere F., Van Camp J., Vanrolleghem P.A., Van Sprang P., Verbeke W., Willems J., 2006. Uncertainty and Variability Modelling of Chemical Exposure through Food. Arch Public Health, 64: 159-173.

Walker W.E., Harremoës P., Rotmans J., Van der Sluijs J.P., Van Asselt M.B.A., Janssen P., Krayer von Krauss M.P., 2003. Defining uncertainty a conceptual basis for uncertainty management model-based decision support. Integrated Assessment 4 (1): 5-17.

Wooldridge, S., 2003. Bayesian Belief Networks. CSIRO – Centre for Complex System Science.

Wu, F.C., Tsang Y.P., 2004. Second-order Monte Carlo uncertainty/variability analysis using correlated model parameters: application to salmonid embryo survival risk assessment. Ecological Modelling 177, 393-414.

Zadeh, L.A. 1965. Fuzzy sets. Information and Control, 8 , 338–353.

CHAPTER 5

DEVELOPMENT OF A TOOL FOR RANKING ENVIRONMENTAL CHEMICAL STRESSORS AT THE REGIONAL SCALE

5.1 INTRODUCTION AND OBJECTIVES

In the framework of the "Environment and Health Action Plan 2004-2010" (illustrated in Chapter 2) emerges the need for developing innovative methodologies and tools for health risk and impact assessment, able to address the complexity of environment-health causal pathways and to effectively support decision-makers in setting up appropriate health protection policies. In this context it becomes useful to develop effective decision-support screening tools able to identify the most critical scenarios and the most dangerous hazards, in order to identify those situations where a detailed assessment of health risks is advisable.

Several methods for screening and ranking chemical substances have been developed at the international level, in particular as results of efforts by US or EU agencies and research institutes, with the aim of estimating the level of concern associated to certain chemicals and identifying therefore "priority substances" to be further investigated (IEH, 2004a). In most of the cases these methods are based on the use of data about intrinsic properties of substances (physico-chemical properties and toxicological and ecotoxicological properties) or estimates of potential population exposure to these substances (for instance, calculated from production tonnages and potential applications/uses) and allow to screen chemicals considering generic exposure scenarios. It is more difficult, however, to find in recent scientific literature structured and quantitative ranking methodologies suitable for screening chemicals in a site-specific context, which could identify, at the local or regional scale, priority environmental chemical stressors on which focus further investigations and analysis.

Taking into account the significant quantity and extension of environmental and health datasets collected in the last years as results of many regional, national and international initiatives (Smolders and Schoeter, 2007), emerges the opportunity to assemble these data from different sources and to exploit them in order to identify priority chemical stressors within a region of interest.

In the following paragraphs, the development of a methodology for ranking environmental chemical stressors at the regional scale is described, aimed at supporting decision-makers in the evaluation of environment and health data collected within a region with the aim of identifying which pairs of

"chemical-health outcome" should become the subject of a detailed assessment. This screening activity should provide the adequate information for addressing the efforts of the further risk assessment towards the most critical scenarios, by identifying an appropriate and manageable number of chemical stressors to be further investigated. For example, their distribution and health effects could be further assessed through the application of predictive models, e.g. fate and transport models to estimate their distribution and fate in the environmental compartments (Fryer et al., 2006), through physiologically-based pharmacokinetic (PBPK) models to estimate their distribution and metabolic transformations within the human organism (USEPA, 2006), through dose-response models to predict the probability of occurrence of specific pathologies (Sarigiannis and Gotti, 2008).

Moreover, the methodology should lead to the identification of priority sub-areas within the region where environmental and health data suggest the possibility of adverse effects on population health and where thus more investigation efforts are required.

One of leading criteria for the methodological development consists in the use of data on actual population exposure to environmental contaminants and on health outcomes measured in the population of interest, i.e. the exploitation of site-specific data rather than data about the intrinsic properties of chemical compounds and general exposure scenarios.

Moreover, the methodology for the ranking of environmental chemical stressors should adopt a spatially-oriented approach. Spatial analysis is indeed an important component of health risk assessment because, most of the times, the addressed problems are inherently spatial (Nuckols et al., 2004): concentrations of chemical contaminants have a specific and not homogenous space distribution, fate and transport of chemicals occur at different scales, targets (i.e. population groups) are unevenly distributed in the space depending on demographic and socio-economic factors. For this reason, in recent years, the application of spatial analysis tools (often realized through the use of Geographic Information Systems) gained an increased attention and interest in the field of environmental epidemiology and originated a dedicated discipline called spatial (or geographic) epidemiology, which can be defined as the *description and analysis of geographically indexed health data with respect to demographic, environmental, behavioural, socio-economic, genetic and infectious risk factors* (Elliott and Wartenberg, 2004). In particular, a typology of spatial studies which play a relevant role in environmental epidemiology is that of ecological studies, defined as *observational studies in which the unit of analysis is a group of individuals, often* geographically defined, rather than the individuals within the groups (Morgenstern, 1982). Ecological studies are aimed at assessing the relationship between health outcome and variables of interest such as exposure to environmental factors, where all variables are defined and measured on an ecologic (i.e. aggregated) scale and target groups are geographically identified (e.g. population living in selected

districts, provinces, census tracts) (Richardson and Monfort, 2000). Ecological studies are particular appealing in the context of environmental health because individual exposure to environmental factors (e.g. contaminants in air, water) are usually complex and expensive to obtain, while the use of aggregated data allow to rely on already existing databases (e.g. routinely monitored environmental indicators). The attention paid to ecological studies confirms the meaning and relevance of considering the spatial dimension in the development of the methodology for the ranking of environmental chemical stressors.

In the following paragraphs the conceptual approach and the main steps in the development of the ranking methodology and its implementation into a prototype software (the "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors") are illustrated in detail.

5.2 CONCEPTUAL APPROACH

In human health risk assessment, the system to be analysed is constituted by a temporal and spatial sequence of events starting from the release of a chemical in the environment and ending to the development of an adverse effect (health outcome) in human body. For pragmatic purposes, this continuous sequence can be divided into discrete steps (DeWoskin et al., 2007), as illustrated in Figure 5.1. For each step, information obtained from experimental, monitoring or modelled data can be used in the assessment process.

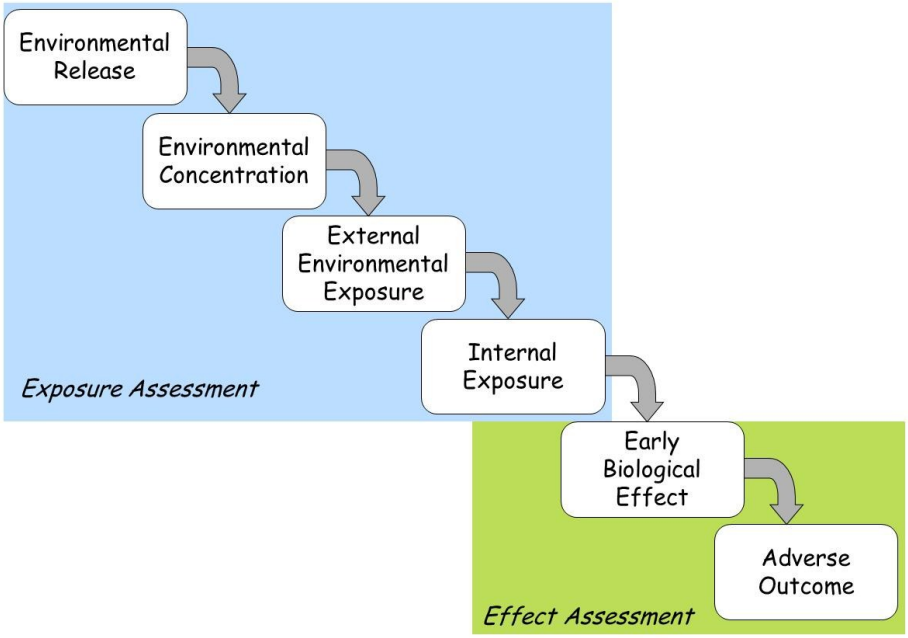


Figure 5.1 Different steps of the exposure-effects sequence (modified from DeWoskin et al., 2007).

The first step concerns the release of a chemical substance in the environment as a consequence of industrial activities, transports, accidental releases, etc. The second step is related to fate and transport processes which determine the presence of a chemical substance with potential toxic health effect in one or more environmental medium (soil, water, air, etc.). The third step concerns the evaluation of the intake, i.e. the quantification of the amount of chemical that may daily enter the body through several exposure routes (inhalation, ingestion, dermal contact). This process is also influenced by the vulnerability of the exposed groups (e.g., children are characterized by a higher contact rate with contaminated media than adults and this fact determines a higher intake if compared to adults in the same exposure conditions).The fourth step consists in the process of absorption of the chemical substance into the body, that determines an internal dose measurable by means of adequate biomarkers of exposure.

Once a chemical stressor has entered the human body, it may cause an early effect on the organism (fifth step). The effects may be measured as changes (often reversible) in the biological systems by using biomarkers of effects, such as measurement of cholinesterase activity in blood, changes in cytochrome P450 enzyme activity, etc. The chain ends with the manifestation of the full disease state (sixth step): at this stage the population health status is measurable by collecting information on the incidence/prevalence of the diseases of interest in a defined area (epidemiological data). For the development of a disease as a consequence of environmental exposure, each step of the sequence has to be “accomplished”.

The basic idea behind the ranking approach of environmental chemical stressors consists in the evaluation, for each chemical and its associated health effects, of the existing evidence for each step of the exposure-effect sequence. As stated in Paragraph 5.1, the ranking methodology will make use only of existing monitoring data about the region under assessment. In particular, for the development of the ranking methodology, three steps of the aforementioned sequence have been chosen, which are more likely to be covered by monitoring data (as illustrated in Chapter 3). These steps can be referred to as three Lines of Evidence (LoE), because data related to each of these steps provide information about a specific aspect of the investigated problem (see Chapter 3).

Specifically, the selected Lines of Evidence are the following:

1) LoE “Environmental Contamination”: this LoE provides information about the distribution and quantity of chemical stressors in the environment, taking different matrices into account (e.g. soil, air, surface water, groundwater), according to the scope of the analysis and the available data. This information can be derived, for example, from existing environmental monitoring data and can be available as single point data or as distribution maps. For evaluating the seriousness of the contamination status, the comparison with reference/threshold values (e.g. Environmental Quality Standards) may be used. This LoE is included in the ranking methodology because it

provides information about the potential contamination to which population is exposed, therefore it can be considered as an indicator of potential exposure (the higher the environmental contamination, the higher the probability that the population is exposed).

2) LoE "Intake": this LoE includes data derived from surveys of exposure biomonitoring parameters. Biomarkers of exposure include *measurements of parent compounds, metabolites, or DNA or protein adducts of parent compound and/or metabolites that indicate a direct exposure to the compound of interest* (Ryan et al., 2007) (see Chapter 3). This LoE has been chosen to introduce in the assessment information about the evaluation of the actual population exposure the selected chemicals. Biomarkers of exposure indeed represent an *integration of exposure from all sources and routes, which provide an important perspective on overall exposure* (Albertini et al., 2006). These data may thus indicate if the population living in the contaminated region is actually exposed in a significant way to specific chemical substances. This LoE will include data provided by biomonitoring campaigns such as the concentration of chemicals or metabolites in blood and other biological matrices (urine, milk, hair, etc.).
3) LoE "Observed Effects": this LoE aims at providing information about health effects measured in the population which are suggested to have, according to available toxicological and epidemiological knowledge, an environmental cause. This LoE may include different types of health effects data, such as epidemiological data and measurement of biomarkers of effects. Epidemiological data consist in information about the distribution and/or the frequency of disease/deaths by means of morbidity and mortality data. Biomarkers of effect reflect early biochemical reactions or modifications that precede actual structural or functional damage (e.g. DNA or haemoglobin adducts, measurement of transcribed protein levels) (Paustenbach et atl., 2006). Health effects may be evaluated as individual-level data or may be aggregated for populations (often identified by administrative units) like those available from local, regional and national surveys. Aggregated data consists in measures of health outcomes frequency and involve the occurrence of new cases or deaths (measure of incidence or mortality) or the presence of existing cases (measures of prevalence) (Morgenstern and Thomas, 1993).

For ranking chemical stressors, each LoE could be considered separately. For example, it is possible to compare existing contamination data for several chemicals within a region and to define accordingly a ranking where chemicals with the highest average concentration or affecting the largest areas are on the top. The same concept may apply to other LoEs. However, instead of considering these aspects separately the approach proposed in this thesis consists in overlapping and integrating the different pieces of information provided by the LoEs for each chemical through a Weight-of-Evidence (WoE) approach (described in Chapter 3) with the aim of achieving a more

robust and complete evaluation of available evidence. WoE, as an approach aimed at synthesizing individual lines of evidence to derive a conclusion about the degree of impairment or risk of a certain situation (Linkov et al., 2009), has been explored as framework for integrating different monitoring information from the environmental domain and the health domain. In particular, the need for structure, transparent, flexible and reproducible WoE methods (Weed, 2005) has guided the methodological development towards the application of Multi-Criteria Decision Analysis (MCDA) for implementing a quantitative WoE. MCDA, indeed, offers flexible options for quantitatively integrating information from different sources including also value-based assessment and expert judgement (Linkov et al., 2011).

The output of the MCDA-based WoE methodology will consist in a ranking list of chemicals. Chemicals resulting on the top of the ranking list are candidates to become the subject of a detailed risk assessment, through the implementation of further monitoring and the use of specific predictive exposure and toxicological models.

The spatial dimension of the assessment requires the identification of spatial entities, called Elementary Geographic Units (EGU), representing the smallest geographical level chosen for data aggregation and allowing the comparison and integration of different types of data (Figure 5.2). These EGUs could correspond to administrative areas, such as municipalities or counties, according to the spatial scale of the assessment, its goals and the availability of monitoring data. Each EGU will be characterized by a set of data (i.e., "attributes") concerning each of the *n* environmental chemical stressors and corresponding *m* health outcomes considered in the assessment.

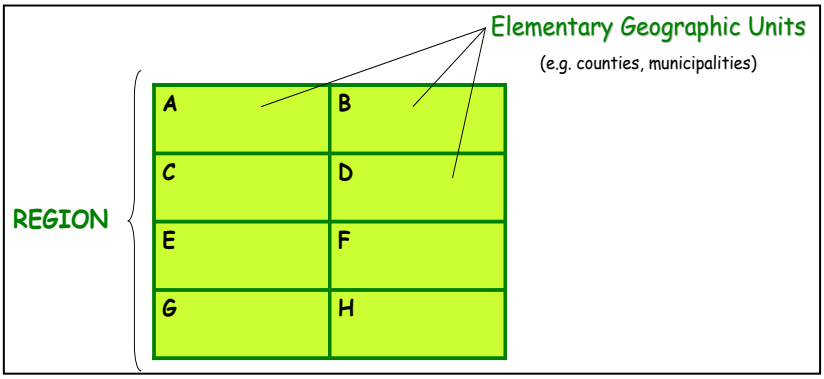


Figure 5.2 Representation of the spatial framework considered in the methodological development.

The information obtained through the integration of the three LoEs will provide the basis for the accomplishment of three methodological steps (which will be explained in detail in the following paragraphs) leading not only to a ranking of chemicals at local scale and at the regional scale but also to a ranking of sub-areas within the considered region.

The identification of the possible causal relationship between a chemical substance and an health outcome should constitute the first step of the assessment. This identification should be based on available toxicological and epidemiological knowledge with the support of expert judgment.

In the assessment, the following elements will be considered:

- **S** = $\{S_1, S_2, \ldots, S_n\}$ is the set of the *n* chemical substances;
- **D** = $\{D_1, D_2, \ldots, D_m\}$ is the set of the *m* diseases.

Taking into consideration all the known relationships, a diagram illustrating the relationships between chemicals and health outcomes can be developed (as illustrated in the example in Figure 5.3). The arrow exiting from the chemical and entering the health outcome indicates that this chemical has been identified among the possible causes of that health effect.

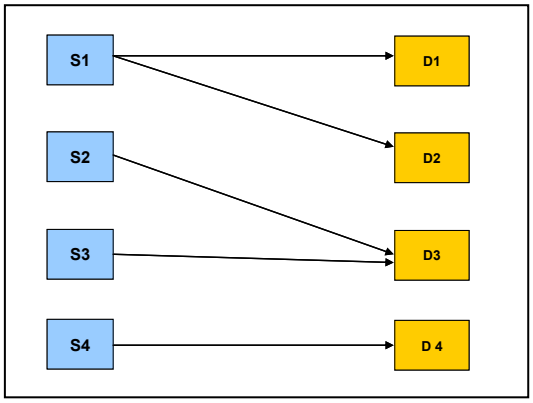


Figure 5.3 A diagram representing an example of possible relationships among chemical substances (S_i) and diseases (D_j).

The same information can be translated into a matrix composed by *n* rows (for the corresponding n chemicals) and *m* columns (for the *m* health outcomes), as illustrated in Figure 5.4.

	D_1	D_2	D_3	...	D_m
S_1	x	x			
S_2			x		
...					
S_n			x		x

Figure 5.4 An example of a (*n* X *m)* matrix representing the relationships between chemical substances (S_i) and diseases (D_j).

It could be useful to highlight that the possible type of relationships could be traced back to three main cases, as reported in Table 5.1. In Paragraph 5.4 it will be explained how the proposed methodology deals with the three situations along the different methodological phases.

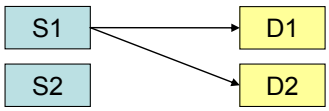
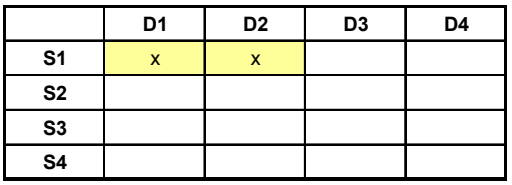
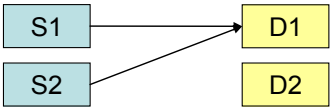
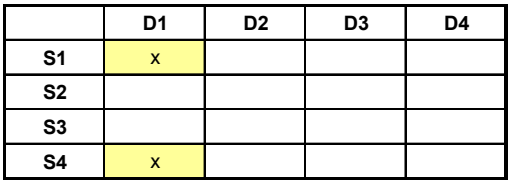
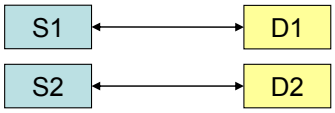
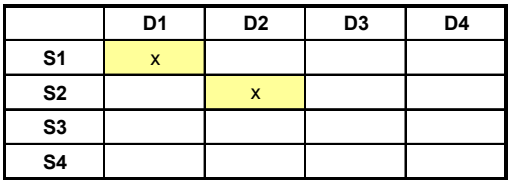
CASE	DIAGRAM	MATRIX OF RELATIONSHIPS
CASE (A) The same stressor (Si) is identified as possible cause of two or more pathologies (M_i)		
CASE (B) Two or more stressors (S_i) are identified as potential causes of the same pathology (M_i)		
CASE (C) Each stressor (S_i) is identified as possible cause of only one pathology (M_i) and this pathology at the same time is connected only to that stressor (i.e. the relationship is biunique)		

Table 5.1 Three possible cases of relationship typology between stressors (S_i) and pathology (M_i).

5.3 METHODOLOGICAL FRAMEWORK

The proposed ranking methodology constitutes the basis for the development of a "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors", a decision-support tool aimed at helping end-users/decision-makers (e.g. local authorities, environmental and public health agencies, etc.) in the selection of priority environmental chemicals and priority areas to be further investigated.

Three different methodological phases have been identified and will be implemented in the "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors": each phase is related to a specific objective and leads to the achievement of a specific ranking as explained in the following paragraphs.

The first phase (PHASE 1) is aimed at obtaining a ranking of the environmental chemical stressors in each Elementary Geographic Unit, for example in each county of the region covered by monitoring data.

Afterwards, the results obtained for the different EGUs will be integrated and properly treated for achieving a ranking of environmental chemical stressors at the regional level (PHASE 2), to select, within the region, those chemicals to be included in a detailed human health risk assessment (e.g. through implementation of further environmental or health monitoring or application of detailed exposure or toxicological predictive models).

The last phase of the Ranking Tool is aimed at providing a ranking of the EGUs within the region (PHASE 3), in order to identify and select those EGUs where existing environmental and health monitoring data suggest a situation of possible or actual impacts on population health.

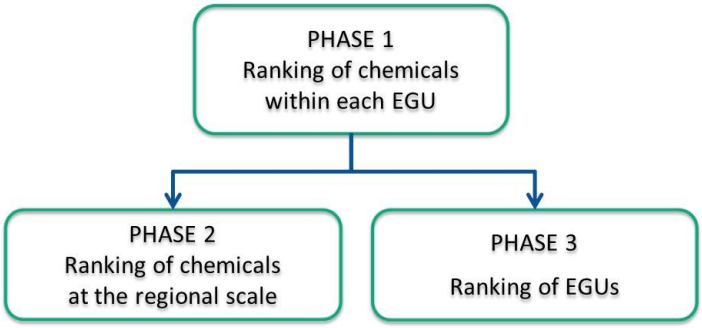


Figure 5.5 Diagram representing the three phases of the "Risk-based Tools for the Regional Ranking of Environmental Chemical Stressors.

In the following paragraphs, a detailed description of the methodology implementing each one of the aforementioned phases is provided.

5.4 RANKING OF CHEMICALS WITHIN EACH ELEMENTARY GEOGRAPHIC UNIT

In this paragraph, the procedure aimed at the ranking of environmental chemical stressors within each Elementary Geographic Unit (PHASE 1) is described.

First, for each Elementary Geographic Unit (EGU), a set of pairs [chemical, disease] has to be identified, for which environmental and health monitoring data are available.

For each EGU and each pair [chemical, disease] a set A including three type of data (corresponding to the three selected Lines-of-Evidence) could be available, i.e.:

$A_{i,j} = [C_i, I_i, D_j]$ (Eq. 5.1)

where:

C_i = concentration of chemical i^{th} in the environmental matrix of interest (e.g. soil, water, air);

I_i = concentration of the chemical i^{th} (or metabolite) in a human biological matrix (e.g. blood, urine);

D_j = indicator of incidence/prevalence of j^{th} health effect in the EGU;

with

i = 1, 2, …, N (number of substances); j = 1, 2, …, M (number of diseases)

Therefore, each EGU will be characterized by a number of sets $A_{i,j} = [C_i, I_i, D_j]$ which equals the number of pairs [chemical, disease] identified in that EGU.

The information provided by the three LoEs has to be merged and evaluated in order to support the decision-maker in the selection of the priority chemicals in the EGU of interest. Different combinations of data from the three LoEs may correspond to different situations: the goal is to evaluate these combinations according to the decision-maker's rules in order to select those chemicals which results to be related to the most critical situations. This goal requires the aggregation and evaluation of heterogeneous data and a suitable approach to deal with this type of issue is provided by MCDA techniques (Figueira et al., 2005). As illustrated in Chapter 3, MCDA supports decision-makers in evaluating and selecting among a number of alternatives (in the case at hand, the pairs [chemical; disease] based on multiple criteria and adopting systematic analysis that overcomes the limitations of unstructured individual or group decision-making.

The methodology for the ranking of environmental chemical stressors within each EGU can be summarized in the following three steps:

1) normalization of criteria values;
2) aggregation and weighting of normalized values into a unique indicator in order to estimate a ranking score for each pair [chemical; disease];
3) estimate of a final score for each single chemical.

