Risk and Environmental Modelling
Delft Institute of Applied Mathematics

Quantification of uncertainty in the dose-response relationships using structured expert judgment

Master's thesis

Patrycja Jesionek

Delft, the Netherlands
July 2006

Members of The Committee

Title: *Quantification of uncertainty in the dose-response relationship using structured expert judgment*

by
Patrycja Jesionek

Chairperson of Graduate Committee:

Prof. dr. Roger M. Cooke
Delft University of Technology, the Netherlands
Resources for Future, United States

Graduate Committee:

Prof. dr. Roger M. Cooke
Delft University of Technology, the Netherlands
Resources for Future, United States

Prof. dr. ir. Arnold W. Heemink
Delft University of Technology, the Netherlands

Dr. Margaret M. MacDowell
Argonne National Laboratory, United States

Dr. Dorota Kurowicka
Delft University of Technology, the Netherlands

Table of contents

List of tables iii

List of figures v

Acknowledgments 1

Abstract 3

1. Introduction 5

1.1. Objectives of the project 5

1.2. Outline of thesis 8

2. Federal guidance report simple risk model 11

2.1. Internal dosimetry 13

2.2. Dose and dose rate effectiveness factor 18

2.3. High-LET relative biological effectiveness factor 20

2.4. Risk coefficient for high dose and dose rate 20

3. Simple risk model for radioactive isotope iodine I^{131} 23

3.1. Biological and physical behavior of I^{131} 23

3.2. Risk per unit absorbed dose to thyroid and dose modifying factor 25

3. 3. Thyroid dose coefficient 25

3.4. Expert judgment and uncertainty in iodine biokinetic model 26

3.4.1. Elicitation process of structured expert judgment study 27

3.4.2. Formulation of the probabilistic inversion problem 28

3.4.3. Solution of probabilistic inversion to iodine biokinetic model 32

3.5. Uncertainty in the simple risk model for radioiodine 37

4. Simple risk model for radioactive isotope cesium Cs^{137} 41

4.1. Biological and physical behavior of Cs^{137} 41

4.2. Risk per absorbed dose to whole body and dose and dose modifying factor 43

4.3. Whole body dose coefficient 44

4.4. Expert judgment and uncertainty in the cesium biokinetic model 46

4.4.1. Results of expert judgment elicitation 47

4.4.2. Formulation of the probabilistic inversion problem 48

4.4.3. Solution of probabilistic inversion to cesium biokinetic model 53

4.5. Uncertainty in the simple risk model for radiocesium 56

5. Conclusions 61

APPENDICES 63

Appendix A: Structured expert judgment 65

Appendix B: Mathematical description of probabilistic inversion 72

Appendix C: Quantification of uncertainty in dose-response relationships of toxic chemical substances using structured expert judgment 79

Appendix D: Uncertainty categories in Federal Guidance Report no. 13 110

Appendix E: Estimation of parameters of the lognormal distribution 111

References 112

List of tables

Table 1: Quantiles of thyroid risk per unit absorbed dose 25
Table 2: Quantiles of retentions of I at selected times with equal (E) and performance based (P) DM 27
Table 3: Quantiles on transfer coefficients after probabilistic inversion with IPF and equal (E) and performance based (P) DM 33
Table 4: Quantiles on retention at selected times after probabilistic inversion for I with IPF and equal weight DM (E) 34
Table 5: Quantiles on retention at selected times after probabilistic inversion for I with IPF and performance based DM (P). 34
Table 6: Rank correlation matrix for transfer coefficients for I and equal weight DM 35
Table 7: Rank correlation matrix for transfer coefficients for I and performance based DM 35
Table 8: Quantiles of $U_{Thyroid}$ with equal (E) and performance based (P) DM 37
Table 9: Quantiles of dose coefficients for thyroid with equal (E) and performance based (P) DM. 38
Table 10: Quantiles of the risk coefficients for thyroid with equal (E) and performance based (P) DM. 38
Table 11: Quantiles of thyroid risk per unit absorbed dose 43
Table 12: Quantiles of retentions of Cs at selected times with equal (E) and performance based (P) DM 47
Table 13: Quantiles on transfer coefficients after probabilistic inversion with IPF and equal (E) and performance based (P) DM 53
Table 14: Quantiles on retention at selected times after probabilistic inversion for Cs with IPF and equal weight DM (E) 54
Table 15: Quantiles on retention at selected times after probabilistic inversion for Cs with IPF and performance based DM (P). 54
Table 16: Rank correlation matrix for transfer coefficients for Cs and equal weight DM 55
Table 17: Rank correlation matrix for transfer coefficients for Cs and performance based DM 55
Table 18: Quantiles of U_{WB} with equal (E) and performance based (P) DM. 57
Table 19: Quantiles of coefficients for whole body dose with equal (E) and performance based (P) DM. 57
Table 20: Quantiles of risk coefficients for whole body with equal (E) and performance based (P) DM 58

List of figures

Figure 1: Probability density and cumulative distribution functions of variable $DDREF_i$ 19
Figure 2: Decay scheme for I^{131}. 24
Figure 3: Acyclic compartment model for I^{131} with transfer coefficients and decay rate. The ULI is the upper large intestinal. 29
Figure 4: Acyclic compartment model for I^{131} with transfer coefficients. The ULI is the upper large intestinal. 32
Figure 5: The cobweb plot of the variables of the compartment model for Cs conditioned on the small values of k_{24} 36
Figure 6: Cumulative distribution function of the thyroid dose coefficient for equal and performance based DM 39
Figure 7:Cumulative distribution function of the thyroid risk coefficient for equal and performance based DM 40
Figure 8: Decay scheme for Cs^{137}. 42
Figure 9: The compartment model for Cs^{137} with transfer coefficients. The ULI is the upper large intestinal. 49
Figure 10: The compartment model for Cs^{137} with transfer coefficients. The ULI is the upper large intestinal. 51
Figure 11: The cobweb plot of the variables of the compartment model for Cs conditioned on large vales of c_{12} 56
Figure 12: Cumulative distribution function of whole body dose coefficient for equal and performance based DM 59
Figure 13: Cumulative distribution function of whole body risk coefficient for equal and performance based DM 60

Acknowledgments

I wish to express a special gratitude to my supervisor, Prof. dr. Roger M. Cooke, for giving me the opportunity to take part in Risk and Modelling program, for his support, insightful comments and helpful advices.

I am also grateful to my parents, sister for their understanding and support they provided me through my entire life. And in particular I must acknowledge Krzysztof without his endless love and encouragement I would not have finished this thesis.

I would also like to thank my colleagues from TUDelft for the time we have had together during these two years.

Patrycja Jesionek

Abstract

The main aim of radiation protection is to prevent adverse health effects form radiation exposure and to enable people to benefit from radiation sources at the smallest level of risk. Radiation risk is estimated based on quantitative models that relate the radiation dose and the response in the exposed population. These models represent the dose-response relationships.

The greatest uncertainty in the estimation of radiation risk is comes form incomplete and sparse databases on parameters of the risk model. For that reason uncertainty analysis on this model based on reliable data concerning its parameters is performed.

In this thesis the application of structured expert judgment for deriving the quantitative data for radiation risk models is described. In our particular research, experts' assessments are used to quantify the uncertainty in the population-averaged cancer mortality risk coefficients for intake of two selected radioelements – radioactive isotopes of iodine and cesium. The crucial part of the study involves gathering structured experts judgment data from relevant studies, analyzing and combining experts' individual assessments. This enables to represent the uncertainty in observable and measurable quantities.

Cancer mortality risk coefficients are calculated based on predictions of biokinetic, dosimetric and radiation models. In this project the parameters of the biokinetic models are regarded as the largest contributors to the uncertainty in the cancer mortality risk coefficients. Since they are not observable, they cannot be directly queried by experts. In this situation, the method that extracts the information on uncertain parameters based on experts' combined assessments on potentially measurable quantities has to be used. The method known as probabilistic inversion technique is used for that purpose.

The calculated uncertainties in the cancer mortality risk coefficients for ingestion of radioiodine and radiocesium are presented and compared with the uncertainties reported in technical guidance published by the U.S. Environmental Protection Agency. This comparison reveals that the uncertainties obtained with structured expert judgment and

probabilistic inversion are larger than subjective judgments made by the authors of the technical report.

The advantage of methodology presented here is that it can be applied to quantify the radiation risk for many radioactive elements and also to estimate the lethal consequences in humans exposed to various toxic chemical substances.

1. Introduction

Radiation is an inherent factor of the environment. Each person is continually exposed to radiation from various natural and man-made sources. It is evident that we cannot stop this radiation, but we can control it.

Governmental agencies are responsible for protecting the general public and workers against loss of life and adverse health effects form radiation exposure. They are charged to formulate and implement the radiation rules and regulations. Regulatory decisions are supported by technical and scientific information for radiation dose and risk assessment provided by specialized organizations and institutions. The most active organizations are the International Commission on Radiological Protection (ICRP), the National Council on Radiation Protection and Measurements (NCRP), the U.S. Environmental Protection Agency (the U.S. EPA) and Committee on the Biological Effects of Ionizing Radiation (BEIR).

Radiation risk is estimated based on quantitative models whose parameters can be highly uncertain, which in turn can influence the regulatory decisions. In addition, the experimental databases on these parameters are usually poor and/or not available. For these reasons, uncertainty analysis has been carried out on these risk models in order to support the regulatory decisions. In situation when substantial uncertainty impacts on decision processes and necessary datasets are sparse or not available, the structured expert judgment as a type of scientific data is sought.

1.1. Objectives of the project

The main purpose of this thesis is

(1) to quantify the uncertainty in the cancer mortality risk coefficient for intake of radionuclides with use of structured expert judgment, and

(2) to compare the uncertainty from structured expert judgment with the uncertainty reported in Federal Guidance Report no. 13 (EPA, 1999).

Federal Guidance Report no. 13 (FGR no. 13) is a document issued by the U.S. Environmental Protection Agency (the U.S. EPA). It provides a methodology for calculating the risk coefficients and tabulates their values for more than 800 radionuclides. The risk coefficient for intake of radionuclides in air, food or water is defined as the probability of radiogenic cancer mortality or morbidity per unit activity ingested or inhaled. The risk coefficient is specific to radionuclide, the environmental medium and mode of exposure (inhalation, ingestion). It can be interpreted as the population average probability of dying (mortality) from or contracting (morbidity) a cancer to an average member of the population exposed throughout life to constant concentration of a radionuclide in the environmental medium.

The computational approach used in FGR no. 13 to calculate the risk coefficients is complex and requires many steps. The risk coefficients were derived based on time-, age- and gender-dependent models representing characteristics of the U.S. population (mortality and usage of air, food and water), biological behavior of elements in different body organs (or/and tissues), the radiation doses to these organs (or/and tissues) and the lifetime cancer risk per unit dose to these organs (or/and tissues). However, uncertainty in the risk coefficients exists due to uncertainties in the predictions of biokinetic, dosimetric and radiation risk models following model structures, incomplete datasets concerning humans, extrapolation from one population to another, etc.

FGR no. 13 contains the estimates of uncertainty in risk coefficients for selected radionuclides and modes of exposure provided based on subjective judgments of the authors of this report. These judgments were obtained from a sensitivity analysis in which various combinations of uncertainty contributors (mentioned above) were used to provide alternative risk coefficients. The sensitivity analysis enabled them to characterize the uncertainty in the risk coefficient in terms of lower and upper bounds X and Y, such that the true value of the risk coefficient is greater than X and lower than Y with probability 90%. The ratio Y/X was then used to assign to risk coefficient one of five uncertainty categories, identified by capital letters A-E. The categories are ordered with respect to increasing uncertainty, where categories A and E represent the narrowest and widest estimations, respectively. The table presenting the possible values of ratios and corresponding to them uncertainty categories is placed in Appendix D.

The standard method of assigning the uncertainty to a quantitative model consists in specifying and propagating the uncertainties associated with the model input parameters. This procedure is difficult to apply for the complex calculation approach presented in FGR no. 13. To circumvent this problem, FGR no. 13 proposed a simpler dose-response model for risk coefficients whose predictions are consistently in the agreement with those of the general method and whose components are easier to asses. This model, called simple risk model, is a mainstay of present study and is briefly described in Chapter 2.

In the simple risk model the risk to a target organ per unit activity for each type of radiation (low- and high-LET) is expressed as a product of the following components: the risk per absorbed dose received by target organ for low-LET high dose and dose rate, the dose coefficient (absorbed dose in target organ per unit activity) and dose modifying factors (dose and dose rate effectiveness factor and relative biological effectiveness). All these components are dependent only on the target organ, but independent of the age at exposure and gender of the exposed individual. The results of the uncertainty analysis on this model were published in 2001 by (D. Pawel et al., 2001). The uncertainty in the risk per unit absorbed dose was quantified based on the expert judgment elicitation performed by Nuclear Regulatory Commission and Commission of European Communities (the U.S. NRC/CEC, 1998), the probability distribution of dose modifying factors were taken from (EPA, 1999).

The largest effort is to quantify the uncertainty in the site- and radionuclide-specific dose coefficients since it involves a consideration of uncertain biokinetic and dosimetric models, parameters and assumptions. The steps undertaken by (D. Pawel et al., 2001) to provide the uncertainty distribution to dose coefficients can be summarized as follows. First, the results of the detailed sensitivity analysis enabled to identify the dominant components of biokinetic and dosimetric models. Those were fraction of radionuclide reaching the stomach absorbed to blood, specific energy (or specific effective energy) and systemic models. Then for each radionuclide different variants of each of those components were constructed. For specified target organ, each of systemic models and variants of two remaining components the dose coefficients were calculated providing a dataset of absorbed doses. Finally, this data set was used to derive continuous distributions relating each of identified components from which the doses were simulated.

The uncertainty analysis on the simple risk model presented in the present report is to large extent based on the indications given in (D. Pawel et al., 2001). However, we try to utilize more of structured expert judgment data from the U.S. NRC/CEC reports and thus the uncertainty in the site-specific dose coefficient will be assessed with use of results of expert judgment elicitation on internal dosimetry (the U.S. NRC/ CEC, 1998).

Roughly, we assume that the largest contributors to uncertainty in the site-specific dose coefficients and ultimately in the risk coefficients are the parameters of the biokinetic models for radioisotopes, represented by transfer coefficients. We make the use of the experts' subjective assessments on observable and measurable quantities such as retention of elements at selected times in body organs after absorption to bloodstream. The uncertainty distributions of all transfer coefficients are then found via probabilistic inversion applied to combined experts' assessments for retention at selected times.

The results of the uncertainty analysis in the cancer mortality risk coefficient are presented here for ingestion of radioactive isotopes of iodine I^{131} and cesium Cs^{137}.

Under the structured expert judgment methodology experts' individual estimates may be aggregated in two different ways:

- experts' distributions are combined with equal weights,
- experts' distributions are combined with weights based on their performance.

The performance of experts can be measured statistically based on so-called calibration variables, that is, variables from their field of expertise whose true outcomes become known post hoc. In this report the results of the uncertainty analysis will be compared with respect to both combination schemes.

1.2. Outline of thesis

The main aim of thesis is to conduct the uncertainty analysis on the simple risk model for ingestion of radioactive isotopes of iodine and cesium. The report is subdivided into five chapters. Chapter 2 introduces the simple risk model, presents all its input parameters and the way in which the uncertainty in the cancer mortality risk coefficient is quantified. Chapter 3 and Chapter 4 contain the results of the uncertainty analysis in the risk coefficients for ingestion of I^{131} and Cs^{37}, respectively. Both chapters consist of five

sections of the same structure, describing (1) the properties and influence of radionuclide on human health and the corresponding mathematical model for the risk coefficient, (2) the risk coefficient for high dose and dose rate, and dose and dose rate effectiveness factor, (3) methods used to estimate the uncertainty distributions of dose coefficient. The parameters of the biokinetic models for both radioisotopes are regarded as the largest contributors to the uncertainty in the dose coefficients and ultimately in the risk coefficients. Section (4) introduces a probabilistic inversion technique as a method of converting experts' combined assessments into probability distributions over parameters of biokinetic model and (5) presents the results of the uncertainty analysis on the simple risk model in terms of probability distributions of the total number of nuclear transformations, dose and risk coefficients. Chapter 5 draws final conclusions on issues covered in this thesis.

The uncertainty analysis in the mortality risk coefficients for both designated radionuclides is performed based on the structured expert judgment and probabilistic inversion technique. For that reason the explanation of the basic concepts of these methods are not included in the main report, but they are presented separately in Appendices A and B.

Human health and life are endangered not only by effects of radiation, but also by incidental releases of chemical substances into environment. The risk of adverse health effects associated with toxic chemical release is quantified based on the dose-response relationships (expressed in form of probit functions) which correlate the doses of chemical materials to the responses in the exposed population. Dose-response relationships allow determining the dose levels realizing different response levels and permits setting regulatory rules.

The estimation of lethal probit relation for humans is based on experiments and data of the toxicity of chemicals. The lack of human data and difficulties in extrapolation from animals to human beings make lethal dose-response relationships uncertain. Similarly to study on the risk coefficients, the uncertainty in the dose-response relationships for toxic chemical substances can be quantified with use of structured expert judgment. Appendix C presents the results of our separate study concerning the uncertainty analysis in the probit relations for acute inhalation of ammonia, acrylonitrile and sulphur trioxide. This study is

not a part of this thesis. It serves an example of alternative use of structured expert judgment in supporting regulatory decisions.

2. Federal guidance report simple risk model

The main goal of this study is to quantify the uncertainty in the cancer mortality risk coefficients for ingestion of radionuclides. This chapter presents the simple risk model proposed in FGR no. 13, describes all its components and provides the sketch of uncertainty analysis.

The cancer mortality risk coefficient for intake of radionuclide is defined as the risk (probability) of dying from cancer per unit activity of a radionuclide ingested with food or water. The risk coefficient is specific to target organ (or tissue), radionuclide, environmental medium and exposure mode, and can be applied to an average member of the population.

The adverse impact of radiation on the absorbing tissue and ultimately on health of the exposed individual depends both on amount of radiation absorbed in the organ and type of radiation. For specified organ i (or tissue) and internal type of exposure the mortality risk per unit activity for each type of radiation (high- or low-LET[1]) is expressed by following formula

$$\mathrm{CancerMortalityRisk}_i = \frac{d_i}{\mathrm{DDREF}_i}\ \mathrm{RBE}_i D_i\ R_i \qquad (1)$$

where

- D_i and d_i are high-LET and low-LET absorbed doses to tissue i integrated over 20 years following acute intake of radionuclide by an average adult, i.e. committed equivalent doses per unit intake or dose coefficients [$Gy \cdot Bq^{-1}$],
- R_i is the lifetime age- and gender-averaged cancer mortality risk estimate for tissue i for low-LET uniform irradiation of the whole body at high dose and dose rate, i.e. risk per absorbed dose received by tissue i for low-LET high dose and dose rate radiation [Gy^{-1}],
- DDREF_i is the low-LET dose and dose rate effectiveness factor for tissue i,
- RBE_i is the high-dose relative biological effectiveness for tissue i.

[1] LET (linear energy transfer) is the average energy loss per unit path length of ionising charged particle.

In accordance with (Pawel et al., 2001) the following assumptions on the simple model have been made:

- the dose coefficients D_i and d_i are independent of individual's age at exposure,
- the uncertainty concerning R_i, high dose RBE_i and $DDREF_i$ are independent of the radionuclide and mode of exposure.

The uncertainty analysis on the simple risk model consists in assessing uncertainty in each parameter occurring in the equation (1). The idea is to assign the continuous distributions to parameters R_i, D_i, d_i, high dose RBE_i and $DDREF_i$ and then to propagate them through the simplified risk model using random sampling methods to obtain the uncertainty distribution of the cancer mortality risk coefficient.

The dose coefficients are determined based on biokinetic and dosimetric models whose parameters are recognized as main contributors to the uncertainty in the risk coefficient. In present study, the assignment of uncertainty to the values of the dose coefficients and risk per absorbed dose is based on results of recent expert judgment studies from the U.S. NRC/CEC reports on internal dosimetry and late health effects. The distributional assumptions for the dose modifying factors, $DDREF_i$ and RBE_i, are the same as those made in EPA report on uncertainties in risk from uniform, low-LET irradiation of the whole body; see (EPA, 1999).

The successive sections of this chapter are addressed to introduce all input parameters to the simple risk model (1) and to indicate the sources of uncertainty.

2.1. Internal dosimetry

This section presents and briefly describes the method of calculating the committed equivalent dose in target tissue (or organ) per unit activity intake. This dose measure is also known as the dose coefficient for a given organ. The methodology submitted is based on the ICRP publication; see (ICRP, 1979, 1995).

When considering the internal exposure to radioactive material one needs to take into account that radionuclide inside the body may lodge or migrate to a particular body organ from where it may continue to irradiate other body organs, it may decay or be excreted. Moreover, different types of radiation emitted during nuclear transformations of a radionuclide are more or less efficient in producing damage in tissue. Furthermore, a radionuclide taken into body will impart a dose to a person not only for the first year of intake, but in all the following years until the radionuclide decays or is eliminated. These complex and time-varying biological and physical situations and the long-lasting effect during specified time period following intake are included in the concept of committed equivalent dose. The dose coefficient is then defined as committed equivalent dose per unit activity intake.

For a given radionuclide and cancer site the dose coefficient is expressed as the absorbed dose for organ (or tissue) accumulated over 20 years due to intake of a radionuclide per unit activity ingested. The dose coefficient is usually expressed in unit of $Gy \cdot Bq^{-1}$ or $Sv \cdot Bq^{-1}$. It can be interpreted as the total energy deposited by radiation in the target[2] region divided by the mass of that region. Total energy deposited is calculated as a product of the total number of the nuclear transformations occurring in the source[3] regions over 20 years and the amount of energy deposited in the target region by each nuclear transformation.

The number of nuclear transformations that occur in each source region over 20 years is calculated as the integral of the time-dependent activity residing in that organ (known as retention function). Thus it reflects the metabolism of the radionuclide in the human body what is predicted by the biokinetic (compartment) models. These models are

[2] Target region is any tissue or organ of the body in which the radiation is absorbed.
[3] Source region is a tissue or organ of the body where the activity of the radionuclide is located or can migrate to other body parts.

based on the assumption that the human body consists of finite number of separate component parts, called compartments, between which the element (both stable and unstable) is moving. In agreement with the physical laws and metabolic data for radioactive element, the loss of radionuclide activity from any compartment is described in terms of first order differential equations with biological and physical (decay) removal rates being parameters.

Total energy deposited in the target region per nuclear transformation occurring in the source region is estimated based on dosimetric model. The difficulty in estimating the dose to members of the public is not only characterization of the emitted type of radiations, but also variability in human bodies (e.g. the mass and geometry of source region and regions around it, the place of energy deposition). To achieve the agreement on standards in radiation protection and to be able to compare the different radiation dose assessments, the reference individual representative of members of a given population was created. The standard parameters of this standard man are: age between 20 - 30 years old, body mass 70 kg and height 170 cm.

The committed equivalent dose is defined as the absorbed dose to target organ T accumulated over 20 years due to intake of a radioactive material and is given by following formula

$$H_{T,\,20} \quad U_S \quad SEE\ (T \quad S) \tag{2}$$

where

- U_S is cumulated activity of radioelement in the source region S 20 years following intake [Bq·day]; or the total number of nuclear transformations (nt) of given radionuclide in source region S over 20 years following intake [nt],
- SEE (T S) is the specific effective energy for radiation emitted by radionuclide deposited in target organ T per nuclear transformation in S [MeV·g^{-1}·nt^{-1}].

The specific effective energy represents the decay characteristics of the radionuclide and is defined as the energy of radiation deposited in target region T per unit mass of T as a result of the nuclear transformation of a radionuclide occurring in the source region S. For a given radionuclide and target organ T it is expressed as

$$SEE(T \leftarrow S) = \frac{\sum_i Y_i E_i AF_i(T \leftarrow S)}{M_T} \tag{3}$$

where the summation is over all types of emitted radiation in S and

- M_T is the mass of the target region (g),
- $AF_i(T \leftarrow S)$ is the absorbed fraction denoting the fraction of energy absorbed in T per nuclear transformation in S for radiation type i (unitless constant),
- Y_i is the yield of radiation of type i per nuclear transformation of the radionuclide that determine the number of particles per nuclear transformation with average energy of radiation i equal to E_i. Product $Y_i \cdot E_i$ is called the total energy of radiation type i per nuclear transformation [$MeV \cdot nt^{-1}$].

The kinetic energy of non-penetrating radiations (beta particles or discrete electrons) is assumed to be completely absorbed in the source region S. The exception is made when S is the part of the walled organ or when S and T are in close proximity e.g. in the respiratory tract or skeleton. For solid regions (all organs except of regions in the respiratory tract and in skeleton) the values of the absorbed fraction (AF) established and expresses as

$$AF(T \leftarrow S) = \begin{cases} 1, & \text{for } T = S \\ 0, & \text{for } T \neq S \text{ and } S \neq BT \\ \frac{M_T}{M_{BT}}, & \text{for } S = BT \end{cases},$$

where BT corresponds to the systemic tissue of the body with mass expressed as M_{BT} and M_T is the mass of the target region.

The dose coefficient for a given radionuclide and organ T, denoted as $h_{T,20}$, is the committed equivalent dose per unit activity intake of 1 Bq. In order to express the dose coefficient in units of $Sv \cdot Bq^{-1}$ one needs to convert the unit of committed equivalent dose[4] to Sv ($J \cdot kg^{-1}$). As a result we get

$$h_{T,20} \quad 1.6 \quad 10^{10} \quad 86400 \quad U_S \quad SEE\ (T \quad S) \qquad [Sv \cdot Bq^{-1}] \tag{4}$$

A dominant source of uncertainty in the ingestion dose coefficient is the variation of parameters of biokinetic models since their predictions are often made with use of incomplete and sparse data. Moreover, some of parameter values do not represent measurable quantities. This makes the uncertainty analysis on dose coefficients hard and difficult task. As a matter of fact, the biokinetic parameters are necessary to estimate the variable U_S. Thus, in present study the great amount of attention and effort will be focused on the uncertainty analysis of this variable.

