



Probabilistic Exposure Assessment Methods in Chemical Safety Assessments (REACH)

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Foreword

The objectives of the project were 1) to introduce the principles of probabilistic exposure assessment and 2) to investigate the applicability and possibilities to use probabilistic methods in human exposure assessments in REACH context. This nature of this report is an eye opener which provides basis for further discussions. The report cannot consider being as a guidance which describes how to make a probabilistic exposure assessment.

The project was funded by the Nordic Council of Ministries through the Nordic Chemicals Group. The project was launched and coordinated by the Nordic Exposure Group, which also act as a project steering group. The practical work was done by a project group, which involved consultants. In addition to the steering and project group, the report was scientifically peer reviewed by Dr. Otto Hänninen (Public Health Institute, Finland).

This report was presented in the Nordic Workshop on Human Exposure Assessment Methods in REACH and Biocide Contexts, on 9th–10th of May 2007 in Oslo.

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Summary

In this report the applicability of the probabilistic methods for the assessment human exposure within the REACH context was investigated. The report and conclusions made were based on a real exposure study.

Based on the case study examples the following main conclusions can be drawn: Although probabilistic technique provides a sophisticated way to characterize exposure, risks and variability it is unlikely that it could be a routine method used in REACH CSA or other regulatory risk assessments (pesticides or biocides). Although there are commercial, user friendly software available (@Risk®, Chrystal Ball®, Analytica®), the probabilistic analysis is still more close to science than practical exposure assessment carried out in workplaces. At the moment also regulatory authorities are lacking experience and competence in using the probabilistic models and interpreting the results.

The most difficult disadvantages using probabilistic techniques are: 1) difficulty of using the models, 2) an algorithm development, 3) collection of good quality input distributions 4) criteria on decision making (what is acceptable and what is not) and 5) communicating the results to the stakeholders. Models, which appear to be easily comprehensible and user-friendly, will definitely be published in the near future. It is crucial that the risk assessors and regulators do not fall for the first impression of simplicity, but understand the pitfalls of modelling. In addition, they must have enough knowledge of the principles of exposure assessment, and the techniques used to describe the exposure and risk. In other words, the risk assessors must be able to ask the right questions.

The probabilistic modelling could, however, be used as a special technique in more complex situations or when deterministic assessments have found exposures of concern (higher tier assessments).

1. Introduction

Characterization of exposure is an essential part in health risk assessments of chemicals for regulatory purposes. Exposure can be best characterized using exposure measurements. However, in the lack of measured data, e.g. for future scenarios, modelling is needed.

Historically, exposure models have been based on point estimates. This deterministic approach has advantage of simplicity and consistency. Moreover, risk characterization is also quite straightforward: comparison of exposure estimate to a health based guidance value. Widely used deterministic models (e.g. EASE) have been evaluated in known setups at least to some extent and their utilization has been accepted by stakeholders. The drawback with the deterministic approach is that it does not incorporate information about the variability of real exposures. Likewise, the uncertainty in the exposure estimate is not assessed or communicated.

A complementary modelling approach is probabilistic technique, which incorporates variability of exposure. In probabilistic modelling distributions of values are used instead of single values. The advantage of probabilistic technique is that the probability of occurrence of exposure is provided giving a sophisticated way to characterize and communicate exposure. Like for deterministic models also in the probabilistic approach the validity of exposure estimate depends on the quality and extent of the input data and the reliability of estimation algorithm.

Probabilistic methods have been used widely in North America in dietary exposure estimations (e.g. USEPA). Over the last few years the regulatory bodies and industry has also moved slightly towards the use of probabilistic techniques in refining exposure estimates in worker exposures (Pesticide Safety Directorate, UK). In operator exposure assessment (plant protection products) the European Commission and OECD working group on Pesticides have prepared reports on the use of probabilistic methods to assess operator exposure to plant protection products. In addition, use of probabilistic methods has been proposed for the effect assessment (both for hazard identification and assessment factors).

There are some published reports and peer-reviewed articles available where probabilistic methods have been investigated. References of this report contain examples of probabilistic analysis carried out, or further references to such case studies. Many of the reports are accessible via internet, but the addresses have been left out, as they tend to change.

It is expected that the probabilistic methods will be used in some extent also in REACH Chemical Safety Assessments. So far there is no experience on the use of this technique in the REACH-context. Furthermore, lessons learned in the Existing Chemicals programme should be

considered in the preparations for the REACH, e.g. concerning available exposure data.

The key concept in REACH Chemical Safety Assessment is the exposure scenario. By definition, an exposure scenario is a the set of conditions that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control exposures of humans and the environment (REACH, Annex I, 2003).

2. Exposure Modelling

Exposure models are conceptual or mathematical representations of exposure. They are used to assess occupational exposure particularly in cases when few or no measurements are available, for example for new uses of chemicals or exposure reduction design. One type of modelling is to use previously measured exposure data along with exposure factors. Exposure models provide an analytical structure for combining different types of data from different studies to make more complete use of existing information. When modelling, it is extremely important to ensure that the data, default values, algorithms and assumptions are valid and relevant for the purpose of the exposure assessment in question.

2.1 Variability and uncertainty

Environmental concentration data and human contact data are both subject to natural variability. Exposure parameters in the real world can seldom be represented by single fixed values. Usually there is a distribution of possible values with each having a probability of occurrence associated with it. Typically, exposures are log-normally distributed. They tend to have many low values and few high or very high values. The variability reflects the true heterogeneity in a well-characterized population across workers, places and time, and is not reducible through additional measurements, while the uncertainty represents our insufficient data and understanding of the phenomenon and related parameters. All exposure assessments include some degree of uncertainty, which is derived from the decisions, judgements and actions during the planning and execution of the assessment procedure. Variability can affect the precision of estimates of exposure and the degree to which they can be generalised, whereas uncertainty can lead to biased or inaccurate estimates. In all exposure assessments, the sources of uncertainty along with their effects on the outcome should be discussed at least qualitatively. A quantitative uncertainty assessment is preferred especially when more complex models are used for exposure assessments (IGHRC, 2004).

In practice, exposure models can be divided into four categories: deterministic or probabilistic, and mechanistic or empirical. Both mechanistic and empirical models can be classified as deterministic or probabilistic (see Table 1). As REACH legislation has raised the question of obtaining good quality exposure data to a new level, it is crucial to develop new approaches for exposure assessment. The main tool used in the existing chemicals programme was EASE, developed by the Health and Safety

Executive in the United Kingdom (CEC, 1996). At the moment, it is somewhat unclear how the deterministic EASE (which combines a decision-tree into measured air concentration and dermal adherence data) meets the requirements set by REACH. Therefore, new models, especially for first tier assessments are currently being developed, and EASE is being developed further for meet the requirements of higher tier demands.

Table 1. Model categories (adapted from IPCS, 2005).

	Mechanistic (= physical)	Empirical (= statistical)
Deterministic	Mathematical constructs of physical and/or chemical processes that predict fixed outputs for a fixed set of inputs (point estimates) (e.g. emission models using vapour pressure and ventilation characteristics, pesticide operator models predicting the exposure from, e.g., use rate. See EUROPOEM, van Hemmen, 2003).	Statistical models based on measured input and output values. A numerical representation of the relationship between input and output variables based on measurements (e.g. relationship between measured dermal contamination, determining process parameters, and personal exposure. See the RISKOFDERM models, Warren et al., 2006).
Probabilistic (= stochastic)	Mathematical constructs of physical and/or chemical processes that predict the range and probability density distribution of an exposure model outcome, which is also a distribution.	Regression-based models, where model variables and coefficients are represented by probability distributions, representing variability and/or uncertainty in the model inputs and parameters.

In the next chapters, deterministic and probabilistic modelling approaches relevant for REACH settings are presented in more detail.

