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# The MCRA model for probabilistic single-compound and cumulative risk assessment of pesticides

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ABSTRACT

Pesticide risk assessment is hampered by worst-case assumptions leading to overly pessimistic assessments. On the other hand, cumulative health effects of similar pesticides are often not taken into account. This paper describes models and a web-based software system developed in the European research project ACROPOLIS. The models are appropriate for both acute and chronic exposure assessments of single compounds and of multiple compounds in cumulative assessment groups. The software system MCRA (Monte Carlo Risk Assessment) is available for stakeholders in pesticide risk assessment at mcra.rivm.nl. We describe the MCRA implementation of the methods as advised in the 2012 EFSA Guidance on probabilistic modelling, as well as more refined methods developed in the ACROPOLIS project. The emphasis is on cumulative assessments. Two approaches, sample-based and compound-based, are contrasted. It is shown that additional data on agricultural use of pesticides may give more realistic risk assessments. Examples are given of model and software validation of acute and chronic assessments, using both simulated data and comparisons against the previous release of MCRA and against the standard software DEEM-FCID used by the Environmental Protection Agency in the USA. It is shown that the EFSA Guidance pessimistic model may not always give an appropriate modelling of exposure.



## 1. Introduction

Cumulative effects on health from multiple similar pesticides ('cocktail' effects) have been overlooked in traditional risk assessments, which only considered single compounds. The European Parliament and the European Council have regulated that for risk assessments leading to decisions on applications concerning maximum residue limits (MRLs) 'account shall be taken of the possible presence of pesticide residues arising from sources other than current plant protection uses of active substances, and their known cumulative and synergistic effects, when the methods to assess such effects are available' (EC, 2005). In addition, it has become clear that multiple routes of exposure (dietary, dermal, inhalation) may be important, especially for professional workers handling pesticides. In response to this perceived lack of sufficient methodology for cumulative risk assessment (Boobis et al., 2008) the EU-funded project ACROPOLIS (www.acropolis-eu.com) has developed strategies for probabilistic aggregate and cumulative exposure and risk assessment. This paper describes a web-based tool for probabilistic cumulative exposure assessment, called MCRA (for Monte Carlo Risk Assessment, available at mcra.rivm.nl). The software also facilitates aggregate single-compound and aggregate cumulative exposure assessments, on which is reported in a companion paper (Kennedy et al., in press). Moreover, the software implements an integration with probabilistic hazard characterisation to allow a full integrated probabilistic risk assessment in terms of probabilistic individual margins of exposure (van der Voet and Slob, 2007; van der Voet et al., 2009).

Different active substances can have the same health effect, and this is commonly expected for substances within a chemical class. For example, many pesticides in the triazole group can lead to neurological damage in embryos. Therefore the European Food Safety Authority (EFSA) has defined Cumulative Assessment Groups (CAGs) containing seven triazole compounds for acute and 11 triazole compounds for chronic risk assessment (EFSA, 2008a, b). Dose–effect studies have been performed to estimate Relative Potency Factors (RPFs), where flusilazole and cyproconazole were the reference compounds for acute and chronic, respectively.

Cumulative effects were also considered in the EFSA guidance on probabilistic modelling (EFSA, 2012). In this work a tiered

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approach was proposed where basic probabilistic assessments would comprise two alternative model runs. Pessimistic and optimistic model runs treat major uncertainties using assumptions expected to give over-estimation and under-estimation of exposure, respectively. The guidance document describes at length how the basic model runs should be performed, both for single-compound and cumulative assessments. In a higher tier refined probabilistic assessments might be needed based on the results of the two basic model runs and additional sensitivity analyses. In this paper the implementation of the EFSA guidance in the MCRA model is described. The application to triazole exposure assessment in eight European countries is reported in a companion paper (Boon et al., in press).

Previous approaches to cumulative risk modelling have been described. Price and Chaisson (2005) presented a conceptual framework for modelling aggregate and cumulative exposures, stressing the importance of person-oriented modelling. Meek et al. (2011) described a WHO/IPCS framework with multiple tiers for both exposure and hazard modelling, where tier 3 corresponds to probabilistic approaches. In practical work, probabilistic cumulative exposure assessments have usually been implemented as index compound equivalent assessments on RPF-weighted total exposure per sample (EPA, 2002, Boon and van Klaveren, 2003, Bosgra et al., 2009, Caldas et al., 2006b, Boon et al., 2008, Jensen et al., 2013, Müller et al., 2009, Petersen, 2010, van Klaveren and Boon, 2009). van Klaveren et al. (2009) compared this sample-based approach to an alternative approach based on modelling each compound separately followed by a summation of the single-compound exposure distributions.

This paper describes the statistical models in the web-based MCRA system for single-compound and cumulative risk assessment. It includes example calculations for the triazole group, and provides validation results.

## 2. Methods

MCRA 8.0 is a research tool implementing many possibilities for modelling single-compound or cumulative exposure, including the procedures as described in the EFSA guidance for acute or chronic exposure assessment according to both an optimistic and a pessimistic model run.

One-day (24 hour) data on food consumption and per-sample residue concentration data are taken as inputs to characterise the short-term exposure distribution relevant for acute risks. The consumption and concentration distributions are integrated by Monte Carlo (MC) sampling. The number of MC iterations can be chosen, a number of 100,000 is typically found to be sufficient.

Estimates of the long-term exposure distribution relevant for chronic risks are obtained from statistical modelling of the 24-hour consumptions multiplied by the average residue concentration, without further modelling. Application of a random or mixed effects model to transformed data separates within- and between-individual variation in exposure. Pesticide exposures per day are often 0, which necessitates the use of two-part models for the frequency of exposure and the amount of exposure, respectively (de Boer et al., 2009; Dodd et al., 2006).

