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Estimation of human intake of pesticides from all potential pathways

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People are exposed to mixtures of pesticides from eating foods containing minute residues of pesticides that were used to treat the products while they were growing, from using products in their home or garden containing pesticides and possibly as part of their work. This project has identified the information that is available to describe the possible sources of pesticide exposure in Great Britain, has collected the available data and devised a model to use this information to estimate the exposure of the population. Results are presented for different groups of people exposed to pesticides mixtures and for the population. In addition, the potential impact of the research on regulation of pesticides is discussed.

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SUMMARY

The uses of pesticides and other similar products are carefully regulated in Great Britain. Before a product can be used it must undergo a review of its toxicity and potential human exposure to ensure that the risks are acceptable. Exposure during application and in other occupational situations is assessed along with people living near to fields or who just happen to be in the vicinity of fields being treated, i.e. bystanders. Consideration is also given to the possible risks to consumers from eating food containing small amounts of pesticide residues. However, the regulatory processes generally only consider individual products and do not take into account exposure to other pesticide active ingredients with similar toxicity, to other products at different times or to the consumption of many different foods that may each contain pesticide residues.

This project has aimed to make an assessment of the exposure to pesticide mixtures from all potential pathways by creating a mathematical model of pesticide exposures from multiple active ingredients in food, or where exposure comes from occupational or bystander scenarios. We have devised a suitable theoretical framework for the exposure modelling, building upon existing models and data. We have collected together data on pesticide residues in food, food consumption, recipes for processed foods, patterns of exposure in agriculture, estimates of the numbers of people employed in agricultural uses of pesticides, numbers of people who may be bystanders when spraying of pesticides takes place in agriculture, and estimates of exposure to agricultural pesticides – both from applicators and bystanders.

A total of 21 pesticides were initially selected for the project, although we were unable to identify food residue data for three of these and so they were dropped from the list for study. The compounds were selected to be representative of substances that have shown anti-cholinesterase activity or which were oestrogen agonists. It was not intended that we select every single compound with these toxicological effects but rather that we selected a representative selection of such materials. The selection was based on the usage of the compounds in the UK, and on their occurrence as residues in food. Compounds of particular concern such as beta oestradiol were also included in the list, which was agreed with FSA at the beginning of the project. The selected pesticides were used in agriculture, as biocides and in a small number of instances as veterinary medicines.

There was a great deal of information available, but equally there were a number of areas where there were little or no data to assist in developing the model. For example, there were data on the levels of exposure likely to occur in the use of biocides containing the same active ingredients, i.e. non-agricultural pesticides, but there was no information about the usage of these materials or the numbers of people exposed. There were no data to develop the model for relevant veterinary medicines, although only one of the selected pesticides was used in these products. There is also no reliable information about the effect of processing on residues on food. In the model we have chosen to assume that processing may have a variable impact on residues with between no reduction and complete removal.

There were also difficulties with the interpretation of the very low levels of contamination that are present in foods. In the majority of cases there was no recorded residue, but for some of these situations there could have been contamination detected but it was below the Reporting Limit or there may have been contamination present below the analytical detection limit. In both of these case there would have been very low levels of pesticides present rather than none. We devised a simple algorithm to estimate the residues in these cases.

The model for food consumption uses summarised data on pesticide residues in combination with data from the National Diet and Nutrition Survey along with data on the basic food

components in common processed foods, i.e. recipe data. Data on occupational exposure were obtained from the EUROPOEM model and from periodic surveys of pesticide usage carried out for PSD. Data on the numbers of potential bystanders were estimated separately.

The model produced simulations of internal dose using a simple single compartment pharmacokinetic model. It simulates the pathways from ingestion (food consumption) or skin exposure (in occupational settings) to the internal dose for each chosen compound separately. The compound mixture internal dose is then estimated as the sum total of the individual compound dose estimates. In this way it was possible to combine data from different exposure pathways in a way that took account of the likely residence of the compound in the body. To assess the effect of the mixture of pesticides we have also simulated the body mass of the "people" and used the Acceptable Daily Intake (ADI) to normalise the internal dose.

We have selected to use ADI rather than the Acceptable Operator Exposure Level (AOEL) or the Acute Reference Dose (ARfD). In practice the AOEL and ARfD are generally quite similar and the exact choice of value would have limited impact on the results of the study. For acute exposures the ARfD would probably be more appropriate, although for simplicity we have used the ADI throughout the report.

Exposure was seen to occur irregularly throughout the year, regardless of whether the source was from food or from use of pesticides in agriculture, although in the latter case there were some seasonal effects. Internal dose was highest for application of pesticides in agriculture (farmers and contractors), next highest for bystanders and lowest for consumers. Internal dose for child consumers was less than for adults. The maximum dose estimates for individual pesticide compounds from food consumption were all much less than the corresponding ADI dose and the aggregate exposure normalised to the ADI dose was also much less than unity, i.e. below an "aggregate" ADI dose. Exposure estimates associated with occupational exposures provided aggregate dose estimates that were in many cases higher than the aggregate dose equivalent to the ADI, particularly for farmers and contractors. Our simulations suggest that there may be some people in the population living near to spraying activities who are bystanders and those who are occupationally exposed who may have unacceptably high exposures, but this conclusion is dependent on the accuracy of the EUROPOEM model and it may be that as a regulatory model it overestimates the true exposure received by individuals.

The impacts upon the regulatory systems in place in the UK were assessed, based on the recommendations of the COT report and the availability of data and information used for the modelling. To respond to the issues of possible human health effects of exposure to a mixture of pesticides the regulatory framework would need a more co-ordinated approach to prioritise the need for risk assessments to be carried out for exposure to more than one pesticide. However such as assessment would need to consider all sources and routes of exposure and could only practically be undertaken as a periodic review of groups of compounds of concern. In cases where exposure to a mixture of compounds was considered to result in a harmful dose there would be a need to regulate for this. In some cases this may require regulatory authorities to consider the removal or restriction of uses of certain compounds that are used in pesticides currently authorised or approved for use. In such cases there could be a conflict of interest, particularly when compounds with very different uses were being evaluated, such as the case where a compound is used for veterinary medicine purposes and also as an insecticide to prevent vector borne crop viruses. Regulatory decisions would need to be taken as to whether it is feasible to restrict the use of one or both products, the implications for restricting use, and the availability of alternative control methods.

The information currently available to regulators is not adequate to allow the risk assessment to be carried out without some degree of associated uncertainty. A limited sensitivity analysis

suggested that the conclusions from our simulations are not unduly sensitive to these uncertainties, particularly in the case of pesticide residues in food. To assess the risk of exposure to mixtures, more detailed information on the sources and routes of exposure, particularly for dietary exposure, would be helpful. This has consequences for the way residue surveillance programmes are organised together with a reduction in the reporting limits for residues in food products. Data would be needed on the patterns of use for biocides and veterinary medicines comparable to that that exists for agricultural pesticides in the UK.

1 INTRODUCTION

Regulation of pesticides, biocides and veterinary medicines in the UK is based on a system of approval for individual products. Although these products have different uses they can share common active ingredients and so it is appropriate to consider exposure to them as a group, and for simplicity in this report we generally refer to all of these as "pesticides". The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has recommended changes to the process of regulating pesticides to provide an integrated assessment of all sources and routes of exposure, both for consumers and people who work with these products. These changes should introduce greater scientific credibility and transparency to the risk assessment process, but to achieve this there must be a paradigm shift for the human exposure assessment away from considering single products towards a more holistic approach.

At present the exposure assessment for pesticides is compartmentalised according to whether it applies to operators, workers, bystanders or consumers, and is completely separate for the three types of use. The regulatory exposure assessment models are historic and generally conservative, i.e. they tend to overestimate actual exposures received.

An important focus of the COT recommendations was the possibility for mixed exposure to the many different pesticides regulated in the UK, along with pesticide residues in imported food and exposure to highly biopersistent compounds. The potential for exposure to mixtures clearly depends on the range of activities and consumption patterns of individuals, but the biological half-life of the pesticides will also determine the chance of mixed "internal" exposure. For example, for someone exposed to a pesticide with a biological half-life of several weeks it is relevant to consider all other co-exposures to pesticides during that time. However, if the half-life of the pesticide were much less than 24-hours then exposure to other pesticides on following days would probably not produce any mixed "internal" exposure.

To accommodate this level of complexity and properly account for the range of variation that may occur with human behaviour it is essential to combine together the estimates of pesticide uptake at the level of "internal" exposure using probabilistic modelling techniques. To do this it is necessary to use simple pharmacokinetic models to combine together the uptake estimates and to use Monte Carlo simulation techniques to provide cumulative assessment of mixed pesticide exposure.

Through the report we use the terms aggregate and cumulative in the sense that is normally accepted in pesticide risk assessment, i.e. aggregate exposure is the exposure from multiple sources of one pesticide active compound and cumulative exposure refers to multiple pesticide compounds from multiple sources.

It is to be expected that those people with occupational exposure to pesticides will have the highest exposures and that will predominate over all other routes of exposure. However, there may be important exposure of some consumers from bystander or "neighbour" exposure situations. In many cases where pesticides are used in the home or garden it is possible that children may have important exposure and for almost everyone there will be pesticide exposure from food consumption. It is possible for a probabilistic assessment to be carried out for the population as a whole, but this could provide an unreliable and difficult to interpret assessment. It is more appropriate to stratify the population at risk into groups with similar patterns of potential exposure, based on their demographic profile. Factors that it may be relevant to stratify on include age, gender, region of residence, occupation, house type and food consumption preferences (e.g. vegetarian). This type of stratification should allow groups who may have greater cumulative exposure to be identified rather than just the likelihood of some unspecified

individuals having greater cumulative pesticide exposure. Having a clearer picture of these groups could provide a basis to further investigate risks and, if appropriate, to intervene to change their exposure. It is still possible to combine the cumulative exposures of these groups to provide an overall distribution of exposure for the population.

In all models there is to some extent uncertainty, either in the models themselves or in the parameters input to the models. It is necessary to simplify the exposure situation so that they can provide a practical basis for modelling a large population with diverse habits. Data to parameterise the models is often only available from historic datasets and these may not have been collected in a way that completely suits the modelling approach. It is important to realise that all models are only valid to the extent that they can be demonstrated to provide reliable predictions of reality and so once a model has been developed it is important to undertake rigorous testing against objective measurements.

This report summarises a research study to make a probabilistic assessment cumulative exposure of the British population and population subgroups to a subset of pesticides. Specific objectives of the work were:

- Identify a subset of pesticide compounds for study;
- Construct a database to hold information on pesticide use and exposure determinants;
- Collect available data about pesticide residues in food, both from Great Britain and other relevant sources;
- Collect available information about British food consumption habits in relation to the food categories identified above;
- Identify the range of occupational scenarios (i.e. operators and workers) applicable to each pesticide or veterinary medicine;
- Estimate the number of people who may be exposed as either bystanders or neighbours;
- Identify the range of exposure scenarios where the identified pesticides may be used by consumers;
- Identify data on residues of pesticides and veterinary medicines in the environment (water and soil) by region;
- Devise a suitable basis for the estimation of dietary uptake (i.e. the mass of residue consumed over a defined period) based on consumption and residue levels;
- Develop the conceptual basis for inhalation, dermal and accidental ingestion uptake of pesticides in occupational and non-dietary consumer scenarios, including bystander, neighbour and environmental exposure;
- Devise a single compartment pharmacokinetic model to enable “internal” exposure to be estimated; and
- Extend the probabilistic simulation to provide a prediction of exposure for the population of Great Britain, overall and in a range of strata defined by the use scenarios and consumption patterns.

Finally, we discuss the extent of additional requirements and associated additional cost for approvals and authorisations of pesticides and related products.

At the beginning of each subsequent chapter we have identified the specific objectives that are dealt with in that section of the report.

2 IDENTIFICATION OF A SUBSET OF PESTICIDES FOR FURTHER STUDY

Objective 01	Identify a subset of pesticides and veterinary medicines for study

A subset of pesticides approved for use in the UK was identified for this study. Two groups of active ingredients were identified: a group of anti-cholinesterase compounds and a group of compounds with oestrogen agonism.

The list of organophosphate and carbamate pesticides were selected from (a) the Pesticides Safety Directorate (PSD) list of anti-cholinesterase pesticides and (b) the Advisory Committee on Pesticides Annual Report (2003). This list was supplemented by a number of pesticides with activities suggestive of oestrogen agonism based on information provided by the Institute for Environment and Health (IEH, personal communication).

The criteria for selections were:
- status: “under review” or “approved”;
- pharmacokinetic data available;
- probability of presence in food and
- availability of information about the biological half-life.

Some of the substances are also used as biocides and/or veterinary medicines.

The availability of information on the biological half-life was identified for each of the compounds selected.

