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ACROPOLIS

Aggregate and Cumulative Risk Of Pesticides: an On-Line Integrated Strategy

SEVENTH FRAMEWORK PROGRAMME

Deliverable 3.2 A European model and case studies for aggregate exposure assessment of pesticides

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A European model and case studies for aggregate exposure assessment of pesticides

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Abstract

Exposures to plant protection products (PPPs) are assessed using risk analysis methods to protect public health. Traditionally, single sources, such as food or individual occupational sources, have been addressed. In reality individuals can be exposed simultaneously to multiple sources. Improved regulation therefore requires the development of new tools for estimating the population distribution of exposures aggregated within individual. A new aggregate model is described, which is designed to be flexible so that individual users can include as much, or as little, information as is available or relevant for their particular scenario. Depending on the inputs provided by the user, the outputs can range from simple deterministic values through to probabilistic analyses including characterisations of variability and uncertainty. Exposures can be calculated for multiple compounds, routes and sources of exposure. The aggregate model links to the cumulative dietary exposure model developed in parallel and is implemented in the web-based software tool MCRA.

Case studies are presented to illustrate the potential of this model, with inputs drawn from existing European data sources and models. These cover exposures to UK arable spray operators, Italian vineyard spray operators, Netherlands users of a consumer spray and UK bystanders/residents. The model could also be adapted to handle non-PPP compounds.

Keywords: common assessment group, probabilistic modelling, occupational exposure, consumer exposure

Running title: Aggregate pesticide exposure assessment

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1. Introduction

Regulation of plant protection products (PPPs) has traditionally been informed by risk assessments based on individual pesticides and exposure sources. In reality individuals may be exposed to a range of compounds from various activities but this presents many challenges for modelling. A simple solution is to combine the single-source assessments, combining conservative assumptions at each step of the calculation. This has the advantage of being protective but may be extremely unrealistic and suitable only for initial screening. There is a need for better tools that can be used routinely in regulating pesticides and other compounds, taking account of multiple sources of exposure.

We describe a general framework for calculating aggregate exposures, where calculations for each of the contributing sources can range from simple deterministic estimates through to fully probabilistic models that account for population variability and uncertainty analysis.

The model was developed as part of the EU Acropolis project, which is creating new models and software tools for aggregate and cumulative exposure to PPPs (www.acropolis-eu.com). It could be adapted to estimate intakes of arbitrary groups of compounds, other than PPPs, if they can be weighted relative to some reference compound. Exposure is *cumulative* in the sense that it can occur from multiple compounds which have similar effect. Such compounds are grouped into cumulative assessment groups (CAGs). *Aggregate* exposures combine dietary and non-dietary sources. Both dietary and non-dietary types of exposure can involve multiple compounds and therefore in general both can be cumulative. Examples of sources are occupational farming activities, use of amateur or consumer products, or incidental exposures experienced by residents or bystanders.

Other probabilistic models for aggregate and cumulative exposure have been developed. The Stochastic Human Exposure and Dose Simulation model for multimedia, multipathway chemicals (SHEDS-Multimedia) was developed by the US EPA (Zartarian *et al*, 2008). The latest version includes cumulative dietary (SHEDS-Dietary) and aggregate residential (SHEDS-Residential) modules.

CARES is a population-based model for performing aggregate and cumulative assessments of pesticide exposures. It is focused on a limited range of exposure situations and uses US datasets, but the model is freely available and has the potential to be adapted for additional scenarios.

Amongst EU member states a variety of databases and models relevant to exposure assessment have been developed independently. The purpose of the current paper is to illustrate a flexible framework in which these may be integrated using the internet based MCRA platform (mcra.rivm.nl). The examples are partly hypothetical and are therefore intended for illustration only. Our focus here is on exposure rather than hazard assessments. In order to describe a good selection of acute and chronic exposure scenarios, it was necessary to select compound groups that are toxicologically relevant to a different subpopulation from the one of interest. Specifically, the only CAGs currently available for triazoles are relevant for developmental effects, and therefore concern exposures to women of childbearing age. Furthermore, some datasets were borrowed across countries if not available for the country-specific scenario. Case studies are presented for population groups in the UK (arable spray operators and bystanders), Italy (vineyard spray operators) and Netherlands (amateur users of a plant spray). Selected single and multiple chemical are used to illustrate some of the possibilities offered by the model and its ability to incorporate results from existing external non-dietary exposure models and databases.

2. Aggregate exposure sources and data

There are many different types of activity through which non-dietary exposure to chemicals may occur. Examples are listed below, together with some relevant data sources and models. These reflect the EU focus of Acropolis, namely PPP usage in the EU.

- Operator activities. Professional users preparing and applying chemicals. The most relevant data in UK and Europe are in the UK-POEM/EUROPOEM databases (EUROPOEM, 1996; 2002). These provide data for actual dermal exposure (ADE), i.e. the mass of active substance (a.s.) on the skin as a proportion of the amount a.s. applied and actual inhalation exposure (AIE). A typical usage scenario involves both mixing/loading and application;
- Worker activities. Individuals entering areas treated with chemical. Operator and worker exposure to biocides can be addressed using the existing models BEAT (JRC, 2007) and ART (Fransman *et al*, 2013).
- Use of consumer products. Exposure from non-professional uses of PPPs or biocides in the home can be calculated using the ConsExpo software (Bremmer *et al*., 2006).
- Bystander and resident activities. Residents are defined as those living near a treated field, whereas bystanders are those passing near a field (EFSA, 2010). The recently developed BREAM model (Kennedy *et al*., 2012) was used to estimate exposures. New models and databases for non-dietary exposure to pesticides are being developed by another EU project, BROWSE (www.browseproject.eu)
- Ongoing activities are developing further data sources such as the AOEM (Agricultural Operator Exposure Model) (Großkopf *et al*, 2013) and the EFSA calculation tool due for public consultation in 2013/2014.

The specific activity scenarios selected as cases studies were: UK operator in arable farming; Italian operator in a vineyard; Netherlands amateur user of a biocides product in the home; UK Bystander/resident; and finally a hypothetical population performing a combination of these activities. Results from applying the aggregate model to these case studies using MCRA are presented in Section 4.

3. Model of aggregate exposure

3.1 Conceptual model framework

The model presented here was designed to be as flexible as possible, to accommodate existing models of non-dietary and dietary exposure, in all their forms, and to facilitate future extensions. Briefly, as summarised in Figure 1, an assessment involves: definition of an exposure question, including selection of an appropriate population, health effect and relevant compound(s); estimation of non-dietary exposures from one or more activities leading to exposure; matching non-dietary exposures with dietary exposures at the individual level; aggregation of those exposures and conversion to an appropriate common unit. If a chronic assessment is required, exposures are calculated per individual, typically representing average daily exposure. In the acute case, exposure values per individual-day should be calculated. To simplify the generic descriptions below we use 'individual' to represent both options.

