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Summary

This report describes the separation of uncertainty and interindividual variability in the predictions of the human exposure model NORMTOX 2.0. NORMTOX models the daily exposure to contaminants from air, soil, drinking and surface water and food products, averaged over a lifetime. NORMTOX 2.0 is an update of NORMTOX 1.0. Input for the model is data on contaminant concentrations in the different media and data on human activity and consumption patterns. These data contains uncertainty, which means that the exact values of the parameters are not exactly known, but could be obtained by additional research. The data also contains variability, which means that there are differences between individuals. Variability is inherent in the system and cannot be reduced by additional research.

True uncertainty and variability are both sources of variance, often they are taken together under the name of uncertainty. Variance may be difficult to interpret when it is a combination of true uncertainty and variability, therefore it may be necessary to separate them. To perform separation of true uncertainty and interindividual variability ANOVA and nested Monte-Carlo simulation are used, this combination seems suitable for this aim. In the output of NORMTOX 2.0 uncertainty and interindividual variability are successfully separated.

The model is applied to calculate the coherence indicator (CI) of standards for different compartments in the Netherlands. A set of standards is called incoherent if simultaneous exposure to all media, which are polluted up to their standard, results in exceeding the acceptable or tolerable daily intake (ADI or TDI). The CI is therefore the ratio between the intake of a compound and its acceptable daily intake. When the CI exceeds one, the standards are incoherent. This study calculates the CI for 54 substances.

For 9 substances the CI is higher than one, which means that the standards are incoherent. For eighteen substances the CI is around one. This means that for a part of the population standards are incoherent, because the variance in the CI distribution originates largely from interindividual variability. One has to keep in mind that these calculations are hypothetical and only qualitative conclusions about the real world situation can be drawn. Variance in the CI originates most of the time from interindividual variability, which means that additional research will not provide a more accurate result. However, for several compounds a large amount of uncertainty is introduced in the calculation of the ADI_{inh}, in which the ratio between the oral and inhalatory coefficient is used. Research on the ADI_{inh} or the absorption coefficients could result in a more accurate estimation of the CI.

Contents

Chapter 1

Introduction

1.1 Deterministic versus probabilistic and variability versus uncertainty

Environmental regulators make decisions about environmental standards and the extent to which exposure of humans and ecosystems to chemical contaminants should be allowed or reduced. These decisions are based on risk assessments which use data about emissions, fate and toxicity of substances. Risk assessment is the process that evaluates the likelihood that adverse ecological or humane effects may occur or are occurring as a result of exposure to one or more stressors (US-EPA, 1998).

Traditionally risk assessment has followed a deterministic approach. This implies that risk assessment models provide the user with a point estimate for a certain quantity (e.g. toxicity). The purpose of such analyses is to provide decision makers with the best estimate. This estimate can subsequently be used in comparison wither assessments. However, in the real world, factors such as toxicity and exposure are not fixed values but are variable. Furthermore, most values affecting risk are not precisely known, but uncertain. Variability may be caused by differences between (groups of) individuals. Each individual within a population has its own characteristic activity and dietary pattern and its own physiological parameters, which in addition may vary in time. These differences lead to variability in exposure and effect between individuals. Parameters can also be uncertain, which can be thought of as gaps in one's knowledge.

A severe drawback of the deterministic approach is that the degree and direction of bias or conservatism are masked by the presentation of a single value. Besides, this approach does not guide decision makers to the most efficient measures, which could be either conducting additional research or drive back exposure levels immediately (Cullen & Frey, 1999).

Growing awareness that deterministic risk assessment procedures can result in conservative or erroneous risk estimates, has resulted in a shift of interest towards probabilistic risk assessment. In the probabilistic approach, uncertainties in model input are propagated to estimate uncertainties in the model output. The probabilistic analysis gives a quantitative insight in the possible range as well as in the relative likelihood of a calculated value. The model output is presented as a distribution, showing a range of possible environmental impacts

and the values within that range that are most likely. Because the full range of possible outcomes can be taken into account, this approach should provide a better basis for decision making.

Most techniques currently used in probabilistic risk assessment have considerable shortcomings from a scientific as well as a management perspective. The process demands a lot of information and concerns may arise that the approach is being used as a smoke screen to confuse issues, because decision makers are glutted with information. Probability distributions give more information, but may also be harder to interpret than point estimates. However, the probabilistic approach does not suffer from the shortcomings of deterministic techniques stated above (Cullen & Frey, 1999). Therefore, the use of probabilistic techniques should be optimized in order to obtain useful and clear model outputs, which can serve to facilitate decision making processes.

Variability and uncertainty are two different characteristics of a model. Understanding variation within a population may lead to recognizing sensitive subpopulations, meriting a more focused study. Knowing uncertainty can aid in determining whether additional research is needed to reduce it. Because variability and uncertainty can have different implications for decision making, it can be useful to consider them separately in an analysis. This report will focus on probabilistic techniques to separate variability and uncertainty.

1.2 Framework

This study is embedded in the NoMiracle project (NOvel Methods for Integrated Risk Assessment of CumuLative stressors in Europe), which is an Integrated Project of the Sixth Framework Programme: 'Global Change and Ecosystems' of the European Union. More in detail it is part of Work Package 4.1 (WP4.1) of this project, entitled: 'New concepts and techniques for probabilistic risk assessment'. The aim of WP4.1 is to develop new concepts and probabilistic risk assessment techniques that are scientifically sound and practicable for management purposes. Part of the project is the use of probabilistic techniques to separate uncertainty and interindividual variability, which is described in this report.

1.3 NORMTOX

NORMTOX 1.0 is an integrated human exposure model, which predicts lifetime averaged daily uptake levels of contaminants (Ragas & Huijbregts, 1998). Uncertain and variable input parameters are defined as probability distributions. By means of Monte Carlo simulation, the variance in these distributions are propagated through the model, resulting in a probability distribution for the output variables. The variance in this distribution has a dual origin, as it originates from interindividual variability as well as from true uncertainty. This impedes an unequivocal interpretation of the model outcome. Therefore, it is important that sources of uncertainty and variability are separated and that they are independently propagated through the model. This report describes how the application of a combination of probabilistic techniques can result in a model outcome in which interindividual variability and true uncertainty are

separated. It describes the development of NORMTOX 2.0 which is an update and extension of NORMTOX 1.0.

1.4 Research question

An important critic on NORMTOX 1.0 is the dual origin of the variance in its output, therefore, the aim of this study is to separate uncertainty and variability in the output of NORMTOX. The main research question in this study is:

> How can the influence of uncertainty and interindividual variability be separated in the predictions of NORMTOX?

1.5 Outline of the report

NORMTOX 2.0 is described in Chapter 2. This chapter gives a general model description and explains the differences between NORMTOX 1.0 and 2.0. Chapter 3 defines the concepts uncertainty and variability and details the techniques which are used to separate those two. Chapter 4 shows an example of an application of the model. The model is used to calculate the coherence of independently derived standards for different media. This chapter also deals with the corresponding parameterization of the model. Results and the way in which to interpret them are given in Chapter 5. The results are discussed in Chapter 6 and conclusions are given in Chapter 7.

Chapter 2

Model description

NORMTOX predicts the lifetime averaged daily intake of substances. The model consists of several mathematical equations and parameters, which together describe the oral and inhalatory intake of a substance through several media. There is no distinction between men and women, and predictions are on a bodyweight basis. A schematic representation of NORMTOX 2.0 is depicted in Figure 2.1. The parameterisation of the model depends on the purpose to which the model is applied. Important input parameters are the consumption patterns of the modeled population and the concentration of the modeled substance in the different media. The model is implemented in Microsoft Excel, which uses Crystal Ball (Decisioneering Inc., 2000) as an add-in to define statistical distributions for the input parameters and run Monte Carlo simulations (Section 3.4).

NORMTOX 2.0 differs at several points from NORMTOX 1.0; differences in the basic model structure are described below and are summarized in Table 2.1, differences in the input parameters will be described in Section 4. For an extensive description of NORMTOX 1.0, see Ragas & Huijbregts (1998).

Table 2.1: Differences between NORMTOX 1.0 and NORMTOX 2.0

NORMTOX 1.0	NORMTOX 2.0
Uptake model (oral, inhalatory and dermal exposure)	Intake model (oral and inhalatory exposure)
Food intake unit: g/day	Food intake unit: $mg/kg_{bw}\,day$
Legumes defined as a separate food category	Legumes included in vegetables
Milk and milk products defined as separate food categories	Milk & milk products defined as one food category
Does not account for sweets, nuts and seeds, oils and fats	Sweets, Nuts & seeds and Oils & fats added to the food categories
Defines food and drinking water intake per age category	Defines food and drinking water intake as a weighted average over all age groups

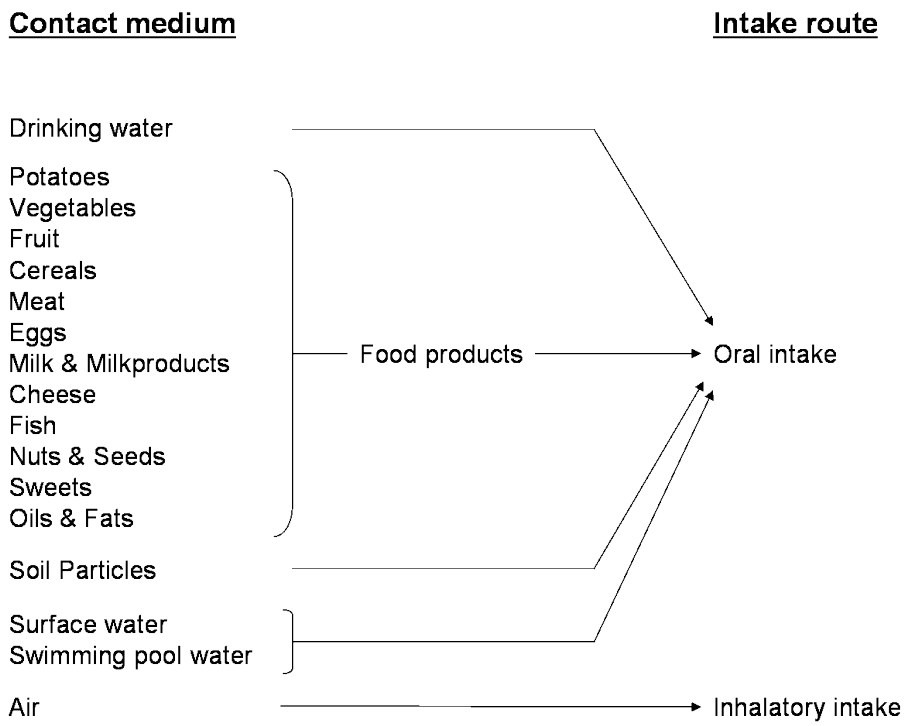

Figure 2.1: Schematic representation of NORMTOX 2.0

2.1 Uptake versus intake

An important difference between the new and the old model is that NORMTOX 2.0 is an intake instead of an uptake model. NORMTOX 1.0 modelled dermal uptake from soil, water and air. However, the contribution of this uptake route turned out to be negligible and is therefore omitted in the new version of the model. The remaining intake routes (oral and inhalatory intake) are discussed below.

2.2 Oral intake

A distinction is made between oral intake from soil particles, surface water, swimming pool water, drinking water and food products. The latter category is subdivided into different food categories (see Figure 2.1). The total oral intake of a contaminant is calculated by adding the intake levels from all individual media, according to Equation 2.1. The meaning and calculation of T_x will be explained in Section 2.4.

$$I_{oral} = \sum_x \frac{C_x \cdot I_x \cdot T_x}{1000} \tag{2.1}$$

In which:

I_{oral}:	Total oral contaminant intake	($\mu g/kg_{bw}\,day$)
C_x :	Contaminant concentration in medium x	(mg/kg)
I_x :	Intake of medium x	($mg/kg_{bw}\,day$)
T_x :	Time correction factor for non-continuous or non-daily exposure rates	($dimensionless$)

There are several differences between the oral intake in NORMTOX 1.0 and 2.0. A first difference is the units of food intake. In the first version of NORMTOX the intake of food is expressed in kg/day. To calculate the intake per kg bodyweight this intake is divided by a bodyweight distribution obtained from literature. In NORMTOX 2.0 the input data for food intake is expressed in kg_{bw} per day, which is more accurate than dividing by a random body weight.

In NORMTOX 1.0 the population is divided in age groups, for which intakes and variances are calculated separately. NORMTOX 2.0 uses age weighted averages and pooled variances for food intake. Age dependence in NORMTOX 2.0 is explained in more detail in Section 2.5.

2.3 Inhalatory intake

Besides the transition from uptake to intake, the inhalatory intake in NORMTOX 2.0 does not differ from that in the earlier model. It is calculated by Equation 2.2.

$$I_{inh} = C_{air} \cdot I_{air} \tag{2.2}$$

In which:

I_{inh} :	Total inhalatory intake	($\mu g/kg_{bw}\,day$)
C_{air}:	Contaminant concentration in air	($\mu g/m^3$)
I_{air} :	Daily inhalation volume	($m^3/kg_{bw}\,day$)

Estimation of an individuals inhalation volume is necessary to calculate the inhalatory intake of a substance. Layton (1993) presented a method for estimating the inhalation volume. It is based on the fact that breathing is controlled primarily by the amount of oxygen consumed in the metabolic conversion of food to energy. The inhalation volume can therefore be described by Equation 2.3.

$$I_{air} = I_{energy} \cdot H \cdot VQ \tag{2.3}$$

In which:

I_{air} :	Daily inhalation volume	($l/kg_{bw}\,day$)
I_{energy}:	Daily intake of energy	($kJ/kg_{bw}\,day$)
H :	Volume of oxygen consumed in the production of 1 kJ of energy	(l/kJ)
VQ :	Ventilatory equivalent	($dimensionless$)

2.4 Time correction for non continuous activities

The calculation of exposures from food and swimming water include a time correction factor, T_x, (Equation 2.1). This factor recalculates the exposure encountered during non continuous (non daily) events into an averaged daily exposure. Time correction factors for food consumption and swimming do not describe exactly the same thing. For swimming the time correction factor describes the averaged time spent swimming in minutes per day (the intake of swimming water is given per minute). For food consumption the time correction factor describes the fraction of days that one consumes a certain food product, therefore it makes a distinction between consumption and non consumption days.

2.4.1 Time correction in swimming

Swimming is a non continuous activity, therefore one is not continuous exposed to swimming water and a time correction factor has to be included in the exposure calculations. From data on swimming behaviour a distribution for the fraction of time spent swimming is easily obtained. This fraction is used as T_x in Equation 2.1.

2.4.2 Time correction in food consumption

The time correction factor for food consumption can be seen as the fraction of days that an individual actually consumes. This fraction is not easily obtained from food consumption surveys, which often have a short duration. This is problematic because these surveys give a biased picture of the consumption frequencies. For example, fish is a seldom consumed product, therefore there will be many individuals who did not consume the product at all during a two days survey. When one just calculates the fraction of days fish is consumed by these individuals, one will conclude that they never consume fish, however, this is not necessarily true. These biased conclusions will be drawn the other way around for frequently consumed products. To overcome this problem it is assumed that the fraction of consumption days can be described by a continuous distribution, which' parameters depend on the consumption frequencies from the survey.

According to Slob & Bakker (2004) the consumption frequency of food products can be assessed by a beta distribution. This distribution has four input variables: a minimum, maximum and two shape parameters; α and β. Because the distribution describes a fraction, all values have to be between 0 and 1, which are therefore the minimum and maximum value. α and β are based on the consumption frequencies of the correspondents (see Section 4.2.1).

2.5 Age dependence

In NORMTOX 1.0 intake of food is related to age. The reason for this is that intakes are in absolute amounts and are divided by a random bodyweight. The intake of food as well as body weight is different for each age group. To prevent that the intake of a child is divided by the bodyweight of an adult or vice versa,

it is necessary to define age groups for both variables. In NORMTOX 2.0 the input data on food intake is already on a bodyweight basis, this cancels the necessity of age groups. Therefore, NORMTOX 2.0 uses a weighted averaged food intake over all ages.

The variance in food intake is not equal for all ages, Slob (1993) mentioned that the interindividual variance increases with age. However, he concluded that implementation of different variances per age group only slightly influenced the variance in lifetime averaged intake distributions. Therefore, the assumption of a constant variance with age can be maintained. The lifetime average intake and variance are calculated by Equations 2.4 and 2.5.

$$I_{averaged} = \sum_i f_i \cdot I_i \tag{2.4}$$

$$\sigma^2_{averaged} = \frac{\sum_i (n_i - 1) \cdot \sigma_i^2}{\sum_i (n_i - 1)} \tag{2.5}$$

In which:

$I_{averaged}$	:	The lifetime-weighted average (lifetime = 75 years; $\mu g/kg_{bw}\, day$)
I_i	:	The average intake in age group i ($\mu g/kg_{bw}\, day$)
f_i	:	The fraction of life spent in age group i ($dimensionless$)
$\sigma^2_{averaged}$	:	The lifetime-weighted interindividual variance ($\mu g^2/kg^2_{bw}\, day^2$)
σ_i^2	:	The interindividual variance in intake in age group i ($\mu g^2/kg^2_{bw}\, day^2$)
n_i	:	The number of individuals in age group i ($dimensionless$)

To obtain a weighted average or variance, NORMTOX 2.0 divides the raw input data in age groups. There should not be too many groups, because, the more groups, the less individuals per group, which means that the average and variance become inaccurate. However, the groups should not be too large, because no age dependent differences should be present within one group. When possible the following eleven age groups are maintained: 0-1, 1-4, 4-7, 7-10, 10-13, 13-16, 16-19, 19-22, 22-50, 50-65 and 65-75.

Chapter 3

Handling uncertainty and variability

One of the aims of this study is to separate uncertainty and variability in the output of NORMTOX. Uncertainty is often used as an umbrella term, which includes true uncertainty as well as variability. Within a model, parameters can be totally determined, uncertain, variable or uncertain as well as variable. This means that there are constants and distributed parameters. The latter can be uncertain, variable or both.

3.1 True uncertainty

Uncertainty can be thought of as a measure of the incompleteness of one's knowledge about the parameter of interest, whose true value(s) could be established if a perfect measuring device would be available. It can lead to inaccurate or biased output values. The cause of uncertainty can be the limited availability of empirical data, imperfections in instruments, models or techniques or a lack of understanding of the true biological or chemical processes (Cullen & Frey, 1999). Theoretically, uncertainty can be eliminated by gathering more information.

There are three types of uncertainty (Cullen & Frey, 1999; Morgan & Henrion, 1990).

- The most obvious form is input uncertainty, which is uncertainty about the true value of an input parameter.
- The second form is model uncertainty, which is uncertainty due to the fact that models are only a simplified representation of a real-world system. The enforced problem boundary of a model may make the model incomplete or incorrect.
- The last form of uncertainty is scenario uncertainty. When a certain (future) scenario has to be chosen, one has to assume or predict things, which takes along a certain amount of uncertainty.

NORMTOX only handles input uncertainty, which will therefore be explained a little further. Input uncertainty is the uncertainty in the measurement of a certain parameter, it can be caused by a random or systematical error

(Morgan & Henrion, 1990). The total random error depends on the number of measurements performed and the variance in these measurements. When there is only a random error, uncertainty will decrease with an increasing number of measurements. Systematical errors are caused by imperfections in measuring devices or research methods and cannot be eliminated by additional measurements. Uncertainty due to systematical errors can be reduced by measurements with different methods.

3.2 Variability

Variability is a true phenomenon of the physical reality. It is a result of differences in time, space or the population. In contrast to uncertainty, it is inherent in the system and cannot be eliminated by gathering more information about the input data. There are several forms of variability namely; temporal variability, which is caused by differences in time, spatial variability, which is caused by differences in space and interindividual variability, which is caused by differences between individuals. Depending on the research question, one can choose which kind of variability is of interest. NORMTOX focuses on interindividual variability, because one is interested in the differences in exposure between individuals. However, there will be temporal and spatial variability in the input data of NORMTOX, in this study these types of variability are not of interest and they are therefore assigned as uncertainty.

3.3 ANOVA

Food consumption data tells which foods are consumed by which individuals, during a certain number of days. When looking at one individual within the population, consumption will differ between days. In addition to this, the average consumption of individual x will differ from that of individual y (interindividual variability). Therefore, the variance in the consumption data is composed of several sources of variance. NORMTOX focuses on interindividual variability, which should therefore be separated from the other sources of uncertainty and variability. ANOVA (ANalysis Of VAriance) will be used to realize this. ANOVA is a technique to separate the observed variance in a sample survey, when it originates from several sources. The technique will be explained below.