In our study we try to utilize the results of expert judgment study from the report of the U.S. Nuclear Regulatory Commission (NRC) and the Commission of European Communities (CEC) on internal dosimetry [1]. The publication contains the results of the expert judgment elicitation process concerning the dose coefficients for inhalation and ingestion of selected radionuclides by children and adults. The uncertainty was addressed to parameters of biokinetic and dosimetric models. For each variable of interest, assumed to be measurable quantity, the nine[5] best experts gave the 5th, 50th and 95th percentile of its distribution. As a part of the elicitation session, experts were asked to assess directly (if possible) the distribution of the dose coefficient to specific organs for selected radionuclides. In addition, they provided the rationale of methodology they applied and indicated the dependencies between elicited variables (reported in separate publication).

---

[4] 1 MeV = $1.6 \cdot 10^{-13}$ J,
1 g = $10^{-3} \cdot$ kg,
1 Bq·d = Bq·24h·d^{-1}·3600s·h^{-1} = 86400·Bq·s = 86400·nt.

[5] Two out of nine experts worked jointly.

Unfortunately, experts' joint estimates on dose coefficients are in large disagreement with assessment of each individual expert. Therefore, one should not recognize them as reliable. Moreover, the absorbed doses for given tissues were integrated over a period of 50 years. Thus, they cannot be directly used for purposes of this report. On the other hand, in present study we make a use of other elicited quantities for which the results are more adequate. Out of seventeen queried variables, the one concerning the retention of selected elements in different parts of the human body at specified times after entry into bloodstream is of our greatest interest. It constitutes the mainstay of the assessment of uncertainty in parameter U_S and ultimately in the dose coefficient.

In the U.S. NRC/CEC report the aggregation of experts' opinions was based on equal weighting method since all experts' ways of reasoning and modeling approaches were assumed to be equally plausible without raising the question of experts' performance. More clearly, the combined distribution on each elicitation variable, called the equal weight decision maker (DM) distribution, is represented as the weighted sum of the individual expert's distributions, where the experts' weights are the same and equal to reciprocal of the number of experts taking part in a study. The tool used to combine experts' assessments was dos program Expo.

Another way to assign the uncertainty to each query variable is to attach to each expert weight that represents his/her performance as probability assessor on "seed variables". These are variables from the experts' field whose real values are become known to experts *post hoc*. Seed questions serve the purpose of quantifying the performance of each expert and to evaluate and validate the combination of groups' judgments. As a result of this combination the distribution of performance based decision maker (DM) is created.

The seed questions for internal dosimetry panel were defined in terms of five case studies concerning the exposure to various radionuclides such as Pu^{239}, Pu^{244}, Am^{241}, Np^{237}, Po^{210}, ^{60}Co, ^{137}Cs and toxic substance $^{160}Tb_4O_7$. For more details see [1].

There are apparent advantageous of performance based combination in rational decision making. Therefore, in present study the results of experts' elicitation session combined according to this scheme are included in uncertainty analysis on dosimetry. The distributions of variables of interest are calculated with help of Excalibur software package (developed at Delft University of Technology) which allows the quantile experts' estimates

for continuous uncertain variables and combine them according to classical model as proposed by Cooke [8]. It is a newer version of Expo dos program used in studies of the U.S. NRC and CEC.

2.2. Dose and dose rate effectiveness factor

The epidemiological studies such as that of Japanese bomb survivors have collected data concerning individuals receiving acutely high doses from low-LET type of radiations. It revealed that the biological effect of radiation at high dose and dose rate for most cancer sites is greater than at low dose and dose rate. To account for this the dose and dose rate effectiveness factor is used to extrapolate the risk of cancer per unit dose at high dose and dose rate to the risk per unit dose at low dose and dose rate.

In present study, based on recommendations of EPA (EPA, 1999) the uncertainty in $DDREF_i$ for all cancers combined (except leukemia) and for uniform whole-body irradiation is represented by mixture of two distributions: uniform distribution on interval [1,2] and exponential distribution for values of $DDREF_i$ grater than 2. This setup was made based on evidence from animal, laboratory and limited epidemiological studies applied to competing dose-response models. The resulting density function of $DDREF_i$ is expressed as

$$f(x) \quad \begin{matrix} 0.5, & 1 \quad x \quad 2 \\ 0.5 \exp(2 \quad x), & x \quad 2 \end{matrix} .$$

Below we present the plots of the probability and cumulative distribution functions for $DDREF_i$. The 5^{th}, 50^{th} and 95^{th} percentiles of that distribution are respectively 1.1, 2 and 4.4.

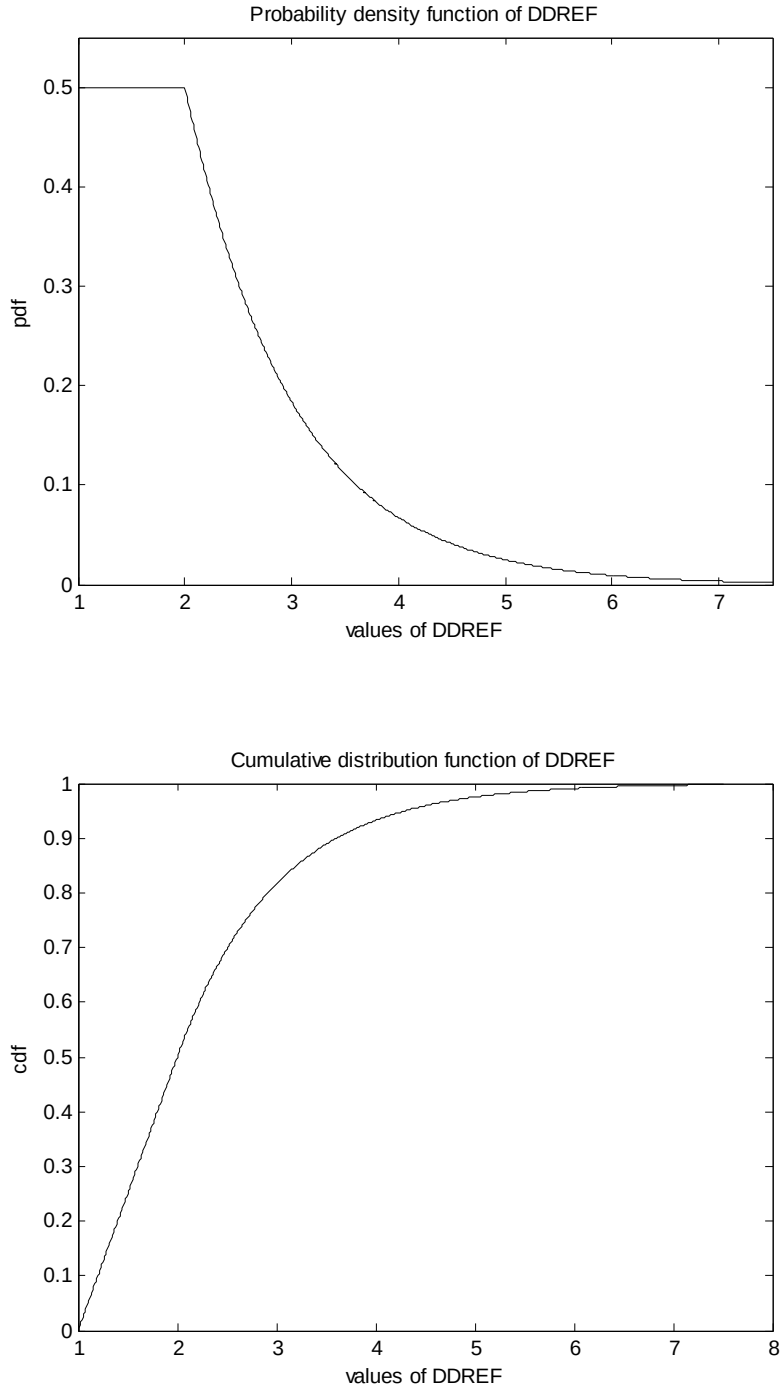


Figure 1: Probability density and cumulative distribution functions of variable $DDREF_i$

2.3. High-LET relative biological effectiveness factor

The radiological data indicates that the high dose of high-LET radiation has bigger biological effect to specific organ than the same dose of low-LET radiation. Thus, for most cancer sites the risk per low dose for low-LET radiation is calculated based on the estimation of risk per high dose of high-LET radiation and high-LET RBE_i. In general, the high-LET RBE_i refers to the relative biological effectiveness of alpha radiation in producing fatal cancers compared with 200 kV X- rays when both are received by organ at high doses.

The uncertainty distribution of parameter high-LET RBE_i adopted in this study is the same as in EPA report (EPA, 1999). It was established based on the ranges of values provided form experimental and epidemiological data on the relative carcinogenic effects of low- and high-LET radiation.

For most cancer (except leukemia) the uncertainty in the high-LET RBE_i is represented by the lognormal distribution with median $\sqrt{50}$ and 90% probability assigned to interval spanned between 2.5 and 20.

2.4. Risk coefficient for high dose and dose rate

The cancer morality risk per unit absorbed dose received by cancer site i, denoted as parameter R_i in the simple risk model (1), is defined as the average[6] site-specific risk (probability) of dying from cancer as a result of whole body uniform irradiation at high dose and dose rate of low-LET radiation.

In this report, the uncertainty on the values of parameter R_i is determined based on results of expert judgment elicitation on late health effects of radiation [2]. This study was also a part of the joint work of the U.S. NRC and CEC.

Ten experts[7] taking part in the study on late health effects were asked to give their subjective estimates in form of median values and 90% confidence bounds on measurable and observable quantities. Elicitation questions concerned the site-specific cancer mortality

[6] Average risk means age- and gender-averaged risk or simply risk per person.
[7] Two out of ten experts gave joint answers.

and morbidity risks per unit absorbed dose for general population and children represented as functions of age at exposure, time after exposure, dose and dose rate in case of low-LET and high-LET types of radiation. The cancer sites considered by experts were: bone, colon, breast, leukemia, liver, lung, pancreas, skin, stomach, thyroid and all other cancer sites, all cancer sites.

In addition, a set of seed questions was prepared and delivered to experts. However, experts' estimates on these questions are not available so far. Detailed information about questionnaires and lists of experts can be found in [2].

As a part of the exercise, experts were asked to asses the uncertainty in the number of radiation-induced cancer deaths over a lifetime (following the population up until it has become extinct) in a typical population of a hundred million persons ($5x10^7$ male, $5x10^7$ female), each receiving a whole body dose of 1 Gy low-LET (gamma) radiation at a uniform rate over 1 minute.

In simple risk model (1) variable R_i is expressed in unit of risk per person. Therefore, experts' individual assessments were first divided by number of population members, i.e. 10^8 and then combined using equal weight aggregation scheme providing assessments for so-called equal weight decision maker (DM).

In the agreement with (Pawel et al., 2001) the lognormal distribution is chosen to represent the uncertainty in parameter R_i. This distribution is constructed in such a way that it realizes the quantile points of distribution of equal weight decision maker.

In general, the lognormal distribution is characterized by two parameters μ R and $\sigma > 0$. They are expresses as $\ln(z_{50})$ and $\frac{\ln(\frac{z_{95}}{z_{50}})}{1.6449}$, where z_{50} and z_{95} are respectively 50^{th} and 95^{th} quantiles of variable Z possessing lognormal distribution. The derivation of parameters of lognormal distribution based on its quintiles is presented in Appendix E.

3. Simple risk model for radioactive isotope iodine I^{131}

In this chapter we present the method of quantification of uncertainty in the cancer mortality risk coefficient from ingestion of radioactive isotope of iodine, I^{131}. It describes the biological and physical properties of radioiodine, provides the model for cancer mortality risk coefficient for thyroid and characterizes all its input parameters. At the end the outcomes of the uncertainty analysis in terms of probability distributions of the number of nuclear transformations over 20 years, dose coefficient and risk coefficients are shown and discussed.

3.1. Biological and physical behavior of I^{131}

The radioactive isotope of iodine I^{131} is present in the environment mainly due to nuclear explosions (weapon testing fallout). It is concentrated in the seawater, grass, leafy vegetables and is also ingredient of the table salt. Therefore the exposure to this radionuclide is almost straightforward. The radioiodine may be ingested directly by people or indirectly due to intake of milk or meat produced by exposed animals. The amount of radioiodine in the environment is relatively low because of it short radiological half-life[8] of time 8.04 days.

After the contaminated iodine is ingested it rapidly moves through gastrointestinal tract from where it is almost entirely absorbed into bloodstream while the rest is excreted in feces. Radioiodine assembles mainly in the thyroid gland. For that reason this organ receives the biggest amount of radioiodine's activity. In adults the biological half-life[9] of radioiodine for thyroid amounts to 80 days. During this time the radioactive decay of I^{131} may appear. If the decay occurs in the thyroid then it does the biggest harm in form of the thyroid nodules and thyroid cancer. I^{131} decays by beta emission and associated gamma emission until the stable isotope of xenon Xe^{131}_{54} is reached. The decay scheme for radioiodine is presented in Figure 1.

[8] Radiological half-life of a radioactive material is defined as the time required to lose 50% of its activity by spontaneous nuclear transformations.

[9] Biological half-life of radioactive material is defined as the time required to reduce the activity of radioactive material by 50% without decay and additional supply of this material.

Thyroid gland is responsible for production of two important hormones triiodothyronine (T3 containing three atoms of iodine) and thyroxin (T4 containing four atoms of iodine) that assure the normal growth, development and metabolism of body cells. The biosynthesis of these hormones is performed only with the presence of iodine which is not produced in the human body. The deficiency of the iodine in human organism predominantly leads to thyroid gland diseases. In medicine, the low doses of radioiodine are used to reduce the activity of the thyroid, lowering the production of hormones while the high doses treat the thyroid cancer.

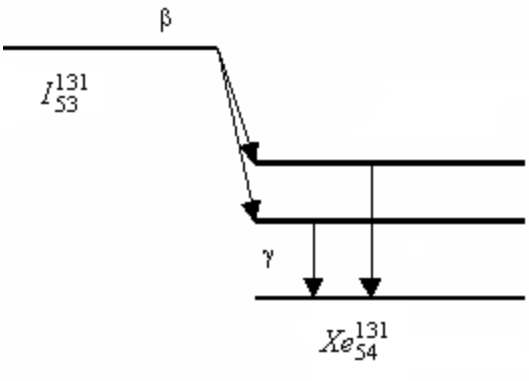


Figure 2: Decay scheme for I^{131}.

As noticed above, radioactive isotope of iodine is an emitter of low-LET radiations and its highest dose is accumulated in thyroid. As a result the mortality risk coefficient following ingestion of radioiodine is calculated only for this organ according the following formula

$$\text{CancerMortalityRisk}_{\text{Thyroid}} = \frac{d_{\text{Thyroid}}}{\text{DDREF}_{\text{Thyroid}}} R_{\text{Thyroid}} \quad [\text{Bq}^{-1}] \tag{5}$$

3.2. Risk per unit absorbed dose to thyroid and dose modifying factor

As mentioned in Chapter 2, experts taking part in the study on the late health effects performed by the U.S. NRC and CEC provided the quintile points (5%, 50%, 95%) of their subjective distributions of age- and gender-averaged site-specific cancer mortality risk for low-LET uniform irradiation of the tissue at high dose and dose rate. Table 1 shows the 5^{th}, 50^{th} and 95^{th} quantiles of resulting distribution of variable $R_{Thyroid}$ representing the estimates of equal based decision maker.

quantile	5%	50%	95%
$R_{Thyroid}$[10]	6.94E-07	5.86E-04	7.08E-03

Table 1: Quantiles of thyroid risk per unit absorbed dose

Moreover, the parameters μ and σ of the lognormal distribution assumed to represent the uncertainty in the $R_{Thyroid}$ equal to -7.4422 and 1.5158, respectively.

In order to assess cancer mortality risk for low doses the site-specific dose and dose rate effectiveness factor has to be used. The probability distribution of variable $DDREF_{Thyroid}$ corresponds to a piecewise-linear distribution as defined in section 2.2 of Chapter 2.

3.3. Thyroid dose coefficient

Thyroid is an organ of the human body in which the activity of radioiodine is lodged and deposited. Thus, thyroid is at once source and target organ for which the dose coefficient is calculated according to formula (6)

$$h_{Thyroid,\,20} \quad 1.6 \quad 10^{\,10} \quad 86400 \quad U_{Thyroid} \quad SEE\,(Thyroid \qquad Thyroid\,) \tag{6}$$

[10] The unit of $R_{Thyroid}$ is cancer deaths per person-Gy. Gy is equivalent to Sv.

It should be noted that $h_{Thyroid,20}$ corresponds to the parameter $d_{Thyroid}$ of the simple risk model (5).

In order to estimate the thyroid dose coefficient it is necessary to assess the number of nuclear transformations of radioiodine in thyroid $U_{Thyroid}$ and the specific effective energy SEE. The number of nuclear transformations of I^{131} occurring in the thyroid over 20 years (equivalently 7300 days) following intake is assumed to be the only one uncertain variable in the dose coefficient model (6). This parameter is also the only varying in time. Thus, in further analysis we will refer to it as $U_{Thyroid}(7300)$ or just $U_{Thyroid}$.

The uncertainty distribution of $U_{Thyroid}$ will be determined based on results of the expert judgment elicitation on the internal dosimetry and presented in next section. On the other hand, the specific effective energy is deterministic and is calculated beneath.

As mentioned in previous section, I^{131} is emitter of beta and gamma radiations. The total energy of beta and gamma radiations emitted[11] in the thyroid amount to 0.192 and 0.382 MeV per nuclear transformation, respectively. Furthermore, in accordance with anatomy of the reference man, the mass of the thyroid is assumed to be 20 grams[12]. Based on this information the specific effective energy is calculated as

$$SEE\ (Thyroid \leftarrow Thyroid) = \frac{0.574}{20} = 0.0287\ MeV\ g^{-1}\ nt^{-1}.$$

3.4. Expert judgment and uncertainty in iodine biokinetic model

This section centers on providing the uncertainty distribution of variable $U_{Thyroid}$. As it is already known, variable $U_{Thyroid}$ is calculated by integrating the retention function for thyroid over 20 years. The retention function represents the relation between time and the amount of activity of the radioactive material in given organ and is derived based on the biokinetic model. The main purpose of this chapter is to reconstruct and to assess the uncertainty in the retention function for thyroid using the results of expert judgment elicitation concerning internal dosimetry and to quantify the uncertainty in the variable

[11] The information about the total energy expressed as $Y_i \cdot E_i$ in equation (3) is drawn form Federal Guidance Report no. 13, Appendix G.
[12] The weights of different body organs of the reference man are taken form ICRP report [3].

$U_{Thyroid}$. The method applied to reconstruct the retention function is probabilistic inversion. First, the results of combination of experts' estimates with use of equal and performance based aggregation schemes are presented and discussed. Then, the way in which the uncertainty to values of retention function can be assigned is introduced.

3.4.1. Elicitation process of structured expert judgment study

Nine experts from internal dosimetry panel were asked to give the 5^{th}, 50^{th} and 95^{th} quintiles of their subjective distribution of the percentage of total amount of I reaching the blood retained in the thyroid as a function of time after its entry into blood. The time periods considered were: 1, 7, 30 and 90 days. Out of nine experts only six assessed the variables of interest. Providing estimates most experts took an advantage of ICRP publications (ICRP, 1979, 1990). It is worth to emphasize that experts considered only the stable iodine and were not constrained to accept any particular biokinetic model.

The results of combination of experts' assessments on the amount of iodine in thyroid 1, 7, 30 and 90 days after being administered intravenously as a single injection into blood using equal and performance based aggregation schemes are presented in Table 2 below.

quantile / t	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
1 day	0.15	0.116	0.28	0.287	0.43	0.563
1 week	0.15	0.112	0.29	0.286	0.44	0.548
1 month	0.11	0.0854	0.23	0.236	0.39	0.457
3 months	0.059	0.0415	0.15	0.154	0.28	0.366

Table 2: Quantiles of retentions of I at selected times with equal (E) and performance based (P) DM

One can observe that the distributions of equal and performance based combinations are not dramatically different. However, the uncertainty bands are narrower for performance based DM. The median estimates for both combinations are in very close proximity and mostly in the agreement with assessments of each individual expert. They also confirm the common use of predictions made by ICRP (ICRP, 1989) among experts. ICRP has used a cyclic three compartment metabolic model describing the biokinetics of iodine in adults after its entry into blood according to which the fractional uptake by thyroid is 0.3. Since the biological half-life of iodine is 80 days then its amount in thyroid after 80 days is 0.15.

Note, that for equal weight DM the amount of iodine in thyroid slowly decreases in time. However, when looking at the median estimates and 95^{th} quantiles of performance based DM (bold numbers in Table 2) one can observe that after first week since injection the amount of this element in thyroid slightly increases and in the next few weeks decreases. This can be explained by the fact that one of the best performing experts chose the same way of reasoning. Form the biological point of view such insignificant increase is not impossible, but perhaps unexpected.

The general conclusion is that distributions of retentions provided by the performance based DM are concentrated on narrower intervals than these of equal weight DM. This indicates that the performance-based retention data placed in Table 1 introduces less uncertainty to the biokinetic models.

The information provided in Table 2 cannot be directly used to quantify the uncertainty in the total number of nuclear transformations of radioiodine occurring in the thyroid since it does not take into account physical properties of radioactive material. The method applied to post-process this information is demonstrated in next subsection.

3.4.2. Formulation of the probabilistic inversion problem

In this subsection the method for quantification of uncertainty in variable $U_{Thyroid}$ based on probability distributions of the retentions at selected times given in Table 2 is presented. The uncertainty in parameter $U_{Thyroid}$ is strictly dominated by the uncertainties in the iodine biokinetic model. We aim to find the distributions over transfer coefficients of the biokinetic model that capture the uncertainties given by experts as given in Table 2.

The biological and physical behavior of unstable isotopes and the loss of the number of nuclei over time are predicted based on the compartment models. The compartment acyclic model[13] for radioiodine is presented in Figure 2. The compartments representing different body parts are labeled by i, i = 1, 2, 3, 4 (which appear in the right-upper corner of each box) while the flow into and out the compartments is marked by arrows.

The exchange of radioiodine between compartments is expressed in terms of transfer coefficients k_{ij} defined as a proportion of the radioactive material moved form compartment i to compartment j in unit time (d^{-1}). The equal flow going out of the model in each compartment represented by λ_1 takes into account the decay properties of radioiodine. Parameter λ_1 is called the decay rate[14] and equals 0.0862 d^{-1} for I^{131}. The compartment model presented in Figure 2 will be used to derive the retention function for I^{131}.

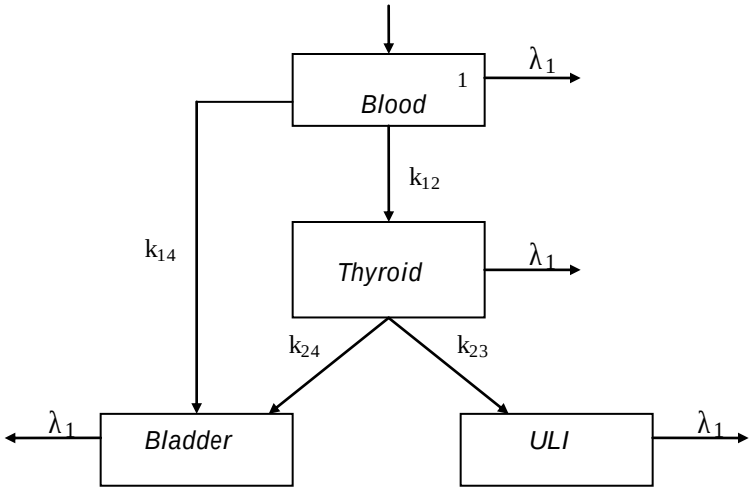


Figure 3: Acyclic compartment model for I^{131} with transfer coefficients and decay rate. The ULI is the upper large intestinal.

[13] The compartment model for radioiodine is taken from the report of the Commission of European Communities [6] and completed with decay rate.

[14] Decay rate is calculated as $\ln 2/T_{1/2}$, where $T_{1/2}$ is the radiological half-life of a radionuclide. For I^{131} the radiological half-life equals 8.04 days.

Let $m_j(t)$ denote the retention (activity) function for compartment j, j = 1, 2, 3, 4. The compartment model provides the set of first order differential equations which with appropriate boundary conditions[15] fully specifies the dynamic of movement of radioiodine between different compartments. Solution of this system for compartment 2 yields:

$$m_2(t) \quad \frac{k_{12}}{k_{12} \quad k_{14} \quad k_{23} \quad k_{24}} [\exp(\quad (\quad _1 \quad k_{23} \quad k_{24}) \quad t) \quad \exp(\quad (\quad _1 \quad k_{12} \quad k_{14}) \quad t))] \qquad (7)$$

As a result the variable $U_{Thyroid}$ is expressed as

$$U_{Thyroid} \quad \int_0^{7300} m_2(t)\,dt \quad \frac{k_{12}}{k_{12} \quad k_{14} \quad k_{23} \quad k_{24}} [\frac{1}{_1 \quad k_{23} \quad k_{24}} (1 \quad \exp(\quad (\quad _1 \quad k_{23} \quad k_{24}) \quad 7300)) \quad \frac{1}{_1 \quad k_{12} \quad k_{14}} (1 \quad \exp(\quad (\quad _1 \quad k_{12} \quad k_{14}) \quad 7300))] \quad [Bq \quad day \quad Bq^{\quad 1}] \qquad (8)$$

It seems apparent that in order to assess the uncertainty in the number of nuclear transformations in thyroid over 20 years one needs to know the distributions over transfer coefficients k_{ij}. However, the transfer coefficients are not observable quantities and cannot be measured by direct experiments or determined by querying experts. For that reason in this report a two-step procedure for specifying the probability distribution of variable $U_{Thyroid}$ is proposed. First, we will find the distributions of transfer coefficients based on combined experts' assessments on the retention of iodine at selected times as given in Table 1 and then we will apply these distributions to equation (8). The first step is described below.