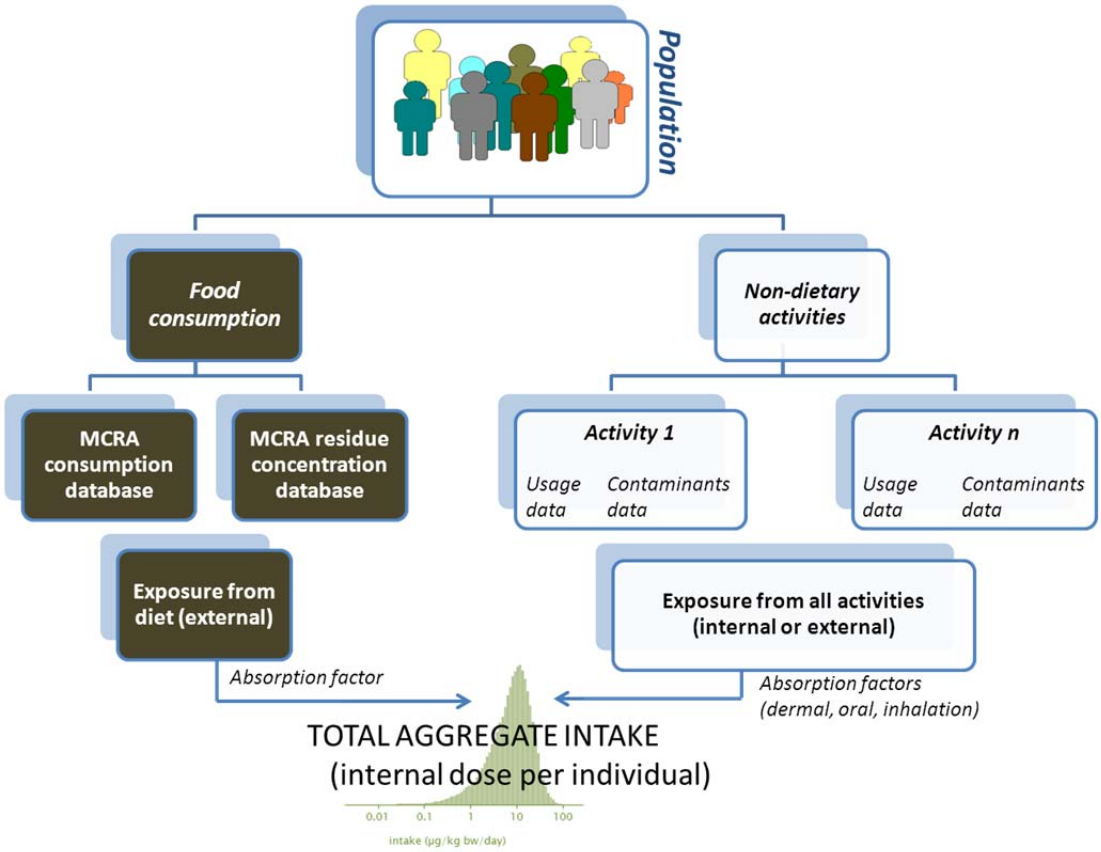


Figure 1. Conceptual model for assessment of (chronic) aggregate exposure, showing how exposure from dietary and non-dietary routes and activities are combined, and the models and databases that may be used. For an acute risk, internal dose per *individual-day* replaces internal dose per individual.

The population could be a national population but will often be a specific subgroup. Any databases used, modelling assumptions or simulated results should all relate to the chosen population. These include the dietary databases, non-dietary databases and models of exposure for relevant routes. It is not necessary for model and data sources to relate to the entire population in both the dietary and non-dietary components, so long as they are compatible in such a way that the aggregated estimates relate to a meaningful subset of the population. For example, current (conservative) models of operator exposure are aimed at the upper end of the actual distribution of exposure among operators, so aggregating these with a distribution of dietary exposures for the general adult population will generate a distribution of operator + dietary exposure that relates to individuals who are at the upper end of the distribution for operator exposure. Whether these estimates are protective relative to actual exposures will depend on the conservatism of the dietary and operator models used, and on the potential contribution from other unmodelled activities of the same individuals (e.g. residential exposures).

Aggregate risk assessments can take various forms, depending on the needs of the risk manager and the availability of quality data. Risk assessment typically uses a tiered approach. The lower (or first) tier models are the simplest to apply and use generic and conservative assumptions, therefore making them well suited to screening assessments. Higher tier models offer refinements in terms of realism at the cost of more detailed data and/or model assumptions, perhaps specific to a particular sub-population. These models can require additional expertise and specialist tools, so are used only when triggered by an inconclusive screening assessment. The aggregate exposure model developed

in the Acropolis project encompasses a wide range of options to allow for simple or complex analyses as required. The following choices are available for non-dietary exposures:

- A single deterministic value applied to all individuals (in the chronic case) or individual-days (acute case). This could represent a point estimate or a conservative upper quantile, for example. The level of conservatism of the model is dependent on the value selected in this case. For an illustration, see Section 4.4.
- A vector of deterministic values, with one value for each individual or individual day in a group. This corresponds to variable exposures, with a known variability distribution.
- A vector corresponding to realisations from an uncertainty distribution of a fixed but unknown non-dietary exposure to apply to all individuals
- Multiple vectors, each of which represents a simulated realisation of the population of individual exposures. Together these realisations quantify uncertainty about the true variability in the population. Such a representation commonly arises as part of a 2-dimensional Monte Carlo (2DMC) analysis (Burmaster and Wilson, 1996; Cullen and Frey, 1999). In our implementation we represent these vectors as a single column of stacked vectors, so that each of the alternative routes of exposure – dermal, oral and inhalation – can be combined and represented as separate columns within a single matrix.

A person-orientated approach is adopted (Figure 1). For every individual of the modelled population a non-dietary exposure value is assigned, using one of the methods described below. Various probabilistic methods are available to simulate exposures for a representative sample of individuals within the population, taking account of individual characteristics and activities, and variations in contaminant levels. The probability of any given individual, or the proportion of the population, exceeding certain exposure thresholds can then be estimated. The final option in the list above quantifies uncertainty, indicating the strength of evidence associated with the exposure estimates given the data and other information used. The treatment of variability and uncertainty more generally within the Acropolis model is described in detail in Kennedy *et al* (2013). Here we present details for the specific models applied in the aggregate case studies.

Making the link with the MCRA implementation, we will refer to the result of a non-dietary exposure calculation as a *non-dietary exposure table*. Each non-dietary table can correspond to a single activity (Section 3.2) or a relevant combination of activities (Section 3.3). The latter is important to allow assessments to reflect the combinations of exposure that may occur in reality (e.g. a person who is exposed through their diet and also as both a worker and a resident). Importantly it also offers the possibility to capture correlations between activities. Even if multiple activities are possible, it can be useful to run models separately for each activity in isolation (e.g. diet only, worker only, resident only), if this is required for regulatory purposes or to analyse the contribution of different components to overall exposure. Examples of different non-dietary tables are presented below. These are aggregated with the dietary exposure values of the modelled population, ensuring that each non-dietary table entry is matched with a compatible dietary record (Section 3.4).

To simplify the model description we refer to *usage* of a product containing a given compound. However, note that exposures may occur incidentally to individuals who are not using the product themselves, e.g. bystanders, so usage refers to a product rather than an individual. Our model separates activities, defined in terms of usage, from contamination per unit of usage, and treats them as independent. This is analogous to many dietary exposure modelling approaches which combine separate models/databases of consumption and residue concentrations. Aspects of dietary models can therefore be adapted and applied within our framework, e.g. to deal with multivariate analysis of pesticide residues if tank-mixes of compounds are applied. It also increases flexibility by

allowing the usage and contaminants model components to be combined in different ways. For example, a scenario in which an individual carries out an activity in their usual way but with an alternative product (or for comparing alternative compound scenarios) can be modelled by switching to a contaminants model specific to that product formulation. General algorithms and code can be developed to combine usage and contaminant models to create inputs suitable for the Acropolis model. Each of the examples presented in Section 4 is a special case of the general acute or chronic model described in sections 3.2.1 and 3.2.2 respectively.

Non-dietary exposures are expressed as matrices. If there are n compounds to which an individual can be exposed, then for every individual, and for every uncertainty realisation if applicable, the concentration and exposure values are $n \times 3$ matrices. Any elements corresponding to non-exposure will be 0. The columns $j = 1,2,3$ correspond to dermal, oral and inhalation exposure routes for all n compounds. We suppose there are I individuals for which to simulate non-dietary exposure. By default this is equal to the number of individual dietary records available for that assessment. For example, if the dietary exposure model generates 100,000 individual days, as is typical for an acute assessment, then we would set I = 100,000.

The following sections explain how to represent a simulated non-dietary exposure table based on a particular combination of activities & contaminants. In practice the data available for non-dietary exposure is most likely to represent a single source/activity. More realistic exposure estimates could be obtained by considering combinations of PPP related activities that an individual might be involved in or exposed to. Someone carrying out mixing/loading and spraying, who also lives near a sprayed field and uses amateur products during the same day, may have several sources of non-dietary exposure. In Section 3.3 we discuss in more detail the process of combining multiple non-dietary activities per person.