Consumption data are assumed to be lognormally distributed. To obtain normally distributed data, which is easier to handle, the data is logtransformed. From the logtransformed observations, the logarithmic individual means and the population mean can be estimated by Equations 3.1 and 3.2.

$$\hat{\mu}_j = \frac{1}{m} \sum_e I_{j,e} \tag{3.1}$$

$$\hat{\mu}_{pop} = \frac{1}{mn} \sum_{j,e} I_{j,e} \qquad \hat{\mu}_{pop} = \frac{1}{n} \sum_j \hat{\mu}_j \tag{3.2}$$

In which:

$\hat{\mu}_j$	:	Estimated mean intake of individual j (= individuals index; $mg/kg_{bw}\,day$)
$\hat{\mu}_{pop}$	:	Estimated mean intake of the population ($mg/kg_{bw}\,day$)
n	:	Number of individuals (*dimensionless*)
m	:	Number of days (*dimensionless*)
$I_{j,e}$	:	Value of individual j on day e (= days index; ($mg/kg_{bw}\,day$)

The estimated logarithmic interindividual and daily variance are described by Equations 3.3 and 3.4. One has to keep in mind that s_{days} can only be calculated when consumption data for more than one day is available. This may drastically decrease n for food consumption surveys of short duration.

$$s^2_{inter} = \frac{1}{n-1}\sum_j (\hat{\mu}_j - \hat{\mu}_{pop})^2 \tag{3.3}$$

$$s^2_{days} = \frac{1}{n}\sum_j \frac{1}{m-1}\sum_e (I_{j,e} - \hat{\mu}_j)^2 \tag{3.4}$$

With the help of ANOVA one can show that the expectation values of s^2_{inter} and s^2_{days} can be described by Equations 3.5 and 3.6. In these equations it is assumed that the number of survey days, m, is constant.

$$s^2_{inter} = \sigma^2_{inter} + \frac{1}{m}\sigma^2 days \tag{3.5}$$

$$s^2_{days} = \sigma^2_{days} \tag{3.6}$$

The real interindividual variability can be obtained by substitution of Equation 3.6 in Equation 3.5 and rewriting this formula, this results in Equation 3.7.

$$\sigma^2_{inter} = s^2_{inter} - \frac{1}{m}s^2_{days} \tag{3.7}$$

In which:

s^2_{inter}	:	Estimated variance between individuals ($mg^2/kg^2_{bw}\,day^2$)
s^2_{days}	:	Estimated variance between days ($mg^2/kg^2_{bw}\,day^2$)
σ^2_{inter}	:	True variance between individuals ($mg^2/kg^2_{bw}\,day^2$)
σ^2_{days}	:	True variance between days ($mg^2/kg^2_{bw}\,day^2$)

3.4 Monte Carlo simulation

Uncertain and variable input parameters in NORMTOX are defined as probability distributions. The influence of true uncertainty and of interindividual variability in the risk predictions of NORMTOX is propagated separately through the model by means of second order Monte Carlo simulation.

First order Monte Carlo simulation is a quite straightforward technique which is used to propagate uncertainty in input parameters to uncertainty in the model output. For each uncertain or variable input parameter, it samples a

value out of the input distribution and calculates an output value. This process is repeated many times, which results in a range of output values, making up the output variables' distribution.

Nested or second order Monte Carlo simulation is an extension of first order Monte Carlo simulation. Each input parameter is classified as either uncertain or variable. First a value for each of the uncertain parameters is sampled, these values are then fixed and a complete Monte Carlo simulation is performed for the variable parameters. This process is repeated many times with each time a new set of uncertain parameters. This results in a model outcome in which variability and uncertainty are separated (EUFRAM, 2004). For NORMTOX 2.0 the outcome specifies the population fraction at risk, due to interindividual variability in consumption and activity patterns, and details the probability of this risk.

3.5 Uncertain as well as variable parameters

Parameters in NORMTOX can be uncertain as well as variable. To deal with this duality, each parameter is defined as follows:

- A distribution describing the interindividual variability is defined (the mean and variance are respectively given by Equations 3.2 and 3.7)
- The parameters of this distribution are assumed to be uncertain and a uncertainty distribution for each of the parameters of the uncertainty distribution is defined

3.5.1 Uncertainty in the population mean

Uncertainty in the mean of a normal distribution (as is the case here because the lognormal data is logtransformed) is determined by its standard error. Although it is often assumed that this uncertainty follows a normal distribution when the parameter of interest is described by a normal distribution, this is not entirely true (Cullen & Frey, 1999). The uncertainty emerges to be best described by a non central Student t-distribution, according to Equation 3.8.

$$\hat{\mu}_{unc} = \hat{\mu}_{pop} + t_{n-1} \cdot \frac{s}{\sqrt{n}} \tag{3.8}$$

In which:

$\hat{\mu}_{unc}$:	Uncertain population mean ($mg/kg_{bw}\,day$)
$\hat{\mu}_{pop}$:	Calculated population mean (Equation 3.2; $mg/kg_{bw}\,day$)
t_{n-1}:	Central Student t-distribution with $n-1$ degrees of freedom
s :	Standard deviation between the measurements ($= \sqrt{\sigma^2_{inter} + \sigma^2_{days}}$; $mg/kg_{bw}\,day$)
n :	Number of measurements ($dimensionless$)

NORMTOX has been set up in Microsoft Excel, which uses Crystal Ball as an add-in to define and calculate the distributions. Because a central student t-distribution is unknown to Crystal Ball, this distribution has to be simulated

according to Equation 3.9 (Cullen & Frey, 1999).

$$t_{n-1} = \frac{N(0,1)}{\sqrt{\frac{\chi^2_{n-1}}{n-1}}} \tag{3.9}$$

In which:

$N(0,1)$:		Standard normal distribution
χ^2_{n-1}	:	χ^2 distribution with $n-1$ degrees of freedom

The χ^2 distribution is also unknown to Crystal Ball. A χ^2 distribution with $n-1$ degrees of freedom can be approximated by a normal distribution with a population mean of $n-1$, and a standard deviation of $\sqrt{2 \cdot (n-1)}$, under the condition that $n > 30$ (Abramowitz & Stegun, 1965). When $n < 30$, a gamma distribution with a location parameter of 0, a scale parameter of 2 and a shape parameter of $(n-1)/2$, can be used to substitute the χ^2 distribution.

3.5.2 Uncertainty in the variance of the normal distribution

According to Cullen & Frey (1999) the uncertainty in the calculated variance of a random survey with a limited number of samples can be described by a χ^2 distribution (Equation 3.10).

$$\sigma^2_{unc} = \frac{(n-1) \cdot s^2}{\chi^2_{n-1}} \tag{3.10}$$

In which:

σ^2_{unc} :		Uncertain variance
n	:	Number of individuals
s^2	:	The calculated variance
χ^2_{n-1}:		χ^2 distribution with $n-1$ degrees of freedom

The uncertainty in the variance in the amount water ingested during swimming and in the time spent swimming, are calculated by Equation 3.10. To calculate the uncertainty in the interindividual variance, σ^2_{inter}, first, Equation 3.7 is rewritten, in which the duration of the food consumption survey is assumed to be two days.

$$\begin{aligned} \sigma^2_{inter} &= \frac{\sum_j (\hat{\mu}_j - \hat{\mu}_{pop})^2}{n-1} - \frac{\sum_{j,e} (I_{j,e} - \hat{\mu}_j)^2}{m \cdot (m-1)} \\ &= \frac{1}{n} \sum_j \left[\frac{n \cdot (\hat{\mu}_j - \hat{\mu}_{pop})^2}{n-1} - \left(\frac{I_{j,1} - I_{j,2}}{2} \right)^2 \right] \\ &= \frac{1}{n} \sum_{j=1}^{n} \gamma_j \end{aligned} \tag{3.11}$$

In Equation 3.11, σ^2_{inter} looks more like an average than like a variance. The components of the sum, the γ's, are more or less normally distributed, therefore,

the uncertainty in σ^2_{inter} can be calculated as it is calculated for the mean of a normal distribution, by Equation 3.8.

3.5.3 Uncertainty in the beta distribution

Section 2.4 explains that consumption frequencies are described by beta distributions. These distributions describe variability within the population. However, there is also a certain amount of uncertainty in consumption frequencies. This is taken into account by uncertainty distributions for α and β. The uncertainty in those parameters is normally distributed and its variance is obtained from the covariance structure of α and β, calculated from consumption frequencies in the survey (for more details see appendix A).

Chapter 4

Model parameterisation for coherence testing

This chapter shows an application of NORMTOX 2.0. The model will be applied to calculate the Coherence Indicator (CI) for Dutch environmental quality standards as was earlier performed with NORMTOX 1.0, in this case study it therefore becomes a risk assessment model instead of an exposure model. In order to calculate a substance's CI the model has to be parameterized. This chapter describes the calculation of the CI, the parameterisation of the model and the classification of parameters as either uncertain, variable or both.

4.1 Case study: The coherence indicator

Environmental quality objectives (EQOs) for surface water, soil, air, drinking water, and food products are often derived independently. This may result in incoherent EQOs. A set of EQOs is called incoherent if simultaneous exposure to all media, which are polluted up to their EQO, results in exceeding the acceptable or tolerable daily intake (ADI or TDI). In this study a coherence indicator (CI) is calculated, to quantify the coherence between EQOs for different media.

NORMTOX predicts the average daily intake of a substance, comparing this value to the acceptable daily intake (ADI) results in the CI, which is defined as the ratio between these two values (Equation 4.1).

$$CI = \frac{I_{oral}}{ADI_{oral}} + \frac{I_{inh}}{ADI_{inhalatory}} \tag{4.1}$$

A coherence indicator over 1 means that the ADI is exceeded by the sum of the intake through all media.

It should be noted that adding up the intakes of different exposure routes is plausible only for substances with a systematic mode of action, that are eliminated or degraded relatively slowly. For substances that do not meet these criteria, oral and inhalatory intake should be compared separately with their respective ADI's. Therefore, adding the intakes of different exposure routes will result in a conservative risk approach and is used as a default in NORMTOX in the absence of data on the mode of action and degradation rates.

The second term in Equation 4.1 is problematic when no $\text{ADI}_{inhalatory}$ is available, which is the case for many substances. Therefore, its value is to be estimated from the ADI_{oral} according to Equation 4.2.

$$ADI_{inhalatory} = \frac{A_o \cdot ADI_{oral}}{A_i} \tag{4.2}$$

In which:

ADI_{oral}:		Acceptable daily intake ($mg/kg_{bw}\,day$)
A_i	:	Inhalatory absorption coefficient ($dimensionless$)
A_o	:	Oral absorption coefficient ($dimensionless$)

4.2 Generic input parameters

The input parameters for NORMTOX 2.0 are different from those in NORMTOX 1.0. Because of the additional techniques in NORMTOX 2.0 more detailed data is necessary. For food intake, inhalatory intake, swimming water intake and soil intake new data has become available since the development of NORMTOX 1.0. The data used to parameterize NORMTOX 2.0 are described below.

4.2.1 Intake of food and drinking water

Food consumption data in NORMTOX is based on the third food consumption survey (VCP-3) of the Dutch population from 1997 and 1998 (Hulshof et al., 1998). In this survey 6250 correspondents wrote down all they consumed during a two days period. The days were evenly spread throughout the week and the seasons. Children under the age of 1 are not included in the survey. According to Löwik et al. (1999) this group consumes 10% more than children of the age 1 to 4 (on a bodyweight basis). This assumption is adopted and implemented in the model.

Food and drinking water intake are variable between individuals (interindividual) as well as within one individual (intra-individual). Intra-individual variability originates from different consumption patterns during week and weekend days, holidays and seasons (temporal variability). Interindividual variability results for example from differences in age, sex and sociocultural group. The intra-individual variation is mostly as large as or larger than the interindividual variability (Löwik et al., 1999). It is assumed that the intake of food and drinks can be modelled by a lognormal distribution. The parameters of the intake distributions are given in Appendix B.1.

Food categories

In NORMTOX 1.0 food intake is subdivided into food categories. Those categories are with some minor changes adopted in NORMTOX 2.0. Food categories in the VCP-3 differ from that in NORMTOX and are therefore converted (Table 4.1).

The intake of fruit and drinking water in NORMTOX, is a combination of the actual intake of respectively fruit and drinking water, supplemented with

Table 4.1: Conversion of food categories from the VCP-3 (Hulshof et al., 1998) to NORMTOX

NORMTOX	**VCP-3**
Drinking water	$(Nalc_{drw}/Nalc_{total})$· Non alcoholic drinks + (Alc_{drw}/Alc_{total})· Alcoholic drinks + Soups [a]
Potatoes	Potatoes + Potato part of the Mixed meals
Vegetables	Vegetables + Legumes + Vegetable and Legume part of the Mixed meals
Fruit	$(Nalc_{fruit}/Nalc_{total})$· Non alcoholic drinks + $(Alc_{fruit}/Alc_{total}$· Alcoholic drinks [b]
Cereals	Bread + Cakes & Cookies + Cereals & Thickenings + Cereal part of the Mixed meals
Meat	Meat, Meat products & Poultry + Meat part of the Mixed meals
Eggs	Eggs
Milk & Milk products	Milk & Milk products
Cheese	Cheese
Fish	Fish + Fish part of the Mixed meals
Nuts & Seeds	Nuts, Seeds & Snacks
Sweets	Sugar, Candy, Sweet sandwich fillings & Sweet sauces
Oils & Fats	Fats, Oils & Savoury sauces + Oils & Fats part of the Mixed meals

[a] $Nalc_{drw}$ = Intake of water based non alcoholic drinks, $Nalc_{total}$ = Total intake of non alcoholic drinks, Alc_{drw} = Intake of water based alcoholic drinks, Alc_{total} = Total intake of alcoholic drinks

[b] $Nalc_{fruit}$ = Intake of fruit based non alcoholic drinks, Alc_{fruit} = Intake of fruit based alcoholic drinks

the intake of fruit and water based drinks. The ratio between water and fruit based drinks in alcoholic and non alcoholic drinks, is obtained from the VCP-3.

The VCP-3 includes a category "mixed meals"; these are for instance ready-made meals and meals from restaurants with an unknown recipe. This category is divided over the food categories in NORMTOX contributing to those meals. The contribution of the mixed meals to a certain food category can be calculated according to equation 4.3. The contribution is small, for oils & fats it is 14%, for the other categories it is less than 7%.

$$FC_{int} = \frac{I_{int}}{I_{pot} + I_{cer} + I_{leg} + I_{soy} + I_{fat} + I_{fish} + I_{meat}} \cdot I_{mixed} \tag{4.3}$$

In which:

FC_{int}:		Contribution of the mixed meals to the food category of interest
I_{int}	:	Intake of the food category of interest
I_x	:	Intake of food category x (potatoes, cereals & thickenings, legumes, soy products, fats, oils & savoury sauces, fish, meat, meat products & poultry and mixed meals)

Food consumption frequencies

Consumption frequencies of food are described by a beta distribution (see Section 4.5). The parameters for these distributions can be obtained from the consumption frequencies of the 2-days VCP-3 (Hulshof et al., 1998) by Equations 4.4 and 4.5 (for more details see Appendix A).

$$\alpha = \frac{(1 + p_2 - p_0) \cdot (1 - p_2 - p_0)}{4p_2 - (p_2 - p_0 + 1)^2} \tag{4.4}$$

$$\beta = \frac{(1 - p_2 + p_0) \cdot (1 - p_2 - p_0)}{4p_2 - (p_2 - p_0 + 1)^2} \tag{4.5}$$

In which:

p_0:	The fraction of correspondents that consumed non of the days
p_2:	The fraction of correspondents that consumed both days

Calculation of the uncertainty in α and β, as explained in Appendix A, is not always possible. For some categories consumption frequencies are very high. In the method described in Appendix A it is tacitly assumed that the uncertainty in p_0, p_1 and p_2 follows a normal distribution, however, in extreme cases, for example a very high consumption frequency, the uncertainty distribution becomes skewed, which makes the described method unsuitable. This is the case for drinking water, fruit and cereals, for these categories it is assumed that they are consumed on a daily basis and no time correction factor is necessary. The parameters of the beta distributions as well as the variance in these parameters are given in Appendix B.2

4.2.2 Intake of soil particles

Soil ingestion by humans is difficult to quantify. In the past it was estimated by taking samples from the soil on the hands of children. Nowadays methods are based on the passage of tracers through the gastrointestinal tract. Mass balances are used to calculate the intake of soil particles (Calabrese & Stanek, 1993, 1994; Stanek & Calabrese, 1995; Stanek et al., 1996; Calabrese et al., 1997b,a; Binder et al., 1986; Davis et al., 1990; Sedman & Mahmood, 1994). The intake of soil can be estimated by the least tracer method, in which soil intake is determined by the tracer which predicts the lowest intake of soil particles. Calabrese & Stanek (1993) replaced this method by the best tracer method, in which the tracer with the lowest food to soil ratio ($Conc_{tracerinfood}/Conc_{tracerinsoil}$) is

chosen as the best tracer. NORMTOX uses data from Stanek et al. (1998) obtained by the best tracer method. They already separated interindividual variability from other sources of variance, the values of the mean and σ^2_{inter}, based on the tracers Al, Si and Y, are copied directly from Table 3 in Stanek et al. (1998). Just as food intake, the intake of soil particles differs from day to day within each individual as well as between individuals. The mean values and variance are adopted from Stanek et al. (1998). Furthermore it is assumed that soil intakes follow a lognormal distribution. The data is given in Appendix B.3.

The intake of soil particles is mainly studied for children; data for adults is scarce. Calabrese & Stanek (1994) estimated the intake of soil particles by persons older than the surveyed population. They assumed that children in the age of 6 to 12 have an intake of 125% of the children in the age of 1 to 6. The intake for individuals over the age of 12 would be 10% of the intake of children from 1 to 6 (all in absolute amounts). These assumptions are adopted in NORMTOX. The intake for children from 0 to 1 is estimated to be 60% of the 1 to 6 years olds. This percentage is based on the fact that these children only get active when they are around 6 or 7 months old. The intake of soil by younger children is minimal as they spent most of their time in a cradle or pen, therefore, only the second half of the first year of life is relevant for soil intake.

4.2.3 Intake of surface and swimming water

Exposure to contaminants in water during swimming, is determined by the time spent swimming multiplied by the volume of water ingested during one time unit of swimming.

The average time spent swimming can be obtained from data of the United States population (US-EPA, 1997a). It is assumed that this data is also applicable to the Dutch population. From the data an average and variance for a lognormal variability distribution are obtained. The time spent swimming consists of swimming in swimming pools (drinking water quality) and swimming in surface water. On basis of personal judgement it is assumed that the ratio in time spent swimming in swimming pools to swimming in surface waters is 5 to 6.

The volume of water ingested during swimming is obtained from a study of Kim & Weisel (1998). They investigated the water intake of four individuals during half an hour of swimming. This resulted in an average water intake of 0.75 ml/min with a standard deviation of 0.51 ml/min. It is assumed that these values are valid for the whole population. A lognormal distribution is assumed to best fit the data. The time spent swimming and the ingestion of water per time unit, are both uncertain as well as variable. Parameters for the time distribution as well as for the intake distribution are given in Appendix B.5

4.2.4 Inhalatory intake

The intake of substances through air is defined by I_{air} and C_{air}, according to Equation 2.2. I_{air} is subsequently defined by H, I_{energy} and VQ. Each of the parameters has its own distribution, contributing to the uncertainty and

variability in the inhalatory intake (I_{inh}), the parameters are summarized in Appendix B.4.

The amount of oxygen consumed in the production of one kJ energy (H) is not constant, it depends on the kind of food that is metabolised. Layton (1993) surveyed several studies on the oxidation of different nutrients. This resulted in a weighted average default oxygen uptake factor of 0.05 $l\,oxygen/kJ$, which is adopted in NORMTOX.

The energy expenditure (I_{energy}) can, according to Layton (1993), be calculated by multiplication of an individual's basal metabolic rate by a certain activity factor. Because NORMTOX predicts a lifetime average, fluctuations in activity can be neglected and the energy expenditure can be simply approximated by food-energy intakes. The VCP-3 (Hulshof et al., 1998) reports energy intakes from food. Therefore, a distribution for I_{energy} can be obtained from this survey in the same way as it was obtained for food intake.

The ventilatory equivalent (VQ) is the ratio of the volume of air exhaled within a minute ($l\,air/min$) to the volume of oxygen absorbed within a minute ($l\,oxygen/min$). Its value differs between individuals as it depends on the lung physiology and the efficiency of metabolism and oxygen uptake. The mean and variance of its variability distribution, respectively 27 and 1.18, were obtained from Layton (1993) and are assumed to follow a lognormal distribution.

4.2.5 Body weight

The predictions of NORMTOX 2.0 are obtained as the daily intake of a certain substance per kg bodyweight. Food and drinking water intake data are on a bodyweight basis. However, the intake of water during swimming and the intake of soil particles are not. Therefore these values have to be divided by the individuals bodyweight. Data on intake of swimming water and soil particles are defined per age class, the intake has to be divided by a weight corresponding to this age class. Bodyweight is assumed to follow a lognormal distribution. Parameters for these distributions are adopted from the Vademecum Gezondheidsstatistiek Nederland 1999 (CBS, 1999), which gives reliable values for the Dutch population. Weight is given for each year separately, parameters for the weight distributions are given in Appendix B.6.