Uncertainty analysis can provide uncertainty limits on exposure percentiles and other statistics in a two-dimensional Monte Carlo approach where datasets are bootstrapped in an outer loop. Uncertainty aspects of MCRA are more fully discussed in a companion paper (Kennedy et al., 2014b).

### 2.1. Food code conversions and processing factors

Food codes used in food consumption surveys are typically not the same as food codes used in residue monitoring programs. For example, the consumption survey may record 'apple pie', whereas pesticide measurements have been made on the raw agricultural commodity (RAC) 'apple'. This requires at least two conversion steps: a recipe of apple pie should specify the proportion of 'peeled apple', and subsequently a processing factor may be known for the residue concentration in 'peeled apple' relative to the concentration in the (unpeeled) RAC 'apple'. MCRA allows the input of both the recipe proportions and the processing factors in relation to a translation of food codes, thus linking foods-as-eaten to foods-as-measured.

Processing factors are defined as the concentration in the processed food divided by the concentration in the unprocessed food. A database of processing factors is available at http://www.bfr.bund.de/cm/349/bfr-compilation-of-processing-factors-for-pesticide-residues.zip or http://chemkap.rivm.nl/groente-fruit/processing-factors/. Such processing factor data can be used as input for MCRA. If no processing factors are available for appropriately coded processed foods, MCRA will use a default factor of 1 (i.e. no processing effect).

Concentration changes can be due to 1) chemical degradation, e.g. in heat treatments, and/or 2) weight changes of the food, e.g. drying of grapes to raisins. Care has to be taken that weight changes are not accounted for in both the recipe and the processing factor data, and therefore would be double-counted. If the same food code translation is made in a recipe and in the table of processing factors then MCRA will adjust the processing factor for the weight change such that only the chemical degradation is reflected in the processing factors that will be applied to the residue concentration data of the RAC.

Processing effects are usually considered as fixed values, as an approximation to the real world where they are usually variable (differing between realisations) and uncertain (not well known). In MCRA both the variability and the uncertainty of processing factors can be modelled using logistic-normal (for processing factors restricted to the interval [0,1]) or log-normal distributions (see appendix A.1 in van der Voet et al., 2009 for details).

### 2.2. Modelling residue concentrations per food

For modelling of acute risk it is necessary to model distributions of residue concentrations from which values can be sampled in the Monte Carlo simulations. For modelling of chronic risk it is sufficient to work with mean residue concentrations, but for non-trivial data, e.g. when not all measurements are positive values, means are still dependent on the type of model assumed.

The two basic concentration models in MCRA are the empirical model and the lognormal model. The empirical model (EFSA optimistic) uses the data as they are, whereas the lognormal model (EFSA pessimistic) fits a lognormal distribution to the available positive residues.

Typically, residue concentration datasets contain only a limited number of positive values and a large number of 'non-detects' or 'less-thans', i.e. measurements censored at a limit value, which depending on the reporting institution may be a formal limit of detection, limit of quantification, or other value. For the purpose of exposure modelling any such limit will be referred to as the Limit Of Reporting (LOR). We will refer to values' <LOR' as non-detects (NDs). Note, that LOR may in principle be different for each measurement, but in practice it is often a constant value for a specific analytical method as applied in a specific laboratory and a specific time period.

For both the empirical and the lognormal model a decision is needed on how to handle the NDs. MCRA implements simple imputation options, such as replacing NDs by zero (EFSA optimistic) or replacing NDs by the LOR (EFSA pessimistic). The EFSA pessimistic model is therefore a mixture distribution of a spike of NDs imputed at LOR and a lognormal distribution fitted to the positive values (lognormal ND-spike model). In a more complex model (Helsel, 2005, EFSA, 2010) the NDs are considered as a censored tail of the lognormal distribution and a censored lognormal distribution is fitted to all data (censored lognormal model). An even more complex model (Paulo et al. 2005) is to assume that the data are a mixture of a certain percentage of true zero concentrations and positive values which may partly be censored. If there are sufficient positive values, the assumption of lognormality may then be used to estimate the percentage of true zeroes as well as the parameters of the lognormal distribution (censored lognormal zero-spike model).

More knowledge may be available from other sources. When agricultural use of a specific compound on the commodity is known to be unauthorised, then NDs can be set to 0 mg/kg (note that positive values in this case would represent unauthorised use). When agricultural use is authorised, then it may be the case that a value for the percentage crop treated (%CT) is available. In that case, an appropriate concentration model is that (100-%CT)% of the concentrations is actually 0, and that NDs are a mixture of true zeroes and censored positive values. If the actual percentage of positive residues in the dataset exceeds the %CT value, the latter will be upwardly adjusted before analysis. In summary, depending on the information of agricultural use that is available, a certain fraction of true zero concentrations is assumed, and the remaining fraction of the data is modelled as sketched above, including the ND imputation options.

The approach to uncertainty analysis depends on the chosen concentration model. In most cases a non-parametric bootstrap is used to generate new consumption and concentration datasets. In the case of the lognormal ND-spike model it is also feasible to specify a parametric uncertainty model, using a beta distribution for the uncertainty in the fraction of positives, an inverse chi-square distribution for the uncertainty in the variance and a normal distribution for the uncertainty in the mean on the log scale (EFSA, 2012, pp. 32, 35).

### 2.3. Modelling single-compound exposure

For acute risk assessment a Monte Carlo procedure combines random draws of consumption patterns (individual-days) with random values sampled from the residue concentration distribution for each relevant food. The residue concentrations are multiplied by a processing factor and/or a stochastic variability factor if needed. Processing factors were already discussed in section 2.1.