2.1 ANTI-CHOLINESTERASE COMPOUNDS

Compounds with anti-cholinesterase activity (note those with an asterisk are also included in the list of oestrogen agonist compounds):

2.1.1 Organophosphates

- Azamethiphos
- Chlorpyrifos*
- Dichlorvos
- Dimethoate
- Ethoprophos
- Fosthiazate
- Malathion
- Pirimiphos-methyl*
- Tolclofos-methyl*

There were 55 approved organophosphate products listed on the PSD website that contain one of the selected compounds. Seventy-five biocides containing one of the selected organophospahte compounds were listed on the HSE website. These biocides contain either azamethipos, chlorpyrifos or dichlorvos. No veterinary medicines were identified containing any of the organophosphate compounds.

Usage of these organophosphate pesticides, based on the most recent DEFRA funded Pesticide Usage Surveys, ranged from zero up to about 47,000 kg per year. Pesticide residue data from selected foods was available for seven of these nine compounds.

2.1.2 Carbamates

- Methiocarb*
- Oxamyl
- Pirimicarb
- Thiodicarb
- Bendiocarb
- Benfuracarb
- Aldicarb

Eighty-nine approved pesticides were identified containing one of the selected carbamate compounds; mostly methiocarb. There were 57 biocidal products containing bendiocarb listed on the HSE website. None of the other selected carbamates were in the list of biocides or veterinary medicines.

The annual estimated usage of the selected carbamates in pesticide also ranged from zero up to 47,000 kg. Pesticide residue data from selected foods was available for four of these seven compounds.

2.2 OESTROGEN AGONISM

For pesticides with activities suggestive of oestrogen agonism, we choose those that were approved by the PSD and are present in a range of foods. The selected compounds are (plus the four compounds shown in the above lists marked with an asterisk):

2.2.1 Pyrethroids

- Cypermethrin
- Cyfluthrin

2.2.2 Others

- Glyphosate
- Triadimenol
- Simazine

There were 28 approved pesticide products containing one of the pyrethroids, mostly cypermethrin. There were 105 biocides listed on the HSE website containing either cypermethrin or cyfluthrin and six veterinary medicines containing cypermethrin. The estimated annual usage of these pesticides is about 60,000 kg. Residue data were available for both of these compounds.

Three other compounds were identified: glyphosate, triadimenol and simazine. There were 263 products listed containing glyphosate and the estimated annual usage was 1.6 million kg. There were 54 pesticides listed containing either triadimenol or simazine with an estimated usage of 13,000 kg and 150,000 kg, respectively. No biocides or veterinary medicines were identified

containing any of these compounds. Residue data were available for all compounds except for simazine.

2.3 SUMMARY

The final list of pesticides consisted of 21 compounds with anti-cholinesterase and oestrogen agonism activities. Pesticides marked with an asterisk in the list have both anti-cholinesterase and oestrogen agonism activities.

3 COLLATION OF DATA FOR RESIDUES IN FOOD

Objective 03	Collect available data about pesticide residues in food, where possible identifying separately food products produced within the EU and food products imported into the EU, using both data from Great Britain and other relevant sources. Add information to database.

3.1 SOURCES OF INFORMATION

The primary source of information relating to the residues of pesticide in food in the UK is the national monitoring programme. Other national governments within the European Union (EU) have similar schemes, which are all part of the EU residue monitoring scheme. Annual European-wide pesticide residues monitoring reports are published on the website http://ec.europa.eu/food/fvo/index_en.htm .

The pesticide residue monitoring programme was set up with a regulatory function, which is now overseen by the Pesticide Residue Committee (PRC), an independent Committee that advises the Government on the programme of pesticide residues surveillance. The programme is administered and carried by the Pesticides Safety Directorate (PSD), who in liaison with other Government Departments are responsible for the regulation of pesticides in the UK. If pesticides have been used in accordance with their approval (i.e. following label recommendations), then the residues in a crop should be within the maximum residue level (MRL). Therefore the main role of MRLs is to check that the approvals system is functioning properly and to regulate trade in treated food. MRLs are set for each pesticide and for food type, although it is important to bear in mind that they are not safety limits.

The definition of MRLs and other terminology used in relation to pesticide residues is defined by the PSD:

Maximum Residue Level (MRL):

> The maximum concentration of a pesticide residue (expressed as mg/kg) legally permitted in or on food commodities and animal feeds. MRLs are based on good agricultural practice data and residues in foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable. MRLs are not in themselves 'safety limits'. MRLs are intended primarily as a check that GAP is being followed and to assist international trade in produce treated with pesticides. MRLs are not safety limits, and exposure to residues in excess of an MRL does not automatically imply a hazard to health.

MRLs (Codex Alimentarius Commission CAC or Codex):

> In cases where there are no UK or EC MRLs, the acceptability of residues may be judged against Codex Maximum Residue Limits. Although not embodied in UK statute, Codex limits are taken as presumptive standards. These limits give an indication of the likely highest residue that should occur in edible crops. These are based on worldwide uses and the residues trials data to support those uses, at the time of evaluation (date of setting the limits is specified and thus the Maximum Residue Limit applicable up to that year, but will not take into account subsequent approved uses.) There are occasions where the MRL that has been set may not reflect UK Good Agricultural Practice (e.g. the Codex MRLs for dithiocarbamates and propamocarb on lettuce). In such circumstances it is possible to exceed the Codex MRL through a UK approved use. This factor needs to be taken into account when assessing results.

Maximum Residue Levels set at the LOD:

> For some pesticides and commodities, insufficient trials data are available on which to set a maximum residue level. In these cases, the MRL may be set at a default level, i.e. at the limit of determination (LOD) where analytical methods can reasonably detect the presence of the pesticide. These MRLs are not based on Good Agricultural Practice (GAP)

Reporting Limit (RL):

> The reporting limit is the lowest calibrated level employed during analysis to detect residues. The reporting limit may vary slightly from laboratory to laboratory depending on the equipment available and operating procedures used.

For the purpose of this project the PRC data from the UK were used to provide data for the occurrence and levels of pesticides in food. Smaller data sets do exist which have been funded by food retailers for example, but these tend to be focussed on specific produce and pesticides, so were not included in the data set. There is also the matter of confidentiality of such information to be considered.

Annually in the UK about 4,000 food samples are analysed for a wide range of pesticides. The annual surveillance programme covers dietary staples (bread, milk and potatoes) and a rolling programme, which monitors different fruit and vegetables, cereals and cereal products, fish and fish products, and products of animal origin every few years. In some instances special problem areas can be addressed, such as rapid response targeted surveys, when information is received about residue levels exceeding the MRL or the presence of non-approved pesticides. For example, in 2006 this occurred with isofenphos methyl residues in peppers imported from Spain.

In this way the PRC provides data for pesticide residues in a wide range of food types. A summary of the results is published in full in Quarterly Reports, which are then used to prepare the Annual Report published in the September following the sampling year.

The range of pesticides that may be used on crops is very wide, with about 350 active substances currently approved for use as agricultural pesticides in the UK and over 850 approved in one or more EU states. It is not practical to monitor a sufficiently representative sample of each of these, therefore a more focussed sampling approach is used, which is done in collaboration with programmes organised by the EU. The range of pesticides being sought in any particular food type depends on the likely prevalence and risk of particular pesticides.
Samples are collected from 24 different UK centres from sources including:

- major supermarkets;
- local shops and market stalls;
- farm shops;
- wholesale;
- ports.

The following laboratories participate in the programme:

- Central Science Laboratory, Defra, Sand Hutton, York;
- LGC Ltd, Teddington;
- Scottish Agricultural Science Agency, East Craigs, Edinburgh;
- Department of Agriculture and Rural Development, Belfast;
- Direct Laboratories, Wolverhampton.

The data used for this project were obtained from PSD and CSL databases. The data as reported by the PRC on the PSD website do not contain sufficient information about the levels of pesticides, and only summarise the number of samples which were found to have residues at or above the above the reporting limit (RL) or the Maximum Residue Limit (MRL).

Table 3.1 shows an example of a selection of summarised data from a CSL database using the following categories:

- Residue;
- Country of origin;
- Commodity;
- Year;
- Reporting limit;
- No of samples tested;
- No of samples above RL;
- No of samples above UK MRL (at that time).

By using the original data for individual samples, supplied by PSD, it is possible to identify the quantity of pesticide for each sample where the level was above the reporting limit. However, this still left the majority of data from the surveillance programme simply quantified as as being below the reporting limit. In reality these values would be a mixture of values between zero and the reporting limit (<RL). Many of these values could in reality be bewteen the Limit of Quantification (LOQ) and the RL. The practical consequences of this issue for the project are dealt with later.

The reporting limit refers to the level at which pesticide residues are quantified for reporting for the PRC. For example, in Table 3.1 it can be seen that for chlorpyrifos in pears from Argentina in 1998 the reporting limit was 0.009 mg/kg. Of the 42 samples tested only 2 were above the reporting limit and none were above the MRL. In this instance the 2 pear samples with residues greater than the RL would have had the residue of chlorpyrifos quantified accurately by the analysts. Samples which contained chlorpyrifos at levels less than the RL but at quantifiable levels would not have the values reported.

The way in which samples are analysed by the laboratories involved in the national residue monitoring programme can also affect the suitability of PRC data for use in risk assessments. The laboratories look for residues of pesticides known to be used on the particular crops, grown in the UK and overseas. The analytical method involves the use of analytical techniques that screen each sample and are capable of detecting a wide range of pesticide residues. However, the analytical methods cannot detect all known pesticides in a single screen, due to the properties of the pesticide active ingredient. Factors such as polarity, volatility and thermal lability affect the suitability for use with liquid chromatography (LC) or gas chromatography (GC) techniques.

It is not always possible to identify all the pesticides in a food sample, and it is possible for samples of produce containing non-approved pesticides to pass through the surveillance programme without detection. To combat this, the EU has a rapid alert system in place that allows Member States to inform one another if pesticide residues are found at elevated levels, or are found in food products where no approval exists.

Table 3.1 Example of the summarised data available for residues of chlorpyrifos (from CSL database)

Residue	Country of origin	Commodity	Year	Reporting limit (mg/kg)	No of samples tested	No of samples above RL	No of samples above UK MRL (at that time)
Chlorpyrifos	Argentina	Kumquats	2002	0.03	1	1	0
Chlorpyrifos	Argentina	Mandarins	2001	0.05	7	2	0
Chlorpyrifos	Argentina	Pears	1998	0.009	42	2	0
Chlorpyrifos	Argentina	Pears	1999	0.009	34	1	0
Chlorpyrifos	Australia	Apples	1997	0.01	2	1	0
Chlorpyrifos	Australia	Apples	2000	0.01	4	2	0
Chlorpyrifos	Australia	Apples	2001	0.01	2	1	0
Chlorpyrifos	Belize	Bananas	1996	0.02	1	1	0
Chlorpyrifos	Brazil	Apples	1998	0.05	2	1	0
Chlorpyrifos	Brazil	Apples	1999	0.01	1	1	0
Chlorpyrifos	Brazil	Apples	2000	0.01	3	1	0
Chlorpyrifos	Brazil	Apples	2003	0.01	3	2	0
Chlorpyrifos	Canada	Carrot	2002	0.004	28	13	0
Chlorpyrifos	Canada	Peanut butter	2000	0.003	5	2	0
Chlorpyrifos	Chile	Apples	1997	0.01	4	1	0
Chlorpyrifos	Chile	Apples	1999	0.003	7	4	0
Chlorpyrifos	Chile	Apples	1999	0.01	4	1	0
Chlorpyrifos	Chile	Apples	2002	0.004	19	1	0
Chlorpyrifos	Chile	Apples	2002	0.01	13	1	0
Chlorpyrifos	Chile	Asparagus	2002	0.004	13	1	0
Chlorpyrifos	Chile	Grapes	2000	0.009	291	64	0
Chlorpyrifos	Chile	Grapes	2001	0.009	705	44	0
Chlorpyrifos	Chile	Grapes	2002	0.05	11	1	0
Chlorpyrifos	Chile	Grapes	2003	0.02	12	3	0
Chlorpyrifos	Chile	Mandarins	2001	0.05	4	1	0

3.2 SEGREGATION OF DATA BY PESTICIDE, COMMODITY TYPE AND ORIGIN

An example of the data as collated is given in Table 3.2 This table shows information for the residues of chlorpyrifos in apples for the following categories:

- Sample identifier;
- Report year;
- Commodity;
- Description;
- Obtained From;
- Origin;
- Pesticide Code;
- Pesticide;
- Value;
- RL;
- MRL.

In this case, the source (usually a supermarket name) has not been shown, to avoid any erroneous conclusions being drawn from showing a small sample of the data.

These data were made available in Excel spreadsheets, allowing sorting for each of the selected pesticides, commodity type and origin.