4.3 Classification of parameters as uncertain, variable or both

The separation of uncertainty and interindividual variability, by means of second order Monte Carlo simulation as described in Section 3.4, requires that each parameter is defined as either uncertain, variable or both.

4.3.1 Variable parameters

There are only two parameters which are assumed to be exclusively variable, namely body weight and the ventilatory equivalent. In practice these variables are also uncertain, for example because of bias in the measuring device. However, these uncertainties are assumed to be negligible compared to the interindividual variability. Both variables are described by a lognormal distribution.

4.3.2 Uncertain parameters

Only two parameters are assumed to be truly uncertain, namely; the oral and inhalatory absorption fractions (see Equation 4.2). These parameters are only known for a limited number of compounds. Absorption fractions will probably also vary between individuals. However, the degree of uncertainty is assumed to be very large compared to the degree of variability, as a result of which variability can be neglected.

4.3.3 Uncertain as well as variable parameters

Most parameters are uncertain as well as variable, this holds for the intake of food, drinking water, soil particles, surface and swimming water, for the fraction of time spent swimming and for consumption frequencies of food. In these cases the parameter distributions are defined as variability distributions in which the distribution parameters are defined uncertain, according to Equations 3.8 and 3.10 and Appendix A for the parameters of respectively the lognormal and beta distribution.

4.4 Substance-specific parameters

The coherence indicator has been calculated for 54 substances; fifty pesticides, 3 heavy metals and nitrate (see Appendix C, D and E). Substances were selected on basis of their relevance for the Dutch population and data availability.

To calculate the CI, NORMTOX estimates the intake of a substance when all media are polluted up to their standards. This means that C_x in Equation 2.1 is a standard instead of a real concentration, which should be used if NORMTOX would be applied as an exposure model. NORMTOX uses different types of standards to calculate the CI. Several agencies are engaged in the determination of these. Sometimes the same type of standard is determined by more than one agency. Therefore it is important to mention which standards are used in the model. When no standard for a certain compound in a certain media can be obtained, the concentration of this compound in this medium is set to zero. This assumption is probably not realistic, however, for testing the coherence of the standards this seems the most reasonable assumption.

4.4.1 Environmental quality standards

The environmental quality standards are the maximum allowed concentrations in air, soil and water. These standards are determined by different agencies. For soil particles NORMTOX uses Dutch standards, stated in the Staatscourant (1994). Dutch standards for surface water and air are formulated by the Netherlands ministry of housing, spatial planning and the environment (VROM, 1997). Drinking water standards are provided by different agencies. For the origin of the values used in NORMTOX the following preference order is used:

1. EU directive 98/83/EC
2. Dijk-Looijaard van (1993)
3. WHO (1996b, 1998)

4. US-EPA (1999)

5. The Dutch drinking water decree (Staatsblad van het Koninkrijk der Nederlanden, 1984)

4.4.2 Food standards

Food standards for pesticides and other environmental hazardous substances are stated by the Dutch government by virtue of respectively article 6 and 13 of the food and drugs act (Staatscourant, 1984, 1993, 1996a,b,c,d).

The food products within this act do not correspond with the food categories in NORMTOX. Therefore, the contribution of the food products to a certain food category has to be estimated. From this estimation, standards for the categories in NORMTOX can be deduced from the statutory standards by Equation 4.6.

$$CS = \sum_{p} PS_p \cdot \frac{I_p}{I_{tot}} \tag{4.6}$$

In which:

CS :	Category standard ($mg\,contaminant/kg\,product$)
PS_p:	Product standard for product p ($mg\,contaminant/kg\,p$)
I_p :	Intake of product p ($g/time\,unit$)
I_{tot} :	Total intake for this category ($g/time\,unit$)

4.4.3 The Acceptable Daily Intake (ADI)

The ADI is determined by different agencies. To decide which value is used in NORMTOX, the following preference order is used:

1. World Health Organisation (FAO/WHO, 1993; FAO/WHO, 1998, 1999; JECFA, 1986, 1989; Lu, 1995)

2. The Dutch national institute of public health and the environment (RIVM) (Vermeire et al., 1991; Janssen et al., 1995, 1998)

3. United States Environmental Protection Agency (US-EPA, 1999, 1997b)

4. Pesticide manual, in which Tomlin (1994) gives a description of pesticides on basis of several sources from literature

The oral and inhalatory absorption coefficients are used to calculate the ADI_{inh} when its value cannot be obtained from literature (see Section 4.1. For seven substances data about the possible value of the absorption coefficients is available (Owen, 1990; WHO, 1993, 1996a). For these substances the possible value is defined as a triangular distribution on basis of data from the literature. When no substance-specific data is available, the oral and inhalatory absorption fractions are modelled with default uniform distributions suggested by Jager et al. (1997).

4.5 Simulation settings

As was mentioned in Chapter 2, NORMTOX 2.0 is set up in Microsoft Excel, in which distributions are defined making use of Crystal Ball. Crystal Ball is a graphically oriented forecasting and risk analysis program (Decisioneering Inc., 2000). The number of runs in the nested Monte Carlo simulation has a considerable influence on the model output, the more runs, the more accurate the results. However, the capacity of the computer may be limited and the calculation time increases with the number of iterations. A number of 101 times 1000 runs seems sufficient to obtain an accurate estimation of the CI and is used in this study. This means that 101 values are drawn for the uncertain parameters and 101 times 1000 values for the variable parameters. A number of 101 is chosen in order to obtain 100 percentiles, the n^{th} model outcome (when model outcomes are modelled from low to highest outcome) gives the $(n-1)^{th}$ percentile.

Chapter 5

Results

5.1 Presentation of the results

NORMTOX generated distributions for the coherence indicator of 54 substances in which true uncertainty and interindividual variability are separated. Because of the two dimensions of the output distribution the plots are somewhat difficult to interpret. As an example a possible plot of the coherence indicator (Figure 5.1) is explained.

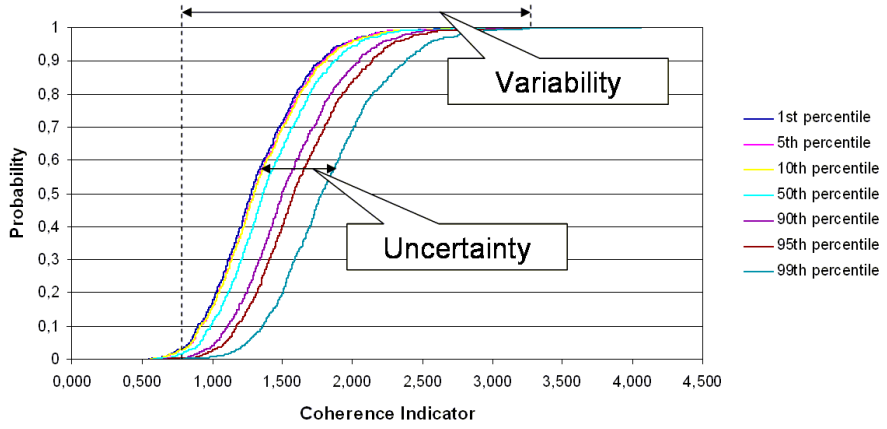

Figure 5.1: Plot of the variability in the percentiles of the uncertainty distribution of the coherence indicator

The curves in Figure 5.1 are percentiles of the uncertainty distribution. Each of them can be seen as one possible population. One can interpret them in the way that there is, for example, a chance of 95% that the true population lies on the left of the curve of the 95th percentile. The spread within one curve represents the interindividual variability within the population. Therefore, the spread within the curve is a measure for the interindividual variability and the spreading between the curves is a measure for true uncertainty represented as percentiles. The x-axis plots the coherence indicator, the y-axis plots the cumulative probability. The way in which Figure 5.1 should be read is that for

example 40% of the population (y-axis) has a chance of 99% (99^{th}-percentile curve) on a coherence indicator below 1.7 (x-axis).

The model produces 101 different graphs, corresponding to the 101 trials for the uncertain parameters. These graphs are ordered and it is assumed that graph number x gives the $(x-1)^{th}$ percentile.

5.2 Outcomes of the Coherence Indicator

Substances can be divided in compounds with a CI over 1, a CI around 1 and a CI below 1. There are nine compounds with a CI over one (see Appendix C). For those substances even the lowest value exceeds one. This means that at lifelong exposure to all media that are polluted up to their standards, the average daily intake exceeds the ADI with 99% certainty for 99% of the Dutch population. The standards for these substances are therefore incoherent.

For eighteen compounds the CI has a value around one (see Appendix D), the minimum value is below one and the maximum value exceeds one. Spreading in the coherence indicator originates from true uncertainty or interindividual variability.

Most (27) compounds have a coherence indicator below one (see Appendix E). This means that the whole graph is below one. It can be concluded that with a certainty of 99%, the coherence indicator will be below one for 99% of the population. The standards for these substances are coherent.

5.3 Variability versus uncertainty

In the output of NORMTOX 2.0 uncertainty and variability are separated as was explained in Section 5.1. For decision making processes it is interesting to know how these sources of variance relate to each other. Analogous to Slob (1994) dispersion factors (DFs) are used to quantify uncertainty as well as variability. The DF is a convenient way to quantify uncertainty, and it surpasses other measures (e.g. the coefficient of variation or the variance) with respect to interpretability. In this study, DF's are defined as the ratio between the 1st and 99th percentile. The DF's of variability, uncertainty and the ratio between these two are presented in Table 5.1.

Generally the amount of uncertainty is very small (a DF of 1 means zero uncertainty). Variance in the CI originates mainly from interindividual variability. This is graphically shown in a typical plot of the CI in Figure 5.2. The dominance of interindividual variability over uncertainty is better understood after a sensitivity analysis of the model. This has been carried out for lead and lindane. Food intake is responsible for over 90% of the variance in the CI. The uncertainty in the mean and variance in these distributions is inversily proportional to the number of correspondents (n). Because, n is high (around 5500, depending on the food category), uncertainty in the parameters is low, therefore, the variance in the CI is mainly caused by interindividual variability.

For six substances an air quality standard and no $ADI_{inhalatory}$ is present. Therefore the $ADI_{inhalatory}$ is calculated from the ratio between the oral and inhalatory absorption coefficient, as is described in Section 4.1. Because these parameters are very uncertain and this counts even more for their ratio, a high

amount of uncertainty is brought into the model. This gives a distorted picture of the variability-uncertainty ratio compared to other substances, for which the air quality standard is set to zero or an $\mathrm{ADI}_{inhalatory}$ is available. Therefore, for substances for which the $\mathrm{ADI}_{inhalatory}$ has to be calculated, a CI oral is calculated, which means that the inhalatory is left aside.

Table 5.1: Comparison of uncertainty and variability, in terms of the dispersion factor, in the output of NORMTOX 2.0

Substance	**Variability**	**Uncertainty**	**Var/Unc**
2,4-D	8,90	1,04	8,54
Acephate	5,47	1,03	5,30
Aldicarb	3,57	1,03	3,48
Anilazine	3,40	1,02	3,33
Atrazine	3,40	1,02	3,34
Azinphos-methyl	8,26	1,04	7,95
Benomyl	4,89	1,04	4,72
Bentazone	4,15	1,03	4,02
Bifenthrin	3,39	1,02	3,31
Cadmium	3,08	1,16	2,67
Cadmium oral	2,59	1,02	2,55
Captan	7,85	1,04	7,58
Carbaryl	4,86	1,03	4,73
Carbendazim	4,93	1,02	4,82
Carbofuran	3,29	1,02	3,23
Chlorfenvinphos	3,71	1,03	3,62
Chlorothalonil	6,26	1,03	6,05
Chlorpyriphos	3,18	1,16	2,75
Chlorpyriphos oral	3,15	1,02	3,10
Deltamethrin	3,81	1,03	3,69
Diazinon	5,02	1,03	4,88
Dichlorvos	4,83	1,03	4,68
Dimethoate	6,60	1,03	6,39
Diphenylamine	12,79	1,04	12,24
Ethoprophos	3,37	1,02	3,30
Fenthion	23,02	1,07	21,53
Fenthion oral	23,02	1,05	21,88
Folpet	7,76	1,03	7,51
Iprodione	6,04	1,03	5,88
Isoproturon	3,40	1,02	3,33
Lead	4,29	1,29	3,32
Lead oral	2,83	1,02	2,78
Lindane	5,61	1,03	5,45
Malathion	4,71	1,03	4,57
Maneb	6,00	1,04	5,79
MCPA	3,39	1,02	3,32
Mercury	2,60	1,03	2,53
Methyl-Mercury	221,13	24,50	9,03
Methyl-Mercury oral	6,07	1,05	5,80
Methomyl	6,96	1,03	6,78

Metolachlor	4,22	1,02	4,12
Mevinphos	4,41	1,03	4,29
Nitrate	13,72	1,04	13,13
Oxamyl	7,64	1,04	7,32
Oxydemethon-methyl	5,59	1,03	5,43
Parathion-ethyl	6,08	1,03	5,88
Parathion-methyl	4,45	1,03	4,32
Permethrin	4,21	1,03	4,10
Pirimicarb	5,85	1,04	5,64
Procymidone	5,37	1,03	5,22
Propoxur	8,05	1,04	7,77
Pyrazophos	3,74	1,03	3,64
Simazine	3,75	1,02	3,68
Thiabendazole	7,03	1,04	6,79
Thiram	6,34	1,53	4,14
Thiram oral	6,03	1,03	5,88
Tolclophos-methyl	3,44	1,02	3,36
Tolyfluanid	6,83	1,04	6,60
Triazophos	3,48	1,02	3,41
Zineb	6,03	1,03	5,85

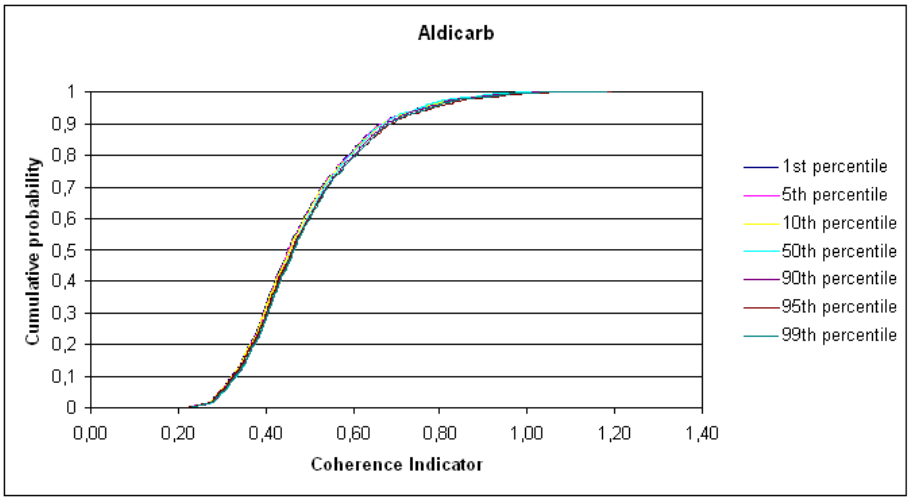

Figure 5.2: Typical plot for the CI, which is in this case is from carbaryl

The ratio between variability and uncertainty is particularly of interest for substances with a CI around one. True uncertainty is only of little importance and interindividual variability plays an important role. This means that a certain part of the population will exceed a CI of one, rather than that there is a certain chance of exceeding one at lifelong exposure to all media that are polluted up to their standards. It can be concluded that the standards are incoherent for a certain part of the population.

Striking is the enormous variability in Methyl-Mercury, which is much higher

than for other substances. Variability and uncertainty are different for each intake route. The intake of a substance trough swimming water is much more variable than for example the intake through soil or food products. The DF is defined by the sum of variability or uncertainty in a certain route times the contribution of that route to the total intake. When the intake trough a certain route is dominant over other routes, the variability in this route will dominate the DF presented in Table 5.1. For Methyl-Mercury no food standards are provided, therefore, the intake through food is zero and other intake routes with a much higher variability dominate the DF.

5.4 NORMTOX 2.0 versus NORMTOX 1.0

Table 5.2 gives the values for the mean and standard deviation of the CI for lead and lindane, calculated by NORMTOX 1.0 and NORMTOX 2.0. For NORMTOX 1.0 the 50^{th} percentile of the uncertainty distribution is chosen as representative, which means that the standard deviation represents only interindividual variability. This is legitimized by the fact that uncertainty is really small, its contribution to the variance will therefore be negligible. Values for the two models are comparable, little differences are assigned to differences in the values of input parameters.

Table 5.2: The Coherence indicator of lead and lindane from NORMTOX 1.0 and NORMTOX 2.0

	NORMTOX 1.0	**NORMTOX 2.0**
Lead		
Mean	1.29	1.40
Standard deviation	0.50	0.34
Lindane		
Mean	6.13	5.23
Standard deviation	2.23	2.07

Chapter 6

Discussion

Only when the predictions of NORMTOX are considered sufficiently accurate one can draw conclusions from its calculations. The validity of its predictions can only be evaluated qualitatively as no experimental validation data is available. As NORMTOX is only a theoretical model a number of simplifications of the real world and several assumptions are necessary.

The first assumption is that the model accounts for all uptake routes of the contaminant of interest. This is not entirely true as the model does not account for dermal uptake from air, soil and water. However, earlier research concluded that dermal uptake is negligible with respect to other uptake routes (Ragas & Huijbregts, 1998).

A second assumption is that there is no correlation between input variables. There may however, be a correlation between the consumption of different food products. Nevertheless, Smith et al. (1992) found that when the relations between model variables are additive, the standard deviations diverge and when the model contains many uncorrelated variables, the correlations are likely to have little or no influence on risk estimates. Therefore, neglecting the correlations between the food intakes is considered to have little effect on the model outcome.

For several input parameters it is assumed that their uncertainty and variability can be described by statistical distributions. It is difficult to outline the influence of the choice of a certain distribution, but it may have a significant influence on the model output. Intakes of soil, air, food and swimming water in NORMTOX 2.0 follow a lognormal distribution. This assumption is to some extent arbitrary, nevertheless lognormally distributed variables have been reported in many scientific fields (Gaddum, 1945). The food intake data was tested on lognormallity, the data fitted reasonably to the defined distributions. All distributions types are obtained on basis of expert judgement and thought to be the best available distribution to describe this data.

The model predicts a lifetime averaged daily intake, which is calculated from weighted averages over several age groups. As one can reason, activity and consumption patterns are not constant in time, but will vary strongly with age. One can therefore only conclude that a substance does not have a chronic effect when the coherence indicator is below one. The substance can however still be of concern, because acute effects of occasional high intakes are not accounted for in the model.

NORMTOX adds up the intakes trough several intake routes to obtain the a total intake of a substance. As was mentioned in Section 4.1, this is only plausible for substances with a systemic mode of action, which are eliminated or degraded relatively slow. The mechanism and metabolism of the 54 substances for which NORMTOX 2.0 calculated the CI, was not investigated. To draw real life conclusions from the output of the model one should first check if the substance satisfy the conditions mentioned above.

Several food products are processed before they are actually consumed (e.g. the washing of fruits or the cooking of potatoes and vegetables). In these processes the concentrations of contaminants can change, however, these processes are not included in NORMTOX, which may give a biased model output (Chavarri et al., 2005; Dejonckheere et al., 1996).

NORMTOX considers the uncertainty and variability in the exposure to a certain substance. The variance in the exposure distribution originates from the uncertainty and variance in the input variance. However, the model may not cover the entire problem, this uncertainty is not included in the output distribution. For the substances modeled in this case study (pesticides and heavy metals), the considered exposure pathways are assumed to be the most important pathways. However, when calculating the exposure to other substances, for example pharmaceuticals or softening agents, for which other pathways may play a considerable role, these pathways should be included or another exposure should be used.

In this study the model is applied to calculate a substances' coherence indicator. It is assumed that all media are polluted up to their standards. The incoherence established in this study should not be confused with exposure concentrations in real life, since the calculations are based on the assumption of lifetime simultaneous exposure. The chance that all media are actually polluted up to their standards during an individuals whole lifetime may generally be considered small. On the other hand it is assumed that the concentration level is assumed to be zero for media for which no standards are provided. A study in which realistic concentrations are implemented in the model should be performed in order to get an idea of which substances may be of real concern.

Chapter 7

Conclusions

There are several conclusions that can be drawn from this study. They can be divided in two groups, namely conclusions about the methods used in NORM-TOX 2.0 and conclusions about the coherence of standards in the Netherlands.

Methods

- Uncertainty and interindividual variability are successfully separated. The combination of ANOVA and second order Monte-Carlo simulation can therefore be considered a good tool to perform this.
- This study clearly presents the ratio between uncertainty and variability (Table 5.1), on basis of which one can decide whether additional research is necessary. When variability is dominant over true uncertainty, additional won't result in more accurate estimations of the output parameter. When true uncertainty is the most important source of variance in the output, additional research will lead to a more precise estimation of the output parameter.