These steps will be described in the following paragraphs and are schematically illustrated in the diagram in Figure 5.6. The results of this first phase (estimate of a final score for each single chemical) represent the starting point also for the other two phases (i.e. ranking of chemicals at the regional scale and ranking of the EGUs).

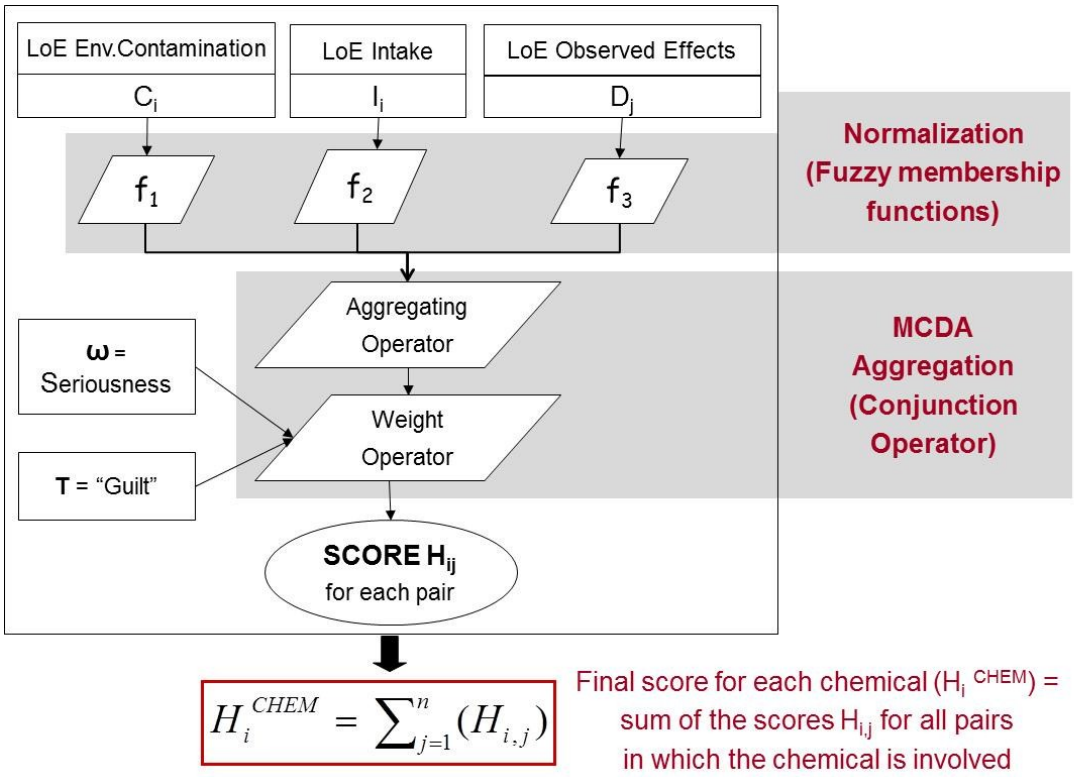


Figure 5.6 Main steps of the MCDA-based methodology applied in PHASE 1(Ranking of chemical within each EGU) for estimating a score for each of the chemical within each EGU.

5.4.1 NORMALIZATION OF CRITERIA VALUES

The data related to each LoE have first to be properly transformed into a common numerical scale (i.e. normalized) in order to allow subsequently their integration. To this purpose, an approach based on Fuzzy logic is proposed. Fuzzy logic allows to define membership functions representing the degree to which a linguistic variable satisfies each term of a Fuzzy set (that is, membership degree) (see Chapter 4). A properly defined normalization function allows to define the "degree of truth" of a sentence such as "*the lead contamination in soil is high*". As an example, the classification and evaluation of the concentration value for the chemical i^{th} can be achieved by a function like the one represented in Figure 5.7. On the *x*-axis there are the values that the variable "Concentration of the i^{th} substance in the environmental medium" (expressed as *mg/kg of dry soil*) can assume, while on the y-axis are the values representing the "degree of truth" of the sentence "*Contamination in the medium due to the i^{th} substance is high*" (expressed on the scale [0,1], but alternatively also the scale [0%, 100%] can be used).

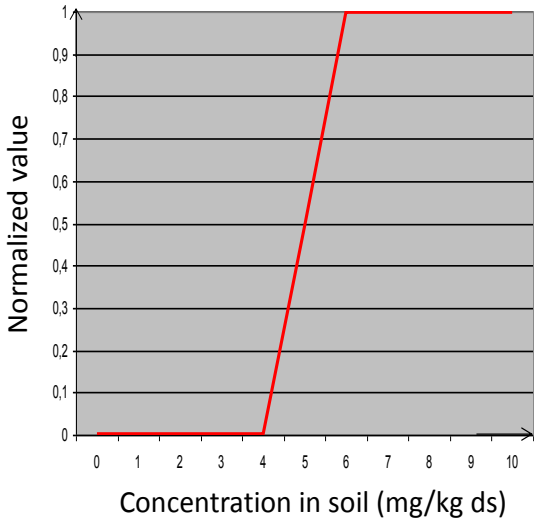


Figure 5.7 Example of a normalization function (fuzzy set membership function) for data of the LoE "Environmental Contamination".

In order to build this membership function, it is necessary to define (and therefore to ask the expert/decision-maker) two numerical thresholds:

- a *lower threshold* below which the degree of truth of the sentence is considered equal to 0 (i.e. the sentence is false);
- an *upper threshold* above which the degree of truth of the sentence is maximum, i.e. equal to 1, or 100% (i.e. the sentence is true).

In the range of values between these two thresholds, the function may have different shapes, but, for the sake of simplicity, it has been set it as a linear continuous function.

Adopting the same approach, two membership functions for the other Loe, i.e. one for the LoE "Intake" and one for the LoE "Observed Effects" respectively, can be defined. In the case of LoE "Intake", on the x-axis the variable "Concentration of the substance i^{th} or its metabolites in a biological matrix" (expressed for example in *ug/dl of blood*) is represented. In the case of LoE "Observed Effects" on x-axis a variable related to the "Incidence or prevalence of the health outcome j^{th}, (e.g., the number of new cases per year each 10.000 people) is represented.

By applying the aforementioned concepts, a set of three normalized data, expressed on the same scale [0,1] is obtained for each pair [chemical, disease], as follows:

$$A'_{i,j} = [x_i, y_i, z_j] \qquad \text{(Eq. 5.2)}$$

where:

x_i = "degree of truth" of the sentence "*the concentration of the chemical substance i^{th} is high in the environmental matrix*";

y_i = "degree of truth" of the sentence "*the concentration of the substance i^{th} or of one of its metabolite in a biological matrix is high*";

z_i = "degree of truth" of the sentence "*the incidence/prevalence of the health effect j^{th} is high*".

5.4.2 AGGREGATION OF NORMALIZED VALUES INTO A UNIQUE INDICATOR AND WEIGHTING

For each alternative (in the case at hand, each pair [chemical, disease]), the normalized values have then be aggregated into a single numerical value, representing the score of that alternative. The selection of the most suitable aggregation operator depends on the relationships among the considered criteria and on the assessment objectives (which are reflected into the meaning of the final single value to be obtained). Many aggregation operators which can be applied in MCDA procedures exists, as mentioned in Chapter 3.

Since it has been chosen to operate in a Fuzzy logic environment, it is necessary to use suitable aggregation operators able to mimic the operations which can be performed among Fuzzy sets. More precisely, for the purpose of this work a conjunction operator has been selected. Conjunction operations (denoted by "AND" and by the symbol $\wedge$) are used when the aim is to highlight situations where all the elements under assessment must be valid at the same time (e.g. my car must be fast AND cheap). In the case at hand, the goal is to identify situations where the values for the three LoEs are contemporary "high", therefore where all operands are contemporary verified (i.e. not null).

In traditional logic, propositions based on conjunction operators are satisfied when all their operands are satisfied, i.e. the proposition is true *if* and *only if* all of its operands are true. Fuzzy logic differs from classical logic because it introduces the concept of different degrees of truth (to be expressed in the range [0,1]). In a fuzzy environment the aforementioned definition of conjunction (demanding that all operands are completely true in order to obtain a true result), cannot be applied because the concept of "truth" may assume a value varying between 0 and 1. In a Fuzzy logic environment Conjunction operators are therefore represented by the set of "Minimum Operators" which correspond to the family of Triangular-norms (abbreviated in *T-Norm*) functions (Klement, 2000).

A T-norms is a function

$T:[0,1] \times [0,1] \rightarrow [0,1]$

having the following properties:

- commutability;
- monotonicity (increasing);
- associativity;

- 1 as the neutral element.

The T-norm providing the maximum results is the minimum function, while the T-norm providing the lowest result is the product (Klement, 2000). The most notable and commonly used T-norms are the minimum, the probabilistic T-norm, the Lukasiewicz T-norm and the drastic T-norm.

The ranking score for each pair "chemical i^{th} and disease j^{th}" can be estimated as the degree of truth of the following statement:

$$H_{i,j} = \left[g(x_i, \delta_x) \wedge g(y_i, \delta_y) \wedge g(z_j, \delta_z) \right] \times T_{i,j}^{\alpha} \times \omega_j \qquad \text{(Eq. 5.3)}$$

The ranking score $H_{i,j}$ related to the i^{th} chemical and the j^{th} observed effect is thus estimated from the elements illustrated in details in the following paragraphs.

First, the ranking score depends on the **normalized values** obtained from each LoE, that are: x_i, y_i and z_i.

As the decision-maker can decide to assign a different importance to each one of the single criterion (i.e. to each single LoE), there is the possibility to assign a **specific Relevance Weight δ_p** to each of them, i.e.:

δ_x = Relevance Weight assigned to LoE "Source";

δ_x = Relevance Weight assigned to LoE "Intake";

δ_x = Relevance Weight assigned to LoE "Observed Effects".

For instance, the decision-maker could decide to attribute a higher weight to the data of LoEs associated to exposure ("Environmental Contamination" and "Intake") in comparison to the LoE "Observed Effects", because he considers the former as more reliable or because he wants to give them a greater relevance in the assessment.

The relevance parameter δ_p can vary on the scale [0,1] and the function g_p is a simple aggregation function between the normalized value for each LoE and the relevance of that LoE, which determines how much the normalized value has to be considered in the aggregation.

As explained earlier, the conjunction operator ($\wedge$) in fuzzy environments is expressed as a T-Norm. Among all possible T-Norms it has been decided to use the minimum function, which is the most widely used function in this kind of elaborations. As shown by the first part of Equation 5.3 (inside the square brackets), a weighted minimum algorithm is applied between the LoEs. According to Yager's definition (Yager, 1981) the weighted minimum can be written as follows:

$$\min\nolimits^{\oplus}_{w_1,\ldots,w_n}(x_1, \ldots, x_n) = \min\nolimits_{i=1}^{n} [\max(1 - w_i, x_i)] \qquad \text{(Eq. 5.4)}$$

Equation 5.4 in the context at hand becomes:

$$\min[\max(1-\delta_x, x_i), \max(1-\delta_y, y_i), \max(1-\delta_z, z_i)] \quad \text{(Eq. 5.5)}$$

Therefore, it results that the *g* function can be written as follows:

$$g(x,\delta) = \max(1-\delta, x) \quad \text{(Eq. 5.6)}$$

To better understand what the weighted minimum means in practice, it should be kept in mind that 1 is the neutral element of the minimum function. This means that an operand whose value is 1 is non-influential in the evaluation of the minimum since we are dealing with numbers in the range [0,1]. Therefore, if an operand has to be non-influential, its value must approach 1.

As argument of the *g* function, the opposite of the Relevance Weight δ is used (i.e., 1- δ), so that the higher δ, the lower its opposite is. Consequently low values of δ (i.e. scarce importance for the associated criterion, i.e. the associated LoE) will likely generate high output values of the *g* function, which will be non-influential in respect to the outputs of the other g functions within the weighted minimum equation.

Another element to be included in the aggregating function is the **parameter** $T_{i,j}^{\alpha}$ **.**

This parameter allows to define how to face the cases in which two or more chemicals are associated to the same disease j^{th}, as in the example illustrated in Figure 5.8.

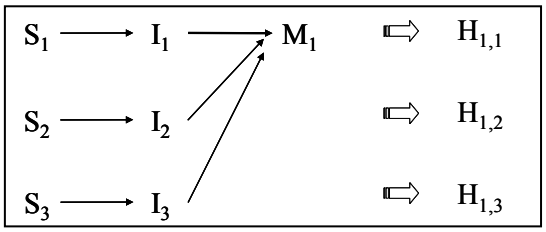


Figure 5.8 An example of a case where more chemicals (S_1, S_2 , S_3) are related to the same disease (M_1) and generate thus different ranking scores for each pair ($H_{1,1}$, $H_{1,2}$, $H_{1,3}$).

In this situation, the decision-maker can decide to evaluate "independently" each set (x_i, y_i, z_j), that is, to consider the value of the LoE "Observed Effects" (z_i) unchanged for each set. Alternatively, the decision-maker can also decide to "subdivide" the value of z_i among the involved chemicals, that is,

to attribute a "portion" of z_i to each set. This choice is determined by his degree of knowledge about the system under analysis and the specific relationship between chemicals and diseases.

To allow the decision-maker to set freely how to deal with this situation, a parameter $T_{i,j}^{\alpha}$ is defined and introduced as an additional element in the aggregation phase.

$T_{i,j}^{\alpha}$ is estimated from a parametric formula defined as follows:

$$T_{i,j}^{\alpha} = \left[\frac{E_i \eta_{i,j}}{\sum_{k \in B} E_k \eta_{k,j}}\right]^{\alpha} \quad \text{(Eq. 5.7)}$$

where

- B is the set including all chemicals associated to the disease j^{th};
- $\eta_{i,j}$ is a parameter representing the "probability" that chemical i^{th} causes disease j^{th} (it is a relative weight, defined on the scale [0, 1] that has to be set a priori by the expert for each pair);
- E_i is an indicator of the "overall evidence of exposure" (because it takes into account information related to both "Environmental Contamination" and "Intake") and is calculated as follows:

  $$E_i = g(x_i, \delta_x) \wedge g(y_i, \delta_y) \quad \text{(Eq. 5.8)}$$

α is defined as a parameter which allows the decision-maker to define how to deal with the situation where more chemicals are associated to the same disease. Specifically, α can take the following values:

1) **α = 0**, (it follows that is $T_{i,j}^{\alpha} = 1$): in this case the decision-maker is evaluating each set independently and is attributing to each chemical all the evidence of effect (z_i);
2) **α = 1**: the decision-maker attributes to each chemical a "partial responsibility" in causing the disease, according to the weights defined *a priori*;
3) **α → ∞** (it follows that Ti,j → 0): in this case, the higher the value of α, the higher becomes the weight given to cases in which only one chemical is associated to a disease (i.e. cases where more chemicals are present tend to be disregarded due to an increasing uncertainty associated to the attribution of effects to one chemicals instead of another one).

The decision-maker who wants to apply the proposed methodology needs to set only few parameters, which are:

- importance of each LoE δ;
- value of α;
- parameter η.

In the software tool, all these values could be asked to the user by means of a scale bar. In the case of the parameters δ and η , the scale bar will be continuous (in the range [0,1]) and will represent the first (δ) the degree of importance and the latter (η) the relative weight of the relationship chemical-disease. In the case of the parameter α, the scale bar will be discrete and each point in the scale will be identified by a label which explains the corresponding logic.

The last element to be included for the estimate of the ranking score is the **parameter ω_j.**

$\boldsymbol{\omega_j}$ is a parameter representing the seriousness of the j^{th} disease in terms of potential disability and thus in terms of potential impacts on society due to occurrence of a case of the disease. The decision-maker can therefore decide if to distinguish further among different pairs [chemical, disease] based not only on the aggregation of information derived from each LoE, but also on the different degrees of seriousness of the considered health effects.

The "seriousness" of the disease could be evaluated by using expert judgement, or a reference scale such as the system of Disability Weights proposed in the framework of assessment of the global/national environmental burden of diseases (WHO, 2004; Stouthard et al. 2000). This consists in a *set of disease-specific empirical weights to evaluate the level of disability, following standardized methods* (Stouthard et al., 2000). These weights are used to translate measures of incidence of environmental diseases (measured or estimated) into cumulative indicators (e.g. Disability-Adjusted Life Years - DALYs) in order to quantify the overall burden of disease for a selected population. According to this reference system, and by adopting expert judgment as appropriate, a "seriousness value" $\boldsymbol{\omega_j}$ could be attributed to each one of the considered disease. This value ω_j is included in the interval [0,1].

As a summary, all parameters which should be set by the end-user in order to apply the proposed methodology are reported in Box 5.1.

BOX 5.1: Information to be set by the end-user

1. <u>for each chemical</u>:
   - definition of the membership function for the LoE "Source" (to set the 2 thresholds)
   - definition of the membership functions for the LoE "Intake" (to set the 2 thresholds)
2. <u>for each disease</u>:
   - definition of the membership function for the LoE "Observed Effects" (set the 2 thresholds)
   - definition of the value of parameter ω_j
3. <u>for each pair [chemical, disease]:</u>
   definition of the value of parameter $\eta_{i,j}$ (relative value associated to the relationship chemical i_{th} and disease j_{th} in the case of more than one chemical related to one disease)
4. <u>for each LoE</u>:
   - definition value of the relevance weight δ_p assigned to each LoE/criterion
5. <u>to define how to deal with cases where multiple substances are associated to one disease</u>:
   - definition of the value of α representing end-user's approach to deal with uncertainty in causes of diseases.

5.4.3 FINAL RANKING OF THE CHEMICALS WITHIN EACH EGU

With the objective of ranking chemicals within the EGU, first it is necessary to sum up the scores $H_{i,j}$ associated to the same chemical in cases where a chemical *i* is associated to more than one health effect; the output of this procedure is a single score $\mathbf{H_i^{CHEM}}$ for each of the considered chemicals, as detailed in Equation 5.9.

$$H_i^{CHEM} = \sum_{J=1}^{n} H_{i,j} \qquad \text{(Eq. 5.9)}$$

Finally, the $\mathbf{H}_i^{\mathbf{CHEM}}$ scores obtained for the different chemicals are compared to obtain the chemicals ranking.

Figure 5.9 illustrates an example for describing the procedure proposed for aggregating $H_{i,j}$ scores for the different cases according to the different relationships among chemicals and diseases (relationship single chemical-single disease, more chemicals associated to the same disease and more diseases associated to the same chemical).

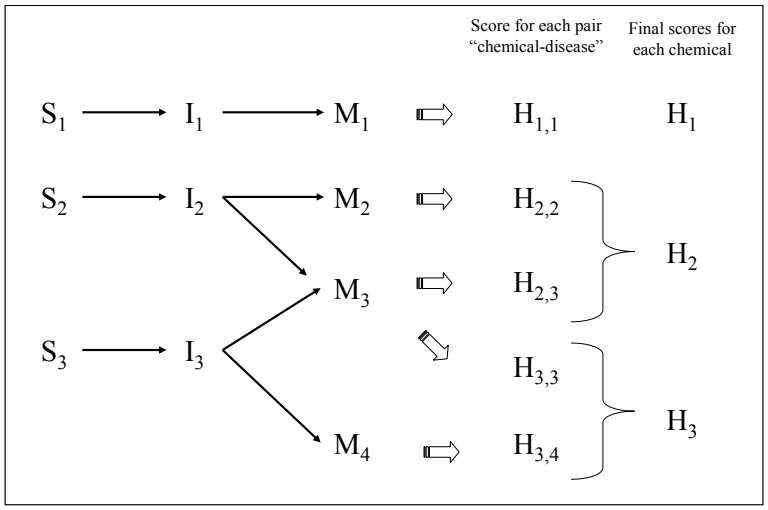


Figure 5.9 An example of aggregation of scores $H_{i,j}$ into a single score H_i^{CHEM} taking into account different types of relationships among chemicals and diseases.

Because the final objective is to achieve a ranking, the different values to be ranked need to be comparable. This implies that it is necessary to have for each pair [chemical, disease] the whole set of three data corresponding to the three LoEs (Environmental Contamination, Intake, Observed Effects). In the proposed methodology, therefore, all sets where the values for one or more LoEs are missing are discarded, and it is therefore important to collect a dataset as much complete as possible.

5.5 RANKING OF CHEMICAL STRESSORS AT THE REGIONAL SCALE

The objective of PHASE 2 consists in selecting the priority chemicals at the regional level, after obtaining the ranking of chemicals within each EGU for which data are available.

Within each EGU, a score for each pair [chemical, disease] $(H_{i,j})_u$ and a final ranking score $(\mathbf{H_i^{CHEM}})_u$ for each chemical have been estimated in PHASE 1 of the methodology.

In PHASE 2, the criteria chosen to rank the chemicals at the regional scale are the following:

- the number of EGU in which the chemical is detected;
- the value of the score $H_{i,j}$ in the u^{th} EGU;
- the population p_u of each EGU.

To include all this information into a single indicator, the Weighted Sum is chosen, where the scores $(\mathbf{H_i^{CHEM}})_u$ obtained by a chemical in different EGUs are summed, after multiplying each of them by the number of inhabitants in the corresponding EGU, as reported in Equation 5.10

$$H_i^{REGIONAL} = \sum_{u=1}^{w} p_r \times (H_i^{CHEM})_u \qquad \text{(Eq. 5.10)}$$

Since values are summed up, the final ranking is influenced by the availability of data for the chemicals of concern within each EGU. Consequently, it could be useful to track the presence of data concerning each chemical. To face this issue, a "precision percentage value" could be attached to each regional score, that is calculated by dividing the number of EGUs (En_i) where the chemical of concern has a score value by the total number of EGUs (En) (Equation 5.11).

$$P_i^{REGIONAL} = \frac{En_i}{En} \qquad \text{(Eq. 5.11)}$$

5.6 RANKING OF ELEMENTARY GEOGRAPHIC UNITS

The objective of PHASE 3 is to obtain a ranking of the Elementary Geographic Units in order to highlight those areas (counties, provinces, etc.) within the region where further investigations can be focused.

The criteria chosen for the evaluation of the "priority score" of each EGU is the sum of all the scores H_i^{CHEM} estimated within that EGU for all the chemicals detected in that EGU. The number of inhabitants of that EGU is considered as well introducing it as a weighting parameter (Equation 5.12).

$$S_u = \left[\sum_{i=1}^{C} (H_i^{CHEM}) \right] \times p_u \qquad \text{(Eq. 5.12)}$$

5.7 SOFTWARE IMPLEMENTATION

The methodology for the ranking of chemical stressors and Elementary Geographic Units illustrated in the previous paragraphs has been implemented into a prototype software, that constitutes the "Risk-based Tool for the Ranking of Environmental Chemical Stressors at the Regional Scale".

The prototype tool allows the user to store and manage data (in an Access database, through a , Visual Basic for Applications (VBA) code), to perform the three assessment steps presented in paragraphs 5.3-5.5 and therefore to obtain the following outputs:

- a ranking of chemical stressors within each EGU;
- a ranking of chemical stressors at the regional level;
- a ranking of EGU within the region of interest.

The tool includes a geo-database linked to a Geographic Information System (G.I.S.) framework which support the visualization and management of spatial information (e.g. visualization of the location of sampling points related to the environmental monitoring and attribution of these points to the different EGUs identified in the region).

To perform the analysis, the user is asked to enter in the prototype two main categories of input data: environmental and health monitoring data from case-study datasets and subjective parameters (to be set by the user himself on the basis of expert judgment) as required by the methodology (e.g. weights assigned to each Lines-of-Evidence).

Values derived from specific case-study databases need to be standardized in the shape and format required by the prototype and is necessary to insert manually these information in each table.