2.2 Deterministic modelling

Deterministic models use and produce point estimates. Each parameter is given as a single default value. Empirical (statistical) models are based on a statistical relationship between input and output variables. They use equations to quantify the exposure setup and relevant exposure determinants. One example of an empirical model is traditional regression analysis. Statistical models cannot be considered reliable for predicting exposures outside the study population.

Since the input parameters in deterministic models are point estimates, the output is also a point estimate. The model input parameters are often chosen in a conservative way, and, therefore, the assessment represents the worst case or realistic worst case situation. The advantages of deterministic models are that they are simple to set up and use, they produce a single point estimate which is easy to interpret, communicate and to use in decision making. The disadvantages, however, are that the variability and uncertainty is not considered and assumptions may be made which are not representative of actual conditions (Cherrie et al. 2003). When the highly conservative parameters are multiplied in a model, the level of

conservatism gets really high. When using a deterministic model, it is not possible to quantify, how high. This kind of analysis is possible to accomplish in probabilistic approach, which can describe the variation much better.

Most of the present regulative human exposure models, such as earlier mentioned EASE, in the EU are deterministic. These models are used in exposure assessments in pesticide and biocide EU-evaluations. Also some process-specific models have been developed, such as a model for spray painting (Brouwer et al., 2001) and for pesticide exposure (Dosemeci et al. 2002). In conclusion, deterministic approach is useful in initial screening level assessments.

2.3. Probabilistic modelling

Theoretically, there is no single risk in a particular scenario, but as many risks as there are individuals in the population studied. Probabilistic modelling techniques make use of whole distributions, and they can be used to quantify the variabilities and uncertainties in the model variables and outputs. Basic feature of probabilistic analysis is the characterization of variability in a population while the characterization of variation together with uncertainty is a more advanced task. For decision-making, a probabilistic distribution gives the opportunity to choose between different percentiles. In the end, the selection of the percentile is a matter of policy.

The advantages of probabilistic techniques are that the input parameters can be expressed as distributions and thus a result of an analysis is also in a shape of distribution. Depending on the availability and quality of data, any exposure variables relevant to the scenario in question can be presented as distributions.

2.3.1 Distributions

Distributions can include the data values themselves, where the “raw” data is used as model inputs as such (in a form of a histogram) or with intermediate points (empirical or non-parametric distribution function). Theoretical or parametric distributions are fitted using statistical techniques. Most common theoretical distributions are normal and log-normal distributions. There is no consensus as to which is the best approach for obtaining representative distributions for modelling. In general, if only a few data is available, the parametric theoretical distributions may be preferable. It must be evaluated carefully, whether the measured data represents the scenario to be assessed. Both empirical and theoretical distributions (and point estimates) can be used in the same model. For instance, in the example of pesticide operator exposure (see Chapter 2.3.3), it is

common that the surrogate exposures are measured in field conditions, but the values for the treated area may come from agricultural statistics or when this data does not exist, the distribution is theoretically formed. It is crucial, however, to know the details about the agricultural practices in order to estimate the minimum and maximum areas. The more there is knowledge of the scenario in question, the more valid modelling can be executed.

When creating distributions, it is essential to evaluate the data carefully. Does it contain values under the detection limit (e.g. measured exposures), are the exceptionally high values “normal”, or do they represent misuse or accidental exposure situations (outliers)? The method and principles used to deal with these situations, for example, by truncating the high end of the distribution, must be transparent and well reported. Another important issue is to handle the correlations among input variables. Some correlations are quite obvious, like body weight and body surface area, but some may not be so easily noticed. All correlations should be identified and addressed a priori. In certain cases statistical relationships between exposure determinants may affect especially estimation of the variability (e.g. SD, GSD) of the exposures significantly (Hänninen et al., 2003, 2005). Risk assessment software allows modelling of such relationships using a rank-correlation method.

2.3.2 Monte Carlo simulation

The most common approach used in probabilistic modelling involves the use of a mathematical sampling technique called Monte Carlo simulation. It combines the results of hundreds or thousands of random samplings of values from input distributions, and produces an output distribution reflecting the expected range and frequency of exposures. A simulation calculates the model repeatedly iterating (sampling) values from the probability distributions describing probabilities of the input variables. The values from variables (distributions) are selected randomly. In Monte Carlo analysis, the sampling from the distribution is usually done either by simple random sampling or Latin hypercube sampling. The latter method is considered to be more efficient.

2.3.3 Worked example on probabilistic pesticide operator exposure assessment

In Figure 1 an example of a probabilistic analysis is presented. In this example (application of pesticide in field) the dermal exposure is expected to be depended on the area treated and the use rate of the chemical. The exposure algorithm is expressed as $E = A * UR * Es$ (E = dermal exposure, A = area treated, UR = Use Rate, Es = Surrogate exposure level). The term “surrogate exposure” refers to the use of other, substitute data

or measurements, i.e. on one substance used to estimate analogous or corresponding values for another substance. In the example of pesticide application, the surrogate levels are presented as one kilogram of the product would have been applied to a one hectare field area. In deterministic modelling, one chooses the percentile, which is to be applied as the default exposure level. In probabilistic approach, the whole distribution can be utilised. The other two parameters (area and use rate) are usually selected to represent the worst case. The maximum area was found from the EU agricultural statistics, and the maximum use rate recommended in the product's use instructions. It is possible, that in the case of the field area, the distribution of the areas may be wide, as can be observed from the figure below (Figure 1). The maximum area may represent a highly extreme situation. If the distribution is not evaluated, this remains to be unnoticed.

The equation used here as an example is used in several deterministic pesticide operator exposure models used in EU's approval procedure of active ingredients. It has been noticed, that the determinants of this model do not explain the exposure very well. With probabilistic techniques, the variability can be taken into account.

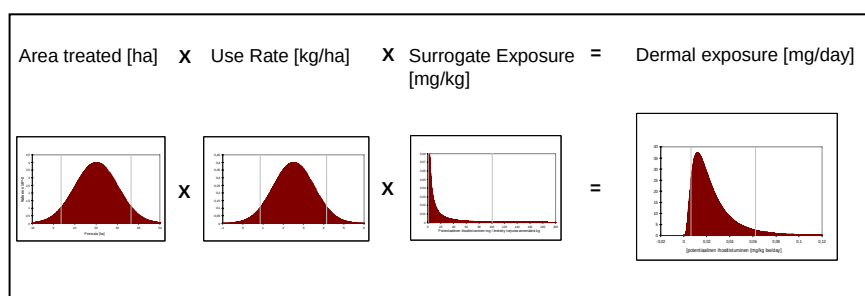


Figure 1. An example of a probabilistic analysis of pesticide exposures in field application.

2.3.4 One- and two-dimensional probabilistic analysis to estimate variability and uncertainty

In principle the probabilistic analysis can be done in one or two dimensions. In one dimensional (1D) analysis the variation and uncertainty are combined, while in two dimensional (2D) analyses they are separated. However, uncertainties related to the model itself or so called “unknown unknowns” situations can never be fully characterized even by 2D-analysis. Examples of one and two dimensional simulation results are shown in Figures 2 and 3. Whether it is necessary and useful for the assessment to evaluate variability and uncertainty separately, must be decided case-by-case for each variable.