The coherence indicator

Conclusions about the coherence indicator depend on the compound of interest. However, some general conclusions can be drawn.

- For 9 substances standards are incoherent, for eighteen substances the standards may be incoherent, for the other substances the standards are coherent. However, one has to keep in mind that these calculations are hypothetical and no conclusions about the real world can be drawn from the results.
- Variance in the CI is for the greater part caused by interindividual variability. Which means that further research to the uncertain parameters is unnecessary as it results in a barely more accurate value for the CI.
- A great amount of uncertainty is introduced into the CI by calculation of the ADI_{inh}. To obtain its value the ratio between the oral and inhalatory absorption coefficients is used. Both coefficients are uncertain and are not correlated to each other, the ratio between them is therefore even more

uncertain. To reduce this uncertainty more information about the ADI_{inh} or about the ratio between the coefficients should be gathered.

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Appendix A

Calculation of the covariance structure of α and β

The consumption frequency of food products can, according to Slob & Bakker (2004), be described by a beta distribution. The parameters of this distribution, α and β can be obtained from the consumption frequencies of the surveyed population. In the 2days VCP-3, there are three possibilities for the consumption frequency:

p_0,	when an individual consumed not at all
p_1,	when an individual consumed one of the days
p_2,	when an individual consumed both days

Given that p is generated by the beta distribution, the probabilities for $p_0\,, p_1$ and p_2 are:

$$\begin{aligned} p_0 &= (1-p)^2 \\ p_1 &= 2 \cdot p\,(1-p) \\ p_2 &= p^2 \end{aligned}$$

The mean and variance of the beta distribution are given by Equations A.1 and A.2 (Abramowitz & Stegun, 1965).

$$\bar{p} = E(p) = \frac{\alpha}{\alpha+\beta} \tag{A.1}$$

$$\sigma_p^2 = E(p^2) - [E(p)]^2 = \frac{\alpha \cdot \beta}{(\alpha+\beta)^2 \cdot (\alpha+\beta+1)} \tag{A.2}$$

Substitution of p and p^2 in the expressions for the consumption frequencies with equations in terms of α and β, results (after rewriting) in equations for α and β in terms of consumption frequencies (Equation A.3 and A.4).

$$\alpha = \frac{(1+p_2-p_0)\cdot(1-p_2-p_0)}{4p_2-(p_2-p_0+1)^2} \tag{A.3}$$

$$\beta = \frac{(1 - p_2 + p_0) \cdot (1 - p_2 - p_0)}{4p_2 - (p_2 - p_0 + 1)^2} \tag{A.4}$$

The beta distribution is used to calculate the consumption frequency as a life long average. Because the data reflects the consumption frequencies of different age groups weighted values have to be taken into account. The weight of each data point can be obtained by Equation A.5.

$$w_j = \frac{a_i}{n_i \cdot life} \tag{A.5}$$

In which:

w_j	:	The weight of the data of individual j
a_i	:	The number of years in the age group i, where i represents the age group of individual j
n_i	:	The fraction of individuals in age group i citepCBS1999
$life$:		The life expectance of the population of interest

To estimate the uncertainty in the α and β, a covariance structure for has to be obtained. This covariance structure gives the variances of α and β on the diagonal. The consumption frequency of each individual can be either p_0, p_1 or p_2. In another notation consumption frequencies are given by:

y_j=(1,0) if the j^{th} individual gives data (0,0)
y_j=(0,0) if the j^{th} individual gives data (1,0) or (0,1)
y_j=(0,1) if the j^{th} individual gives data (1,1)

The parameters (p_0, p_2) can be estimated by Equation A.6.

$$(\hat{p}_0, \hat{p}_2) = \sum_j w_j \cdot y_j \tag{A.6}$$

The covariance structure of this estimate is given by Equation A.7.

$$S = \sum_i \sum_{j \, \varepsilon \, i} w_j^2 \cdot \frac{1}{n_j - 1} \cdot (y_j - \bar{y_i}) \cdot (y_j - \bar{y_i})^T \tag{A.7}$$

The so called Delta method (Rao, 1965) tells us that the covariance structure of α and β can be obtained by Equation A.8.

$$(\phi_1(\hat{p}_0, \hat{p}_2), \phi_2(\hat{p}_0, \hat{p}_2)) = (D\phi) S (D\phi)^T \tag{A.8}$$

ϕ_1 and ϕ_2 are the equations for α and β which are given by Equations A.3 and A.4 respectively.

$D\phi$ stands for the Jacobian matrix which contains the partial differential equations of ϕ_1 and ϕ_2 to p_1 and p_2, according to:

$$D\phi = \begin{pmatrix} \partial_1\phi_1 & \partial_2\phi_1 \\ \partial_1\phi_2 & \partial_2\phi_2 \end{pmatrix}$$

Using this matrix, Equation A.8 results in the covariance structure for α and β, from which the variance in those parameters can be obtained.

Appendix B

Input parameters for calculation of the CI with NORMTOX 2.0

B.1 Food intake

Food intake follows a lognormal distribution. The parameters of the lognormal variability distribution are given below. The uncertainty in these its parameters is defined by the number of individuals that consumed the product (n), which is therefore also given below. Data originates from Hulshof et al. (1998)

Food category	**Symbol**	**Unit**	**Mean**[a]	**Variance**[a]	n_1[b]	n_2[c]
Drinking water	I^o_{dw}	$\mu l/kg_{bw}\,day$	9.80	0.18	45	5889
Potatoes	I^o_{potato}	$mg/kg_{bw}\,day$	7.90	0.18	2629	2325
Vegetables	I^o_{veg}	"	7.70	0.23	1845	3669
Fruit	I^o_{fruit}	"	7.84	0.34	29	5911
Cereals	I^o_{cereal}	"	8.04	0.17	89	5845
Meat	I^o_{meat}	"	7.46	0.14	1059	4664
Eggs	I^o_{eggs}	"	6.36	0.40	2364	508
Milk & Milk products	I^o_{milk}	"	8.53	0.61	511	5204
Cheese	I^o_{cheese}	"	6.32	0.24	1758	2755
Fish	I^o_{fish}	"	7.36	0.33	810	95
Nuts & Seeds	I^o_{nut}	"	6.63	0.61	2134	1317
Sweets	I^o_{sweet}	"	6.34	0.57	870	4455
Oils & Fats	I^o_{oil}	"	6.46	0.29	414	5425

[a] In the lognormal domain
[b] Number of individuals that consumed the product at least on one day
[c] Number of individuals that consumed the product both days

B.2 Food consumption frequencies

Food consumption frequencies are described by beta distributions, parameters for each food category are given below. α, β and the variance in these values are calculated by the methods described in Appendix A.

Food category	p_0	p_2	α	β	SD of α	SD of β
Potatoes	0.1658	0.3942	7.97	10.71	0.061	0.085
Vegetables	0.0707	0.6212	5.916	4.066	0.033	0.024
Meat	0.0374	0.7862	3.566	1.232	0.015	0.006
Eggs	0.5159	0.0860	11.954	46.677	0.273	1.075
Milk & Milkproducts	0.0381	0.8768	1.238	0.223	0.004	0.001
Cheese	0.2356	0.4705	1.017	1.114	0.002	0.003
Fish	0.8435	0.0168	0.651	7.916	0.004	0.049
Nuts & Seeds	0.4240	0.2199	1.151	2.772	0.003	0.008
Sweets	0.1068	0.7462	0.811	0.324	0.002	0.001
Oils & Fats	0.0174	0.9136	2.224	0.284	0.010	0.001

B.3 Soil intake

The intake of soil particles (I_{soil}) in mg/day is variable as well as uncertain. The parameters of the lognormal variability distribution are given below. The uncertainty distribution depends on the number of individuals (n), which is therefore also given in the table below. Data is obtained from Table 3 in Stanek et al. (1998).

Parameter	Age groups (years)			
	0-1	1-6	6-12	12-75
n	64	64	64	64
Mean[a]	2.019	2.530	1.144	0.227
Standard deviation[a]	0.582	0.582	0.582	0.582

[a]In the lognormal domain

B.4 Inhalatory intake

The inhalatory intake is determined by three parameters; the energy intake, I_{energy}, the oxygen uptake factor, H, and the ventilatory equivalent, VQ. Data for I_{energy} originates from Hulshof et al. (1998), H and VQ originate from Layton (1993).

Parameter	Units	Classification	Distribution	Mean[a]	Variance[a]
Energy intake	$kJ/kg_{bw}\,day$	Unc & Var	Lognormal	4.97	0.09
Oxygen Uptake Factor	m^3O_2/kJ	Constant	-	0.00005	-
Ventilatory Equivalent	-	Var	Lognormal	1.50	3.61

[a]In the lognormal domain

B.5 Intake of Swimming water

The intake of swimming water is determined by the amount of water taken in per time unit and the fraction of time one spent swimming. Values for both parameters are given below (US-EPA, 1997a; Kim & Weisel, 1998).

Parameter	Units	Age groups (years)				
		1-5	5-12	12-18	18-65	65-75
Intake of water	ml/min					
Mean[a]		-0.478	-0.478	-0.478	-0.478	-0.478
Variance[a]		0.380	0.380	0.380	0.380	0.380
Time spent swimming	min/day					
Mean[a]		0.608	0.859	0.817	0.321	0.342
Variance[a]		0.527	0.335	0.367	0.545	0.446

[a]In the lognormal domain

B.6 Bodyweight

Bodyweight, G, in kg, is distributed, data originates from CBS (1999).

Body-weight	Age groups (years)								
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9
Mean	7.73	11.65	14.06	16.37	18.76	21.27	24.11	27.12	30.38
SD	1.45	2.20	2.70	3.28	3.95	4.74	5.73	6.80	8.16

Age groups (years)									
9-10	10-11	11-12	12-13	13-14	14-15	15-16	16-17	17-18	18-19
33.82	37.45	41.77	46.93	52.31	57.27	61.40	64.47	66.66	68.27
9.59	11.21	12.88	14.39	15.34	15.81	16.08	16.13	16.29	16.32

Age groups (years)						
19-20	20-30	30-40	40-50	50-60	60-70	70-75
69.54	71.93	74.10	75.05	75.75	75.25	72.22
16.31	11.16	12.14	15.76	13.69	11.50	9.90

B.7 Absorption fractions

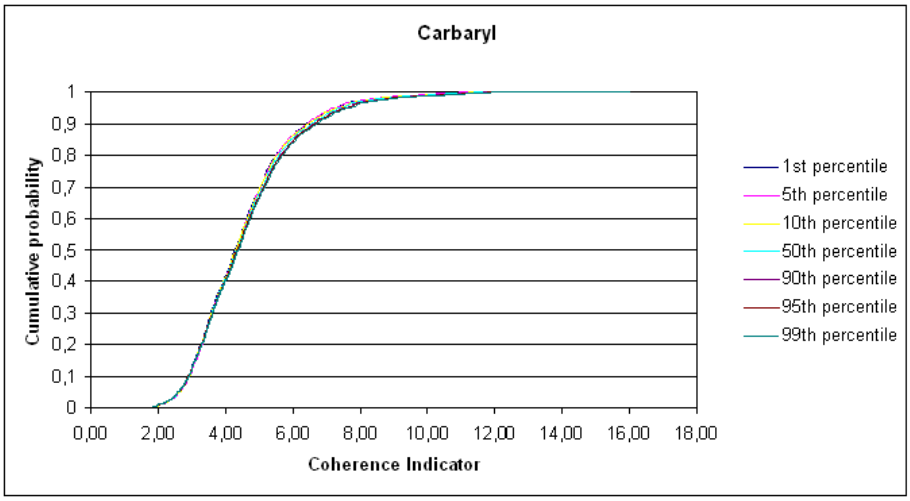
Absorption fractions are uncertain and are described by a triangular distribution when data is available. For substances for which no data is available a default uniform distribution is used.

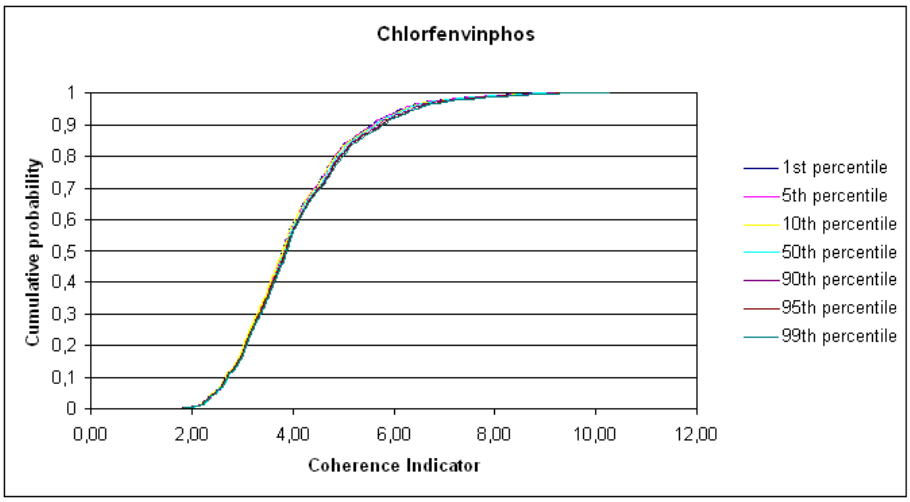
Substance	$\mathbf{A}_{inhalatory}$			$\mathbf{A}_{oral}$			Source
	Min	Likeliest	Max	Min	Likeliest	Max	
Cadmium	0.05	0.40	0.60	0.01	0.06	0.23	Owen (1990)
Carbendazim	-	-	-	0.00	0.82	1.00	WHO (1993)
Chlorothalonil	-	-	-	0.00	0.30	1.00	WHO (1996a)
Lead	0.20	0.50	0.62	0.01	0.10	0.14	Owen (1990)
Mercury	0.50	0.75	1.00	1.00e-10	1.00e-4	0.45	Owen (1990)
Methyl-Mercury	0.80	0.95	1.00	-	-	-	Owen (1990)

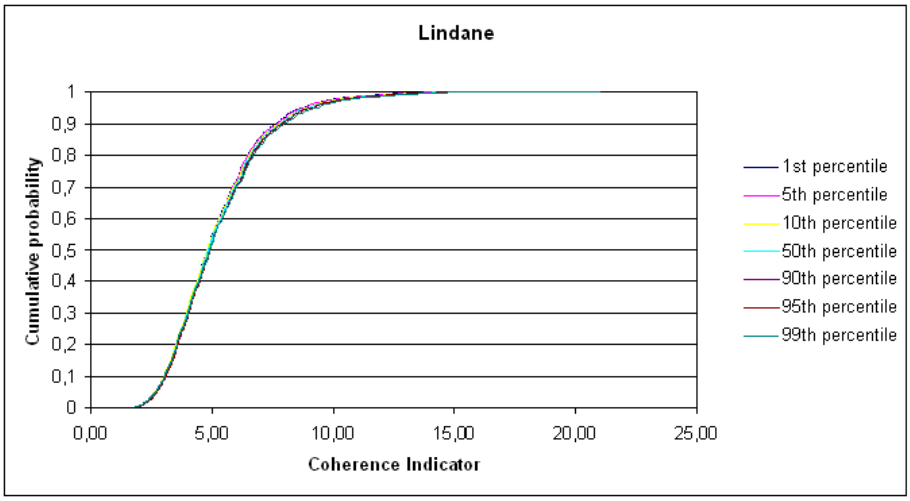
Appendix C

Compounds with a coherence indicator over 1

Carbaryl Chlorfenvinphos Lindane
Oxydemethon-methyl




Chlorfenvinphos
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
2,00
4,00
6,00
8,00
10,00
12,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile


Lindane
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
5,00
10,00
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25,00
Coherence Indicator
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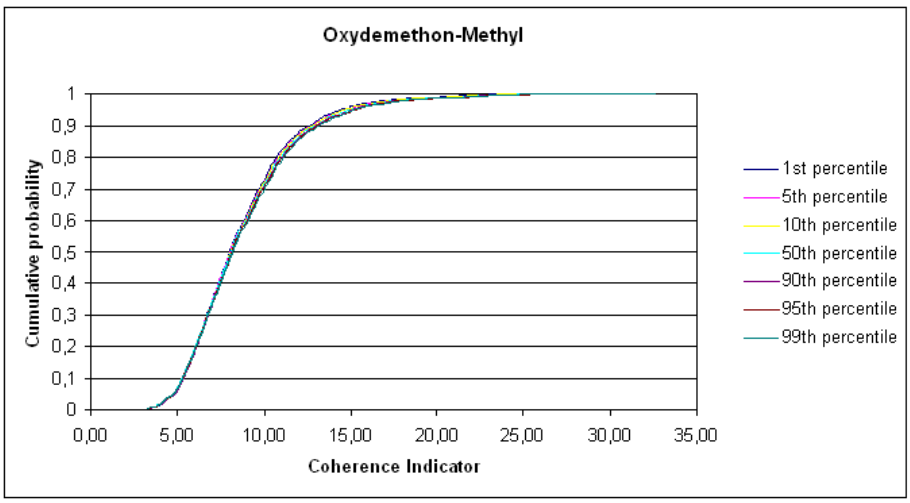
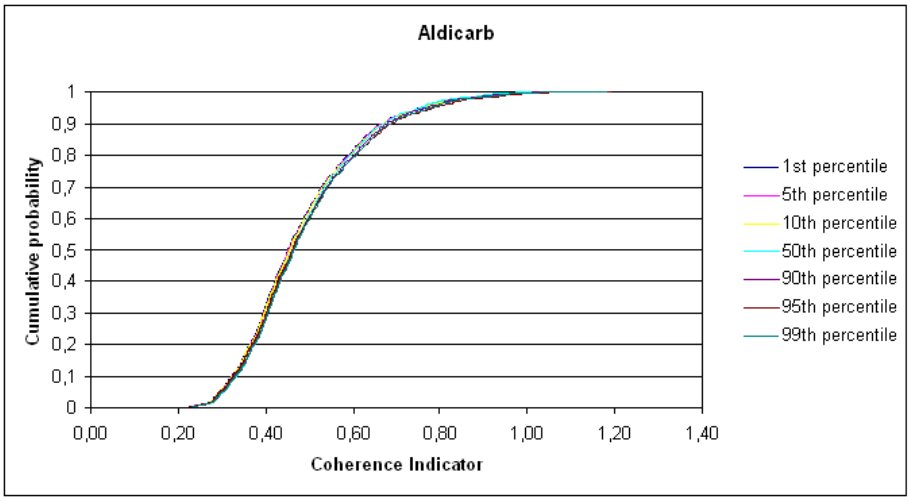
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

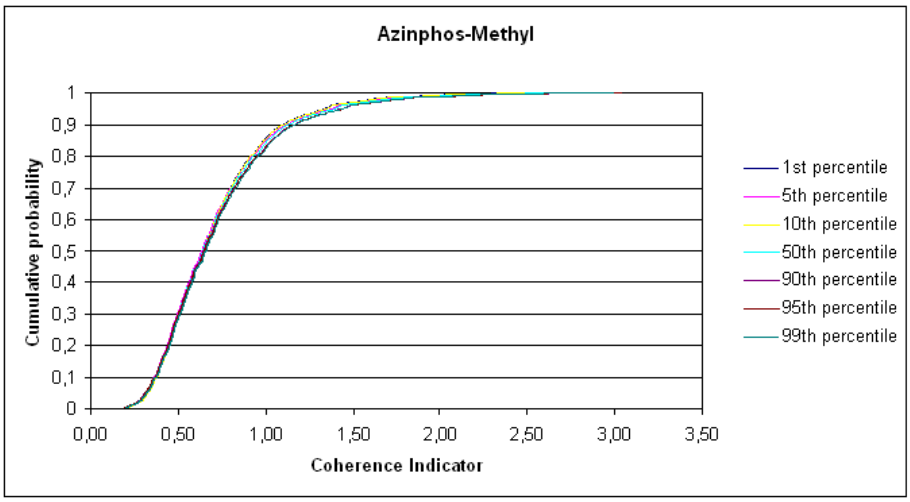

Oxydemethon-Methyl
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
5,00
10,00
15,00
20,00
25,00
30,00
35,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