The subjective parameters to be set by the user can be defined according to different factors, such as:

- specific aims of the assessment;
- national legislations considered in setting the thresholds for the Fuzzy normalization functions;
- relative importance given to each Line-of-Evidence on the basis of expert judgment;
- kind of pollutants considered in the assessment and their specific relationships with the considered health effects.

In Figure 4.10 the basic relationships among the tables of the prototype software are shown.

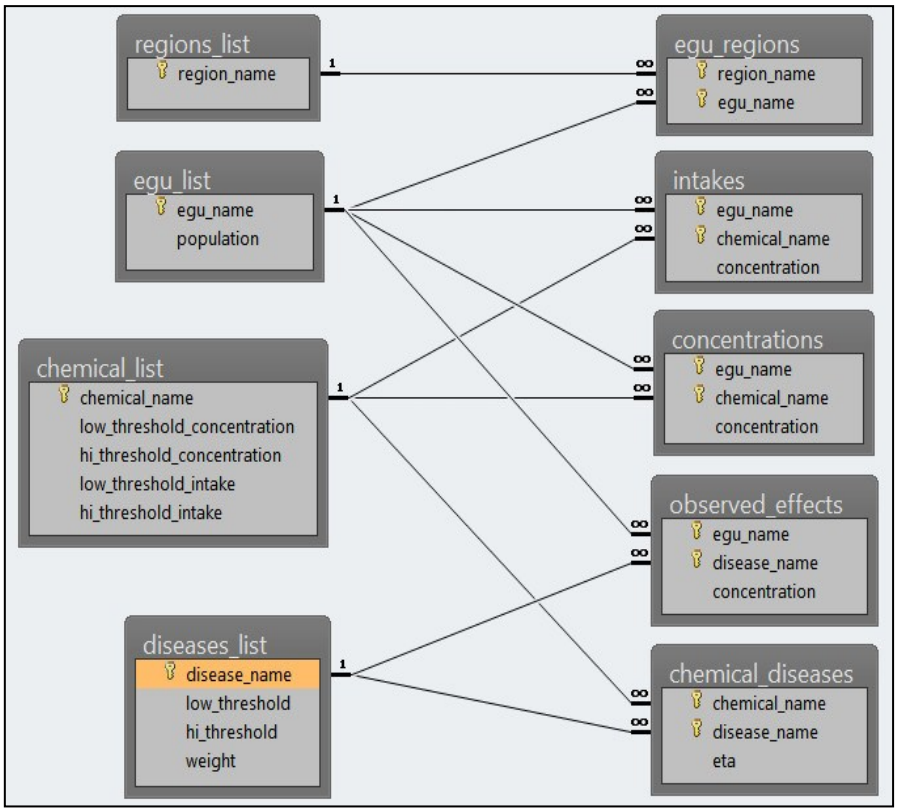


Figure 4.10 Relationships among tables in the prototype tool database.

In the tool database there is a table with the list of the EGUs considered in the case-study at hand where the demographic data associated with each EGU are included. The data for the three LoEs are included in three distinct tables, and they are associated to the EGUs considered in the assessment (that means, for each EGU there is a list of contamination data, effect biomarkers data and health effects data). A specific table reports the relationship of association between chemical substances and possible health effects considered in the assessment.

After running the prototype, three output reports are produced and made available to the user:

1) a report where all the chemical stressors considered in the assessment are scored and ranked within every single EGU;
2) a report where the chemicals are scored and ranked within the considered region;
3) a report where the EGUs within the considered region are scored and ranked according to the urgency for further, more detailed investigations and health risk assessment.

5.8 REFERENCES

Albertini R., Bird R., Doerrer N., Needham L., Robinson S., Sheldon L., Zenick H., 2006. The use of biomonitoring data in exposure and human health risk assessment. Environmental Health Perspectives 114 (11): 1755-1762.

DeWoskin R., 2007. PBPK Models in Risk Assessment – A focus on Chlorophene. Chemico-Biological Interactions 166: 352-359.

Elliott P. and Wartenberg D., 2004. Spatial Epidemiology: Current Approaches and Future Challenges. Environmental Health Perspectives 112 (9): 998-1006.

Figueira J., Ehrgott M., Greco S., 2005. Multiple Criteria Decision Analysis: State of the Art Surveys. Springer, Berlin.

Fryer M., Collins C.D., Ferrier H., Colvile R.N., Nieuwenhuijsen M.J., 2006. Human exposure modelling for chemical risk assessment: a review of current approaches and research and policy implications. Environmental Science and Policy 9: 261-274.

IEH, 2004. A Review of Prioritisation Methodologies for Screening Chemicals with Potential Human Health Effects as a Result of Low-Level Exposure. IEH Web Report W13. MRC Institute for Environment and Health, Leicester, UK. Report available at http://www.le.ac.uk/ieh/.

Klement E. P., Mesiar R., Pap E., 2000. Triangular norms. Trends in Logic, Studia Logica Library, Vol. 8, Kluwer Academic Publishers.

Linkov I., Satterstrom F.K., Kiker G., Batchelor C., Bridges T., Ferguson E., 2006. From comparative risk assessment to multi-criteria decision analysis and adaptive management: recent developments and applications. Environment International 32: 1072-1093.

Morgenstern H. and Thomas D., 1993. Principles of study design in Environmental Epidemiology. Environmental Health Perspectives Supplements 101 (S4).

Nuckols J.R., Ward M.H., Jarup L., 2004. Using Geographic Information System for Exposure Assessment in Environmental Epidemiology Studies. Environmental Health Perspectives 112 (9): 1007-1015.

Paustenbach D. and Galbraith D., 2006. Biomonitoring: is body burden relevant to public health? Regulatory Toxicology and Pharmacology 44: 249-261.

Richardson S. and Monfort C., 2000. Ecological Correlation Studies. In: Spatial Epidemiology: methods and applications. Elliott P., Wakefield J.C., Best N.G., Briggs D.J. (Eds), Oxford, Oxford University Press, pp.205-220.

Ryan P.B., Burke T.A., Cohen Hubal E.A., Cura J.J., McKone T.E., 2007. Using biomarkers to inform cumulative risk assessment. Environmental Health Perspectives 115(5): 833-840.

Sarigiannis D.A., Gotti A., 2008. Biology-based dose-response models for health risk assessment of chemical mixtures. Fresenius Environmental Bulletin 17 (9B): 1439-1451.

Smolders R. and Schoeters G., 2007. Identifying opportunities and gaps for establishing an integrated EDR-triad at the European level. International Journal of Hygiene and Environmental Health 210: 253-257

Stouthard M.E.A., Essink-Bot M.L., Bonsel G.J., 2000. Disability Weights for Diseases: a Modified Protocol and Results from Western European Region. European Journal of Public Health 10 (1): 24-30.

US EPA, 2006. Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. EPA/600/R-05/043F. National Center for Environmental Assessment, Office of Research and Development, United States Environmental Protection Agency, Washington DC.

WHO, 2004. Global Burden of Disease 2004 Update: Disability Weights for Diseases and Conditions. World Health Organization, Geneva.

Yager R.R., 1981. A new methodology for ordinal multiple aspect decisions based on Fuzzy sets. Decision Science 12: 589-600.

CHAPTER 6

CASE-STUDY: SOIL CONTAMINATION AND ADOLESCENTS' HEALTH IN FLANDERS (BELGIUM)

6.1 CASE-STUDY DESCRIPTION AND AVAILABLE DATA

6.1.1 THE FLEMISH CASE-STUDY

With the aim of performing a testing application of the Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors and to evaluate strengths and weaknesses of this tool, a suitable case-study has been identified in collaboration with the Flemish Institute of Technological Research (VITO). The case-study concerns the region of Flanders, the Dutch speaking region of Belgium, and has been selected because, thanks to the dense Flemish environmental monitoring and health monitoring networks, environmental contamination data, human biomonitoring data and health effects data are available for the same region.

The Flemish region (Figure 6.1) is a densely populated areas (6.211.065 inhabitants in 2009, with a population density equal to 456 inhabitants/km^2), divided into 5 Provinces (Antwerp, Limburg, East Flanders, Flemish Brabant, West Flanders).

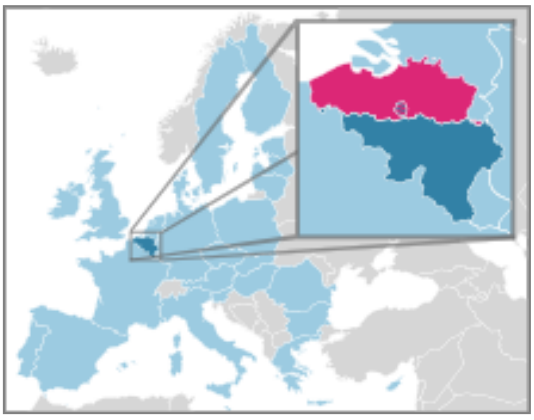


Figure 6.1 The region of Flanders (in red) in Belgium

The Flemish region is characterized by different anthropic pressures on the environment, due to the presence of many industrial activities (e.g., chemical, petroleum, metal, textile and automotive

industries), intensive agriculture and horticulture. Moreover, Flanders have five harbours (Antwerp's harbour is the fifth largest in the world) and a one of the world's highest density networks of road and rail. Therefore, considering the relevant presence of many potential chemical health stressors in a densely populated area, it results useful to analysis the relationships between population exposure and health effect and the application of the developed tool could offer helpful insights for this purpose.

In this chapter, the data collected for the testing application are presented and described. According to the requirements of the proposed methodology, it is necessary to have for each pair of chemical stressor and associated health effect the data corresponding to the three Lines-of-Evidence (i.e. contamination data, exposure biomarker data, health effects). The analysis of available data for the Flemish region and the matching of data for each LoE lead to choose the following chemicals for the testing application:

- Lead;
- Cadmium;
- Benzene;
- Benzo(a)pyrene.

A remark is needed to explain the choice to include Benzo(a)pyrene among the considered substances. Polycyclic Aromatic Hydrocarbons (PAHs) were one of the category of chemicals of interest for the application, because this category is covered by data available from the Flemish Biomonitoring Programme 2002-2006. Specifically, data on concentration of 1-hydroxypyrene (1-OH-pyrene) in urine are available for the Flemish region. 1-OH-pyrene is a specific metabolite of pyrene, but it has been established as an indicator of uptake not only for pyrene, but also as indirect indicator of all PAHs (Jongeneelen, 2001). Currently it is the most relevant and widely used biological indicator of exposure to PAHs, due to its sensitivity and the availability of effective measurement methods (Toriba and Hayakawa, 2007).

For the environmental monitoring of PAHs, benzo(a)pyrene has been used as the most important PAHs indicator in many studies, because it is always present in PAHs mixtures and its environmental behaviour is well known. Therefore, considering the low number of soil contamination data on pyrene in the available Flemish database, it was decided to use benzo(a)pyrene as an alternative in the testing application. For the sampling points where both pyrene and benzo(a)pyrene concentrations were available, a correlation analysis was also performed, and the significant correlation between the two chemicals further confirmed the choice of using the more abundant soil benzo(a)pyrene concentrations in the application.

6.1.2 SOIL CONTAMINATION DATA

Data on soil contamination used in the testing application were provided by the Public Waste Agency of Flanders (OVAM - Openbare Vlaamse Afvalstoffenmaatschappij), that is the Flemish agency responsible for soil remediation and waste management.

OVAM database includes all data collected in the frame of contaminated sites assessment and management procedures. The actual legal framework of reference for the action of the OVAM is the 2006 "Decree regarding the soil sanitation and the soil protection" (also "Soil decree") that is the natural evolution of the law in force during the collection of the database, the 1996 "Flemish regulation concerning soil remediation" (Vlaams Reglement betreffende de bodemsanering – known as VLAREBO). These decrees regulate the identification and registration of contaminated soils, the duty and the liability of the remediation process that differs according to whether the soil pollution can be considered as a new or a historical one *(*Lavrysen, 2007).

The OVAM database used here for the testing application is composed by data collected during the descriptive soil survey of potentially contaminated sites in the whole Flanders region between 1988 and 2010.

The database contains the following information:

1) chemical concentration data: reporting the concentration values of the different chemicals measured in soil, expressed as mg/Kg of dry soil;
2) spatial data: reporting the spatial coordinates of each sample site based on "Lambert conformal conic 1972" projection, the municipality (*gemeente*) where the soil was sampled, and the sampling depth;
3) time data: reporting the date of the sampling.

6.1.3 THE FLEMISH HUMAN BIOMONITORING PROGRAMME 2000-2006

Exposure biomarkers data and early health effects data used in the application come from an important biomonitoring campaign funded by the Flemish government conducted in selected areas of Flanders. This biomonitoring project started in 2002 and was directed by the Centre for Environment and Health in Flanders (http://www.milieu-en-gezondheid.be/), that is the result of a cooperation between the universities of Antwerp, Brussels, Ghent, Leuven, Hasselt and Maastricht and the research institutes VITO (Flemish Institute for Technological Research) and PIH (Provincial Institute for Hygiene). The project consists in a large scale biomonitoring programme realized in the

period 2002-2006 and involving three main age categories: neonates, adolescents and elderly people (Den Hond et al., 2009).

The programme aimed in particular at estimating the internal exposure to pollutants by measuring different blood and urine biomarkers among the population in function of the area of residence, and at starting investigating the relationship between this exposure and early health effects (Den Hond et al., 2009; Schroijen et al., 2008)

The study areas (Figure 6.2) where the biomonitoring was carried out have different characteristics and are scattered around the whole region of Flanders, covering about the 22% of the surface and about 20% of the Flemish population (Croes et al., 2009). Nine study areas have been selected, taking into account land use, population density, production activities, presence of infrastructures and, accordingly, different types of pollution pressure.

The list of study areas is presented in Table 6.1 and represented in Figure 6.2.

AREA	CHARACTERISTICS
Albert Canal	Chemical industries, energy production
Antwerp City	Industrial city (404.000 inhabitants)
Ghent City	Industrial city (213.000 inhabitants)
Antwerp Harbour	Petrochemical and chemical industries
Ghent Harbour	Metallurgic industries
Olen	Non-ferrous smelters, chemical and car industries
Fruit Area	Rural area, with intensive apple/pear cultivation
Surrounding of incinerators	6-12 km NE from incinerators
Rural Flanders	<250 inhabitants/Km^2, 9 different areas, no motorways, no industries

Table 6.1 Study areas assessed in the Flemish Biomonitoring Programme 2002-2006 and their main features (from Schroijen et al., 2008; Croes et al. 2009).

Antwerp harbour and Ghent harbour were originally one single area called “Harbours” but they have then been split into two areas due to a substantial difference in the characteristics of the pollution later detected.

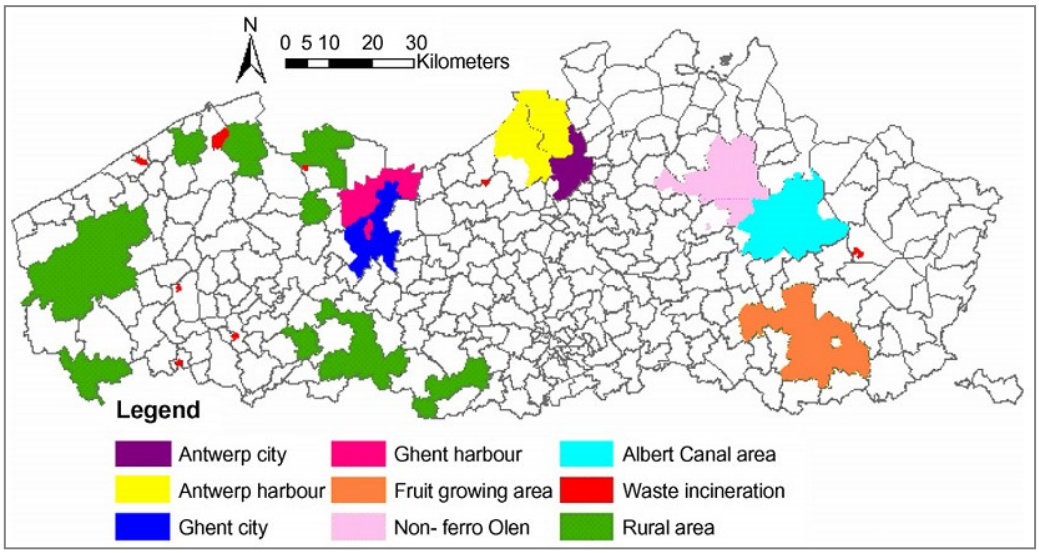


Figure 6.2 Map of study areas investigated in the Flemish Biomonitoring Programme 2002-2006 (from: Schroijen et al., 2008)

For the testing application, only contiguous areas where considered, that means all areas except for the areas named “Rural areas” and “Waste Incineration”.

The study takes in consideration different kinds of pollutants and effect categories: in the three age groups, different exposure and effect biomarkers were measured, as summarized in Table 6.2.

	Newborns N = 1200	**Adolescents (14-15 y) N = 1600**	**Adults (50-65 yr) N =1600**
Markers of exposure	Cord blood: Cadmium, Lead Cord blood serum: markers of PCBs, pesticides, dioxin-activity	Blood: Cadmium, Lead Serum: marker PCBs, pesticides Urine: 1-OH pyrene, t-t’-muconic acid, Cadmium	Serum: marker PCBs, pesticides, dioxin-activity Urine: Urine: 1-OH pyrene, t-t’-muconic acid
Markers of effects	Biometry, TSH, Apgar score, Time to pregnancy Questionnaire: asthma & allergy Follow up of part of the children	Blood: Comet test Serum: Hormone balance, biometry, sexual development Questionnaire: asthma & allergy	Blood: Comet test Serum: Tumor markers Urine: 8-OH dG Questionnaire: asthma & allergy
Co-variables	Questionnaire: general + food Biochemical analyses: cholesterol, iron status cord blood	Questionnaire: general + food Biochemical analyses: cholesterol, iron status blood, urinary creatinine	Questionnaire: general + food Biochemical analyses: cholesterol, iron status blood, urinary creatinine

Table 6.2 Overview of biomarkers of exposure and early health effects monitored in the Flemish Biomonitoring Programme 2002-2006 (from Den Hond et al., 2009)

The exposure biomarker measured in the study were selected because validated analytical procedure were available for them, and because they had known human health effects (Den Hond et al., 2009). Moreover, health history and food behaviour of the people included in the target sample have been investigated trough questionnaires for the whole length of the project.

For the test application, it has been chosen to focus on available data concerning adolescents, taking into account the relevance of assessing and protecting children's and young people's health as highlighted in recent EU policy documents (e.g., Environment and Health Action Plan 2004-2010; Parma Declaration; see Chapter 2).

The Flemish Biomonitoring programme 2002-2006 focused on teenagers between 14 and 15 years old and the inclusion criteria for the target sample are the following:

a) being born in 1988 or 1989;
b) studying in the third year of secondary school;
c) living for at least five years in the same area;
d) giving informed consent.

The total size of the target sample is of 1679 adolescents (Croes et al., 2009).

A stratified clustered multi-stage designed was chosen to select participants as a random sample of the population under investigation (Den Hond et al., 2009).The target sample size is kept around 200 in each study area, since "a power calculation demonstrated that this appears to be statistically sufficient to detect differences of 20% between study areas while the efficiency in estimation is the same for all study areas" (Schroijen et al,. 2008; DeJonge et al., 2003). All the data used in the application have been adjusted for sex, age and smoking habits.

The causal relationship between environmental exposure to chemicals and health effects considered for adolescents are reported in Table 6.3.

	Comet assay	Thyroid hormones	Sex hormones	Pubertal stages	Gynecomastie	Menarche	Growth	ADHD	Asthma	Allergy	Airway infections
PCB's	X	X	X	X	X	X	X	X	X	X	X
DDE/HCB	X	X	X	X	X	X	X	X	X	X	X
Cadmium	X		X	X		X		X	X	X	X
Lead	X		X	X		X		X	X	X	X
Benzene	X								X		X
PAHs	X	X	X	X	X	X			X		X

Table 6.3 The studied associations between environmental exposure to chemical stressors and early health effects investigated in the Flemish Biomonitoring Programme (from Elly Den Hond – VITO, personal communication, 2010).

In the following paragraphs, a detailed description is offered only for those exposure biomarkers and early health effects indicators that have been selected for being used in the testing application, namely:

- chemicals: lead, cadmium, benzo(a)pyrene, benzene;
- early health effects indicators: sex and thyroid hormones, allergies and respiratory diseases.

6.1.4 EXPOSURE BIOMARKERS DATA

As illustrated in Chapter 3, a biomarker of exposure consists in the measure of a chemical or its metabolites in human tissues or specimen such as blood, urine or milk (NRC, 2006; Albertini et al., 2006; Needham et al., 2007). A biomarker of exposure provides direct evidence of human exposure to natural or synthetic substances and, specifically, is a measure of the internal exposure to a chemical (Clewell et al., 2008). Among the exposure biomarkers measured in the Flemish Biomonitoring Programme, biomarkers of exposure for two metals (lead and cadmium) and for organic compounds (polycyclic aromatic hydrocarbons and benzene) were of interest for our case-study.

Measurements of heavy metals in whole blood

Lead and Cadmium can be found in blood as dissolved ions (Pb^{2+} and Cd^{2+}) and their concentrations in this matrix are commonly used to monitor environmental exposure to these metals.

Blood lead concentration is currently considered as the most reliable index of exposure to lead, it is the most widely used for clinical use and public health surveillance, and generally reflect relatively recent exposure (ATSDR, 2007b ; Sakai, 2000).

Blood cadmium concentration is usually assessed in whole blood and is regarded as the most valid marker of recent exposure, but is also an estimate of the accumulated body burden years after the exposure (ATSDR, 1999; Jarup and Akesson, 2009).

In the Flemish Biomonitoring Programme 2002-2006, Cd and Pb blood levels have been detected using high resolution mass spectrometry on samples of whole blood previously treated with acid digestion to destroy the organic fraction. The detection limits were 2,0 ηg l^{-1} for Cadmium and 0,09 ηgl^{-1} for Lead (Schroijen et al,. 2008).

Measurements of PAHs and benzene metabolites in urine

As biomarker of exposure to Polycyclic Aromatic Hydrocarbons (PAHs), 1-hydroxypyrene (1-OH-pyrene), a product of pyrene metabolism, is measured in urine. Pyrene is one of the most representative compounds of the Polycyclic Aromatic Hydrocarbons (PAHs) family and is always present in relevant amount in every PAHs mixture (Jongeneelen, 2001). Pyrene can be absorbed through inhalation and dermal contact and is present both in gas or on particulate matter. These reasons lead many researchers to use 1-OH-pyrene as an indicator not only of pyrene, but as an indirect indicator of all PAHs exposure (Jacob and Seidel, 2002; Jongeneelen, 2001).

Human exposure usually is assessed by monitoring 1-hydroxypyrene (1-OH-pyrene) in urine samples because pyrene is the major component in PAH mixtures and its urinary metabolites (1-OH-pyrene and 1-OH-pyrene glucuronide) usually are abundant and relatively easy to measure (Huang et al., 2006).

Because the volume of urine excreted from day to day both within a person and among individuals varies and is largely depending on the hydration of the participant, the concentration of 1-OH-pyrene, such as for many other urinary metabolites, is usually normalized to the excreted creatinine level (Huang et al., 2006).

In the Flemish Biomonitoring Programme 2002-2006, high performance liquid chromatography (HPLC) with fluorescence detector is used in order to determine the 1-OH-pyrene concentration measured in ηg l^{-1} of urine. The detection limit is here of 0,060 ηg l^{-1} (Schroijen et al., 2008).