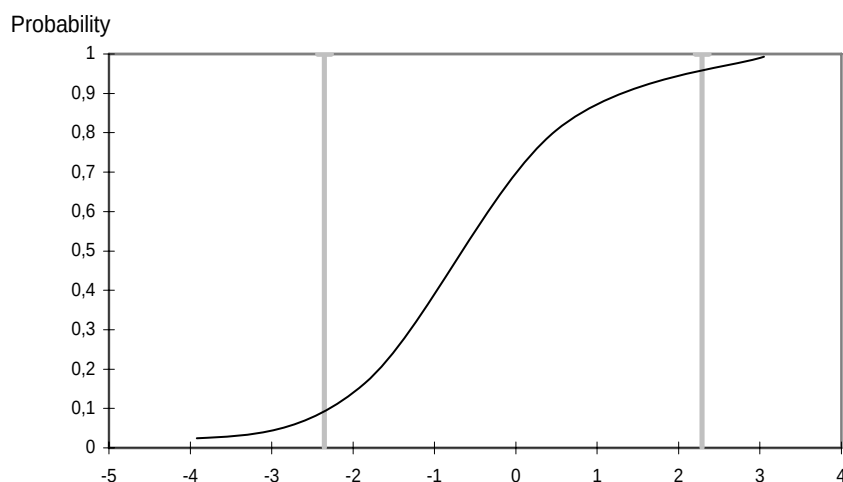


Figure 2. Output distribution in 1D-analysis (variation and uncertainty combined). The parameter is estimated to lie between ≈ -4 and ≈ 4 .

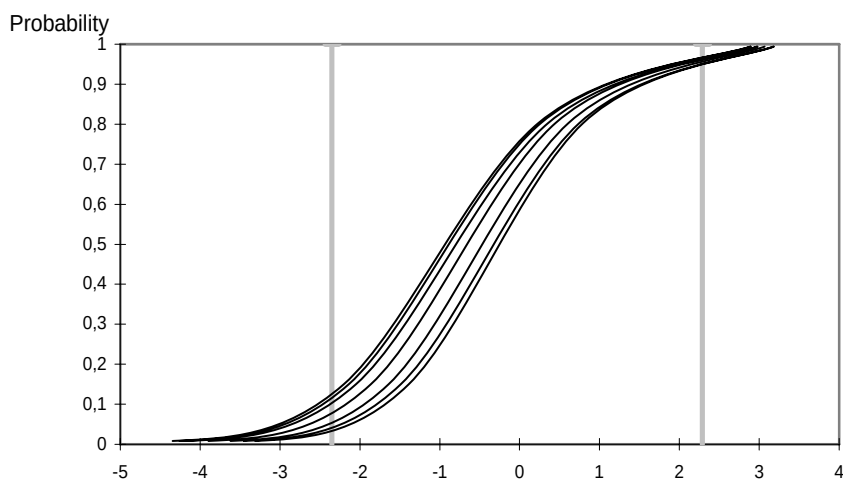


Figure 3. Output distribution in 2D-analysis (variation and uncertainty separated). The parameter is estimated to lie between ≈ -4 and ≈ 4 . Also the uncertainty associated with the values is shown. A statement of confidence that the true value will be within certain limits; thinner curve means less uncertainty.

2.3.5 Sensitivity analysis

The probabilistic technique allows to use sensitivity analysis to identify the most important and influential parameters. This is also important when designing new studies (field studies, questionnaires) for collecting new data. The most important focuses of these studies can be selected. Clear focus, and more resources, can be put into describing determinants which are the most influential, and the parameters with less importance can be handled “lighter”. In other words, the key parameters can be selected for deeper analysis, and for the less important ones it is possible to rely on data with less quality and extent. In Figure 4, it can be noticed

that concentration (85%) and exposure time (35%) are the two most influential determinants of exposure in this case. A sensitivity analysis attempts to provide a ranking of the model's input parameters with respect to their contribution to model result. The purpose of sensitivity analysis is to quantify the influence of input variables on the output variable and develop bounds on the model output. Also in a probabilistic model, some parameters can be presented as point estimates. It is advisable to conduct sensitivity analysis to identify which key parameters should be added into the model as distributions, and in which cases that does not add much value to the assessment. Some parameters may only have a weak effect on the outcome, or they are not very variable. In principle, sensitivity can refer to how conclusions may change if input parameters are changed. In theory, sensitivity analysis can be used in deterministic and statistical models too, but then it requires many data points. In Figure 4 is an example of sensitivity analysis made using @Risk-program. The algorithm and input distributions are presented in Chapter 3. Figure 4 shows that the parameter "concentration" [mg/m³ or mg.../G4] has strongest influence to the results, while parameter "normal/dermal" has only weak effect to the outcome.

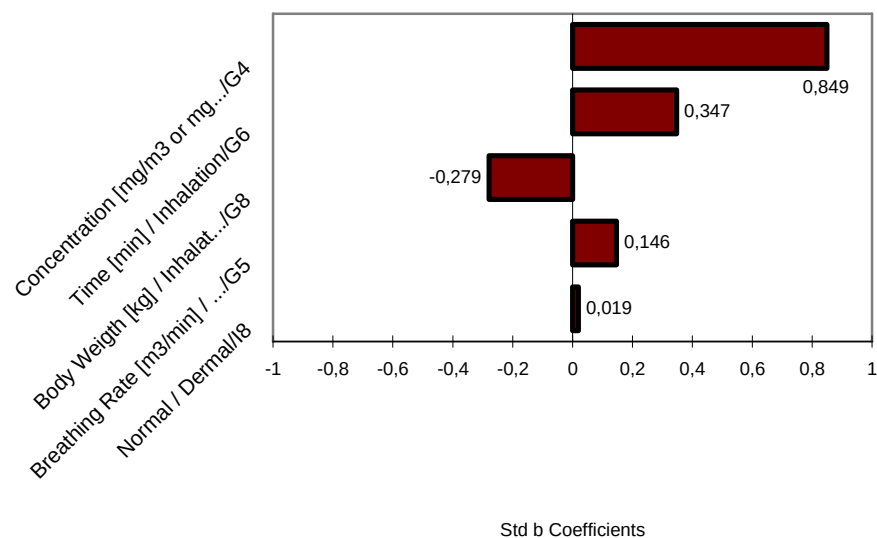


Figure 4. Sensitivity analysis from Equation 1 (see algorithm in Chapter 3)

2.4 Probabilistic models and software

In Table 2 a summary of some commercial probabilistic software is presented.

Table 2. A Summary of some commercial probabilistic software

Software	Short description	Users	Pros and cons
@Risk ®	Add-in spreadsheet model	STTV, KTL, FIOH	Easy to use, commercial training courses available. Only 1D-analysis
Crystal Ball®	Add-in spreadsheet model	KTL, FIOH	Easy to use, commercial training courses available. 1D and 2D-analysis
Analytica®	Stand-alone software for probabilistic modelling, developed in Harvard University	KTL	Graphical model building with reusable modules; requires substantial training
MATLAB®		HSE/HSL	Comprehensive mathematical software that lends itself to probabilistic modelling with proper libraries. Requires substantial training. Powerful but expensive.

STTV = National Product Control Agency for Welfare and Health, Finland

KTL = National Public Health Institute, Finland

FIOH = Finnish Institute of Occupational Health, Finland

HSE/HSL = Health and Safety Executive, Health and Safety Laboratory, UK

3. Exposure assessment in REACH

European Union new chemical regulation REACH enters into force on 1st of June 2007. One core element in REACH is that registrants should describe how the substance is manufactured and used safely. The safe use is described and justified by “exposure scenarios”. According to REACH regulation, exposure scenarios must be prepared when a substance is manufactured or imported in quantities of 10 tonnes per year and above and classified as dangerous or as PBT/vPvB.

An exposure scenario is a set of conditions that describe how a substance (as such, in a preparation or in an article) is manufactured or used during its life-cycle and how the manufacturer or importer or downstream user controls or recommends controlling exposure of humans and the environment. An exposure scenario includes the risk management measures (RMM) and operational conditions (OC) that ensure that the risks are adequately controlled.

The development of an exposure scenario is an iterative process. Once the registrant or downstream user has identified the relevant uses of his chemical substance he may derive a tentative exposure scenario on the basis of a first set of defined operational conditions of use, risk management measures and local conditions. From this tentative exposure scenario the exposure and risk can be estimated. If risk is not adequately controlled, then further refinement of either the exposure assessment or risk management measures may be done. The output of this iterative process will be the final exposure scenario (safe use). It is expected that a modelling will be one of the most important methods that are used for estimating exposure levels.