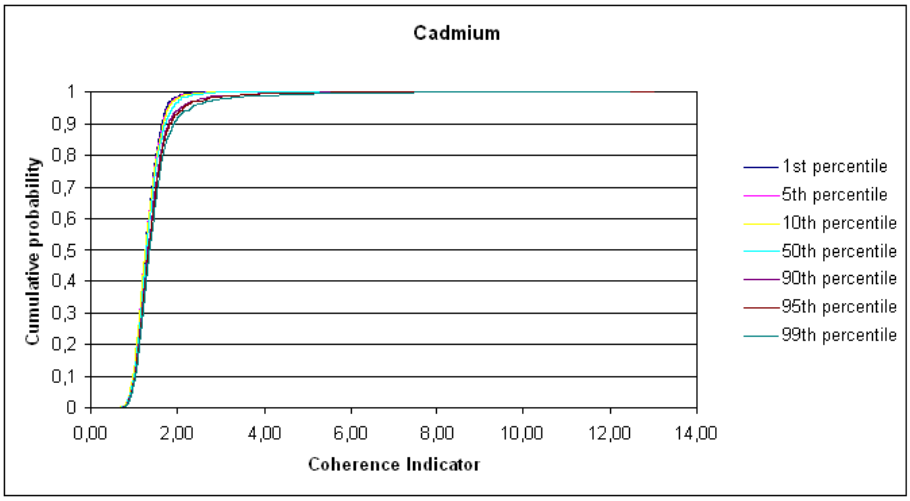
Appendix D

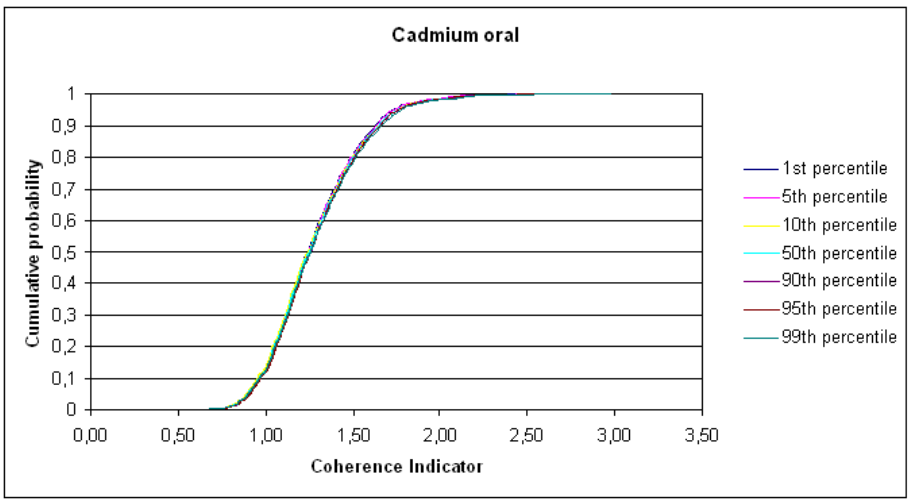
Compounds with a coherence indicator around 1

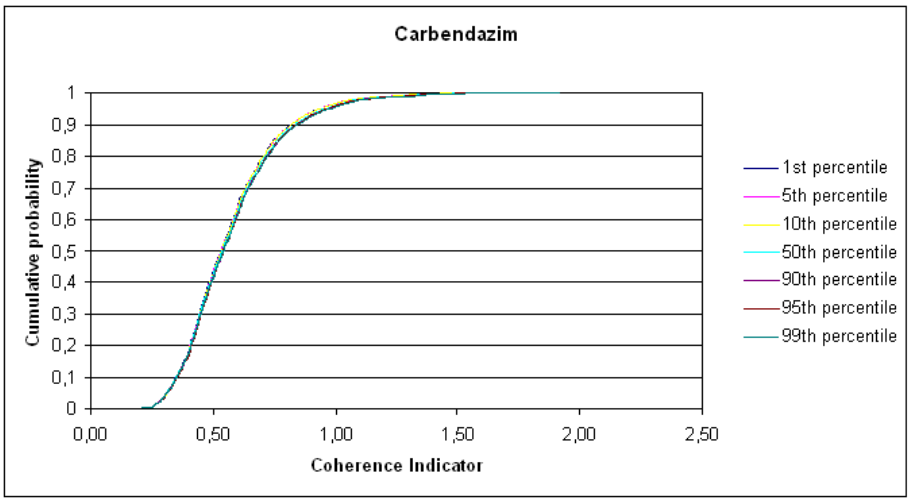
Aldicarb	Azinphos-methyl	Cadmium
Cadmium oral	Carbendazim	Carbofuran
Chlorpyriphos	Chlorpyriphos oral	Diazinon
Dichlorvos	Dimethoate	Ethoprophos
Iprodione	Lead	Lead oral
MCPA	Mercury	Methyl-Mercury
Mevinphos	Parathion-Ethyl	Parathion-Methyl
Propoxur	Thiram	Thiram oral
Triazophos		

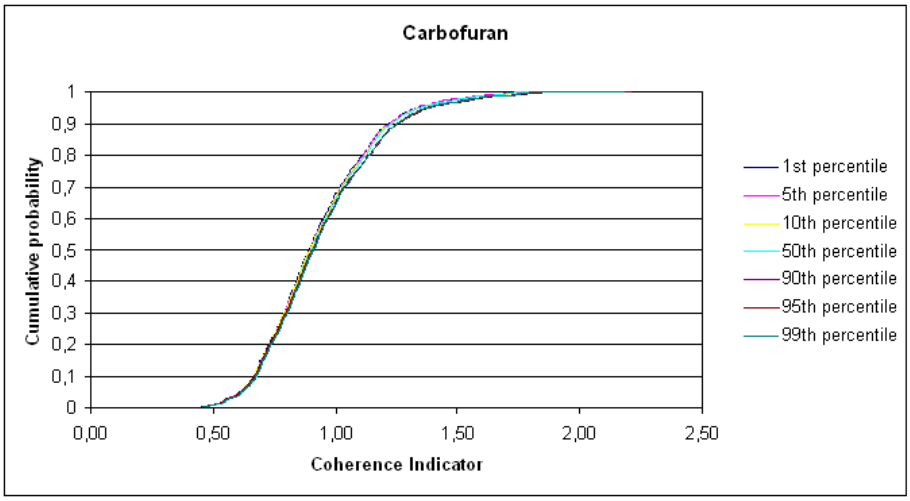


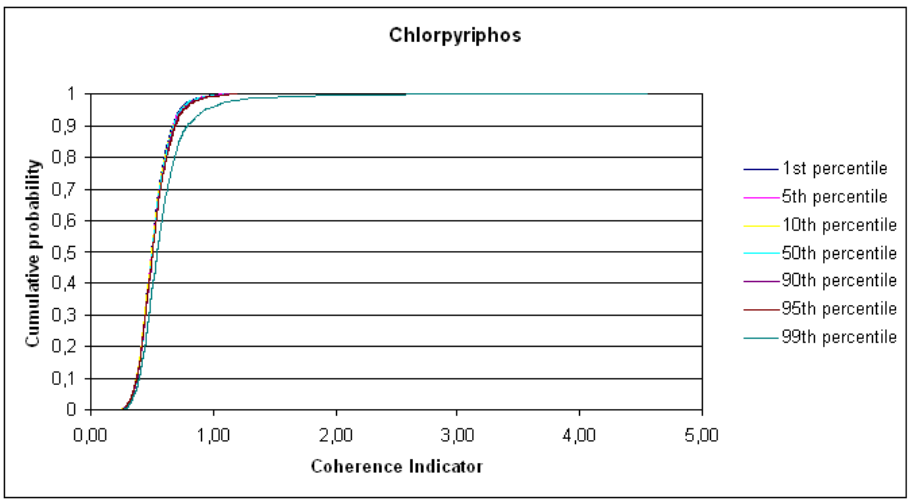

Azinphos-Methyl
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
3,00
3,50
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

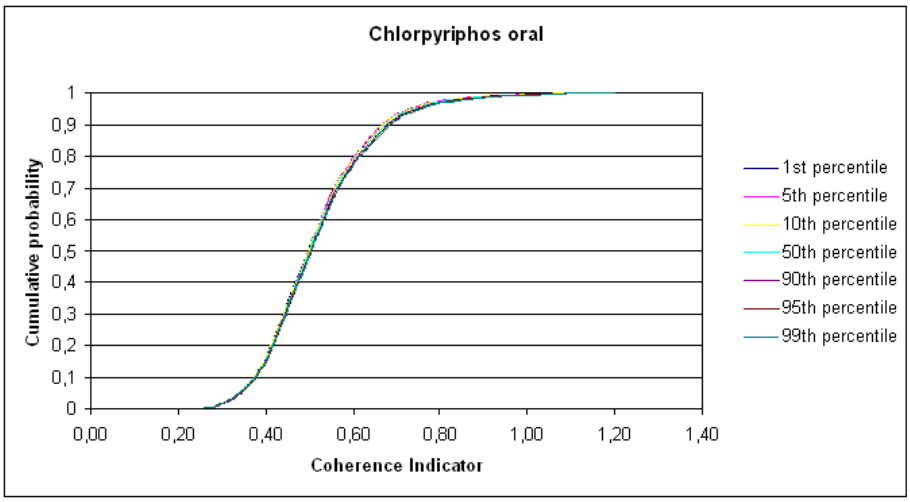

Cadmium
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
2,00
4,00
6,00
8,00
10,00
12,00
14,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

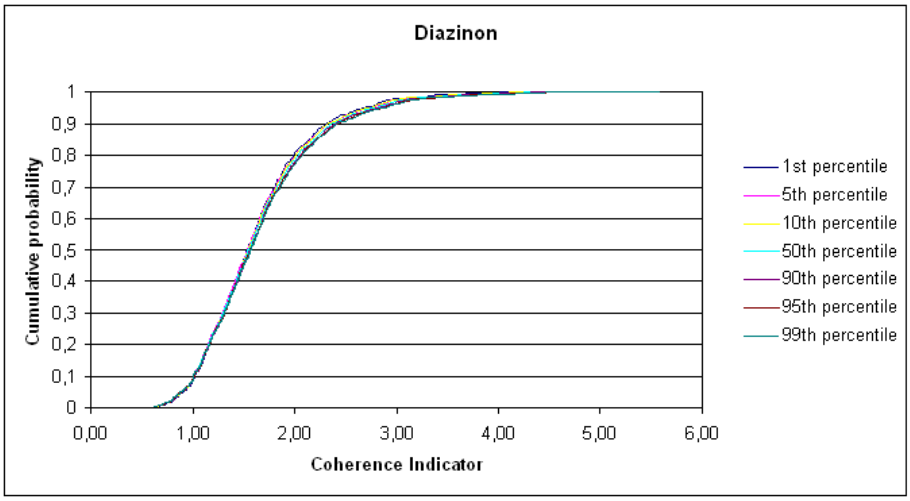

Cadmium oral
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
3,00
3,50
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

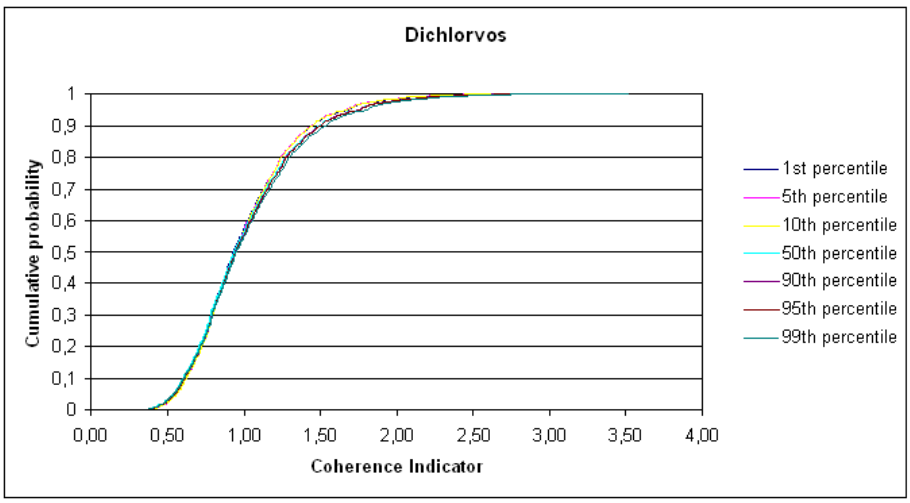

Carbendazim
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

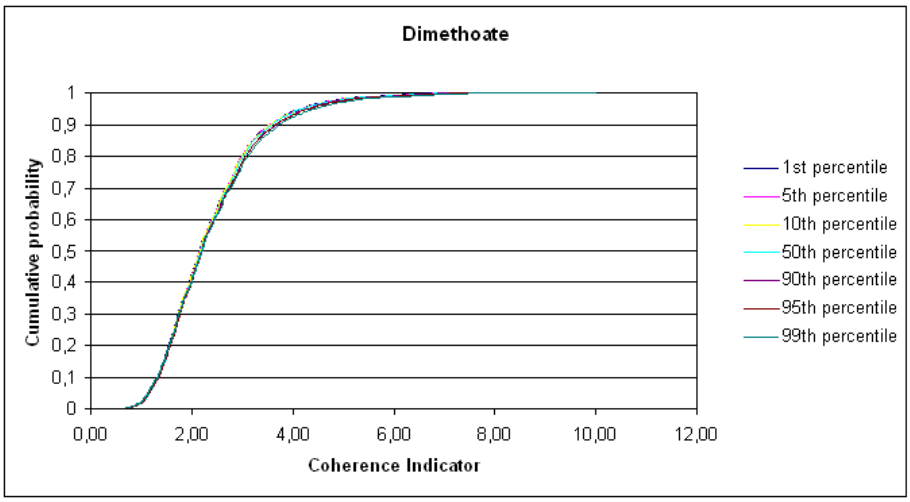

Carbofuran
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

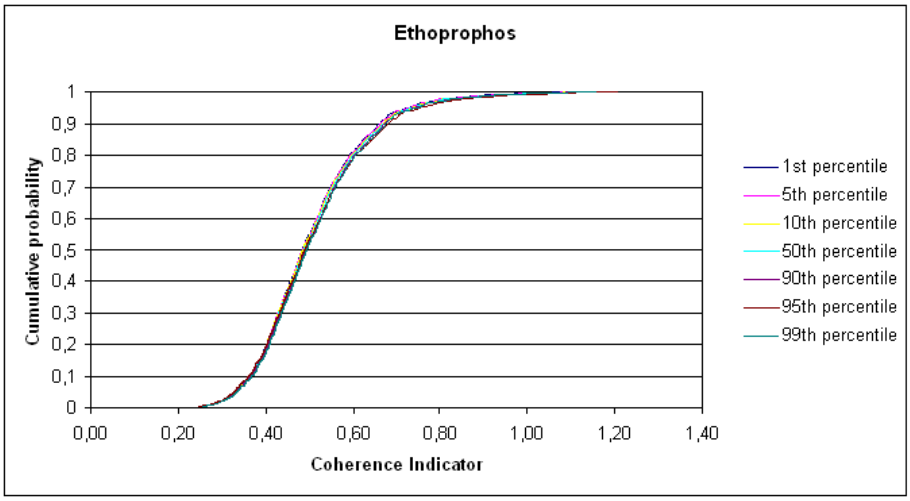

Chlorpyriphos
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
1,00
2,00
3,00
4,00
5,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

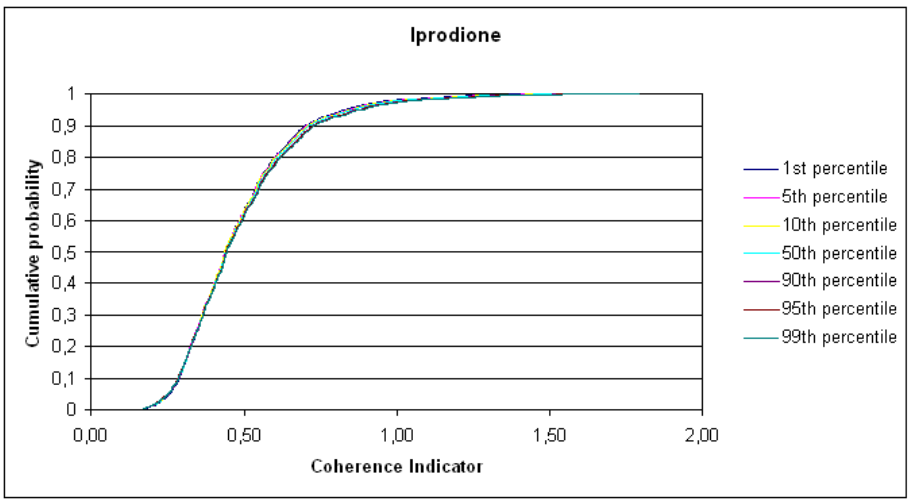

Chlorpyriphos oral
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,20
0,40
0,60
0,80
1,00
1,20
1,40
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

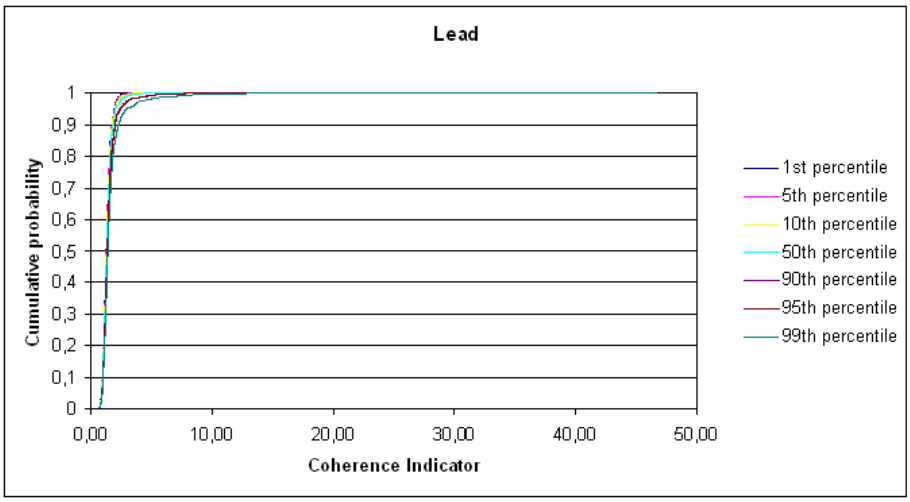

Diazinon
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
1,00
2,00
3,00
4,00
5,00
6,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

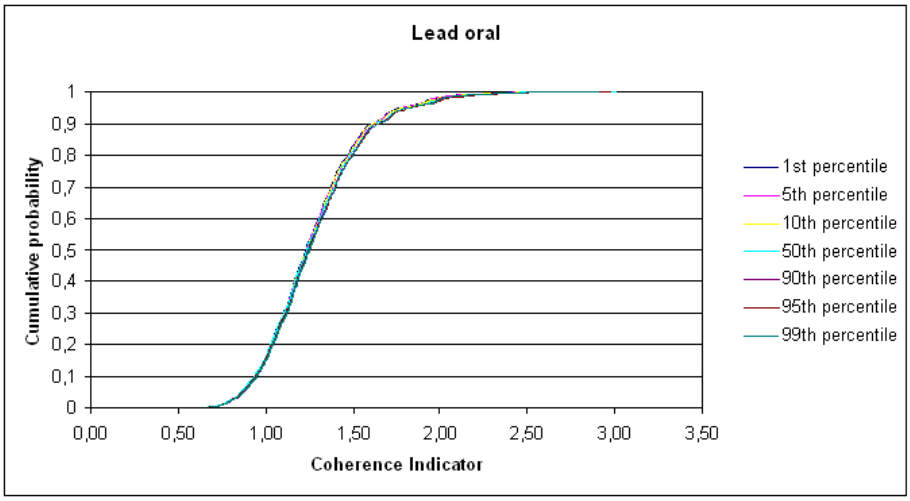

Dichlorvos
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
3,00
3,50
4,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

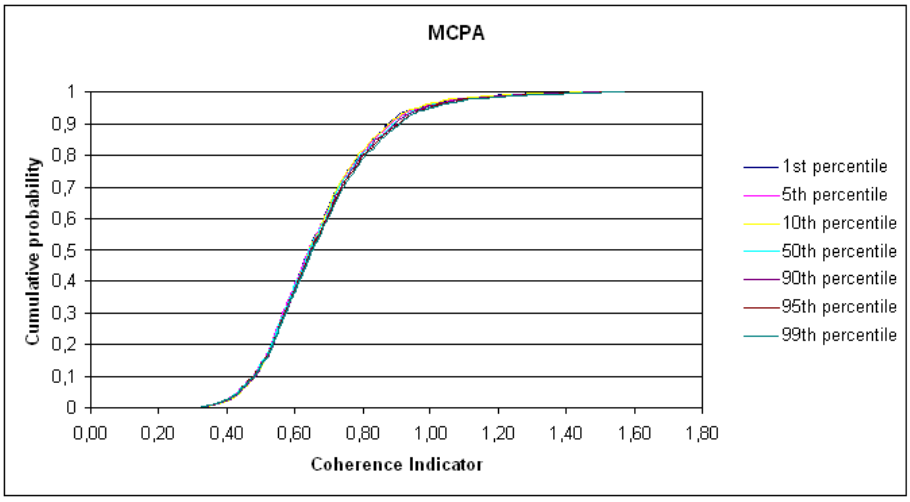

Dimethoate
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
2,00
4,00
6,00
8,00
10,00
12,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