Unit variability factors (EFSA, 2012) were introduced in pesticide exposure modelling to account for the fact that RAC measurements are normally made on composite

samples (say 12 apples mixed together), whereas consumers are confronted with single units (e.g. one apple). Residue concentrations in composite samples underestimate the variation. Variability factors are defined as the 97.5th percentile divided by the mean of the distribution of residue found in single units. Stochastic variability factors are the probabilistic equivalents of unit variability factors. Stochastic variability factors are random draws from a suitable distribution characterised by a mean that is equal to a sampled composite residue, and a given ratio p97.5/mean. In MCRA the lognormal distribution or a scaled beta distribution can be chosen. The motivation for the latter is that a single unit in a composite sample cannot contain more residue than the composite sample as a whole, and therefore there is a maximum to the possible concentration. For example, if all residue in a composite sample of 12 apples would reside in one 'hot' apple, then the concentration would be 12 times the measured composite sample concentration.

Exposures $y_i$ for an individual-day $i$ are simulated according to

$$y_i = \sum_{j}^{foods} \sum_{h}^{proctypes} \sum_{u}^{units} x_{ijhu} \cdot svf_{ijhu} \cdot pf_{jh} \cdot c_{ijh} \Big/ BW_i$$

where the consumption $x_{ijhu}$ relates to unit portion $u$ of food $j$ of processing type $h$. Individual consumed amounts $x_{ijhu}$ are derived from resampled consumption patterns $x_{ijh}$ and a dataset of unit weights per food type. Resampling can use sampling weights $w_i$ when available in the food consumption data. The individual has body weight $BW_i$. Residue concentrations $c_{ijh}$ are sampled from the residue concentration distribution fitted before, and multiplied by the processing factor $pf_{jh}$. Note that separate draws from the same distribution are made for different processing types of the same food, but that different units $u$ in the same consumption dataset entry start from the same sampled residue value, which is then modified by a stochastic variability factor $svf_{ijhu}$ sampled from the unit variability distribution. Of course, in practice unit variability may only apply to some foods and some processing types, for all other cases $svf_{ijhu}$ is just taken to be 1, so the calculated exposure may be based partly on unit concentrations and partly on composite concentrations.

For chronic risk assessment, different models to assess the long-term exposure (also called usual or habitual intake) may be employed. In the Observed Individual Means (OIM) method, the intakes calculated for the different days of a person are just averaged to obtain an estimated long-term exposure distribution (EFSA, 2012). However, it is well-known that OIM, like the direct use of short-term (e.g. per-day) data leads to an over-estimation of upper tails in chronic risk assessment (e.g. Dodd et al., 2006, Goedhart et al., 2012). In addition to OIM, MCRA implements various models for usual exposure, such as the BetaBinomial-Normal (BBN) model and the Iowa State University Foods (ISUF) model, as were previously described (de Boer et al., 2009). More recently, the Logistic-Normal-Normal (LNN) model was added, which is very similar to the National Cancer Institute (NCI) model (Goedhart et al., 2012; Tooze et al., 2006). However, all these models are based on assumptions about the statistical distribution of exposures, which never can be fully tested in practice (de Boer et al., 2009). For this reason, and to avoid unwanted over-optimism, the EFSA Guidance prescribed the use of a simpler non-parametric OIM method for basic chronic assessments.

### 2.4. Modelling cumulative exposure

In cumulative acute risk assessment two main approaches have been identified (van Klaveren et al., 2009), which are both available in MCRA. In Approach 1, or the **sample-based approach**, residue concentrations are recalculated in terms of an index compound, and then summed:

$$y_i = \sum_{j}^{foods} \sum_{h}^{proctypes} \sum_{u}^{units} x_{ijhu} \cdot \sum_{k}^{compounds} \left( RPF_k \cdot pf_{jhk} \cdot svf_{ijhuk} \cdot c_{ijhuk} \right) \Big/ BW_i$$

In Approach 2, or the **compound-based approach**, exposures are calculated independently for each compound, and then the cumulative exposure is calculated as a weighted sum:

$$y_i = \sum_{k}^{compounds} \left( RPF_k \cdot \sum_{j}^{foods} \sum_{h}^{proctypes} \sum_{u}^{units} x_{ijhu} \cdot pf_{jhk} \cdot svf_{ijhuk} \cdot c_{ijhuk} \right) \Big/ BW_i$$

In both equations $k$ identifies the compound, and $RPF_k$ is the Relative Potency Factor for compound $k$ relative to the index compound.

In Approach 1 correlations between compounds in the residue concentrations are retained simply by resampling concentration vectors for all compounds simultaneously from the set of samples. Residue concentrations are made comparable between compounds by weighing with relative potency factors (RPFs), and may be modified by applying processing factors $pf$ and/or stochastic variability factors $svf$.

A simplified version of the sample-based approach uses the same processing factors $pf$ and stochastic variability factors $svf$ for all compounds $k$. Then the sample-based approach can be performed whenever a program for single-compound probabilistic exposure assessment is available. It is only necessary to calculate the RPF-weighted sums of concentrations in the chemical samples as input for a standard single-compound assessment. This simplified approach has been used previously in several studies (*e.g.* Boon et al., 2008; Caldas et al., 2006).

In some datasets not all compounds of the CAG are measured in all samples. Approach 2 avoids the need of Approach 1 to impute concentration values for non-measured samples. Approach 2 can also be used when the residue data are only available without sample identification. The compound-based approach was used in van Klaveren et al. (2009) because the assumption of zero values for unmeasured residues in the alternative sample-based approach was shown to lead to under-estimation.