4. Case example: probabilistic exposure assessment in floor lacquering

To demonstrate application of probabilistic techniques in an occupational exposure setup, a probabilistic analysis was conducted for parquet floor lacquering. The contaminant of interest in the lacquer products was 2-(2-butoxyethoxy) ethanol, CAS 112-34-5 (hereafter referred to as DEGBE). It belongs to the group of glycol ethers, which are mainly used as solvents. The floor lacquering task with a certain solvent could be a practical example of an exposure scenario which should be analysed within a REACH chemical safety assessment in future.

The data used in the probabilistic analysis was obtained from a DEGBE exposure study conducted during the RISKOFDERM project by the Finnish Institute of Occupational Health (Laitinen & Pulkkinen, 2005). In this study, respiratory and hand exposures of nineteen workers were measured. No respiratory protection or gloves were used by the workers. In addition to the concentration measurements, also exposure determinants were recorded (working time, lacquered surface area and lacquer consumption volume).

The results of measured exposures and the exposure factors, i.e., the variables relating to working activities, are presented in Appendix 1 (Table A1-1). A correlation analysis showed that there is no relationship between exposure and lacquer use volumes, lacquering times or areas (Appendix 1, Table A1-2). The lack of correlation means that these available exposure determinants do not explain the exposure, as could be assumed a priori. The determinants of exposure are, therefore, not known and therefore neither deterministic nor probabilistic modelling is possible using these parameters. The true determinants remain unexplained. This emphasises the difficulty of exposure data collecting and using exposure databases.

Therefore, as the exposure determinants could not be identified, a different approach was chosen to demonstrate the use of probabilistic methods. The sampled inhalation and dermal exposure data was used together with physiological exposure factors (inhalation rate, body weight, and absorption data) in order to characterize systemic exposure. Algorithms used in probabilistic analysis are presented below (Equations 1 and 2) the input distributions are showed in Figures 6–9. The simulation was made using Excel based @Risk-software (v. 4.0).

$$\text{Exposure}_{\text{inhalation}} = E_i \times \text{BR} \times t \times \text{Abs} / \text{BW} \quad (\text{Equation 1})$$

$$\text{Exposure}_{\text{dermal}} = E_d \times \text{Abs} / \text{BW} \quad (\text{Equation 2})$$

Where

E_i = Measured DEGBE concentration in breathing zone (mg/m^3)

E_d = Measured DEGBE concentration in hands (mg)

BR = Breathing Rate (m^3/min)

t = Time (min)

Abs = Inhalation or dermal absorption fraction (%)

BW = Body Weight (kg)

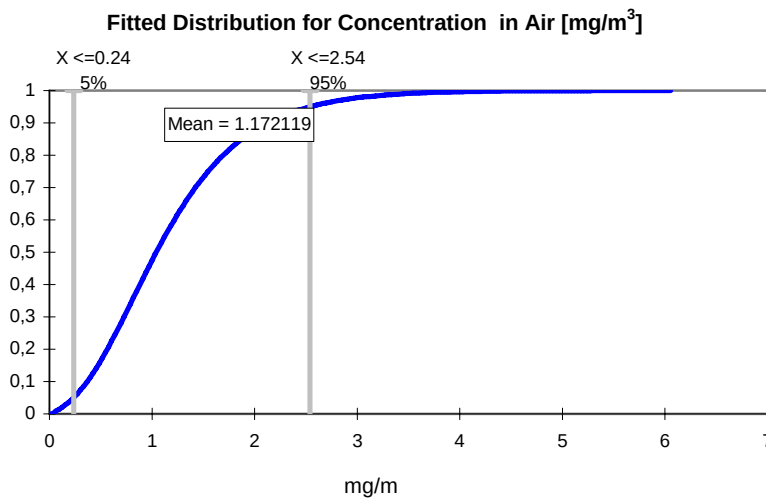


Figure 6. DEGBE concentration in air, mg/m^3 (data from FIOH exposure study)

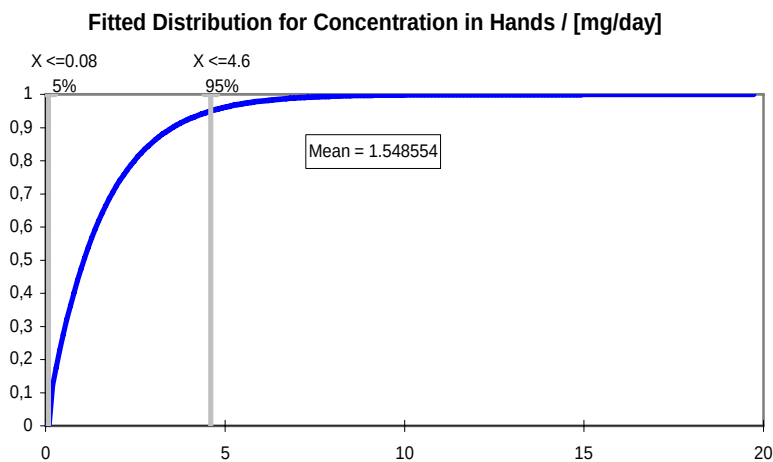


Figure 7. DEGBE concentration in hands, mg/day (Data from FIOH exposure study)

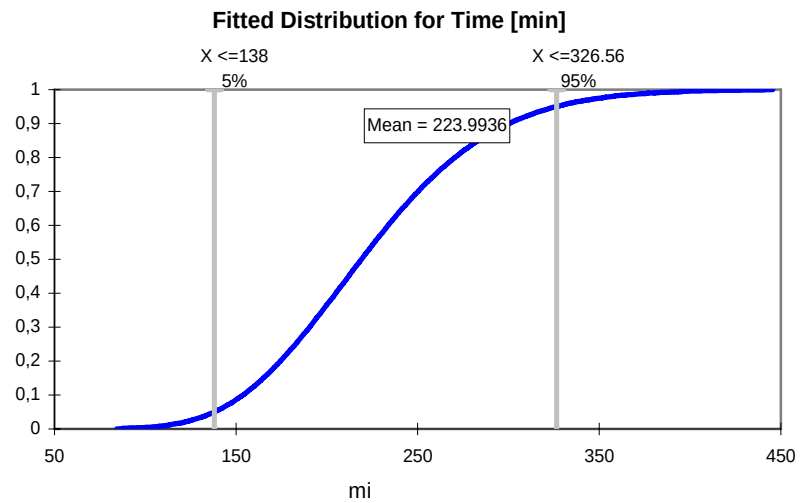


Figure 8. Working time, minutes (Data from FIOH exposure study)

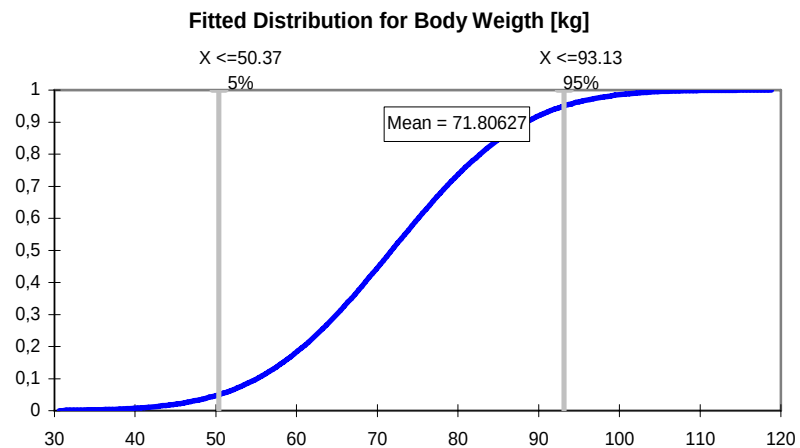


Figure 9. Body weights, kg (Data from US EPA exposure factors handbook)

The description of parameters used in @Risk simulations and the simulation settings are presented in Tables 3 and 4. The type of distribution in the Table 3 refers to a @Risk-distribution type which gives best fit to the corresponding data. The distribution types of “Ext Value”, “Gamma” and “Expon” are log-normal type of distributions. The body weight, as always, is a normally distributed and the “Uniform” type of distribution (breathing rate) gives equal probabilities for all data points.