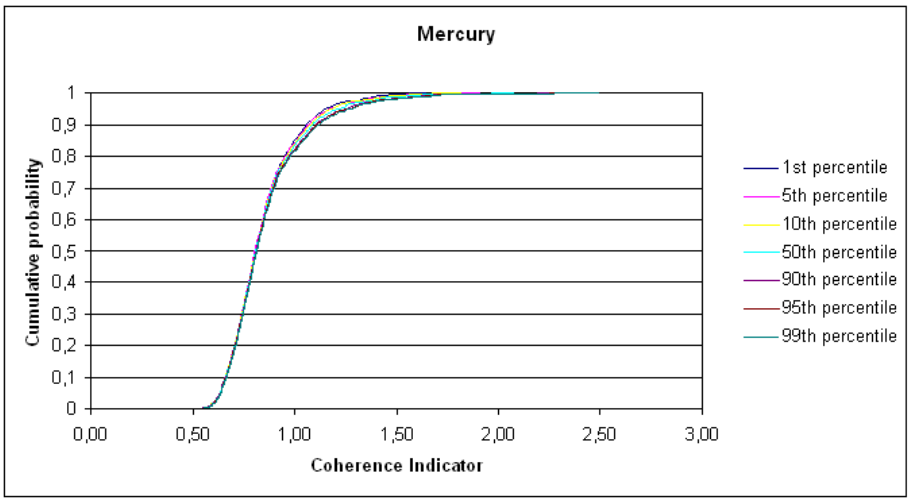

Ethoprophos
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,20
0,40
0,60
0,80
1,00
1,20
1,40
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

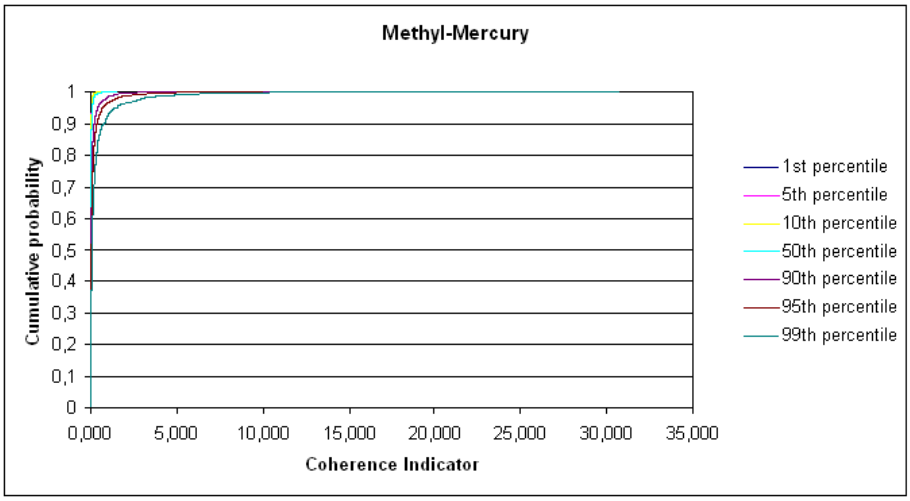

Iprodione
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

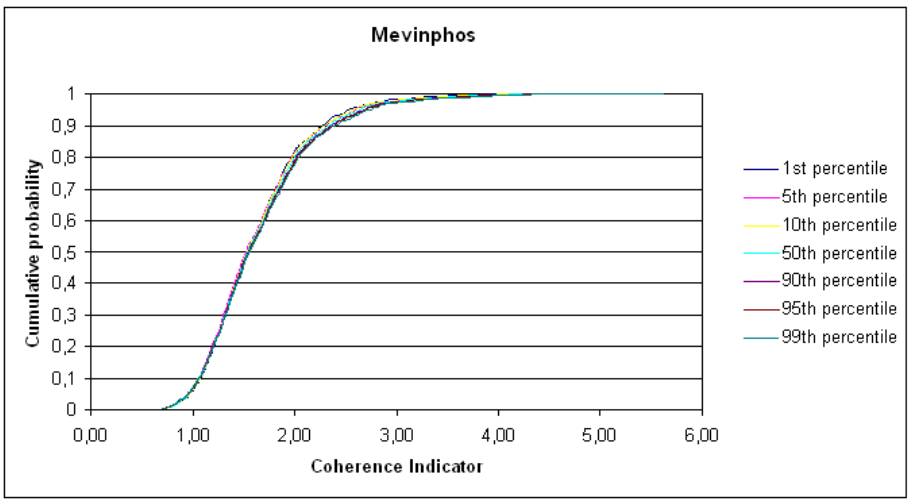

Lead
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
10,00
20,00
30,00
40,00
50,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

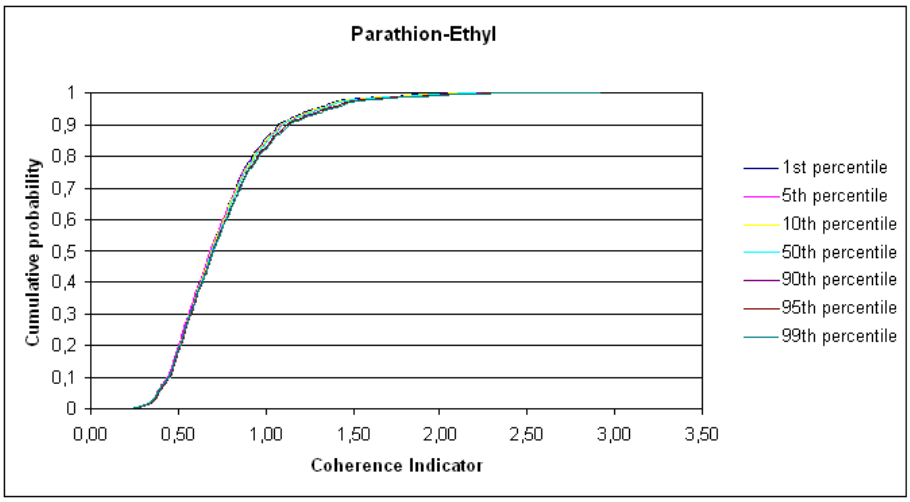

Lead oral
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
3,00
3,50
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

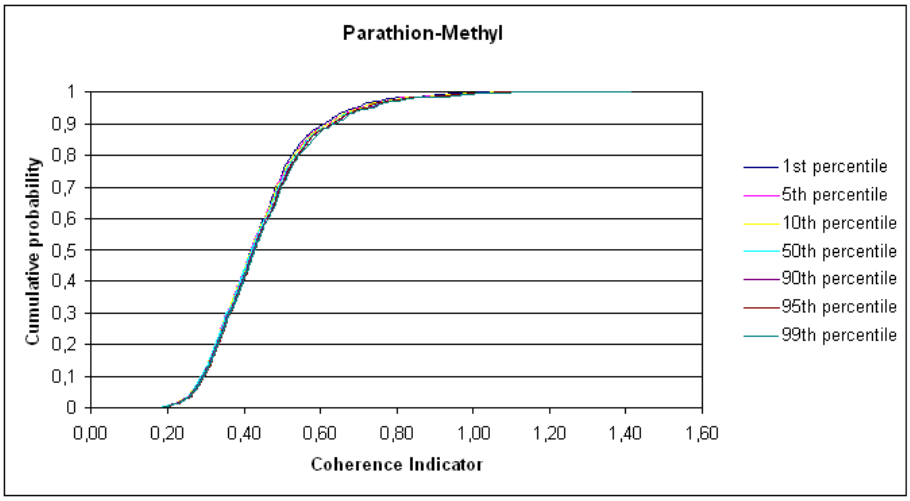

MCPA
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,20
0,40
0,60
0,80
1,00
1,20
1,40
1,60
1,80
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

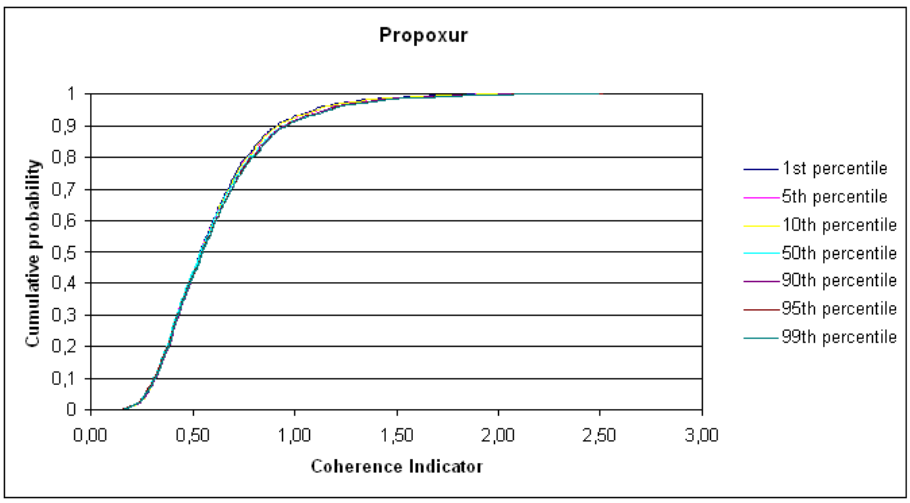

Mercury
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
3,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

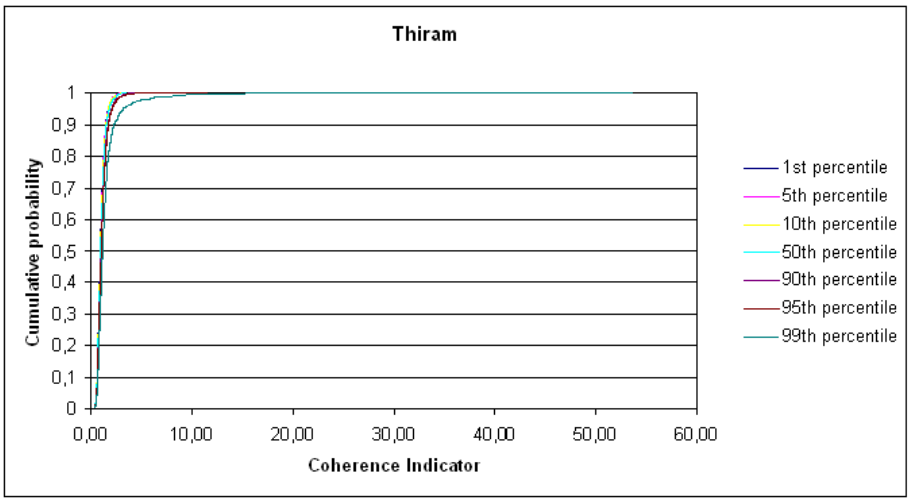

Methyl-Mercury
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,000
5,000
10,000
15,000
20,000
25,000
30,000
35,000
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

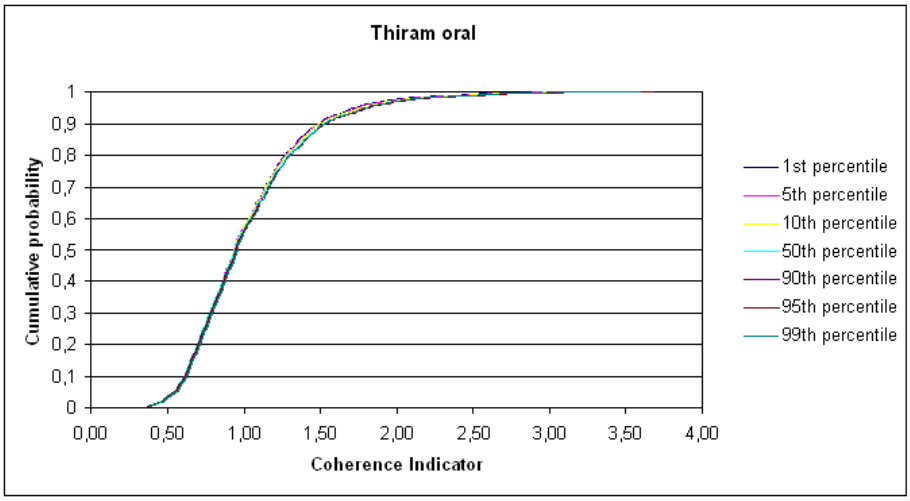

Mevinphos
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
1,00
2,00
3,00
4,00
5,00
6,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

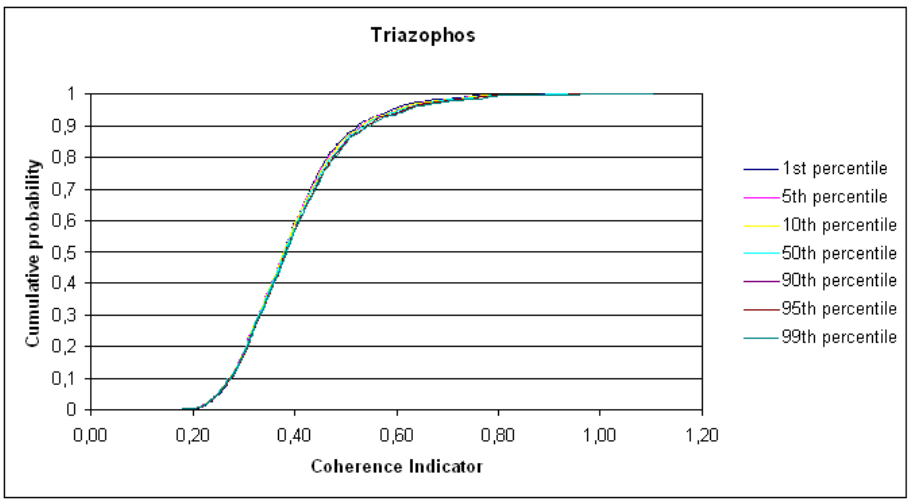

Parathion-Ethyl
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
3,00
3,50
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile


Parathion-Methyl
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,20
0,40
0,60
0,80
1,00
1,20
1,40
1,60
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile


Propoxur
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
3,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile


Thiram
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
10,00
20,00
30,00
40,00
50,00
60,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

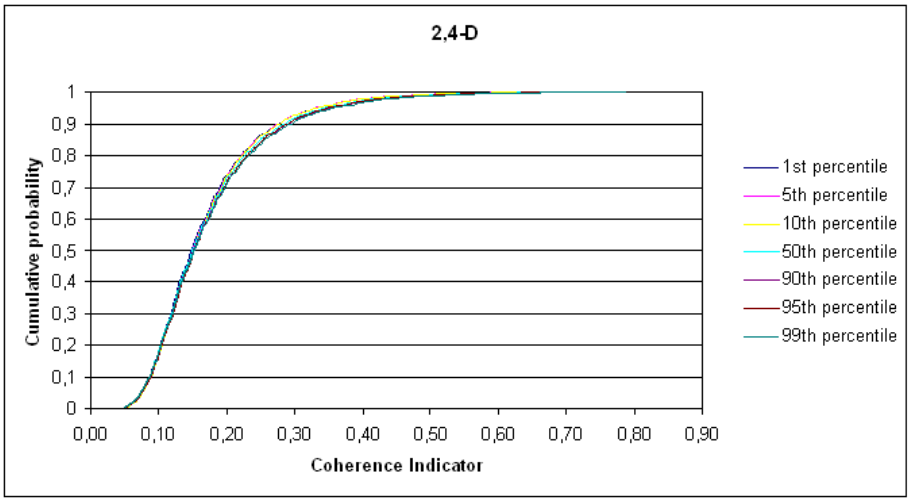

Thiram oral
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,50
1,00
1,50
2,00
2,50
3,00
3,50
4,00
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

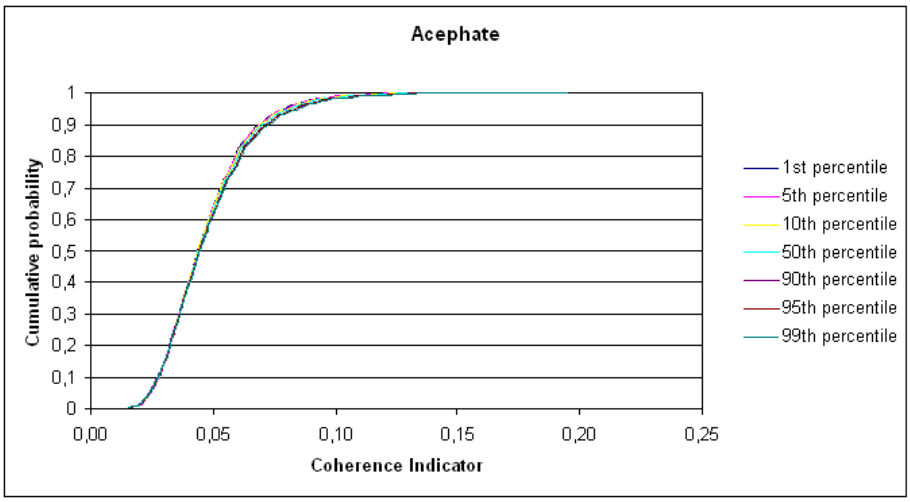

Triazophos
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,20
0,40
0,60
0,80
1,00
1,20
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

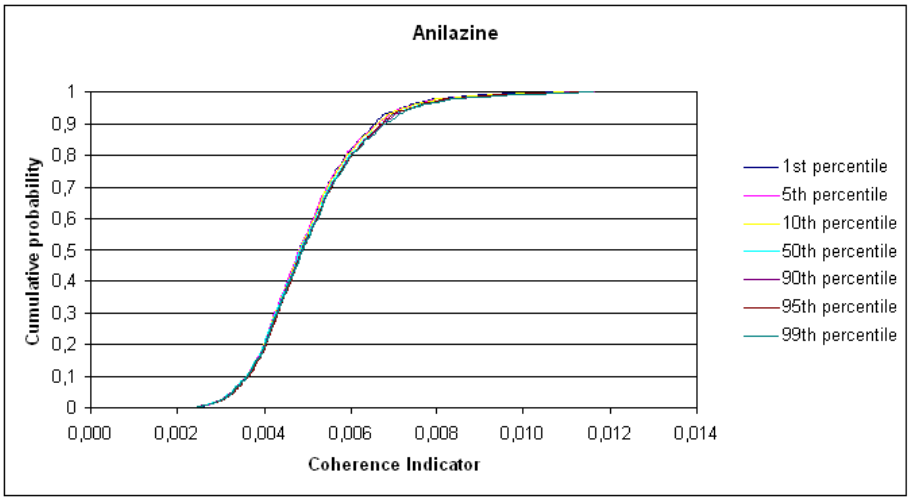
Appendix E

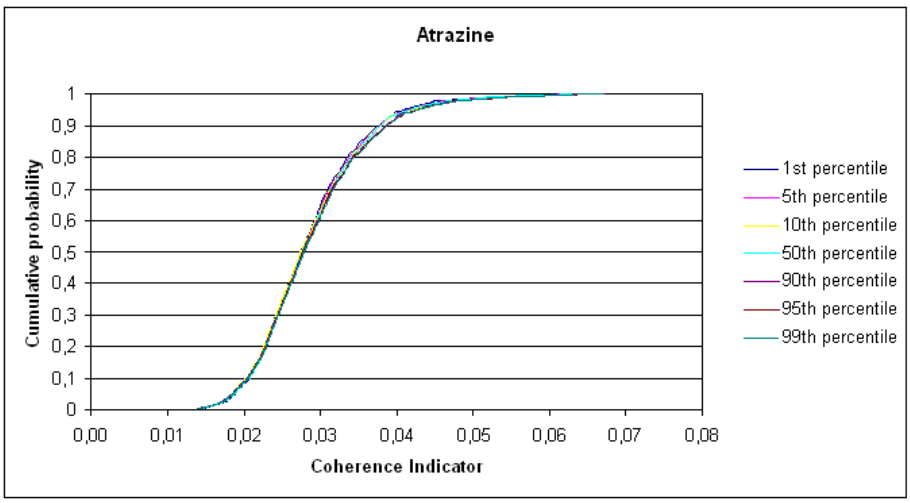
Compounds with a coherence indicator below 1