Table 3.2 Example of the data available for residues of chlorpyrifos in apples (from PSD database)

Sample ID	Report Year	Commodity	Description	Origin	Pesticide Code	Pesiticide	Value	Reporting Limit	MRL
0403/1999	1999	APPLES	Variety: Golden Delicious	France	CPF	chlorpyrifos	0	0.01	0.5
0404/1999	1999	APPLES	Variety: Braeburn Class 1	France	CPF	chlorpyrifos	0	0.01	0.5
0661/1999	1999	APPLES	Class II Variety: Golden Delicious	Italy	CPF	chlorpyrifos	0	0.01	0.5
0662/1999	1999	APPLES	Class I Variety: Empire	USA	CPF	chlorpyrifos	0	0.01	0.5
0663/1999	1999	APPLES	Class I Variety: Red Delicious	USA	CPF	chlorpyrifos	0	0.01	0.5
0693/1999	1999	APPLES	Class II Variety: Empire	USA	CPF	chlorpyrifos	0	0.01	0.5
0694/1999	1999	APPLES	Class I Variety: Royal Gala	Chile	CPF	chlorpyrifos	0.03	0.01	0.5
0695/1999	1999	APPLES	Variety: Red Delicious	USA	CPF	chlorpyrifos	0	0.01	0.5
0735/1999	1999	APPLES	Variety: Golden Delicious	Unknown	CPF	chlorpyrifos	0	0.01	0.5
0736/1999	1999	APPLES	Variety: Royal Gala	UK	CPF	chlorpyrifos	0	0.01	0.5
0737/1999	1999	APPLES	Variety: Washington Red Delicious	USA	CPF	chlorpyrifos	0	0.01	0.5
0773/1999	1999	APPLES	Class I Variety: Empire	USA	CPF	chlorpyrifos	0	0.01	0.5
0774/1999	1999	APPLES	Class I Variety: Jonagold	UK	CPF	chlorpyrifos	0	0.01	0.5
0775/1999	1999	APPLES	Class 1 Idared	UK	CPF	chlorpyrifos	0	0.01	0.5
0810/1999	1999	APPLES	Class I Variety: Cox	New Zealand	CPF	chlorpyrifos	0.03	0.01	0.5
0811/1999	1999	APPLES	Variety: Golden Delicious	South Africa	CPF	chlorpyrifos	0	0.01	0.5
0812/1999	1999	APPLES	Variety: Granny Smiths	Unknown	CPF	chlorpyrifos	0	0.01	0.5
0848/1999	1999	APPLES	Class I Variety: Golden Delicious	South Africa	CPF	chlorpyrifos	0.1	0.01	0.5
0849/1999	1999	APPLES	Apples Variety: Granny Smiths	UK	CPF	chlorpyrifos	0	0.01	0.5
0850/1999	1999	APPLES	Apples	USA	CPF	chlorpyrifos	0	0.01	0.5
0974/1999	1999	APPLES	Class I Variety: Granny Smiths	Chile	CPF	chlorpyrifos	0	0.01	0.5
0975/1999	1999	APPLES	Class I Variety: Limousin Golden	France	CPF	chlorpyrifos	0	0.01	0.5
0976/1999	1999	APPLES	Class I Variety: Gala	Brazil	CPF	chlorpyrifos	0.02	0.01	0.5

3.3 HOW TO ESTIMATE THE DISTRIBUTION OF DATA BELOW THE REPORTING LIMIT

The majority of data that are available from the residue monitoring programme fall into the category "below reporting limit". A number of approaches have been considered to deal with the problem of how to attribute values to these data. It is clear that any approach that results in a value between zero and RL being assigned could greatly influence the result of the risk assessment, and may not take into account the probability that a particular pesticide was used on the crop. Use of probabilistic methods is one approach, but this still requires data for the distribution of values, which are not available from the PRC. Assuming particular distributions for the data between zero and RL will result in uncertainty factors in any model outputs.

The approach used for the residues of pesticides is based on data from the Pesticide Usage Survey in the UK. This dataset has comprehensive data on the pesticides used on each crop, identifying the time of year that the crop was treated and the amount of pesticide that was used. In the UK this data is generated for PSD, and provides detailed information on the use of pesticides, to pick up trends in overall use and specific uses on crops and in regions of the UK.

Much of the pesticide usage data comes from stratified arable and horticultural surveys. A recent arable survey with a smaller sample size than normal (402 farms rather than 950) had a standard error (%) for factors occurring on most farms ranging from 1.47 to 5.75 by farm size group and 0.88 to 6.58 by region. Most arable surveys, being larger, would be expected to have lower standard errors. For arable surveys approximately 4% of the area grown is sampled, so in the horticultural sector, where 25-33% of the area grown is sampled, a much higher level of accuracy in the data is expected.

Using these data it is possible to identify the proportion of the UK area for each crop treated with a particular pesticide, and where appropriate the number of times the crop has been treated with the same pesticide. Using information on the area treated in each case, it is possible to estimate the proportion of the national crop that has not been treated with that same pesticide. Therefore it is possible to take into account the use of each of the selected pesticides on each crop. For example, if the pesticide was not used on a particular crop, then the data that have been reported as less than the RL in the residue monitoring are likely to be zero. Similarly, in cases where 25% of the crop has been treated, there is some justification for assuming that 75% of the less that RL values would be zero. The method for assigning the residue level to the non-zero proportion of the crop is described later (Section 5.3). We realise that the assumption that a proportion of the crop is not contaminated with pesticide on the basis of the proportion of the total crop sprayed may underestimate the amount of residues in food because of atmospheric transportation of pesticides from regions where spraying had taken place to other areas, but we consider that this spread of contamination would produce negligable levels of contamination.

The data for areas of the UK treated with the selected pesticides are shown in Table 3.4 for orchards and soft fruit. Pesticides that are not included in the list were not used on any of the crops in the table. Using data for the number of times a crop has been treated provides an indication of how the residues are likely to be distributed between true zero and the RL.

The US EPA employs data for pesticide usage to estimate the proportion of home grown produce likely to have been treated with each pesticide, in a similar way to that used in this report. For imported produce, the EPA has started to use a probabilistic approach to estimate values <LOD in dietary risk assessments. In the UK, risk assessments are based on data from the residue field studies, submitted to regulatory authorities as part of the data package. Normally the highest value from these field studies is used to assess the risk by comparing with ADI and ARfD values, based on the food consumption survey data. For aggregate exposure,

two food commodities with typically high residues (such as apples and pears) are considered in the risk assessment. Discussions are taking place to consider the development of probabilistic methods for dietary risk assessment.

Table 3.3 Number of times (national average) crops treated with selected pesticides

Produce	Aldicarb	Chlorpyrifos	Cypermethrin	Dichlorvos	Dimethoate	Glyphosate	Malathion	Pirimicarb	Simazine	Toclofos-Methyl	Triadimenol
Beans			1.3			1.2		1.2	1.0		
Beet	1.0		1.1		1.0	1.2		1.2			
Linseed			1.1		1.0	1.5					
Oats		1.0	1.1			1.2					
Peas			1.2			1.4		1.2			
Potatoes seed	1.0		4.0			1.0		2.9			
Potatoes ware	1.0		1.0		1.0	1.1		1.4			
Rye			1.2			1.1					
Spring barley		1.0	1.1		1.0	1.1		1.1			
Spring oilseed rape		1.0	1.7			1.5		1.0			
Triticale			1.0			1.0					
Wheat		1.0	1.2		1.0	1.1		1.0	1.0		1.0
Winter barley		1.0	1.1			1.2			1.0		
Winter oilseed rape			1.6			1.2		1.0	1.0		
Celery (protected)			1.0					1.0		1.0	
Cucumber				1.0		1.0		1.0			
Edible plants in propagation		2.0	2.1			2.0		2.0		2.1	
Fruit (protected)								1.0			
Lettuce (protected)			1.2		2.0	1.0		1.4		1.1	
Other vegetables (protected)			5.6			2.4	2.0	2.0		2.0	
Pepper				3.0		1.0	1.0	1.0			
Strawberry (protected)						1.7		1.6	1.0		
Tomato						3.0		3.0			

Table 3.4 Percentage of national crop treated with each pesticide

		Chlorpyrifos	Cypermethrin	Malathion	Methiocarb	Pirimicarb	Thiodicarb	Glyphosate	Triadimenol	Simazine
Orchards										
	Cherries	0.61%	27%			48%		71%		
	Cider apples & perry pears	35%	5.7%			4.7%		78%	13%	28%
	Culinary apples (Bramley)	95%	3.6%			6.2%		98%		36%
	Culinary apples (others)	62%	8.9%					81%		100%
	Dessert apples (Cox)	93%	6.8%			13%		92%		23%
	Dessert apples (others)	94%				7.5%		99%		26%
	Other top fruit (incl. nuts)	2.9%						8%		6.7%
	Pears	21%				17%		100%		33%
	Plums	50%	4.7%			31%		57%		2.1%
	Hops		2.1%		1.8%			41%		58%
Soft fruit										
	Blackberry	48%	1.2%	0.0%	0.91%	4.1%		2.8%		24%
	Blackcurrant - market	11%	0.25%			1.7%		7.1%	0.39%	25%
	Blackcurrant - processed	33%	3.9%			31%		29%		56%
	Gooseberry	23%	4.2%			1.4%		8.5%		20%
	Hybridberry	23%	0.37%	1.1%		1.3%		18.3%		15%
	Raspberry	56%	0.42%	0.0%	0.85%	19%		5.1%		43%
	Red/white currant	14%	0.0%			1.3%		3.5%		12%
	Strawberry	45%	1.6%	0.32%	24%	16%	0.42%	9.2%		50%
	Vine							76%		2.8%

3.4 POSSIBLE ERRORS WITH THE OVERSEAS PRODUCE AND LACK OF PESTICIDE USAGE INFORMATION

Using the trend of residue data in the UK, i.e. the occurrence of data for <RL for particular food produce, it is possible to extrapolate to the food that is imported into the UK. There is no detailed pesticide usage data for overseas crops, although this is being rectified as part of the requirements for the Common Acceptance Directive (EEC 91/414). At this stage, in the absence of such pesticide usage data, we believe the trend of usage and appearance of residues in UK produce provides the most appropriate way of estimating residues below the RL.

This approach is useful where similar pesticides are used on the crops in question, as is most likely to occur in the EU where pesticides only on the "Annex I" listing should be used.

For non-EU produce there is likely to be a wider range of pesticide available to growers, and so occur as residues. However the trend of pesticide usage could be expected to be the same where similar pest and diseases occur. The critical issues for pesticide residues are the timing of use, and the persistency of the pesticide. Pesticides used close to harvest or post harvest are the ones that tend to occur as detectable residues in the monitoring programme.

In this case, where we have looked at the residues of similar compounds, using data for pesticide usage on the crop will give the best indication of the likelihood of pesticide residues being present. A probabilistic approach would need to have input criteria, such as expected use of pesticide to be able to accurately estimate the distribution of residues which are reported as below the reporting limit in the residue monitoring programme in the UK.

4 COLLATION OF DATA FOR DIETARY INTAKE

Objective 04	Collect available information about British food consumption habits in relation to food categories identified above. Add information to database.

4.1 NATIONAL DIET AND NUTRITION SURVEY

The information for the food consumption of the UK population was taken from Volume 5 of the National Diet and Nutrition Survey (NDNS) published in December 2004. This data has detailed information for the individuals taking part on the survey (a national sample of adults aged 19 to 64 years). In addition to food consumption it has data for nutrient intake, nutritional status, obesity, blood pressure and physical activity.

The data have been collated to allow factors related to the region in which they are living and, types of employment and income.

The regions are based on the Government standard regions as follows:

1. Scotland
2. Northern
    - North
    - Yorkshire and Humberside
    - North West
3. Central, South West and Wales
    - East Midlands
    - West Midlands
    - East Anglia
    - South West
    - Wales
4. London and South East
    - London
    - South East

The social class assignment was based on the Registrar General's Standard Occupational Classification, TSO (2001). Social class was ascribed on the basis of the occupation of the household reference person. As some of these grouping contained insufficient numbers for adequate statistical analysis the standard categories for social class were further grouped as follows:

Non-manual: professional, managerial and technical professions; Social Class IIINM skilled non-manual occupations.
Manual: Social Class IIIM – skilled manual occupations; Social Classes IV and V – unskilled occupations.
Unclassified: Those who were not allocated a social class either because their job was inadequately described, they were a member of the armed forces, had never worked, or where it was not known whether they had ever worked.

4.2 DESCRIPTION OF THE INFORMATION PROVIDED FOR NATIONAL DIET

In addition to the background information relating to the survey described in Section 4.1, there are details of the daily intake of food and drink for each individual, including how much food was prepared, how it was cooked, and how much was left after the meal. Individuals therefore had to record details of ingredients that were used during cooking, to determine the weight of the different food types that had been consumed

A list of food codes was assigned by the original researchers for each of the surveys, although care was needed in using these codes as there were some changes between surveys 4 and 5. In Table 4.1 these food-codes and other data relating to the amount eaten and demographic information can be seen for an extract from the survey data.