Table 3. The input parameters and type of distributions. The numeric values represent the mean value of corresponding distributions.

Parameter	Inhalation	Type of distribution	Dermal	Type of distribution
Concentration [mg/m ³] or mg/day]	1.17	ExtValue	1.53	Expon
Breathing Rate [m ³ /min]	0.02	Uniform	***	***
Time [min]	220	Gamma	***	***
Absorption [%]	100	***	100	***
Body Weight [kg]	72	Normal	72	Normal
Sys Exposure [mg/kg/day]	0.08	***	0.02	***
Tot. Systemic Exposure	0.097			

*** No value

Table 4. The simulation settings used in analysis (@Risk-software)

Type of setting	Parameters chosen in the analysis
Iterations	10.000
Sampling Type	Latin Hypercube
Standard Recalc	Expected value
Random Generation Seed	Choose Randomly
Collect Distribution Samples	All
Correlations (in data)	0.430 between dermal and inhalation exposures

5. Results

A Monte Carlo simulation with 10.000 iterations was made using inhalation and dermal exposure data together with physiological parameters (inhalation rate, body weight, and absorption data) in order to characterize systemic exposures (See Figures 10–12).

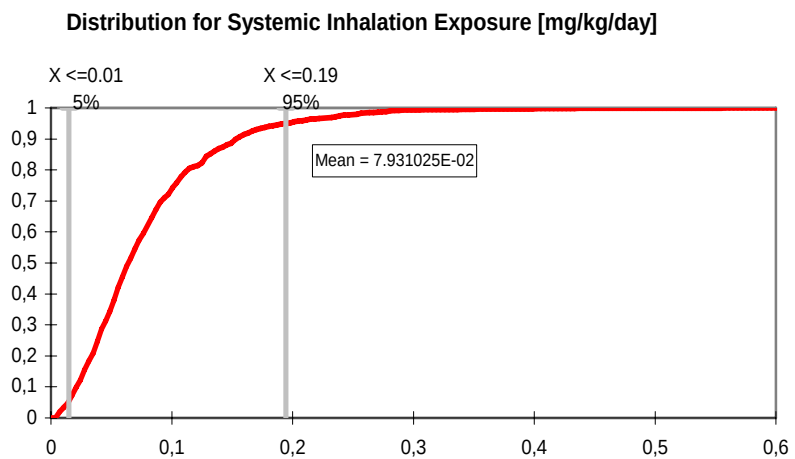


Figure 10. Systemic inhalation DEGBE exposure mg/kg/day (no PPE).

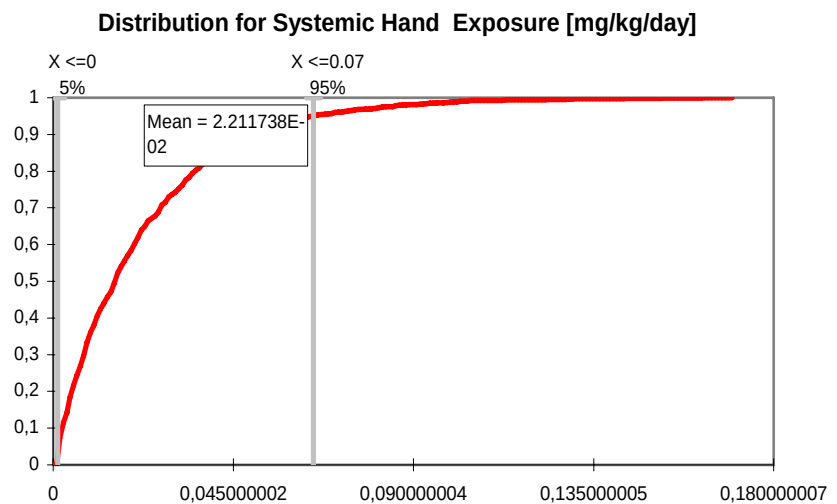


Figure 11. Systemic hand DEGBE exposure mg/kg/day (no PPE).

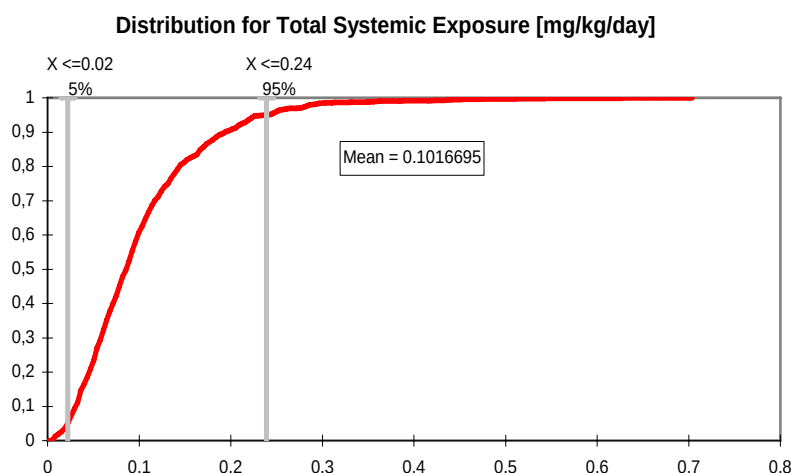


Figure 12. Systemic DEGBE exposure without PPE (inhalation + hand) mg/kg/day. The 50th, 75th and 90th percentiles are indicated with dash lines.

The total systemic exposure (Figure 12) ranged from 0.001 to 0.72 mg/kg/day with the mean and median values of 0.100 and 0.072 mg/kg/day. The 75th and 90th percentiles were 0.122 and 0.193 mg/kg/day, respectively.

5.1 Comparison of the probabilistic results to DEGBE assessment results in existing substance program

The DEGBE has been evaluated also in the Existing Substances programme by the Netherlands. In the risk assessment report (RAR), occupational exposure during manual application of products containing DEGBE was assessed. Manual application was described to contain spray application, brushing, rolling and cleaning (including manual transferral and mixing of such products). The task discussed in this study can be compared with brushing or rolling, as a comb-like tool is used to spread the lacquer.

The conclusions about *inhalation exposure* in RAR are based on few measured data. The only study found by the authors of the risk assessment report that discussed exposure to DEGBE in brushing or rolling of paint (4% of DEGBE in paint) was published by Hansen et al. 1987. Short-term measurements showed exposure of 4–5 mg/m³ to DEGBE. Number of measurements was 15. These concentrations locate in upper end of the distribution used in probabilistic assessment here (see Figure 6).

For assessing *dermal exposure*, the EASE model was the only method used in RAR. For scenarios as brushing and rolling, an estimated exposure of 0.005–0.1 mg/cm² was calculated. If it is assumed that fingers of one hand are exposed (200 cm²), the daily exposure would be 1–20

mg/day. These values were equal with the hand exposure data used in a probabilistic simulation.

In the case of DEGBE exposure assessment in painting and brushing tasks, it seemed that the probabilistic analysis did not provide any additional and useful information compared to the conclusions obtained in the RAR. The assumptions and models in RAR assessments probably involve rather high uncertainties, but on the other hand, also the dermal and inhalation surrogate exposures input distributions used in probabilistic simulations are quite uncertain ($n=19$). The sensitivity analysis indicated that these parameters have the most significant effect to the results. The body weight and the breathing rate data can be considered as information with rather low uncertainties.