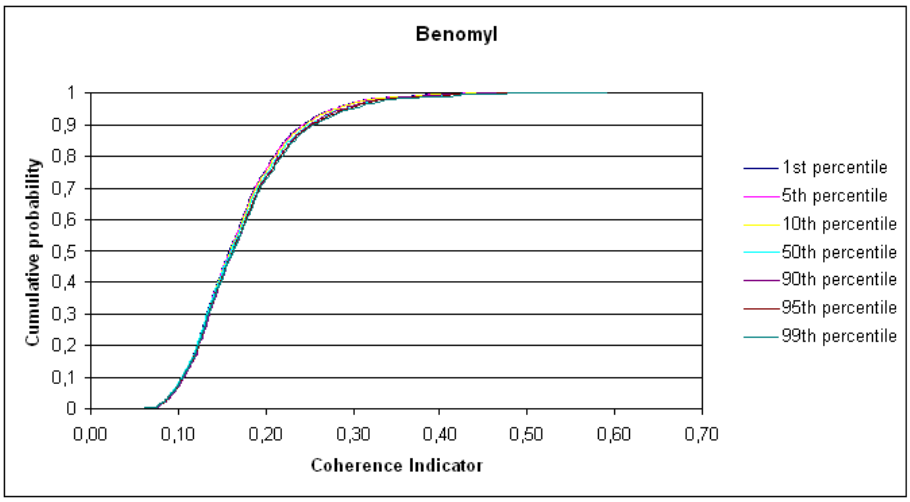
2,4-D	Acephate	Anilazine
Atrazine	Benomyl	Bentazone
Bifenthrin	Captan	Chlorothalonil
Deltamethrin	Diphenylamine	Fenthion
Fenthion oral	Folpet	Isoproturon
Malathion	Maneb	Methomyl
Metholachlor	Methyl-Mercury oral	Nitrate
Oxamyl	Permethrin	Pirimicarb
Procymidone	Pyrazophos	Simazine
Thiabendazole	Tolclophos-Methyl	Tolylfluanid
Zineb		

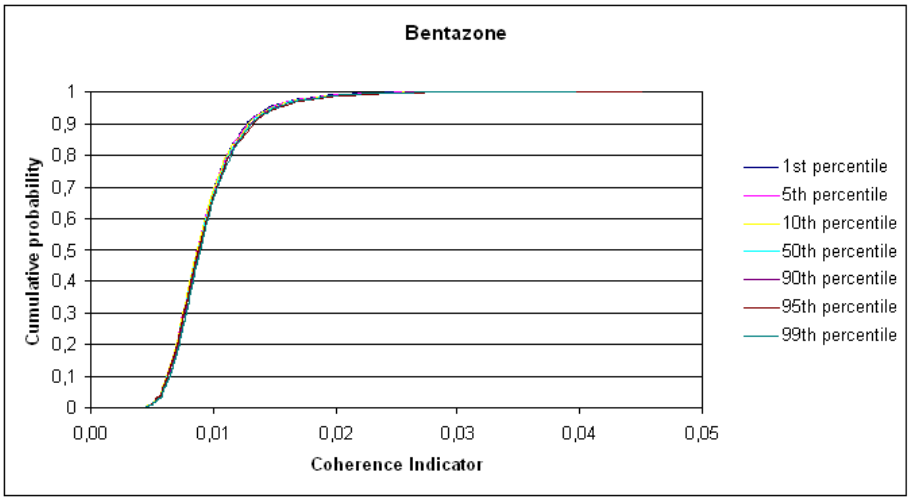


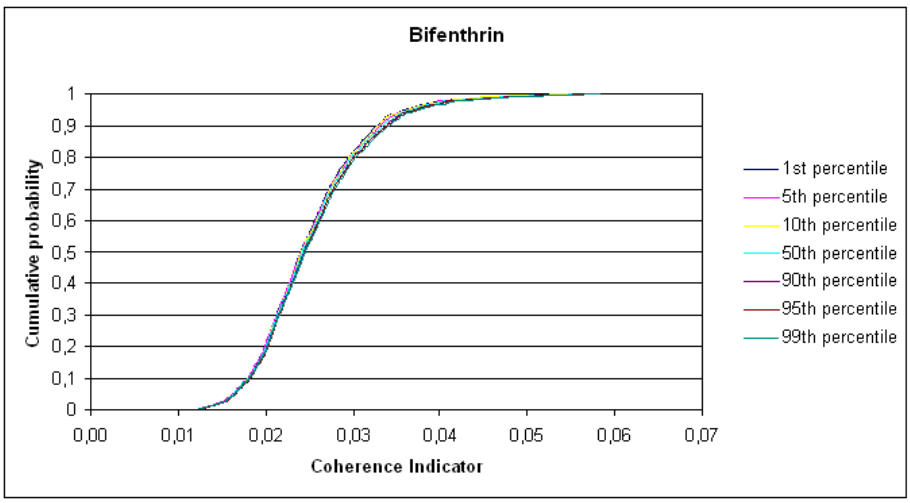

Acephate
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,05
0,10
0,15
0,20
0,25
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

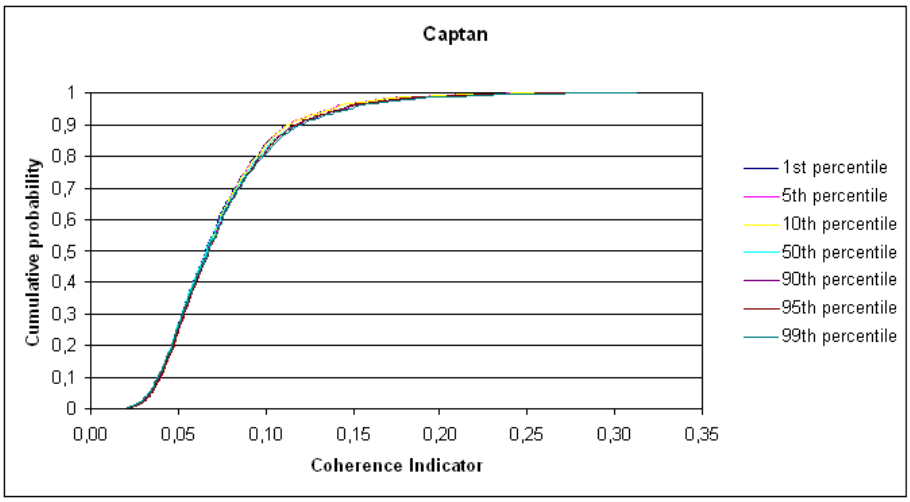

Anilazine
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,000
0,002
0,004
0,006
0,008
0,010
0,012
0,014
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

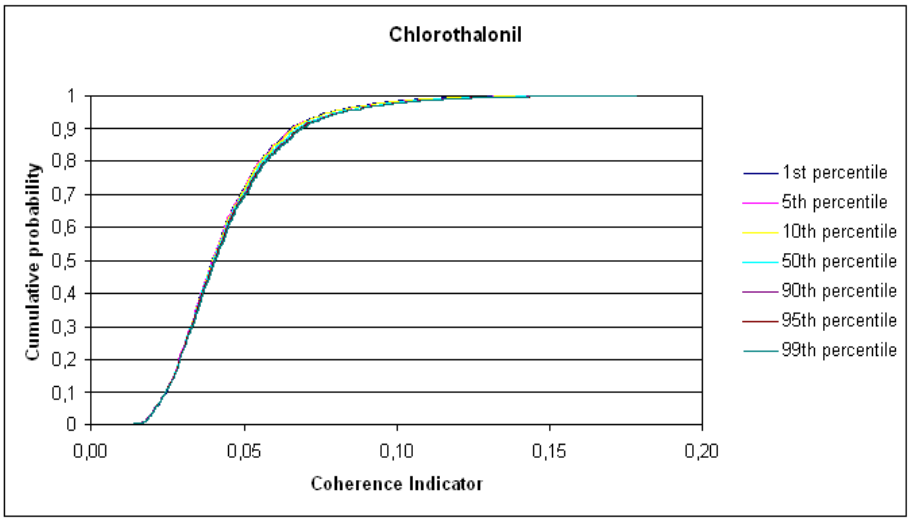

Atrazine
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,01
0,02
0,03
0,04
0,05
0,06
0,07
0,08
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

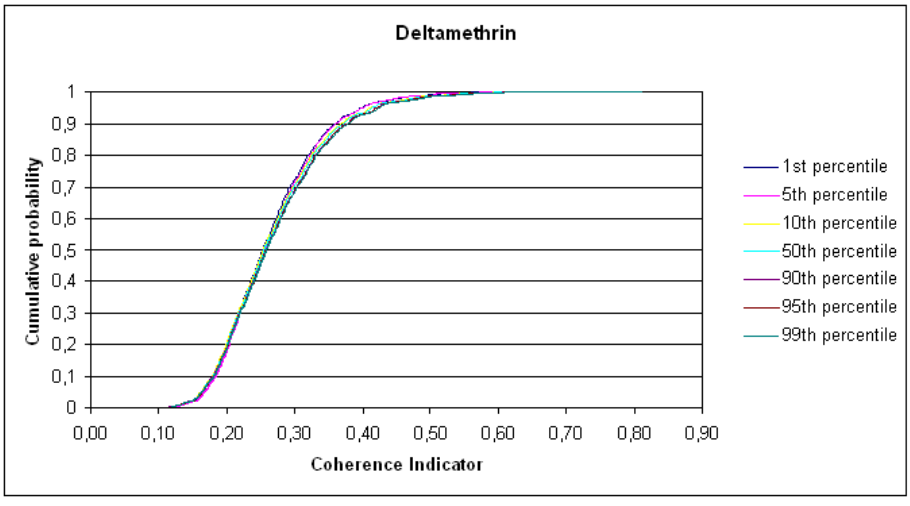

Benomyl
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,10
0,20
0,30
0,40
0,50
0,60
0,70
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

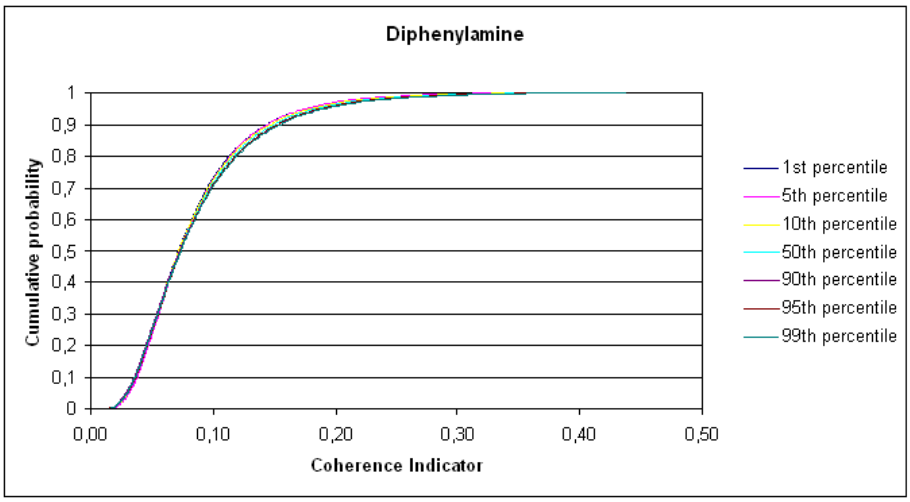

Bentazone
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,01
0,02
0,03
0,04
0,05
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

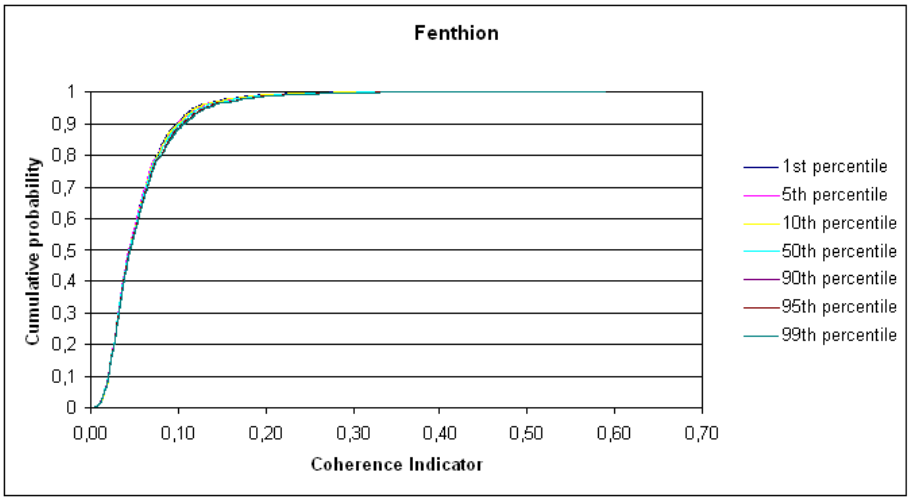

Bifenthrin
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,01
0,02
0,03
0,04
0,05
0,06
0,07
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

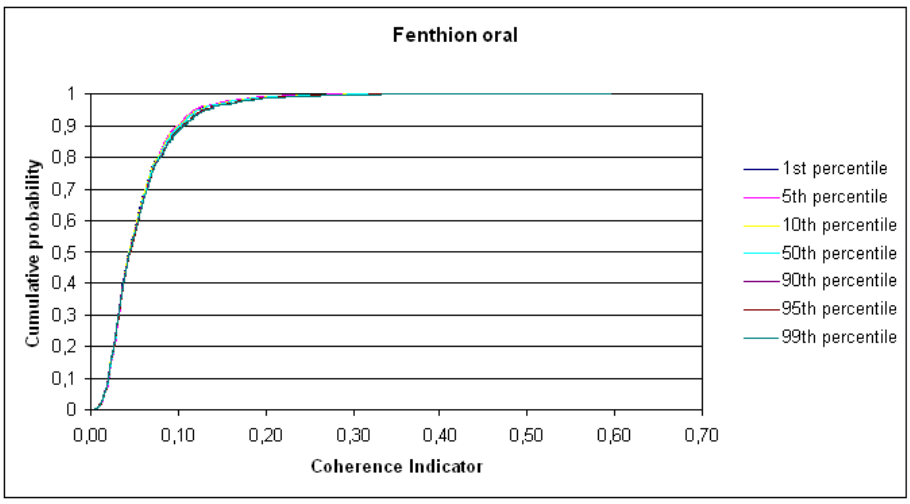

Captan
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,05
0,10
0,15
0,20
0,25
0,30
0,35
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

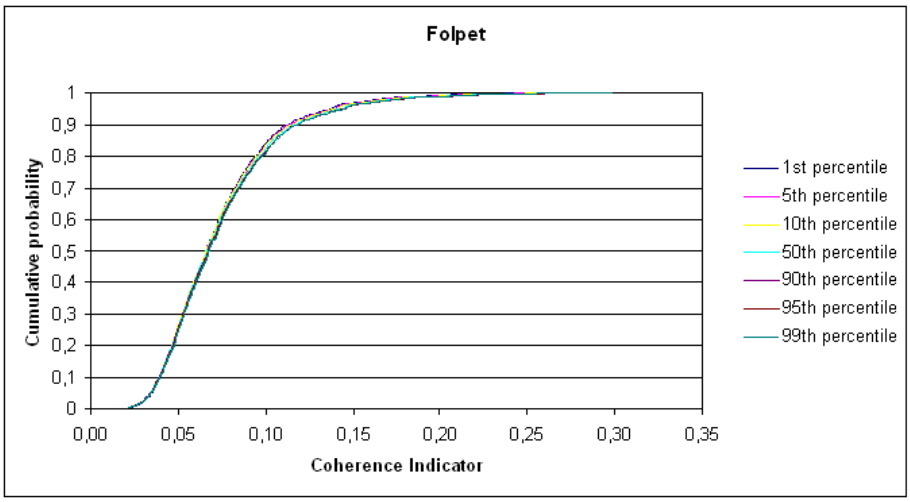

Chlorothalonil
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,05
0,10
0,15
0,20
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

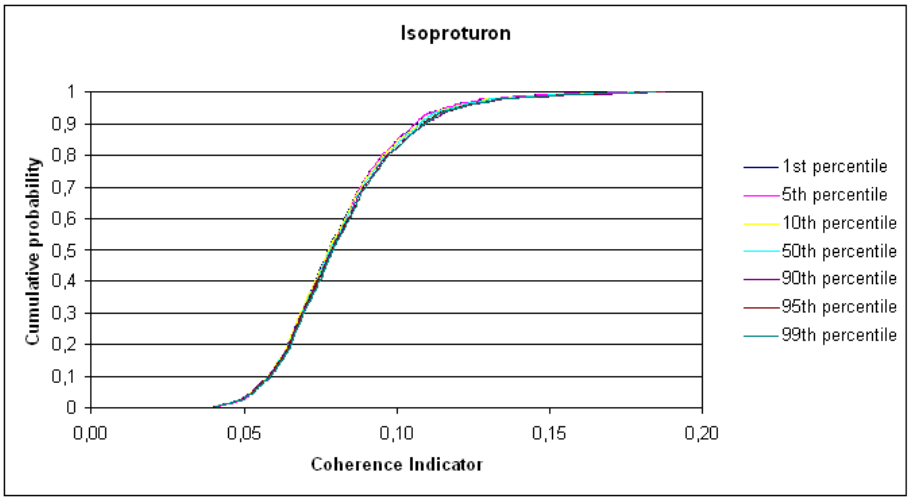

Deltamethrin
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,10
0,20
0,30
0,40
0,50
0,60
0,70
0,80
0,90
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

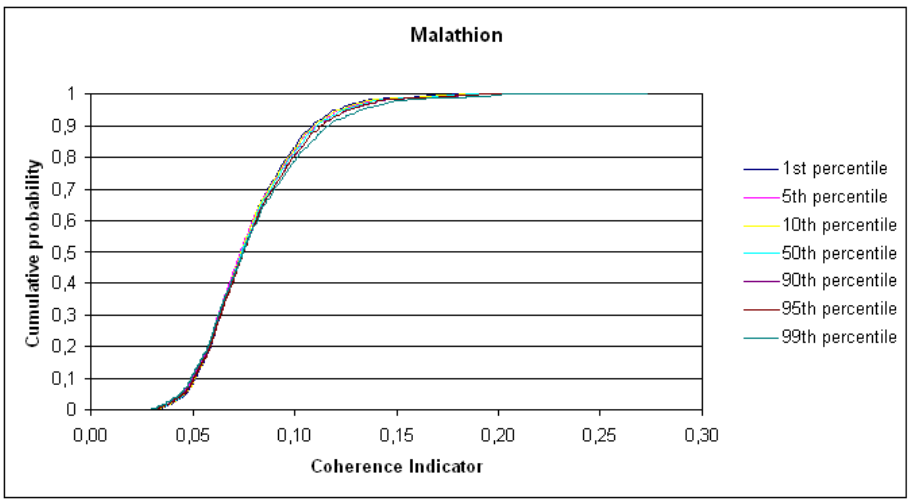

Diphenylamine
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,10
0,20
0,30
0,40
0,50
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

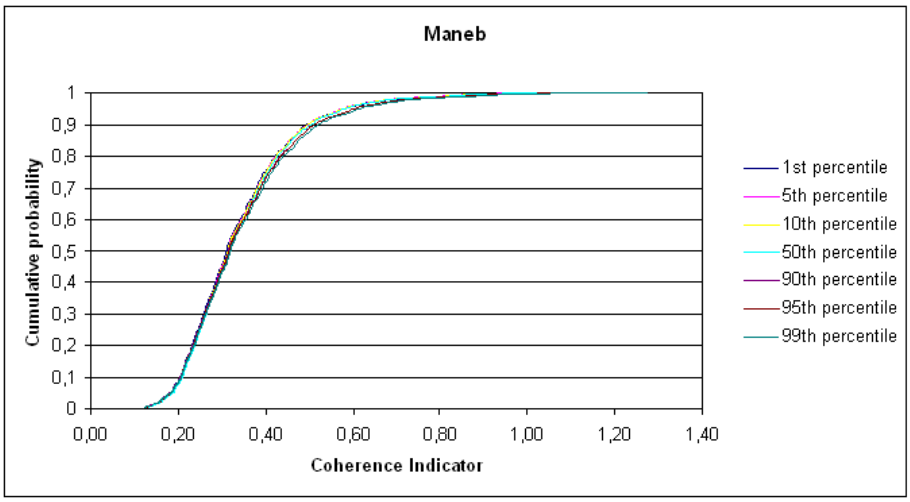

Fenthion
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,10
0,20
0,30
0,40
0,50
0,60
0,70
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

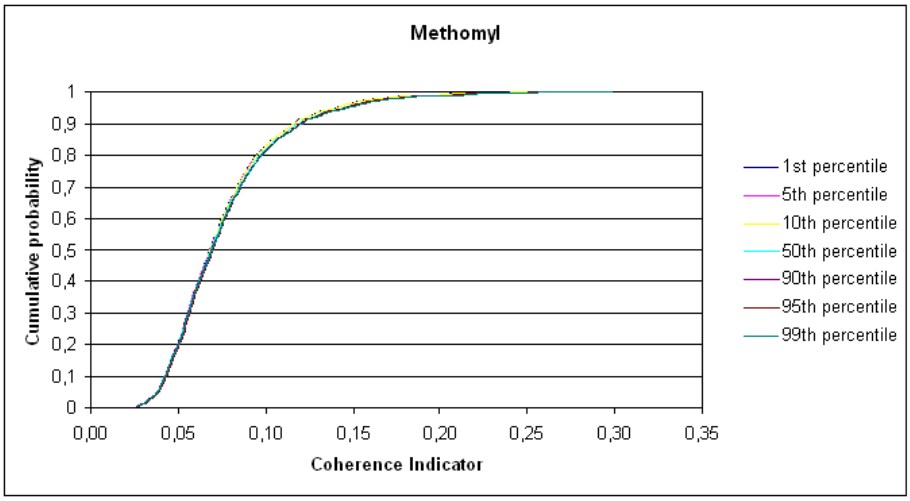

Fenthion oral
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,10
0,20
0,30
0,40
0,50
0,60
0,70
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