Table 4.1 Example of output from the diet survey

Survey ID	Subject ID	Sex	Region	Benefit	Hohscln	Age	Weight (kg)	Height (cm)	Id	Day No.	Plate No.	Item No.	Food code	Brand	Weight Eaten (g)	Food Group Code	Food item
2	101	1	1	2	3	6	22.7	117.45	568	5	3	1	1875	-9	90	66	Chips frozen, straight cut, fried in ps oil or marg
2	101	1	1	2	3	6	22.7	117.45	776	6	1	2	7775	-9	8	39	Reduced fat spread (60%) not polyunsaturated not low in trans not olive oil based
2	101	1	1	2	3	6	22.7	117.45	777	6	1	3	2215	-9	13	77	Jam with edible seeds purchased
2	101	1	1	2	3	6	22.7	117.45	778	6	2	1	2308	-9	1	96	Coffee instant powder or granules
2	101	1	1	2	3	6	22.7	117.45	779	6	2	2	2205	-9	15	76	Sugar, white
2	101	1	1	2	3	6	22.7	117.45	780	6	2	3	5103	-9	153	96	Water as a diluent for instant coffee
2	101	1	1	2	3	6	22.7	117.45	781	6	2	4	603	-9	60	17	Milk whole pasteurised winter
2	101	1	1	2	3	6	22.7	117.45	782	6	3	1	761	-9	109	28	Egg fried in pufa
2	101	1	1	2	3	6	22.7	117.45	783	6	4	1	1900	-9	25	79	Potato crisps
2	101	1	1	2	3	6	22.7	117.45	784	6	5	1	1952	-9	164	70	Apples eating raw flesh & skin only
2	101	1	1	2	3	6	22.7	117.45	785	6	6	1	7894	413	296	111	Cola cherry cola canned not low calorie
2	101	1	1	2	3	6	22.7	117.45	786	6	7	1	7894	413	295	111	Cola cherry cola canned not low calorie
2	101	1	1	2	3	6	22.7	117.45	787	6	8	1	204	-9	35	10	Cocoa pops cocoa krispies
2	101	1	1	2	3	6	22.7	117.45	788	6	8	2	603	-9	96	17	Milk whole pasteurised winter
2	101	1	1	2	3	6	22.7	117.45	789	6	9	1	308	-9	1	13	Sponge chocolate marg not pufa h/made butter icing
2	101	1	1	2	3	6	22.7	117.45	790	6	9	2	2205	-9	14	76	Sugar, white

4.3 OVERCOMING PROBLEMS WITH USING DATA IN THIS WAY

One of the main problems with using this type of information relates to the consumption of processed food, partly from the composition of the food items and partly because of the effects that processing may have on the presence of residues. Access to some of the recipe information is dealt with in Section 4.4 in more detail.

Although it is possible to have information for the pesticides residue levels in apples from a variety of different origins, this cannot be matched to the data from the diet survey. So for example, it is not possible to take account of whether a person has eaten an apple from the UK or from South Africa or Chile. Coding of these food items has necessarily had to be done at the lowest common level, which in this case is “apples”.

Access to recipe information to allow residues in constituents to be estimated was obtained from the FSA through CSL.

4.4 DEFAULT VALUES FOR FOOD PROCESSING

There are few reliable data published for the effect of food processing on the residues of pesticides in food. Although limited studies have been carried out by the CSL on cooking of pizzas for example, these data are not adequate to use in this study, as they involved too few pesticides and food item types. For the risk assessment of dietary exposure the Pesticides Safety Directorate (PSD) use a transfer factor of one, which implies that they consider the whole residue in the food is available after processing and cooking. This would appear to be the most appropriate approach to transfer factors, by taking what is the worst case and assuming no degradation of residues. There are cases where the residues can be concentrated during processing, which is due to the loss of water from the fruit or vegetable, or concentration of juice extracts. In such cases the processing factors can be estimated from the changes in weight that occur. This is most common with the processing of baby foods and with dried fruits.

In rare instances the effect of food processing can actually result in an increase in residues. The most notable case is with the dithiocarbamate fungicides. For crops treated with the pesticide Mancozeb the occurrence of residues of ethylenethiourea (ETU) can increase after cooking. Watts et al. (1974) reported an increase in ETU after cooking spinach fortified with mancozeb. The amount of ETU formed by cooking was about 20% of the weight of mancozeb originally added. Newsome and Laver (1973) reported similar results after cooking spinach, potatoes and carrots containing residues of mancozeb and metiram.

As indicated in Section 3.1 the residue data is generated on the whole food item, so includes residues in parts of the food not eaten. For example in the case of bananas and oranges, the peel is not usually eaten, whereas in the case of apples and pears the peel can be eaten or discarded. As with the transfer factors during cooking there are insufficient data available for the separate amounts of pesticide residues in the flesh and peel of fruit and vegetables.

For the purposes of the modelling we consider that it would be appropriate to assume that processing has some variable effectiveness in removing contamination, i.e. by assuming that the processing can reduce the dietary exposure between zero and 100%

5 PRODUCTION OF STUDY DATABASE FOR PESTICIDE RESIDUES AND FOOD INTAKE

Objective 02	Construct a database to hold information on pesticide use and exposure determinants.

This section describes the work that was done to collate the pesticide residue data and dietary intake information used for this study. The details of the sources of these are more fully described in chapters three and four, respectively. After investigating the most appropriate available sources of information required for the intake model and considering the elements that would need to be imputed or estimated through the absence of real data, a database was designed and implemented to process and link four main datasets and several other accessory datasets and coding lists.

Key datasets contained information on:

- levels of pesticide residues in food commodities;
- coverage of pesticide application per selected crops;
- the consumption of food items in dietary of samples of the UK population;
- recipe data itemising the components of foods consumed in the dietary study.

1 Pesticide Residue Data:
18 Pesticides
327 food/crop commodities
(98% zero values)

2 Pesticide Crop Application Data:
720 Pesticide & Crop combinations of percentage coverage

3 NDNS Data:
Case personal, Demographics & Dietary Diary Data
3 Studies of age groups

4 NDNS food codes and ingredient codes
4612 food codes
11791 ingredients codes

These different data sets were obtained via CSL from separate sources. All had been originally collected for different purposes, with different formats, different identifiers and different coding schemes. There was therefore no inherent or natural inbuilt way to link together the residue and food data so as to be able readily to relate food consumption and pesticide intake. Therefore a large part of the work in database production was spent initially in normalising and encoding as far as possible the data into common shared formats. Then, through a combination of expert knowledge of the datasets, information from descriptive analysis, and other qualitative assessments, tasks were carried out to devise and implement common coding schemes, so that the different datasets could be related, and appropriate summary measures derived, for the purposes of modelling in this study.

5.1 PESTICIDE DATA - RESIDUES IN FOOD AND CROP APPLICATION DATA

A fuller background and description of these data are given in chapter 3. The data were handled in two major parts: residue levels in food commodities; and crop application data, which were used to impute values for large proportions of otherwise "missing" data (below RL) in the residue data files, for use by the ingestion model. The handling and processing of each of these for the database is described in detail below.

5.2 PESTICIDE RESIDUE LEVELS IN FOOD COMMODITIES

Of the twenty-one selected pesticides data files for 18 different pesticides were ultimately supplied by CSL. These were uploaded to the database and normalised to standardise for contents, variable names and formats, and combined into one large data table. They were then analysed and screened with summary frequencies and cross tabulations to discern the overall coverage (food commodity types, country of source, etc) and verify ranges and variability in reporting limits, pesticide values, etc, and to facilitate the normalisation process for identifiers, encoding and labelling. The number of records for each different pesticide represented is given in Table 5.1.

Table 5.1 Number of records of pesticide residue data available for analysis

Pesticide name	Number of records Processed
Aldicarb	4376
Bendiocarb	3652
Chlorpyrifos	14601
Cyfluthrin	5399
Cypermethrin	10934
Dimethoate	10103
Dichlorvos	6832
Ethoprophos	5537
Fosthiazate	2461
Glyphosate	2033
Malathion	12660
Methiocarb	2044
Oxamyl	1501
Pirimicarb	9065
Pirimiphos-methyl	12750
Thiodicarb	308
Tolclofos-methyl	7473
Triadimenol	1665
Total	113394

Within all pesticides, there were records for 327 different food commodities that were sampled. These were examined and in order to move towards a more unified and compact coding scheme, (and one that could be related to the dietary data to be used in the study) it was found that many of these different items could be grouped into same basic commodity, so that they were collapsed into Residue Commodity Groups. A careful clerical collation exercise was carried out to create a linked-list coding scheme to allow these equivalences to be encoded and used in the database. Examples of this coding for apples and bananas may be seen in Table 5.2. Seven variations on Apple item residue commodities were coded down (collapsed) to one Apple Commodity Group, and similarly, seven banana item commodities were collapsed down to one Banana Commodity Group. After this process the 327 Residue Commodity Items were allocated to 138 Residue Commodity Groups.

Table 5.2 Examples of the coding for apples and bananas

Residue Commodity ID	Residue Commodity	Residue Commodity Group Code	Residue Commodity Group Name
31	APPLES PART 2	1	APPLE
30	APPLES PART 1	1	APPLE
29	APPLES	1	APPLE
28	APPLE SCHOOL 8	1	APPLE
27	APPLE SCHOOL 7	1	APPLE
26	APPLE SCHOOL 4	1	APPLE
25	APPLE SCHOOL 3	1	APPLE
229	PLANTAIN/GREEN BANANAS	8	BANANA
42	BANANA SCHOOL 3	8	BANANA
43	BANANA SCHOOL 7	8	BANANA
44	BANANA SCHOOL 8	8	BANANA
45	BANANAS PART 1	8	BANANA
256	SCHOOL BANANA 4	8	BANANA
46	BANANAS PART 2	8	BANANA

5.3 ESTIMATING THE DISTRIBUTION OF DATA BELOW THE PESTICIDE RESIDUES REPORTING LIMIT

As noted in chapter 3, the majority of the pesticide residue data records contain no actual values for residue level values: Records do specify the quantity of pesticide (mg/kg) for each sample where the level was above the reporting limit, but most records are below the reporting limit, with the data value presented as a zero (0). In reality these values would be a mixture of values below the limit of Quantification (<LOQ) and below the reporting limit (<RL), values that were not contained in the actual data files. In fact 98.8% of the records contained zero values.

For the modeling process in this project this absence of values represented a large area of missing data that would not in fact actually be zero, and a way of estimating these lower values, below the reporting limit was required. In exploratory discussions between CSL and IOM it was agreed that there was no absolute method to produce these estimates. However, based upon the Pesticide Usage Survey, as described in Chapter 3, CSL provided estimates for the percentage of the UK fruit and vegetable crops treated with each individual pesticide. By using these figures the proportion of the crop not treated with a particular could be estimated, and from this the proportion of values reported as below reporting limit that could be assumed to be zero. The remaining values were assumed to have a distribution between zero and the reporting limit. Relating incurred residues to the use of the pesticide on a particular crop allows residues in particular fresh food commodity to be estimated using best available information.

Data files containing the estimated percentage of the various crops were processed. In all, 1,887 records were received for 18 pesticides combined with 109 different crops. Similar to the original residue commodities it was necessary to aggregate and re-code the crop treatment data to give equivalence to the pesticide residue commodity groups, so that relations and calculations between the datasets could be made. For example, for chlorpyriphos treatment six different

cabbage types were coded to Cabbage, and the lowest minimum and highest maximum percentages treated were taken to represent the lower and upper range of percentage treatment for that group. After this processing this provided crop coverage data for 720 different crop and pesticide applications in all, including null applications where the pesticide was not estimated to have been used on a particular crop.

It was agreed that estimated (to provide non-zero) values within the range of 0 to RL would then be imputed (by the model, external to the database) for the same proportion (percentage) of the overall records for a pesticide/crop combination as were estimated to have been treated with a given pesticide. Conversely, the number of records with zero values would be proportionate to the percentage not pesticide treated. For modelling purposes this was done for both the minimum and maximum treatment percentages supplied by CSL, so that both, or a range of estimates between, could be used in the modelling process as required. The calculation was expressed as follows;

> New count of records with non-zero values =
>
> Total count of records - (Total Count of records / 100) * (100 – Percentage Sprayed)
>
> For example on this basis, for pesticide "A" used on cabbages where there were 175 data records of which 166 were zero, and the max crop coverage was 36%:
>
> Number of pesticide residue records for cabbage: 175
> Number of zero value records: 166
> Number of records with non-zero (<>0) values: 9
> Max percentage crop sprayed: 36%
>
> New count of records with <>0 values =
>
> 175 – ((175/100) * (100 – 36)) = 63
>
> No of records that would have <>0 values based on 36%: 63
>
> New no of O values: (175-63) = 112
> Original (<>0) values: 9
> New values to impute: (63-9) = 54

In this example, when used by the ingestion model pesticide residue values were allocated to 54 of the previously zero value records. Equivalent calculations are carried out for minimum percentages sprayed.