3.2 Creating a non-dietary exposure table

3.2.1. Acute non-dietary exposure

Acute exposure is taken to mean total 1 day exposures. We describe the general case in which several different activities or products are used, and the results combined into a single table[1]. This can be useful, for example, to account for correlations between those activities observed directly in data (see below). Suppose that an individual may use up to p products potentially containing one or more of the n contaminants of interest. For $i = 1, \dots, I$, let $\boldsymbol{y}_{ij}$ denote the n-vector of exposures for person-day i and route $j = 1,2,3$. Let x_{ik} denote the amount of product k used for individual i, and let $\boldsymbol{c}_{ijk}$ be the n-vector of concentrations in product k exposed to by individual i via route j. For the acute model the daily exposures are expressed as

$$\boldsymbol{y}_{ij} = \sum_{k=1}^{p} x_{ik} \boldsymbol{c}_{ijk} \tag{1}$$

Fixed units are not assumed in this equation, as different sources and routes of exposure can have different representations. Aggregation is described in Section 3.4, including the use of route-specific conversion factors. For a given route j, it is important however that in the sum (1) the same units are used for all k, between products. Dietary exposure is typically expressed as amount per kg body weight (e.g. mg/kg-bw or µg/kg-bw) in terms of external dose (as this is the unit assumed for toxicological reference values against which exposures are compared), so the non-dietary exposure

[1] Here and in Section 3.4 a single uncertainty realisation is presented to simplify the notation. Multiple realisations would simply involve calculating the same quantities repeatedly with new simulated values for uncertain variables.

needs to be scaled appropriately. This is taken care of in MCRA. In particular, bodyweight scaling of the non-dietary exposures takes place *after* aggregation.

In general notation we use $f_{Xk}(\cdot;\ \boldsymbol{\theta}_{Xk})$ and $f_{Ck}(\cdot;\ \boldsymbol{\theta}_{Ck})$ to denote the probability distributions of usage and concentration for product/activity k, with parameters $\boldsymbol{\theta}_{Xk}$ and $\boldsymbol{\theta}_{Ck}$ if a parametric form is assumed. These describe variability in usage and concentration with the latter being a multivariate distribution. These distributions may be estimated empirically, i.e. sampling from observed data, selected from a parametric family, or generated as output from a simulation model. Options for fitting a parametric distribution include statistical inference from data or the use of expert opinion. Uncertainty about $\boldsymbol{\theta}_{Xk}$, $\boldsymbol{\theta}_{Ck}$ may also be included. Usage and concentration are assumed to be independent in our case studies so the uncertainty distributions of their respective parameters are expressed separately as $\boldsymbol{\theta}_{Xk} \sim f_{\Theta x}(\cdot)$; $\boldsymbol{\theta}_{Ck} \sim f_{\Theta c}(\cdot)$. This independence assumption could be relaxed if required.

3.2.2. Chronic non-dietary exposure

For a chronic assessment the long-term average, rather than single day, exposures are calculated per individual and per route. For person i and route j this is expressed as

$$E(\boldsymbol{y}_{ij}) = \sum_{k=1}^{p} E(x_{ik}) E(\boldsymbol{c}_{ijk}) \tag{2}$$

where the expectations are over time, using a timescale appropriate for the toxicological endpoint of interest, e.g. average *daily* exposure. The same distributions of usage and concentration are relevant, although calculations will be simplified if the mean summaries of these distributions are available directly.

3.3 Multiple non-dietary exposure sources

In some cases it will be necessary for the analyst to carry out assessments for multiple routes and activities per individual and record total exposures in a single table as explained in Section 3.2.1. This would be particularly appropriate if there are dependencies between activity patterns for each individual, and a model is available to account for those, or if the data source is a detailed survey of PPP related activities. In this case for each individual i the model or survey would provide $(x_{i1}, \ldots, x_{ip})$ from the appropriate multivariate distribution that includes any correlations between activity types. The simplest approach, if an activity survey is available, would be to sample multivariate usage records empirically, using data from activities such as EFSA funded studies (Glass *et al*, 2012), UK Pesticide Usage Survey (PUS) (Garthwaite *et al*. 2011, 2012). Other options include computer simulation or probabilistic modelling, which can be designed to capture any relationships by approximating the underlying processes involved. The concentrations $(\boldsymbol{c}_{i11}, \ldots, \boldsymbol{c}_{i1p}, \ldots, \boldsymbol{c}_{i31}, \ldots, \boldsymbol{c}_{i3p})$ will also in general be correlated, as each individual will use certain types of formulations and in a certain way. Usage and concentrations are assumed to be independent. Given samples from multivariate activity and concentration distributions, these can be combined using (1) or (2) to give a single non-dietary exposure table for use in the aggregate calculation. Any correlation structure is automatically carried through to this aggregated survey. There is a parallel in modelling of multivariate food intakes in dietary risk models (Van Klaveren *et al*, 2012; Kennedy, 2010)

The multivariate model described above can require detailed multivariate data or models developed for a very specific scenario which will not be available in many practical situations. A simpler and more flexible approach is available that makes use of any combination of single source non-dietary tables. A single table is created by simulating from the marginal distributions $x_{ik} \sim f_{Xk}$ and $(\boldsymbol{c}_{i1k}, \boldsymbol{c}_{i2k}, \boldsymbol{c}_{i3k}) \sim f_{Ck}$ independently for each k. The process is repeated for all simulated individuals.

The drawback here is the assumption of independence, which could lead to less accurate results, but it offers more flexibility in terms of the available sources to combine.

3.4 Aggregating dietary and non-dietary exposures

The dietary assessment is described in Van der Voet *et al* (2013). It is assumed to be cumulative involving n compounds, and generates simulated exposure values for a sample of individuals from the population. The compounds of interest are those in the CAG for the selected health endpoint. For aggregation there are 3 important issues of consistency that must be addressed:

1. The units of dietary and non-dietary exposure must match exactly, which usually requires the application of relevant absorption factors;
2. If the purpose of the study is to assess relative contributions to exposure within the overall population, then dietary and non-dietary methods should be of a similar type if possible. This will ensure the dietary and non-dietary results can be interpreted and compared in a consistent way. If a parametric approach is used to extrapolate into the extreme tails of the dietary exposure distribution, for example, then something similar should be used for non-dietary exposure. Some examples are discussed below. Exact correspondence is not practical, or necessarily desirable given the need for flexibility. As explained in Section 3.1, it can be useful to consider a mix of conservative and un-conservative features to represent a specific subgroup, but this should be made clear when presenting results and conclusions;
3. The dietary and non-dietary exposure values must be correctly matched. It would be unrealistic, for example, to match the exposure of an operator with the dietary intake of a child. In our model each non-dietary exposure can be matched to a specific individual in the food survey, randomly assigned to any individual, or randomly assigned to individuals from a selected sub-population. The type of matching is specified through the use of a particular input file format, as described in the MCRA 8 user guide. The matched case would be ideal if both dietary and non-dietary information were available for the same group of individuals, but this situation is rare in practice.

The principles of the approach apply to both acute exposure (focusing on one-day exposures) and chronic exposure (averaged over longer time periods). Whichever interpretation applies, the units and timescale of exposure estimates, and the population to which they refer, must be compatible between the different parts of the aggregated assessment. Dietary exposure is normally estimated as external dose for comparison with the acute reference dose (ARfD) or acceptable daily intake (ADI), while operator exposures may be estimated as internal (systemic) doses, for comparison with the systemic acceptable operator exposure level (AOEL). When conducting aggregate exposure assessments, the final aggregate exposures must be expressed in the same form as the toxicological reference dose to which they will be compared, which may be internal or external and usually expressed relative to bodyweight. A necessary first step in aggregation is therefore to convert the individual routes (dermal, oral, inhalation) into a single value for each compound that is consistent with the unit of dietary exposure. Appropriate absorption factors are applied so that the 'doses' can be aggregated appropriately. Absorption factors can vary between compounds and sources. For example, the guidance of EFSA (2012a) recommends a default dermal absorption value of 25% be applied for products containing > 5% (50 g/L for liquids) a.s. and a default value of 75% should be used for products or in use dilutions containing ≤ 5% a.s. In our examples we have assumed 75% dermal absorption and 100% absorption for inhalation and oral intakes, as conservative choices. More generally, distinct absorption factors may be specified for each compound and non-dietary table in an assessment. Each compound is aggregated separately, before a suitable weighted sum is derived to give a total exposure. The weights are derived based on relative potency factors (RPFs), which are toxic potencies expressed relative to a selected index compound (EFSA 2009).