Benzene is a toxic and carcinogenic chemical, often related to occupational exposure and traffic exposure, present in tobacco smoke, many foodstuff and consumer products. Trans-trans muconic

acid (t,t'-muconic acid) is a product of benzene metabolism and its concentration in urine is the most used biomarker (along with S-phenylmercapturic acid) to estimate the exposure to benzene (ATSDR, 2007a).

In the Flemish Biomonitoring Programme, High Performance Liquid Chromatography with a solution of methanol and acetic acid is used to separate t,t'-muconic acid from other compounds to which it is associated in urine, and then the concentration values are determined through ion chromatography. The detection level is 8,6 ηg l^{-1} (Schroijen et al,. 2008).

6.1.5 EARLY HEALTH EFFECTS DATA

Within the Flemish Biomonitoring Programme 2002-2006, several biological and health effects were monitored in the selected group of adolescents. The collected data include information on: sex hormones and thyroid hormones (measured in blood samples with commercial immunoassays), pubertal stages and sexual developments (through school doctors examinations), respiratory diseases and allergies (information collected through self-reporting questionnaires completed by adolescents and their parents).

Thyroid hormones

Thyroid hormones play a crucial role as a regulator of nervous system myelination, of growth and puberty, and also of metabolism and organ functions. Disorders affecting the thyroid gland represent the most common endocrine pathology during childhood (Wu et al., 2006).

The thyroid hormones measured in the Flemish Biomonitoring Programme are the Thyroid-Stimulating Hormone, free triiodothyronin and free thyroxine (Croes et al., 2009).

The Thyroid Stimulant Hormone (TSH, also named thyrotropin) is a product of the adenohypophysis, which is directly under the control of the hypothalamus. TSH acts on the thyroid gland to trigger the production and release of thyroid hormones, in particular triiodothyronin (T_3) and thyroxine (T_4) (Bursell and Warner, 2007). T4 (Thyroxine) and T3 (Triiodothyronine) regulate a series of body functions concerning mainly energy supply and usage. They stimulate the metabolism, the consumption of oxygen and the production of proteins. They are also really important to body development during pregnancy and childhood. FT4 (free T4) and fT3 (free T3) are the unbound fraction of T4 and T3 hormones. They are a small percentage of the total amount, around 0,03% and 0,3%, and they are referred to as the active fraction, because that they are free to bind to their receptors while the rest is bound to particular proteins. Thyroid dysfunction may result not only in metabolic abnormalities but can also seriously affect growth and development.

Sex hormones

The Luteinizing hormone (LH), or lutropin is produced in the adenohypophysis and it triggers important but different hormonal reactions in women and men, mainly for the production of estrogens and androgens and the following appearance of feminine and masculine characters. Ovulation and the development of the corpus luteum (from which the word "luteinizing") in females are directly linked to the LH, and so also the further production of testosterone and oestradiol. In males, instead, the LH acts mainly at the level of testicles and adrenal cortex triggering the production of testosterone.

Testosterone is probably the most important androgen, used also in therapies, present in both males and females but in very different amounts. In men it is the main actor in the development of primary (genital organs) and secondary sexual characters and of the libido. It also takes part in the regulation of the skeletal growing. Testosterone male level starts to rise abruptly during puberty until reaching a peak around the age of 30. Then it decreases at an average rate of 1% per year.

In children, elevated serum testosterone concentrations indicate over-production by the testes or by the adrenals and can result in premature pubarche (Soldin et al., 2009).

Testosterone is not soluble in water. This means that in blood most of it is bound to particular proteins: Sex Hormone Binding Globulin (SHBG) and albumin. SHBG binds testosterone firmly, creating a temporary inactive reserve, while Albumin binds it really loosely putting it in a condition of quicker bioavailability. The small unbound fraction is called active or Free Testosterone (Raverot et al., 2010) The levels of active and inactive testosterone can be extrapolate from the levels of serum testosterone and SHBG.

Oestradiol is a very important feminine sex hormone, produced from testosterone through a transformation led by the enzyme aromatase**.** Oestradiol is involved in development of primary and secondary feminine sex characters. It represents the major estrogen in humans, and has an important role in both females and males in the maturation of the nervous system, reproductive system, bone metabolism (Soldin et al., 2005). As the testosterone, oeastradiol is found in blood bound to SHBG and albumin and free (bioactive fraction).The bound and unbound levels can be extrapolated, similarly to testosterone, once the levels of serum oestradiol, aromatase and SHBG are determined (Croes et al., 2009).

Respiratory diseases and allergies

The Flemish Biomonitoring Programme 2002-2006 also took into account different kinds of health effects which are investigated and measured through self-reported questionnaires and individual medical examinations.

For the purposed of the testing application, asthma (doctor-diagnosed), hay fever (doctor diagnosed), food allergy and animal allergy, airway infections and eczema are considered. All of them are pathologies potentially linked to environmental exposure to different kind of pollutants.

6.2 DATA TREATMENT AND APPLICATION OF THE RISK-BASED TOOL FOR THE REGIONAL RANKING OF ENVIRONMENTAL CHEMICAL STRESSORS

6.2.1 DATA PRE-PROCESSING

A pre-processing of the collected data was needed in order to build a dataset with the characteristics required by the Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors.

For data of exposure biomarkers and early health effects, the data were already available in an aggregated form, since for each of the considered Flemish areas a single aggregated date (arithmetic or geometric mean value) was publicly available.

On the contrary, the database with soil contamination data provided by OVAM required a preliminary treatment, in order to obtain from single measurement values the aggregated data (at the level of single areas) required by the applied methodology.

First of all data errors or anomalies in the soil contamination database were identified and isolated, such as errors of dates and concentration values equal to zero.

Soil contamination data for the four chemicals of interest were selected according to the following criteria:

a) sampling date between 2000 and 2003, to have an overview of regional contamination status in the years immediately before the biomonitoring campaign;
b) sampling depth less or equal to 1 meter, since it is assumed that only surface contamination is relevant for population exposure; in case different concentration values measured at different depths for the same site at the same date were present in the database, the highest values has been chosen following a precautionary approach.

Moreover, since the sampling locations for the selected chemicals covers the whole Flemish region, it was necessary to select only those sampling points included in the considered EGUs. To this purpose, an ArcGis layer of all the areas of Flanders considered in the Flemish Biomonitoring Programme was overlapped to the sampling points map and the sampling points of interest were identified (Figure 6.3).

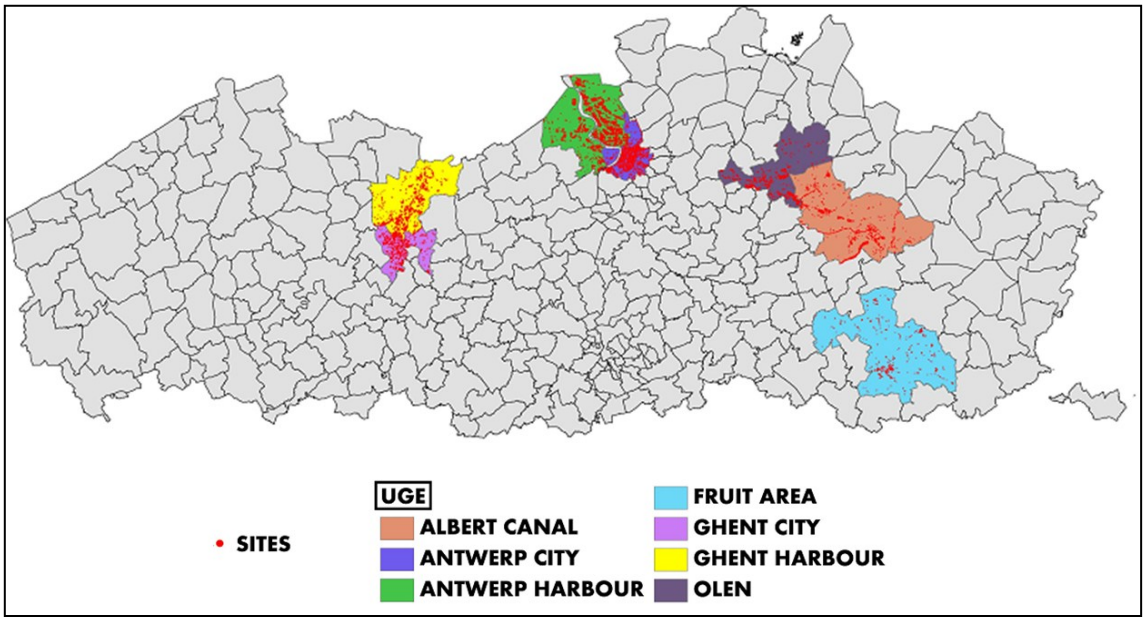


Figure 6.3 Sampling point for soil pollution monitoring in the areas within Flemish region of interest for the case-study application.

According to the requirements of the methodology implemented in the prototype tool, a single soil contamination value for each chemical is needed for each EGU. The 95% Upper Confidence Limit (95%UCL) of the mean of soil contamination data has been selected as metric to characterize the soil contamination status of each EGU. The 95% UCL of a mean is defined as a value that, repeatedly calculated on a random data group, is over (or equal to), in the 95% of the times, the real mean value for which represents a highly conservative estimate.

The 95%UCL was calculated using the statistical programme ProUCL (US EPA, 2010), a software developed by the US Environmental Protection Agency to support the statistical treatment of data for environmental risk assessment (US EPA, 2006). ProUCL can perform different goodness-of-fit tests for different types of distribution, and can then calculate the 95%UCL according to the selected distribution.

The 95% UCL values obtained for each chemical and for each EGU were then taken as input data for the LoE “Environmental Contamination”.

6.2.2 SETTING INPUT PARAMETERS

Before running the Risk-based Tool for Regional Ranking of Environmental Chemical Stressors, some input parameters have to be set by the user.

Specifically, the input parameters to be defined by the user are the following (see Chapter 5):

1. for each chemical:
   - definition of the membership function for the LoE "Source" (to set the two thresholds)
   - definition of the membership functions for the LoE "Intake" (to set the two thresholds)
2. for each disease:
   - definition of the membership function for the LoE "Observed Effects" (to set the two thresholds)
   - definition of the value of parameter ω_j
3. for each pair [chemical, disease]:
   - definition of the value of parameter $\eta_{i,j}$ (relative value associated to the relationship chemical i^{th} and disease j^{th} in the case of more than one chemical related to one disease)
4. for each LoE:
   - definition value of the relevance weight δ_p assigned to each LoE/criterion
5. to define how to deal with cases where multiple substances are associated to one disease:
   - definition of the value of α representing end-user's approach to deal with uncertainty in causes of diseases.

In the following paragraphs, the values of parameters chosen for the testing application is illustrated and the decisional criteria leading these choices is briefly explained.

Membership Functions for the Loe "Environmental Contamination"

To define the Fuzzy membership function, two thresholds have to be set (see Chapter 4).

For the definition of the thresholds concerning soil contamination, Flemish and other national regulations addressing contaminated soil assessment and management were considered.

The lower threshold for the considered contaminants are set on the basis of the Background Values defined by the Flemish "Soil Decree" ("Decree regarding the soil sanitation and the soil protection" of October 27, 2006, Belgian Official Gazette January 22, 2007).

Background Values reflect the concentration of chemical contaminants found in unpolluted soil. Background values for metals consist in the 90^{th} percentile of metals concentrations measured in Flemish top soil, while for most organic contaminants the Background Values are equal to the limit of

detection of each substance (with the exception of cases where they show a diffuse enrichment) (Carlon, 2007).

For the definition of the Upper Threshold, the Intervention Values, one of the two types of soil screening values set by the Dutch legislation, namely the Dutch Soil Protection Act (VROM, 1994), were considered. Specifically, soils where Intervention Values are exceeded are considered as seriously contaminated soils where remediation is necessary (Lijzen et al., 2001). Soil Intervention Values are based on "potential risks", i.e. risk occurring under standardized condition, that means they are used independently from soil use (e.g. industrial, residential, etc.) (Carlon, 2007). Soil Intervention Values are derived based on both human health and ecotoxicological risk assessment: it means that first an Ecological Serious Risk Concentrations (SRC_{ECO}) is calculated, as well as a Human Serious Risk Concentration (SRC_{HUMAN}). Then, to derive the final Intervention Value, the two SRCs are integrated: the most stringent (i.e. the lower) between the two values is chosen. According to the purposes of our application, focused on human health risks posed by environmental contamination, the SRC_{HUMAN} for the chemicals of interest have been selected, as reported in Lijzen et al. (2001).

The thresholds for Fuzzy membership functions defined according to the abovementioned criteria are reported in Table 6.4.

	SOIL CONCENTRATIONS (mg/Kg dm)	
	Flanders (Belgium)	The Netherlands
	Background Values	Intervention Values (human health)
Cadmium	0,8	28
Lead	40	622
Benzene	0,1	1,1
Benzo(a)pyrene	0,1	280
	Lower Thresholds	***Upper Thresholds***

Table 6.4 Lower and Upper Thresholds selected for the definition of Fuzzy membership functions for the LoE "Environmental Contamination".

Membership Functions for the Loe "Intake"

The definition of thresholds for building the Fuzzy membership functions for data concerning the LoE "Intake" was hampered by the substantial lack of international reference values for the interpretation of human biomonitoring data in a risk assessment context.

In recent years, many large biomonitoring programmes have been realized (or are currently on-going) at regional or national level, such as the German Environmental Survey (Schulz et al., 2007b), the Environmental Health Monitoring System in the Czech Republic (Černa et al., 2007) or the National Health and Nutrition Examination Surveys the United States (CDC, 2009). However, these programmes were not implemented to test specific exposure-effect hypothesis, rather are designed to generate population-representative data on the presence of environmental contaminants in human biological specimen (e.g. blood, urine) (Hays et al., 2008). Therefore, these programmes provide Reference Values which are statistically derived from the data obtained from the monitored population (e.g. mean value, 90^{th} percentile, etc.) but are not suitable to provide risk-based biomonitoring limits. Recently, efforts were also devoted to derive this latter type of values (i.e. toxicologically derived biological exposure limits), in order to support the interpretation of human biomonitoring measurements in a health risk assessment context. The available information on risk-based limits for the biomarkers of exposure considered in the testing application was reviewed, and lower and upper thresholds for building Fuzzy membership functions were proposed accordingly.

Blood Lead

For a risk-based interpretation of lead concentration in blood, information was collected from the reports of the German Biomonitoring Commission (Schulz et al., 2007a).

This Commission set 2 types of biomonitoring guidance values: besides Reference Values (which are statistically derived, and represent the upper margin of background exposure to a given chemical in a given population at a given time), the Commission set Human Biomonitoring Values (named HBM), derived on the basis of toxicological and epidemiological studies by expert judgement.

Two HBM levels are defined as follows (Schulz et al., 2007a):

a) The HBM I value represents *the concentration of a substance in human biological material below which – according to the knowledge and judgement of the commission and with regard to the substance under consideration – there is no risk for adverse health effects and, consequently, no need for action*.

b) The HBM II value represents *the concentration of a substance in human biological material above which – according to the knowledge and judgement of the commission and with regard to the substance under consideration – there is an increased risk for adverse health effects and, consequently, an urgent need to reduce exposure and to provide individual biomedical care (advice). The HBM II value should thus be regarded as an intervention or action level*.

The German Biomonitoring Commission states that, if the biomarkers measurement is between HBM I and HBM II, it is necessary to control the results by further measurements (Figure 6.4). If initial results are confirmed, the potential exposure source has to be identified and proper measure for

reducing or eliminating human exposure has to be implemented. The HBM I value should be considered as a *verification or control value* (Schulz et al., 2007a).

	Damage to health	Recommendation
	Possible	- Care by experts in environmental medicine - Immediate action to reduce exposure
HBM II	----------	----------
	Cannot be excluded with sufficient certainty	- Check analytical results - Identify specific sources of the exposure - Reduce exposure in adequate way
HBM I	----------	----------
	Not to be expected according to current knowledge	No need for action

Figure 6.4 Definition of HBM I and HBM II guidance values and recommendations for different biomarkers values ranges (from Schulz et al., 2007a)

In 1996, the Commission defined a HBM I of 100 µg/l for lead in blood of children and females of a reproductive age, and a HBM II of 150 µg/l, while for other persons these limits were 150 µg/l and 250 µg/l respectively. These values were re-evaluated and confirmed in 2002 (Wilhelm et al., 2010). In the following years, lead pollution underwent a general decline and this allowed recent studies to include cohorts with blood lead level mostly below 100 µg/l. These studies confirmed that adverse health effect of lead exposure, particularly on the nervous system and endocrine system during the development age, can occur at level below 100 µg/l, and also support the hypothesis of persisting lead-induced effects into adulthood. For these reasons, and also because IARC included Inorganic Lead Compounds in group 2A (probably carcinogenic to human), the Commission decided that the definition of a threshold level for blood lead was unjustified, and therefore suspended HBM values for both children and adults (Wilhelm et al., 2010).

According to this information, for building the Fuzzy membership functions it was decided to set the lower threshold equal to **0 µg/l.**

The upper threshold was set equal to **150 µg/l**, because this is the HBM II value indicated by the German Biomonitoring Commission, i.e. the value above which there is an increased risk for adverse health effects and public health actions should be proposed.

<u>Blood Cadmium</u>

In order to build the membership function for the concentration of cadmium in blood, Biomonitoring Equivalents derived by Hays and Aylward (2009) were considered.

A Biomonitoring Equivalent (BE) is defined as the *concentration of a chemical or metabolite in a biological medium that is consistent with an existing exposure guidance value such as a tolerable daily intake (TDI) or reference dose (RfD)* (Hays and Aylward, 2009). The BE approach integrate available pharmacokinetic data and forward dosimetry to convert existing exposure guidance into an equivalent concentration value in a biological matrix (e.g. blood, urine) (Hays et al., 2007).

BEs are screening values, which cannot be used as diagnostic criteria, but could provide a screening level assessment. BE values can be used for prioritization when multiple chemicals are being assessed, with the aim of identifying those resulting below, near or above levels consistent with the underlying exposure guidance values and suggest relative priority for further risk assessment follow up or risk management actions (Hays and Aylward, 2009).

The process for deriving BE values lead to two estimates of the biomarker concentration at relevant points in the risk assessment process (as illustrated in Figure 6.5):

a) **BE_{POD}**: it is the Biomonitoring Equivalent (biomarker concentration) associated with the human point of departure (derived from the NOAEL for the animal species after application of all adjustment factors to account for duration and interspecies extrapolations),

b) **BE**: it is the final Biomonitoring Equivalent value consistent with the exposure guidance value considered in the evaluation (RfD, TDI, …) and derived after application to the BE_{POD} of intraspecies and other uncertainty factors (such as database uncertainty factors).

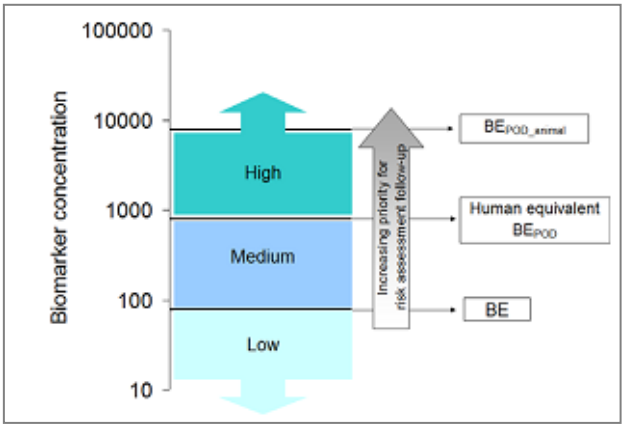


Figure 6.5 An example to illustrate the relative ranges of biomarkers concentrations (hypothetic values) associated with increasing levels of priority for health risk assessment follow-up (from Hays et al., 2008)

Hays et al. (2008) applied the Biomonitoring Equivalent approach to derive BE for cadmium in blood and for cadmium in urine. They reviewed the available exposure guidelines for cadmium, available pharmacokinetic data and models and integrating this information to derive BE_{POD} and BE.

The results of this assessment is reported in Figure 6.6.

BE derivation step	USEPA chronic RfD			ATSDR chronic MRL			WHO JECFA PTWI	
Target organ	Kidney			Kidney			Kidney	
POD	200 μg g^{-1} Renal cortex Cd concentration			0.0021 mg kg^{-1} d^{-1} Dietary Cd intake			2.5 μg g^{-1} cr Urinary Cd concentration	
Matrix	*Urine*		*Blood*	*Urine*		*Blood*	*Urine*	*Blood*
BE_{POD}	6.3 μg g^{-1} cr[a]	4.6 μg L^{-1}[b]	5.3 μg L^{-1}[c]	5.4 μg g^{-1} cr[d]	3.8 μg L^{-1}[b]	4.4 μg L^{-1}[c]	2.5 μg g^{-1}	1.8 μg L^{-1} [b]
Intraspecies uncertainty factors[e]							Not specified	
Pharmacodynamic	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$		
Pharmacokinetic	1	1	1	1	1	1		
BE value	2.0 μg g^{-1} cr	1.5 μg L^{-1}	1.7 μg L^{-1}	1.7 μg g^{-1} cr	1.2 μg L^{-1}	1.4 μg L^{-1}	Not calculated	
Confidence rating[e]	High	High	Medium	High	High	Medium	Not evaluated	

[a] Calculated using Eq. (1) discussed in text.
[b] Calculated assuming a ratio of 0.73 g crL^{-1} urine. See text for discussion.
[c] Calculated using the average of Eqs. (4) and (5) in text.
[d] Calculated as the average of values for men and women reported in Table 1 from Nogawa and Kido (1993).
[e] See discussion in text.

Figure 6.6 Biomonitoring Equivalents (BE) for exposure guidance values and underlying POD (from Hays et al. 2008)

The value of interest for 2-FUN case-study are the BE values concerning cadmium concentration in blood. Two couples of values are available, because Hays and colleagues (2008) estimated BE from two exposure guidance values: the first is the chronic Reference Dose (RfD) set by the US Environmental Protection Agency (USEPA), the second is the Minimal Risk Level (MRL) set by the Agency for Toxic Substances and Disease Registry (ATSDR).

For our purposes, the most conservative value is chosen (that derived by ATSDR MRL): the lower threshold is thus set equal to **0 μg/L,** and the upper threshold is set equal to the BE_{POD} corresponding to a cadmium blood concentration of **4,4 μg/L**.

<u>1-OH-pyrene in urine</u> and <u>t,t'-muconic acid in urine</u>

From a detailed literature research, it resulted that no health-based reference values for environmental exposure scenarios are currently available for the other two biomarkers of exposure considered in the testing application, i.e. 1-OH-pyrene in urine and t,t'-muconic acid in urine.

For these biomarkers, only reference values for occupational exposure are available, such as the Biological Exposure Index (BEI) defined by the American Conference of Governmental Industrial Hygienists (ACGIH). These are reference values intended as guidelines for the evaluation of potential health hazards in the practice of industrial hygiene (Morgan, 1997), therefore are based on occupational exposure scenarios (e.g. exposure time calculated as 5 days/week, 8 hours/day).

Due to the lack of other biomonitoring reference values, it was thus decided to use occupational biomonitoring guidance values. Specifically, the Biological Exposure Index (BEI) for the two biomarkers of interest are the following (Lauwereys and Hoet, 2001):

1) BEI for 1-OH-pyrene in urine: **2 μg/g creatinine**
2) BEI for t,t'-muconic acid in urine: **0,5 mg/g creatinine**

Since these values are set for adult worker while the testing application is focused on adolescent exposed to environmental concentration, these BEI values were set as Upper Thresholds for the two biomarkers for the respective Fuzzy membership functions.