Based upon this, the database calculated the figures required for the intake model to take account of the percentage sprayed. These figures, for all combinations of crop and pesticides, for maximum and minimum pesticide application, along with the frequency distribution of the original actual values, and appropriate reporting limits as parameters, were output from the data base in a spreadsheet form for input to the ingestion model.

5.4 FOOD INTAKE DATA

After an initial quantitative and qualitative assessment of possible sources of information on dietary intake and nutrition in the UK, and the examination of test datasets, the actual data on food intake was sourced from the National Diet and Nutrition Survey (NDNS) via CSL. The background to this series of studies is described more fully in chapter 4.

The first main dataset used was from volume 5 of the National Diet and Nutrition Survey, (NDNS), national sample of adults aged 19 to 64 years, published in December 2004 (The Adult Study). This was the principal dataset of interest but after initial routines and procedures for data coding, processing and programming were established for the study database, further data were also uploaded from the related National Diet and Nutrition Survey, young people aged 4 to 18 years, published 2000 (the Youth Study), and the National Diet, Nutrition and Dental Survey of Children Aged 1 1/2 to 4 1/2 Years, 1992-1993, published 1995 (The Infant Study).

The three main data components to be used from each these studies were:

- basic anonymised personal and demographic information relating to the characteristics of the cases (individuals), their households and relating coding schemes;
- detailed dietary diaries of food intake recorded by or on behalf of the individuals;
- food item coding information and recipe data identifying the individual components of the food items recorded in the food intake diaries.

In addition, a great deal of other nutritional and other health information (food intake, nutrition, health, etc) related to cases, or at several levels of aggregation, was available from these studies, and in the published statistics arising from the NDNS. The latter helped to inform the design of the present study. Although there was not the scope to employ some of these other quantitative measures directly in this study, they would provide a rich source of additional material and more detailed analysis possibilities in future studies.

Each study provided substantial datasets to be uploaded to the study database (Table 5.3). Each dataset was quantitatively and qualitatively assessed and summary statistics and tabulations examined to verify contents and suitability for use in the study. Files from each study were different in layout and format, had different variable names used, and these all had to be accommodated and normalised. Due to their very large size, and the results of queries that commonly produced more than 500,000 large records at a time, the study database had to be split into several separate physical files and linked into one large virtual database.

Table 5.3 Number of subjects and records in database

Study	Subjects	Food diary records	Number of different food items
Adult	2251	312631	4612
Youth	2127	216470	4238
Infant	1859	145047	2614

The information about each case, with a subset of personal and demographic information was as follows:

Caseid - numeric subject identifier
Startdat – Date subject started participation
Regsumm – Summary regional identifier
Respage – Respondents age
Ragegp - Age group
Scresp - Social class of respondent
Vegi - Vegetarian?
Ethnic – Ethnic group

Each subject kept a complete food diary for up to seven days, and had an average (for adults) of 25 food records per day. Each record itemised a food item consumed, with several per meal. The record held the following details:

Caseid – numeric subject identifier
Dayno - in the series of seven
Cntnrno – serial number for meal or "consumption event"
Itemno – item number within the meal
Homegrow – was it home grown commodity
Wtserved – the weight served
Leftind – any leftovers
Estimate – weighed or estimated
Foodcode – code for the food item (apple, beef steak, chicken curry, etc)
Brand – brand, if purchased food product, where known/noted
Spillage – any losses
Wteaten – actual weight eaten of food item
Dilute - for drinks etc was it dilute?

Example records for food diaries are shown in chapter 4.

In all there were 4612 unique food items from the three studies (the adult study, being the first processed was used as the "master"), each being identified by the food code from the NDNS. Although in practice many of these items were very close to being the same thing, they were expressed in the data files somewhat differently, or were a different brand, with a differing recipe.

Each food item could be made up of one or more constituent components or ingredients. Some items such as "fresh apple" would have just one ingredient – (Apple – raw), unprepared or uncooked, and many, such as apple crumble (not wholemeal), comprise several ingredients (Apple – raw, sugar – white, plain flour, margarine – block, cinnamon) and are prepared and cooked.

To enable this study to look at the individual food items that may contain pesticides we required to identify likely candidate fresh food items that related to the pesticide residue data levels in the database. A list of ingredients used in the creation and analysis of the NDNS was made available via CSL. In this file there were up to 11791 "parent" food items that consisted of 1 or more of "child" ingredients. Each of the child ingredients had a number representing the ingredient's percentage of the whole item. In all the 11791 parent food items were composed from 60572 ingredient records.

In the study database it was possible, with well-designed tables and queries, to use the food-codes in the diary data, to link to the individual ingredients, so that each food item (e.g. apple crumble), could be expanded out into its individual ingredients (apples, flour, margarine, etc). Further, by knowing the weight of the food item (or portion) in the diary, and the percentage of the ingredient from the ingredients table, an estimate of the weight of each single ingredient for that item, and collectively the meal, could be made. Queries to produce results of over 500,000 records of data for all diary records, for each NDNS database were produced by the database using this method.

5.5 BUILDING THE LINKAGE BETWEEN FOOD ITEMS AND PESTICIDE RESIDUE LEVELS

In order to model pesticide ingestion it was necessary that a method was devised to relate the residue levels in the pesticide data to the food ingredient intake levels from the dietary diary data, but the codes and descriptions were not directly equivalent. As can be seen from the figures above, the coding lists for food items and their ingredients is huge. An efficient and sufficiently accurate way was needed to link Residue Commodity Group codes in the residue data, to the Food Ingredients in the food intake data, without having to individually encode each ingredient.

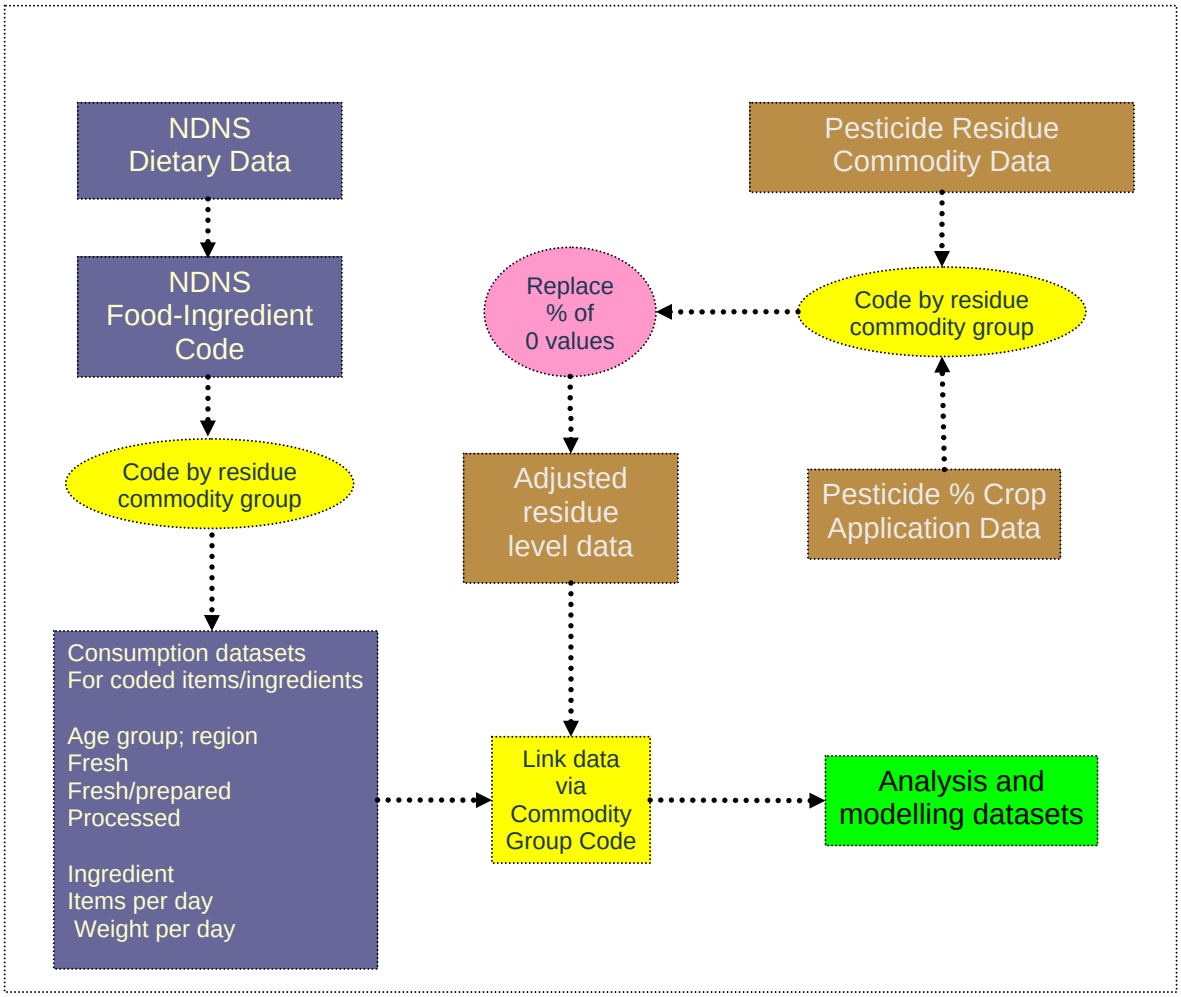
Processing the residue data had already created a coding list for Residue Commodity Group, but unfortunately these were not directly equivalent to the descriptions in the food data. However, most of the 136 residue commodity groups were individual fresh or raw products (meat, fruit, veg and other basic staples like wheat-flour, milk etc) that were separately identifiable, and not composed of a set of ingredients. For the majority of these items, it was then possible to identify an equivalent individual ingredient item, and link them together with a common code. Using the term, or fragments of terms from the Residue Commodity Group descriptions it was possible to search for equivalences between the two areas and to build a linked list of common codes that related the food ingredient items to pesticide residue items.. For example “APPLES” in the residue data were linked to 11 fresh ingredients in the food intake data.

Furthermore at the same time, this set of items was allocated a treatment code that identified it as being in one of three classes for treatment or preparation of the food item:

- Raw/Fresh - such as fresh meat or fresh fruit and vegetables (e.g. fresh unpeeled apples eating raw)
- Raw/Prepared – such as peeled or outer leaves removed (e.g. peeled apples – chopped into salad)
- Cooked/Processed – cooked, processed or treated beyond raw (e.g. tinned apple sauce)

Because there had been some changes in the ingredient coding systems used by NDNS between the three major studies, in the interests of accuracy only ingredient items that were consistent across the three studies were allocated a residue group code. This exercise identified 685 different ingredients that were given a Residue Commodity Group code (ie equivalent to the codes in the residue data) and also a treatment code. 107 different residue commodity codes occurred in those 685 items.

The overall linkage of the main datasets in this study is illustrated in the diagram below.



5.6 PROVIDING COMBINED FOOD INTAKE AND PESTICIDE BURDEN DATA FOR MODELLING

Data about Pesticide Residues could now be linked to the food consumption data, and combined with the information needed to impute non-zero pesticide values. These were output to be fed into the ingestion model. Since the actual weight of the ingredient was known from the food diary, and the concentration of pesticide it was related to was known or could be derived, then estimates of pesticide intake were now possible for a substantial subset of food items.

This food intake data were aggregated by day to give an estimate of daily pesticide intake per pesticide. Variations in preparation and several other exposure modifiers are incorporated into the model, as described in detail in chapter 7. Consideration of other factors such as variations in sex, age, vegetarianism, regional differences and other factors, could be incorporated in analysis and modelling, using the linkages available in the database.

Datasets of coded food intake, coded residue levels, and distribution information to allow the creation of imputed or adjusted pesticide levels in items via Commodity Group were provided for use by the ingestion model for each of the three NDNS studies described earlier. Data files of individual personal food consumption were first output from the database and aggregated using the software package SPSS, so that descriptive frequencies and tables could be examined prior to their full application in the mathematical model.

6 EXPOSURE SCENARIOS

Objective 05	Identify the range of occupational scenarios (i.e. operators and workers) applicable to each pesticide or veterinary medicine.
Objective 06	Estimate the number of people who may be exposed as either bystanders or neighbours. Link these data to the information on occupational exposure and enter into the database.
Objective 07	Identify the range of exposure scenarios where the identified pesticides may be used by consumers.
Objective 08	Identify data on residues of pesticides and veterinary medicines in the environment (water and soil) by region.