The EFSA Guidance (EFSA, 2012) has proposed the use of the sample-based approach for basic cumulative acute assessments, using an imputation method to replace missing values in the data matrix for each food. For basic optimistic model runs missing values are replaced by zero. For basic pessimistic model runs, after setting all residue levels below the LOR to LOR, provisional RPF-weighted sums per sample are used for sorting the samples from highest to lowest cumulative exposure. For each pesticide–RAC combination as many residues as there are MVs are sampled from the already fitted binomial-lognormal distribution, and also these are sorted from high to low. Then the first MV is imputed by the highest sampled residue, and the RPF-weighted sum and sorting of samples is adapted if necessary. This is continued until all sampled residues have been used and all MVs have been imputed. A worked example was provided (EFSA, 2012, appendix 1).

We describe an adaptation of the sample-based cumulative imputation approach for the case when data on agricultural uses (AUs) (authorization status and/or %CT) are available. The EFSA Guidance only uses available knowledge about the authorization status of agricultural uses (combinations of pesticides) to prevent unauthorised combinations to be generated in the imputation (a zero value is imputed instead). In the Acropolis project a more complete model was developed. With $p$ compounds in a CAG there are in principle $2^p$-1 possible AUs (combinations), with between 1 and $p$ pesticides. In practice, there is only a limited number ($n_{AAU}$) of authorised agricultural uses (AAUs), and the remaining $n_{NAAU} = 2^p - n_{AAU} - 1$ non-authorised agricultural uses (NNAUs) can be lumped into one group. For example, if a CAG consists of three compounds (A, B, C) and the AU data specify 10% CT for A alone and 5% CT for A + B, then the non-authorised AUs are B alone, C alone, A + C, B + C and A + B + C. In 100 – 10 – 5 = 85% of cases the crop can be considered to be untreated with any compound if authorisation status is used. On this assumption we can also derive %CT per compound ($\%CT_{compound}$), which in the example will be 10 + 5 = 15% for compound A, 5% for compound B and 0% for compound C.

If AU authorization data are available, then there are still four ways to obtain residue values in the modelling, depending on the dichotomies sample- or compound-based and use %CT data or not. In a sample-based acute cumulative assessment the imputation of MVs will be a value from the residue model with probability $\%CT_{compound}$ and zero otherwise. If no %CT data are used, then there are only zeroes for the non-authorised combinations (EFSA Guidance method). In a compound-based acute cumulative assessment Monte Carlo simulations start by sampling an AU for each simulated sample. This already fixes zero residue values for the compounds which are not in the sampled AU. For the compounds included in the AU a value from the residue model is simulated with probability $\%CT_{compound}$ (100% if no %CT data are used), and zero otherwise.

Whenever pesticides are used together, their levels may be correlated. This is automatically addressed in the sample-based approach, but not in the compound-based approach. Co-occurrences of positive values in practical datasets are often so sparse (see Kennedy et al., 2014b), that correlations between residues are difficult to estimate. As an alternative, MCRA allows to perform a sensitivity analysis. In the standard analysis residues are sampled independently (zero correlation). In an alternative run the sampled residues within each sampled AU group are re-ordered according to their ranks. So in the A + B group the highest sampled residue for A will coincide with the highest sampled residue for B. This should give a more pessimistic estimate in the upper tail if the food under consideration is a risk driver.

In cumulative chronic risk assessment the issues are partly simpler, e.g. there is no distinction between sample or compound based as only the mean residue concentrations (derived from the chosen concentration models) are needed. Unit variability and correlations between residues do not need to be addressed. MCRA implements cumulative exposure assessment for both acute and chronic risks. Moreover, it can be applied as well in the context of a multi-source (aggregate) assessment (Kennedy et al., in press).

### 2.5. Validation of models and software

Validation is the process of evaluating models and software to determine whether they are fit for purpose (Gibney and van der Voet, 2003). In probabilistic exposure assessment of pesticides the main purpose is to obtain reliable estimates of the upper tail percentiles of the exposure distribution. In addition, the purpose is to estimate reliably the contributions to exposure from different sources (foods in the diet, and, in aggregate assessments, also dermal and inhalatory contributions) and, in cumulative assessments, from different compounds.

Validation compares model output to reference values. The reference values may be true values or values from a historically accepted procedure. A practical validation of dietary exposure assessment models against true values can be obtained from a duplicate diet study (Boon and van Klaveren, 2003). Another possibility is comparison of predicted exposures with measured biomonitoring data. While this

validation approach can be challenging, particularly in the absence of reasonable toxicokinetic models, it can sometimes provide an objective evaluation if sufficient information is available. The possibilities to use duplicate diets and biomonitoring data for validation have been investigated in the ACROPOLIS project and are reported in a companion paper (Kennedy et al., 2014a). Given the high costs and low precision of such a study it is often preferable to obtain true values (and model input data) from a simulation model. Historically accepted procedures for exposure assessment are typically other software tools which have been used for a longer time than the software to be evaluated.

In the current study MCRA 8.0 was validated against true simulated values at several levels of complexity, and against results from the previous release of the same software (MCRA 7.1) and the DEEM-FCID 3.16 software used by the Environmental Protection Agency in the United States (EPA-US).

#### 2.5.1. Synthetic data validation

The computer code of MCRA 8.0 includes a large number of automatic tests that run on a set of prepared synthetic datasets which are simple enough to know the desired outcome. These tests are ordered in three categories: 1) Data integrity tests to validate that all inputs are correctly transferred to the internal database structures, 2) Unit and modular tests to validate the outcomes of specific calculations, and 3) Scenario tests to validate the outcomes of complete runs of the program. A test report, generated from a run of all tests, is generated automatically, and is available at any time.