Experts form the internal dosimetry panel provided their subjective assessments on the amount of stable iodine retained in thyroid after its single injection into bloodstream. Let consider the iodine biokinetic model[16] as shown in Figure 3 and let $m_j'(t)$ denotes the

[15] Assuming unit deposition in blood we get $m_1(0) = 1$, $m_j(0) = 0$ for j = 2, 3, 4.

[16] The biokinetic model for radioiodine is taken from the report of the Commission of European Communities (CEC) and is applied to both stable and unstable isotopes of iodine [6].

amount of stable iodine in the compartment j at time t, j = 1, 2, 3, 4. Then, the experts estimates corresponds to $m'_2(t)$ for t = 1, 7, 30, 90 where

$$m'_2(t) \quad \frac{k_{12}}{k_{12} \quad k_{14} \quad k_{23} \quad k_{24}} \exp(\quad (k_{23} \quad k_{24})\ t) \quad \exp(\quad (k_{12} \quad k_{14})\ t) \qquad (9)$$

Note, that equation (7) is a product of $m'_2(t)$ and term $e^{-\lambda_1 t}$. In accordance with physical laws, the term $\lambda_1 \cdot t$ is interpreted as the probability of decay in unite time t while the exponential term $e^{-\lambda_1 t}$ represents the probability that the atom of iodine does not decay before time t. This means that the activity of radioiodine in thyroid at time t is equal to number of atoms of I^{131} in thyroid at time t times the probability that there was no decay before time t.

The problem of finding the distributions over transfer coefficients is an inverse problem. It can be described shortly as follows.

Experts provided the combined distributions of equal and performance based DMs of the amount of iodine retained in thyroid at selected times as given in Table 2. The probabilistic inversion problem is to find the distribution over parameters (k_{12}, k_{14}, k_{23}, k_{24}) which, when applied in equation (9), yield as well as possible the quantiles over the retentions as summarized in Table 2. However, one has to keep in mind that experts did not consider any particular biokinetic model for iodine. Therefore the choice of the biokinetic model presented in Figure 3 should be also validated somehow. Both problems are well solved with use of probabilistic inversion technique. The results of the probabilistic inversion applied separately to both combined distributions are presented in next subsection while a brief description of steps of probabilistic inversion method is the content of Appendix B.

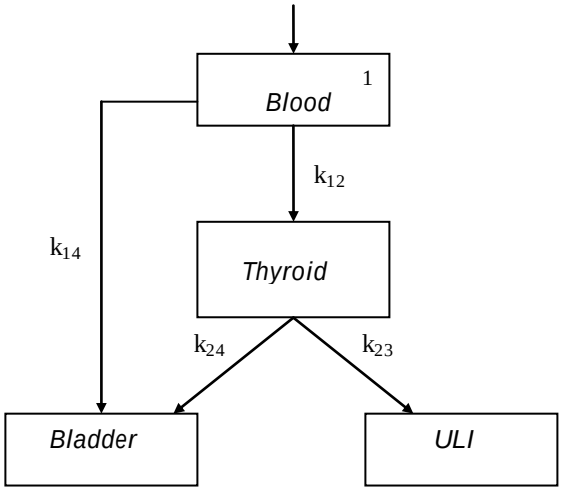


Figure 4: Acyclic compartment model for I^{131} with transfer coefficients. The ULI is the upper large intestinal.

3.4.3. Solution of probabilistic inversion to iodine biokinetic model

There are number of approaches that could be used to find the distribution over transfer coefficients. However, in this report the probabilistic inversion technique based on sample re-weighting has been applied to biokinetic models presented. The idea of the strategy for sample re-weighting can be shortly described as follows. Let vectors X and Y denote respectively the vector of transfer coefficients and retentions $m'_2(1)$, $m'_2(7)$, $m'_2(30)$, $m'_2(90)$. First we choose the initial distribution for X. Then we sample this distribution large number of times, say N, and compute N samples for Y according to formula (9) yielding N samples of (X, Y). When we have drawn N samples of initial distribution of X then each sample has the same probability of occurring 1/N. Now, we want to re-weight these N samples such that if we re-sample this distribution, drawing each sample with probability given by its weight, the quantile constraints on Y are satisfied in the re-sampled distribution. In this study we decided to find the weights with use of iterative algorithms, namely IPF (Iterative Proportional Fitting) and Parameter Fitting for Uncertainty Models (PARFUM). However, in the main reports we present the results

obtained with IPF because of its advantages in solving feasible problems. For more details see Appendix B.

Probabilistic inversion technique can be also used for model validation or criticism. If the re-weighted distributions agree to large extent with the decision maker distributions then the model is suitable to represent the decision maker uncertainty. However, the model considered does not have to be the only one which satisfies these constraints. In the opposite situation the conclusion is not that the model is wrong, but it means that we cannot capture experts' uncertainty via joint distribution over the transfer coefficients.

All calculations were carried out with UNICORN software (developed at Delft University of technology) which is equipped with satellite program provided for probabilistic inversion. The detailed description of probabilistic inversion based on sample re-weighting applied to biokinetic models and the results of PARFUM can be found in Appendix 2 while the general information about probabilistic inversion and iterative algorithms the reader can find in references [9, 10, 12].

Initially, the unknown transfer coefficients k_{12}, k_{14}, k_{23}, k_{24} were assumed to be independent and to posses log-uniform distribution. With this set-up the IPF algorithm was run. Table 3 presents the 5^{th}, 50^{th} and 95^{th} quantiles of the distribution obtained for transfer coefficients occurring in compartment model for equal and performance based DMs. Moreover, Table 4 and Table 5 compare the quantile information between the equal and performance based DMs and those reproduced when the distributions of transfer coefficient obtained from probabilistic inversion are "pushed-through" the equations (9).

quantile / transfer coefficient	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
k_{12}	0.184	0.154	0.833	1.07	4.58	6.48
k_{14}	0.211	0.157	1.43	1.5	8.55	7.77
k_{23}	7.52E-6	7.49E-6	8.71E-5	9.97E-5	2.09E-3	2.63E-3
k_{24}	0.0102	0.0101	0.0113	0.0122	0.0188	0.0221

Table 3: Quantiles on transfer coefficients after probabilistic inversion with IPF and equal (E) and performance based (P) DM

quantile t	5%		50%		95%	
	Probabilistic Inversion	E.DM	Probabilistic Inversion	E.DM	Probabilistic Inversion	E.DM
1 day	0.114	0.116	0.288	0.287	0.563	0.563
1 week	0.115	0.112	0.285	0.286	0.742	0.548
1 month	0.0858	0.0854	0.226	0.236	0.572	0.457
3 months	0.0416	0.0415	0.122	0.154	0.289	0.366

Table 4: Quantiles on retention at selected times after probabilistic inversion for I with IPF and equal weight DM (E)

quantile t	5%		50%		95%	
	Probabilistic Inversion	P.DM	Probabilistic Inversion	P.DM	Probabilistic Inversion	P.DM
1 day	0.146	0.15	0.280	0.28	0.435	0.43
1 week	0.151	0.15	0.356	0.29	0.659	0.44
1 month	0.114	0.11	0.29	0.23	0.517	0.39
3 months	0.0472	0.059	0.151	0.15	0.28	0.28

Table 5: Quantiles on retention at selected times after probabilistic inversion for I with IPF and performance based DM (P)

We observe the agreement between distributions of retentions at selected times corresponding to combined DMs and those reproduced with use of probabilistic inversion. This also indicates that the compartment model shown in Figure 3 is suitable to represent the distributions of decision makers and is appropriate to predict the uncertainty in the transfer coefficients. However, the compartment model for radioactive isotope of iodine chosen in this study dose not has to be the only one that captures *experts' uncertainty*.

Table 3 shows that the quantiles of the transfer coefficients corresponding to equal and performance based DMs coincide with minor differences. These differences are reflected in the spread of distributions which is larger for the equal weight DM (except k_{14}).

Another attractive feature of the probabilistic inversion is that it determines not only the marginal distributions of the target variables, but it also specifies the dependencies between them. Table 6 and Table 7 present the rank correlation matrices for transfer coefficients obtained form distributions of equal and performance based DMs, respectively.

One can observe that for equal weight DM the transfer coefficients are mostly positively correlated while for performance based DM all dependencies are positive. However, for both combination schemes the strongest monotone dependence is between variables k_{14} and k_{12}.

k_{12}	1	0.60	0.02	0.20
k_{14}	0.60	1	0.12	0.12
k_{23}	0.02	0.12	1	0.06
k_{24}	0.20	0.12	0.06	1

Table 6: Rank correlation matrix for transfer coefficients for I and equal weight DM

k_{12}	1	0.76	0.08	0.04
k_{14}	0.76	1	0.12	0.16
k_{23}	0.08	0.12	1	0.08
k_{24}	0.04	0.16	0.08	1

Table 7: Rank correlation matrix for transfer coefficients for I and performance based DM

One of the graphical outputs of UNICORN software is the cobweb plot. It is helpful in understanding relationships between variables in the structure of multivariate distributions. As an example Figure 4 presents the cobweb plot corresponding to the high dimensional distribution obtained as a result of probabilistic inversion and combined experts' assessments using equal weighting scheme when conditioning on the small values taken by variable k_{24}.

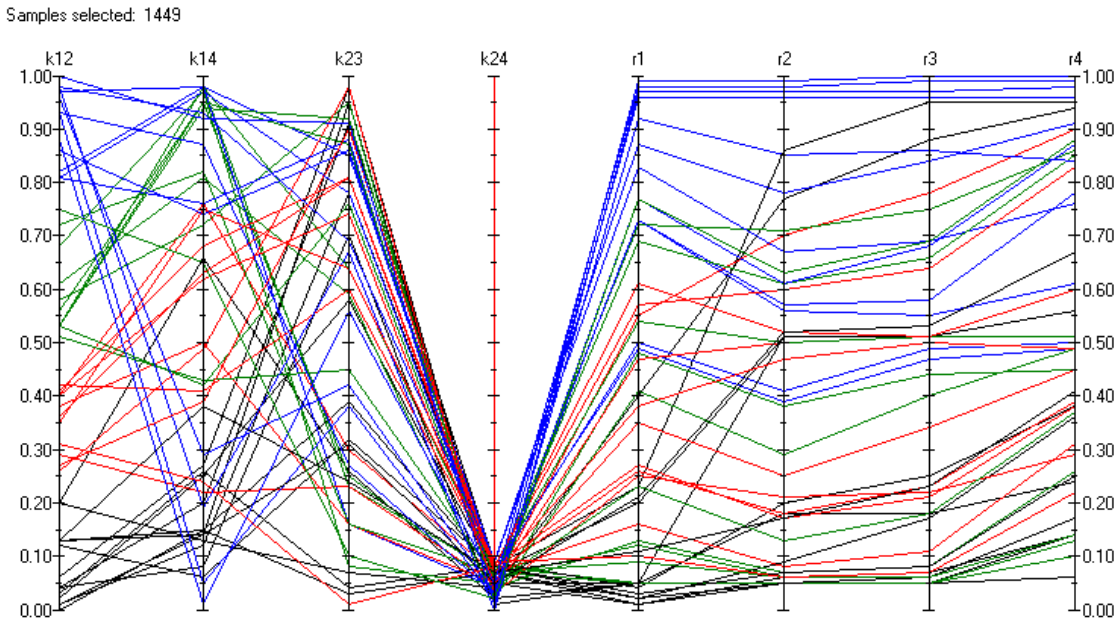


Figure 5: The cobweb plot of the variables of the compartment model for Cs conditioned on the small values of k_{24}

The axes represent the variables of the iodine compartment model (see Figure 3), i.e. transfer coefficients k_{12}, k_{14}, k_{23}, k_{23} and retention functions $m'_2(1)$, $m'_2(7)$, $m'_2(30)$, $m'_2(90)$ (from left to right). One multivariate sample, of set of 30,000 samples of form (k_{12}, k_{14}, k_{23}, k_{24}, $m'_2(1)$, $m'_2(7)$, $m'_2(30)$, $m'_2(90)$) obtained with use of probabilistic inversion technique, is illustrated by a line joining one coordinate of each variable. The picture shows the following conditional dependencies: the negative rank correlation between variables k_{24}, $m_2(1)$ since smaller values of coefficient k_{24} correspond to larger values of variables $m_2(1)$, almost zero rank correlation between k_{24} and k_{23}, strictly positively correlation between pairs of the retention functions $m'_2(1)$ and $m'_2(7)$, $m'_2(7)$ and $m'_2(30)$, $m'_2(30)$ and $m'_2(90)$.

3.5. Uncertainty in the simple risk model for radioiodine

In this section we present the results of the uncertainty analysis of the simple risk model (1) that was carried out with use of equal and performance based combinations of experts' assessments and probabilistic inversion technique.

Since the distributions of the transfer coefficients present in the compartment model for iodine are already known, it is now possible to estimate the number of nuclear transformations of radioiodine in thyroid after 20 years following intake. Following previous notation, this variable is denoted as $U_{Thyroid}$. It is worth to mention, that since the retention function $m_2(t)$ given by equation (7) decreases quickly and approaches zero value after a short time, the number of nuclear transformations after 20 and 50 years coincide. Thus, it is possible to compare obtained results with that recommended by ICRP (ICRP, 1979).

Drawing 30.000 samples from distribution of each transfer coefficient k_{ij} obtained form equal and performance based combinations we have found distribution of variable $U_{Thyroid}$. The 5th, 50th and 95th quantiles of these uncertainty distributions are shown in Table 8.

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$U_{Thyroid}$[17]	1.28E5	1.00E5	2.68E5	2.45E5	5.16E5	5.97E5

Table 8: Quantiles of $U_{Thyroid}$ with equal (E) and performance based (P) DM

One sees that the probability distribution of performance based DM is concentrated on a smaller range of values than the one resulting equal weighting combination of experts' assessments. In spite of closeness of the median estimates, the one representing performance based DM is closer to the value 2.9E5 reported by ICRP.

As all input parameters occurring in model equation (6) are known we can find the distribution of the dose coefficient and subsequently of risk coefficient. Table 9 and Table

[17] The unit of variable $U_{Thyroid}$ is given in nuclear transformations (nt), i.e. $86400 \cdot Bq \cdot sec \cdot Bq^{-1} = 86400 \cdot nt \cdot Bq^{-1}$.

10 show medians and bounds of confidence intervals corresponding to the resulting distributions.

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$h_{Thyroid,\ 20}$[18]	5.74E-7	4.60E-7	1.16E-6	1.13E-6	2.37E-6	2.75E-6

Table 9: Quantiles of dose coefficients for thyroid with equal (E) and performance based (P) DM

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$Cancer\ Mortality Risk_{Thyroid}$	2E-11	1.94E-11	3.11E-10	3.26E-10	4.64E-9	5.07E-9

Table 10: Quantiles of the risk coefficients for thyroid with equal (E) and performance based (P) DM

Again, the uncertainty distributions of both dose and risk coefficients are very similar for both combination schemes, but the ones corresponding to the performance based DM are concentrated on narrower intervals. Both central estimates of $h_{Thyroid,\ 20}$ are far form value 4.8E-7 reported by ICRP while the median estimate of risk coefficient representing distribution of performance based DM is almost in a perfect agreement with FGR no.13[19].

The uncertainty in the risk coefficient is represented by the ratio between 95th and 5th percentiles of its distribution. For performance (equal) weight combinations, this ratio equals to 232 (277). This ratio is smaller for the performance based DM than for the equal weight DM. However, both ratios indicate that the risk coefficient is highly uncertain and the uncertainty category remains unchanged - E of the scale provided in FGR no.13. Furthermore, it is still two uncertainty categories higher than that reported in FGR no.13, where were it was judged as C. The proximity of the median estimates of equal and performance based DMs and value reported in FGR no. 13, and the large discrepancy between the uncertainties are worth emphasizing.

Figure 5 and Figure 6 present the plots of cumulative distribution functions of performance and equal based DM for dose and risk coefficients. The green points

[18] Unit of the dose coefficient is in $Sv \cdot Bq^{-1}$.
[19] Mortality risk coefficient for ingestion of tap water and dietary intake is 3.16E-10.

correspond to the 5th, 50th and 95th quantile points while the circles - published values of dose and risk coefficients.

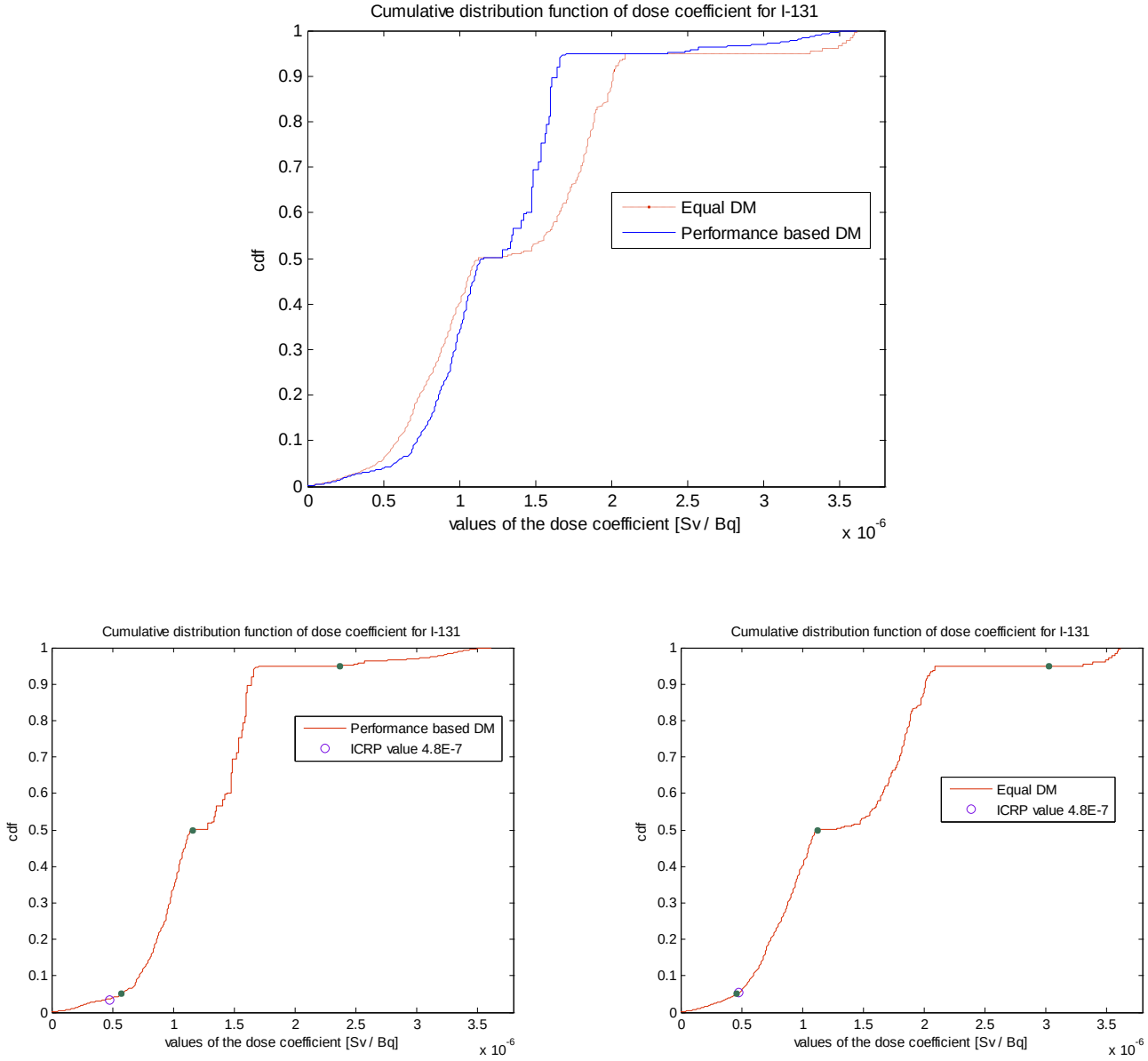
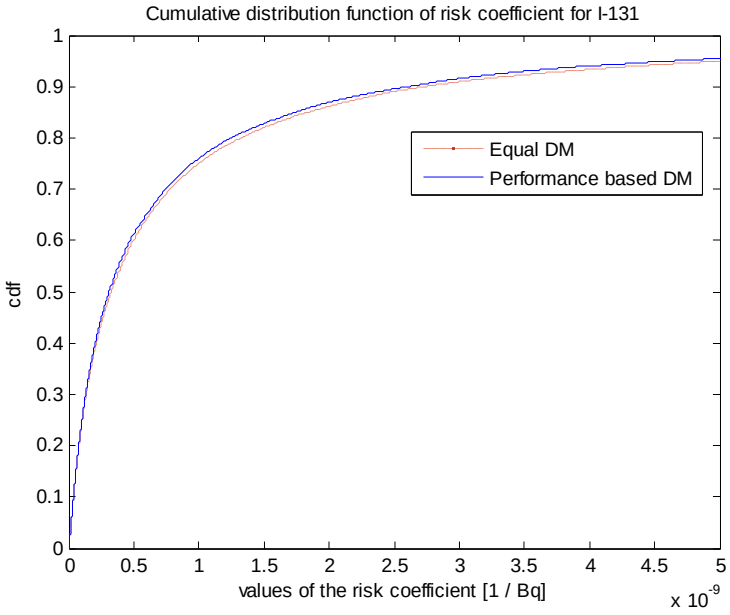
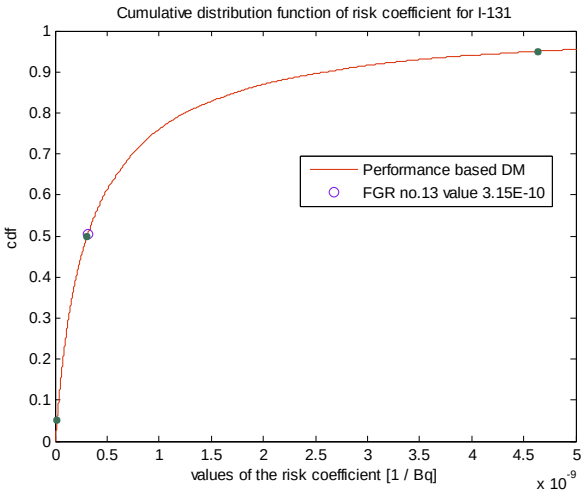


Figure 6: Cumulative distribution function of the thyroid dose coefficient for equal and performance based DM





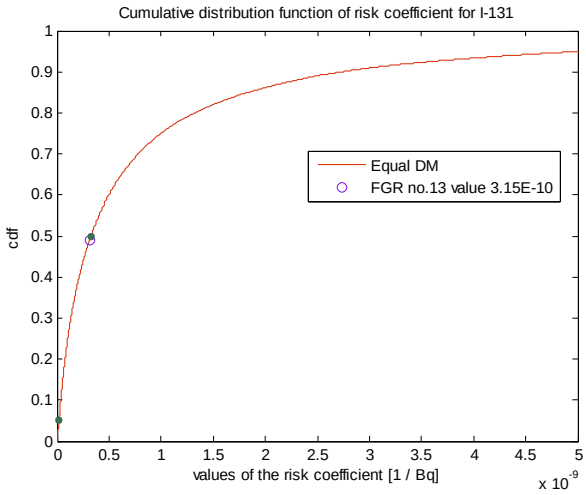


Figure 7:Cumulative distribution function of the thyroid risk coefficient for equal and performance based DM

4. Simple risk model for radioactive isotope cesium Cs^{137}

This chapter presents intermediate steps and the results of the uncertainty analysis on the cancer mortality risk resulting ingestion of radioactive isotope of cesium Cs^{137}. It provides the underlying methods used to determine the probability distributions of both input and output variables of the simple risk model for this radionuclide as well as their representations.

4.1. Biological and physical behavior of Cs^{137}

The radioactive isotope of cesium, Cs^{137}, is formed by nuclear fission. Nuclear fission is used to produce the energy for nuclear power and to drive the explosion of nuclear weapons. Thus Cs^{137} is present in the environment as the fallout of the nuclear reactor accidences and nuclear weapon testing. Trace amount of this radionuclide can be found in soil, water, meat, fish, mushrooms and other food products. The exposure to radioactive cesium isotope is very long due to its physical half-life of 30 years.

If radiocesium enters the body, it is rapidly and totally absorbed into bloodstream. Cesium behaves in the similar manner to potassium and absorbed in blood is uniformly distributed throughout all tissues and organs in the human body. Therefore the doses to particular organs are similar. Formally, the whole body consists of the entire body minus the contents of the gastrointestinal tract, the unitary bladder and heart. The tissues and organs occupied by radiocesium are distinguished with respect to velocity of the turnover of the Cs^{137}. In adults the biological half-lives for the fast and slow turnover compartments are 2 and 110 days, respectively. Thus, the latter compartment is significant to dosimetric calculations. Cesium is eliminated from the body through urine and feces.

Exposure to radiation form Cs^{137} results in malignant cancers and shortening life. In case of very high exposure the serious burns, or even death, may happen. As other radionuclides radiocesium is also used in medical therapy to treat the cancer.

Cs^{137} decays by emission of the beta radiation (low-LET) into the unstable barium isotope Ba^{137m}, which further decays into its stable state by emitting gamma radiation. The decay scheme for radiocesium is shown in Figure 7 below.

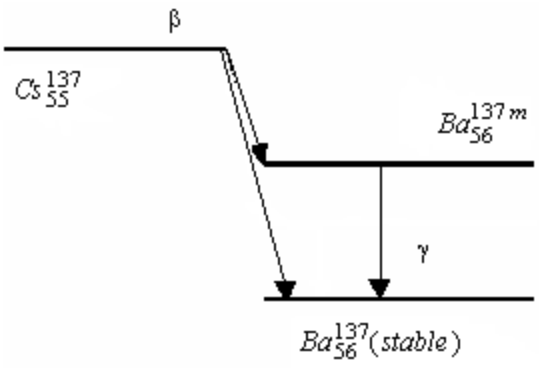


Figure 8: Decay scheme for Cs^{137}.