5.2 Comparison of the probabilistic analysis results to deterministic model results

The exposures were re-calculated using the point estimates (deterministic approach) by Equations 1 and 2 instead of distributions. The point estimates for dermal and inhalation exposures are shown in Table 5 and they should reflect realistic worst case exposures. The 90th percentile of exposure data was chosen for the realistic worst case exposure value. Instead, 50th percentile for painting time was considered reasonable and having not too much conservatism.

Table 5. Parameters in deterministic model

Parameter	Inhalation exposure	Dermal exposure
Surrogate exposure	1.8 mg/m ³ (90 th percentile)	3.7 mg/hands (90 th percentile)
Exposure time	111 min (50 th percentile)	***
Body Weight	70 kg	70 kg
Absorption	100 %	100%

*** No value

The deterministic realistic worst case calculation resulted total systemic exposure of 0.111 mg/kg/day. The total systemic exposures in probabilistic simulations ranged from 0.001 to 0.72 mg/kg/day with the mean and median values of 0.100 and 0.072 mg/kg/day. The deterministic model results are close to the mean value in the exposure distribution obtained by probabilistic analysis. Assuming that the probabilistic model would capture the exposure variability correctly the results of the deterministic model does not reflect realistic worst case exposure.

It must be noted that in this example, the total distribution has been available to find and select different percentiles to be used as default values in deterministic model. Therefore, the model parameters are probably of better quality in this case than normally. As it has been mentioned

before, quite often when default values are defined, the characteristics of the data, e.g., the shape of the distribution, are not known.

6. Conclusions

6.1 Advantages of probabilistic approach

Probabilistic techniques can be used to characterize the variability of exposures in a population.

- Quantitative assessment of exposure variability provides more comprehensive picture of exposures in real settings than using conservative assumptions and estimating high-end exposures using point-values. Such models may be a potential alternative especially in higher tier assessments in REACH Chemical Safety Assessment.
- Probabilities can also be used in quantifying uncertainties (e.g. as used when estimating confidence intervals in traditional statistical analysis). Quantitative analysis makes uncertainties in model results explicit and thus supports rational decision making.
- The use of a probabilistic model may also be feasible when assessing cumulative/aggregate exposures (different sources) and when characterizing risks for highly exposed groups.
- Correlations between exposure determinants can be modelled.
- Sensitivity analysis can be used for investigating how changes in input parameters affect the results.
- Commercial, user friendly software is available (@Risk®, Chrystal Ball®, Analytica®).
- Fitted input distributions can be created from statistical values/estimates of observations (e.g. mean variation or range).

6.2 Disadvantages of probabilistic approach

- Interpretation of results from probabilistic analysis may be difficult. Probabilistic analysis provides more detailed risk assessment than deterministic analysis. If this additional information is not utilised by the assessor due to the lack of knowledge, or the modeller fails to communicate all relevant information related to the exposure assessment procedure, the advantage given by the powerful methodology remains low.
- The choice of the percentile is a matter of policy; how to decide which is acceptable or not? Before probabilistic methods can be used in regulatory risk assessments, a mutually accepted criterion on the use of percentiles has to be achieved.
- Advanced skills for using a probabilistic analysis are needed.

- A critical issue in probabilistic as well as in deterministic modelling seems to be developing a reliable algorithm for predicting exposures. For predictive models a relationship between exposure factors (time, consumption, area, etc.) must be found. It is likely that for certain tasks this kind of relationship cannot be established. This is especially difficult for tasks that include manual handling, as between worker variation may be large. Especially the level of dermal exposure is highly influenced by the personal work habits and hygiene, which cause variation between workers. Furthermore, if there is a relationship it may not be linear.
- Collection of good quality distributions that are representative of input parameters. An inappropriately defined parameter distribution, either empirical or theoretical, may significantly effect the estimated exposure distribution. The selection of input distributions require more time and attention than selecting point estimates for deterministic models.
- Manipulation of input and output distribution (filtering, truncating, shifting etc.) in a case of result falsification.

6.3 Specific questions

- In which circumstances it is appropriate to use a point values in a probabilistic assessment, for example dermal and inhalation absorptions, the efficiency of personal protective equipment, etc.?
- How to collect representative and harmonized input distributions (utilization of RARs, existing databases etc.)? In Europe, the European Exposure Factors database (ExpoFacts) is the latest approach to enhance the exposure factor data availability. It is an internet-based, free access database with data from 30 European countries and links to other sources of data (<http://envi.uku.fi/expofacts2006>, CEFIC, 2005).
- In which cases a two-dimensional analysis is recommended instead of a one-dimensional analysis? When it is necessary to quantitatively characterize uncertainty and variability? When do these techniques really improve the quality of risk assessment and the decision-making?
- Do we need “common rules” in reporting results of occupational hygiene surveys? For example, guidelines for occupational hygiene studies that keeps in mind the needs of modelling. All usable information about the exposure determinants, and process and workplace conditions should be collected and reported (peer-reviewed or other) along with the results. All relevant factors do not seem to be known, as could be seen in the worked example in this report. There is also still diversity among the measurement methods, especially in the field of dermal exposure, which lacks standardised methods. All this is crucial if we want to use good quality databases of exposure as the basis of the modelling in the future.

7. Probabilistic modelling used for risk assessments

Probabilistic approach has been utilised so far more in North America (e.g. US EPA, Cal EPA, and Health Canada) than in Europe by the regulatory authorities in the higher tier assessments. As early as in 1997, the US EPA listed eight conditions for an acceptable risk assessment that uses probabilistic risk analysis techniques (see Appendix 3).

Models have been built especially to assess risk occurring from dietary or residential exposure to agricultural pesticides. The aims of the assessments include acute and chronic (DEEM™), and aggregate/cumulative exposure over different time periods (Calendex™) or lifetime (LifeLine™). Another advanced field is environmental health.

DEEM™ is a dietary exposure analysis system for performing chronic and acute exposure assessments, first introduced in the mid 1990s. DEEM™ employs Monte Carlo Analysis (MCA) techniques in order to provide probabilistic assessments of dietary pesticide exposures when residue data for targeted foods are available as distributions. DEEM™ has been used by the Office of Pesticide Programs at EPA, CalEPA and Health Canada to evaluate human exposures to pesticide residues in food, and establish tolerances for those pesticides. It has also been used by agricultural chemical companies in the US and abroad. For more information, see the company website <http://www.durango-software.com/software/deem.html>.

Calendex™ is an exposure and risk analysis tool for estimating exposure of the U.S. population and its subgroups to pesticides in food and the residential environment, food, air and water contaminants, and chemical ingredients in formulated products. The model assesses acute, short-term, intermediate, or chronic time periods. Multiple routes of exposure can be aggregated. The model simultaneously accounts for the temporal, spatial, and demographic variation in chemical use and chemical users. The Calendex™ model is a calendar-based system that uses Monte Carlo sampling techniques to estimate the distributions of exposure. The company website gives more details <http://www.exponent.com/practices/foodchemical/calendex.html>.

LifeLine™ models longitudinal exposures to the same individual over periods longer than one season using data from a number of surveys of exposure-related factors, like daily activity or dietary patterns, performed in the US. Further information about the LifeLine™ 4.3 model can be found from the internet, <http://www.thelifelinegroup.org/>, or from an article by Price et al., 2001.

Consumer exposure model used widely across Europe, ConsExpo (latest version 4.1) developed in RIVM (see <http://www.rivm.nl/en/health->

[anddisease/productsafety/ConsExpo.jsp](#)) has been used, for example, to assess biocide exposure of amateur users of biocidal products. ConsExpo can carry out not only calculations with point values but also calculations with distributions. Sensitivity analyses can be carried out as well. ConsExpo includes assessment of inhalation, dermal and oral exposure.