Dietary exposure is calculated for multiple compounds, whereas non-dietary exposures as described above can include multiple compounds as well as multiple routes per compound. For individual i, with body weight bw_i (in kg), the n-vector of exposures is

$$\boldsymbol{y}_i^A = \frac{\boldsymbol{y}_i^D A^D + (\boldsymbol{Y}_i^N \odot \boldsymbol{A})\mathbf{1}}{bw_i} \tag{3}$$

where $\boldsymbol{y}_i^A, \boldsymbol{y}_i^D$ are vectors of length n, corresponding to modelled aggregate and dietary exposures for individual (or person day) i, for all compounds $1, \ldots, n$. $\boldsymbol{Y}_i^N$ is an $n \times 3$ matrix generated using (1) or (2) with columns for dermal, oral, and inhalation non-dietary exposures of individual i for all compounds. The matrix $\boldsymbol{A}$ is an $n \times 3$ matrix of absorption factors with the ith row being the absorption factors for (dermal, oral, inhalation) exposures relevant to compound i and A^D is a dietary absorption factor. When $\boldsymbol{Y}_i^N$ is calculated as internal dose, the matrix $\boldsymbol{A}$ consists entirely of 1s. The vector $\mathbf{1} = (1,1,1)^T$ sums over the columns to aggregate the non-dietary routes. The operator $\odot$ represents element-wise matrix multiplication. The ARfD or ADI must be adjusted to be on the same scale as $\boldsymbol{y}_i^A$. Separate oral absorption factors are possible for dietary and non-dietary exposure, as eating is considered to be a different type of activity.

Two basic alternatives are available for matching dietary and non-dietary records, which we refer to as *individual* and *random* matching. In both cases each simulated dietary record is considered in turn and a suitable non-dietary exposure selected if appropriate. For individual i, individual matching allows for correlation between rows of $\boldsymbol{Y}_i^N$ and elements of $\boldsymbol{y}_i^D$. As with correlated inputs of non-dietary sources, suitable models are outside the scope of this paper, but can be considered in future work. The random matching case proceeds by selecting at random a non-dietary exposure value from each of the non-dietary tables included. Some of those tables are appropriate for a specific sub-population only, defined in terms of age and/or sex, in which case a non-dietary exposure will only be selected if the corresponding dietary record individual is a member of that sub-population.

Finally, after aggregation, cumulative exposures are given by $y_i = \boldsymbol{w}^T \boldsymbol{y}_i^A$ where $\boldsymbol{w}$ is a vector of weights. RPFs or TEFs can be used as weights. The unit used for the weight simply has to be meaningful compared with the toxicological reference value). Repeating for a large sample produces a sample $(y_1, \ldots, y_I)$ that is then used to produce summaries of the distribution of exposures within the population. In addition, the intermediate calculations are used to generate distributions of the contributions from individual compounds, routes and sources.

3.5. Implementation

The case studies were implemented using the MCRA software version 8 (mcra.rivm.nl). The user manual gives details of the various modelling options and input file formats. Briefly, a user has options to input non-dietary exposure in terms of internal or external dose units, combine multiple non-dietary tables stored independently, specify different absorption factors for each survey and compound, and select a matching strategy. For an uncertainty analysis, repeated realisations of $\boldsymbol{y}_{ij}$ can be generated using (1) within a 2DMC probabilistic modelling framework. In each uncertainty loop of the 2DMC algorithm, those parameters considered uncertain will be simulated from their joint uncertainty distribution.

Non-dietary input files for our case studies were created using routines created in R version 2.15.0 (R Development Core Team, 2012). This code is available from the authors and was used to:

- Create a single source exposure scenario from a selection of typical activity and contaminant options;
- Combine multiple tables and absorption factors into a single internal absorbed dose.

The first of these includes very simple deterministic approximations that will be sufficient in many practical situations. In Section 3.3, options to combine exposures from multiple activities were outlined. The aggregate exposure model and MCRA software can accept multiple non-dietary surveys each derived separately. However, for any specific application it is the responsibility of the user to combine these to create a single set of exposures and tables in the correct format. The R code generates example CSV files that can then be combined and converted to a file suitable for input to MCRA, and therefore provides a practical set of templates.

4. Results: Case studies

The conazole group of compounds has been selected for the case studies as they are commonly used in PPPs. The primary purpose here is to illustrate the range of possible exposure scenarios available through the aggregate model, rather than detailed exposure assessments. Many of the basic scenario features are common to all of the case studies. The health endpoint for the chronic case studies in Sections 4.3 and 4.5 is hepatoxicity (liver damage) in the foetus, which implies the following set of triazoles in the CAG and associated RPFs (EFSA, 2009): Bitertanol (2), Cyproconazole (1), Difenoconazole (2), Diniconazole (0.4), Epoxiconazole (2.5), Flusilazole (4), Myclobutanil (0.05), Propiconazole (0.6), Tebuconazole (0.1), triadimefon (0.1) and triadimenol (0.4). For the other scenarios an acute effect is considered. The endpoint is cranio-facial effects in the developing foetus with RPFs of Bitertanol (2.1), Cyproconazole (2.2), Diniconazole (1), Epoxiconazole (1.5), Flusilazole (1), Propiconazole (0.1), and Triadimefon (1.2). The concentration model followed the EFSA guidance for optimistic or pessimistic assumptions (EFSA, 2012b) and included a beta model for unit-to-unit variability. The UK and Italian operator case studies (sections 4.1, 4.3, 4.6) use the optimistic concentration model for consistency with the empirically-based non-dietary models. All others use the pessimistic model because their non-dietary models include similar conservative assumptions. Dietary and residue data were extracted from national surveys for UK, Italy and Netherlands from the period 2007-10 (see Boon *et al.* 2013 and Van der Voet *et al*., 2013). Percentage exposure contributions presented below are relative to the estimates of mean exposure. Unless stated otherwise, any references to percentiles are with respect to the variability distribution of exposures within the defined population. Uncertainties should also be considered in practice, as discussed in Kennedy *et al* (2013).

4.1 UK operator acute exposures

The most common operator scenario in the UK is arable boom spraying. Spray operators generally also perform mixing and loading of pesticides, and can be exposed through dermal or inhalation routes. A population of males aged 19-64 was considered, for which 766 UK dietary records were available in the National Diet and Nutrition Survey (NDNS) (Henderson *et al*, 2002). Following our general approach to create non-dietary exposure tables, pesticide usage was considered separately from exposure per unit applied. Relevant UK external exposure data (per kg of active substance applied) were selected from the EUROPOEM database as summarised in Figure 2. These included 44 actual hand exposures (AHE), 16 actual dermal exposures on the body (ADE) and 33 actual inhalation exposure (AIE) values. Only 12 individual records include both hand and body exposure, and none were available with hand, body, and inhalation exposures, making it impossible to estimate correlations reliably. In a separate investigation with a larger EUROPOEM dataset, we found no evidence of correlations between these exposures routes. One explanation is that exposure route is linked to specific activity types and product formulation, e.g. hand exposures from mixing and loading. We therefore simulated 3 values (ADE, AHE, AIE) independently for each individual for this

illustrative example. More realistic correlations would require more data or could be simulated via a mechanistic model output.