Since absorption into bloodstream cesium distributes uniformly in all body tissues and organs. Thus the ingestion dose coefficient and then the risk coefficient are calculated for the whole body (WB). Thus, in this particular case the simple risk model (1) takes the following form

$$\text{CancerMortalityRisk}_{WB} = \frac{d_{WB}}{\text{DDREF}_{WB}} R_{WB} \quad [Bq^{-1}] \tag{10}$$

In the contrary with the iodine dosimetry calculations, the dose coefficient for cesium has to into account its decay product Ba^{137m}. This is motivated by the fact that approximately 94.6% of decays of Cs^{137} go to radioactive Ba^{137m} and the energy emitted by this progeny is the largest contributor to the dose delivered to tissues and organs in the human body.

4.2. Risk per absorbed dose to whole body and dose and dose modifying factor

As in the example concerning radioactive isotope of iodine, the distribution of the risk coefficient for high dose and dose rate for whole body resulting ingestion of Cs^{137} is determined based on expert judgment study on the late health effects performed by the U.S. NRC and CEC [2].

Recalling, experts were asked to estimate the number of radiation-induced cancer deaths over a lifetime (following the population up until it has become extinct) in a population of a hundred million persons ($5x10^7$ male, $5x10^7$ female) each receiving a whole body dose of 1 Gy low-LET (=gamma) radiation at a uniform rate over 1 minute. Experts provided their subjective distributions of elicited variable with respect to many single cancer sites and for all cancer sites combined. In this report the risk for high dose and dose rate for all cancer sites, i.e. the total risk, is of great interest.

Table 11 presents 5^{th}, 50^{th} and 95^{th} quantiles of the distribution of variable R_{WB} expressed in units of cancer deaths per person-Gy. It is also worth to mention that the aggregation of experts' assessment was carried out according to equal weighting scheme only.

quantile	5%	50%	95%
R_{WB}	0.0348	0.102	0.285

Table 11: Quantiles of thyroid risk per unit absorbed dose

In accordance with assumptions made in Chapter 2, the lognormal distribution is assigned to represent the uncertainty in variable R_{WB}. Parameters μ and σ corresponding to this distribution are equal to

$$\begin{matrix} 2.2828 \\ 1.2784 \end{matrix}.$$

As it is already known, two piecewise-linear distribution is assigned to the dose and dose rate effectiveness factor $DDREF_i$ for each cancer site i. Depending on the information available the alternative distributions for certain cites may be considered. According to EPA [3] more careful choice of the $DDREF_i$ probability distribution would be needed for cases where the dose is heavily concentrated in a few specific target tissues. Therefore, in this report for all cancer combined, and for uniform whole-body irradiation the distribution of $DDREF_{WB}$ is the same as given in Chapter 2.

4.3. Whole body dose coefficient

The whole body dose coefficient resulting intake of Cs^{137} with food products or water can be estimated using formula (11)

$$h_{WB,20} \quad 1.6 \quad 10^{10} \quad 86400 \quad U_{WB} \quad SEE\ (WB \quad WB) \quad [Sv \cdot Bq^{-1}] \qquad (11)$$

As mentioned in section 4.1 the radioactive progeny of Cs^{137}, namely Ba^{137m}, is responsible for most of the dose received by all body tissues and organs. It is thus required to take into account its biokinetic behavior and decay properties when calculating $h_{WB,20}$. However, it should be noted that due to very short half-life of Ba^{137m} the sites in which it decays are assumed to be the same as those for its parent Cs^{137}. Therefore the separate biokinetic model for Ba^{137m} is not considered.

In general, when radionuclide i has a radioactive daughter j then the total value of the dose coefficient in target region T is then expressed as

$$h_{T,20} \quad 1.6 \quad 10^{10} \quad 86400 \quad U_S \quad SEE\ (T \quad S)_i \quad U_S \quad SEE\ (T \quad S)_j \quad [Sv \cdot Bq^{-1}] \qquad (12)$$

In our particular case equation (12) takes the following form

$$h_{WB,20} \quad 1.6 \quad 10^{\ 10} \quad 86400 \quad U_{WB} \quad SEE\ (WB \quad WB)_{Cs\ 137} \quad U_{WB} \quad SEE\ (WB \quad WB)_{Ba\ 137m} \tag{13}$$

In order to assess the whole body dose coefficient for Cs^{137} it is necessary to calculate the number of nuclear transformation in the whole body and the specific effective energy for Cs^{137} and Ba^{137m} separately.

The number of nuclear transformations U_{WB} is calculated as the time dependent activity (retention) function of the radionuclide in the whole body integrated over 20 years following intake. In situation when the parent radionuclide is long-lived relative to its daughters, the activity of the daughters ($i = 2, 3, \ldots, n$) at times t such that $\lambda_i \cdot t > 5$ can be approximated as

$$A_i(t) \quad A_1(t) \quad \prod_{j\ 1}^{i\ 1} f_{j,j\ 1} \tag{14}$$

where:

- $A_i(t)$ represents the activity of the daughter i in the source region at time t, with i = 1 indicating parent radionuclide,
- $f_{j,\,j+1}$ is the fraction of the nuclear transformations of chain member j forming member j + 1,
- λ_i is the decay constant for radionuclide i.

Since the physical half-life of Ba^{137m} is much shorter than the one for Cs^{137} (2.552 min), the activity of Ba^{137m} at time t is just

$$A_{Ba\ 137m}(t) \quad 0.946 \quad A_{Cs\ 137}(t) \quad [Bq] \tag{15}$$

The relationship obtained enables to reduce the expression for the dose coefficient to following form

$$h_{WB,20} \quad 1.6\ 10^{\ 10}\ 86400\ \ U_{WB}\ \ SEE\ (WB \quad WB)_{Cs\ 137} \quad 0.946\ \ SEE\ (WB \quad WB)_{Ba\ 137m} \qquad (16)$$

It is now noticeable that parameters that need to be estimated are U_{WB} for Cs^{137} and specific effective energy both for Cs^{137} and Ba^{137m}. The variable U_{WB} will be determined based on the expert judgment study and presented later in the report while the values of SEE are assessed without uncertainty below.

According to the FGR no. 13 the total energy of emitted beta radiation is 0.187 MeV per nuclear transformation of Cs^{137}. Moreover, the total beta and gamma energies emitted per nuclear transformation of Ba^{137m} in the human body are 0.065 MeV and 0.597 MeV, respectively. The dose coefficient is provided for the reference man of the population whose body mass is assumed to be 70 kg, see (ICRP, 1979). Based on latter the specific effective energies for Cs^{137} and Ba^{137m} in the whole body equal to 2.671E-6 and 9.457E-6, respectively.

4.4. Expert judgment and uncertainty in the cesium biokinetic model

This section is intended to provide the probability distribution of variable U_{WB}. It is attained by integrating the retention function specific to the whole body over period of 20 years. The retention function takes into account both biological and physical properties of radionuclide and is determined based on the biokinetic model for Cs^{137}. As in the iodine example, we try to reconstruct the retention function for the whole body compartment by converting the quantile information gathered from experts taking part in the joint NRC/CEC study into distributions of parameters of the biokinetic model (transfer coefficients) with use of probabilistic inversion method. This section contains the results of the combination of experts' estimates with use of equal and performance based aggregation schemes, outcome of the probabilistic inversion and resulting uncertainty distributions of number of total nuclear transformations in the whole body, dose and risk coefficients.

4.4.1. Results of expert judgment elicitation

Seven out of eight experts' groups working at the internal dosimetry have provided their subjective assessments concerning the whole body retention of stable cesium in an adult as a function of time after entry into bloodstream. The time periods taken into consideration were: 1 day, 1 week, 1 month, 1 year and 5 years. The probability distributions were specified in terms of 5^{th}, 50^{th} and 95^{th} percentiles. It should be noted that experts considered only the biological behavior of designated element without taking into account its decay properties.

When assessing the retention of Cs in the human body many experts made the use of datasets reported in ICRP publications 30, 56 and 67 (ICRP 1979, 1990, 1994b) where the two whole body compartment model was studied. Moreover, experts allowed the differences in deposition of elements among genders what is included in their answers.

Since cesium is regarded as the best understood element the big consistency among experts' central estimates for each selected time was observed. For purposes of our study experts' assessments were combined using equal and performance based aggregation schemes. The resulting 5^{th}, 50^{th} and 95^{th} quantiles are placed in Table 1 below.

quantile / t	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
1 day	0.92	0.870	0.96	0.962	0.9803	0.992
1 week	0.8	0.745	0.85	0.859	0.9004	0.943
1 month	0.6	0.545	0.7001	0.724	0.8008	0.893
1 year	0.01	2.38E-3	0.04003	0.0648	0.1019	0.264
5 years	9.011E-9	1.21E-10	1E-7	1.08E-5	0.009988	6.3E-3

Table 12: Quantiles of retentions of Cs at selected times with equal (E) and performance based (P) DM

One can observe that the distributions of equal and performance based DMs are in close proximity. However, the spreads of retention values, represented by the ratio between 95^{th} and 5^{th} quantiles, are (sometimes very much) larger for the equal weight DM. This indicates that the probability distributions corresponding to performance based combination should provide lesser uncertainty in the predictions of the biokinetic model.

Table 12 also reveals that the amount of the cesium in the human body slowly decreases with time (see median values) and at the end of the 5^{th} year is almost insignificant. It can be explained by choice of biokinetic model for cesium. Experts relied on the model provided by ICRP consisting of two compartments for the whole body. According to it 90% of cesium absorbed into bloodstream locates in the long-term compartment with biological half-life of 110 days while the rest 10% leaves the second compartment with biological half-life of 2 days.

Next subsection shows the way in which the uncertainty data gathered in Table 12 can be used to provide the probability distribution of variable U_{WB}.

4.4.2. Formulation of the probabilistic inversion problem

At it is already known, in order to assign the uncertainty to the number of nuclear transformation of Cs^{137} in whole body occurring during 20 years following its intake one has to gain the information about the changes of activity of this radionuclide in the human body. The main goal of this subsection is to reconstruct and to assess the uncertainty in the values of the retention (activity) function for the whole body with use of experts' combined distributions on the amount of stable cesium in the whole body at selected times as given in Table 12 and probabilistic inversion technique.

The retention function for whole body is determined based on a compartment model specific for radiocesium that includes both biological and decay properties of designated isotope. Figure 8[20] presents a compartment model for Cs^{137}. The boxes numbered 2 and 3 correspond to the short- and long-term whole body components and together represent the

[20] The compartment model for radiocesium is taken from the report of the Commission of European Communities [6] and completed with decay rate.

whole body. Parameters c_{ij} represent transfer coefficients and λ_2 is a constant decay rate[21] for Cs^{137} equal to $6.22 \cdot 10^{-5}$ (day^{-1}).

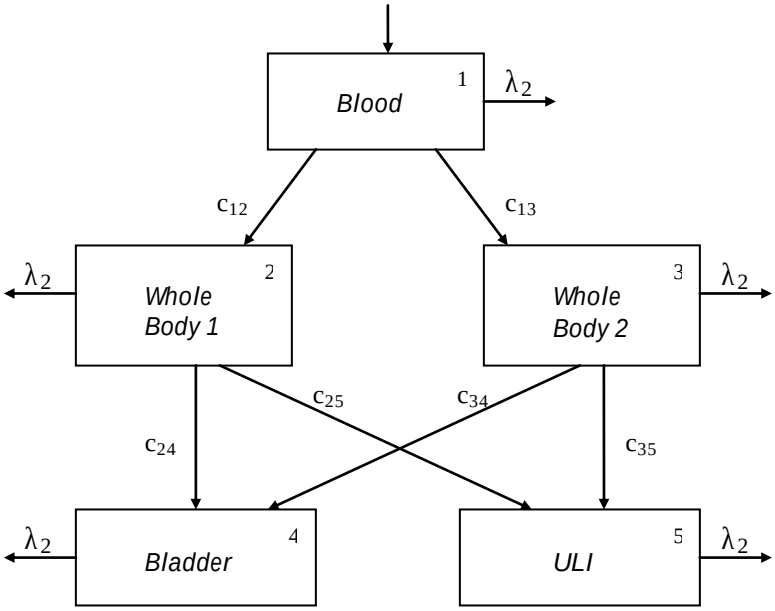


Figure 9: The compartment model for Cs^{137} with transfer coefficients. The ULI is the upper large intestinal.

Let $r_j(t)$ denote the amount of unstable isotope of cesium retained in the compartment j at time t, j = 1, 2, 3, 4, 5. Based on Figure 8 the transfer of the ingested radionuclide between different compartments can be fully described as a system of linear differential equations. Solving this system under appropriate initial conditions [22] the retention functions corresponding to compartments 2 and 3 are expressed as

$$r_2(t) \quad \frac{c_{12}}{c_{12} \quad c_{13} \quad c_{24} \quad c_{25}} \exp \quad (\quad _2 \quad c_{24} \quad c_{25}) \; t \quad \exp \quad (\quad _2 \quad c_{12} \quad c_{13}) \; t \qquad (17)$$

$$r_3(t) \quad \frac{c_{13}}{c_{12} \quad c_{13} \quad c_{34} \quad c_{35}} \exp \quad (\quad _2 \quad c_{34} \quad c_{35}) \; t \quad \exp \quad (\quad _2 \quad c_{12} \quad c_{13}) \; t \qquad (18)$$

[21] The decay rate is calculated as the $\ln 2/T_{1/2}$, where $T_{1/2}$ is the physical half-life of Cs^{137} equal to 30 years.
[22] Assuming unit deposition in blood we get $r_1(0) = 1$, $r_j(0) = 0$ for j = 2, 3, 4, 5.

Since the number of nuclear transformations of Cs^{137} in the whole body over 20 years is calculated by integrating the appropriate retention function, the parameter U_{WB} is represented by equation (20)

$$U_{WB} \int_0^{7300} r_2(t)\ r_3(t)dt \quad \frac{c_{12}}{c_{12}\ c_{13}\ c_{24}\ c_{25}}\left[\frac{1}{{}_2\ c_{12}\ c_{13}}(\exp(\ (\ {}_2\ c_{12}\ c_{13})\ 7300\ )\ 1)\right.$$

$$\left.\frac{1}{{}_2\ c_{24}\ c_{25}}(\exp(\ (\ {}_2\ c_{24}\ c_{25})\ 7300\ )\ 1)\right]$$

$$\frac{c_{13}}{c_{12}\ c_{13}\ c_{34}\ c_{35}}\left[\frac{1}{{}_2\ c_{12}\ c_{13}}(\exp(\ (\ {}_2\ c_{12}\ c_{13})\ 7300\ )\ 1)\right. \tag{19}$$

$$\left.\frac{1}{{}_2\ c_{34}\ c_{35}}(\exp(\ (\ {}_2\ c_{34}\ c_{35})\ 7300\ )\ 1)\right]\ \ [\text{Bq day Bq}^{\ 1}]$$

In this report the following strategy has been undertaken for assigning the uncertainty to the values of variable U_{WB}. First, since the transfer coefficients c_{ij} are associated with biological behavior of stable isotope are cannot be measured by direct observations, their probability distributions are found based on uncertainty data concerning the amount of stable cesium retained in the whole body at selected times as given by equal and performance based DMs (see Table 12). It is apparent that the distributions of transfer coefficients cannot be straightforward derived form experts' combined assessments. The mathematical technique that translates the experts' uncertainty into distributions over parameters of the biokinetic model is probabilistic inversion. Finally, when the distributions of transfer coefficient become known, they are applied in equation (19) to assess the uncertainty in the values of variable U_{WB}. The detailed description of first step of the strategy is submitted beneath.

Consider the biokinetic model for cesium[23] as presented in Figure 9. Experts taking part in elicitation session on the internal dosimetry have provided their subjective distributions in form of 5^{th}, 50^{th} and 95^{th} quantiles of amount of cesium retained in the

[23] The compartment model for cesium is taken from the report of the Commission of European Communities (CEC) and was not known to experts (see, [6]).

whole body, i.e. joint amount accumulated in the compartments *Whole Body1* and *Whole Body2*.

If we denote the amount of stable Cs retained in compartment j at time t as $r_j'(t)$, j = 1, 2, 3, 4, 5, the elicited variable referred to $r_2'(t)$ $r_3'(t)$.

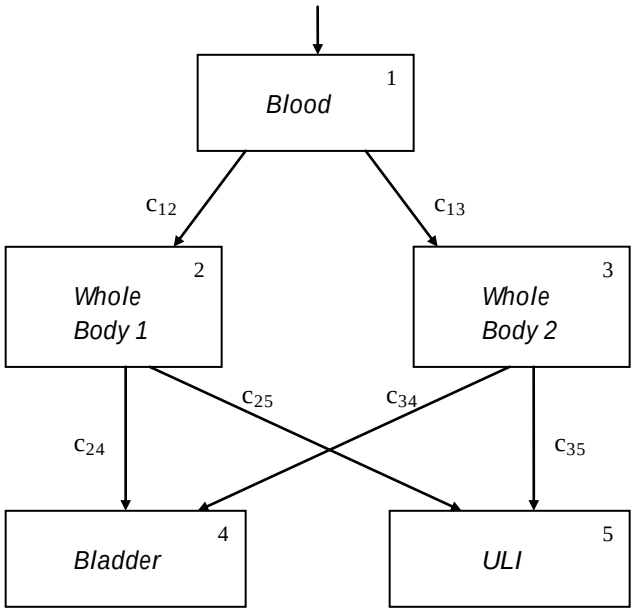


Figure 10: The compartment model for Cs^{137} with transfer coefficients. The ULI is the upper large intestinal.

However, when looking at equations (17) and (18) we see that in each the term $e^{-\lambda_2 t}$ can be separated. Then, what remains is nothing but the retention functions corresponding to the compartments 2 and 3 of the model shown in Figure 9, i.e.

$$r_2'(t) \quad \frac{c_{12}}{c_{12} \quad c_{13} \quad c_{24} \quad c_{25}} \exp \quad (c_{24} \quad c_{25})\ t \quad \exp \quad (c_{12} \quad c_{13})\ t \tag{20}$$

$$r_3'(t) \quad \frac{c_{13}}{c_{12} \quad c_{13} \quad c_{34} \quad c_{35}} \exp \quad (c_{34} \quad c_{35})\ t \quad \exp \quad (c_{12} \quad c_{13})\ t \tag{21}$$

As a result, the retention function for whole body compartment and for stable isotope of cesium is given by

$$r'_{WB}(t) \quad r'_2(t) \quad r'_3(t) \quad \frac{c_{12}}{c_{12} \quad c_{13} \quad c_{24} \quad c_{25}} \exp \quad (c_{24} \quad c_{25})\ t \quad \exp \quad (c_{12} \quad c_{13})\ t$$
$$\frac{c_{13}}{c_{12} \quad c_{13} \quad c_{34} \quad c_{35}} \exp \quad (c_{34} \quad c_{35})\ t \quad \exp \quad (c_{12} \quad c_{13})\ t \qquad (22)$$

As one recognized, the estimation of transfer coefficients is an inverse problem. As we have already shown on the iodine example this type of problems are well solved with use of probabilistic inversion technique. In this particular case the idea of the probabilistic inversion can be described as follows.

The aggregation of experts' individual assessments on the retention of cesium in the whole body after 1day, 1 week, 1 month, 1 year, 5 years following intake with use of equal and performance based combination schemes resulted in combined distributions of equal and performance based DMs as given in Table 12. For each combination separately, we seek a distribution over transfer coefficients which, when pushed through equation (22), yields quantiles over retentions of cesium in whole body agreeing with those of equal and performance based DMs, respectively.

Note that the cesium biokinetic model shown in Figure 9 was not known to experts when giving their subjective assessments. Probabilistic inversion will enable to state whether the *model is suitable to represent experts' quantile specifications.*

The results of the probabilistic inversion applied to cesium compartment model are presented in the next subsection. The details concerning probabilistic inversion method the reader can find in Appendix B.

4.4.3. Solution of probabilistic inversion to cesium biokinetic model

For each combination of experts' assessments separately, the distributions of transfer coefficients of the cesium biokinetic model were found via sample re-weighting method. The vectors of sample weights that are minimally informative with respect to starting weights were obtained with iterative algorithm IPF (Iterative Proportional Fitting). The results of sample re-weighting with IPF are presented below, while the results of PARFUM the reader can find in Appendix B.

Initially, variables c_{12}, c_{13}, c_{24}, c_{25}, c_{34}, c_{35} were assumed to be independent of each other and log-uniformly, but not identically, distributed. Table 13 shows the 5^{th}, 50^{th} and 95^{th} quantiles of the marginal distributions of transfer coefficient corresponding to assessments of equal and performance based DM after re-weighting the original samples according to weights found by IPF. In addition, Table 14 and Table 15 compare the quantile points of distributions of the retentions of cesium in whole body corresponding to equal and performance based DMs with those re-predicted emerging after probabilistic inversion.

quantile / transfer coefficient	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
c_{12}	0.0119	0.00253	4.11	2.27	17.6	16.2
c_{13}	0.377	0.367	1.31	2.59	5.86	6.47
c_{24}	0.00113	2.55E-4	0.00776	0.0072	0.403	0.537
c_{25}	3.72E-4	3.51E-4	1.14E-3	1.23E-3	3.11E-3	3.09E-3
c_{34}	4.13E-4	2.35E-4	0.161	9.66E-3	0.905	0.709
c_{35}	1.73E-5	1.94E-5	5.39E-4	1.26E-3	0.0164	0.0192

Table 13: Quantiles on transfer coefficients after probabilistic inversion with IPF and equal (E) and performance based (P) DM

quantile	5%		50%		95%	
t	Probabilistic Inversion	E.DM	Probabilistic Inversion	E.DM	Probabilistic Inversion	E.DM
1 day	0.869	0.870	0.962	0.962	0.992	0.992
1 week	0.745	0.745	0.864	0.859	0.944	0.943
1 month	0.545	0.545	0.724	0.724	0.893	0.893
1 year	2.51E-3	2.38E-3	0.0656	0.0648	0.267	0.264
5 years	1.02E-10	1.21E-10	1.08E-5	1.08E-5	6.41E-3	6.3E-3

Table 14: Quantiles on retention at selected times after probabilistic inversion for Cs with IPF and equal weight DM (E)

quantile	5%		50%		95%	
t	Probabilistic Inversion	P.DM	Probabilistic Inversion	P.DM	Probabilistic Inversion	P.DM
1 day	0.92	0.92	0.959	0.96	0.98	0.9803
1 week	0.801	0.8	0.85	0.85	0.9	0.9004
1 month	0.6	0.6	0.7	0.7001	0.801	0.8008
1 year	0.0105	0.01	0.0379	0.04003	0.103	0.1019
5 years	8.60E-9	9.011E-9	9.69E-8	1E-7	0.0101	0.009988

Table 15: Quantiles on retention at selected times after probabilistic inversion for Cs with IPF and performance based DM (P)

Tables 14 - 15 show a high degree of coincidence between the re-sampled distributions and distributions of equal and performance based DMs. The differences in fit are hardly observable what supports the choice of compartment model for cesium shown in Figure 9 in representing the estimates made by experts.

Table 13 reveals the discrepancy in the median estimates of transfer coefficients between equal and performance based DMs and agreement on the 5^{th} and 95^{th} quantiles for most variables. However, the spread of values of all transfer coefficients represented by ratio between 95^{th} and 5^{th} quantiles is smaller for performance based DM.

The uncertainty in the unknown variables resulting probabilistic inversion is represented not only by marginal distributions of each transfer coefficient, but also by specifying the correlation matrices between those distributions. Table 16 and Table 17

show the rank correlation matrices between distributions transfer coefficients with regard to equal and performance based DMs, respectively.

c_{12}	1	0.30	0.25	0.13	0.51	0.05
c_{13}	0.30	1	0.21	0.01	0.36	0.03
c_{24}	0.25	0.21	1	0.22	0.42	0.03
c_{25}	0.13	0.01	0.22	1	0.11	0.06
c_{34}	0.51	0.36	0.42	0.11	1	0.25
c_{35}	0.05	0.03	0.03	0.06	0.25	1

Table 16: Rank correlation matrix for transfer coefficients for Cs and equal weight DM

c_{12}	1	0.33	0.38	0.15	0.66	0.22
c_{13}	0.33	1	0.37	0.19	0.60	0.25
c_{24}	0.38	0.37	1	0.21	0.46	0.18
c_{25}	0.15	0.19	0.21	1	0.10	0.08
c_{34}	0.66	0.60	0.46	0.10	1	0.32
c_{35}	0.22	0.25	0.18	0.08	0.32	1

Table 17: Rank correlation matrix for transfer coefficients for Cs and performance based DM

One can observe that the values of the rank correlations for transfer coefficients are very similar for both combination schemes. The largest positive monotone dependency occurs between variables c_{12} and c_{34} while the largest negative between c_{24} and c_{34}. The latter statements are graphically confirmed with use of the cobweb plot (see Figure 10) when condition on large values of c_{12}. The vertical axes (from left to right) represent the elicited and target variables: c_{12}, c_{13}, c_{24}, c_{25}, c_{24}, c_{35}, $r'_{WB}(1)$, $r'_{WB}(7)$, $r'_{WB}(30)$, $r'_{WB}(356)$, $r'_{WB}(1825)$.