As an example of a scenario test we describe here a test written to validate a cumulative exposure assessment where additional data on agricultural use are available. This test can also be used to illustrate the potential advantage of the models described in section 2.4. The consumption data for this test are simplified to just two individuals (with body weights 65 and 75 kg) who both consume 100 g of banana on each of two survey days. The concentration data describe 100 samples all measured with an analytical method which can measure two compounds, bitertanol and triadimefon, with an LOR of 0.05 mg/kg for the non-detects. In one of the samples both compounds are found (bitertanol at 0.08 mg/kg, triadimefon at 0.03 mg/kg, note that individual positive values can be below the LOR for non-detects). In four more samples only bitertanol is found (at levels 0.12, 0.10, 0.10 and 0.10 mg/kg) and in one other sample only triadimefon is found (at 0.07 mg/kg). In the remaining 94 samples there are only non-detects. The agricultural use data specify three authorised uses: a formulation with only bitertanol is used in 10% of the crop, a formulation with only triadimefon in 5% of the crop, and a formulation containing both compounds in 2% of the crop. The RPFs of bitertanol and triadimefon are 2.1 and 1.2, respective to the index compound flusilazole.

Given these input data it is possible to calculate exactly all possible exposure values for each of the four person-days as well as their probabilities under an empirical resampling model for concentrations (as in the EFSA optimistic run). These exact exposures (see Supplementary Material) were compared with the results from the program. The synthetic data were also used to compare upper exposure percentiles and exceedance probabilities under various probabilistic methods (see Results section).

#### 2.5.2. Validation against other software

MCRA 8.0 was validated against results from other software. As a first example we show a comparison of the results of a chronic lead exposure assessment using MCRA 8.0 and the previous release of the same software (MCRA 7.1). The Dutch consumption data for children between 2 and 6 years were combined with lead monitoring data using the LNN model for long-term exposure, with age as a cofactor in the model. These data were analysed before (Boon et al., 2012), but in the current validation only a subset of the foods were used (excluding cereals, eggs and rice) therefore the results presented here are different. In the second example a comparison of acute exposure results is made between MCRA 8.0 and the DEEM-FCID 3.16 software used by the Environmental Protection Agency in the United States (EPA-US). It is in the interest of future harmonization to compare the results obtained with US and European software tools using the same basic data. DEEM-FCID is the standard program for the exposure assessment of pesticides in the US (Petersen, 2010). Models for exposure assessment of pesticides have developed quite independently on both sides of the Atlantic. For example, the US DEEM model incorporates a fixed US consumption database, whereas the EU MCRA model allows users to link any consumption database. Obviously then, given the architecture of DEEM the validation had to use the US WWEIA-FCID consumption data.

The DEEM-FCID Version 3.16 software was downloaded from http://www.epa.gov/pesticides/science/deem/. This version incorporates the NHANES What We Eat in America – Food Commodity Intake Database (WWEIA-FCID) dietary survey data for the years 2003–2008. The consumption data are separately available at http://fcid.foodrisk.org/.

For the calculations with MCRA the WWEIA-FCID 2003-08 food consumption WWEIA codes were translated to FCID codes using the Recipes table. Several databases were constructed which differ in the residue concentrations. As a first check an artificial concentration value 1 was used for nine FCID codes of apple products to generate a consumption distribution for the individual-days in the WWEIA dataset including sampling weights. Secondly, a true Monte Carlo analysis was performed to calculate the acute captan exposure distribution using Dutch captan monitoring data for apple (n = 260). For this the nine FCID codes for apple products were linked to the single Dutch Raw Agricultural Commodity (RAC) code for apple. Processing factors were not available for the FCID codes within the Acropolis project, therefore validation was restricted to the basic exposure calculation.

## 3. Results

### 3.1. Synthetic data validation cumulative exposure

The first step in cumulative exposure modelling is the modelling of the cumulative residue concentrations expressed as equivalents of the index compound flusilazole. The EFSA basic pessimistic model requires to replace the non-detects by the LOR, and fit the weighted sum by a lognormal distribution. The results in Fig. 1a show that this may lead to a high spike in the flusilazole

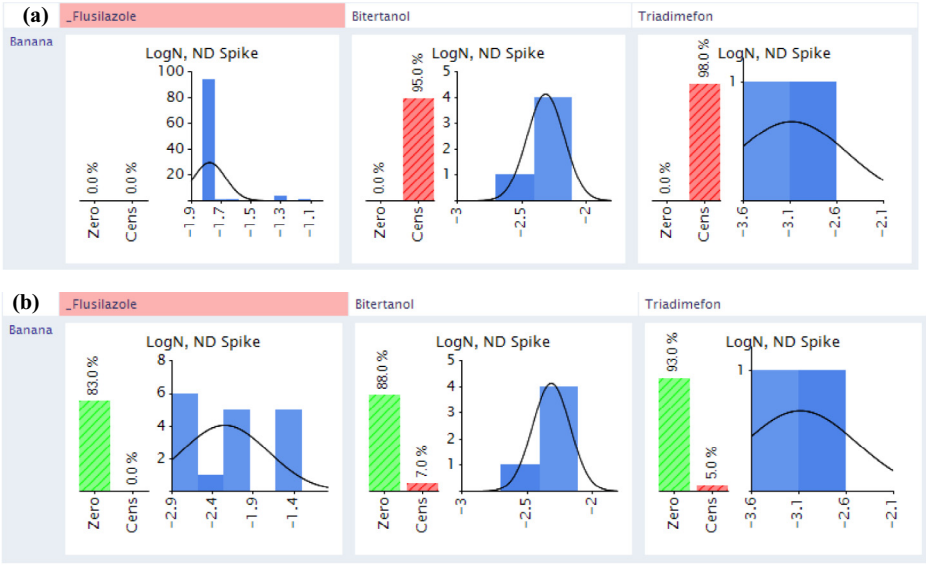


**Fig. 1.** Synthetic example. MCRA output showing histograms of ln(concentration) of calculated flusilazole equivalents (left) from measured bitertanol (middle) and triadimefon (right) in banana. Calculation according to EFSA Guidance, basic pessimistic model (fit of LogNormal Non-Detect Spike model is shown), (a) without and (b) with using data on agricultural use.