The purpose of this part of the study was firstly to identify the range of occupational scenarios applicable to each pesticide identified as containing one of the active ingredients of interest and the number exposed for each scenario. Secondly, the number of people who may be exposed as bystanders (people in the vicinity) when pesticides or veterinary medicines are applied) or neighbours (people living in relatively close proximity to areas where pesticides or veterinary medicines are applied) was estimated and the ways in which they might become exposed. Finally, the exposure scenarios where the identified pesticides may be used by consumers were considered. For each of the above cases: occupational; bystanders/neighbours and consumers, exposure was estimated.

6.1 OCCUPATIONAL SCENARIOS AND EXPOSURE

6.1.1 Agricultural pesticides

The main occupational use is in the agricultural sector, where pesticides may be used by farm owners, farm employees or contractors. Information on pesticide usage is collected as part of the Pesticide Usage Survey, which has a series of rolling programmes carried out by survey teams at the Central Science Laboratory (CSL) and the Scottish Agricultural Science Agency. Although such information is freely available on the web (http://pusstats.csl.gov.uk/), this was not in the format required for this study. Therefore, for each of the active ingredients of interest used in the agricultural sector (only 20 since azamethiphos is only present in veterinary medicines and biocide products), the CSL supplied information on annual usage for 2004, though it should be noted that each crop may not be surveyed in that year. This information was supplied by crop group, region, method of application and month. There were 23 crop groups: beet crops; carrots & parsnips; cereals; grassland; lettuce & other leafy salads; maize & sweetcorn; mushrooms; oilseeds, onions & leeks, other arable crops, other fodder crops; other outdoor vegetables; other root vegetables; other soft fruit; outdoor ornamental crops; peas & beans; potatoes; protected edible crops; protected ornamental crops; set aside; strawberries; top fruit & hops and vegetable brassicas. Ten regions were defined: East Midlands; Eastern; London and South East; North East; North West; South West; West Midlands and Yorkshire and the Humber, plus Scotland and Wales. The method of application was divided into two groups: “hand-held” and “other” which included boom spraying and air-assisted spraying.

Another related source of exposure in this category is seed treatment. However, this was not considered since there is insufficient information and it is thought that exposure will be relatively limited. Seed treatment is either carried out at a factory or on site using mobile seed

processors. It is not generally carried out by farmers or farm workers. It is possible that farmers may have contact with treated seed, for example during drilling, however, this again was thought to be minimal and was not considered.

Characteristics of sprayers and spraying

Spray operators can be categorised into one of three main groups: farmers whose main business is farming, but who also act as contractors on nearby farms; specialist spray contractors whose main business is pesticide spraying and contractors who offer a range of agricultural contracting services including pesticide spraying.

The following information was abstracted from "A survey of current farm sprayer practices in the United Kingom 2004"[1] and supplemented by information supplied by Garthwaite (personal communication). About 50,150 people are involved with spraying pesticides in Great Britain. There are an estimated 5,450 companies and 7,100 spray operators are employed in spray contracting. Approximately 49,100 farm owners and employees are involved in arable spraying on arable farms in the UK, although this number also includes people who also undertake contract spraying. The estimated number of farm-based spray operators fell from 60,500 in 2001 to 49,100 in 2004, an 18% reduction, reflecting both the increased use of spray contractors and the fall in the number of UK arable holdings.

The average age of spray operators is 44, with ages ranging from 18 to 77 years old. The breakdown in age by region is shown in Table 6.1.

Table 6.1 Average and range of ages of spray operators

Region	Farm based		Contractor	
	Average	Range	Average	Range
East Midlands	43	22-67	38	25-55
Eastern	46	22-76	40	22-58
London & South East	44	21-77	42	25-63
North East	46	30-60	43	26-67
North West	48	21-65	24	24-24
Scotland	44	22-69	49	36-58
South West	46	20-69	37	23-61
Wales	50	23-63	36	24-48
West Midlands	44	26-66	42	24-65
Yorkshire & the Humber	45	18-72	40	24-62

Table 6.2 shows the average number of farms sprayed per year by region for the three groups of operators.

[1]http://www.voluntaryinitiative.org.uk/_Attachments/Second%20Farm%20Application%20Practice%20Survey%20June%202005.pdf

Table 6.2 Average number of farms sprayed per year by a given operator

Region	Contractor	Employee	Owner/tenant
East Midlands	13	4	1
Eastern	21	2	2
London & South East	18	2	2
North East	18	1	1
North West	4	1	1
Scotland	27	2	2
South West	28	2	2
Wales	37	1	1
West Midlands	31	2	1
Yorkshire & the Humber	34	1	2

The greatest number of farms were sprayed by contractors, with between 4 and 37 being sprayed. There is little difference between employees and owners/tenants who sprayed between one and four farms.

Table 6.3 shows the average number of days spraying for each of the above groups by region.

Table 6.3 Average number of days spraying per year by a given operator

Region	Farm based	Contractors
East Midlands	39	75
Eastern	45	185
London & South East	40	127
North East	26	45
North West	18	
Scotland	24	137
South West	25	151
Wales	13	260 *
West Midlands	30	107
Yorkshire & the Humber	35	88
National average	35	135

* This is based on only one operator sampled and is unlikely to be representative, therefore the national average was used.

When the total number of farms sprayed by an operator employed by a spray contractor is taken into account the average number of spraying days or part-days was 135 per year.

Information on the number of holdings and the size range was obtained for regions in England from the June Agricultural Survey 2004[2] and is summarised in Table 6.4. No such figures exist for Scotland and Wales.

[2] http://www.defra.gov.uk/esg/work_htm/publications/cs/farmstats_web/2_SURVEY_DATA_SEARCH/COMPLETE_DATASETS/regional_level_datasets.htm

Table 6.4 Number of holdings in England by size

Region	Size (hectare)				
	<5	5 - <20	20 - < 50	50 - <100	≥100
East Midlands	8078	3646	2804	2319	3554
Eastern	9647	3853	2649	2167	4337
London & South East	11018	5678	3310	2161	3318
North East	2281	997	717	866	1660
North West	9861	3993	3242	3033	2489
South West	21518	9670	6748	5484	5181
West Midlands	10907	5153	3497	2883	2874
Yorkshire & the Humber	8815	3820	2734	2571	3343

6.1.2 Dermal exposure for spraying operators

Estimates of dermal exposure estimates were based on data in the EUROPOEM database[3]. This database contains information on the exposure of sprayers, bystanders and post application workers. For spraying, information on potential and actual exposure related to mixing/loading, application and mixing/loading/application related to different scenarios is recorded. For the purposes of this project, actual exposure data were used to estimate exposure for sprayers. No distinction was made between mixing, loading and application, i.e. we used aggregate data for all phases of use. Also, no account was taken of the physical form of the pesticide. Information on actual exposure extracted from the EUROPOEM database for sprayers is shown in Table 6.5.

Table 6.5 Dermal exposure (mg/kg active substance) – summary statistics

	Hand held		Other	
	ADE	AHE	ADE	AHE
Minimum	0.06	0.01	0.0001	0.0002
Median	1.82	0.09	0.03	0.02
Maximum	1364.80	71.51	2.11	18.59

where ADE is actual dermal exposure (mg/kg active substance) and AHE is actual hand exposure (mg/kg active substance). ADE and AHE were summed and re-expressed as a proportion of the amount being sprayed (k_f) as shown in Table 6.6.

Table 6.6 Proportion of pesticide sprayed which is deposited on skin (k_f)

	Hand held	Other
Minimum	1.60×10^{-7}	3.00×10^{-10}
Median	1.91×10^{-6}	5.00×10^{-8}
Maximum	1.44×10^{-3}	2.07×10^{-5}

6.1.3 Veterinary pesticides

Using the Veterinary Medicines Directorate website[4] the "Electronic Summary of Product Characteristics for relevant products" was searched for information about the active ingredients of interest for this project. Of the 1,834 products listed on this site, only seven contained any of the active ingredients of interest. Six veterinary products contained cypermethrin and one

[3] http://europoem.csl.gov.uk/
[4] http://www.vmd.gov.uk/

contained azemethiphos. Two of the cypermethrin products were used for the treatment of sheep, two for horses and ponies, one for cattle and one for salmon (the azemethiophos containing product). The marketing authorisations for cypermethrin-based sheep dip products were suspended on 21st February 2006. However, the recall of products supplied to agricultural merchants and other authorised retailers before this date was not required and so it was still legal to purchase and use these stocks. However, since these products are being phased out, they are unlikely to contribute significantly to exposure. Similarly, ear tags which are typically applied to the ear of cattle once per season to protect against flies, are considered unlikely to contribute significantly to exposure.

Over 95% of the UK's farmed salmon is produced in Scotland[5]. In 2000 there were over 530 registered salmon farming businesses in Scotland[6] and there were 1,711 full and part time employees involved in fish farming[7]. As part of a study into the ecological effects of sea lice medicines in Scottish sea lochs, the Scottish Association for Marine Science carried out a measurement programme at four active salmon farms[8]. The use of veterinary medicines from 1999 to 2004 was reported. Since the farms chosen were thought to be representative, it is reasonable to assume that the information on veterinary medicines can be generalised. The number of applications per year for one product (Electis) ranged from 0 to 10, median 1 and for the other (Salamoson), the range was 0 to 4, with a median of zero. All four farms used Electis, whereas only three of the four used Salamoson. The amount of cypermethrin used per application ranged from 0.43 to 18 litre, with a median 8 litre and the amount of azamethiphos ranged from 200 to 2880 g, median 1520 g.

These researchers reported that the use of azamethiphos for the control of sea lice on salmon farms was limited and will probably continue to decline as the use of in-feed treatments increased and that it was most often used in conjunction with cypermethrin treatments. This is supported by the figures quoted in their report.

It is possible that those working in industries associated with fish farming, for example, processors and suppliers, may be potentially exposed, however, it is not likely to be significant.

No information on the overall pattern of use or the frequency of use of these veterinary medicines or potential exposure of salmon fish farmers was available.

Although veterinary medicines are widely used in the UK there is no information on detailed use and frequency for individual veterinary medicines. Further usage may vary according to the fly or lice season. As such it is very difficult to estimate the number of individuals who might be exposed to any particular scenario.

6.1.4 Non-agricultural pesticides and biocides

Seven of the active ingredients of interest are listed as being notified in the Third Review Regulation (EC No 1048/2005) of the biocides review programme[9]. These are listed in Table 6.7, along with the product type and use.

[5] http://business.scotsman.com/topics.cfm?tid=1080&id=1502662006
[6] http://www.sac.ac.uk/consultancy/farmdiversification/database/fishfarming/salmon
[7] http://www.scotland.gov.uk/Publications/2004/03/19038/34138
[8] http://www.sams.ac.uk/research/coastal%20imapcts/ecol.htm
[9] http://ecb.jrc.it/legislation/2005R1048EC.pdf

Table 6.7 Active ingredients used in biocidal products

Active ingredient	Product type	Use
Azamethiphos	Veterinary hygiene biocidal products	Professional
Bendiocarb	Insectides, acaracides and other arthropods	Professional
		Non professional
Chlorpyrifos	Insectides, acaracides and other arthropods	Professional
		Non-professional
Cypermethrin	Wood preservatives	Professional
		Non professional
	Fibre, leather, rubber and polymerised materials preservatives	Professional
	Insectides, acaracides and other arthropods	Professional
		Non-professional
Dichlorvos	Insectides, acaracides and other arthropods	Professional
		Non-professional
Malathion	Insectides, acaracides and other arthropods	Professional
		Non-professional
Pirimiphos-methyl	Insectides, acaracides and other arthropods	Professional
		Non-professional

The use of azamethiphos has been considered under veterinary medicines (section 4.1.2). The remaining six active ingredients are used in pest control and both professional and non-professional use is possible. Cypermethrin is also used as a preservative for wood and fibre, leather, rubber and polymerised materials.

The HSE lists products registered with its Biocides & Pesticides Unit as antifouling products, aquatic algicides & molluscicides, biocidal paints, bird stupefying baits, insect repellents, insecticides (including insecticidal paints), rodenticides, surface biocides, wood preservatives and wood treatments. Each of the 13 sections was searched for products containing the active ingredients of interest. Products containing the active ingredients of interest were found under Insecticides[10] and Wood Preservatives[11]. These data were compiled on 19th January 2007. No products containing dichlorovos, malathion or primiphos-methyl were found. The remaining five active ingredients that were identified are listed under insecticides and their use is summarised in Table 6.8.

Table 6.8 Use of active ingredients in biocide products

	Total number of products listed	Number of Amateur products	Number of Professional products
Azamethiphos	2	1	1
Bendiocarb	44	38	6
Chlorpyrifos	19	8	11
Cyfluthrin	2	2	0
Cypermethrin	71	48	44

In addition, 15 products containing cypermethrin were listed under wood preservatives, of which seven were listed for amateur use and 11 for professional use and eight for industrial use.