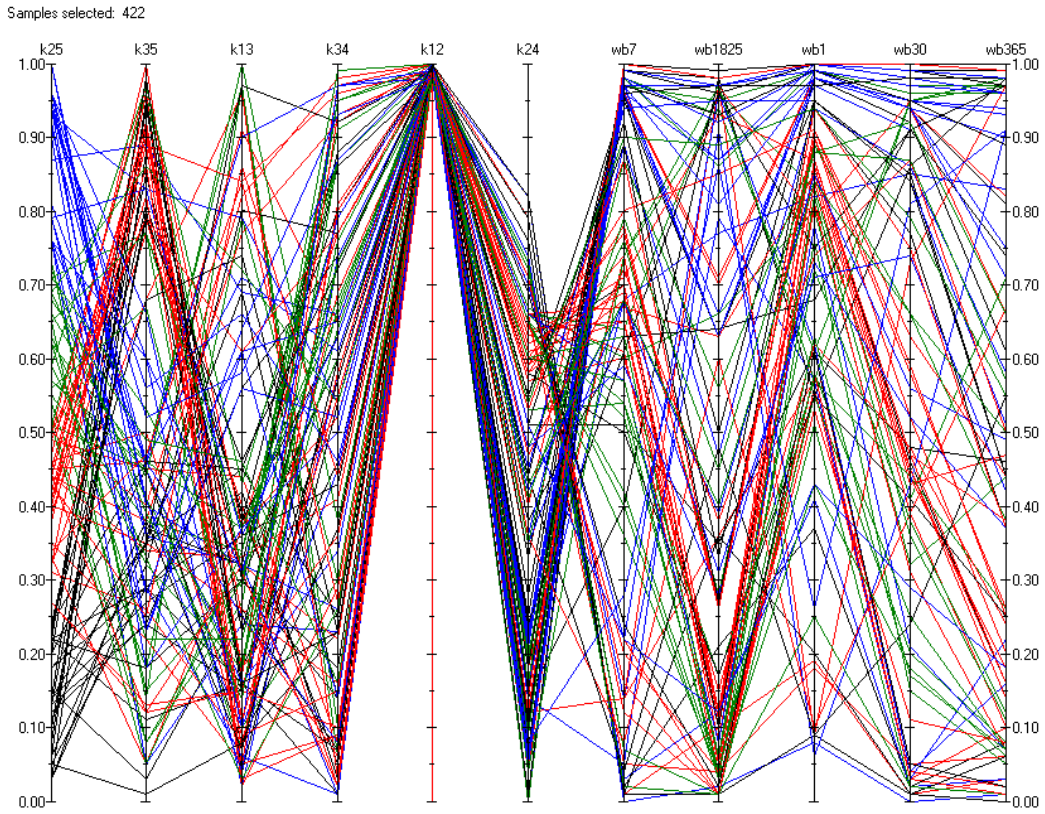


Figure 11: The cobweb plot of the variables of the compartment model for Cs conditioned on large vales of c_{12}

4.5. Uncertainty in the simple risk model for radiocesium

This section summarizes the findings collected Chapter 4. It presents the results of uncertainty analysis on simple risk model for whole body in form of probability distributions of the total number of nuclear transformations of radioactive Cs^{137} occurring in whole body over 20 years following intake, dose and risk coefficients for whole body. The distributions obtained will be compared with point estimates or uncertainties available in the literature with respect to both equal and performance based combinations.

The probability distributions of transfer coefficients c_{ij} and formula (19) were sufficient to assign the uncertainty to the values of accumulated activity in the whole body 20 years following intake. The resulting 5^{th}, 50^{th} and 95^{th} quantiles are shown in Table 18.

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
U_{WB}[24]	5.82E6	4.60E6	8.91E6	1.05E7	1.64E7	2.46E7

Table 18: Quantiles of U_{WB} with equal (E) and performance based (P) DM

It is easy to see that the distribution of variable U_{WB} corresponding to performance based DM is constructed on a narrower interval with comparison to equal weight DM. Since the number of nuclear transformations of Cs^{137} in the whole body is the same after 20 and 50 years after ingestion we can compare our results to those reported by ICRP (ICRP, 1979). The median estimate of equal weight combination is greater than that of performance based DM and is also smaller than the value published by ICRP (ICRP, 1979) where the number of nuclear transformations over 50 years in the whole body per unit intake of activity of Cs^{137} is 1.2E7. However, the difference is not so significant.

The distribution of the dose coefficient for the whole body due to intake of radioactive isotope cesium Cs^{137} was obtained by drawing 30.000 samples from the distribution of variable U_{WB} and pushing them trough equation (16). The 5^{th}, 50^{th} and 95^{th} quantiles of $h_{WB,\,20}$ distribution of equal and performance based DMs are presented in Table 19.

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$h_{WB,\,20}$	1.07E-8	8.48E-9	1.66E-8	1.95E-8	3.09E-8	4.65E-8

Table 19: Quantiles of coefficients for whole body dose with equal (E) and performance based (P) DM

Despite of closeness between median estimates, the range of values on which the distribution of the whole body dose coefficient is concentrated, is smaller for performance based DM. As the whole body dose coefficient represents the dose absorbed uniformly in all parts of human body (with the exception of gastrointestinal tract, unitary bladder and

[24] The unit of U_{WB} is $nt \cdot Bq^{-1}$.

heart) it can be compared with the estimates of the *effective dose*[25] (or *effective dose committed*). The effective dose reported in ICRP publication ICRP (ICRP, 1996) equals 1.3E-8 higher that central values shown in Table 19, but closer to predictions of the performance based DM.

Finally, since the uncertainty to all input parameters to the simple risk model (10) has been assessed, the probability distribution of the whole body risk coefficient can be found. The resulting 5th, 50th and 95th quantiles are shown in Table 20.

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$Cancer\ MortalityRisk_{WB}$	2.03E-10	1.98E-10	8.14E-10	9.60E-10	3.85E-9	5.16E-9

Table 20: Quantiles of risk coefficients for whole body with equal (E) and performance based (P) DM

Table 20 reveals that although the median values of whole body risk coefficients are close to each other for both experts' aggregation schemes, the 90% central confidence intervals are wider for equal based DM. Moreover, the central estimate of $CancerMortalityRisk_{WB}$ is more in line with the values in FGR no.13[26] for equal weight DM.

The uncertainty in the risk coefficient is represented by ratio between 95th and 5th quantiles of its distribution which amounts to 26 and 19 for equal and performance based DMs, respectively. These two scores correspond to uncertainty category B of FGR no. 13. Furthermore, they are one uncertainty category higher than that reported in FGR no. 13, where it was judged as A.

Plots of the cumulative distribution functions of dose and risk coefficients both for equal and performance based DMs are placed below.

[25] The effective dose is defined as $e(\tau) = \sum_T w_T H_T(\tau)$ where w_T is the weighting factor for tissue/organ T, $H_T(\tau)$ is the dose coefficient for tissue/organ T and τ is the time since absorption into blood.

[26] The total mortality risk coefficient for Cs^{137} is 1.254E-9 which is the sum of the mortality risk coefficient for ingestion of tap water (5.66E-10) and dietary intake (6.88E-10). This value for risk coefficient already introduces the contribution to dose from prediction of decay chain members in the body after intake of the parent.

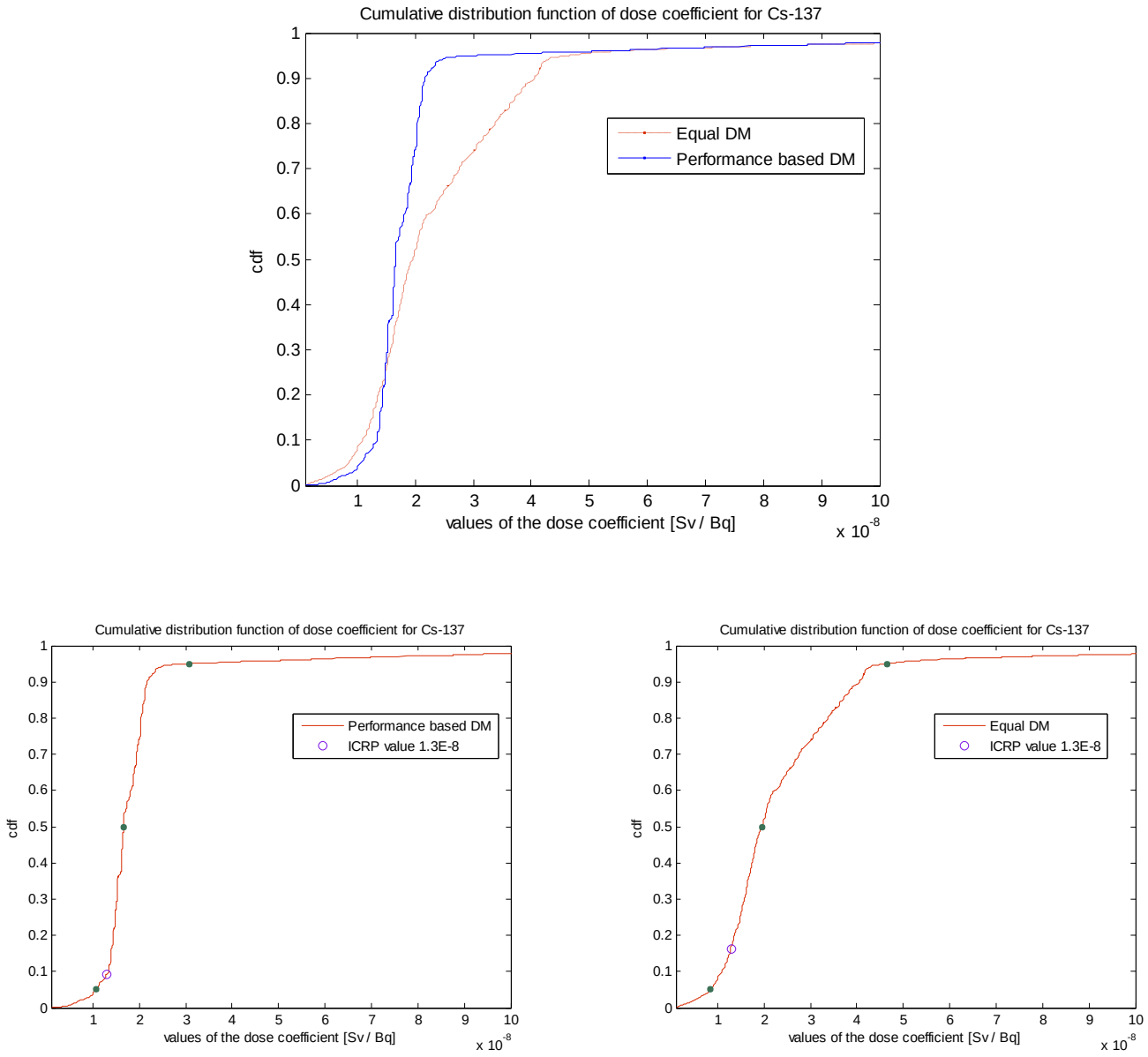


Figure 12: Cumulative distribution function of whole body dose coefficient for equal and performance based DM

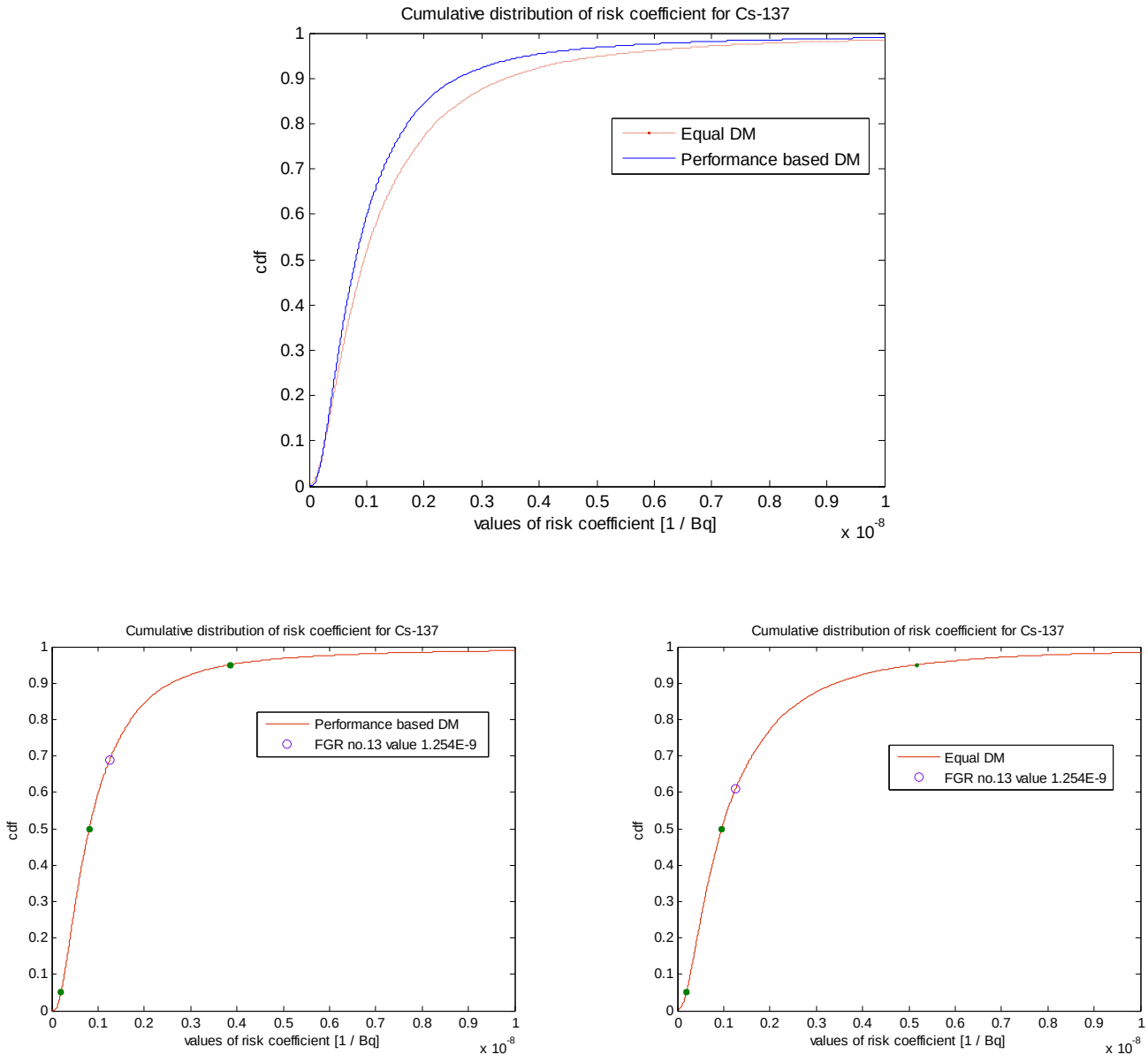


Figure 13: Cumulative distribution function of whole body risk coefficient for equal and performance based DM

5. Conclusions

This chapter summarizes the essential elements of the uncertainty analysis on the cancer mortality risk coefficients following ingestion of two radionuclides, radioiodine and radiocesium, and presents the valuable findings that have been obtained during the study.

The following fundamental problems have been formulated and solved during the research:

- the input parameters of simple risk model may be highly uncertain what may influence the regulatory decisions; thus the investigation of uncertainties associated with model input and output parameters is crucial,
- the uncertainty in the cancer mortality risk result form poor or unavailable experimental and epidemiological datasets; the alternative and reliable source of information is essential to generate;

The main elements of the project are summarized below.
In the study we have conducted the uncertainty analysis on the simple risk models for ingestion of two radionuclides, I^{131} and Cs^{137}, representing the cancer mortality risk coefficients. The risk per unit absorbed dose and the dose coefficients were assumed to be the least known model input parameters and the largest contributors to the uncertainty in the risk coefficients. Because the data on the parameters of biokinetic, dosymetric and risk models are sparse and/or not available we decided use the results of structured expert judgment elicitation on the internal dosimetry and late health effects being a part of the joint study of the U.S. NRC/CEC. Before the uncertainty analysis could be undertaken the subjective assessments of different experts had to be combined. Two aggregation methods- equal and performance weighting schemes- were applied in the internal disimetry, and only equal weighting in late health effects. The probability distributions of the parameters of the biokinetic models for both radionuclides were found by converting the combined experts' distributions on the retentions of designated radioactive materials in specified organs at selected times since injection into bloodstream. The probabilistic inversion technique was

used for that purpose. Finally, the calculated uncertainties in total number of nuclear transformations occurring in specified organs over 20 years and the dose coefficients were compared with their values published by ICRP. These distributions enabled to assign the uncertainties to the values of the cancer mortality risk coefficients for thyroid and whole body following ingestion of radioiodine and radiosecium, respectively, which were further compared with their values and subjective judgments of uncertainties reported in FGR no. 13.

The following final conclusions common for both radionuclides may be drawn:

1. Structured expert judgment has been successfully applied to quantify the uncertainty in the simple risk model.
2. Iterative sample re-weighting methods are adequate to quantify the uncertainty in non-measurable model parameters that capture uncertainties given by experts and provide the opportunity for model validation or criticism.
3. The performance based combination of experts' individual assessments always gives narrower spread of values both of elicited variables and variables of interest, namely total number of nuclear transformations in the source region, dose and risk coefficients. However, the differences between both combinations are not so big.
4. The median values of variables form the internal dosimetry are in the agreement with estimates reported by ICRP, while the central estimate of the risk coefficient is in line with FGR no. 13. Moreover, mostly the statements of the performance based decision maker are closer to their published values.
5. The uncertainty in the mortality risk coefficient, represented by ratio between 95^{th} and 5^{th} quantiles of its distribution, obtained form expert judgment and probabilistic inversion is larger than the subjective judgments of the authors of FGR no. 13.

APPENDICES

Appendix A: Structured expert judgment

This appendix presents the goals of the structured expert judgment and provides an explanation of the main concepts of the classical model and underlying measures of performance.

Expert judgment has always played an important role in science, engineering and technology. Roughly, expert judgment is recognized as another type of scientific data, and methods are developed for treating it as such. It is most appropriate in situations when data on parameters or variables of interest are lacking, difficult to obtain form regular experiments or poorly understood. Thus, when there is not sufficient data and hence substantial uncertainty experts' opinions (in form of subjective probabilities) is used as a dominate source of information.

The main aim of applying structured expert judgment is to enhance a rational consensus. The necessary conditions and principles that scientific methodology for using experts opinion should satisfy to achieve this goal are:

> *Accountability*: all data, including experts' names, individual assessments and scores, and all processing tools are open to peer review by competent reviewers and results must be reproducible,
>
> *Empirical control*: expert' assessments must be in principle susceptible to empirical control; in other words it must be in principle possible to evaluate experts' opinions on the basis of possible observations,
>
> *Neutrality*: method for combining/evaluating expert opinions should encourage experts to state their true opinions, and not bias the results,
>
> *Fairness*: experts are treated equally, prior to processing the results of observations.

In this project in order to estimate the parameters we are looking for we have used so-called Classical Model for combining experts' judgments. It is a performance based linear pooling or weighted averaging model which fulfils above mentioned principles. The

term "classical" indicates the analogy between the concepts of this model and classical hypothesis testing.

Below we present the background concepts and methods underlying the classical model. But we restrict the description to the case when experts are asked to assess their uncertainty for quantities taking values in a continuous range. For more details, see [8].

Experts are asked to give their uncertainty assessments on each query variable in form of quantiles of his/her subjective distributions, say 5%, 50% and 95%. The classical model constructs the weighted combination of expert probability assessments, where the weights are derived based on the performance measures and satisfy the strictly proper scoring rule. There exist two quantitative measures of performance of experts - calibration and information (or informativeness), which are assessed based on experts estimates on so-called *seed* or *calibration* variables. These are variables from experts' field whose true values are unknown to experts when giving their opinion, but whose values are known post hoc. Loosely, calibration measures the statistical likelihood that a set of experimental results correspond, in a statistical sense, with the experts' assessments. Information represents a degree to which a distributions provided by experts are concentrated. Both measures can be applied both to experts' assessments and to the combination of experts' assessments.

Calibration score

Calibration measures the statistical likelihood. It is the p-value for the hypothesis that a given expert's probability statements are accurate.

Each expert is asked to asses the probabilities of N fixed uncertain quantities and simultaneously he/she states three quantiles[27] of subjective distribution of these quantities. Suppose that we know the realizations (real values) of these quantities, say $x_1, x_2, \ldots, x_N$. Hence, there are four inter-quantile intervals into which these realizations may fall and the theoretical probability vector associated with these intervals is p = (0.05, 0.45,0.45, 0.05). It means, the expert believes that there is 5% probability that the realization falls between

[27] Let X be random variable defined on probability space Ω. The smallest number z from Ω such that $P(X \leq z) = p/100$ is called p% quantile and is denoted by q_p.

his/her 0% and 5% quantiles, a 45% probability that the realization falls between his/her 5% and 50% quantiles, and so on.

Let $s = (s_1, s_2, s_3, s_4)$ denotes the empirical probability vector, reflecting the relative frequencies with which the realizations fall in the inter-quantile intervals stated by expert e, i.e.

$s_1(e) = \#\{ i \mid x_i \leq 5\% \text{ quantile}\}/N$

$s_2(e) = \#\{ i \mid 5\% \text{ quantile} < x_i \leq 50\% \text{ quantile}\}/N$

$s_3(e) = \#\{ i \mid 50\% \text{ quantile} < x_i \leq 95\% \text{ quantile}\}/N$

$s_4(e) = \#\{ i \mid 95\% \text{ quantile} < x_i \}/N$

If the expert e is well calibrated we should expect that approximately 5% of the true values fall beneath 5% quantile, 45% should fall between 5% and 50% quantiles, etc. Under the hypothesis that the true values of seed variables are drawn independently from a distribution with quantiles as given by expert the quantity

$$2 N I(s(e), p) \quad 2 N \sum_{i=1}^{4} s_i \ln \frac{s_i}{p_i}$$

is asymptotically Chi-square distributed with 3 degrees of freedom for large number of seed questions.

Calibration score of expert e, denoted as C(e), is defined as the probability that the discrepancy between distributions s(e) and p is at least as large as I(s(e), p) under assumption that the expert's true distribution is p. Thus, if χ^2_3 is the cumulative distribution function for a Chi-square variable with 3 degrees of freedom, then

$$C(e) \quad p \quad value \quad 1 \quad \chi^2_3(2 N I(s(e), p)),$$

where I(s(e),p) is relative information of s(e) with respect to p and

$$\chi^2_3(2 N I(s(e), p)) \quad P(\chi^2_3 \quad 2 N I(s(e), p)).$$

Relative information I(s(e),p) takes value zero only if $s_i = p_i$ for all i. Thus, the closer to 1 the C(e) is, the better calibration of the expert e.

Informativeness

To measure information of expert the background measure is assigned to each query variable. Background measure can be uniform or log-uniform over an intrinsic range I on which these measures are concentrated. The background measure is not elicited from experts as indeed it must be the same for all experts, but instead it is chosen by the analyst. The *intrinsic range* is the *smallest interval containing all the expert's specified quantiles and* the realization enlarged above and below by overshot K% (default K=10%). The value of K is chosen by the analyst. Its large value tends to make all experts look quite informative, and tends to suppress the relative differences in information scores. The intrinsic range is obtained in the following way.

Let $q_i(e)$ denote the i% quantile of expert e for query variable X. Assuming that E experts take part in the elicitation process, we find the lowest and highest values of the smallest interval containing all assessed quantiles of all experts and the realization as follows

$$L = \min \{ q_5(1), q_5(2), \ldots, q_5(E), r \},$$
$$H = \max \{ q_{95}(1), q_{95}(2), \ldots, q_{95}(E), r \},$$

where r (if known) is the value of the realization of X. Then for overshot K we can calculate lower and upper bounds for intrinsic range $I = [q_L, q_H]$ as

$$q_L = L - K \cdot (H - L),$$
$$q_H = H + K \cdot (H - L).$$

The information is scored per expert per variable by computing the Shannon's relative information with respect to a user-selected background measure. It is expressed as follows

$$I(e) \quad \sum_{i=1}^{4} p_i \ln \frac{p_i}{r_i},$$

where $p = (0.05, 0.45, 0.45, 0.05)$ is the expert's probability while r_i is the background measure of the corresponding interval i (i = 1, … , 4), i.e.

$$r_1 = F(q_5(e)) - F(q_L(e)), \ldots, r_4 = F(q_H(e)) - F(q_{95}(e)),$$

where F is uniform or log-uniform distribution on the intrinsic range given respectively by

$$F(q_j) \quad \frac{q_j \quad q_L}{q_H \quad q_L}$$

and

$$F(q_i) \quad \frac{\ln(q_j) \quad \ln(q_L)}{\ln(q_H) \quad \ln(q_L)}$$

for j = L, 0.05, 0.5, 0.95, H.

The overall informativeness per expert is the mean of the information scores for all N variables. Information scores are always positive and experts with high information score are preferred, since increasing values indicate greater information relative to the background measure.

Combination

When experts have given their subjective probability assessments of each variable, the final step is to combine these distributions into one distribution, called a "decision maker" (DM) distribution.

In the classical model the decision maker distribution for each variable is derived as a weighted sum of experts' individual distributions, i.e.

$$f_{DM,i} \quad \sum_{k \ 1}^{E} w_k \quad f_{k,i},$$

where w_k, k = 1, … , E are non-negative normalized experts' weights and $f_{k,i}$ is the density of k^{th} expert for variable *i*. Depending on way of assigning the weights to experts we obtain different combination schemes.

We distinguish:

Equal weight decision maker

Equal weights are assigned to each expert. If we have E experts then the weight is $w_k = 1/E$ for $k = 1, \ldots, E$. Then the equal weight decision maker's density for variable i is given by

$$f_{DM,i} \quad \frac{1}{E} \sum_{k=1}^{E} f_{k,i},$$

where $f_{k,i}$ denotes density of k^{th} expert for variable i.

Global weight decision maker

The weight for each expert is defined by product of his/her calibration score and his/her overall information score on seed variables, and by an optimization routine described below. These weights satisfy strictly proper scoring rule. That is an expert receives his maximal expected score if his/her stated assessments correspond to his/her true, actual belief. For expert k, the same weight is used for all variables assessed. Thus, the density of global weight decision maker for variable i is thus

$$f_{DM,i} \quad \sum_{k=1}^{E} w_k \quad f_{k,i}, \quad \sum_{k=1}^{E} w_k \quad 1$$

where w_k is the normalized weight of k^{th} expert and $f_{k,i}$ as above.