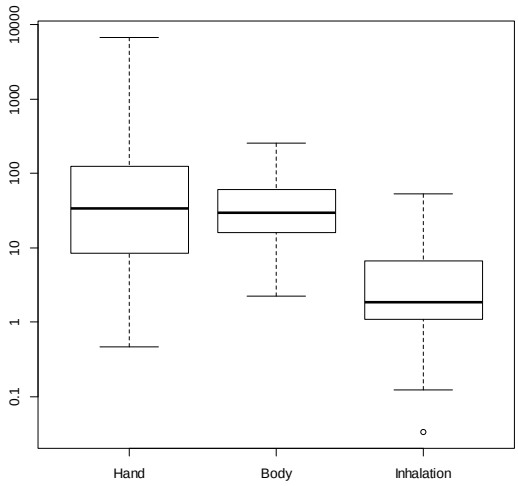


Figure 2. Summaries of independent samples of exposure data from EUROPOEM for Mixing/Loading/Applicator for arable boom spraying via the dermal hand, dermal body and inhalation routes expressed as (µg/kg a.s. applied)

Representative usage data, including typical triazole combinations sprayed and total amounts applied on different days, were extracted from the UK Pesticide Usage Survey (Garthwaite *et al*. 2011, 2012) and are summarised in Table 1. These comprised 10 farms, with between 3 and 36 spray days per farm. In total there were 124 spray days and various combinations of between 1 and 4 triazoles sprayed per day from a selection of 8 triazoles – Metconazole, Cyproconazole, Propiconazole, Tebuconazole, Epoxiconazole, Prothioconazole, Difenoconazole and Flusilazole. The corresponding areas worked per day ranged from around 10 to 150 ha. These individual spray day records were randomly sampled with replacement 1000 times to build up a simple approximated distribution of amounts used. The multivariate structure of conazole co-usage is retained by simulating whole records. Any 0 entries for a particular are included in the simulated usage records. Metconazole and Prothioconazole did not appear in the CAG and were therefore removed.

For an acute assessment, the *distribution* of total person-day exposures was derived by combining the usage and exposure data randomly as described in Section 3.2.1.

Table 1: Summary of daily conazole usage amounts (kg a.s. applied) extracted from PUS data

Farm	Number of spray days	Number of compounds	Max number of compounds per day	Total kg a.s. per day (range)
1	11	6	3	0.42 – 21.24
2	5	6	3	0.67 – 25.47
3	3	5	2	2.34 – 13.98
4	9	4	2	0.94 – 12.65
5	14	6	4	1.12 – 13.74
6	4	4	2	0.07 – 4.59
7	15	6	3	0.57 – 19.00
8	15	5	3	0.09 – 6.15
9	36	6	2	0.18 – 9.98
10	12	4	3	1.02 – 20.28

Some outputs from MCRA are presented in Figure 3, showing how the aggregate exposure can be expressed in total or separated by route and/or compound. As a proportion of total exposure, the relative contributions were dermal (96.6%), oral (0%), inhalation (2.6%), and dietary (0.5%). MCRA also generated estimates of the upper tail intakes, and in this case dermal was even more influential with 99.5% contribution, compared with 0.5% for inhalation and 0% dietary. Median, 90th 95th percentile aggregate exposures were estimated as 0.65, 14.7 and 35.1 µg/kg bw/day. As seen in Figure 3, Epoxiconazole, Cyproconazole and Flusilazole are the top contributors to dermal exposure. This is due a combination of usage frequency and relatively large RPF values. The true percentiles (median, 90th, 95th) are summaries of the distribution for variability between person-day exposures. Uncertainty in these percentiles, due to limitations in our approximation, is not quantified here and may be substantial. Methods for evaluating uncertainty are discussed in Kennedy *et al* (2013). Uncertainty about quantiles of a population's exposure should be considered if an assessment was to be used for regulatory purposes.

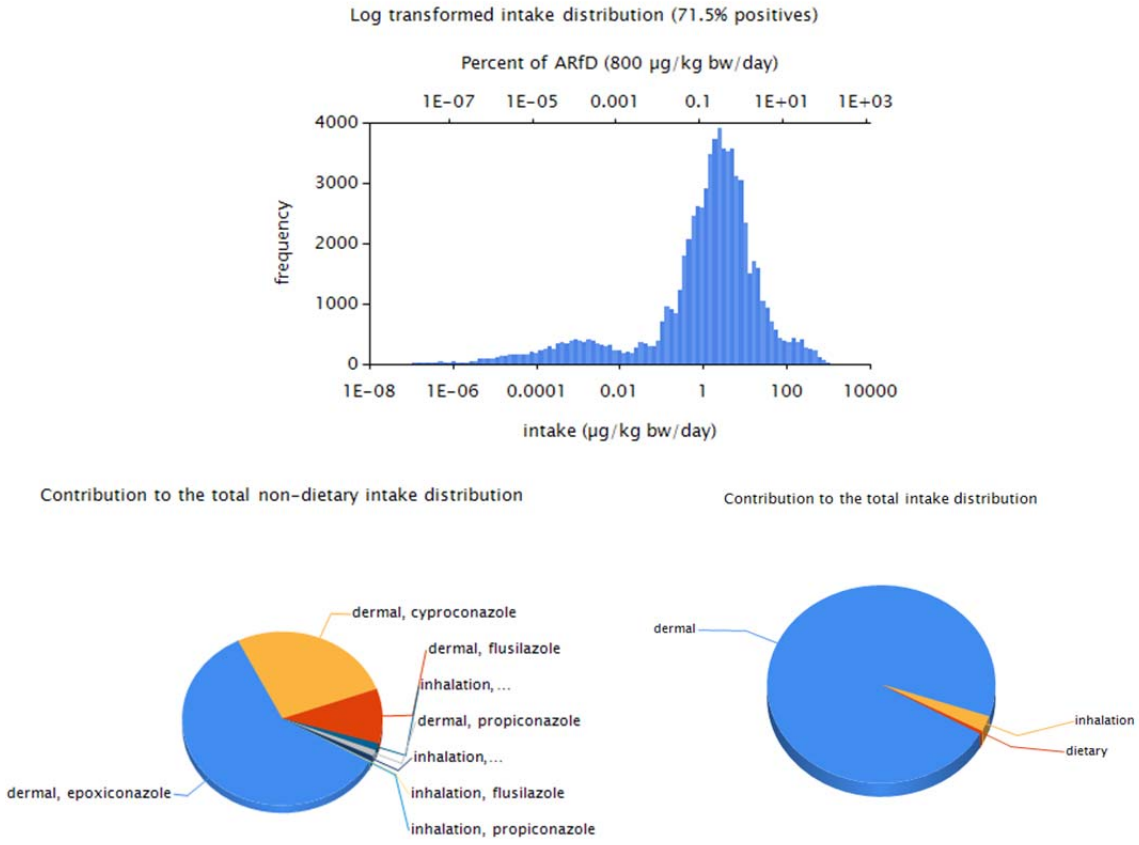


Figure 3. Estimated distribution of acute total aggregate UK operator exposure and relative contributions of exposure routes

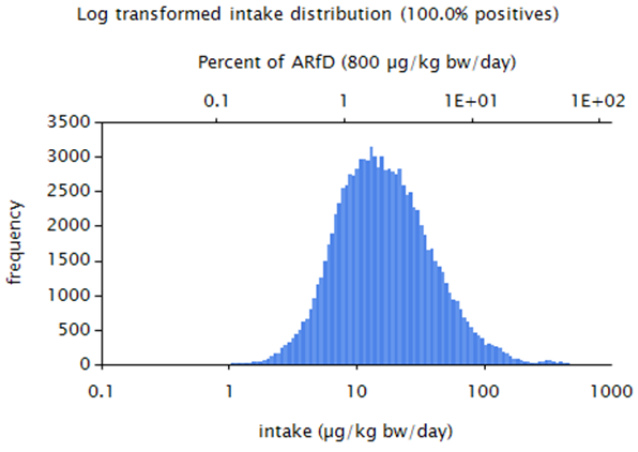
4.2 NL amateur user, acute exposure

Predictions of exposure to consumer products such as amateur PPPs and amateur biocides were generated using the ConsExpo model version 4.1 (Bremmer *et al., 2006)*. The first tier models in ConsExpo 4.1 are based on mathematical-mechanistic equations. The higher tier models are physics based models, e.g. those accounting for diffusion processes. The higher tier evaporation and spray models for inhalation exposure have been validated using experimental data on release from several types of consumer products (Delmaar and Bremmer, 2009).