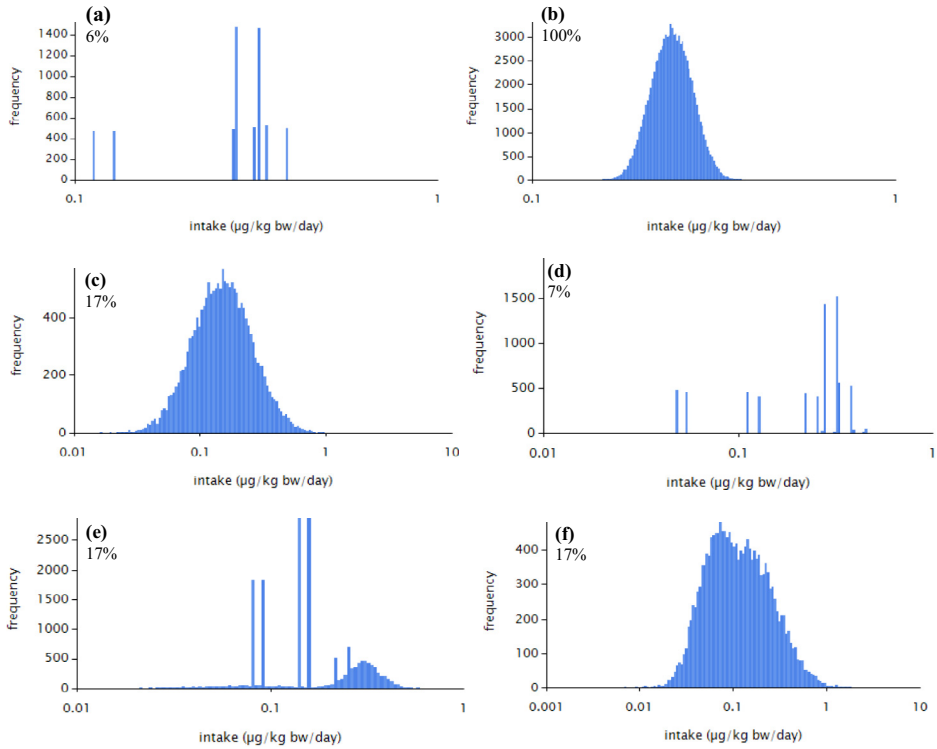


**Fig. 2.** Synthetic example. MCRA output showing simulated positive flusilazole equivalents exposures in 100,000 Monte Carlo runs according to (a) EFSA Guidance optimistic; (b) EFSA Guidance pessimistic, AU data not used; (c) EFSA Guidance pessimistic, AU data used; (d) compound-based empirical, NDs set to 0; (e) compound-based ND spike lognormal, NDs set to LOR, AU data used; (f) compound-based censored lognormal, AU data used. Percentages indicate the positive and displayed fraction of the distribution.

equivalents distribution corresponding to the samples where only non-detects have been registered. The lognormal distribution could be reasonable for the measured compounds, but gives an inappropriate fit to the flusilazole equivalents distribution, and this leads to unconservative estimates of the upper tail of the distribution. Data on the percentages crop treated (agricultural use data) can at least partly remedy this problem, as is shown in Fig. 1b. In accordance with the supplied agricultural use data 88% of samples is free of bitertanol and 93% is free of triadimefon. Recognizing that a large part of the samples is untreated (and thus corresponds to true zero values) leads in this case to 83% zero concentrations and a more acceptable fit of the lognormal model.

Using the flusilazole equivalents distribution the cumulative exposure has been estimated. The EFSA basic optimistic model replaces non-detects by zero, and therefore the flusilazole equivalents distribution calculated by MCRA consists of a spike of 94% zeroes plus a pattern of spikes which corresponds with the exact values calculated outside the program from all possible combinations of concentrations on samples and body weights in the input data (Fig. 2a, see also Supplementary Material). The cumulative exposure estimated with EFSA basic pessimistic model is again dependent on the use of agricultural use data. Without such data all estimated exposures are positive because in this example banana was consumed on all days, and the flusilazole equivalents distribution also had no zeroes (Fig. 2b). Based on the agricultural use data there are only 17% positives, and the estimated distribution is broader (Fig. 2c). The estimated 99.9th percentiles for the three cases were 0.39 (optimistic), 0.35 (pessimistic, no AU) and 0.58 (pessimistic, AU) µg/kgBW/d (Table 1).