Due to the lack of information to set the Lower Thresholds, these have been conservatively set to 0 for both biomarkers, i.e. **0 μg/g creatinine for 1-OH-pyrene** and **0 mg/g creatinine for t,t'-muconic acid**.

Membership Functions for the LoE "Observed Effects"

In order to build the Fuzzy membership functions for the parameters of the Line-of-Evidence "Observed Effects", reference ranges, representing acceptable values for healthy people (Horn and Pesce, 2003), were derived for the hormones considered in the case-study (thyroid hormones and sex hormones) from a literature review.

The selected ranges and the corresponding references are reported in Table 6.5.

Effect Category	Effect Parameter	Unit	Range	Reference
Thyroid Hormones	TSH	mlU/L	0,51 - 4,6	Kratzsch et al., 2008
Thyroid Hormones	Free T3	pg/ml	2,878 - 5,143	Kratzsch et al., 2008
Thyroid Hormones	Free T4	ng/dL	0,93-1,71	Kratzsch et al., 2008
Sex Hormones	Oestradiol	pg/ml	7-42	UIHC, 2009
Sex Hormones	Free oestradiol	pg/ml	0,30 - 0,90	Nichols Institute, 2004
Sex Hormones	Testosterone	ng/dL	42 - 880	Soldin et al., 2009
Sex Hormones	Free Testosterone	ng/dL	0,14 - 15,60	LabCorp, 2005
Sex Hormones	Luteinizing Hormone (LH)	lU/ml	1 - 3,7	Soldin et al., 2005
Sex Hormones	Sex Hormone Binding Globulin (SHBG)	lU/ml	13 - 93	LabCorp, 2005

Table 6.5 Reference ranges for thyroid and sex hormones considered in the case-study application.

To define the Fuzzy membership functions for hormones parameters, the upper values of the identified reference ranges were set as the Lower Thresholds, while the Upper Thresholds were derived according to a conservative approach by multiplying the upper value of the range for a factor of 10.

Finally, it was necessary to set the Fuzzy membership thresholds for the following indicators of early health effects:

- respiratory disease: doctor diagnosed asthma, doctor diagnosed hay fever
- allergies: airways infections, food allergy, eczema and allergy to animals.

Since all these indicators are expressed as percentage (%) of affected persons within the monitored population, and considering the lack of reference values in the available literature, the Lower Threshold was set at 0%, and the Upper Threshold was set at 100%.

Setting Other Tool Parameters

Besides the thresholds for building the Fuzzy membership functions, other parameters of the tool have to be set by the user (for a detailed description of each parameter, see Chapter 5).

The values chosen for the testing application are reported in the following list:

a) the weights assigned to each LoEs (δ_x, δ_y, δ_z) are all set to **1**; it means that the same importance is assigned to all LoEs;
b) the weights ω_j assigned to the health effects are all set to **1**;
c) the value of α (representing the user's approach to deal with uncertainty concerning the causes of the diseases) is set to **0**; it means that, when more chemicals are associated with the same disease, the contribution given by each substance is not weighted, and each pair "chemical-health effect" is considered independently (the evidence of effect is attributed completely to each chemical).

Considering that we are dealing with a preliminary testing application, it was decided to set all parameters to their "default value" without adopting specific preferences.

6.3 RESULTS AND DISCUSSION

The Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors has been applied to the dataset including environmental and health data from the Flemish region described in Paragraph 6.1 , after setting the tool parameters according to the criteria and choices illustrated in Paragraph 6.3. In this paragraph, the outcomes of this testing application are illustrated and briefly discussed.

As explained in detail Chapter 5, the tool provides three types of outcomes:

a) a ranking of chemical stressors within each Elementary Geographic Unit (EGU);

b) a ranking of chemical stressors at the regional level;

c) a ranking of the Elementary Geographic Units within the region.

6.3.1 RANKING OF CHEMICALS WITHIN EACH EGU

The scores provided for each environmental chemical stressors within each EGU are reported in Table 5.1, and these outcomes are represented in the chart in Figure 6.6.

Lead results to be in all EGUs the chemical with the highest score, except for the area named Albert Canal, where Cadmium is receiving the highest score. Benzo(a)pyrene, as can be observed in Figure 6.7, turns out to be the chemical with the lowest score in all EGUs.

EGU	Benzene	Benzo(a)pyrene	Cadmium	Lead	
ALBERT CANAL	0,390	0,009	0,491	0,057	**SCORES**
ANTWERP CITY	0,322	0,033	0,172	0,778	
ANTWERP HARBOUR	0,335	0,029	0,630	0,805	
FRUIT AREA	0,341	0,033	0,042	0,599	
GHENT CITY	0,377	0,057	0,409	0,753	
GHENT HARBOUR	0,339	0,025	0,450	0,809	
OLEN	0,345	0,001	0,322	0,747	

Table 6.6 Scores obtained by each considered environmental chemical stressor within each EGU considered in the case-study application.

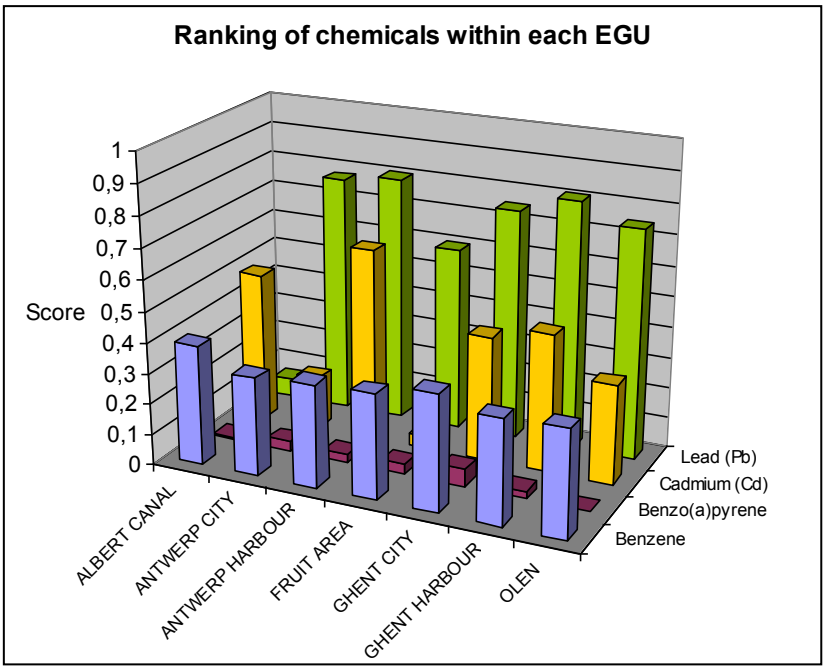


Figure 6.7 Graph comparing the scores obtained by each chemical within each EGU.

In order to allow a comparison of the obtained scores to the "worst case" situation, the scores obtained for each chemical within each EGU are normalized by dividing them for the maximum score achievable by each chemical, that means: the highest score for each pair chemical-observed health effects (that is 1) multiplied by the highest number of health effects associated with a single chemical in the case-study at hand (in the case of the testing application, 11).

Results obtained after this normalization process are reported in Table 6.7 and represented by the graph in Figure 6.8.

	Benzene	Benzo(a)pyrene	Cadmium (Cd)	Lead (Pb)	
ALBERT CANAL	0,035	0,001	0,045	0,005	**Normalized Scores**
ANTWERP CITY	0,029	0,003	0,016	0,071	
ANTWERP HARBOUR	0,030	0,003	0,057	0,073	
FRUIT AREA	0,031	0,003	0,004	0,055	
GHENT CITY	0,034	0,005	0,037	0,068	
GHENT HARBOUR	0,031	0,002	0,041	0,074	
OLEN	0,031	0,001	0,029	0,068	

Table 6.7 Scores obtained by each chemical stressors within each UGE, after normalization for the maximum number of health effects associated to a chemical.

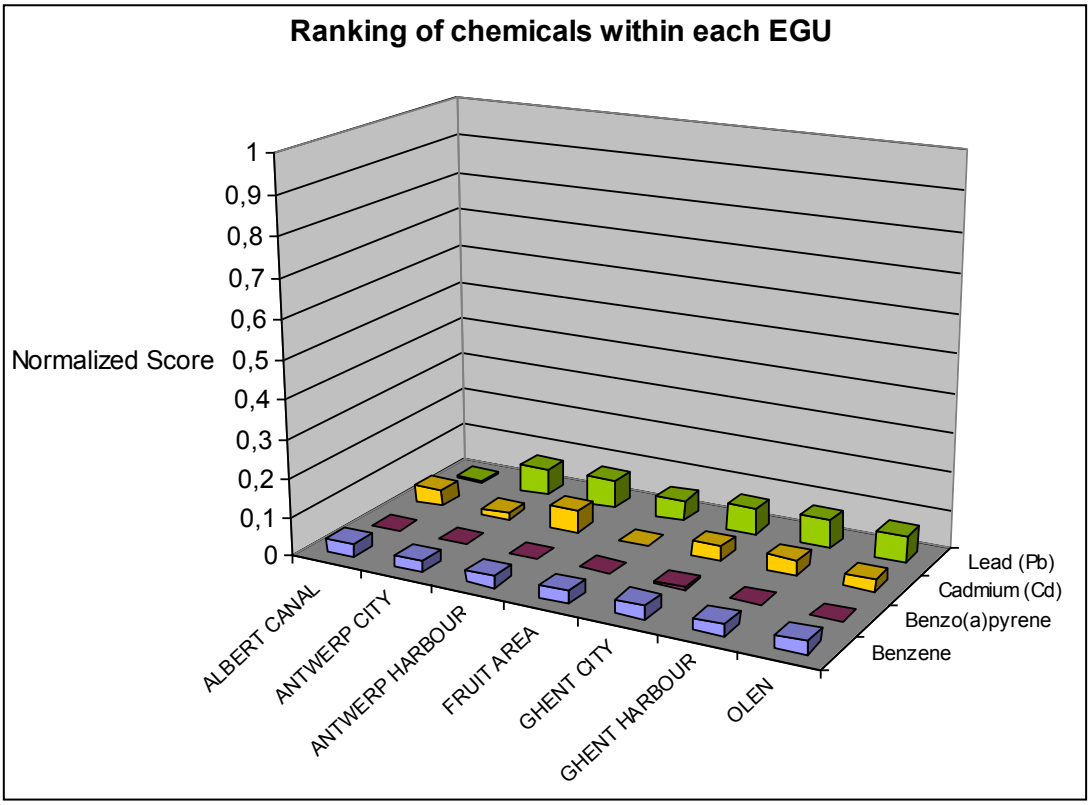


Figure 6.8 Graph comparing the scores obtained by each chemical within each EGU after normalization process.

In general terms, it can be said that the application of the methodology for ranking the chemical stressors within each EGU allows to differentiate among the chemicals under assessment (see Figure 6.7). This first phase of the assessment permits to achieve a first overview of the relative priority attributable to each chemical within the individual sub-areas (EGUs). This outcomes could allow to define a preliminary ranking of chemicals and associated health effects to be further investigated within each area.

At the same time, it is important to highlight that the normalization process permits to compare the obtained scores to the "worst case" scenario and, as can be observed from Figure 6.8, it results that the situation depicted for each chemical and its associated health effects is definitely far from being critical in terms of potential health risks. In all the EGUs considered in the assessment, indeed, a "flattening" of all chemical normalized scores towards zero can be noticed. That means that, according to the criteria used for building up and applying the ranking methodology, there is no chemical within the individual areas that needs an urgent detailed health risk assessment.

6.3.2 RANKING OF CHEMICALS AT THE REGIONAL LEVEL

After estimating a (normalized) score for each chemical within each EGU and thus obtaining a ranking of the chemicals within each EGU, these scores are aggregated for each chemical (see the procedure illustrated in Chapter 5) in order to obtain a ranking of chemicals at the regional level (i.e. for the whole of areas monitored by the Flemish Biomonitoring Programme 2002-2006 in the case-study of interest). In this case, since the score for each chemical is estimated through a weighted sum using the EGU's population as weighting factor, the final scores are normalized with reference to the maximum population within a EGU multiplied for the number of chemicals considered in the assessment.

The scores obtained by each chemical at the regional level are included in Table 6.8 and represented by the graph in Figure 6.9.

Region	Chemical	Normalized Score	Rank
Flanders	Lead	0,0619	1
	Benzene	0,0314	2
	Cadmium	0,0268	3
	Benzo(a)pyrene	0,0029	4

Table 6.8 Scores of chemicals at the regional level and associated position in the ranking.

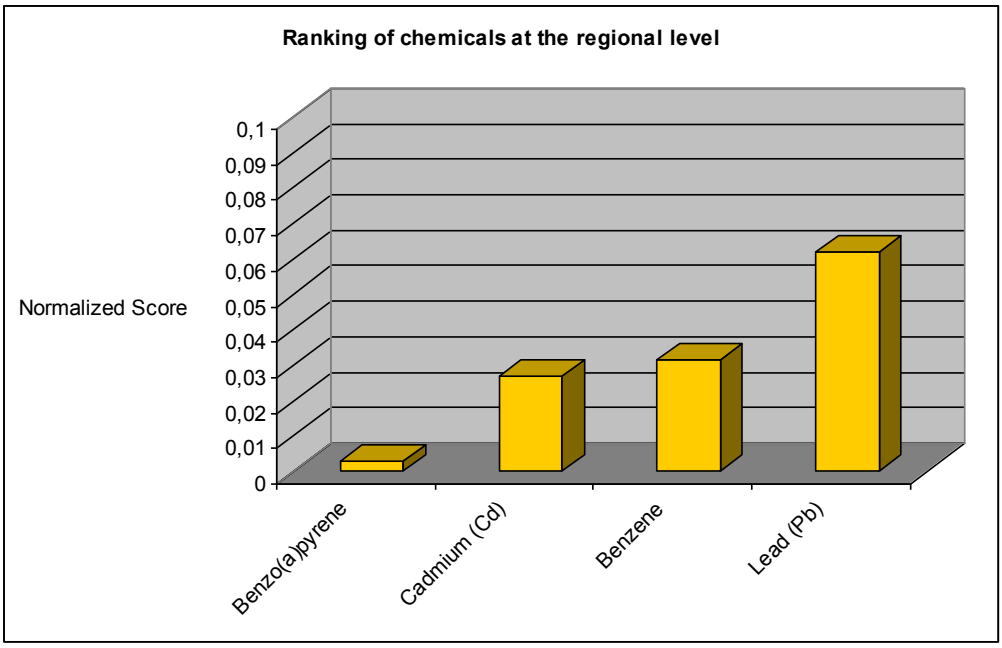


Figure 6.9 Graph representing the score obtained by each chemical at the regional level.

As can be noticed from Table 6.8, the chemical contaminant receiving the highest score at the regional level is Lead, followed by Benzene, Cadmium and Benzo(a)pyrene. Also in this case, the normalization process based on the consideration of the "worst case scenario" allows to observe that none of the chemicals considered in the assessment is associated to a critical situation, since all values are quite distant from 1.

6.3.3 RANKING OF EGUS

The third output provided by the Tool consists in a ranking of the Elementary Geographic Unit (EGUs) assessed in the case-study. The score of each EGU is derived by integrating the normalized scores of each chemical monitored in that EGU (see the first assessment step) by weighting the scores for the population of the EGU.

The normalized score assigned to each EGU and the final ranking are reported in Table 5.9 and illustrated by the graph in Figure 6.10.

Elementary Geographic Unit	Normalized Score	Rank
ANTWERP CITY	0,0341	1
GHENT CITY	0,0195	2
ANTWERP HARBOUR	0,0079	3
FRUIT AREA	0,0072	4
GHENT HARBOUR	0,0066	5
OLEN	0,0060	6
ALBERT CANAL	0,0056	7

Table 6.9 Scores of the EGUs and associated position in the ranking.

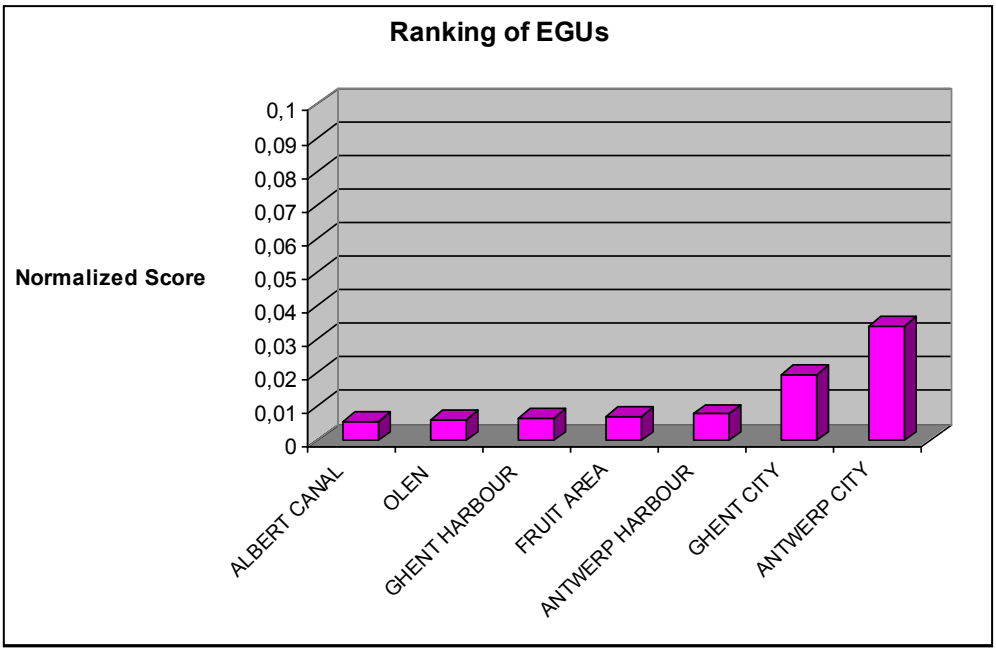


Figure 6.10 Chart representing the scores obtained by each EGU.

The EGU ranked first in the assessment is Antwerp City, which shows a score which is 3-times higher than the score of the second-ranked EGU, Ghent City. It is however important to bear in mind that, as previously described, the top-ranked EGU is quite far from the most critical situation, receiving a score of 0,0341 over the range from 0 to 1.

6.4 CONCLUSIONS TO CHAPTER 6

This chapter describes the testing application of the "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors", implementing the methodology illustrated in Chapter 5.

A case-study has been identified in the region of Flanders (Belgium), and a dataset including data for the three Lines-of-Evidence considered in the model (i.e., Environmental Contamination, Intake and Observed Effects) has been built. Specifically, this dataset includes data on soil contamination, data on four exposure biomarkers measured in adolescents, and data on early health effects indicators monitored in the same population group.

The outcomes of the testing application demonstrate that the proposed tool can support the identification of priority chemicals and associated health effects within individual sub-areas, as well as at the regional level. Moreover, the tool can provide a preliminary screening of priority areas (EGUs) within the assessed region, where further environmental health assessments should be focused.

It is important to highlight that the outcomes of the tool deeply depends on the quality and quantity of environmental and health data available for the region of interest, and for each sub-areas within this region. The use of data which are representative for the region under assessment, derived by large scale monitoring campaign of environmental pollution, human internal exposure and health effects, is needed in order to obtain reliable results.

In this context, it should be reported that the identification of a case-study suitable for testing the developed methodology constituted a challenging task. This was due mainly to the difficulties in selecting a region where environmental contamination and biomonitoring/health data were contemporary available for suitable time periods. Different types of agencies or authorities are responsible for the collection of the required data, and in most of the considered cases data cannot be integrated because they were collected in different "hot-spot" areas or only for restricted time periods and purposes and, as a consequence, cannot be used for depicting the whole region. Moreover, such types of data are often not publicly available. This is the case especially for biomonitoring and health effect data, that, when existing, cannot be accessed as individual data due to confidentiality issues, neither are made available as aggregated data (e.g. averaged data). The situation is slightly better, even if not ideal, for environmental data, since many environmental agencies and other monitoring authorities more often publish monitoring data (in reports or on websites) or make them available on request. The experienced difficulties demonstrate that an improvement of the understanding of the links between environmental and health quality should start from more integrated monitoring systems, able to provide datasets truly representative of the environmental health status of a region. Since often environmental data are aimed at describing environmental quality but are not meant to be interpreted in the context of human risk assessment, much more efforts are needed from regional and national authorities in order to include in environmental monitoring campaigns those environmental factors which are more significant from the public health perspective, with the aim of using them in integrated environmental health studies.

From an overall point of view, in order to achieve a detailed understanding of the methodology outputs, it would be important to identify and characterize all the different types of uncertainty which may affect the final results. Among these uncertainties, it would be for example interesting to analyse the uncertainty associated to monitoring data and how it is transferred along the model (integration of data, weighting processes, etc.) until the final outcomes. If a probabilistic description of input data would be available, this aim could be achieved for example through a Monte Carlo simulation (see Chapter 4). Moreover, another relevant source of uncertainty emerged in the case-study application and gaining relevance in the context at hand, is related to the choice of the assessment scale and to introduction of an aggregation procedure for monitoring data. When working with geographically distributed data, the choice of different scales and distinct aggregation

strategies can provide different outcomes (i.e. different maps of the represented region), none of which can be considered "incorrect" but each one calling attention to different features of the analysed data. This issue is called by geographers the Modifiable Areal Unit Problem (MAUP) (Openshaw, 1984), that is the dependence of the results on the set and the shape of regions within which aggregation occurs. MAUP is a "*a problem arising from the imposition of artificial units of spatial reporting on continuous geographical phenomenon resulting in the generation of artificial spatial patterns*" (Heywood et al., 1998). The effects of the MAUP can be split into two components: the *scale effect* (i.e. the variation in numerical results caused by the number of zones chosen for the analysis) and the *zonation effect* (i.e. the variation in numerical results originated from the grouping of small areas into larger units). It is important to detect which may be the main effects of MAUP in the analysis of the available data set, because generalizations may lead to critical results. In general, the selection of the scale and methodology of aggregation should be equilibrated between the need for small areas with population of homogeneous characteristics and the preference for wider areas where the larger population guarantee more precise and stable risk estimates (Elliott and Wartenberg, 2004). In the Flemish case-study, the choice of aggregation areas was forced by the availability of aggregated biomonitoring data (sub-areas identified in the Flemish biomonitoring programme). However, when individual data are available for both environmental and health data, it should be surely relevant to investigate the effect of the aggregation scale on each parameter and on the final ranking of chemicals and of sub-areas.

The application of the developed tool to the Flemish case-study also allows to observe that the identification of "guidance values" for assessing environmental pollution, biomarkers of exposure and early health effects indicators is a relevant but challenging task. For some fields (such as soil pollution, and environmental pollution in general, considering also other media) these guidance values/limits can be quite easily identified, because there are many regional and national regulations which set reference values derived by using different environmental, health and socio-economic criteria and priorities, on the basis of the available knowledge.

On the contrary, in the context of human biomonitoring risk-based guidance values for evaluating the internal exposure of population groups are still largely missing. In the case-study application presented in this thesis, for example, it has been necessary for some chemicals to resort to guidance values set for occupational exposure in order to define normalization thresholds. However, this choice has been forced by the complete lack of other guidance values for the substances of interest, and it implies the application of uncertainty factors to account for the specific features of occupational human biomonitoring references (e.g. they are set for occupation exposure of adults and therefore are not suitable for younger people).