Little is currently known about the frequency of PPP and biocide use by amateurs. Therefore, we consider the exposure of a single event. Our exposure scenario consists of the spraying of bitertanol from a can by adult women of reproductive age (18-44 years), for example on household plants. A selection of uniform and lognormal distributions was specified for the inputs to ConsExpo. The ConsExpo calculations result in a lognormal distribution LN(GM = 0.033, GSD = 2.6) for inhalation exposure $D_{bw=1}$ (mg per event) for a reference bodyweight of 1 kg. Back-transformed individual exposures (mg/kg-bw/event) are then derived using the equation $D_{bw} = D_{bw=1}\, bw^{0.65}$. This requires the bodyweight of the individual, which in practice corresponds to an individual from the dietary survey. A similar process is repeated for the dermal and oral exposure scenarios, using LN(0.06, 2.1) and LN(0.000056, 2.4) distributions respectively. Figure 4 shows the result of simulating combined exposures, as the sum of independent inhalation + dermal + oral simulations, and assuming a fixed bodyweight of 60 kg[2].

Note that because of the way the scenario was constructed, the distribution in Figure 4 estimates the variability of acute (one day) exposures within a sector of the population that experiences a high percentile of exposure via consumer products, in addition to the general contribution to exposure from the diet. The assumption of a single spray event per individual day is also a simplification. The exposure is dominated by inhalation exposure. A useful extension of this case study would be to obtain information about realistic frequency of use of these products, and this would be essential for chronic assessments. This could involve data collection through surveys or expert opinion. Similarly, we might also consider the level of conservatism represented by the ConsExpo output distribution as described above. The level of conservatism of the exposure is unknown, because uncertainty and variability are not separated. It also depends on conservatism of the input parameters, which are derived from Bremmer and van Veen (2000), Bremmer *et al*. (2006), Delmaar and Bremmer (2009), RIVM (2010) and ECHA (2010). The parameter values given in these documents are not primarily defined as distributions required for probabilistic exposure assessment. Therefore, it is emphasized that the parameter values applied here are open for discussion and improvement. Additional literature searches and experimental work may provide more informed parameter value distributions.

This scenario is represented in the general model (1) by setting $J = 1, n = 1, p = 1, I = 1000$ and $bw = 60$ kg for a single compound, single product case. Concentration and product used are not separated, so we take $x_{i1} = 1$, $\boldsymbol{c}_{i1} = (c_{i11}, c_{i21}, c_{i31} bw^{0.65})$ where $c_{i11} \sim LN(0.06, 2.1)$, $c_{i21} \sim LN(0.000056, 2.4)$, $c_{i31} \sim LN(0.033, 2.6)$ are independently simulated concentrations per spray event for dermal, oral and inhalation routes.



[2] This is the recommended bodyweight value in the draft guidance of EFSA (2010), and is used here because it is not generally possible to extract individual bodyweights for the linked dietary survey records.

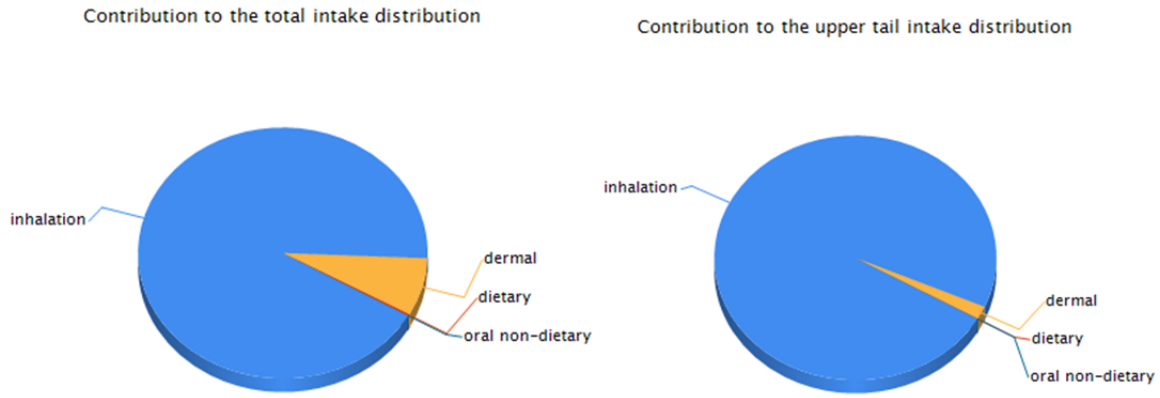


Figure 4. Distribution of acute aggregate bitertanol exposure and relative contributions from different routes, assuming a single spray event assuming a default 60 kg bodyweight.

The estimated contributions to total aggregate exposure are given as inhalation 92.3%, dermal 7.4%, dietary 0.2%, oral non-dietary 0%. Corresponding median and (p25-p75) summaries produced by MCRA are 13.9 (7.18 – 26.6) for inhalation, 1.35 (0.82 – 2.22) for dermal, 0 (0 – 0.005) for dietary and 0.002 (0.001 – 0.003) for non-dietary oral exposure (µg/kg-bw/day). The percentage contribution from inhalation is further increased in the upper tail exposure (to 98.2%).

4.3 Italy worker, chronic exposure

An Italian case study was developed considering male vineyard workers. The scenario was similar to the UK operator case study but used Italian EUROPOEM data relevant to vine spraying and Italian dietary survey from 2005-6 (Leclercq *et al.*, 2009) and triazole dietary residues from the Italian monitoring 2007-10. The population of Italian males aged 19-64 was considered based on the CAG associated with the hepatotoxic health effect due to chronic exposure. A single study was available in EUROPOEM, providing only 12 records of dermal and inhalation exposure data, per kg a.s. applied. These were repeatedly sampled and multiplied by a randomly sampled value from the 31 usage amounts (kg a.s. applied) collected in the EFSA survey (Glass *et al*, 2012). The triazoles used were penconazole and tebuconazole, although penconazole does not appear in the CAG and was therefore omitted. As tebuconazole appears in the chronic CAG but not in the acute CAG, this case study was used to illustrate chronic exposure. Effectively, we imagine that the simulated exposures represent average daily exposures per individual. MCRA8 was run as in the UK operator case study, and the general pattern of results is similar (Figure 5). Of the total intake, approximately 91% is due to dermal exposure, with 6.5% from inhalation and 2.5% from dietary.

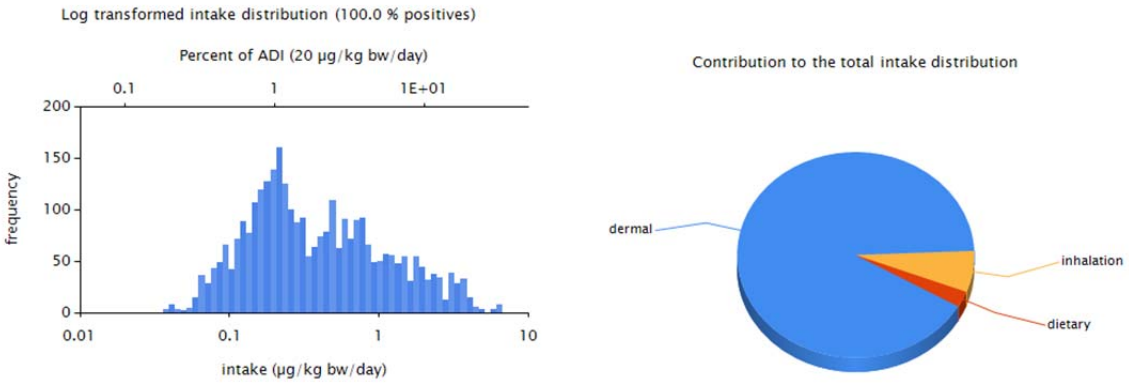


Figure 5. MCRA output showing estimated distribution of chronic aggregate exposure and proportion contributions from different routes, in the Italy vineyard case study.