Although exposure levels for a number of active ingredients have been well documented, with part 2 of the Technical Notes for Guidance compiled by the European Chemicals Bureau (2002)

[10] http://www.hse.gov.uk/pesticides/bluebook/section08.pdf
[11] http://www.hse.gov.uk/pesticides/bluebook/section12.pdf

summarising information from all available studies[12], there is no information on quantities used annually, usage patterns or the number of people potentially exposed (HSE personal communication).

6.2 BYSTANDERS AND NEIGHBOURS

6.2.1 Numbers potentially exposed

The main exposure of bystanders or neighbours will be to pesticides used for spraying crops. Exposure to veterinary medicines and biocides for the active ingredients of interest in this report is unlikely and will not be considered further in this report.

The number of neighbours potentially exposed to agricultural pesticides was calculated using information in report from the Centre for Ecology and Hydrology (Stuart, 2005), using Table 6.9.

Table 6.9 Number of occupants of residential properties adjacent to arable and horticultural broad habitat land

Country	Environmental zone	Number of residents ('000s)	Coefficient of Variation	Lower 95% confidence interval	Upper 95% confidence interval
England & Wales	1	702	17	489	943
	2	386	19	259	520
	3	4	55	0.65	8.65
	1-3	1092	13	855	1356
Scotland	4-6	116	27	61	182
Great Britain	1-6	1209	12	967	1479

Great Britain is split into Environmental zones, with England and Wales being covered by zones 1 (south and east lowlands), 2 (north and west lowlands) and 3 (uplands) and Scotland by zones 4 (lowlands), 5 (marginal uplands and islands) and 6 (uplands).

For England and Wales it was necessary to link up environmental zones with GOR (Scotland is one region in the model). This was done by considering a map of the environmental zones with one of the GORs and assigning the GORs to an environmental zone or zones. For example, both East Midlands and Eastern were assigned wholly to environmental zone 1, whereas 50% of Wales was assigned to environmental zone 1 and 50% to environmental zone 2.

Information on the population in each region was obtained from the Office of National Statistics website[13] and the figures from the 2001 census were used.

The number of people adjacent to farms is then calculated using the following equation:

$$\sum_{i=1}^{3} \frac{No.\ in\ \ region}{total\ \ in\ zone_i} \times no.\ adjacent\ to\ zone_i \qquad (6.1)$$

The numbers and percentages of the population likely to be adjacent to farms are given in Table 6.10.

[12] http://ecb.jrc.it/documents/Biocides/TECHNICAL_NOTES_FOR_GUIDANCE/TNsG_ON_HUMAN_EXPOSURE/Report_2002_part_2.doc

[13] http://www.statistics.gov.uk/

Table 6.10 Number of people and percentage of the regional population estimated to be adjacent to farms

Region	No. adjacent to fields ('000s)	Percentage adjacent to fields
East Midlands	122	2.9
Eastern	158	2.9
London and South East	435	2.9
North East	39	1.5
North West	60	0.9
Scotland	116	2.3
South west	85	1.7
Wales	26	0.9
West Midlands	90	1.7
Yorkshire & The Humber	77	1.6

The number of people who are bystanders, i.e. in the vicinity of pesticide spraying, but who are not residents is assumed to be very small and is not considered further in this report.

6.2.2 Dermal exposure of bystanders

Information on potential bystander exposure was collected from EUROPOEM and reported as a percentage of the applied dose (l or kg/ha as applied to 2 m^2 (assumed surface area of a subject)) per pass of the sprayer. A summary of exposures as a proportion for arable spraying is given in Table 6.11.

Table 6.11 Proportion of applied dose rate per pass of the sprayer which contaminates bystander

	Proportion
Minimum	0.0003
Median	0.002
Maximum	0.032

The exposure per pass of sprayer can then be calculated as follows.

$$E = 2.\frac{M_{Appl}}{A}.k_p \qquad (6.2)$$

where M_{Appl} is the mass of pesticide applied (kg), A is the area sprayed (m^2) and k_p is the proportion of contamination per pass. In order to calculate the total exposure per pass of the sprayer, an average of three passes per field were assumed (maximum 15), (Twining, 2006). It should be stressed that only potential exposure for bystanders is available from EUROPOEM. Since no information is available about the protection afforded by ordinary clothing, the actual exposures were assumed to be equivalent to the potential exposures, which is the worst scenario whereby ordinary clothing is assumed to provide no protection.

6.3 CONSUMERS

Consumers are exposed to pesticides through food, which is considered elsewhere, through secondary exposure as a result of professional treatment of, for example, pests in the home and

as a result of direct contact with products used in the home and the garden. Only direct use is considered here.

No studies of non-agricultural pesticide use in homes and gardens have been carried out in the UK. Grey *et al.* (2006) investigated the level and extent of pesticide use in homes and gardens in the UK in a sample of parents participating in a longitudinal study of parents and children in and around Bristol in 2001. Of the 147 subjects interviewed, 93% had used at least one pesticide in the preceding year and 76% two or more pesticides. The main use was in the garden (75%) followed by treating the inside of homes (57%), treating pets (33%) and head lice (16%). The majority (80%) had used one to five different products (median 3) over the last year. Insecticides in the home were the most commonly applied pesticides (21% of total pesticides and were applied a median of three times. A total of 76 different active ingredients were identified. Of the active ingredients of interest in this study, only three were listed in the paper amongst the most commonly stored products (% of total product): bendiocarb (4.8%), glyphosate (4.2%) and malathion (2.6%). It is unclear how representative these results are of the UK as a whole. However, it is clear that the use of the active ingredients of interest in the study represent only a small fraction of overall active ingredient use.

In 1999, the IEH reported a study to assess the current exposure of the UK general population to pesticides in the indoor domestic environment (IEH, 1999). They reported that the pesticide products most likely to be used indoors were non-agricultural surface biocides, insecticides and wood preservatives, vertebrate control agents and agricultural insecticides approved for amateur use. They reported that such pesticides accounted for over 2,100 products and contained over 150 active ingredients. They concluded that there were insufficient data to enable an accurate estimation of the exposure of the UK general population to pesticides from indoor sources; this was mainly due to a lack of information on type of pesticide used, usage pattern and frequency of application. They concluded that although indoor sources of pesticides may make an important relative contribution to an individual's total daily exposure to pesticides, this exposure is likely to be very low.

The PSD database[14] was searched to identify pesticides used in gardens and on houseplants by amateurs. Seventy-six products were identified as being approved for use that contained the active ingredients of interest. One of these products contained malathion, three contained methiocarb and the remaining 72 contained glyphosate. This compares with over 600 products listed for amateur use, though it should be noted that despite efforts to eliminate duplicates, it is likely that a number are the same. It can therefore be concluded that with respect to the active ingredients of interest it is unlikely that garden exposure contributes importantly to overall exposure.

With respect to biocide use (see section 4.1.3 above), there is no information on the quantities used annually, usage patterns, or the number of people potentially exposed (HSE, personal communication).

Very little information on exposures resulting from home or garden use exist, although the PSD has commissioned two studies to investigate exposures arising from the use of home garden pesticides (PSD, personal communication).

This study investigated differences in exposure between professional and amateur usage and found that skin contamination from application tasks by amateurs was less than 25 mls potential dermal exposure from a 30 minutes exposure, which was less than predicted by POEM.

[14] https://secure.pesticides.gov.uk/pestreg/ProdSearch.asp

However, the data from mixing and loading suggested that the exposure for these tasks may be higher than predicted by POEM.

Further experiments were undertaken to assess exposure from concentrate handling operations for amateur users. Ten participants were observed, using three different applicators (one of which was a garden watering can). Hand contamination predicted by POEM, using a container less than 1 litre is 0.01mls contamination per pouring action. The majority of pouring actions in the study resulted in a value lower than this, although some users received exposures higher than this level. Hand exposures from the removal of the second seal was found to be a major source of contamination.

For single pouring operations using a 1 litre sprayer, the maximum hand contamination was found to be 0.04mls (although the average exposure was closer to 0.002mls). For single pouring operations using 3 and 5 litre sprayers, higher hand contamination was associated with containers where the inside of the cap was used to measure and decant the pesticide stimulant; overfilling the inner measure in the cap led to spillage which ultimately contaminated the hand. In addition, it was found that 50% of users did not wash the cap after use as there were no instructions to do so on the packaging, and they did not want to risk contamination of the container with water.

6.4 IDENTIFY DATA ON RESIDUES OF PESTICIDES AND VETERINARY MEDICINES IN THE ENVIRONMENT (WATER AND SOIL) BY REGION.

The Environment Agency (EA) report the most frequently occurring pesticides in rivers and groundwater, with monitoring sites where data have been recorded consistently for several years. The EA report data for the nine pesticides that are most commonly found at relatively high levels. River samples at indicator sites are assessed against a threshold of 0.1µg/l for each pesticide to look at trends of pesticides in the environment. It is not a measure of environmental damage. In 2005 almost 8% of the indicator samples contained pesticide concentrations above that required for drinking water (0.1µg/l). All of the most frequently found pesticides are herbicides, which tend to be both mobile and persistent. Pesticides were found to exceed the indicator threshold (0.1µg/l) more often in all regions except South West in 2005, as shown below.

Pesticides in surface waters by region in England and Wales, 1998 to 2005. Percentage of samples exceeding 0.1µg/l)

	1998	1999	2000	2001	2002	2003	2004	2005
Anglian	7.36	6.41	6.70	7.93	6.25	4.18	5.68	9.50
Midlands	7.68	7.51	6.13	8.64	6.91	6.21	5.70	8.58
North East	11.12	9.93	10.60	12.64	9.97	10.90	9.03	11.82
North West	3.68	4.56	5.42	7.43	7.55	5.03	6.23	6.87
Southern	8.03	6.70	6.32	5.33	6.73	4.97	3.72	6.37
South West	1.38	3.02	0.79	0.57	1.62	1.15	2.47	1.99
Thames	10.18	11.91	11.16	11.86	10.05	7.84	6.55	13.46
Wales	1.68	1.78	1.88	2.19	1.14	1.71	1.68	2.21

Source: Environment Agency

In 2005 the most frequently occurring pesticides in river water were Simazine, Atrazine (which are now subject to restricted use and will be withdrawn completely after 2007), Diuron (also due to be phased out in 2008), Mecoprop, Isoproturon, 2,4-D, MCPA, Chlortoluron and Dichlorprop (which have all been reviewed recently). The EA monitor for pesticides in rivers

under requirements for the Water Framework Directive, and target the monitoring for the pesticides most likely to be found.

In groundwater the most frequently occurring pesticides in 2005 are shown below.

	% of samples above level of detection	% of samples greater than 0.1µg/l
Atrazine	11.4	1.7
Atrazine desethyl	7.3	2.5
Simazine	8.6	0.5
Atrazine desisopropyl	4.4	1.0
Bentazone	1.6	0.9
Diuron	1.8	0.3
Mecoprop	1.3	0.7
Clopyralid	1.2	0.8
Isoproturon	1.3	0.5
Ethofumesate	1.3	0.4
Metazachlor	1.3	0.3
Propazine	1.5	0.0

Source: Environment Agency

Simazine was the only pesticide on the list of compounds chosen for the project that appeared in the EA monitoring data in 2005, but has now been withdrawn. There are not sufficient data to consider the contribution of drinking water as a source of exposure to mixtures of pesticides. It is possible that residues of pesticides are present in water but below the limit of detection with current analytical techniques. Legislation within the EU is now covered by the Water Framework Directive (2000/60/EC), which allows limits for individual pesticide active substances (including metabolites and degradation products) in drinking water of 0.1 µg/l, with a total content of not more than 0.5 µg/l for total pesticides.

The data have been presented to illustrate the type of data that are collected for pesticides and metabolites, and how these data could be used in assessing exposure to mixtures on a wider scale.

7 MODELLING THE INTAKE OF PESTICIDES

Objective 09	Devise a suitable basis for the estimation of dietary uptake (i.e. the mass of residue consumed over a defined period) based on consumption and residue levels.
Objective 10	Develop the conceptual basis for inhalation, dermal and accidental ingestion uptake of pesticides in occupational and non-dietary consumer scenarios, including bystander, neighbour and environmental exposure.
Objective 11	Devise a single compartment pharmacokinetic model to enable "internal" exposure to be estimated.
Objective 12	Extend the probabilistic simulation to provide a prediction of exposure for the population of Great Britain, overall and in a range of strata defined by the use scenarios and consumption patterns.

7.1 DEVISE A SUITABLE BASIS FOR THE ESTIMATION OF DIETARY UPTAKE BASED ON CONSUMPTION AND RESIDUE LEVELS.

The model is designed with many parameters. While these parameters are random, the probability distribution of each of the parameter is fixed, e.g. the mean and standard deviation of which define the distribution are fixed. These statistics are either estimated from the data or chosen according to expert judgement. The model simulations reflect the variation from a population. The uncertainty of the model outputs can be made by attributing a random distribution to the parameter statistics is not pursued in this project but can be an area for further investigation.