The most valuable and interpretable guidance values for exposure biomarkers remain those based on human exposure-response data (Angerer et al., 2011), however such data are scarce and this kind of guidance values have been thus derived only for a very restricted set of chemicals. Therefore, efforts are being devoted to derive risk-based guidance values in which external dose-based guidance values (e.g. Tolerable Daily Intake) are translated (through the application of pharmaco-kinetic models) into equivalent biomonitoring levels. This modelling approach has been developed almost in parallel by the German Human Biomonitoring Commission (Schulz et al., 2007a) and by the Summit Toxicology team (Hays et al., 2007) and is very promising for enlarging considerably in the next future the number of chemicals for which risk-based guidance values can be derived.

In any case, it is important to remark that, when setting normalization thresholds, whenever the guidance values available in the literature or in regulatory documents, the choices must follow a conservative approach, taking into account existing uncertainties and applied extrapolation processes, in order to guarantee an adequate level of protection of the considered targets (especially in the case of vulnerable individuals).

In the proposed methodology, the uncertainty associated to the setting of thresholds for the normalization of environment and health monitoring data is managed through the inclusion of Fuzzy membership functions. This approach is beneficial because it allows the user to include a certain degree of uncertainty while classifying monitoring data concerning the three LoEs, and this uncertainty is then quantitatively accounted for in the ranking process.

Finally, as a general remark, it can be said that the testing application demonstrates how the integration of different types of data (environmental monitoring, human biomonitoring and health effects data) can be effective for preliminarily exploring environment-health relationships and thus in offering a more complete view on the environmental health status of a region of interest. The case-study permits to notice that this integration process, even if at a screening level, can support the identification of those scenarios where additional investigation and assessment efforts are needed, optimizing then the distribution of resources and research efforts.

In conclusion, the described features of the proposed “Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors” make it interesting as a support tool in the decisional process concerning the screening assessment and management of environmental health risks and it would be advisable to test it on additional case-studies in the European context.

6.5 REFERENCES

Albertini R., Bird R., Doerrer N., Needham L., Robinson S., Sheldon L., Zenick H., 2006. *The Use of Biomonitoring Data in Exposure and Human Health Risk Assessment.* Environmental Health Perspectives 114 (11): 1755-1762.

Angerer J., Aylward L.L., Hays S.M., Heinzow B., Wilhelm M., 2011. Human biomonitoring assessment values: approaches and data requirements. International Journal of Hygiene and Environmental Health 214: 348-360.

ATSDR, 1999. *Toxicological Profile for Cadmium*. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services.

ATSDR, 2007a. *Toxicological profile for Benzene*. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services.

ATSDR, 2007b. *Toxicological Profile for Lead*. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services.

Bursell J.D.H. and Warner J.T., 2007. *Interpretation of thyroid function in children*. Pediatrics and Child Health 17(9): 361-366.

Černà M., Spevackova V., Batariova A., Smida J., Cejchanova M., Ocadlìkova D., Bavorova H., Benes B., Kubınova R., 2007. *Human biomonitoring system in the Czech Republic*. International Journal of Hygiene and Environmental Health, 210: 495-499.

Carlon, C. (Ed.), 2007. *Derivation methods of soil screening values in Europe*. A review and evaluation of national procedures towards harmonization. European Commission, Joint Research Centre, Ispra, EUR 22805-EN, 306 pp.

CDC, 2009. *Fourth National Report on Human Exposure to Environmental Chemicals.* Centers for Disease and Control Prevention, US Department of Health and Human Services, Atlanta, USA.

Clewell H.J., Tan Y.M. Campbell J.L., Andersen M.E., 2008. *Quantitative Interpretation of Human Biomonitoring Data.* Toxicology and Applied Pharmacology, 231: 122-133.

Croes K., W. Baeyens, L. Bruckers, E. Den Hondd, G. Koppend, V. Nelene, E. Van de Mieroope, H. Keune, W. Dhooge, G. Schoeters, N. Van Larebeke, 2009. *Hormone levels and sexual development in Flemish adolescents residing in areas differing in pollution pressure.* International Journal of Hygiene and Environmental Health, 212 (6): 612-625.

De Jonge J.D, Kleinjans J., 2003. *The Flemish biomonitoring study, part 3: Minimal group sizes yielding sufficient statistical power for particular biomarker analysis*. Maastricht University,

Department of Health Risk Analysis and Toxicology. Available at http://www.milieu-en-gezondheid.be.

Den Hond E., H. Chovanova, B. Dumez, H. Keune, G.. Schoeters, C. Teughels, K. Van Campenhout, 2009. *Human biomonitoring in Flanders: some aspects related to study design, future, communication and ethics.* Bulletin épidémiologique hebdomadaire, 16 june 2009 - Special edition: 9-13.

Elliott P. and Wartenberg D., 2004. *Spatial Epidemiology: Current Approaches and Future Challenges.* Environmental Health Perspectives 112 (9): 998-1006.

Hays S.M. and Aylward L.L., 2009. *Using Biomonitoring Equivalent to interpret human biomonitoring data in a public health risk context*. Journal of Applied Toxicology, 29: 275-288.

Hays S.M., Becker R.A., Leung H.W., Aylward L.L., Pyatt D.W., 2007. *Biomonitoring equivalents: A screening approach for interpreting biomonitoring results from a public health risk perspective*. Regulatory Toxicology and Pharmacology 47: 96-109.

Hays S.M., Nordberg M., Yager J.W., Aylward L.L., 2008. *Biomonitoring Equivalents (BE) dossier for cadmium (Cd) (CAS No. 7440-43-9).* Regulatory Toxicology and Pharmacology, 51:S49-S56.

Heywood I., Cornelius S., Carver S., 1998. *Introduction to Geographical Information Systems.* Addison Wesley Longman, New York.

Horn P.S. and Pesce A.J., 2003. *Reference Intervals: an update*. Clinica Chimica Acta 334:5-23.

Huang W., Caudill S.P., Grainger J., Needham L.L., Patterson D.G., 2006*. Levels of 1-hydroxypyrene and other monohydroxy polycyclic aromatic hydrocarbons in children: A study based on U.S. reference range values*. Toxicology Letters 163:10-19.

Jacob J. and A. Seidel, 2002. *Biomonitoring of polycyclic aromatic hydrocarbons in human urine*. Journal of Chromatography B, 778 : 31–47.

Jarup L. and Akensson A., 2009. *Current Status of Cadmium as an Environmental Health Problem*. Toxicology and Applied Pharmacology, 238: 201-208*.*

Jongeneelen *F., 2001*. *Benchmark guideline for urinary 1-hydroxypyrene as biomarker of occupational exposure to polycyclic aromatic hydrocarbons*. The Annals of Occupational Hygiene, 45 (1): 3-13.

Kratzsch J., Schubert G., Pulzer F., Pfaeffle R., Koerner A.,Dietz A., Rauh M., Kiess W., Thiery J., 2008. *Reference intervals for TSH and thyroid hormones are mainly affected by age, body mass index and number of blood leucocytes, but hardly by gender and thyroid autoantibodies during the first decades of life*. Clinical Biochemistry, 41:1091-1098.

LabCorp, 2005. *Pediatric Endocrinology Reference Guides*. Laboratory Corporation of America, USA.

Lauwereys R.R., Hoet P, 2001. *Industrial chemical exposure. Guidelines for Biological Monitoring*. Third edition. Lewis Publishers, CRC Press, 2001 (ISBN 1-56670-545-2).

Lavrysen L., 2007. *Legislation on soil remediation in the Flemish Region of Belgium*. Proceedings of the International Seminar on Law Regulating Soil Contaminations, Lanzhou (China), 2007.

Lijzen J.P.A., Baars A.J., Otte P.F., Rikken M.G.J., Swartjes F.A., Verbruggen E.M.J. and. van Wezel A.P., 2001. *Technical Evaluation of the Intervention Values for Soil/Sediment and Groundwater Human and Ecotoxicological Risk Assessment and Derivation of Risk Limits for Soil, Aquatic Sediment and Groundwater*. National Institute for Public Health and the Environment, Bilthoven, the Netherlands. RIVM report 711701 023.

Morgan M.S., 1997. *The Biological Exposure Indices: A Key Component in protecting workers from Toxic Chemicals*. Environmental Health Perspectives Supplements, 105 – S1.

Needham L.L., Calafat A.M., Barr D.B., 2007. *Use and issues of biomonitoring*. International Journal of Hygiene and Environmental Health, 210: 229-238.

Nichols Institute, 2004. *Pediatric Endocrinology Reference Guide*. Quest Diagnostic Nichols Institute, Madison (USA).

NRC, 2006. *Human Biomonitoring for Environmental Chemicals*. National Research Council, National Academies Press, Washington DC.

Openshaw S., 1984. The Modifiable Areal Unit Problem. GeoBooks Ed., Norwich, UK

Raverot V., Lopez J., Grenot C., Pugeat M., Déchaud H., 2010. *New approach for measurement of non-SHBG-bound testosterone in human plasma*. Analytica Chimica Acta 658:87-90.

Sakai, 2000. *Biomarkers of Lead Exposure*. Industrial Health, 38: 127-142.

Schroijen C., W. Baeyens, G. Schoeters, E. Den Hond, G. Koppen, L. Bruckers, V. Nelen, E. Van DeMieroop, M. Bilau, A. Covaci, H. Keune, I. Loots, J. Kleinjans, W. Dhooge, N. Van Larebeke, 2008. *Internal exposure to pollutants measured in blood and urine of Flemish adolescents in function of area of residence*. Chemosphere, 71: 1317–1325.

Schulz C., Angerer J., Ewers U., Kolossa-Gehring M., 2007a. *The German Human Biomonitoring Commission*. International Journal of Hygiene and Environmental Health, 210: 373-382.

Schulz C., Conrad A., Becker K., Kolossa-Gehring M., Seiwert M., Seifert B., 2007b. *Twenty years of the German Environmental Survey (GerES): Human biomonitoring – Temporal and spatial (West Germany/East Germany) differences in population exposure.* International Journal of Hygiene and Environmental Health, 210: 271-297.

Soldin O.P., Hoffman E.G., Waring M. A., Soldin S.J., 2005. *Pediatric reference intervals for FSH, LH, estradiol, T3, free T3, cortisol, and growth hormone on the DPC IMMULITE 1000*. Clinica Chimica Acta 355: 205-210.

Soldin O.P., Sharma H., Hustede L., Soldin S.J., 2009. *Pediatric reference intervals for aldosterone, 17α-hydroxyprogesterone, dehydroepiandrosterone, testosterone and 25-hydroxy vitamin D3 using tandem mass spectrometry.* Clinical Biochemistry 42: 823-827.

Toriba A. and Hayakawa K., 2007. *Biomarkers of Exposure to Polycyclic Aromatic Hydrocarbons and Related Compounds.* Journal of Health Science 53(6): 631-638.

UIHC, 2009. *Laboratory Service Handbook*. University of Iowa Health Center, Department of Pathology, Iowa City (USA).

US EPA, 2006. *Data Quality Assessment: Statistical Methods for Practitioners*. EPA QA/G-9S, United Stated Environmental Protection Agency, Washington DC, USA. .

US EPA, 2010. *ProUCL Version 4.00.05 Technical Guide.* EPA/600/R-07/041, U.S. Environmental Protection Agency, Office of Research and Development, Washington DC, USA.

VROM, 1994. *Ministerial Circular on second phase remediation paragraph, Soil Protection Act, the Netherlands*, Reference DBO/16d94001.

Wilhelm M., Heinzow B., Angerer J, Schulz C., 2010. *Reassessment of critical lead effects by the German Human Biomonitoring Commission results in suspension of the human biomonitoring values(HBM I and HBM II) for lead in blood of children and adults*. International Journal of Hygiene and Environmental Health, 213:265-269.

Wu T., Flowers J.W., F. Tudiver, J.L. Wilson and N. Punyasavatsut, 2006. *Subclinical thyroid disorders and cognitive performance among adolescents in the United States*. BMC Pediatrics 6:12.

CHAPTER 7

SENSITIVITY ANALYSIS

7.1 INTRODUCTION

Uncertainty is an inherent characteristic of every risk assessment procedure and it could be ascribed to several sources, as illustrated in Chapter 4. This consideration is even more valid when a Multi-Criteria Decision Analysis (MCDA) model is considered, where preferential judgements are incorporated, implying thus the inclusion of subjective judgement (even if in a transparent way) in the assessment. Sensitivity analysis could support in investigating the uncertainties involved in the decisional process and the impacts they have on the conclusions that can be drawn from the model; moreover, it can be the means to explain to the decision-maker the implications (and possible inconsistencies) of his judgements (Rios Insua, 1999; Saltelli et al., 1999). Specifically, in a MCDA model sensitivity analysis methods aim at investigating the relationship between changes in input parameter and subsequent alterations in the ranking of alternatives following the completion of the decision analysis (Hyde et al., 2005). In this context, it may be important to bear in mind the definition of robustness. A ranking may be considered robust if little variations in the input data do not cause a significant variations in the position of the alternatives in the ranking. The analysis of the robustness of a MCDA model consists in determining how likely is that a reversal of the ranking of the alternatives will occur as a result of a change in one or more of the input factors (Hyde et al., 2005). It other words, it can mean to seek that alternative which is the most superior to others (in a robust ranking the difference between the best and the "second best" alternative is maximized) (Jessop, 2004).

Weighting the criteria is one of the crucial steps and often the more difficult of applying a MCDA method and is a potential source of significant uncertainty (Triantaphyllou and Sànchez, 1997). The weights assigned to criteria attempt to represent the importance of criteria and allow decision-makers' perspectives and their impact on the ranking of alternatives to be explicitly expressed. It may be difficult for decision-makers to provide precise numbers for criteria weights, so that their values may be affected by imprecision, contradiction, arbitrariness or lack of consensus in case many decision-makers are contemporary involved (Mousseau et al., 2003). Although the availability of several elicitation methods for supporting the definition of criteria weights, it seems

that no method could guarantee a very accurate result and it is possible that the same decision-maker come to choose different weights if different elicitation methods are applied (Hyde et al., 2005).

It is therefore important to investigate how the uncertainty in criteria weights could influence the resultant ranking of alternatives, also with the aim of providing the decision-maker with information about how likely is that a reversal of the alternatives' ranking occur as a result of a change in the criteria weights. It has thus been decided to perform a sensitivity analysis for the risk-based methodology for the ranking of environmental chemical stressors illustrated in Chapter 5, with the specific objective of testing the role of weights in determining the final output.

Many researchers proposed sensitivity analysis methods which can be applied for specific MCDA methodologies developed in different disciplinary fields, thus several approaches have been considered for the purposes of the present work. Sensitivity analysis can be performed either on a local or on a global level. A local method restricts *the analysis to the neighbourhood of a working points where the factors are fixed at their nominal value* (Saltelli et al., 1999). A Global sensitivity analysis, instead, investigates *how the uncertainty in the output of a model can be apportioned to different sources of uncertainty in the model inputs* (Saltelli et al., 2004) and, as it allows the input factors to vary over their whole range of uncertainty, it involves a multi-dimensional integration over the space of variations of the input factors (Saltelli et al., 1999). Moreover, the methods could be classified according to whether they vary a single parameter or whether they allow multiple parameters to vary simultaneously (Lindstedt et al., 2001). An exhaustive overview of sensitivity analysis methods could be found in Saltelli et al. (2005).

Taking into account the specificities of the proposed MCDA-based methodology for ranking environmental chemical stressors, it has been decided to apply a sensitivity analysis method based on Monte Carlo approach. The description of the proposed sensitivity analysis method, its application and the results are described in detail in the following paragraphs.

7.2 SENSITIVITY ANALYSIS BASED ON MONTE CARLO APPROACH

If sufficient information is available to define probability distributions for likely values of each input parameter, a stochastic approach can be used to analyse the likelihood of alternatives achieving a particular ranking (Hyde et al., 2006). The method involves the application of Monte Carlo simulation in which statistical sampling techniques are used to obtain a probabilistic approximation to the solution of a model (USEPA, 2001).

In Monte Carlo simulation (as illustrated in Chapter 4), a deterministic model is run repeatedly using for each run combination of values of input parameter randomly sampled from the probability distributions describing the input values. The procedure is repeated for a fixed number of times, typically between 500 and 1000, and through these iterations a distribution of output is generated. The set of simulations propagates defined uncertainties from model inputs through to model outputs. The output dataset can be analysed statistically, to estimate its descriptive parameters, such as the mean and the variance in order to define the probability distribution of the dependent variable of interest.

In the case at hand, the Monte Carlo simulation enables repetition of the selected MCDA model with the range of possible input values defined by probability distributions (Hyde and Maier, 2006).

The proposed method includes the following steps:

a) probability distributions are defined for the input factors of interest; if many decision-makers are involved in the assessment, the distribution can be derived from the values they choose for each input factors; if the process involves only one decision-maker, probability distributions can be built as Gaussian distributions around the median value selected by the decision-maker.
b) input values are then sampled from their respective probability distributions (by using a random sampling or a stratified sampling such as Latin Hypercube sampling) ;
c) the selected MCDA model is run with the sampled values and a ranking of alternatives is obtained for each sampling;
d) the process is repeated for a pre-defined number of times (to be selected) and a corresponding number of ranking is obtained.

Usually, from each run of the model (e.g., a fate and transport model for estimating chemical distribution) a single output value is obtained. In a MCDA model, the output consists not in a single value but in a ranking of alternatives. Changes in input values (weights or other parameters) affect the final scores of alternatives. These modifications can be more or less relevant, switching a “high” position of an alternative to a “low” one (or vice versa) or leaving an alternative with about the same score. As a result, the rankings obtained from multiple simulations can be more or less similar one to the others.

Accordingly, it is necessary to define a way to compare different ranking or, if the alternatives (in the case at hand, chemical stressors) are considered one by one, a way to compare the different position of each alternative in a set of different rankings. To this aim, indicators and indices are already available in literature, which have been reviewed and properly adapted to the case at hand.

For the graphic visualization of results, suitable graphs can be chosen to represent variations in alternatives ranking or in the score received by each alternative according to different choice of input factor (some examples are reported in Figure 7.1).

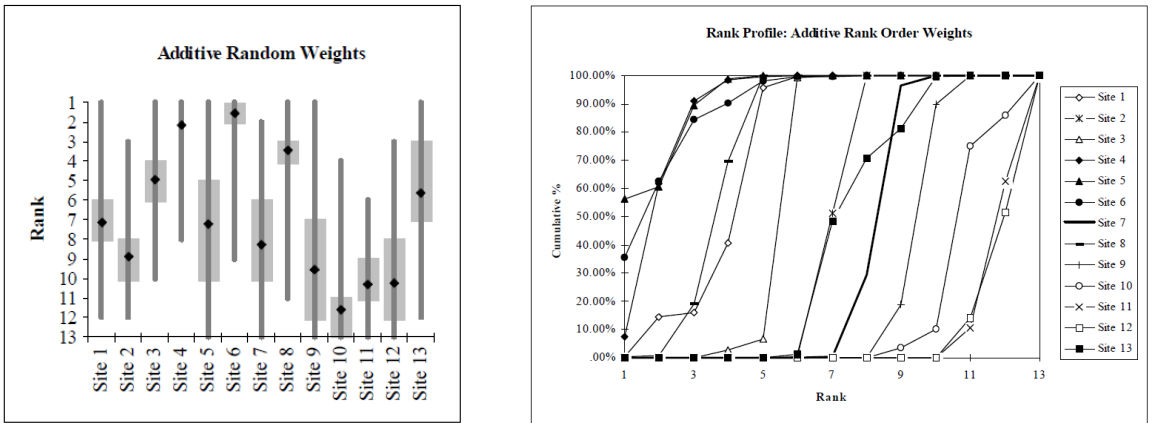


Figure 7.1 Possible visualization of results obtained with a simulation approach for a sensitivity analysis performed on criteria weights (from Butler et al., 1996).

7.3. A SENSITIVITY ANALYSIS TO EXPLORE THE ROLE OF LOES' WEIGHTS IN THE "RISK-BASED TOOL FOR THE REGIONAL RANKING OF ENVIRONMENTAL CHEMICAL STRESSORS"

7.3.1 PROPOSED METHODOLOGY FOR SENSITIVITY ANALYSIS

The application of a sensitivity analysis method based on Monte Carlo approach aimed at exploring the role of criteria weights (i.e., LoE's weight) in the "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors" (presented in Chapter 5) is illustrated in this paragraph. In particular, the sensitivity analysis will focus on PHASE 2, i.e. it will take into account the ranking of chemical stressors at the regional scale.

Since the sensitivity will explore in particular the role that the weights assigned by the user to each Line-of-Evidence have in affecting the final results, the following parameters will be considered in the sensitivity analysis:

δ_x = Relevance Weight assigned to LoE "Environmental Contamination"

δ_y = Relevance Weight assigned to LoE "Intake"

δ_z = Relevance Weight assigned to LoE "Observed Effects"

At least one of the weights, (δ_x or δ_y or δ_z), has to be set equal to 1 as a reference. This is due to the fact that for the decision-makers at least one of the criteria has to be considered "very important"

for the purposes of the assessment, and that one is set equal to 1. Moreover, this is also motivated by the need to have a reference value for the definition of the weights of the LoEs which do not receive the “maximum relevance”.

For each of the selected parameters, a Probability Distribution Function (PDF) of possible values has to be defined. In the case at hand, a Gaussian function (normal function) has been chosen as PDF for the weight associated to each LoE.

The mean of the function is set equal to the value initially chosen by the decision-maker for each parameter (that is, the value used in the Flemish case-study, chosen as reference application), and a pre-defined standard deviation has been chosen, representing the uncertainty about this value.

After having defined the distribution functions, the MCDA model is run for a pre-defined number of times. The results provided by Monte Carlo model consists in a set of L ranking, where L correspond to the number of simulations performed.

The analysis of the results can be done focusing on each single chemical stressor independently, or by evaluating the “degree of similarity” (or “degree of concordance”) among multiple rankings.

In the former case, two types of analysis can be performed:

a) it is possible to focus on the score obtained by the i-th chemical, using a bar chart to represent how frequent is each score in the simulation results;

b) it is possible to focus on the position (rank) achieved by the i-th chemical, using a bar chart representing how often the chemical occupies each one of the possible position in the ranking. For each substance, the mean and the variance (considering scores or ranks or both) can be calculated and analysed.

Moreover, a further assessment step consists in applying a method based on *Borda count* to aggregate, for each substance, the results of multiple rankings (derived from multiple simulations).

The Borda count is a method originally developed for elections purposes by Jean Charles de Borda in 1770 and that can be applied to several situations where multiple decision-makers are involved. In group decision there is indeed an aggregation problem to be faced, i.e. how to aggregate the ranking defined by each decision-maker. This relatively simple approach determines an aggregate rank (R_i) for option i^{th} by determining the sum of ranks ($r_{h,i}$) across all stakeholders (h = 1, 2, …, k), as reported in Equation 7.1.

$$R_i = \sum_{k=1}^{L} r_{k,i} \qquad \text{(Eq. 7.1)}$$

In the case of interest, the sum of ranks and the sum of scores is calculated for each chemical across all simulations (k = 1, …, L). The Borda count is thus used to estimate, for each substance, an indicator of the rank (or score) achieved by each substance taking into account the results obtained in all simulations.

After the analysis of the alternatives (chemicals) one by one, the second proposed way to analyse the results obtained from Monte Carlo simulations consists in evaluating the "degree of similarity" (or degree of concordance) among multiple rankings. That means to evaluate how much the obtained rankings differs one from the other, i.e. to explore the average shift in the rank of chemicals among multiple rankings.