In September 2000 an international workshop called “Innovative exposure assessment of pesticide uses for appropriate risk assessment” was held. A series of papers published in the *Annals of Occupational Hygiene* (2001, Vol 45, No 1001, Supplement, pp 174) describe several approaches of probabilistic assessment, and critical opinions, on worker and residential exposure. Experiences from different countries are also presented.

Probabilistic approach is applied also in environmental studies. A good example is the Superfund, an US EPA program. In this program, probabilistic modelling has been used to create information that may support remedial action decisions at hazardous waste sites. Both ecological and human risks are considered. A guidance document for conducting probabilistic risk assessment for Superfund can be found from EPA’s website <http://www.epa.gov/oswer/riskassessment/rags3a/>. The document is a profound presentation of probabilistic techniques and serves even as a handbook in this area.

In an EU 4th framework study EXPOLIS (Air pollution exposure distributions of adult urban populations in Europe), probabilistic techniques were used to assess the population exposure to air pollutants in urban air. More details can be found from Dr. Otto Hänninen’s (scientific peer reviewer of this report) doctoral thesis (http://www.ktl.fi/attachments/-suomi/julkaisut/julkaisusarja_a/2005/2005a10.pdf) and from the original publications it is based on.

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Optional summaries¹

I denna rapport undersöktes användbarheten av probabilistiska metoder för bedömning av human exponering i samband med REACH-förordningen. Rapporten och dess slutsatser gjordes på basen av en verklig exponeringsstudie.

På basen av exemplen i fallstudien (case study), kan följande slutsatser antas: Även om probabilistiska metoder möjliggör förfinad karakterisering av exponering, risk och variation, är det ändå inte sannolikt att dessa metoder skulle rutinmässigt användas vid kemikaliesäkerhetsbedömningar (CSA) enligt REACH, eller inom andra system för regulatorisk riskbedömning (växtskyddsmedel eller biocider). Även om det finns kommersiella, lätt användbara dataprogram till hands (@Risk®, Chrystal Ball®, Analytica®), är probabilistiska analyser ändå mera användbara för akademiska ändamål än för praktisk exponeringsbedömning vid arbetsplatser. För tillfället saknar myndigheterna erfarenhet och kompetens för användning av probabilistiska modeller och hur man tolkar resultaten.

De mest betydande nackdelarna och frågeställningarna med användningen av probabilistiska metoder är: 1) svårigheter med att använda modellerna, 2) utvecklingen av algoritmer, 3) insamlande av data (fördelning) med god kvalitet, 4) kriterier för beslutsfattande (vad är acceptabelt och vad är inte acceptabelt) och 5) informering av resultaten till intressegrupper. Modeller som verkar att vara lättbegripliga och lätt användbara, kommer högst sannolikt att publiceras i en nära framtid. Det är ytterst viktigt att riskbedömare och myndigheter inte faller för de probabilistiska modellernas skenbara enkelhet, utan förstår fallgrupparna vid modelleringen. Dessutom måste användare av modeller ha tillräckliga insikter i principerna för bedömning av exponering, samt erfarenhet av olika tekniker som används för att beskriva exponering och risk. Med andra ord måste riskbedömare kunna ställa de rätta frågorna.

Probabilistisk modellering kan eventuellt användas som specialteknik vid mera komplexa exponeringssituationer, eller då deterministiska bedömningar pekar på oacceptabelt höga exponeringsnivåer, varvid förfinad (higher tier) bedömning av exponering behövs.

¹ If the main language of the report is English (or any other non-Scandinavian language), the summary must be translated into one Scandinavian language (Danish, Norwegian or Swedish). Summaries in Finnish or Icelandic should be included if considered relevant.

APPENDIX 1. Observed exposures in the parquet lacquering study

Table A1-1. Results of a parquet lacquering exposure study (19 workers, one application each) (Laitinen & Pulkkinen, 2005).

Descriptive statistics	Exposure time (min)	Area treated (m ²)	Consumption of the product (s) (l)	Consumption of DEGBE (mg)*	Respiratory exposure (mg/m ³)	Hand exposure (mg/hands)
AM	126	169	22	669	1,144	1,568
GM	111	122	16	487	0,808	0,849
median	120	80	14	420	1,148	1,100
95th	231	380	65	1950	2,471	4,750
90th	230	334	51	1542	1,769	3,716
75th	148	260	28	840	1,519	2,480
min	30	36	6	180	0,068	0,030
max	243	380	65	1950	3,443	4,840

* Estimated DEGBE concentration 3 %, density ~ 1 g/cm³ (0.948-0.960 g/cm³ according to the EXICHEM report).

Table A1-2. Correlations between variables

	Time (min)	Area (m ²)	Product cons. (l)	DEGBE cons. (l)	Inhalation exp. (mg/m ³)	Dermal exp. (mg/hands)
Time	1,0000	0,5975	-0,1050	0,5954	0,3386	0,2698
Area	0,5975	1,0000	0,4831	0,8129	0,0140	0,1458
Product consump.	-0,1050	0,4831	1,0000	0,5018	-0,3213	-0,2965
DEGBE consump.	0,5954	0,8129	0,5018	1,0000	0,1252	0,0576
Inhalation Exp	0,3386	0,0140	-0,3213	0,1252	1,0000	0,4258
Dermal exp.	0,2698	0,1458	-0,2965	0,0576	0,4258	1,0000

APPENDIX 2. Determinants of inhalation and dermal exposures

Inhalation and dermal exposure determining factors in occupational settings have been discussed by several work groups. A conceptual source-receptor model of exposure has been presented by Creely et al. 2005 (Figure A2-1). The model shows potential pathways of the contaminants from the source through different compartments to the receptor, i.e., exposed person (respiratory tract and skin contaminant layer). Room air and surfaces are the so called work environment compartments. Breathing zone air and clothing (inner and outer layers) are recognised as compartments strongly influenced by personal behaviour. Outside air and surfaces are the so called work environment compartments. Breathing zone air and clothing (inner and outer layers) are recognised as compartments strongly influenced by personal behaviour.

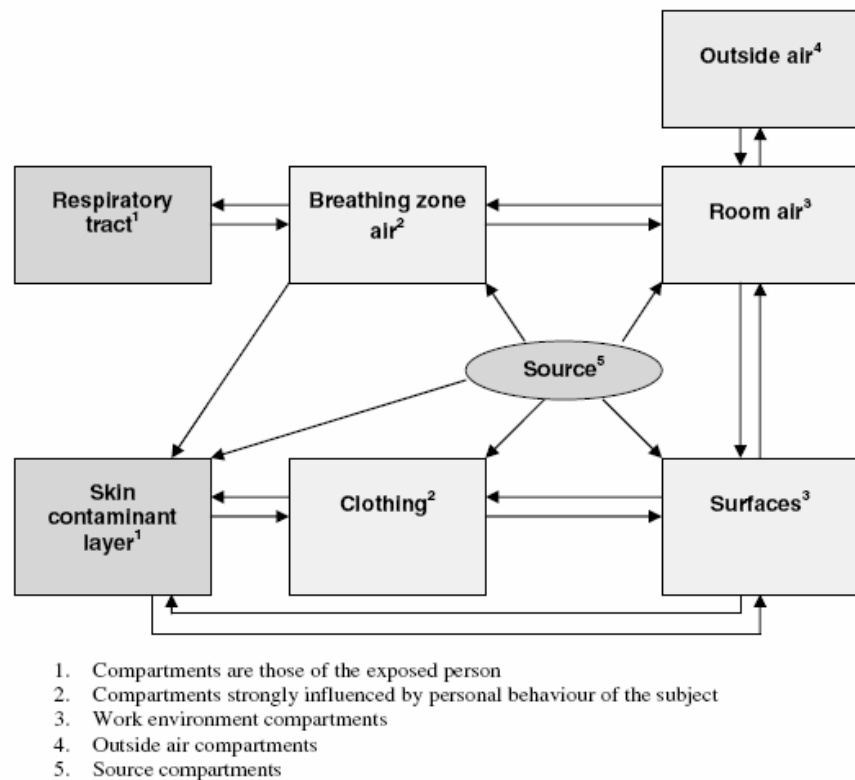


Figure A2-1. Simplified conceptual model of inhalation and dermal exposure (adapted from Creely et al. 2005).