4.4 UK/NL Bystander/Resident, acute exposure

As an example of a bystander exposure, dietary records from male and female children aged 2-6 were taken from the NL database, together with triazole residues 2007-2010 in MCRA. The sprayed compound was assumed to be Cyproconazole, which is commonly applied in the UK. For non-dietary exposure we generated some output from the BREAM model, representing a single pass of a boom sprayer application to an arable crop under the following conditions: Forward Speed = 8 km/h, Boom Height = 0.5 m, Wind Speed = 2 m/s, with a child bystander located 2m downwind of a sprayer with 48 nozzles. The BREAM model is probabilistic, in that it generates random variation around the default wind angle, boom height and wind speed input values (Kennedy *et al.*, 2012) as would occur during a real spray event. BREAM was run with 1000 randomly simulated input values, and resulting estimates of the 75th and 95th percentile dermal exposures are shown in Table 2 for this case. Percentiles are often used as simple summaries that represent typical high input values. The 75th percentile of 0.27 was used, in addition to the values simulated from a distribution, to illustrate the different types of input that can be provided to our aggregate model and the impact on results. It is anticipated that the BROWSE model will provide output data in a similar format.

Table 2: Mean and quantile summaries of output from the BREAM model (ml spray liquid). The modelled population corresponds to children, each exposed to a single boom spray event, under varying wind angle, wind speed and boom height conditions. The line highlighted in bold is the case considered further below.

		Mean	75th percentile	95th percentile
Adult	Dermal (external)	0.28	0.35	0.79
	Dermal (internal)	0.028	0.035	0.079
Child	**Dermal (external)**	**0.22**	**0.27**	**0.61**
	Dermal (internal)	0.022	0.027	0.061

Comparing with the general model (1), it can be seen that $p = 1, n = 1$ as this is a single pass of a sprayer and a single compound is considered. We have also considered a single source for the exposure, i.e. dermal so $j = 1$. For future analysis, the BROWSE model will also provide inhalation and oral exposure. The BREAM model output (taken here as the unit of product, x) is ml spray liquid on the skin. Before aggregation the concentration factor c is applied to convert this to mg active substance (a.s.). Additional information is required to calculate c. In the current example we used the following typical values for illustration: Volume applied = 120 l/ha, dose rate = 1 l/ha, concentration of active in product = 350g/l. This implies 350/120 = 2.9 g a.s. per litre sprayed, so $x =$ 1 ml spray becomes 2.9 mg a.s. when aggregating with dietary exposure values. The appropriate concentration factor is therefore $c = 2.9$. Alternative concentration models could be included, for example to account for different dose and product concentration, dilution, or tank mixtures. Finally, $I = 1000$ individuals were simulated in this case for illustration. Larger I could be used if the extreme tails of the distribution are of interest.

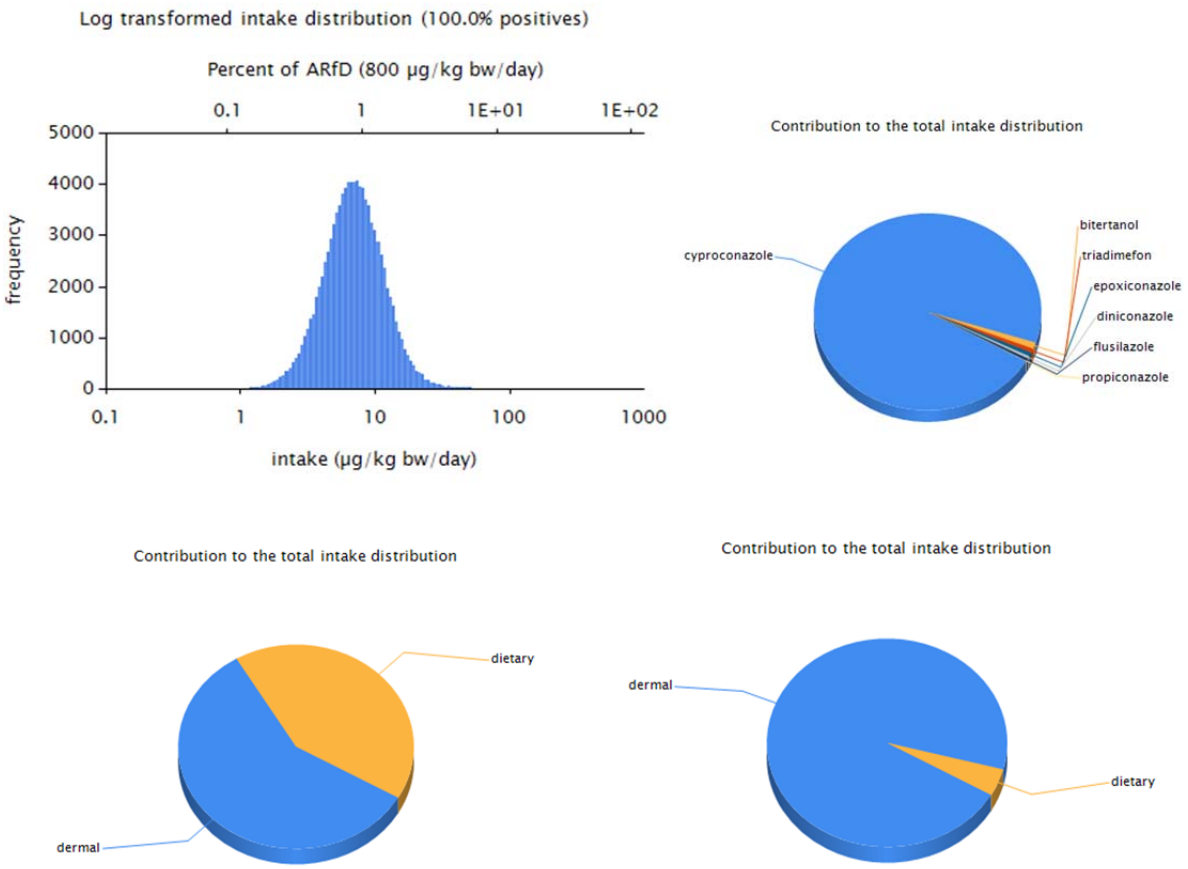


Figure 6: Distribution of acute aggregate exposure and percentage of dietary vs. dermal exposure in UK/NL child bystander case study, with either a conservative deterministic choice (right) and a variability distribution choice (left) for dermal exposure. Inhalation exposure is not included.

The deterministic estimate of non-dietary exposure leads to a larger contribution to the total exposure (Figure 6), with 95.8% compared with 58.2%. Median aggregate exposures were respectively 76.8 and 6.97 µg/kg bw/day for the deterministic and probabilistic cases. Note that Cyproconazole has the highest RPF (2.2) of all compounds in the CAG, and dominates the aggregate exposure (Figure 6).

4.5 UK/NL Resident, chronic exposure

Finally, an example of chronic resident exposure was generated to represent daily average exposure during a typical spray season. Average daily exposure to the compound tebuconazole was taken as the hypothetical scenario, combining exposure from crop spraying (as a resident living adjacent to an arable field) with chronic dietary exposure. The interval between the first and last spraying events in our UK operator usage dataset (Section 4.1) was 84 days, so we used this as a typical spray season length. We also selected farm 2 as our scenario, which had 5 spray days during the season and considered typical for a single field relevant to the resident scenario. For each individual, 5 spray days were randomly sampled from the same data as used in the operator case study of Section 4.1. This corresponds to Equation (2) in which $E(c_{i11}) = 2.9$ as this is constant, and $E(x_{11})$ is calculated as the average of 5 randomly simulated spray days drawn from the total collection of spray day data, i.e. divide the sum of the 5 amounts by the season length of 84. The percentage due to dermal exposure was 0.1%, with the remaining 99.9% from the diet. The median exposure was estimated as 9 µg/kg bw/day. The actual period over which PPP are used will be variable in reality, as will the

number of spray days (Table 1). The length of the exposure period could be altered depending on what is considered a chronic exposure period when exposures are pre-calculated by the user, and the impact of any Unquantified uncertainty in this value should be reported. Note also that by combining spray records from all farms this assessment does not attempt to consider separately between- and within-farm variability. Alternative models are mentioned in Section 5.