To this purpose, the statistic indicated in Equation 7.2 has been chosen. This statistic, proposed by Nardo et al. (2005), captures in a single number the relative shift in the position of the entire system of alternatives (i.e. chemicals in the case at hand). It can be quantified as the average of the absolute differences in alternatives' rank with respect to a reference ranking over the M alternatives (Nardo et al., 2005).

$$V_k = \{ \frac{1}{N_S} \sum_{i=1}^{N_S} \left| R_0(i) - R_k(i) \right| \} \qquad \text{(Eq. 7.2)}$$

where:

i = 1, …, N_S are the alternatives (i.e. chemicals)

$R_k(i)$ = rank of the i^{th} chemical in the k^{th} ranking (obtained from the simulation)

$R_0(i)$ = reference rank of the i^{th} chemical

In the case of concern, the reference ranking is the ranking obtained with the set of parameters initially defined by the decision-maker (i.e. the ranking obtained in the Flemish case-study application illustrated in Chapter 6). V_k represents the mean of the distance from the reference ranking for the k^{th} ranking, this implies that also the standard deviation can be evaluated.

Once estimated V for all *L* simulations, the trend of this indicator is analysed (e.g. mean, standard deviation). The characteristics of the probability density function of V are also considered.

7.3.2 SOFTWARE IMPLEMENTATION OF THE PROPOSED SENSITIVITY ANALYSIS METHOD

The methodology illustrated in Chapter 5 has been implement in a prototype software, the "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors. The proposed sensitivity analysis is performed by a specific module which has been included in the Tool and supplies all the required statistical evaluations.

In order to apply the sensitivity analysis module, the following parameters have to be set by the user:

- number of model simulations (which corresponds to the number of generated rankings);
- reference values of LoE weights δ_x, δ_y and δ_z;
- which one of δ_x, δ_y and δ_z should be considered as reference for the others and therefore fixed to 1;
- standard deviation of the probability distribution functions for the "non-fixed" weights to be used to generate the input values for the selected number of runs.

In addition to the final sensitivity results, intermediate results are generated for all the steps of the procedure allowing for a more precise, stepwise assessment of the outcomes.

7.4 RESULTS AND DISCUSSION

The procedure for sensitivity analysis illustrated in Paragraph 7.3 has been applied to the methodology implemented in the "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors". The dataset used to perform this analysis is the same used in the testing application of the tool, concerning a case-study in the Flemish region (Belgium); this dataset has been described in Chapter 6. The sensitivity analysis has been focused only on one phase of the ranking methodology (PHASE 2), that is the phase providing as output the ranking of chemicals at the regional scale.

The reference application consists in the testing application to the Flemish dataset, where all LoE weights were set equal to 1 (i.e., the same relevance was given to all LoEs). For the purposed of the sensitivity analysis, it has been decided to fix to the value 1 the weight δ_x related to the LoE "Environmental Contamination".

A normal probability distribution has been chosen to described the other two weights (δ_y and δ_z, related to the LoEs "Intake" and "Observed Effects", respectively). The values of mean and standard deviation describing these normal distribution, needed for input data creation in the Monte Carlo random sampling, are based on experts judgments as reported in Table 7.1. Since the maximum value of each weight is 1, the probability distributions considered in the simulations consist actually

only in the “first half“ of a normal distribution with mean 1 and standard deviation 0.5 (and minimum value 0).

The number of simulations of the Monte Carlo random sampling has been set equal to 1000.

	Mean	Standard deviation
δ_x	1	0
δ_y	1	0.5
δ_z	1	0.5

Table 7.1 Mean and standard deviations of the probability distributions for the LoE’s weights used in the sensitivity analysis .

The sensitivity analysis has then been performed with the described parameters values, and the results are illustrated in the following paragraphs.

The first way to investigate the results of the analysis consists in analysing the alternatives ranked by our model (i.e., chemicals) one by one, that means to look at the scores obtained by each single chemical in the different simulations. As a first approach, these scores are evaluated with the Borda count approach, consisting in summing up for each chemical all the normalized scores obtained in the 1000 performed simulations. Figure 7.2 offers a visualization of these results; it is important to remind that the maximum value of Borda count for each chemical would be 1000 in case a chemical would receive the score 1 (i.e. the maximum score) for all 1000 performed simulations.

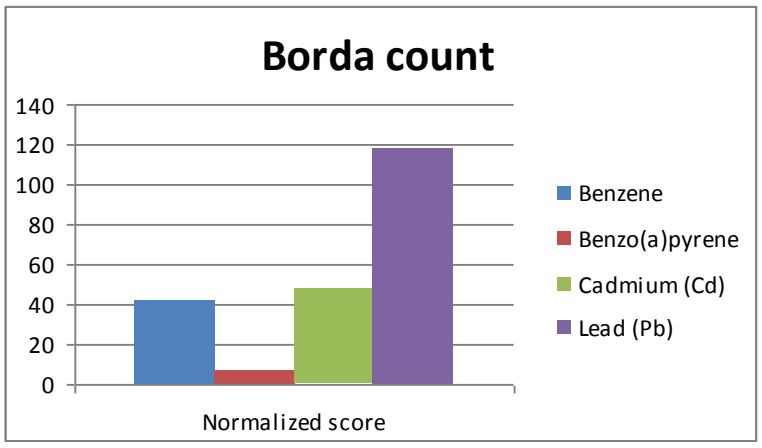


Figure 7.2 Borda count histogram considering the normalized scores received by the chemical substances.

By examining the bar chart reported in Figure 7.2, it appears that Benzo(a)pyrene received the lowest Borda count, and we can thus say it is likely to be very often the “least dangerous” substance; on the opposite, Lead has the highest Borda count and so it is supposed to be very often the “priority substance” with the highest score.

Cadmium and Benzene obtain a quite similar Borda count, and it means that their scores in the different simulations are often very close. As a consequence, it is possible to conclude that small changes in their scores are sufficient to let them exchange their relative positions in the ranking.

In Figure 7.3, the graphs illustrating the variations of the normalized scores for each single chemical are reported. In these graphs, the mean and standard deviation of scores, along with the empirical Cumulative Probability Distribution (CDF) are shown. These graphs confirm the observations made about Borda count results. The Benzo(a)pyrene scores are indeed always the lowest; while, Benzene and Cadmium scores have a similar mean value (which can be noticed also in Table 7.2) but the latter presents a slightly higher standard deviation. This implies that Cadmium and Benzene are likely to exchange their positions in the ranking as was already arguable from the Borda count results.

	Mean	**Standard Deviation**
Benzene	0,0421	0,0212
Benzo(a)pyrene	0,0067	0,0039
Cadmium	0,0476	0,0231
Lead	0,1182	0,0822

Table 7.2 Mean and standard deviation values of normalized scores for the assessed chemical substances.

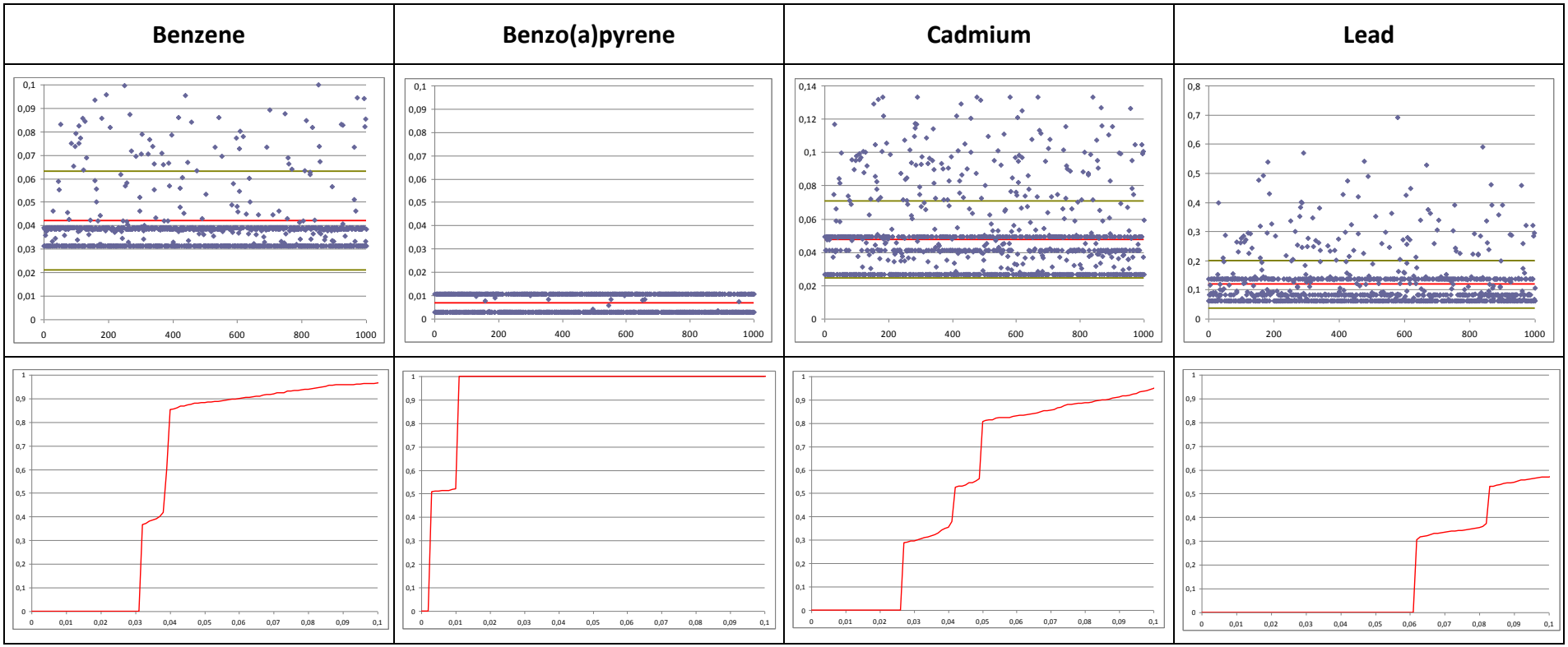


Figure 7.2 Scores distribution of the assessed chemical substances as obtained from Monte Carlo simulations (number of simulations set to 1000). In the first row dispersion graphs of scores for each chemical are presented along with the mean line (in red) and standard deviation (in green); the scale for the y-axis is not the same for all graphs, since it is set according to the range of values covered by the scores for each substance, In the second row cumulative distribution functions of the same data are presented.

The described outcomes can be observed also by examining Figure 7.4 where the box plots related to the scores (Figure 7.4a) and the positions (Figure 7.4b) in the regional rankings of the chemical substances obtained in the different simulations are presented. The box plot in Figure 7.4b (based on chemical positions) clearly identify a quasi-identical distribution of positions for Benzene and Cadmium, that is supported by the box plot based on chemical scores (Figure 7.4a) as well. It also clearly confirms the stable positioning of Lead on the top of the rankings, such as the stable positioning of Benzo(a)pyrene at the last location of the rankings.

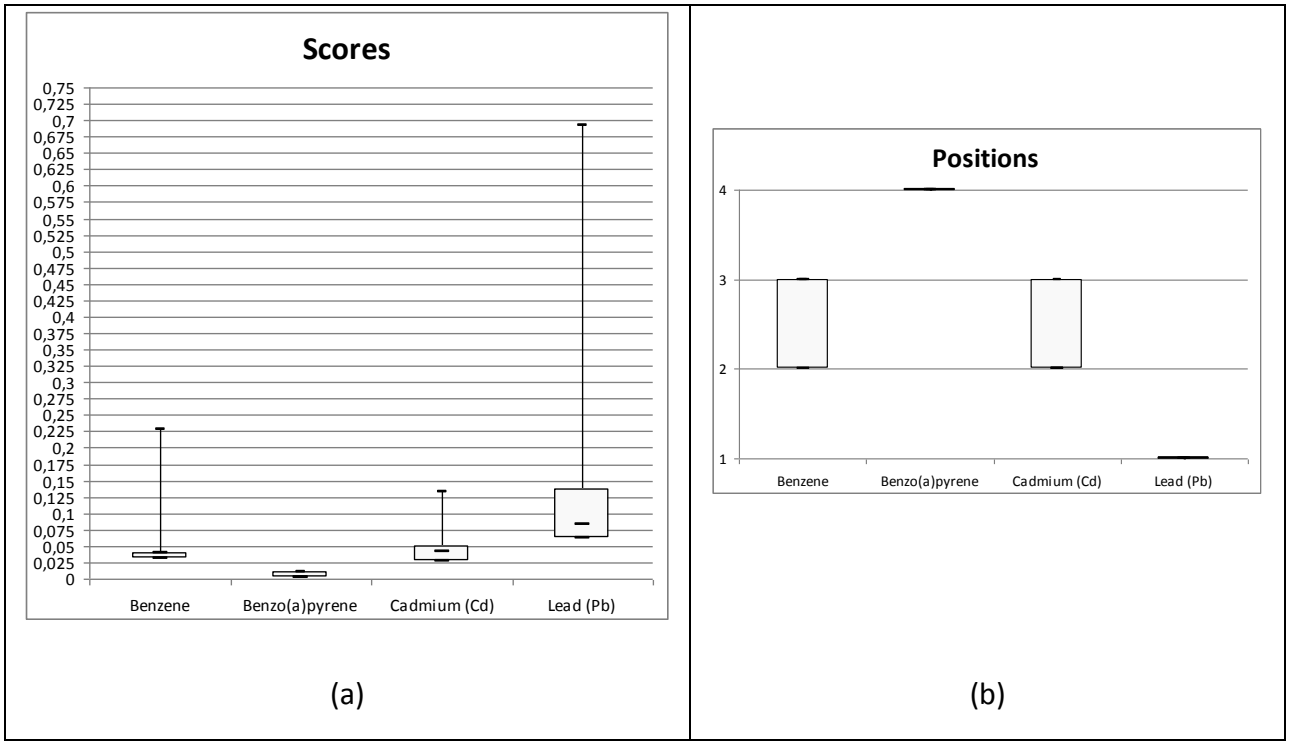


Figure 7.4 (a) Box plots of scores distributions the assessed chemical substances.
(b) Box plots of positions distributions for the assessed chemical substances.

As can be noticed from graphs presented so far in Figures 7.3 and 7.4, the scores for the chemicals Benzene and Benzo(a)pyrene are limited to the [0 - 0,1] interval, while those for Cadmium are limited to the interval [0 - 0,14]. The only chemical that in some simulations exceed these ranges is Lead, reaching as maximum value (in a single simulation) a score equal to 0,692.

This can be noticed also from the graph reported in Figure 7.5, where scores distributions of all four chemical substances are presented all together in the [0 - 1] original scale. This distribution is strictly dependent on the specific environmental and health monitoring data used in the application. As already explained in Chapter 5, a "flattening" of all chemical normalized scores towards zero can be noticed, in both the assessment within each EGU and at the regional scale. It means that, according to the criteria used for building up and applying the ranking methodology, for no chemical a situation of need for a urgent, detailed risk assessment can be noticed. From the sensitivity analysis results, it can be observed that for very few simulations (considering that the total number of simulation is 1000) the score of Lead can reach more relevant scores.

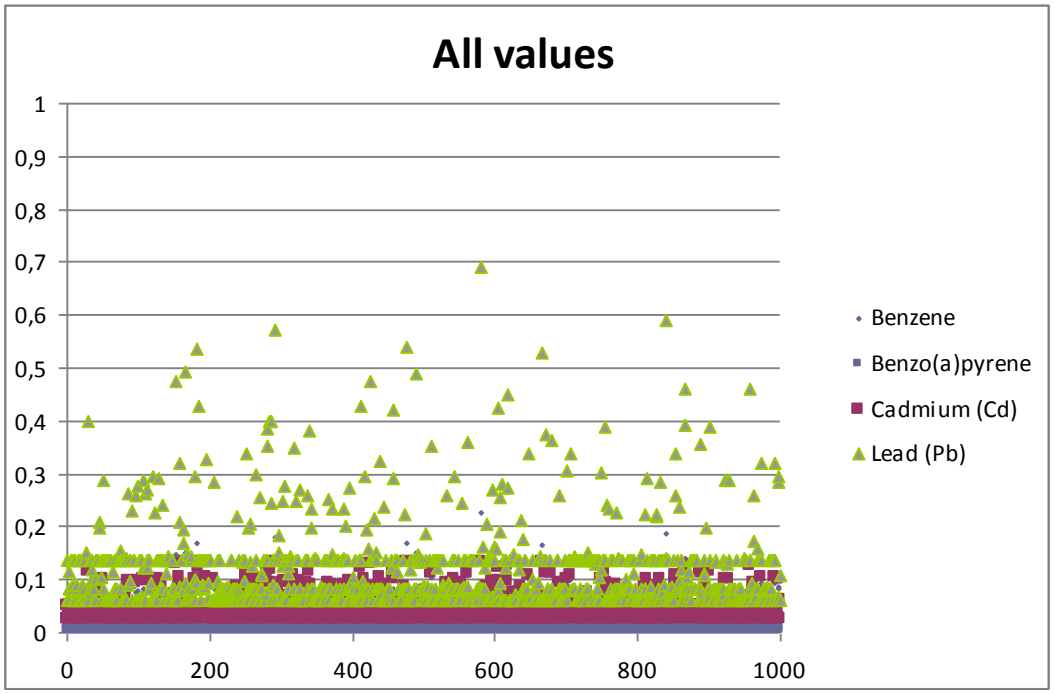


Figure 7.5 Scores distribution of all assessed chemical substances in the original [0,1] scale.

As illustrated in Paragraph 7.3 of this report, another way to analyse the results of Monte Carlo simulations for the applied MCDA methodology can consist in considering the degree of concordance among the several rankings obtained from the repeated simulations, in order to evaluate and quantify how much each ranking differs from all the other. To this aim, the indicator V (Equation 7.2) is estimated and some statistics describing its trend are reported.

The indicator V represents the mean of the differences between the scores obtained by the substance in the "reference ranking" and the scores obtained in the simulated rankings, taking into account all chemicals. It can be therefore used to describe the "degree of similarity" among the rankings obtained in the Monte Carlo simulation. The "reference ranking" in case at hand is the ranking obtained by setting all the LoEs' weights to 1 (as done in the testing application described in Chapter 6).

Since the chemical scores at the regional scale obtained in the reference ranking are already very small (in the [0 - 0,1] scale), as a consequence the mean of the differences between these reference scores and the simulated scores is even smaller and densely clustered around a mean value of 0,023, with standard deviation 0,032 (as presented in Figure 7.6).

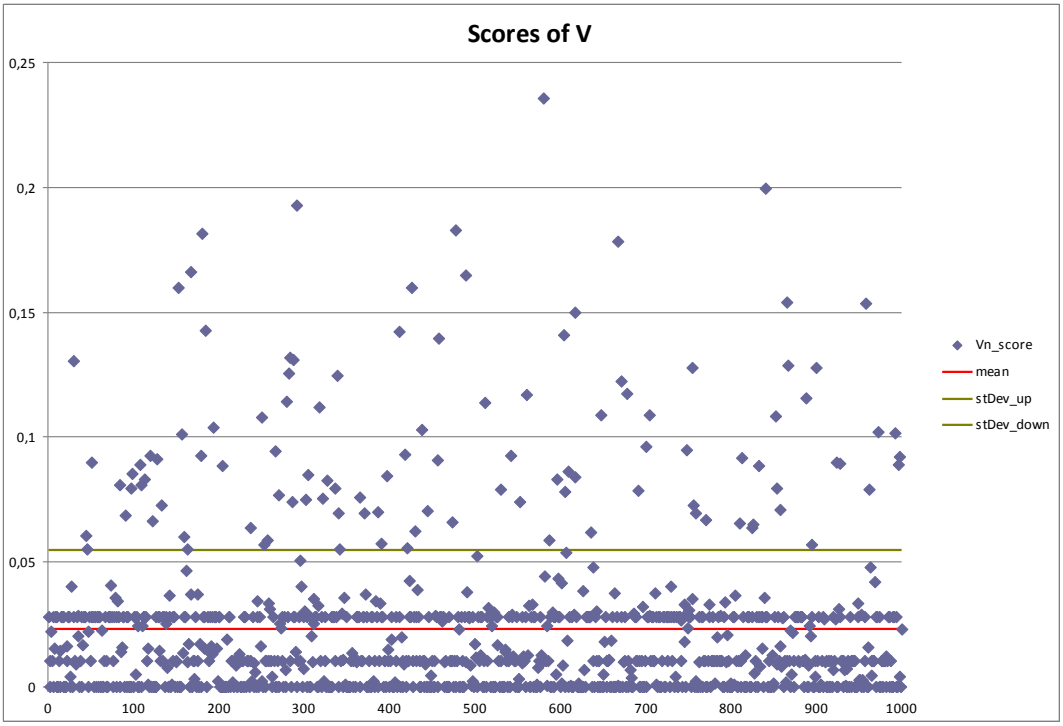


Figure 7.6 V score distribution along with mean (red) and standard deviation (green).

Moreover, in Figure 7.7 the empirical cumulative distribution of V is represented; since the maximum value achieved by V is 0,235 (i.e., for V equal to 0,235, the cumulative function has already achieved the value 1), only the range (0 - 0,5) is represented.

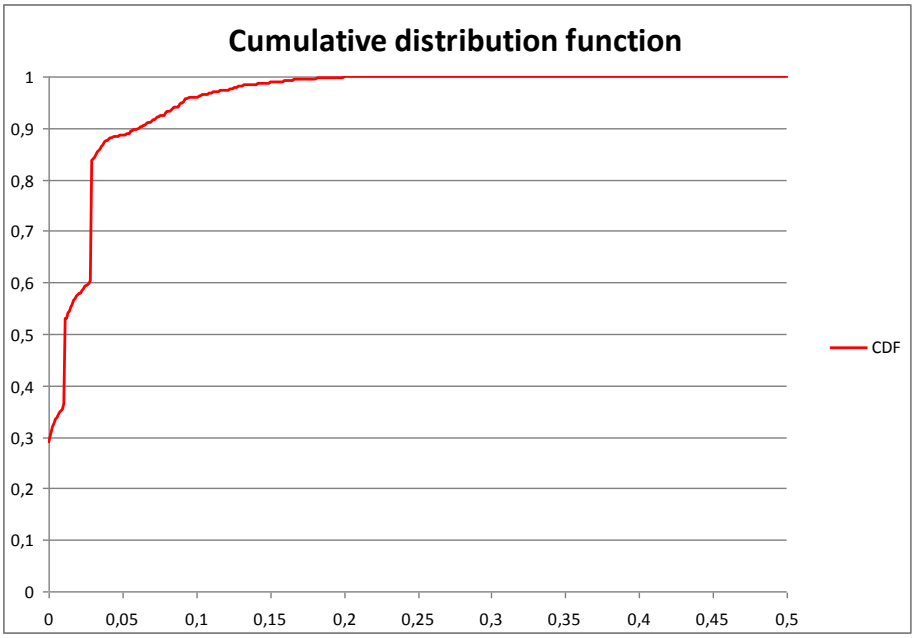


Figure 7.7 Empirical Cumulative Distribution Function for the scores achieved by indicator V

7.5 Conclusions to Chapter 7

The described outcomes demonstrate that results of the ranking methodology concerning the ranking of chemicals at the regional scale are not much dependent on user's selection of the weights assigned to each LoE for the case-study application of interest.

The considered case study in fact presents very limited variations in terms of "assessment priority" of one substance in comparison to others, and therefore only small variations arose from the analysis.

In the sensitivity analysis presented in the previous paragraphs, the weight for the LoE "Environmental Contamination" was set to 1, while a probability distribution was set for the weights assigned to the other two LoEs. The same procedure has been applied for sensitivity analysis to other two hypothetical situations: in the first case, the weight for the LoE "Intake" was set to 1 while the other two weights were variable, in the second case the fixed weight was that for the LoE "Observed Effects".