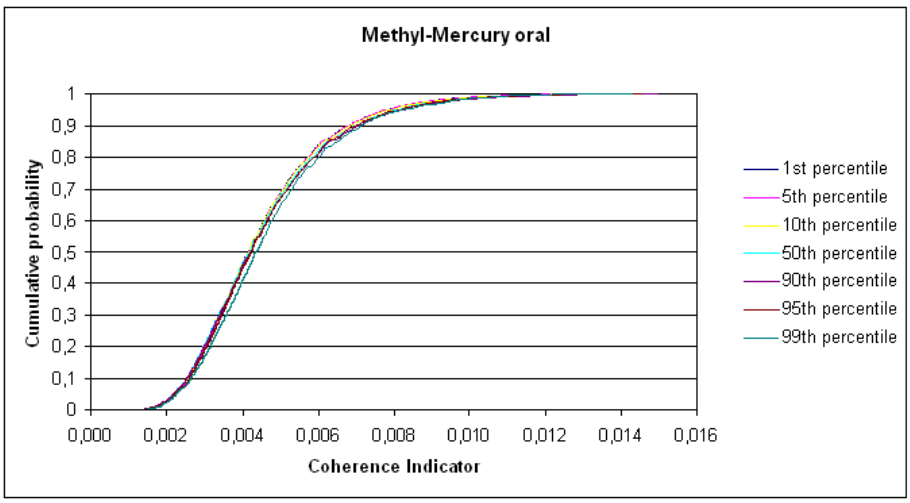

Folpet
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,05
0,10
0,15
0,20
0,25
0,30
0,35
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

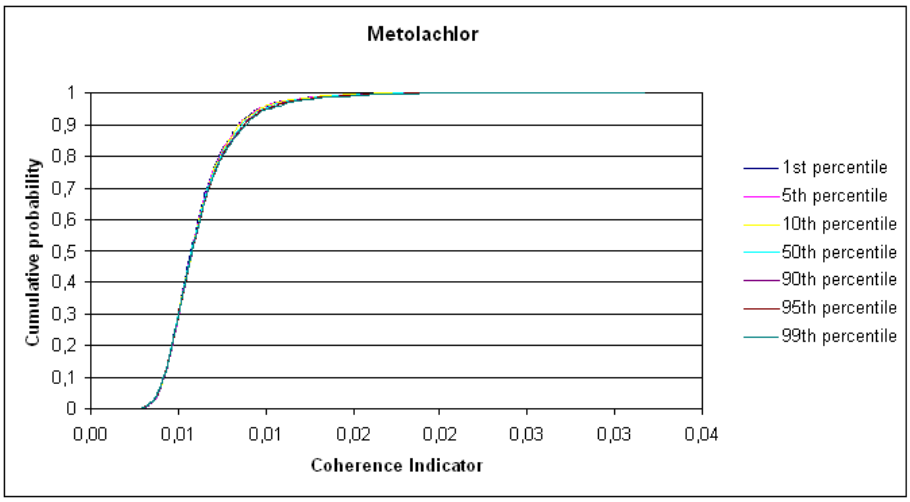

Isoproturon
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,05
0,10
0,15
0,20
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

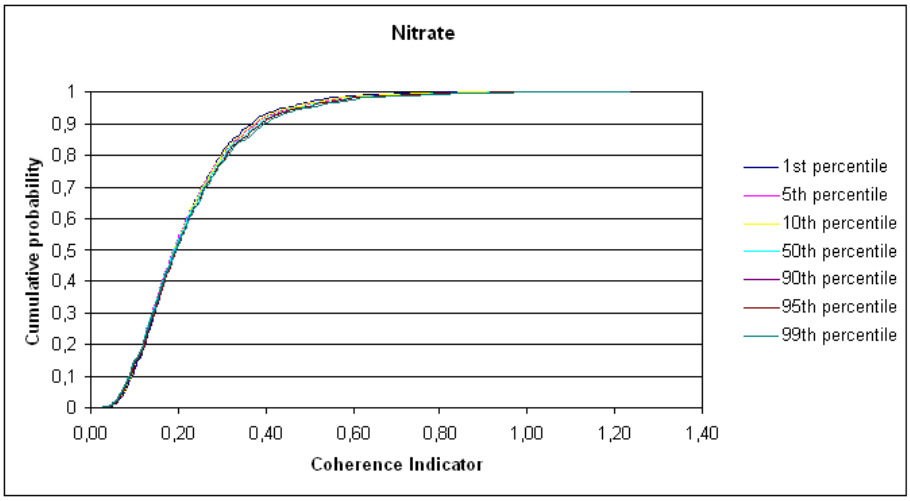

Malathion
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,05
0,10
0,15
0,20
0,25
0,30
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

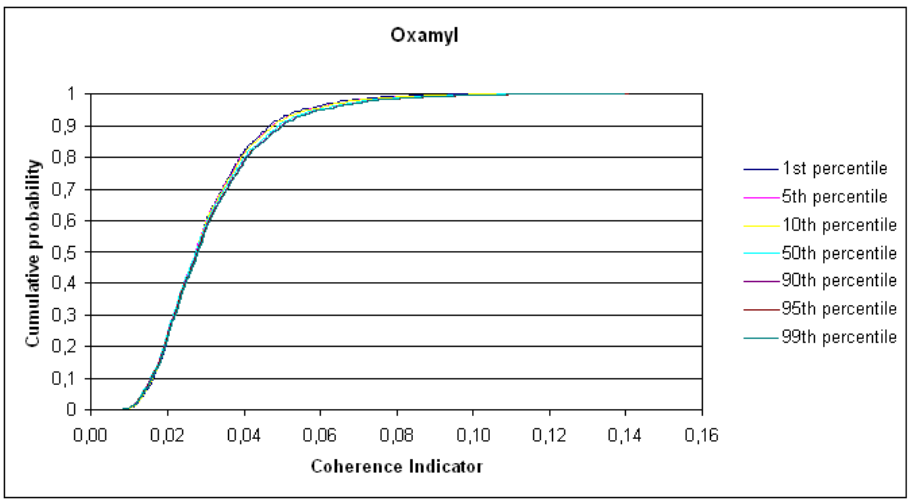

Maneb
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,20
0,40
0,60
0,80
1,00
1,20
1,40
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

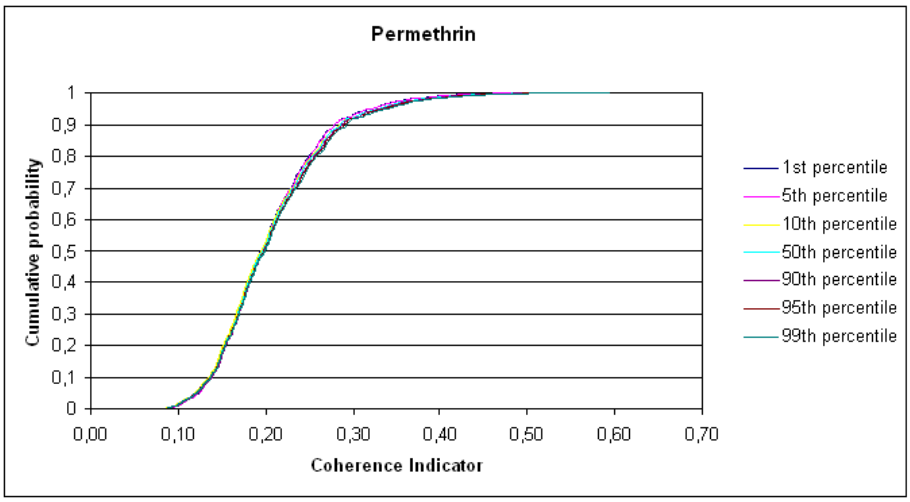

Methomyl
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,05
0,10
0,15
0,20
0,25
0,30
0,35
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

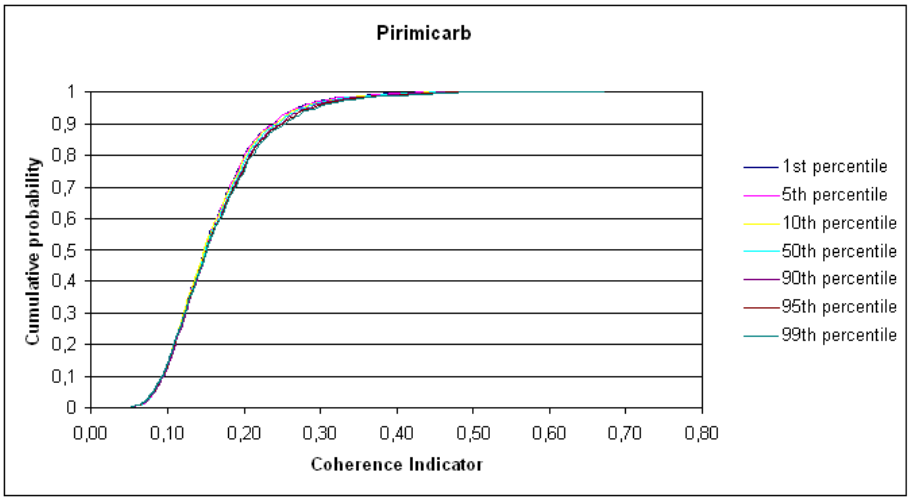

Methyl-Mercury oral
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,000
0,002
0,004
0,006
0,008
0,010
0,012
0,014
0,016
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

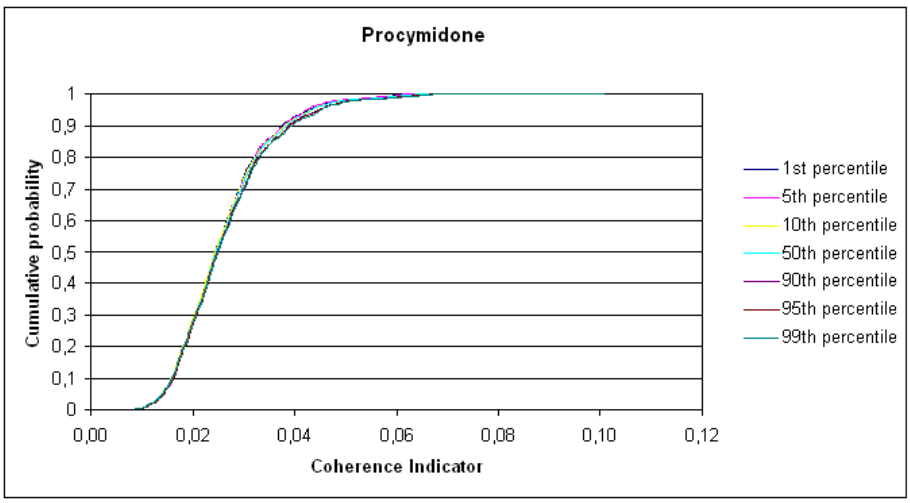

Metolachlor
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,01
0,01
0,02
0,02
0,03
0,03
0,04
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

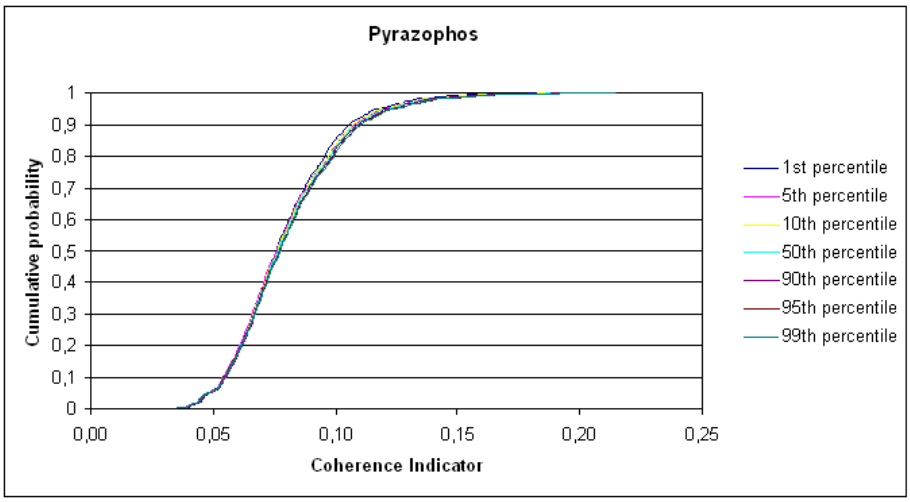

Nitrate
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,20
0,40
0,60
0,80
1,00
1,20
1,40
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

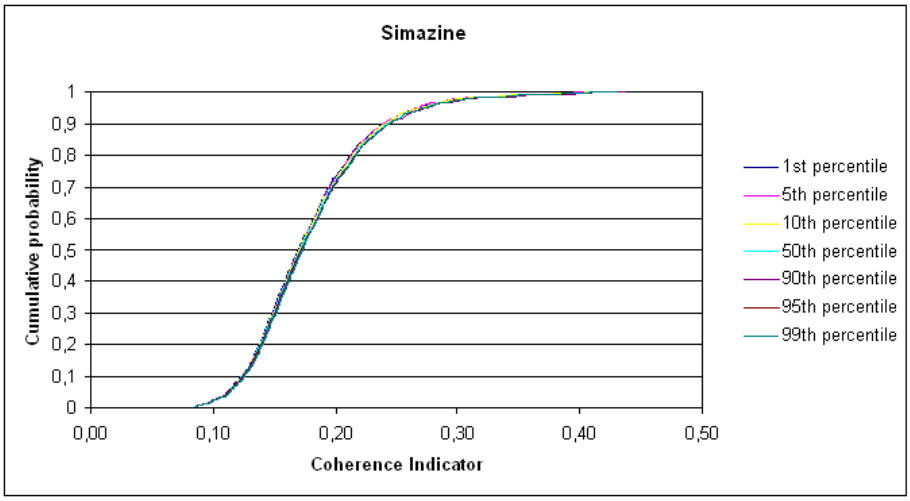

Oxamyl
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,02
0,04
0,06
0,08
0,10
0,12
0,14
0,16
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

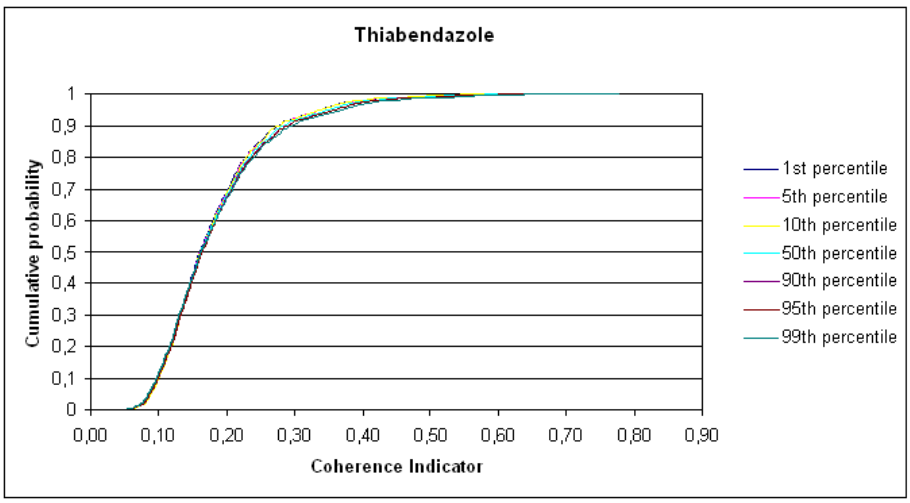

Permethrin
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,10
0,20
0,30
0,40
0,50
0,60
0,70
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

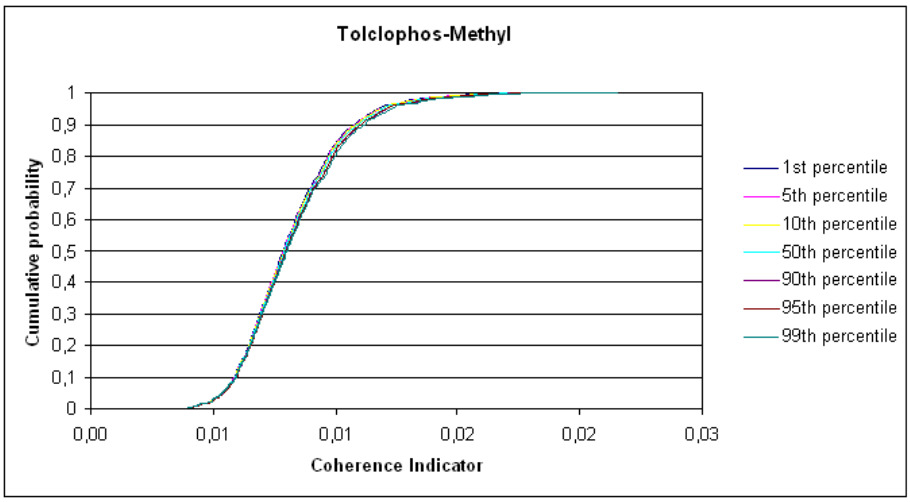

Pirimicarb
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,10
0,20
0,30
0,40
0,50
0,60
0,70
0,80
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

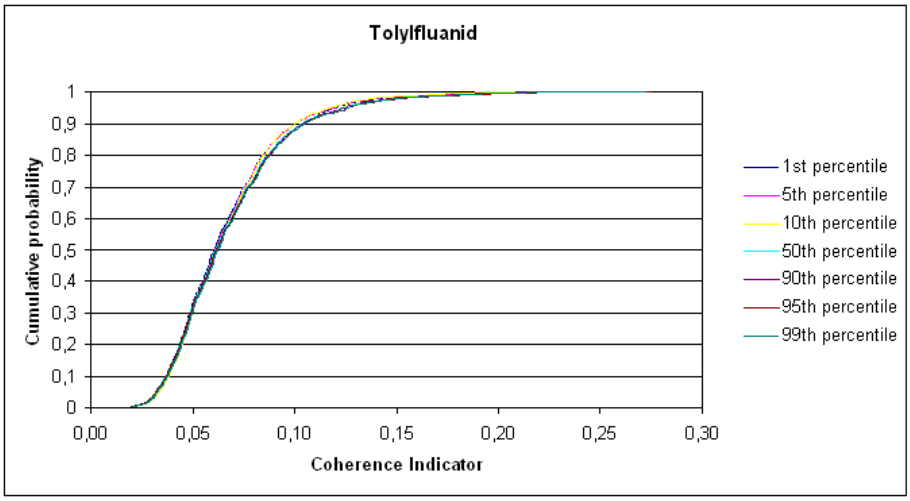

Procymidone
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,02
0,04
0,06
0,08
0,10
0,12
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile

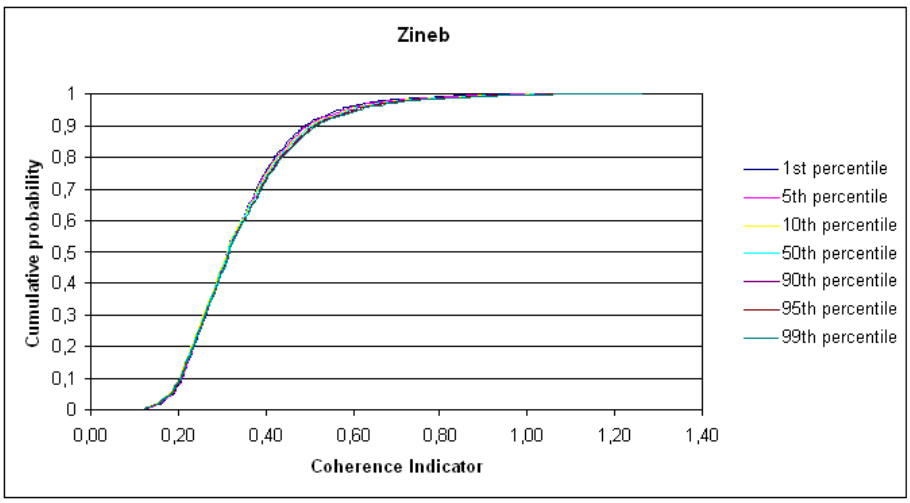

Pyrazophos
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,05
0,10
0,15
0,20
0,25
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile


Simazine
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,10
0,20
0,30
0,40
0,50
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile


Thiabendazole
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,10
0,20
0,30
0,40
0,50
0,60
0,70
0,80
0,90
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile


Tolclophos-Methyl
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,01
0,01
0,02
0,02
0,03
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile


Tolylfluanid
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,05
0,10
0,15
0,20
0,25
0,30
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile


Zineb
Cumulative probability
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0,00
0,20
0,40
0,60
0,80
1,00
1,20
1,40
Coherence Indicator
1st percentile
5th percentile
10th percentile
50th percentile
90th percentile
95th percentile
99th percentile