4.6 UK cumulative, acute exposure, from multiple sources

To illustrate the multiple source exposure (Section 3.2.1) we consider a hypothetical population that combines aspects of 3 of our existing case studies. The hypothetical population considered is person-day exposures for UK adult male operators who are also considered as bystanders and users of the amateur spray product on the same day. A single exposure table was created by sampling independently from the individual component tables, as outlined in Section 3.2.

Table 3. Quantiles from the distribution of dietary and aggregated exposures calculated in MCRA for a multi-source exposure scenario

Percentage	Exposure (µg/kg bw/day)	
	Dietary	Aggregated
50%	0	23.34
90%	0.01	71.71
95%	0.24	111.4
99%	1.53	311.3

The breakdown of contributions to the overall mean aggregated exposure is 52.9% dermal, 46.9% inhalation, and 0.1% dietary. Contributions to the upper tail of the distribution, above the 97.5th percentile, are 89.5% dermal, 10.5% inhalation, and 0% dietary. As expected if we compare this example to the previous ones, there is now a more even split of exposures between dermal exposure arising from crop spraying and inhalation from consumer product spray.

In future multi-source aggregate exposure assessments, more realistic assumptions about individual activity patterns will be considered when generating input tables for the MCRA Acropolis model.

5. Discussion, future improvements required

A flexible, general framework has been described for incorporating non-dietary sources of exposure within a risk assessment. The implementation of this method offers the possibility to improve on existing methods which account for single sources or a combination of conservative assumptions. A significant challenge in this area is the communication of risks and probabilities. The outputs available from the aggregate model provide estimates of the relative exposure from various sources, which may be more effective for communication. A comparison of risks is easier to process than an individual exposure or probability value in isolation.

Input tables for non-dietary activities can be collected or simulated, and methods of creating these have been explained. The case studies presented in Section 4 cover various possibilities, ranging from simple deterministic estimates though to multi-compound non-dietary exposures with multiple

routes of exposure and uncertainty analyses, which demonstrate the flexibility of the approach. Although our examples are for illustration only, they demonstrate how the relative contributions to exposure can be shown to differ between particular scenarios and populations. For example, based on our hypothetical scenarios the main routes of exposure are seen to be inhalation for the spray user, and dermal for the UK operator. Section 4.4 results show that for child bystanders, exposure through non-dietary dermal exposure is estimated to be small compared with dietary exposure. This example also demonstrates how alternative model specifications can influence the results (Figure 6). In any future assessment, particularly to inform a risk assessment, the selected scenario parameters and distributions would require specific and detailed justification. A small selection of MCRA outputs has been presented here, relevant to aggregate modelling. More detailed outputs are also available as described in Van der Voet *et al* (2013).

Further refinements will be made based on feedback from stakeholder groups testing and using the model in practice. Particular computation issues may arise as larger CAGs become available and are included. Ideally, account should be taken of the fact that the same person may undertake multiple activities of a similar type, e.g. different worker activities such as harvesting, grading and packing treated fruit. However, to do this reliably would require surveys of non-dietary activities, in which large samples of subjects record their activities in detail over representative periods of time, similar to the consumption surveys that are used in dietary exposure assessment. The US SHEDS model (Zartrian *et al*, 2008) is an example that does incorporate comprehensive activity databases (Comprehensive Human Activity Database - CHAD, McCurdy *et al*., 2000). CHAD includes almost 17000 person days of activities and includes about 140 distinct activity codes. At the present time, very little EU data of this type is available, although this is improving slowly with more detailed farm surveys collecting activity data referred to in the EFSA funded projects. Consequently, it is envisaged that the BROWSE project will develop models which consider only one activity of each type in each assessment, but assume that this activity fills all the time spent on the activity type (e.g. workers spending all their work time harvesting fruit in one assessment, and all their time grading fruit in a separate assessment). This should be a conservative approach, in the sense that exposure for more complex combinations of activities should be lower than the highest exposure for a single activity. In a cumulative assessment, however, there could be instances where a combination of activities and therefore combination of compounds in the CAG represents a worse case. More sophisticated models reflecting complex combinations of activities could be developed in the future, if detailed activity data become available. In Section 3.3 the method of incorporating these multivariate data was outlined.

When interpreting results, care must be taken to recognise possible differences in the degree of conservatism between dietary and non-dietary exposure models. As an illustration, the Italian case study of Section 4.3 was rerun using the pessimistic option for the residue concentration model. This led to an increase in predicted dietary exposure to the extent that dietary became the dominant route. The median estimate of total exposure was 9.6 µg/kg bw/day, although the estimated median exposure from spraying was only 0.3 µg/kg bw/day. The contributions to total exposure were estimated as 95.1% from dietary sources, 4.7% from dermal and 0.2% from inhalation. The difference in this case between dietary and non-dietary sources arises because the empirical sampling used in the Italian vine spraying model is not particularly extreme, so combining with a conservative dietary model may be unhelpful. The pessimistic dietary exposure model itself is relatively new and requires further testing before being used routinely in risk assessments (van der Voet *et al*., 2013). To understand results in detail we therefore advise sensitivity analyses in which the assessment is repeated using alternative plausible assumptions, so that any important differences can be identified. Other explanations can be found by examining the detailed breakdown of the results. For example Bitertanol from dietary residues contributes 50.4% to the overall intake and has an RPF of 2. Flusilazole contributes a further 14.6% and has RPF = 4. Tebuconazole has a

much smaller RPF of 0.1, and therefore contributes less to the weighted intake even though exposure is greater.

In the Acropolis model as described above, we allow for chronic (daily average) exposure and quantify between-individual variability, or acute exposure (individual-days combined across all individuals). Within and between individual variability are not separately characterised in the output. However, it would be possible to extend this by including multiple 'individual' codes per person that would correspond to multiple days for each individual. This would allow for investigation of variations, between individuals, of the individual patterns of exposure, and would be useful if individual health impacts were dependent on short term exposures over more than one day.

Account should be taken of the real within- and between-farm variability structure, particularly when performing a chronic assessment where the focus is individual operators, some of whom (e.g. contract spray operators) could be exposed to higher usage and therefore this should not be averaged across all farms. Larger sample sizes, particularly for the operator case study, would be desirable to generate a distribution of exposures that more accurately represents the true underlying population. Further software tools are being developed to help produce suitable non-dietary inputs for the aggregate model and this will continue as more data are made available. In the ongoing EU project BROWSE (www.browseproject.eu), various models and software tools are being developed to predict exposure from pesticides to the following population groups: bystanders, residents, operators and workers. The outputs from these models will be available as inputs to MCRA. As guidance (e.g. from EFSA) is developed in future for such things as standard bodyweights and absorption factors, the most recent values should be included as standard options when using the MCRA aggregate modelling software.

When interpreting results, users should take into consideration other sources of variability and uncertainty that have not been quantified in the assessment and may influence the overall conservatism of the results. This is essential when the assessment is intended for regulatory use, as risk managers need to understand how much higher or lower the real exposures might be. Approaches for quantifying additional sources of variability and uncertainty, and for evaluating the impact of unquantified variability and uncertainty, are presented by Kennedy *et al*. (2013). We have emphasised the need for more data on non-dietary exposure sources, such as realistic consumer product use, actual operator activities and bystander activities, so this should be a priority area if these models are to be used for routine assessments.

Acknowledgements

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