The results obtained with these two analysis are quite similar to those described here, and confirmed that, even with some changes in the obtained scores, Lead is the chemical most likely to hold the first

position in the ranking, Benzo(a)pyrene the lowest position, while Cadmium and Benzene are always in the intermediate positions and can exchange their relative rank. Therefore, with the available dataset, the most probable ranking is the same already obtained in the testing application.

With the aim of achieving a better understanding of the relevance of different input parameters in the MCDA model, a more comprehensive assessment could include also a sensitivity analysis on the thresholds set by the user for the definition of Fuzzy membership functions (normalization function). This analysis would help in understanding the role that the choice of normalization thresholds have on the score achieved by each stressor and on the final ranking of chemicals and sub-areas, and could thus offer also useful indications about the main factors to be considered when the user sets these thresholds. Moreover, another further development could focus on the role that the uncertainties associated to input monitoring data plays in influencing the ranking of chemicals and of sub-areas. The proposed Monte-Carlo procedure for sensitivity analysis could be extended to input monitoring data through an extension of the module currently implemented for sensitivity analysis in the developed tool. All these aspects will be included in a further development of the work presented in this thesis.

7.6 REFERENCES

Butler J., Jia J., Dyer J., 1997. *Simulation techniques for the sensitivity analysis of multi-criteria decision models*. European Journal of Operational Research 103: 531-546.

Hyde K.M., Maier H.R., Colby C.B., 2005. *A distance-based uncertainty analysis approach to multi-criteria decision analysis for water resource decision making*. Journal of Environmental Management 77: 278-290.

Hyde K.M. and Maier H.R., 2006. *Distance-based and stochastic uncertainty analysis for multi-criteria decision analysis in Excel using Visual Basic for Applications*. Environmental Modelling and Software 21: 1695-1710.

Jessop A., 2004. *Sensitivity and robustness in selection problems*. Computers and Operations Research 31: 607-622.

Mousseau V., Figueira J., Dias L., da Silva C.G. and Clìmaco J., 2003. Resolving inconsistencies among constraints on the parameters of an MCDA model. European Journal of Operational Research 147: 72–93.

Nardo M., Saisana M., Saltelli A., Tarantola S., 2005. *Tools for Composite Indicators Building*. EUR 21682 EN, European Commission, Institute for the Protection and Security of the Citizen, Joint Research Centre - Ispra, Italy.

Saltelli A., Tarantola S., Campolongo F., Ratto M., 2004. *Sensitivity Analysis in Practice. A Guide to assessing Scientific Models*. John Wiley & Sons Ltd., Chichester, England.

Rios Insua D., 1999. Introduction to the Special Issue on Sensitivity Analysis. Journal of Multi-Criteria Decision Analysis 8:117-118.

Triantaphyllou E. and Sanchez A., 1997. A sensitivity analysis approach for some deterministic Multi-Criteria Decision Making methods. Decision Sciences 28 (1): 151-194.

Saltelli A., Tarantola S. and Chan K., 1999. A role for sensitivity analysis in presenting the results from MCDA studies to decision-makers. Journal of Multi-Criteria Decision Analysis 8: 139-145.

Lindstedt M.R.K., Hamalainen R.P., Mustajoki J., 2001. Using intervals for global sensitivity analysis in multiattribute value trees. In: Lecture notes in economics and mathematical systems, Koksalan M. and Zionts S. (Eds.), 2001, pp.177-186.

CHAPTER 8

CONCLUSIONS

The work presented in this thesis was sparked by the need to develop new methods and tools for ranking health chemical stressors at the regional scale, able to support decision-makers in identifying priority scenarios where to focus further efforts and resources with the aim of improving environmental health protection.

For this purpose, a "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors" has been developed, able to provide as main outputs a ranking of health chemical stressors in individual sub-areas within the region of interest, a ranking of health chemical stressors at the regional level and a ranking of priority sub-areas to be further assessed. The tool implements a methodology based on the integration of three "Lines-of-Evidence" (LoEs), namely environmental contamination data, biomarkers of exposure and observed health effects. The integration of information from the environmental and the health domains has indeed been recognized as an essential approach for gaining insight into the different steps of the complex environment-health knowledge chain (even if it still remain a challenging task). A Weight-of-Evidence (WoE) approach, quantitatively implemented through a Multi-Criteria Decision Analysis (MCDA) procedure, demonstrates its strengths in merging typologies of information from different sources and in providing an effective framework where quantitative and qualitative data could be properly allocated and effectively integrated with expert judgement. The choice of MCDA assures flexibility to the ranking approach, because the procedure allows to incorporate the individual decision-maker's preference structure in the evaluation (for example through the relevance weight assigned to the LoEs). At the same time, the MCDA procedure guarantees transparency, since the obtained results could be traced back to the input datasets and considerations and assumptions underlying each assessment phase are clear and communicable.

Potentialities and weaknesses of the developed methodology have been explored through the testing of the Tool in a real case-study, focused on soil contamination and health outcomes in adolescents in the Flemish region (Belgium). The application shows that the tool can support the identification of priority chemical stressors within individual sub-areas as well as at the regional scale, and also allows to screen among sub-areas. These results demonstrate the validity of an approach that relies on different environmental and health data for supporting the identification of criticalities in the environmental health status of a region. However, according to the features of the

developed methodology, a reliable assessment should be based on the use of data truly representative for the region of interest, derived by large scale monitoring campaigns on environmental contamination, human internal exposure and health effects. Many efforts are being devoted at local, regional and national level for monitoring effectively environment and health components, however there are still many knowledge gaps and data comparability issues related to the spatial and temporal scales. Therefore, as recently highlighted also in the Parma Declaration on Environment and Health (WHO, 2010), reinforcing the monitoring of environmental and health parameters at different scales should still be considered as a priority issue at different administrative scale.

During the case-study application, the identification and selection of "guidance values" for the evaluation of environmental pollution, internal exposure and early health effects turned out to be a sensitive and challenging task. In particular, this issue is very relevant in the context of human biomonitoring data: risk-based guidance values for evaluating exposure biomarkers data are indeed currently available only for a restricted set of chemicals, and therefore much efforts are needed to use all available approaches (e.g., Biomonitoring Equivalents method) to face this lack. This consideration goes beyond the application of the methodology presented in this thesis, and it is desirable it could be rapidly addressed by the environmental health scientific community in order to fully exploit the potentialities of biomonitoring as complementary tool to assist evidence-based public health and environment measures.

This thesis also tried to deal with the thorny issue of uncertainty in health risk assessment. As an inherent component of health risk assessment, the role of uncertainty in this field is emphasized, for instance, by the complexity of the environmental health systems under observation, the high degree of "contamination" across multiple disciplines, the integration of information (often incomplete) from very different domains, the considerable knowledge gaps still existing. A literature review permitted to have a quite wide overview about how uncertainty is commonly classified, assessed and managed in environmental health risk and impact assessments. In the work presented in this thesis, the attempts to manage the uncertainty in the methodological development focused on the choice of a Fuzzy logic approach for normalization of monitoring data pertaining to the three LoEs, an approach that may support the decision-maker in accounting for the uncertainty associated to the classification process. Moreover, with the aim of investigating the role that the selection of criteria weights (LoEs' weight) may have in influencing the final ranking of health chemical stressors, a sensitivity analysis based on Monte Carlo approach has been performed.

Nonetheless, it must be recognized that an overall assessment of all uncertainties characterizing to the proposed methodology should adopt a much wider (and also resource-demanding) approach for

encompassing and considering all uncertainty sources (as described in Chapter 4) and evaluating their relative impacts on the final outputs of the proposed tool.

Finally, the application of the developed Tool to other case-studies (in different European contexts and considering different target age groups, chemical stressors and health endpoints) is advisable since it would offer the opportunity to test its flexibility and could suggest further improvements of the proposed methodology, also through the dialogue with different experts.

ACKNOWLEDGEMENTS

I kindly thank Prof. Antonio Marcomini and Dr. Andrea Critto for supervising my PhD and for following my research activity along these years.

A special thanks is due to Prof. Silvio Giove and to Alex Zabeo for their relevant contribution to the development of the MCDA methodology and its application, and for the long, very fruitful discussions we had.

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I special thank all my colleagues at the University of Venice (Dept. of Environmental Sciences and Centre IDEAS) and at CVR for sharing with me the difficulties and joys of everyday life in the office and for contributing to my personal and professional development with their constant inputs, suggestions and support.

I am heartily thankful to all my friends, in Italy and throughout the world, for supporting me and let me forget my concerns with their precious friendship.

Finally, my very special thanks go to my parents for their love and their presence in difficult moments and for supporting my choices and contributing to let me be as I am, and to Luca for being everyday so close to me.

ANNEX 1

MONITORING DATA USED IN THE FLEMISH CASE-STUDY

TABLE 1. SOIL CONTAMINATION DATA USED IN THE TESTING APPLICATION

Source of data: raw soil contamination data were provided by OVAM (Openbare Vlaamse Afvalstoffenmaatschappij - Public Waste Agency of Flanders) - contact person: Griet van Gestel.

Chemical	Elementary Geographic Unit	Soil Concentration (UCL95% of the mean) (mg/kg ds)
Benzene	Albert Canal	1,89
Benzene	Antwerp City	1,76
Benzene	Antwerp Harbour	2,61
Benzene	Fruit Area	11,21
Benzene	Ghent City	0,24
Benzene	Ghent Harbour	3,45
Benzene	Olen	4,38
Benzo(a)pyrene	Albert Canal	0,95
Benzo(a)pyrene	Antwerp City	3,19
Benzo(a)pyrene	Antwerp Harbour	2,79
Benzo(a)pyrene	Fruit Area	3,17
Benzo(a)pyrene	Ghent City	5,44
Benzo(a)pyrene	Ghent Harbour	2,47
Benzo(a)pyrene	Olen	0,21
Cadmium	Albert Canal	18,94
Cadmium	Antwerp City	1,59
Cadmium	Antwerp Harbour	3,92
Cadmium	Fruit Area	0,99
Cadmium	Ghent City	3,91
Cadmium	Ghent Harbour	8,84
Cadmium	Olen	2,26
Lead	Albert Canal	45,57
Lead	Antwerp City	586,70
Lead	Antwerp Harbour	168,00
Lead	Fruit Area	214,40
Lead	Ghent City	727,80
Lead	Ghent Harbour	651,60
Lead	Olen	176,20

TABLE 2. EXPOSURE BIOMARKERS DATA USED IN THE TESTING APPLICATION

Source of data:

Schroijen C., W. Baeyens, G. Schoeters, E. Den Hond, G. Koppen, L. Bruckers, V. Nelen, E. Van DeMieroop, M. Bilau, A. Covaci, H. Keune, I. Loots, J. Kleinjans, W. Dhooge, N. Van Larebeke, 2008. *Internal exposure to pollutants measured in blood and urine of Flemish adolescents in function of area of residence.* Chemosphere, 71: 1317–1325.

Exposure Biomarker	Unit	Elementary Geographic Unit	Concentration
Lead in blood	µg/L	Albert Canal	17,5
Lead in blood	µg/L	Antwerp City	25,1
Lead in blood	µg/L	Antwerp Harbour	23,2
Lead in blood	µg/L	Fruit Area	15,4
Lead in blood	µg/L	Ghent City	21,0
Lead in blood	µg/L	Ghent Harbour	23,4
Lead in blood	µg/L	Olen	22,6
Cadmium in blood	µg/L	Albert Canal	0,36
Cadmium in blood	µg/L	Antwerp City	0,47
Cadmium in blood	µg/L	Antwerp Harbour	0,48
Cadmium in blood	µg/L	Fruit Area	0,16
Cadmium in blood	µg/L	Ghent City	0,30
Cadmium in blood	µg/L	Ghent Harbour	0,33
Cadmium in blood	µg/L	Olen	0,32
1-0H-pyrene in urine	ng/g creatinine	Albert Canal	104
1-0H-pyrene in urine	ng/g creatinine	Antwerp City	95
1-0H-pyrene in urine	ng/g creatinine	Antwerp Harbour	122
1-0H-pyrene in urine	ng/g creatinine	Fruit Area	98
1-0H-pyrene in urine	ng/g creatinine	Ghent City	116
1-0H-pyrene in urine	ng/g creatinine	Ghent Harbour	106
1-0H-pyrene in urine	ng/g creatinine	Olen	115
t,t'-muconic acid in urine	µg/g creatinine	Albert Canal	76
t,t'-muconic acid in urine	µg/g creatinine	Antwerp City	72
t,t'-muconic acid in urine	µg/g creatinine	Antwerp Harbour	68
t,t'-muconic acid in urine	µg/g creatinine	Fruit Area	71
t,t'-muconic acid in urine	µg/g creatinine	Ghent City	72
t,t'-muconic acid in urine	µg/g creatinine	Ghent Harbour	70
t,t'-muconic acid in urine	µg/g creatinine	Olen	73

TABLE 3. EARLY HEALTH EFFECTS DATA USED IN THE TESTING APPLICATION

Source of data:

- **Sex and thyroid hormones:** from Croes K., W. Baeyens, L. Bruckers, E. Den Hondd, G. Koppend, V. Nelene, E. Van de Mieroope, H. Keune, W. Dhooge, G. Schoeters, N. Van Larebeke, 2009. *Hormone levels and sexual development in Flemish adolescents residing in areas differing in pollution pressure.* International Journal of Hygiene and Environmental Health, 212 (6): 612-625.
- **Asthma and allergies** data: data from the Flemish Biomonitoring Programme 2002-2006, provided by Elly den Hond (VITO).

Health Effect Category	Health Effect Indicator	Unit	Elementary Geographic Unit	Value	Monitored groups
Thyroid Hormones	TSH	mlU/L	Antwerp City	2,18	Boys and girls
	TSH	mlU/L	Antwerp Harbour	1,96	Boys and girls
	TSH	mlU/L	Fruit Area	2,27	Boys and girls
	TSH	mlU/L	Olen	2,29	Boys and girls
	TSH	mlU/L	Ghent City	2,33	Boys and girls
	TSH	mlU/L	Albert Canal	2,36	Boys and girls
	TSH	mlU/L	Ghent Harbour	2,10	Boys and girls
	free T4	ng/dL	Antwerp City	1,24	Boys and girls
	free T4	ng/dL	Antwerp Harbour	1,23	Boys and girls
	free T4	ng/dL	Fruit Area	1,25	Boys and girls
	free T4	ng/dL	Olen	1,26	Boys and girls
	free T4	ng/dL	Ghent City	1,25	Boys and girls
	free T4	ng/dL	Albert Canal	1,25	Boys and girls
	free T4	ng/dL	Ghent Harbour	1,25	Boys and girls
	free T3	pg/ml	Antwerp City	3,91	Boys and girls
	free T3	pg/ml	Antwerp Harbour	3,93	Boys and girls
	free T3	pg/ml	Fruit Area	3,85	Boys and girls
	free T3	pg/ml	Olen	3,98	Boys and girls
	free T3	pg/ml	Ghent City	3,83	Boys and girls
	free T3	pg/ml	Albert Canal	3,92	Boys and girls
	free T3	pg/ml	Ghent Harbour	3,99	Boys and girls

Sex Hormones	Testosterone	ng/dL	Antwerp City	388	Only boys
	Testosterone	ng/dL	Antwerp Harbour	415	Only boys
	Testosterone	ng/dL	Fruit Area	405	Only boys
	Testosterone	ng/dL	Olen	419	Only boys
	Testosterone	ng/dL	Ghent City	413	Only boys
	Testosterone	ng/dL	Albert Canal	362	Only boys
	Testosterone	ng/dL	Ghent Harbour	398	Only boys
	Free Testosterone	ng/dL	Antwerp City	8,46	Only boys
	Free Testosterone	ng/dL	Antwerp Harbour	8,80	Only boys
	Free Testosterone	ng/dL	Fruit Area	8,82	Only boys
	Free Testosterone	ng/dL	Olen	9,06	Only boys
	Free Testosterone	ng/dL	Ghent City	9,21	Only boys
	Free Testosterone	ng/dL	Albert Canal	7,65	Only boys
	Free Testosterone	ng/dL	Ghent Harbour	8,31	Only boys
	Oestradiol	pg/ml	Antwerp City	14,9	Only boys
	Oestradiol	pg/ml	Antwerp Harbour	14,8	Only boys
	Oestradiol	pg/ml	Fruit Area	16,2	Only boys
	Oestradiol	pg/ml	Olen	15,7	Only boys
	Oestradiol	pg/ml	Ghent City	14,8	Only boys
	Oestradiol	pg/ml	Albert Canal	15,2	Only boys
	Oestradiol	pg/ml	Ghent Harbour	13,9	Only boys
	Luteinizing Hormone (LH)	lU/ml	Antwerp City	2,75	Only boys
	Luteinizing Hormone (LH)	lU/ml	Antwerp Harbour	2,61	Only boys
	Luteinizing Hormone (LH)	lU/ml	Fruit Area	2,90	Only boys
	Luteinizing Hormone (LH)	lU/ml	Olen	2,77	Only boys
	Luteinizing Hormone (LH)	lU/ml	Ghent City	2,96	Only boys
	Luteinizing Hormone (LH)	lU/ml	Albert Canal	2,55	Only boys
	Luteinizing Hormone (LH)	lU/ml	Ghent Harbour	2,48	Only boys

Sex Hormones	Sex Hormone Binding Globulin (SHBG)	IU/ml	Antwerp City	29,1	Only boys
	Sex Hormone Binding Globulin (SHBG)	IU/ml	Antwerp Harbour	30,5	Only boys
	Sex Hormone Binding Globulin (SHBG)	IU/ml	Fruit Area	28,3	Only boys
	Sex Hormone Binding Globulin (SHBG)	IU/ml	Olen	31,6	Only boys
	Sex Hormone Bindign Globulin (SHBG)	IU/ml	Ghent City	27,2	Only boys
	Sex Hormone Binding Globulin (SHBG)	IU/ml	Albert Canal	31,0	Only boys
	Sex Hormone Bindign Globulin (SHBG)	IU/ml	Ghent Harbour	32,8	Only boys
Asthma and Allergy	Asthma (doctor diagnosed)	%	Antwerp City	9,2	Boys and girls
	Asthma (doctor diagnosed)	%	Antwerp Harbour	8,5	Boys and girls
	Asthma (doctor diagnosed)	%	Fruit Area	8,6	Boys and girls
	Asthma (doctor diagnosed)	%	Olen	6,0	Boys and girls
	Asthma (doctor diagnosed)	%	Ghent City	9,7	Boys and girls
	Asthma (doctor diagnosed)	%	Albert Canal	8,6	Boys and girls
	Asthma (doctor diagnosed)	%	Ghent Harbour	8,5	Boys and girls
	Hay fever (doctor diagnosed)	%	Antwerp City	22,3	Boys and girls
	Hay fever (doctor diagnosed)	%	Antwerp Harbour	25,2	Boys and girls
	Hay fever (doctor diagnosed)	%	Fruit Area	22,9	Boys and girls
	Hay fever (doctor diagnosed)	%	Olen	21,5	Boys and girls
	Hay fever (doctor diagnosed)	%	Ghent City	22,3	Boys and girls
	Hay fever (doctor diagnosed)	%	Albert Canal	31,4	Boys and girls
	Hay fever (doctor diagnosed)	%	Ghent Harbour	25,2	Boys and girls
	Food Allergy	%	Antwerp City	25,2	Boys and girls
	Food Allergy	%	Antwerp Harbour	29,5	Boys and girls
	Food Allergy	%	Fruit Area	22,8	Boys and girls
	Food Allergy	%	Olen	23,3	Boys and girls
	Food Allergy	%	Ghent City	27,7	Boys and girls
	Food Allergy	%	Albert Canal	27,6	Boys and girls
	Food Allergy	%	Ghent Harbour	29,5	Boys and girls

Asthma and Allergy	Eczema	%	Antwerp City	22,2	Boys and girls
	Eczema	%	Antwerp Harbour	23,6	Boys and girls
	Eczema	%	Fruit Area	22,0	Boys and girls
	Eczema	%	Olen	18,7	Boys and girls
	Eczema	%	Ghent City	21,7	Boys and girls
	Eczema	%	Albert Canal	17,0	Boys and girls
	Eczema	%	Ghent Harbour	23,6	Boys and girls
	Allergy Animals	%	Antwerp City	9,8	Boys and girls
	Allergy Animals	%	Antwerp Harbour	14,2	Boys and girls
	Allergy Animals	%	Fruit Area	10,7	Boys and girls
	Allergy Animals	%	Olen	9,6	Boys and girls
	Allergy Animals	%	Ghent City	9,6	Boys and girls
	Allergy Animals	%	Albert Canal	12,7	Boys and girls
	Allergy Animals	%	Ghent Harbour	14,2	Boys and girls
	Airway Infections	%	Antwerp City	8,6	Boys and girls
	Airway Infections	%	Antwerp Harbour	11,4	Boys and girls
	Airway Infections	%	Fruit Area	11,3	Boys and girls
	Airway Infections	%	Olen	13,9	Boys and girls
	Airway Infections	%	Ghent City	14,9	Boys and girls
	Airway Infections	%	Albert Canal	16,0	Boys and girls
	Airway Infections	%	Ghent Harbour	11,4	Boys and girls

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Studente: Elisa Giubilato Matricola: 955528

Dottorato: Scienze Ambientali

Ciclo: XXIII

Titolo della tesi[1] **:** Exploring Environmental Quality and Human Health Relationships: a Risk-based Tool for Ranking Environmental Chemical Stressors at the Regional Scale

Abstract:

The EU Environment and Health Strategy (2003) asks for the development of innovative tools for health risk and impact assessment, including screening methods suitable to identify the most critical scenarios. A "Risk-based Tool for the Regional Ranking of Environmental Chemical Stressors" has been developed to support decision-makers in the identification of priority environmental contaminants, as well as priority areas, to be further assessed. The tool implements, through a Multi-Criteria Decision Analysis procedure, a quantitative Weight-of-Evidence approach integrating data on environmental contamination, exposure biomarkers and health effects. The tool has been applied to a case-study in Flanders (Belgium), using soil contamination data and data on biomarkers of exposure and effect measured in adolescents. A Monte Carlo-based sensitivity analysis permits to investigate the role of criteria weights in influencing the final ranking of chemical stressors.

La Strategia Europea per l'Ambiente e la Salute chiede lo sviluppo di strumenti innovativi per la valutazione di rischi e impatti sanitari, inclusi metodi di screening per identificare gli scenari più pericolosi. Uno strumento per la prioritizzazione a scala regionale degli stressori ambientali chimici sulla base del rischio posto per la salute umana è stato sviluppato per supportare i decisori nell'individuare i contaminanti e le aree prioritarie da analizzare in dettaglio. Lo strumento implementa, attraverso l'Analisi Multi-Criteriale, un approccio *Weight-of-Evidence* che integra dati di contaminazione ambientale, biomarker di esposizione ed effetti sanitari. La metodologia è stata applicata ad un caso studio nella regione delle Fiandre, utilizzando dati di contaminazione del suolo e biomarker di esposizione ed effetto misurati in adolescenti. L'analisi di sensitività ha permesso di analizzare il ruolo dei pesi attribuiti ai criteri nell'influenzare il ranking finale delle sostanze.

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Matricola (se posseduta): 955528 Autore della tesi di dottorato dal titolo:

EXPLORING ENVIRONMENTAL QUALITY AND HUMAN HEALTH RELATIONSHIPS:

A RISK-BASED TOOL FOR RANKING ENVIRONMENTAL CHEMICAL STRESSORS

AT THE REGIONAL SCALE……

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