Item weight decision maker

As with global weights, item weights are performance based weights which satisfy a proper scoring rule constraint, and are based on calibration and informativeness, with an optimization routine described below. In this case, however, weights depend on expert and on the item. Item weights are determined per expert and per variable, which is sensitive to the expert's informativeness for each variable. Then the density of item weight decision maker for variable i is

$$f_{DM,i} \quad \frac{\sum_{k=1}^{E} w_{k,i} \; f_{k,i}}{\sum_{k=1}^{E} w_{k,i}}.$$

Optimization

In the classical model the proper scoring rule entails that the expert should be unweighted if his/her calibration score is under a certain minimum, so called cut-off-level, $\alpha > 0$, which is determined based on optimization. That is, for each possible value of α, a certain group of experts will be unweighted, namely those whose calibration score is less than α. The weights of the remaining experts will be normalized to sum to unity. For each value of α we thus define a decision maker dm computed as a weighted linear combination of the experts whose calibration score exceeds α. dm is scored with respect to calibration and information. The weight which this dm would receive if he were added as a "virtual expert" is called the "virtual weight" of dm. The value of α for which the virtual weight of dm is greatest is chosen as the cut-off value for determining the unweighted expert. In other words, the aim is to choose α that maximize the decision maker's virtual weight, i.e.

$$\alpha' = \text{argmax}(w_{dm}(\alpha)),$$

where $w_{dm}(\alpha)$ is unnormalized weight of decision maker ($0<\alpha<1$).

Appendix B: Mathematical description of probabilistic inversion

This appendix presents the way in which the probability distributions over input parameters to the biokinetic models for radionuclides can be derived based on combined experts' distributions over retentions at selected times. In other words, we show how the inverse problems can be solved using probabilistic inversion. The steps of probabilistic inversion are the same for both designated radionuclides. Therefore we present them here on the example of radioiodine biokinetic model.

The elicitation variables $Y_1, Y_2, \ldots, Y_n$ can be expressed as functions of model input parameters $X_1, X_2, \ldots, X_m$ as

$$Y_i = G_i(X_1, X_2, \ldots, X_m) \quad \text{for } i = 1, \ldots, n.$$

From the expert judgment elicitation we obtained the 5^{th}, 50^{th} and 95^{th} quantiles of the marginal distributions of the elicitation variables Y_i. The probabilistic inversion problem is to find a distribution on the parameters $(X_1, X_2, \ldots, X_m)$ such that $G_i(X_1, X_2, \ldots, X_m)$ satisfies the quantile constraints imposed on Y_i for each $i = 1, 2, \ldots, n$.

For the inverse problem defined in the thesis, the coordinates of vector X are transfer coefficients k_{ij}, model predictor functions G_i are represented by equation (9) and coordinates of vector Y correspond to the aggregated distributions on the amount of iodine retained in the thyroid after 1, 7, 30 and 90 days since single injection in the blood.

The main steps of probabilistic inversion technique are explained below. All calculations are carried out with help of UNICORN software (developed at TU Delft) which is equipped with satellite program provided for probabilistic inversion.

Initially, the transfer coefficients k_{ij} are assumed to be independent of each other and log-uniformly, but not identically, distributed. The choice of starting distributions on the transfer coefficients is rather hard since they should cover the range of realistic values.

In the next step, we generate N = 30,000 samples form distributions on transfer coefficients yielding $X_i = (k_{12,i}, k_{14,i}, k_{23,i}, k_{24,i})$ for $i = 1, \ldots, N$. For each X_i we calculate corresponding N samples of $G_i = (G_{1,i}, \ldots, G_{4,i})$ using equation (9), $i = 1, \ldots, N$. In result

we get N samples for (X,G) = (k_{12}, k_{14}, k_{23}, k_{24}, G_1, … , G_4). It should be noted that the initial distributions of k_{ij} has to be chosen such that some calculated samples of G_i fall within each inter-quantile interval for each Y_i.

Let $u_i = (X_i, G_i)$ denotes the i-th sample. Since we have drawn N samples form initial distribution, each sample u_i has the same probability of occurrence equal to $p(u_i) = p_i = 1/N$. As result the probability vector $p = [p_1, p_2, \dots, p_N]$ is created.

After that, the values of G_1, … , G_4 are transferred to the EXCEL spread sheet where the subsequent steps of probabilistic inversion are performed. Now, we try to change the probabilities p_i so as ensure that the distributions of G_1, … , G_4 satisfy the specified quantile constraints of Y_1, … , Y_4 given by the decision maker. In other words, we want to find vector of probabilities $p' = [p_1', p_2', \dots, p_N']$ such that, if we re-sample this distribution with respect to probability given by its weight p_i' the quantile constraints for Y_1, … , Y_4 (i.e. 5th, 50th, 95th percentiles) are satisfied, or satisfied "as close as possible", in the re-weighted distribution. The "closeness" of two distributions is usually measured by relative information[28].

There are many strategies of finding the weights. However, in the present study we made a use of the iterative algorithms available to solve the probabilistic inversion problems. These iterative solvers do not require model inversion, but they are based on sample re-weighting. In other words, they involve successively updating initial probability vector p as to find the vector of weights p' for which the quantile constraints on Y_i are satisfied or satisfied as close as possible.

Two iterative algorithms have been developed, namely Iterative Proportional Fitting (IPF) and Parameter Fitting for Uncertain Models (PARFUM). Both of them are quite fast and easy to implement. We do not provide the formal description of these two strategies, they can be found in [9, 10, 12].

However, both of them were applied to find the distributions of the transfer coefficients for radioiodine and radiocesium biokinetic models. But only the results of IPF were presented in the main report. This is explained by the fact that for feasible problems

[28] Let $S^n = \{p \in \mathbb{R}^n \mid p_i \geq 0, \Sigma p_i = 1\}$. For $p, q \in S^n$, the relative information of p with respect to q, I(p|q), is defined as

$$I(p|q) = \sum_{i=1}^{n} p_i \ln(p_i / q_i).$$

(as we have here) the IPF algorithm has more advantages than PARFUM. It means that, if IPF converges, then it converges to the vector p' has minimum information relative to the starting distribution p, in the set of probability vectors satisfying the constraints.

Below we present the results of PARFUM algorithm and the resulting uncertainty distributions for the number of nuclear transformations of I^{131} and Cs^{137} in specified organs over 20 years following ingestion, dose and risk coefficients. Of course, the results will be given for both combination schemes applied to aggregate experts' distributions on the retentions of radionuclides in given organs and at specified times.

As one can observe the results of PARFUM are very close to those obtained with IPF.

1. Radioiodine

quantile / transfer coefficient	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
k_{12}	0.184	0.152	0.833	1.08	4.69	6.84
k_{14}	0.211	0.158	1.44	1.49	8.55	7.78
k_{23}	7.52E-6	7.49E-6	8.71E-5	9.97E-5	2.08E-3	2.68E-3
k_{24}	0.0102	0.0101	0.0113	0.0122	0.0378	0.022

Quantiles on transfer coefficients after probabilistic inversion with PARFUM and equal (E) and performance based (P) DM

quantile / t	5%		50%		95%	
	Probabilistic Inversion	E.DM	Probabilistic Inversion	E.DM	Probabilistic Inversion	E.DM
1 day	0.116	0.116	0.29	0.287	0.563	0.563
1 week	0.117	0.112	0.368	0.286	0.547	0.548
1 month	0.0863	0.0854	0.292	0.236	0.437	0.457
3 months	0.0417	0.0415	0.154	0.154	0.235	0.366

Quantiles on retention at selected times after probabilistic inversion for I with PARFUM and equal weight DM (E)

k_{12}	1	0.61	0.03	0.19
k_{14}	0.61	1	0.12	0.11
k_{23}	0.03	0.12	1	0.07
k_{24}	0.19	0.11	0.07	1

Rank correlation matrix for transfer coefficients and equal weight DM and PARFUM

quantile	5%		50%		95%	
t	Probabilistic Inversion	P.DM	Probabilistic Inversion	P.DM	Probabilistic Inversion	P.DM
1 day	0.146	0.15	0.28	0.28	0.423	0.43
1 week	0.149	0.15	0.335	0.29	0.437	0.44
1 month	0.0813	0.11	0.29	0.23	0.374	0.39
3 months	7.65E-3	0.059	0.151	0.15	0.194	0.28

Quantiles on retention at selected times after probabilistic inversion for I with PARFUM and performance based DM (P)

k_{12}	1	0.69	0	0.15
k_{14}	0.69	1	0.07	0.05
k_{23}	0	0.07	1	0.12
k_{24}	0.15	0.05	0.12	1

Rank correlation matrix for transfer coefficients for I and performance based DM and PARFUM

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$U_{Thyroid}$	1.26E5	1.001E5	2.53E5	2.8E5	3.73E5	4.55E5

Quantiles of $U_{Thyroid}$ with PARFUM, equal (E) and performance based (P) DM

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$h_{Thyroid,20}$	5.73E-7	4.58E-7	1.15E-6	1.13E-6	1.71E-6	3.3E-6

Quantiles of dose coefficients for thyroid with PARFUM, equal (E) and performance based (P) DM

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
Cancer MortalityRisk $_{Thyroid}$	2.07E-11	2.04E-11	3.1E-10	3.28E-10	4.61E-9	4.99E-9

Quantiles of the risk coefficients for thyroid with PARFUM, equal (E) and performance based (P) DM

2. Radiocesium

quantile transfer coefficient	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
c_{12}	0.0105	2.66E-3	4.11	2.33	17.6	16.2
c_{13}	0.365	0.350	1.31	2.58	5.78	6.47
c_{24}	1.08E03	4.6E-4	7.76E-3	6.94E-3	0.403	0.515
c_{25}	3.68E-4	3.49E-4	1.14E-3	1.24E-3	3.11E-3	3.08E-3
c_{34}	3.92E-4	2.42E-4	0.161	9.94E-3	0.905	0.709
c_{35}	1.73E-5	1.89E-5	5.39E-4	1.14E-3	0.0173	0.0192

Quantiles on transfer coefficients after probabilistic inversion with PARFUM and equal (E) and performance based (P) DM

quantile t	5%		50%		95%	
	Probabilistic Inversion	E.DM	Probabilistic Inversion	E.DM	Probabilistic Inversion	E.DM
1 day	0.871	0.870	0.962	0.962	0.992	0.992
1 week	0.745	0.745	0.859	0.859	0.945	0.943
1 month	0.528	0.545	0.722	0.724	0.891	0.893
1 year	2.43E-3	2.38E-3	0.0667	0.0648	0.267	0.264
5 years	9.27E-11	1.21E-10	1.11E-5	1.08E-5	6.56E-3	6.3E-3

Quantiles on retention at selected times after probabilistic inversion for Cs with PARFUM and equal weight DM (E)

c_{12}	1	0.29	0.24	0.13	0.51	0.06
c_{13}	0.29	1	0.21	0.02	0.36	0.04
c_{24}	0.24	0.21	1	0.23	0.43	0.03
c_{25}	0.13	0.02	023	1	0.1	0.05
c_{34}	0.51	0.36	0.43	0.1	1	0.24
c_{35}	0.06	0.04	0.03	0.05	0.24	1

Rank correlation matrix for transfer coefficients for Cs and equal weight DM and PARFUM

quantile	5%		50%		95%	
t	Probabilistic Inversion	P.DM	Probabilistic Inversion	P.DM	Probabilistic Inversion	P.DM
1 day	0.921	0.92	0.959	0.96	0.98	0.9803
1 week	0.797	0.8	0.85	0.85	0.901	0.9004
1 month	0.6	0.6	0.7	0.7001	0.8	0.8008
1 year	0.0109	0.01	0.038	0.04003	0.105	0.1019
5 years	9.22E-9	9.011E-9	1.32E-7	1E-7	0.0101	0.009988

Quantiles on retention at selected times after probabilistic inversion for Cs with PARFUM and performance based DM (P)

c_{12}	1	0.31	0.38	0.16	0.66	0.23
c_{13}	0.31	1	0.37	0.17	0.60	0.26
c_{24}	0.38	0.37	1	0.21	0.47	0.17
c_{25}	0.16	0.17	0.21	1	0.11	0.07
c_{34}	0.66	0.60	0.47	0.11	1	0.34
c_{35}	0.23	0.26	0.17	0.07	0.34	1

Rank correlation matrix for transfer coefficients for Cs and performance based DM and PARFUM

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
U_{WB}	5.82E6	4.44E6	8.92E6	1.03E7	1.66E7	2.3E7

Quantiles of U_{WB} with PARFUM, equal (E) and performance based (P) DM

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$h_{WB,20}$	1.08E-8	8.18E-9	1.66E-8	1.91E-8	3.19E-8	4.3E-8

Quantiles of coefficients for whole body dose with PARFUM, equal (E) and performance based (P) DM

quantile	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$\text{Cancer MortalityRisk}_{WB}$	2.08E-10	1.96E-10	8.22E-10	9.45E-10	3.77E-9	4.93E-9

Quantiles of risk coefficients for whole body with PARFUM, equal (E) and performance based (P) DM

Appendix C: Quantification of uncertainty in dose-response relationships of toxic chemical substances using structured expert judgment

Introduction and summary

The purpose of this study is

(1) to quantify the uncertainty in the dose-response relationships with use of structured expert judgment, and
(2) to compare the uncertainty from expert judgment with the range of published values in the literature.

The relation between the dose of inhaled chemical material (expressed as a function of exposure concentration and exposure time) and the response of the exposed individuals is represented by probit functions. Probit relations can be used to implement regulatory rules e.g. by determining allowable concentration levels. We utilize structured expert judgment data for acute lethal effects in humans exposed to inhalation of three toxic chemical substances, namely ammonia, acrylonitrile and sulphur trioxide [1, 2].

The estimation of lethal probit relation for humans is based on experiments and data of the toxicity of chemicals. Obviously, the experiments at high doses are not carried out on human beings. Therefore, the probit functions are derived by extrapolation from animal experiments.

The lack of human data and difficulties in extrapolation from animals to human beings make lethal dose-response relationships uncertain. The crucial part of our study is to quantify the uncertainty in probit relations using the data provided by the structured expert judgment elicitation process performed for the Dutch Ministry of Housing, Physical Planning and Environment [1, 2]. The study concerned ammonia, acrylonitrile, sulphur trioxide, hydrogen fluoride and azinphos-methyl, but the expert data for the last two was not sufficient for the present analysis.

Roughly, the idea is to have experts quantify their uncertainty on dose which realizes various given risk levels, and to find a distribution over the parameters of a

mathematical dose-response relation (in this case the probit relation) which capture that uncertainty. If the dose-response relation were known with certainty, the dose realizing a given risk level would be known with certainty. The distribution over possible doses, for a given risk level therefore reflects the uncertainty in the dose-response relation. The mathematical technique which translates the experts' uncertainty in doses into distributions over the parameters of the probit relation is called probabilistic inversion.

We make the use of the experts' individual estimates in form of 5^{th}, 50^{th} and 95^{th} quantiles of the concentration values that cause death within 24 hours in 10, 50 and 90 percent of the exposed population after exposure of 60 minutes for ammonia and acrylonitrile and 30 minutes exposure for sulphur trioxide. These assessments are combined with equal and performance based aggregation schemes according to methods described in (Cooke, 1991). A combination scheme is called a "decision maker" (DM), thus we speak of equal and performance based DMs.

Tables 4.4 - 4.6 (see next page) present the published probit relations for ammonia, acrylonitrile and sulphur trioxide; and in addition the probit relations based on the median estimates of the equal and performance based DMs. For all probit relations the concentration values (in units of parts per million, ppm) which realize given risk levels in certain exposure conditions are calculated. The risk levels are chosen arbitrarily and serve an example.

These tables present a plume of different probit relations, but do not yield an uncertainty distribution over dose-response models. Hence, they do not constitute a quantification of model uncertainty.

The probit relations documented in the literature often exhibit large disagreements. This holds in particular for ammonia and acrylonitrile whose toxicity and health impact are rather well understood. For all three substances the probit parameters corresponding to equal and performance based DMs are close to each other.

Study	Ammonia probit parameters			$C^1(r)$ - ppm for risk of death within 24 hours after exposure of 60 minutes			
	a_1	b_1	n	0.00001	0.0001	0.01	0.1
SAFETI	-9.82	0.71	2	218	321	855	1784
Goossens (1998)	-35.02	2.01	2	941	1078	1525	1977
CCPS (2000)	-35.9	1.85	2	2576	2986	4351	5770
TNO (Aarts and others 2000)	-16.5	1	2	714	938	1881	3171
Canvey Island study (1978)	-46.95	2.205	2.75	587	642	808	960
AIChE	-16.14	1	2	596	783	1572	2649
CPR 18E (2005)	-14.92	1	2	324	426	854	1439
Perry and Articola (1980)	-28.33	2.27	1.36	630	753	1185	1665
CPD Green Book (1992)	-15.12	1	2	358	471	944	1591
Rijnmond (1982)	-30.57	1.385	2.5	1642	1923	2874	3885
This study P.DM	-36.9	2.05	2	1251	1430	2008	2591
This study E.DM	-38.7	2.18	2	1094	1240	1706	2168

Table 4.4: Probit parameters for exposure to ammonia and their published counterparts. P.DM and E.DM are the median values for the probit parameters for the performance based and equal weight DM.

Study	Acrylonitrle probit parameters			$C^2(r)$ - ppm for risk of death within 24 hours after exposure of 60 minutes			
	a_2	b_2	n	0.00001	0.0001	0.01	0.1
Goossens (1998)	-6.88	0.96	1	46	82	350	1038
CCPS (2000)	-29.42	3.008	1.43	64	72	100	127
AIChE	-7.81	1	1.3	31	47	137	306
CPR 18E (2005)	-9.61	1	1.3	123	188	548	1224
CPD Green Book (1992)	-9.61	1	1.3	123	188	548	1224
This study P.DM	-9.09	1.2	1	60	95	302	720
This study E.DM	-12.1	1.57	1	59	84	204	396

Table 4.5: Probit parameters for exposure to acrylonitrile and their published counterparts. P.DM and E.DM are the median values for the probit parameters for the performance based and equal weight DM.

Study	Sulphur trioxide probit parameters			$C^3(r)$ - ppm for risk of death within 24 hours after exposure of 30 minutes			
	a_3	b_3	n	0.00001	0.0001	0.01	0.1
Goossens (1998)	- 4.46	0.68	2	8	12	35	75
TNO (1989)	-11.41	1	2	79	104	209	352
This study P.DM	-9.1	1.01	2	24	31	62	104
This study E.DM	-9.33	0.938	2	39	52	110	191

Table 4.6: Probit parameters for exposure to sulphur trioxide and their published counterparts. P.DM and E.DM are the median values for the probit parameters for the performance based and equal weight DM.

The diversity among probit functions is reflected in the concentration levels realizing given lethality levels (see the last four columns in tables above). One can see that the spread of concentrations for risk level 10^{-1} overlap the spread for risk level 10^{-5} for ammonia and sulphur trioxide and risk level 10^{-4} in case of acrylonitrile. This indicates how uncertain the existing probit relations are. In our study we quantify the uncertainty in the parameters of the probit relations for ammonia, acrylonitrile and sulphur trioxide (see Chapter 2). This yields probability distributions of concentration values $C^i(r)$ for substance *i* that realize lethality level *r* (the same as in Tables 4.4 - 4.6). The results are shown in Tables 4.7 - 4.9.

quantile / Concentration	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$C^1(10^{-1})$	2300	649	2700	2400	3100	4700
$C^1(10^{-2})$	1500	410	2120	1790	2510	3800
$C^1(10^{-4})$	771	219	1480	1240	1920	2900
$C^1(10^{-5})$	587	178	1300	1070	1720	2620

Table 4.7: Uncertainty distributions of the concentration of ammonia realizing given risk level for equal (E) and performance based (P) DM

quantile / Concentration	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$C^2(10^{-1})$	329	62.9	649	512	1540	4490
$C^2(10^{-2})$	126	33.9	292	252	754	1790
$C^2(10^{-4})$	34.2	12.1	95.3	97.1	360	683
$C^2(10^{-5})$	20.5	8.07	60	66.5	268	510

Table 4.8: Uncertainty distributions of the concentration of acrylonitrile realizing given risk level for equal (E) and performance based (P) DM

quantile / Concentration	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$C^3(10^{-1})$	4.43	6.6	79.2	178	1300	5920
$C^3(10^{-2})$	1.42	2.24	30.7	90.2	729	1810
$C^3(10^{-4})$	0.292	0.765	16.7	39.2	340	697
$C^3(10^{-5})$	0.213	0.559	13.1	28.5	256	510

Table 4.9: Uncertainty distributions of the concentration of sulphur trioxide realizing given risk level for equal (E) and performance based (P) DM

For ammonia the distributions provided by the performance based DM are narrower than the spreads of concentrations calculated from existing certain probit functions. For acrylonitrile and sulphur trioxide these distributions are wider than the spreads of published values. This evidently reflects the fact that there are more published probit relations for ammonia than for the other two. In any case, it demonstrates that a plume of published values will not necessarily correspond with the results of a structured expert judgment quantification.

It is worth emphasizing that the structured expert judgment process involves empirical quality controls. In addition to the variables of interest, experts are queried about calibration variables, that is, variables from their field of expertise whose true values are known post hoc. On the basis of these variables, statistical accuracy and informativeness are measured (Cooke 1991). Statistical accuracy is the p-value for the hypothesis that a

given expert's probability statements are accurate. Low values (say, beneath 0.05) indicate that the hypothesis would be rejected. Informativeness is measured as Shannon relative information with respect to a background measure. The combinations can also be empirically controlled in this way. Table 2.4 shows the statistical accuracy and informativeness for the equal and performance based DMs for the three substances.

	Combination scheme	Statistical accuracy (p-value)	Informativeness	number of seed variables
ammonia	E. DM	0.28	0.9714	10
	P. DM	0.11	1.591	10
acrylonitirle	E. DM	0.28	1.327	10
	P. DM	0.24	3.093	10
sulphur trioxide	E. DM	0.14	1.957	7
	P. DM [29]	0.42	4.03	7

Table 2.4: Statistical accuracy and informativness scores for equal (E) and performance (P) based combinations

No such empirical control is possible for an ensemble of dose-response relations gathered from the published literature. In this sense, an uncertainty distribution over dose-response models based on structured expert judgment is preferable to a distribution based simply on a plume of published relations.

The report is subdivided into six chapters. The first chapter presents basic information about probit relations and the way in which the uncertainty in probit parameters can be quantified. Chapter 2 presents and discusses the results of the equal and performance based combinations of experts' estimates on the concentration values of toxic substances that cause given lethality response in the exposed population under certain exposure conditions. Chapter 3 describes the probabilistic inversion technique and presents its solution in the form of uncertainty distributions over probit parameters when applied to ammonia, acrylonitrile and sulphur trioxide probit models. The comparison between the probit relations for ammonia, acrylonitrile and sulphur trioxide obtained in our study and those documented in the literature with regard to their impact on the regulatory rules is the

[29] The performance based DM used to provide the probit relation in this study does not correspond exactly to the performance based DM in study for Dutch Ministry (see Table 2.3 and Table 4.6), due to minor changes in the software used to combine experts' individual assessments.

content of Chapter 4. Chapter 5 gives the final conclusions and the last chapter presents the list of references.

1. Dose-response relationships of toxic chemical substances

This chapter presents basic information about probit functions that represent the dose-response relationships of toxic chemical substances and provides the sketch of the uncertainty analysis of these relations. For details about the probit method, see (Finney, 1980).

In our study, the dose-response relationships represent the lethal responses of population of human beings as a result of exposure to disperse cloud of toxic gases. It is known that the physiological effects of toxic gases depend on their concentration in the air being inhaled and the period of time an individual is exposed to this concentration. The product of the concentration raised to a power (termed the concentration exponent) and exposure time is referred to as *dose* or *toxic load*. The dose to which the population is exposed is related to the lethal responses of that population via *probit equation* expressed in the following form

$$\Pr(C^n t) \quad F^{-1}(r) \tag{1.1}$$

where

- r is percentage of lethal responses observed at dose $C^n t$,
- F is cumulated normal distribution function with mean 5 and standard deviation 1,
- Pr is probit value of the percentage of lethal responses corresponding to dose $C^n t$,
- C is the concentration of toxic substance in parts per million [ppm] or milligrams per meter cube [mg/m^3],
- t is the exposure time in minutes [min],
- n is the exponent indicating the relative influence of C to the probit value with respect to values of t.

In practical applications the probit relation is represented as

$$\Pr \quad a \quad b \ \ln (C^{n} \quad t) \tag{1.2}$$

or according to (1.1)

$$^{1}(r) \quad 5 \quad a \quad b \ \ln (C^{n} \quad t) \tag{1.3}$$

where a is a dimensionless constant indicative for the dose at which lethal effect begins (or intercept of probit function), whose value depends on the dimensions of the concentration and exposure time, b is the slope of the probit curve, Φ is cumulated normal distribution function with zero mean and standard deviation 1. The other variables are defined as above.

The literature provides many different probit functions for well understood chemicals such as ammonia and acrylonitrile (see Table 1.1 and Table 1.2). Since toxicity of sulphur trioxide is related to that of sulfuric acid and exposure to this substance is very harmful, the experimental data and the information on its probit relation are sparse (see Table 1.3).

Study [Reference]	Ammonia probit parameters[30]		
	a	b	n
SAFETI [5]	-9.82	0.71	2
Goossens (1998) [3]	-35.02	2.01	2
CCPS (2000) [6]	-35.9	1.85	2
TNO (Aarts 2000) [7]	-16.5	1	2
Canvey Island study (1978) [1]	- 46.95	2.205	2.75
AIChE [8]	- 16.14	1	2
CPR 18E (2005) [9]	- 14.92	1	2
Perry and Articola (1980) [5]	- 28.33	2.27	1.36
CPD Green Book (1992) [5]	- 15.12	1	2
Rijnmond (1982) [1]	- 30.57	1.385	2.5

Table 1.1: Probit parameters for ammonia (NH_3)

[30] The probit parameters were derived based on concentration of toxic substance given in unit of parts per million (ppm) and exposure time in minutes. The probit relations for Goossens, Canvey Island study, CPR 18E and CPD Green Book were converted from mg/m^3.