In Fig. 2 and Table 1 also some results for alternative cumulative methods are shown, which are variations of Approach 2 (compound based). Using empirical distributions and setting non-detects to zero (a compound-based 'optimistic' approach, Fig. 2d) gives very similar results as the EFSA sample-based optimistic approach: there are 7% positive exposures as a result of randomly combining 5% positive bitertanol with 2% positive triadimefon exposures ($1 - 0.95 \times 0.98$). The empirical distribution is different because other combinations can be made, e.g. there are now results below 0.1 µg/kgBW/d because the lowest triadimefon residue could be sampled without the positive bitertanol value which was actually found on the same sample. In a compound-based model where AU data are combined with the ND-spike LogNormal model, and NDs are imputed by the LOR (this is the same concentration model as in the EFSA pessimistic model) a slightly lower tail percentile is found than with the AU-adapted EFSA pessimistic model. The

**Table 1**
Synthetic example. Summary statistics for flusilazole equivalents exposure distributions using various probabilistic methods. ND = non-detect, LOR = limit of reporting, AU = agricultural use, maxcor = maximized correlation in sensitivity analysis (see text).

| | Positive exposure (% of population) | 99.9th percentile (µg/kgBW/d) | Exceedance of 0.5 µg/kgBW/d (% of population) |
|---|---|---|---|
| **Sample based cumulation** | | | |
| EFSA optimistic | 6 | 0.39 | 0 |
| EFSA pessimistic | 100 | 0.35 | 0 |
| EFSA pessimistic + AU | 17 | 0.58 | 0.2 |
| **Compound-based cumulation** | | | |
| Empirical, ND→0 | 7 | 0.39 | 0 |
| Empirical, ND→0, maxcor | 7 | 0.39 | 0 |
| NDSpike-LogN, ND→LOR + AU | 17 | 0.46 | 0.03 |
| NDSpike-LogN, ND→LOR, maxcor + AU | 17 | 0.50 | 0.09 |
| CensLogN, + AU | 17 | 0.81 | 0.5 |
| CensLogN, maxcor + AU | 17 | 0.84 | 0.6 |

**Table 2**
Exposure of Dutch children 2 and 6 years old to lead. Percentiles and top-5 of consumed foods contributing to the exposure of 2- to 6-year-old children according to LNN model in MCRA 8.0 and MCRA 7.1.

| Exposure at age 2 (ng/kgBW/day) | | | Exposure at age 6 (ng/kgBW/day) | | | Contribution by food (%) | | |
|---|---|---|---|---|---|---|---|---|
| Percentage | MCRA 8.0 | MCRA 7.1 | Percentage | MCRA 8.0 | MCRA 7.1 | Food | MCRA 8.0 | MCRA 7.1 |
| 50% | 468 | 469 | 50% | 311 | 311 | Milk | 31.8 | 31.8 |
| 90% | 636 | 637 | 90% | 422 | 424 | Apple | 13.6 | 13.6 |
| 95% | 694 | 694 | 95% | 460 | 462 | Drinking water | 9.0 | 9.0 |
| 99% | 816 | 817 | 99% | 542 | 541 | Potatoes | 8.1 | 8.1 |
| | | | | | | Pork/piglet | 6.4 | 6.4 |

exposure distribution however looks very weird (Fig. 2e) because of the spikes caused by the imputed non-detects (10% of the population). An alternative censored lognormal model combined with AU data in the same way results in a more reasonably looking exposure distribution (Fig. 2f), and a higher tail percentile (0.81 μg/kg bw/d).

A sensitivity analysis was performed to correct for the lack of modelling correlation between pesticides in the compound-based approach. The results, shown in Table 1, show only slightly higher tail percentiles when the sampled residues are paired based on their ranking.

### 3.2. Validation MCRA 8.0 against MCRA 7.1

The percentiles calculated with MCRA 8.0 and MCRA 7.1 for the long-term exposure to lead distribution of Dutch children aged 2 and 6 years old are reported in Table 2, and differed by less than 0.5%, which can be explained by the stochastic nature of the Monte Carlo method. The estimated contributions of the top-5 foods were the same.

**Table 3**
Consumption of the US population of apple products (g/kgBW/day). Percentiles MCRA and DEEM.

| Percentage | MCRA | DEEM |
|---|---|---|
| 60.00% | 0 | 0 |
| 70.00% | 0.02788 | 0.02961 |
| 80.00% | 0.7995 | 0.8027 |
| 90.00% | 2.863 | 2.871 |
| 95.00% | 6.079 | 6.075 |
| 97.50% | 11.17 | 11.17 |
| 99.00% | 19.89 | 19.85 |
| 99.50% | 27.84 | 27.83 |
| 99.75% | 37.85 | 37.92 |
| 99.90% | 53.79 | 54.09 |

### 3.3. Validation MCRA against DEEM

The percentiles calculated with MCRA 8.0 and DEEM 3.16 for the total consumption distribution of apple products are reported in Table 3, and differed by less than 0.5%, except for the very low exposure at p70 (6% difference) and in the extreme upper tail, at p99.9 (0.6% difference).

The differences between MCRA and DEEM may be related to technical differences in the algorithms. Whereas MCRA stores all the exposures for the simulated individual-days, the older DEEM program applies a binning algorithm to reduce storage requirements and gain speed. DEEM applies different binning systems below and above the mean exposure. Above the mean the bin width is 1% of each bin lower limit, therefore the bins are of equal width at a logarithmic scale. Below the mean, DEEM creates 100 bins of width 0.01*mean. These bins are therefore of increasing width at the logarithmic scale if we consider decreasing exposure levels. The consequence of this is seen in Fig. 3: MCRA shows a trimodal distribution for the 42.6% positive consumptions. In DEEM the two lower components are not distinguished.

In the second validation a full two-dimensional Monte Carlo assessment was run with MCRA. Individual-days and captan concentrations were resampled in the inner loop of 100,000 Monte Carlo iterations and percentiles were calculated. In the outer loop the datasets themselves were bootstrapped 100 times to generate uncertainty limits on the percentiles. The comparison with DEEM (Table 4) showed DEEM estimates to fall between the MCRA uncertainty limits with the exception of p70, where again the binning algorithm of DEEM may have caused additional deviations.