Creely and her co-workers have also listed several exposure determinants based on the conceptual model. In the first table (Table), determinants associated with source compartment have been presented. In most cases

same factors play an important role both in inhalation and dermal exposure, but it must be noted that sometimes not in the same way.

Table A2-1. Exposure determinants associated with the source compartment (adapted from Creely et al. 2005).

Inhalation emission factor	Increase in emission potential with...	Dermal emission factor	Increase in emission potential with...
Physical state	Gases and vapours	Physical state	Liquids
Volatility of liquids	Higher volatility	Volatility of chemicals	Lower volatility
Area of volatile chemicals in contact with air	Larger area	Area of volatile chemicals in contact with surfaces	Larger area
Air temperature and flow rate over liquid surfaces	Higher temperature or airflow	Air temperature and flow rate over surfaces	Negligible effect
Agitation of liquids or solids	More agitation	Agitation of liquids or solids	More agitation (splashes)
Particle size of solids	Finer particles	Particle size of solids	Coarser particles
Presence of other substances in mixtures	Unpredictable	Presence of other chemicals in mixtures	Unpredictable
Process for handling the chemical (e.g. spraying, scooping, grinding, etc.)	More energetic processes	Process for handling the chemical (e.g. spraying, scooping, grinding, etc.)	More energetic processes
Localised ventilation close to the source	Less efficient ventilation	Localised ventilation close to the source	Small effect
Other control measures	Less efficient containment	Other control measures	Less efficient containment

The same work group also pointed out the factors affecting transfer from room to breathing zone air (Table x), and correspondingly, factors affecting transfer to the skin contaminant layer (Tables below) in their previous study report (Cherrie et al. 2003). It can be seen that many determinants are not easily predictable, they tend to be hardly measurable or generalised across different workplaces. Especially in the case of dermal exposure, many strong determinants depend on personal behaviour.

Table A2-2. Factors affecting transfer from room to breathing zone air.

Factor	Increase in net transfer with...
Location of air inlets and exhaust points for forced ventilation	Unpredictable (depends on the location of source and worker in relation to the airflows)
Presence of air jets emitting contaminant	Distance of worker from air jet
Room shape	Unpredictable (depends on the location of source and worker in relation to the shape)
Air temperature gradients	Unpredictable
Presence of hot equipment or processes	Unpredictable (depends on the location of source in relation to the worker)
Movement of people in room	Unpredictable (although more movement tends to promote more homogeneous conditions in the work room)
Opening of doors and windows	Should reduce transfer
Duration workers close to sources	Increased duration generally increases transfer
Physical work rate	Increased work rate tend to reduce net transfer

Table A2-3. Factors affecting transfer to the skin contaminant layer

Factor	Increase in net transfer with...
Agitation or pouring of liquids promoting splashing	More splashing increases transfer
Spills of chemicals onto surfaces or clothing	More spills will increase transfer
Accidental pouring of chemicals onto skin	More accidents increases transfer
Deliberate immersion of hands in chemicals	Less care in working with chemicals will increase transfer
Number of contacts with contaminated surfaces	Increases in the number of contacts will increase transfer
Area of skin in contact with contaminated surfaces	Greater skin area contacting surfaces (or less clothing worn)
Working in high aerosol concentrations	Poor local control measures may increase transfer rate to the skin
Infrequent laundering or work clothing	Less frequent laundering of clothing

Dermal exposure determinants were also discussed in the RISKOFDERM project. An inventory of potential determinants of dermal exposure for exposure modelling was collected and evaluated recently by Marquart et al. (2003). The determinants estimated to have scientific evidence of effect were divided into six categories (Table A2-4). This approach has been used in practice in the model development process included in the RISKOFDERM (Warren et al. 2006).

Table A2-4. Categorised presentation of potential dermal exposure determinants with examples or the parameters found in the literature and judged by experts (adapted from Marquart et al., 2003).

Category of determinants	Examples of the parameters
Substance and product characteristics	Physical state, viscosity, particle size, moisture, organic content (soil)
Task done by the worker	Frequency, intensity, duration, number of items handled, volumes handled, concentrations, treated area, level of contamination
Process technique and equipment	Distinguishing type of process or equipment, orientation, pressure
Exposure control measures	Gloves: use, material; clothing: use, material, skin area covered, organisation of work
Worker characteristics and habits	Accuracy of working: training, touching contaminated surfaces; skin moistness and roughness, personal hygiene: frequency of hand washing, personal manner of working
Area and situation	Type of contaminated surfaces: roughness; weather conditions: temperature, wind speed

Many of the established determinants have not shown a uniform direction of effect in the studies reviewed, and only a few parameters have been identified as independent determinants of exposure. The effect and its direction also depend on the type of exposure (i.e., whether the exposure is caused by direct contact with contamination [splashing, immersion, etc.], contact with contaminated surfaces, or deposition). For example, it has been found that using a solvent-based formulation as a wood preservative leads to higher dermal exposure than work with a water-based one. However, when surfaces treated earlier with a solvent-based formulation are touched, the exposure is lower than when surfaces treated with a water-based substance are touched, due to the difference in the evaporation rate (Roff, 1997a; Garrod et al., 1999).

APPENDIX 3. USEPA conditions for an acceptable probabilistic risk analysis (US EPA, 1997). Policy for use of probabilistic analysis in risk assessment)

The eight conditions listed by US EPA for an acceptable risk assessment that uses probabilistic analysis techniques:

1. The purpose and scope of the assessment should be clearly articulated in a "problem formulation" section that includes a full discussion of any highly exposed or highly susceptible subpopulations evaluated (e.g., children, the elderly, etc.). The questions the assessment attempts to answer are to be discussed and the assessment endpoints are to be well defined.
2. The methods used for the analysis (including all models used, all data upon which the assessment is based, and all assumptions that have a significant impact upon the results) are to be documented and easily located in the report. This documentation is to include a discussion of the degree to which the data used are representative of the population under study. Also, this documentation is to include the names of the models and software used to generate the analysis. Sufficient information is to be provided to allow the results of the analysis to be independently reproduced.
3. The results of sensitivity analyses are to be presented and discussed in the report. Probabilistic techniques should be applied to the compounds, pathways, and factors of importance to the assessment, as determined by sensitivity analyses or other basic requirements of the assessment.
4. The presence or absence of moderate to strong correlations or dependencies between the input variables is to be discussed and accounted for in the analysis, along with the effects these have on the output distribution.
5. Information for each input and output distribution is to be provided in the report. This includes tabular and graphical representations of the distributions (e.g., probability density function and cumulative distri-

bution function plots) that indicate the location of any point estimates of interest (e.g., mean, median, 95th percentile). The selection of distributions is to be explained and justified. For both the input and output distributions, variability and uncertainty are to be differentiated where possible.

6. The numerical stability of the central tendency and the higher end (i.e., tail) of the output distributions are to be presented and discussed.
7. Calculations of exposures and risks using deterministic (e.g., point estimate) methods are to be reported if possible. Providing these values will allow comparisons between the probabilistic analysis and past or screening level risk assessments. Further, deterministic estimates may be used to answer scenario specific questions and to facilitate risk communication. When comparisons are made, it is important to explain the similarities and differences in the underlying data, assumptions, and models.
8. Since fixed exposure assumptions (e.g., exposure duration, body weight) are sometimes embedded in the toxicity metrics (e.g., Reference Doses, Reference Concentrations, unit cancer risk factors), the exposure estimates from the probabilistic output distribution are to be aligned with the toxicity metric.