Study [Reference]	Acrylonitrle probit parameters[1]		
	a	b	n
Goossens (1992) [1,2]	- 6.88	0.96	1
CCPS (2000) [6]	- 29.42	3.008	1.43
AIChE [8]	- 7.81	1	1.3
CPR 18E (2005) [9]	- 9.61	1	1.3
CPD Green Book (1992) [5]	- 9.61	1	1.3

Table 1.2: Probit parameters for acrylonitrile (CH_2)

Study [Reference]	Sulphur trioxide probit parameters[1]		
	a	b	n
Goossens (1998) [3]	- 4.46	0.68	2
TNO (1989) [1]	- 11.41	1	2

Table 1.3: Probit parameters for sulphur trioxide (SO_3)

The above tables show (in some cases very large) disagreement on parameters *a* and *b* of the probit relations for all designated substances. The values of intercepts vary between around - 47 and -10, -30 and -7, -12 and -5, respectively for ammonia, acrylonitrile and sulphur trioxide. For ammonia and acrylonitrile different studies do not agree on the exponent of the concentration *n*. None of the above probit relations enjoys universal acceptance.

The above tables indicate that the dose-response relations are uncertain. They do not tell us what the uncertainty is. In other words, they point to substantial model uncertainty, but do not provide for the quantification of this model uncertainty. That will be the goal of the present study.

Direct toxicology data on lethal consequences to humans are sparse, and extrapolations from animal experiments involve many additional uncertainties. In this study, we derive uncertainty distributions on the parameters of the probit function (1.3) using structured expert judgment. Although the probit model (1.3) is widely accepted, there are other mathematical forms for capturing dose-response relations. The techniques and data used here could also be applied to other mathematical models as well, but that is not undertaken in this study.

The structured expert judgment data is taken from an elicitation on toxicology of hazardous materials performed for the Dutch Ministry of Housing, Physical Planning and

Environment [1, 2]. The study was investigated the following substances: acrylonitrile, ammonia, sulphur trioxide, hydrogen fluoride and azinphos-methyl[31]. In total twenty-seven experts were selected and took part in the study. They assessed their uncertainty in the concentration causing given levels of response in a reference population. For each substance experts' estimates were combined using both equal and performance based aggregation schemes providing assessments for the so-called equal and performance based decision maker (DM), respectively. The details concerning the study for Dutch Ministry can be found in [1, 2]. However, its results for ammonia, acrylonitrile and sulphur trioxide obtained with use of median estimates of performance based DM are presented in tables above and will further serve a comparison scale.

2. Acute toxicity data and structured expert judgment

The main goal of this report is to use structured expert judgment to quantify the uncertainty in dose-response models for ammonia, acrylonitrile and sulphur trioxide. This chapter contains the description and the results of the expert judgment analysis performed with use of the results of elicitation session which was a part of the study on the toxicology of chemical substances carried out for Dutch Ministry [1, 2]. The description of experts' groups working at ammonia, acrylonitirle and sulphur trioxide, the structure of the questionnaires and the results of combination of experts' estimates with use of equal and performance based weighting schemes are presented and discussed in the subsequent sections.

2.1. Experts description and elicitation

Experts taking part in the study on the lethal toxicity of inhaled chemicals carried out for the Dutch Ministry were selected based on their achievements in the field of interest and the familiarity with the practical aspects of human exposure. The toxicity of ammonia, acrylonitrile and sulphur trioxide was assessed by three separate groups of six, seven and

[31] For the latter two substances, the expert data was insufficient to support the analysis of the present study, owning to dearth of expert data and calibration variables.

four experts over the world, respectively. The selected experts came form industrial and academic environments, and governmental agencies.

Experts were asked to give their subjective estimates in the form of median values and 90% confidence intervals on observable and measurable quantities. There were two types of questions which were related only to fatal consequences after inhalation of substances in the exposed population. One type of questions gave fixed inhalation concentrations of toxic substance and requested the assessment of the exposure time by which 10, 50 and 90% of the exposed population will die. The other type of questions requested the assessment of the concentrations by which 10, 50 and 90% of the exposed population will die under varying assumptions. For both sets of questions the varying assumptions were the exposure time (15, 30, 60 minutes), observation period (30 and 60 minutes, 24 hours) and the breathing rate (15 or 45 m^3/day).

The exposed population was defined as a general population of a typical industrialized and developed nation like the Netherlands including vulnerable groups. Vulnerable groups consist of individuals sensitive to inhalation of given substances because of age (approximately 20% of the population: 10% children (< 10 years), 10% old persons (> 70years)) and because of illness (5% of the population). Moreover, the exposed group could be considered to be a large and representative sample of this general population.

In order to measure the experts' individual performance and to obtain a performance based combination of the experts, a set of calibration (or *seed*) questions was prepared. The seed questions are questions which true answers are known post hoc but not to the experts at the time of the elicitation. In the light of sparse data concerning human responses to large exposures to toxic substances, the seed variables for all chemicals and experts' groups were related to animal experiments and human epidemiological research reported in the literature. For ammonia and acrylonitrile ten seed variables were elicited while for sulphur trioxide – seven. Detailed information about questionnaires and lists of experts can be found in [1, 2].

2.2. Results of expert judgment elicitation

The elicitation questionnaire was prepared to obtain the acute toxicity data required to quantify the uncertainty in parameters of the probit relations for ammonia, acrylonitrile and sulphur trioxide. The elicitation variables which have the greatest importance for our study are the concentration levels of designated substances that cause death in a given percent of the reference population within 24 hours after exposure of 60 minutes to ammonia and acrylonitrile and 30 minutes exposure to sulphur trioxide. The exposure time of 30 minutes for sulphur trioxide was chosen with regard to the severe effects of exposure to this substance like burns and blindness.

According to probit relation (1.3), experts' assessments reflect the 5th, 50th and 95th quantile points of the distribution of concentration $C^i(r)$ given in the following form

$$C^i(r) \quad \frac{\exp\left(\frac{^1(r) \quad a}{b}\right)}{t}^{1/n} \tag{2.1}$$

where index i corresponds to the chemical substance, r equal to 0.1, 0.5 and 0.9, t amounts for 30 and 60 minutes.

In our study, we assume that constants a and b are unknown parameters of the probit relations while the exponent of the concentration $C^i(r)$ is fixed. In the agreement with (Goossens, 1998) the value of exponent n equals to 2 for ammonia and sulphur trioxide and 1 for acrylonitrile. Thus, the concentrations of chemicals can be expressed by equations (2.2), (2.3) and (2.4) respectively for ammonia, acrylonitrile and sulphur trioxide

$$C^1(r) \quad \frac{\exp\left(\frac{^1(r) \quad a_1}{b_1}\right)}{60}^{0.5} \tag{2.2}$$

$$C^{2}(r) \quad \frac{\exp\left(\frac{^{1}(r) \quad a_{2}}{b_{2}}\right)}{60} \tag{2.3}$$

$$C^{3}(r) \quad \frac{\exp\left(\frac{^{1}(r) \quad a_{3}}{b_{3}}\right)}{30}^{0.5} \tag{2.4}$$

The results of combination of experts' assessments on the concentrations of toxic materials causing death in a given percent of the exposed population using both equal and performance weighting schemes are shown in Table 2.1, Table 2.2 and Table 2.3 below[32]. In the present study the distributions of variables of interest were calculated with help of the Excalibur software package (developed at Delft University of Technology) which allows the quantile experts' estimates for continuous uncertain variables and combine them according to classical model as proposed by Cooke [10].

quantile r	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
10%	2295	517.14	2700	2399	3105	4718.4
50%	3213	1074.6	4158	3526.9	4782	8152.5
90%	4208	1568.8	4950	4454.2	5693	11912

Table 2.1: Concentration of NH_2 for equal (E) and performance based (P) DM

[32] Concentration of toxic substance is given in units o parts per million (ppm) for the exposure time expressed in minutes (min).

quantile r	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
10%	325.2	81.07	650.4	512.19	1300.8	2468.9
50%	1084	139.1	2168	1389.8	4336	12298
90%	3252	286.04	6504	3191.2	13008	21997

Table 2.2: Concentration of CH_2 for equal (E) and performance based (P) DM

quantile r	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
10%	0.83	1.83	79.3	180.3	1508.5	2660.1
50%	18.5	22.1	305.8	510.7	2585.3	19060.8
90%	35.4	39.1	459.8	857	4865.8	50590.2

Table 2. 3: Concentration of SO_3 for equal (E) and performance based (P) DM

One can see that for all toxic materials and all percentages of lethal responses *r*, the probability distributions of concentrations $C^i(r)$ corresponding to the performance based DM are concentrated on narrower intervals and show lower spread (the ratio between 95th and 5^{th} quantiles) than these of equal weight DM. Moreover, one can observe that the probability distributions of concentrations of sulphur trioxide are concentrated on large intervals, even for performance based DM. This can be explained by the fact that the acute toxicity of this chemical is poorly known to experts.

The decision whether to choose equal or performance based DM can be motivated by the performance of these DMs. There are two measures of statistical performance: *statistical accuracy (*or *calibration)* and *information* (or *informativeness*). These measures are related to standard statistical methods and are based on the assessments of the seed variables. Moreover, they can be applied both to experts' assessments and to the combination of experts' assessments. *Statistical accuracy* is the p-value of the hypothesis that the experts' performance on seed variables supports the hypothesis that experts' probability statements are true; that is, the probability of falsely rejecting this hypothesis given the data. *Informativeness* represents the degree to which the distributions provided by expert are concentrated. In general, experts and decision makers with good calibration

and high information are preferred. Moreover, calibration should dominate over information, but information serves to discriminate between more or less equally calibrated experts (or/and DMs). The mathematical details about performance measures can be found in (Cooke, 1991).

The information and calibration scores for equal and performance based DMs calculated using all seed questions for ammonia, acrylonitirle and sulphur trioxide are presented in Table 2.4.

	Combination scheme	Statistical accuracy (p-value)	Informativeness	number of seed variables
ammonia	E. DM	0.28	0.9714	10
	P. DM	0.11	1.591	10
acrylonitirle	E. DM	0.28	1.327	10
	P. DM	0.24	3.093	10
sulphur trioxide	E. DM	0.14	1.957	7
	P. DM [33]	0.42	4.03	7

Table 2.4: Statistical accuracy and informativeness scores for equal (E) and performance (P) based combinations

For all designated toxic substances both equal and performance based DMs present acceptable statistical performance. For ammonia the equal weight DM is better calibrated than the performance based DM. Since calibration dominates over information the equal weight combination shows a bit better performance. For acrylonitrile both DMs represent comparable calibration. However, informativeness of the performance based DM is higher and thus his overall performance is better. Finally, the scores obtained for sulphur trioxide indicate that the performance based DM represents better quality of assessments. There is a scientific basis for preferring assessments of the performance based DMs when making quantitative statements on the toxicity of acrylonitirle and sulphur trioxide. For ammonia the performance of the equal weight DM is a bit better. (The choice between different combinations may depend on other factors than the statistical performance).

One more remark is in order: the numerical results given in this report differ slightly from those reported in [2]. The difference arises from the fact that in the study for the

[33] The performance based DM used to provide the probit relation in this study does not correspond to the performance based DM in study for Dutch Ministry (see Table 2.3 and Table 4.6). The difference arises by choice of software applied to combine experts' individual assessments.

Dutch Ministry the combined probability distributions were calculated using the older EXPO software package, which is a previous version of presents Excalibur.

Although the performance based combination of experts' assessments provides narrower confidence bounds for elicited variables and presents (in most cases) better statistical performance, the results of both weighting schemes will be used to obtain probability distributions on probit parameters.

It is apparent that the distributions of constants a and b in the probit relations cannot be derived directly form the experts' combined assessments and further post-processing of data contained in Tables 2.1 - 2.3 is required. The method that solves the problem is probabilistic inversion.

The description of the probabilistic inversion problem and its results are presented in the Chapter 3.

3. Probabilistic inversion technique and probit parameters

As mentioned in previous chapter, the uncertainty distributions of probit parameters can not be directly estimated based on experts' combined assessments on the concentration values causing death within a day in 10%, 50% and 90% of the population exposed to toxic release of ammonia, acrylonitrile and sulphur trioxide during prescribed time periods. The problem of assessing the uncertainty in parameters of dose-response relationship expressed in form of probit function (1.3) is an inverse problem. It can be described shortly as follows.

Subjective judgments of experts provide the combined distributions of the concentrations of ammonia, acrylonitrile and sulphur trioxide as given in Tables 2.1 – 2.3. For each chemical separately, the probabilistic inversion problem is to find the distributions of parameters a_i and b_i (i = 1, 2, 3) which, when applied in equations (2.2), (2.3) and (2.4), yield as well as possible the quantiles over the concentrations as summarized in Tables 2.1 – 2.3, respectively.

The first section of this chapter briefly describes the steps of probabilistic inversion method applied to the general probit function (1.3) while the second section presents and discusses the results of this method applied to ammonia, acrylonitrile and sulphur trioxide probit models.

3.1. Mathematical formulation of probabilistic inversion

The elicitation variables $Y_1, Y_2, \ldots, Y_n$ can be expressed as a functions of model input parameters $X_1, X_2, \ldots, X_m$ as

$$Y_i = G_i(X_1, X_2, \ldots, X_m) \quad \text{for } i = 1, \ldots, n.$$

From the expert judgment elicitation one has obtained 5^{th}, 50^{th} and 95^{th} quantiles of the marginal distributions of the elicitation variables Y_i. The probabilistic inversion problem is to find a distribution on the parameters $(X_1, X_2, \ldots, X_m)$ such that the distribution of $G_i(X_1, X_2, \ldots, X_m)$ satisfies the quantile constraints imposed on Y_i for each $i = 1, 2, \ldots, n$.

In our study, the coordinates of vector X are probit parameters *a* and *b*, model predictor functions G_i are represented by equation (1.3) and coordinates of vector Y correspond to the combined experts' assessments of the concentration C of the toxic substance causing death in 10, 50 and 90 percent of the reference population if exposed during time *t*.

The main steps of probabilistic inversion technique are explained below. The calculations are carried out with help of UNICORN software developed at Delft University of Technology which is equipped with satellite program provided for probabilistic inversion.

Initially, the unknown parameters of probit relations are assumed to be independent of each other and posses the uniform distributions on the intervals encompassing all their plausible values.

In the next step, we generate N = 30,000 samples form distributions of probit parameters yielding $X_i = (a_i, b_i)$ for $i = 1, \ldots, N$. For each X_i we calculate corresponding N samples of $G_i = (G_{1,i}, G_{2,i}, G_{3,i})$ using equation (1.3), $i = 1, \ldots, N$. In result we get N samples for $(X,G) = (a, b, G_1, G_2, G_3)$.

Let $u_i = (X_i, G_i)$ denotes the i-th sample. Since we have drawn N samples form initial distribution, each sample u_i has the same probability of occurrence equal to $p(u_i) = p_i = 1/N$. As a result the probability vector $p = [p_1, p_2, \ldots, p_N]$ is created.

After that, the values of G_1, G_2, G_3 are transferred to the EXCEL spread sheet where the subsequent steps of probabilistic inversion are performed. Now, we try to re-weight the N samples so as the obtained distribution of G_1', G_2', G_3' agrees with specified distributions of Y_1, Y_2, Y_3 given by the decision makers. In other words, we want to find vector of probabilities $p' = [p_1', p_2', \ldots, p_N']$ such that if we re-sample this distribution with respect to probability given by its weights p' the quantile constraints for Y_1, Y_2, Y_3 (i.e. 5th, 50th, 95th percentiles) will be satisfied, or satisfied "as close as possible", in the re-weighted distribution. The "closeness" of two distributions is measured by relative information[34].

There are many iterative algorithms available to solve the probabilistic inversion problems based on sample re-weighting. These algorithms involve successively updating initial probability vector p as to find the vector of weights p'. From description above one easily sees that the iterative solvers for probabilistic inversion do not require model inversion. There are various strategies for finding the weights. However, in this report one of the probabilistic inversion problem solvers, Iterative Proportional Fitting (IPF) is applied. The detailed information about IPF and other algorithms the reader can find in [11, 12, 13].

3. 2. Results of probabilistic inversion

In this section the results of probabilistic inversion applied to probit models (2.2), (2.3) and (2.4) are presented.

With the initial distributions assigned to each pair of probit parameters (a_i, b_i) IPF algorithm was run. It provided the distributions of probit parameters a and b that are minimally informative with respect to starting distributions and that reproduce the experts' quantiles as given in Tables 2.2 – 2.4. The 5th, 50th and 95th quantiles of resulting distributions are presented in Tables 3.1 – 3.3 for ammonia, acrylonitrile and sulphur trioxide, respectively. The next six tables show the 5th, 50th and 95th quintile points of concentrations obtained when the probit coefficients resulting probabilistic inversion are

[34] Let $S^n = \{p \in \mathbb{R}^n \mid p_i \geq 0, \Sigma p_i = 1\}$. For $p, q \in S^n$, the relative information of p with respect to q, I(p|q), is defined as $I(p|q) = \sum_{i=1}^{n} p_i \ln(p_i / q_i)$.

applied in equations (2.2), (2.3) and (2.4) and those representing the combined experts' distributions.

quantile	5%		50%		95%	
Probit parameters	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
a_1	-51	-53.5	-36.9	-38.7	-20.6	-17.2
b_1	1.51	1.17	2.05	2.18	2.79	3

Table 3.1: Quantiles on probit parameters after probabilistic inversion for NH_3 with equal (E) and performance based (P) DM

quantile	5%		50%		95%	
Probit parameters	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
a_2	-16.5	-18.1	-9.09	-12.1	-6.81	-7.01
b_2	1.01	1.08	1.2	1.57	1.81	1.96

Table 3.2: Quantiles on probit parameters after probabilistic inversion for CH_2 with equal (E) and performance based (P) DM

quantile	5%		50%		95%	
Probit parameters	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
a_3	-14.5	-14.5	-9.10	-9.33	0.306	-1.36
b_3	0.502	0.46	1.01	0.938	1.82	1.69

Table 3.3: Quantiles on probit parameters after probabilistic inversion for SO_3 with equal (E) and performance based (P) DM

quantile	5%		50%		95%	
r	IPF	E.DM	IPF	E.DM	IPF	E.DM
10%	649	517.14	2400	2399	4700	4718.4
50%	1080	1074.6	3530	3526.9	7850	8152.5
90%	1570	1568.8	4490	4454.2	1.19E4	1.1912E4

Table 3.4: Quantiles on the concentration of NH_3 causing death in given percent of exposed population with IPF and equal weight (E) DM

quantile	5%		50%		95%	
	IPF	P.DM	IPF	P.DM	IPF	P.DM
10%	2300	2295	2700	2700	3100	3105
50%	3230	3213	3890	4158	4800	4782
90%	4220	4208	5050	4950	6600	5693

Table 3.5: Quantiles on the concentration of NH_3 causing death in given percent of exposed population with IPF and performance based (P) DM

quantile	5%		50%		95%	
	IPF	E.DM	IPF	E.DM	IPF	E.DM
10%	62.9	81.07	512	512.19	4490	2468.9
50%	128	139.1	1360	1389.8	12700	12298
90%	273	286.04	3160	3191.2	27900	21997

Table 3.6: Quantiles on the concentration of CH_2 causing death in given percent of exposed population with IPF and equal weight (E) DM

quantile	5%		50%		95%	
	IPF	P.DM	IPF	P.DM	IPF	P.DM
10%	329	325.2	649	650.4	1540	1300.8
50%	1080	1084	2160	2168	4390	4336
90%	3210	3252	6430	6504	13200	13008

Table 3.7: Quantiles on the concentration of CH_2 causing death in given percent of exposed population with IPF and performance based (P) DM

quantile	5%		50%		95%	
	IPF	E.DM	IPF	E.DM	IPF	E.DM
10%	6.6	1.83	178	180.3	5920	2660.1
50%	22.5	22.1	450	510.7	1.93E4	19060.8
90%	39.3	39.1	852	857	4.93E4	50590.2

Table 3.8: Quantiles on the concentration of SO_3 causing death in given percent of exposed population with IPF and equal weight (E) DM

quantile	5%		50%		95%	
r	IPF	P.DM	IPF	P.DM	IPF	P.DM
10%	4.43	0.83	79.2	79.3	1300	1508.5
50%	17.8	18.5	290	305.8	2660	2585.3
90%	34.6	35.4	498	459.8	5810	4865.8

Table 3.9: Quantiles on the concentration of SO_3 causing death in given percent of exposed population with IPF and performance based (P) DM

We observe that the agreement between distributions of concentrations of toxic substances corresponding to equal and performance based DMs and those reproduced with use of probabilistic inversion, though not perfect, is good.

For ammonia and sulphur trioxide the median estimates of probit parameters a_i and b_i (i = 1, 3) for equal and performance based DMs are very close to each other, but only for ammonia and acrylonitrile the 90% confidence bounds are wider for the equal weight DM. For sulphur trioxide, the ranges of values of parameters a_3 and b_3 are larger for the performance based DM.

Another attractive feature of the probabilistic inversion tool is that it returns not only the marginal distributions of parameters we are looking for, but it also specifies the dependencies in the model equations (2.2) - (2.4). Tables 3.10 – 3.15 below present the rank correlation[35] matrices for ammonia, acrylonitrile and sulphur trioxide probit models.

For all toxic substances under study the parameters of the probit relations are (strongly) negatively correlated.

[35] Rank correlation or Kendall's Tau is a measure of monotone relationship between random variables, i.e. the degree to which large or small values of one random variable associate with large or small values of another. It is attractive since it is invariant to the choice of marginal distributions.

a_1	1	0.80	0.29	0.14	0
b_1	0.80	1	0.13	0.28	0.42
C_{10}^1	0.29	0.13	1	0.98	0.94
C_{50}^1	0.14	0.28	0.98	1	0.98
C_{90}^1	0	0.42	0.94	0.98	1

Table 3.10: Rank correlation matrix for NH_2 probit model with equal weight DM

a_1	1	0.85	0.04	0.38	0.59
b_1	0.85	1	0.17	0.58	0.79
C_{10}^1	0.04	0.17	1	0.78	0.63
C_{50}^1	0.38	0.58	0.78	1	0.93
C_{90}^1	0.59	0.79	0.63	0.93	1

Table 3.11: Rank correlation matrix for NH_2 probit model with performance based DM

a_2	1	0.68	0.52	0.40	0.29
b_2	0.68	1	0.15	0.29	0.41
C_{10}^2	0.52	0.16	1	0.99	0.96
C_{50}^2	0.40	0.29	0.99	1	0.99
C_{90}^2	0.29	0.41	0.96	0.99	1

Table 3.12: Rank correlation matrix for CH_2 probit model with equal weight DM

a_2	1	0.88	0.28	0.28	0.05
b_2	0.88	1	0.26	0.07	0.40
C_{10}^2	0.58	0.26	1	0.93	0.73
C_{50}^2	0.28	0.07	0.93	1	0.93
C_{90}^2	0.05	0.40	0.73	0.93	1

Table 3.13: Rank correlation matrix for CH_2 probit model with performance based DM

a_3	1	0.51	0.34	0.23	0.13
b_3	0.51	1	0.52	0.63	0.71
C_{10}^3	0.34	0.52	1	0.99	0.97
C_{50}^3	0.23	0.63	0.99	1	0.99
C_{90}^3	0.13	0.71	0.97	0.99	1

Table 3.14: Rank correlation matrix for SO_3 probit model with equal weight DM

a_3	1	0.48	0.46	0.34	0.21
b_3	0.48	1	0.41	0.54	0.66
C_{10}^3	0.46	0.41	1	0.99	0.95
C_{50}^3	0.34	0.54	0.99	1	0.98
C_{90}^3	0.21	0.66	0.95	0.98	1

Table 3.15: Rank correlation matrix for SO_3 probit model with performance based DM

4. Dose-response relationships for ammonia, acrylonitrile and sulphur trioxide – comparison with existing probit relations

As shown in the previous chapter, the expert judgment elicitation process and data processing using probabilistic inversion proceeded successfully. It allowed establishing the uncertainty in probit relations for ammonia, acrylonitrile and sulphur trioxide. In this chapter the resulting uncertainty in probit relations will be compared with ranges of values reported in the literature.

The dose-response relationships derived using the median estimates of probit parameters corresponding to equal and performance based DMs are summarized in Tables 4.1 – 4.3.

	Probit relation for ammonia
equal weight DM	$Pr = -36.9 + 2.18 \cdot \ln(C^2 \cdot t)$
performance based DM	$Pr = -38.7 + 2.05 \cdot \ln(C^2 \cdot t)$

Table 4.1: Median probit relations for ammonia with equal (E) and performance based (P) DM

	Probit relation for acrylonitrile
equal weight DM	$Pr = -12.1 + 1.57 \cdot \ln(C \cdot t)$
performance based DM	$Pr = -9.09 + 1.2 \cdot \ln(C \cdot t)$

Table 4.2: Median probit relations for acrylonitrile with equal (E) and performance based (P) DM

	Probit relation for ammonia
equal weight DM	$Pr = -9.33 + 0.938 \cdot \ln(C^2 \cdot t)$
performance based DM	$Pr = -9.36 + 1.02 \cdot \ln(C^2 \cdot t)$

Table 4.3: Median probit relations for sulphur trioxide with equal (E) and performance based (P) DM

In the risk assessment one often needs to measure the responses to very low concentrations such as ppm or ppb (parts per billion). A typical dose-response curve, however, has sigmoid shape of the log-normal distribution and is difficult to use at these low concentrations. In the probit method the sigmoid plot is transformed into the straight

line what allows to easily estimating concentration (dose) of toxic substance at given lethality levels, including threshold concentrations (doses) [36] and LC_i (LD_i)-values[37].

The next figures present the plots of the number of fatalities (probit) versus the level of (natural logarithm of) concentration (dose) for ammonia, acrylonitrile and sulphur trioxide as given in Tables 4.1 – 4.3.