## 4. Discussion

In this study the methods for probabilistic exposure assessment as described in the EFSA Guidance were implemented, and compared to alternative methods using a validation on simulated data. In pesticide monitoring the common pattern is to find a few positive values and a far greater number of non-detects. For statistical modelling this means that parametric distributions like

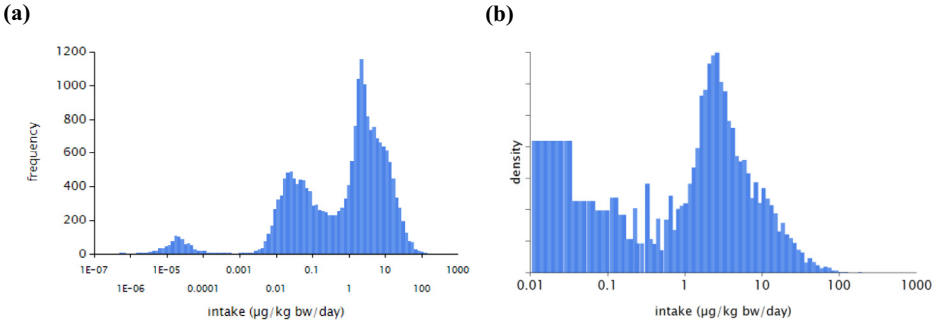


**Fig. 3.** WWEIA-FCID data for nine apple products. Total daily consumption distribution (42.6% positive consumptions only) according to (a) MCRA and (b) DEEM.

**Table 4**
Exposure of the US population to captan in apple (μg/kgBW/day). Percentiles MCRA and DEEM.

| Percentage | MCRA Exposure | MCRA Lower Bound (p2.5) | MCRA Upper Bound (p97.5) | DEEM Exposure |
|---|---|---|---|---|
| 60.00% | 0 | 0 | 0 | 0 |
| 70.00% | 0.0005497 | 3.277E-06 | 0.001238 | 0.003063 |
| 80.00% | 0.04209 | 0.02555 | 0.055 | 0.03905 |
| 90.00% | 0.4547 | 0.3518 | 0.5517 | 0.4458 |
| 95.00% | 1.512 | 1.2 | 1.919 | 1.521 |
| 97.50% | 3.782 | 2.801 | 4.564 | 3.672 |
| 99.00% | 8.727 | 6.424 | 10.38 | 8.451 |
| 99.50% | 14.42 | 10.26 | 16.99 | 14.03 |
| 99.75% | 22.11 | 15.49 | 26.63 | 21.69 |
| 99.90% | 33.4 | 24.7 | 41.83 | 34.32 |

the lognormal often have to rely on small numbers of observations. The problem is more severe in cumulative exposure assessment where also less important pesticides (with even fewer positive observations) are included in the CAG. The EFSA Guidance (EFSA, 2012) has offered a proposal on how a pessimistic cumulative assessment could be done. Our results show that the EFSA method may not work well. Due to all imputed LORs for NDs the cumulative distribution shows a strong spike and is not well modelled by a lognormal distribution. In our example the 99.9th percentile estimated by the 'pessimistic' approach was even lower than the one from the 'optimistic' approach. It may be concluded that further development of methodology is needed. This study presented some alternatives such as the censored lognormal model in combination with the use of additional data on agricultural use.

Validation of models and software has been approached from different angles, using external data from duplicate diets and biomonitoring (see Kennedy et al., 2014a), and, as reported in this paper, by comparing model output against known values from synthetic data or other programs. For the latter types MCRA includes automated testing of specific endpoints in specific examples. Whereas this is a great help in ensuring the quality of the software, it is also clear that complex software like MCRA allows for immense numbers of combinations of data sets and model settings, and any validation exercise is bound to test only a minute fraction of all possibilities. Therefore, selecting a sufficiently representative set of validation tests is still needed, and such a selection should be based on examples of the practical use of the program.

The results of the comparison between MCRA 8.0 and DEEM show in general a very good correspondence between the exposure percentiles calculated with the two programs. Extreme exposures in the upper tail of the distribution were almost identical. In the details there are some differences. Due to the binning system used for the Monte Carlo results in DEEM this program cannot give an accurate estimate of the left-hand side of the exposure distribution. MCRA on the other hand stores all Monte Carlo values and therefore is able to estimate the complete distribution. The consequence of this validation exercise is that users should be aware of these differences when they are interested in lower percentiles. Another outcome of the comparison is that the percentages contribution per food are calculated differently. MCRA applies the sampling weights per individual of the consumption database when calculating the percentages contribution for each food, whereas DEEM calculates from the unweighted exposures.

Discussions are on-going about the proper methods for probabilistic risk assessment. On the one hand it is attractive to keep models as simple as possible, however this may lead to very unrealistic results, e.g. as was found in our case for the EFSA pessimistic model (see also Boon et al., in press). On the other hand, more realistic models may require data which are currently not always available. In this paper we showed that agricultural use data may add to the realism of the models, but such data should be made available from existing farmer registrations by national agencies, as for example given by Kennedy et al. (2014b) for pesticide usage on crops in Great Britain.

It is likely that further harmonization of methodology for probabilistic risk assessment in Europe, North America and the rest of the world will lead to further needs to be able to perform these assessments using available data from many different sources. For example, not all people may experience the same average residue concentrations over time due to regional differences in consumed products, and therefore the current chronic models may underestimate the higher tail of the exposure distribution for some of the subgroups. As another example of further work, the integration of exposure assessment and hazard characterization already implemented in MCRA can be further connected to recent proposals for human health risk assessment (e.g. Embry et al. 2014, Pastoor et al. 2014). Therefore the MCRA 8.0 model as developed in the ACROPOLIS project should not be seen as an endpoint, but as a step towards further model development and integration.

## Conflict of interest

The authors declare that there are no conflicts of interest.

## Transparency document

The Transparency document associated with this article can be found in the online version.

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## Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.fct.2014.10.014.

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