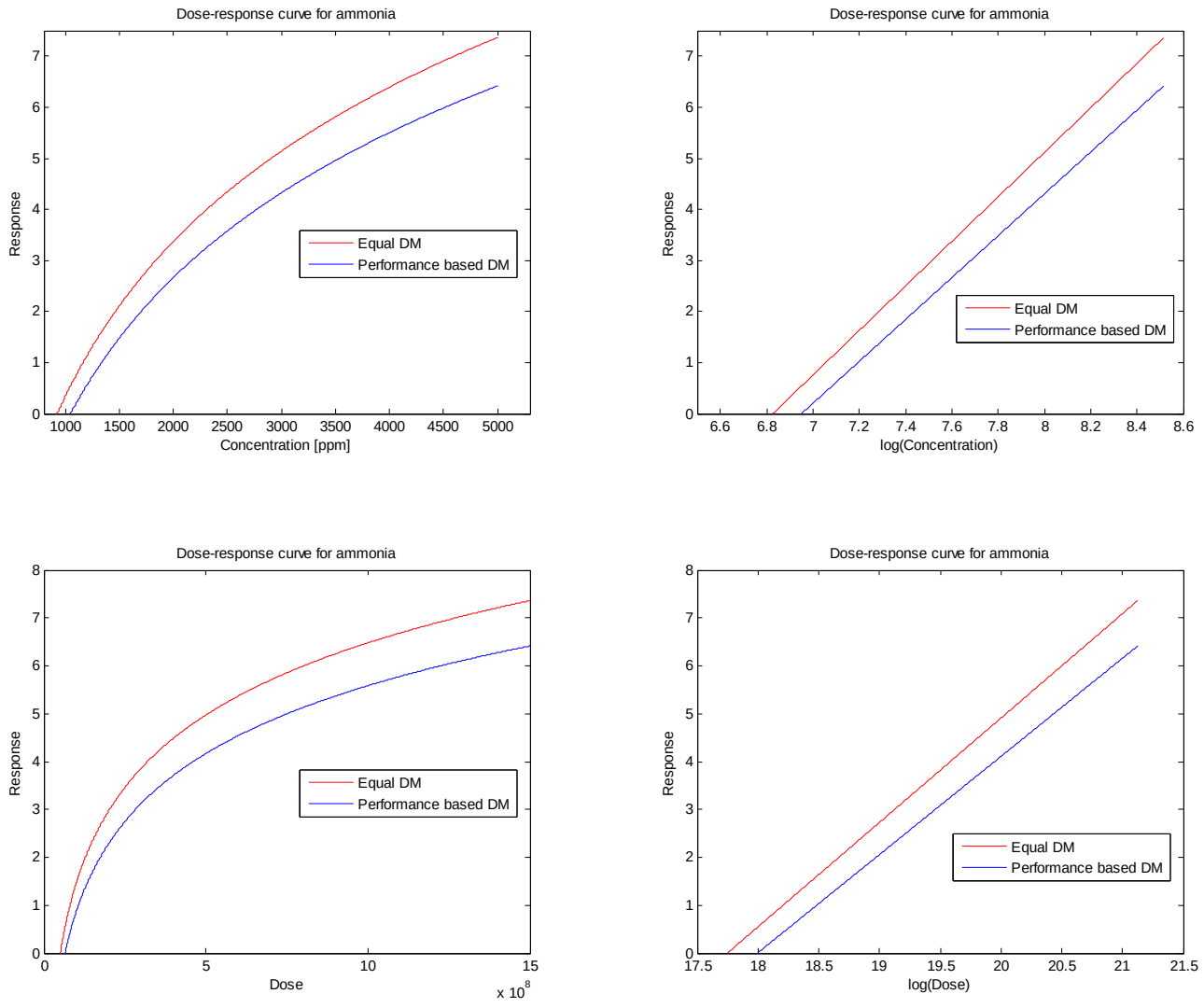


Figure 1: Probit function for ammonia; Response = Φ^{-1}(% of exposed population which dies)+5

[36] Threshold concentration (dose) denotes exposure concentration (dose) below which an effect is not expected.

[37] LC_i (LD_i)- value represents lethal concentration (dose) i.e. the concentration (dose) of the chemical substance at which i% if the exposed population will die.

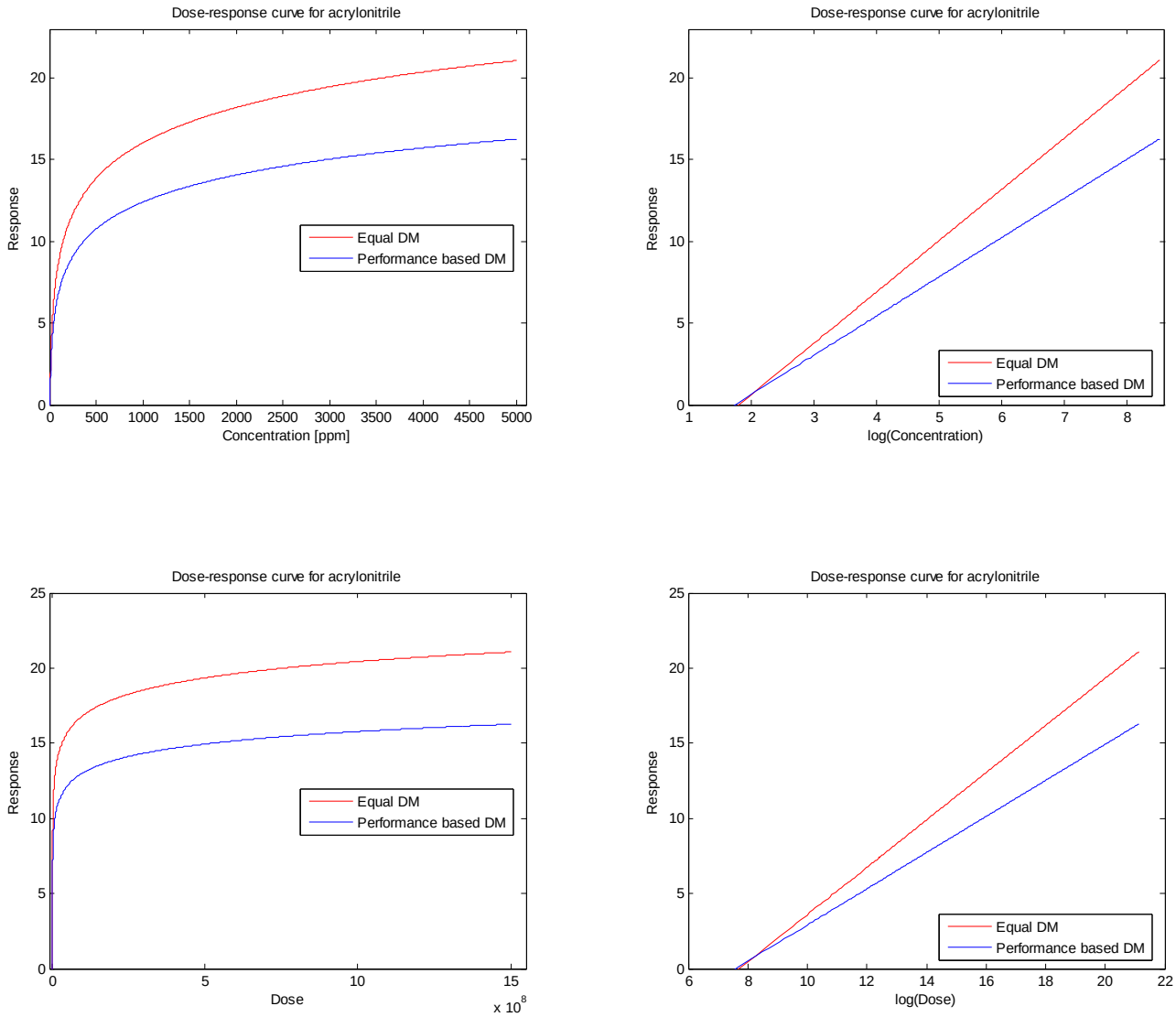


Figure 2: Probit function for acrylonitrile; Response = Φ^{-1}(% of exposed population which dies)+5

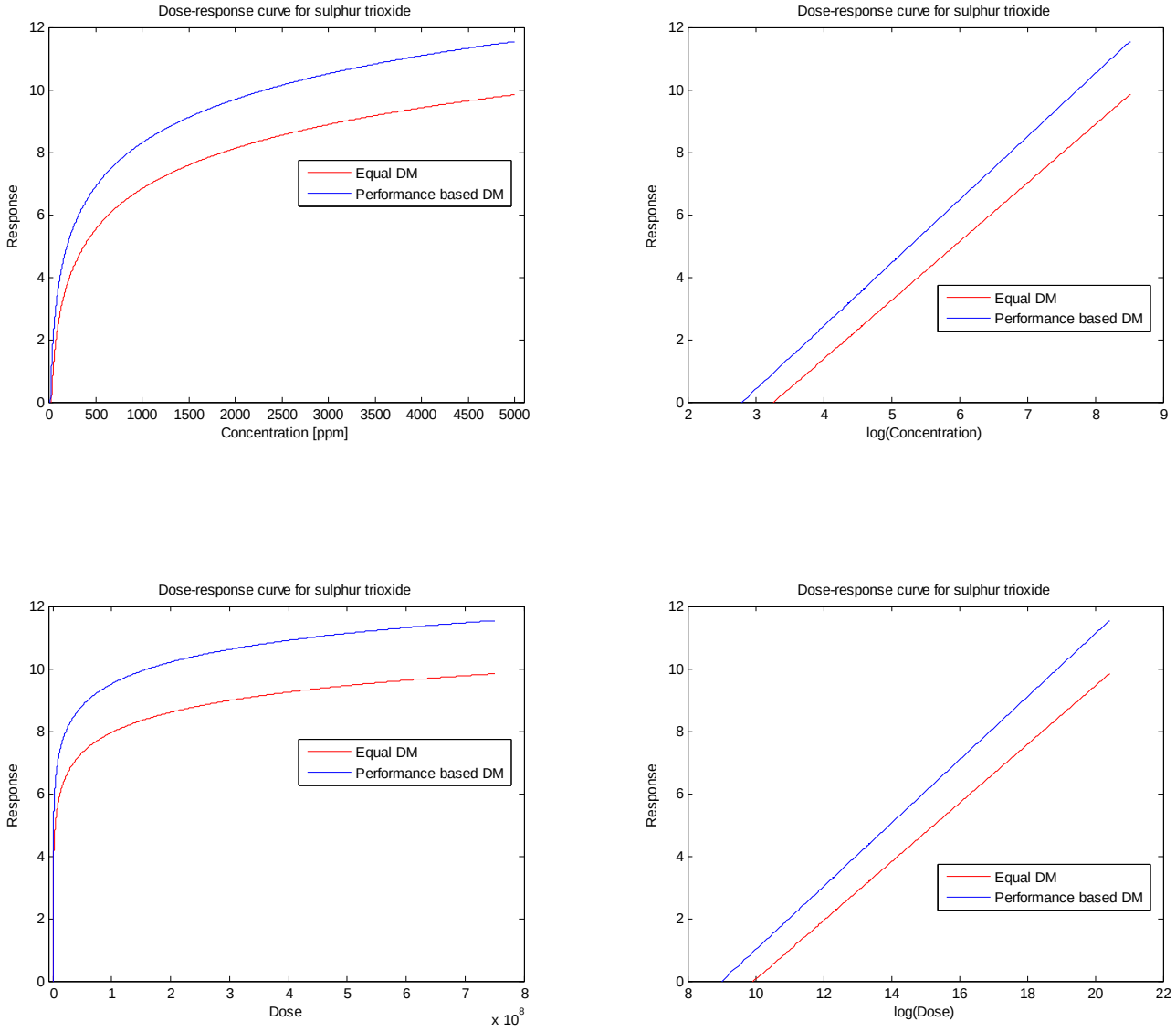


Figure 3: Probit function for sulphur trioxide; Response = Φ^{-1}(% of exposed population which dies)+5

The published dose-response relationships and those derived using the median estimates of probit parameters are presented in Tables 4.4 – 4.6 for ammonia, acrylonitrile and sulphur trioxide, respectively. In addition, four last columns in each table show the concentration values in ppm of substance *i* which realize the following risk levels *r*: 10^{-1}, 10^{-2}, 10^{-4}, 10^{-5} given the time of exposure.

Study	Ammonia probit parameters			$C^1(r)$ - ppm for risk of death within 24 hours after exposure of 60 minutes			
	a_1	b_1	n	0.00001	0.0001	0.01	0.1
SAFETI	-9.82	0.71	2	218	321	855	1784
Goossens (1998)	-35.02	2.01	2	941	1078	1525	1977
CCPS (2000)	-35.9	1.85	2	2576	2986	4351	5770
TNO (Aarts and others 2000)	-16.5	1	2	714	938	1881	3171
Canvey Island study (1978)	-46.95	2.205	2.75	587	642	808	960
AIChE	-16.14	1	2	596	783	1572	2649
CPR 18E (2005)	-14.92	1	2	324	426	854	1439
Perry and Articola (1980)	-28.33	2.27	1.36	630	753	1185	1665
CPD Green Book (1992)	-15.12	1	2	358	471	944	1591
Rijnmond (1982)	-30.57	1.385	2.5	1642	1923	2874	3885
This study P. DM	-36.9	2.05	2	1251	1430	2008	2591
This study E. DM	-38.7	2.18	2	1094	1240	1706	2168

Table 4.4: Probit parameters for exposure to ammonia and their published counterparts. P.DM and E.DM are the median values for the probit parameters for the performance based and equal weight DM.

Study	Acrylonitrle probit parameters			$C^2(r)$ - ppm for risk of death within 24 hours after exposure of 60 minutes			
	a_2	b_2	n	0.00001	0.0001	0.01	0.1
Goossens (1992)	-6.88	0.96	1	46	82	350	1038
CCPS (2000)	-29.42	3.008	1.43	64	72	100	127
AIChE	-7.81	1	1.3	31	47	137	306
CPR 18E (2005)	-9.61	1	1.3	123	188	548	1224
CPD Green Book (1992)	-9.61	1	1.3	123	188	548	1224
This study P. DM	-9.09	1.2	1	60	95	302	720
This study E. DM	-12.1	1.57	1	59	84	204	396

Table 4.5: Probit parameters for exposure to acrylonitrile and their published counterparts. P.DM and E.DM are the median values for the probit parameters for the performance based and equal weight DM.

Study	Sulphur trioxide probit parameters			$C^3(r)$ - ppm for risk of death within 24 hours after exposure of 30 minutes			
	a_3	b_3	n	0.00001	0.0001	0.01	0.1
Goossens (1998)	-4.46	0.68	2	8	12	35	75
TNO (1989)	-11.41	1	2	79	104	209	352
This study P. DM	-9.1	1.01	2	24	31	62	104
This study E. DM	-9.33	0.938	2	39	52	110	191

Table 4.6: Probit parameters for exposure to sulphur trioxide and their published counterparts. P.DM and E.DM are the median values for the probit parameters for the performance based and equal weight DM.

The probit relations for ammonia obtained in present study appear to be consistent with the proposals given by study for Dutch Ministry (Goossens, 1998) and American Institute of Chemical Engineers (CCPS, 2000). The acrylonitrile probit relations are more in line with statements of Publication Series on Dangerous Substances (CPR 18E, 2005) and Committee for the Prevention of Disasters (CPD Green book, 1992). Since there is (almost) no data available on the toxicity and dose-response following exposure to sulphur trioxide, effective comparisons can not be made. However, according to Table 4.6 results of our study are closer to proposal of The Netherlands Organization (TNO, 1989).

The diversity in probit relations for designated toxic substances results in the significant differences in the values of concentrations that cause given lethality response of the exposed population. One can observe that the spread of concentrations for risk level 10^{-1} overlap the spread for risk level 10^{-5} for ammonia and sulphur trioxide and risk level 10^{-4} in case of acrylonitrile. Such differences imply large uncertainties in the regulatory decisions. Moreover, the concentration values calculated from median probit relations of equal and performance based DMs are situated approximately in the middle of concentration intervals realizing each considered risk level determined by published relations.

All probit relations for ammonia, acrylonitrile and sulphur trioxide presented in tables above are assumed to be known with certainty. However, in our study with help of experts' combined assessments and probabilistic inversion technique we have derived the probability distributions of probit parameters a_i and b_i, i = 1, 2, 3. They can be subsequently used to find the distributions of concentration values $C^i(r)$ for substance i realizing given risk level $r = 10^{-1}, 10^{-2}, 10^{-4}, 10^{-5}$ when exposure to chemicals lasts accordingly 30 and 60 minutes. Tables 4.7 – 4.9 show the 5^{th}, 50^{th} and 95^{th} quantiles of resulting distributions when experts' assessments were combined using equal and performance based aggregation schemes.

quantile / Concentration	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$C^1(10^{-1})$	2300	649	2700	2400	3100	4700
$C^1(10^{-2})$	1500	410	2120	1790	2510	3800
$C^1(10^{-4})$	771	219	1480	1240	1920	2900
$C^1(10^{-5})$	587	178	1300	1070	1720	2620

Table 4.7: Uncertainty distributions of the concentration of ammonia realizing given risk level for equal (E) and performance based (P) DM

quantile / Concentration	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$C^2(10^{-1})$	329	62.9	649	512	1540	4490
$C^2(10^{-2})$	126	33.9	292	252	754	1790
$C^2(10^{-4})$	34.2	12.1	95.3	97.1	360	683
$C^2(10^{-5})$	20.5	8.07	60	66.5	268	510

Table 4.8: Uncertainty distributions of the concentration of acrylonitrile realizing given risk level for equal (E) and performance based (P) DM

quantile / Concentration	5%		50%		95%	
	P.DM	E.DM	P.DM	E.DM	P.DM	E.DM
$C^3(10^{-1})$	4.43	6.6	79.2	178	1300	5920
$C^3(10^{-2})$	1.42	2.24	30.7	90.2	729	1810
$C^3(10^{-4})$	0.292	0.765	16.7	39.2	340	697
$C^3(10^{-5})$	0.213	0.559	13.1	28.5	256	510

Table 4.9: Uncertainty distributions of the concentration of sulphur trioxide realizing given risk level for equal (E) and performance based (P) DM

We see that the uncertainty distributions of concentrations $C^i(r)$ corresponding to all performance based DMs are narrower than the equal weight DMs (what should not be a surprise). For ammonia the spreads of concentrations for given risk levels in Table 4.4 is much larger than the confidence bands of performance based DM's concentrations shown in Table 4.7. For other toxic materials, the ranges of concentration values obtained by pushing the probability distributions of probit parameters through equations (2.3) and (2.4) are larger than the ranges calculated from published probit relations. The reason for that is evidently that the acute toxicity of ammonia is the most studied of three substances.

5. Conclusions

Several conclusions have been adduced during the report. In this chapter we point out the essential findings and the summary conclusions.

The following final conclusions may be drawn from the case study:

1. There are many published probit relations ammonia, which has been very well studied, and fewer for acrylonitrile and sulphur trioxide. The published values indicate very substantial disagreement. A exposure realizing a risk level of 10^{-5} according to one relation may realize a risk level of 10^{-1} according to another.
2. Structured expert judgment has been successfully used to quantify the uncertainty in dose-response relations.
3. The performance-based combination of experts usually gives more informative distributions with greater statistical accuracy.
4. The uncertainty in dose-response relations obtained from expert judgment with probabilistic inversion is sometimes narrower than the spread of published values, and sometimes broader.

Appendix D: Uncertainty categories determined in Federal Guidance Report no. 13

Let X and Y are the lower and upper bounds of the 90% confidence interval for the values of risk coefficient. Based on the ratio between X and Y the following categories has been distinguish

Uncertainty category	*Definition*
A	$(Y / X) < 15$
B	(Y / X) 25
C	(Y / X) 50
D	(Y / X) 100
E	$(Y / X) > 150$

Note: A derived value Y/X in the range 15 - 35, 35 - 65, or 65 - 150 wan considered be approximately 25, 50, or 100, respectively.

Appendix E: Estimation of parameters of the lognormal distribution based on quintile points

Let Z and X denote variables possessing respectively lognormal and normal distributions with parameters $\mu \in R$ and $\sigma > 0$. It is known that lnZ has the same distribution as variable X. Furthermore, the standardization of variable X leads to

$$\frac{\ln Z - \mu}{\sigma} \stackrel{d}{=} \frac{X - \mu}{\sigma} \stackrel{d}{=} Y,$$

where Y is standard normal variable. Thus, $\frac{\ln z_a - \mu}{\sigma} = y_a$, where z_a and y_a are the a^{th} quantiles of variable Z and Y. As a result the quantiles of the Z are expressed as

$$z_a = \exp(\mu + \sigma y_a).$$

Since the median of the standard normal random variable is zero then the parameter μ is the natural logarithm of median of Z, i.e. $\mu = \log(z_{50})$. Moreover,

$$\frac{\log z_a - \mu}{y_a} = \frac{\log z_a - \log z_{50}}{y_a} = \frac{\log \frac{z_a}{z_{50}}}{y_a}.$$

Recalling that the 95^{th} percentile of standard normal distribution equals 1.6449 one ends up with $\sigma = \frac{\log \frac{z_{95}}{z_{50}}}{1.6449}$.

References

Cancer mortality risk coefficient

1. Goossens L.H.J, Harrison J.D., Kraan B.C.P., Cooke R.M., Harper F.T., Hora S.C. *Probabilistic Accidence Consequence Uncertainty Analysis. Uncertainty Assessment for Internal Dosimetry*. NUREG/CR-6571, EUR 16773, SAND98-0119, Vol. 1 and 2, 1998.
2. Little M.P., Muirhead C.R., Goossens L.H.J., Kraan B.C.P., Cooke R.M., Harper F.T., Hora S.C. *Probabilistic Accidence Consequence Uncertainty Analysis. Late Health Effects Uncertainty Assessment*. NUREG/CR-6555, EUR 16774, SAND97-2322, Vol. 1 and 2, 1997.
3. International Commission Radiological Protection. *Limits for intake of radionuclides by workers*. Oxford: Pergamon Press; ICRP Publication 30, 1979.
4. Eckerman K.F., Leggett R.W., Nelson C.B., Puskin J.S., Richardson A.C.B. *Cancer Risk Coefficients for Environmental Exposure to Radionuclides.* Washington, DC: U.S. Environmental Protection Agency. Federal Guidance Report No.13; EPA 402-R-99-001, 1999.
5. Washington DC: U.S. Environmental Protection Agency. *Estimating Radiogenic Cancer Risk, Addendum: Uncertainty Analysis.* EPA 402-R-99-003, 1999.
6. Goossens L.H.J., Cooke R.M., Kraan B.C.P., Ehrhardt J., Fisher F., Hasemann I., Jones J.A., Brown J., Khursheed A., Phipps A. *Probabilistic accidence consequence uncertainty assessment using Cosyma. Uncertainty from the dose module*. EUR 18825 EN, 2001.
7. Pawel D.J., Leggett R.W., Eckerman K.F., Nelson C.B. The U.S. Environmental Protection Agency, Office of Radiation and Indoor Air Oak Ridge National Labolatory, Life Sciences Division. *Uncertainties in Estimates Of Cancer Risk From Environmental Exposure To Radionuclides*.
8. Cooke R.M. *Experts in Uncertainty*. Oxford University Press, 1991.

9. Kurowicka D., Cooke R.M. *Uncertainty Analysis with High Dimensional Dependence Modelling.* Delft Institute of Applied Mathematics, Delft University of Technology.
10. Cooke R.M., Nuta M., Havelaar A.H., van der Fels I. *Probabilistic Inversion for Chicken Processing Lines.* Department of Mathematics, Delft University of Technology, 2002.
11. Kraan B.C.P., Cooke R.M. *Uncertainty in compartmental models for hazardous materials - a case study.* Journal of Hazardous Materials, 71:253-268, 2000.
12. Du C., Kurowicka D., Cooke R.M. *Techniques for Generic Probabilistic Inversion*. Delft Institute of Applied Mathematics, Delft University of Technology.

Probit relation

1. Goossens L.H.J, Cooke R.M, Woudenberg F., van den Torn P. *Probit Functions and Expert Judgment: Protocol and Results*. Report prepared for the Ministry of Housing, Physical Planning and Environment, the Netherlands; Delft University of Technology, Safety Science Group and Department of Mathematics, Municipal Health Service, Rotterdam, Section Environmental Health, 1992.
2. Goossens L.H.J, Cooke R.M, Woudenberg F., van den Torn P. *Probit Functions and Expert Judgment: Backgrounds, Variables and Data*. Report prepared for the Ministry of Housing, Physical Planning and Environment, the Netherlands; Delft University of Technology, Safety Science Group and Department of Mathematics, Municipal Health Service, Rotterdam, Section Environmental Health, 1992.
3. Goossens L.H.J, Cooke R.M, Woudenberg F., van den Torn P. *Expert judgment and lethal toxicity of inhaled chemicals*. Journal of Risk Research vol. 1 no.2, p. 117-133, 1998.
4. Finney D.G. *Probit Analysis*, 4th edition, Cambridge University Press, 1980.
5. Lees F.P. *Loss Prevention in the Process Industries.* 2nd edition, Butterworths, 1996.
6. Center for Chemical Process Safety, *Guidelines for Chemical Process Quantitative Risk Analysis.* American Institute of Chemical Engineers, 2nd edition, 2000.

7. Aarts J.H.E, Mommers C. Muijser H., *Toxic Effects from Accidental Releases of Hazardous Substances (TEARHS) - Lethal and non-lethal effects in rats upon exposure during short periods of time,* Vol. V99.1136, TNO Nutrition and Food Research, Zeist, the Netherlands, 2000.
8. Prugh R.W. *Quantitative Evaluation of Inhalation Toxicity Hazards.* Proceedings of the 29th Loss Prevention Symposium, American Institute of Chemical Engineers, July 31, 1995.
9. Uijt de Haag P.A.M., Ale B.J.M. *Guidelines for Quantitative Risk Assessments, Purple Book, Part 1: Establishment.* Ministerie van Verkeer en Waterstraat, CPR 18E, Publication Series on Dangerous Substances (PGS 3), December 2005.
10. Cooke R.M. *Experts in Uncertainty*. Oxford University Press, 1991.
11. Kurowicka D., Cooke R.M. *Uncertainty Analysis with High Dimensional Dependence Modelling.* Delft Institute of Applied Mathematics, Delft University of Technology.
12. Cooke R.M., Nuta M., Havelaar A.H., van der Fels I. *Probabilistic Inversion for Chicken Processing Lines.* Department of Mathematics, Delft University of Technology, 2 002.
13. Du C., Kurowicka D., Cooke R.M. *Techniques for Generic Probabilistic Inversion*. Delft Institute of Applied Mathematics, Delft University of Technology.