We created a database of the 21 compounds. For each compound, we had:

1. the residue data for a range of food ingredients and
2. the bio-kinetics (e.g. excretion rate).

The database also contained the dietary intake information for a typical child, youngster, adult and old age pensioner, separated by sex. The information consists of:

1. The number of meals per day;
2. The weight of the meal;
3. The type of meal, as consisting of several food items (e.g. pie, cake etc…);
4. The recipe for each food item.

For each variable above, a probabilistic distribution was attributed to describe the variability in the assigned value. A further probabilistic distribution was attributed to each of the parameters of the first distribution to describe the uncertainty regarding the quantification of the variable in question.

The number of meals per day, the weight of each food item making up the meal, the recipe of each food item allowed linkage of the residue data through the recipe and the meal information to calculate the daily intake of the compound. This daily intake was used as the input to the simple pharmacokinetic model.

7.1.1 Description of model inputs

Specifically, the data structure is as follows:

I. Data Structure

1. The individual:
   (S)he will have the following characteristics:
   a. Demography: Scotland, England (regions within England), Wales;
   b. Age (0-5 years, 6-10 etc…);
   c. Statistics of population per demographic region by age group, by gender;
   d. Gender (Male/Female);
   e. Preference (Vegetarian/Non-Vegetarian);
   f. Profession (Worker/Bystander). Used later on for occupational exposure.

2. Meal:
   Dependent on the individual's characteristics, (s)he will eat:
   a. a certain type of meal (i.e. (s)he is restricted to only a subset of meal types; from the set of all possible meals available in the UK);
   b. at certain frequency (in number of time per day);
   c. with a meal weight (gm).

3. Food item:
   Each meal type consists of a number of food items (e.g. Pie, Steak, etc…):
   a. each food item is made of certain food ingredients (the Recipe);
   b. each food item is measured as weight (gm). A meal weight is the sum of food items' weight;
   c. each ingredient can be of EU/UK or non–EU provenance;
   d. each ingredient can be processed or non-processed.

4. Pesticide residual:
   For each food ingredient, we will have residue data for the pesticide of interest.
   a. pesticide residue is of unit of μg/gm.

With the data described above, we will calculate a daily intake of that particular pesticide. We plan to simulate the one-year time course of the daily intake for an individual using data available for the last 5 years. Figure 7.1 represents the schema for matching pesticide residues with food intake.

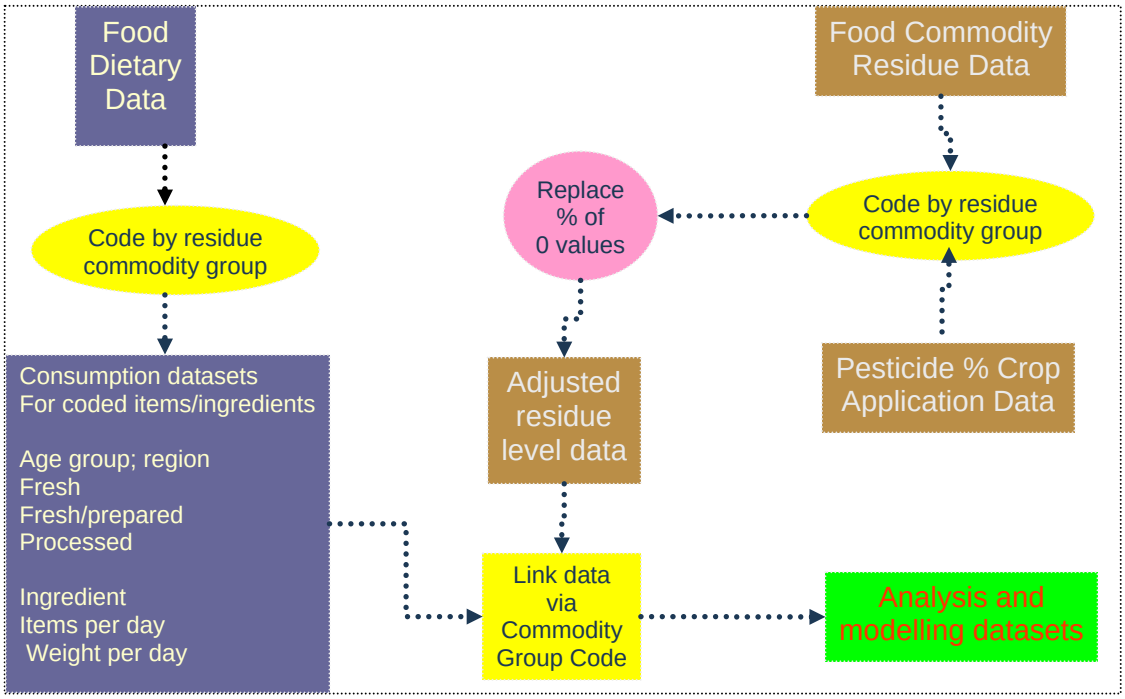


Figure 7.1 Schema for matching pesticide residues with food intake

7.1.2 Description of model for dietary intake

The daily intake (DI_l) of pesticide P_l (μg/day) is calculated as follows:

$$DI = \sum_{j=1}^{N} M_j \qquad (7.1)$$

where

N Number of meals *per* day

M_j Amount of *per* meal (μg)

and

$$M_j = \sum_{k=1}^{M} F_{j_k} \qquad (7.2)$$

where

F_{j_k} food item k in meal j (gm)

$$F_{j_k} = \sum_{l=1}^{K} I_{j_{kl}} \qquad (7.3)$$

where

$I_{j_{kl}}$ ingredient l in meal food item F_{j_k} (gm)

7.1.3 Description of model outputs

Let ρ_l be the residue in ingredient $I_{j_{kl}}$ then combining the equations above,

$$DI = \sum_{j=1}^{N} \sum_{k=1}^{M} \sum_{l=1}^{K} \rho_l I_{j_{kl}} \quad (7.4)$$

7.1.4 Description of the approach in quantification of uncertainty and variability in model inputs/outputs

We incorporated uncertainty and variation in our simulation.

1. For a given individual (we choose a 'typical individual' so this is fixed, but we will simulate for many typical individuals).
2. The meal type will be selected randomly within the subset of meal type available to this individual. The multinomial distribution is based on the data available from the CSL and reflects the frequency of certain meal (or fruit) being eaten and therefore takes into account the popularity of choice for certain food type over others. By sampling on the multinomial distribution we are replicating the pattern as seen in the data.
3. The meal frequency will vary (min, mean, max, in integer). The meal frequency is a triangular distribution with parameters (Min, Mean, Max). While Min and Mean is fixed (1 and 2) Max is a uniform random variable between (Max_{min} (=3) and Max_{max} (=6)).
4. The amount will vary (distribution shape, summary statistics.). The distribution of amount of food consumed is obtained from the consumption data and is a multinomial distribution based on a series of weight range. Within a weight range the actual amount is chosen a uniformly distributed value within the range.
5. Each meal type will consist of fixed list of food item each food item is allowed to vary (Distribution shape, summary statistics) or fixed (i.e. 0). Again, we used the multinomial distribution which is constructed from the data.
6. Their provenance is allowed to vary randomly (binary distribution), i.e. we simulated the vegetarians separately from the non-vegetarians.
7. They can be either processed or unprocessed depending on the meal type. Food can either be processed or unprocessed. The choice of variability between processed and unprocessed is modelled according to a binomial distribution and processed food is equalled to unprocessed food multiplied by a random factor chosen from a uniform distribution between 0 and 1.
8. The pesticide residual data can also vary (Distribution shape, summary statistics). Residual data come with a minimum and maximum level of residue. The actual value is a uniformly distributed variable between min and max. The minimum and maximum are kept fixed.
9. Fruits can either be 'fresh' or 'processed'. For fresh fruits the pesticide concentration is calculated as above. For 'processed' fruit, some of the residue level will be washed out. The fraction representing the reduction level is described as an uniform random variable between 0 and 1 (see Figure 7.1).

These sources of randomness will be introduced as part of the simulation in order to estimate the one-year time course of the daily intake of a chosen individual.

7.1.5 A single compartment pharmacokinetic model to enable "internal" exposure to be estimated.

The simple one-compartment model consists of two parts:

a. the daily ingestion of the compound (and mixture);
b. the excretion of the compound(s)

The internal dose is currently modelled as:

$$\frac{dC}{dt} = DI - k.C \qquad (7.5)$$

where C is the internal dose of the compound and k is its excretion rate. Excretion rates were obtained from toxicology data for a simple one-compartment model.

The issue of uncertainty/variability regarding the parameter k was implemented in the same way as in the exposure model.

Figure 7.2 describes the logical steps, the various random distribution used in simulating a one-year pattern of exposure and internal dose for an individual consuming fresh and fresh/prepared/processed fruits. Because the distributions are drawn from the data we tend to use multinomial instead of a continuous distribution, which has the advantage of reproducing the pattern seen in the data.

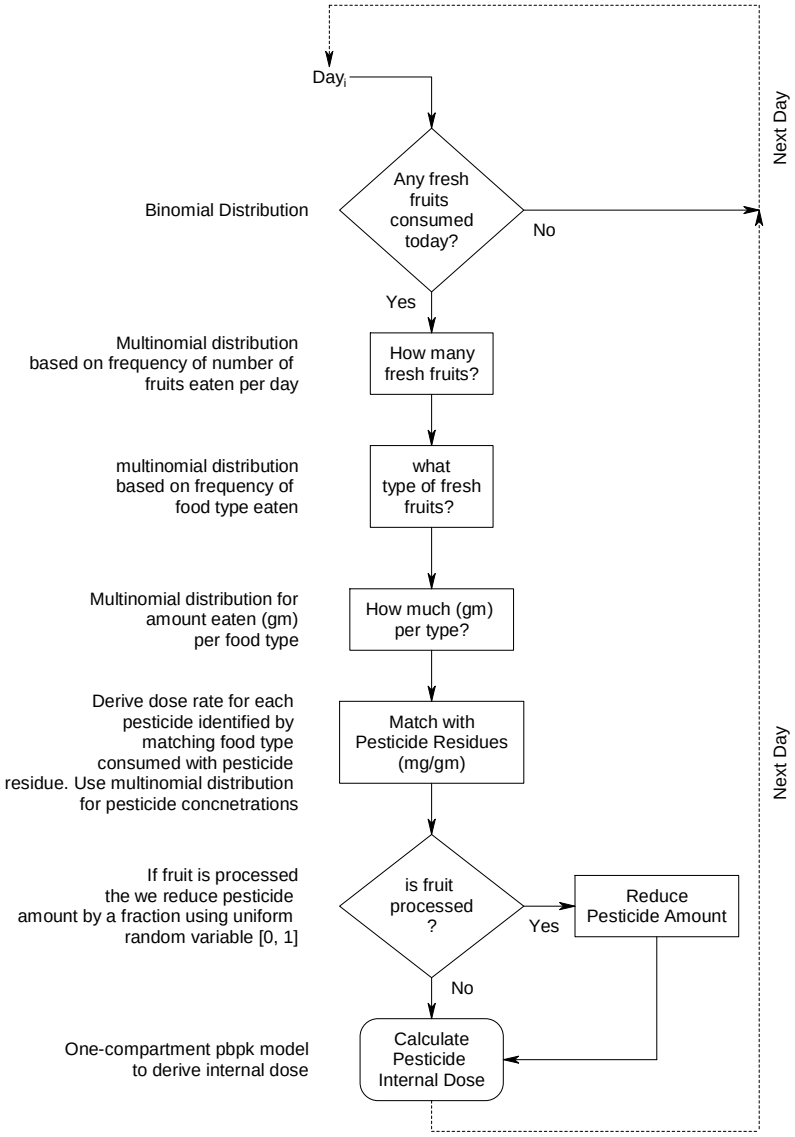


Figure 7.2 Schema for the simulation of daily intake of pesticides through fresh fruits and fresh/prepared/processed fruits.

7.2 MODEL OUTPUTS FOR TYPICAL CONSUMER GROUPS

The model was implemented using the Matlab language and the corresponding Statistics Toolbox. The following results are for an adult whose exposure comes solely from food consumption.

Figure 7.3 describes the daily time course of the internal dose of various pesticides associated with the fresh and fresh-processed fruits and vegetables consumed by a single adult – only nine pesticide compounds are shown in this example because there were only these pesticides consumed by this individual. The horizontal axis covers the 365 days in a year and the vertical axis is the dose in μg. In general, the fast clearance of the pesticides implies that pesticide body level remains low but there is a possibility of repeated exposure, which gives rise to an irregular "spiky" pattern of internal dose over time. Note, the scales on the graphs are not identical so for

cypermethrin and glyphosate the maxumum internal dose on any one day is about 5 to 10 μg, whereas for the other compounds the maximum is more typically around 1 μg. It is also noteworthy that the frequency of "spikes" is determined by the frequency with which residues are found in food and the pattern of consumption of these foods.

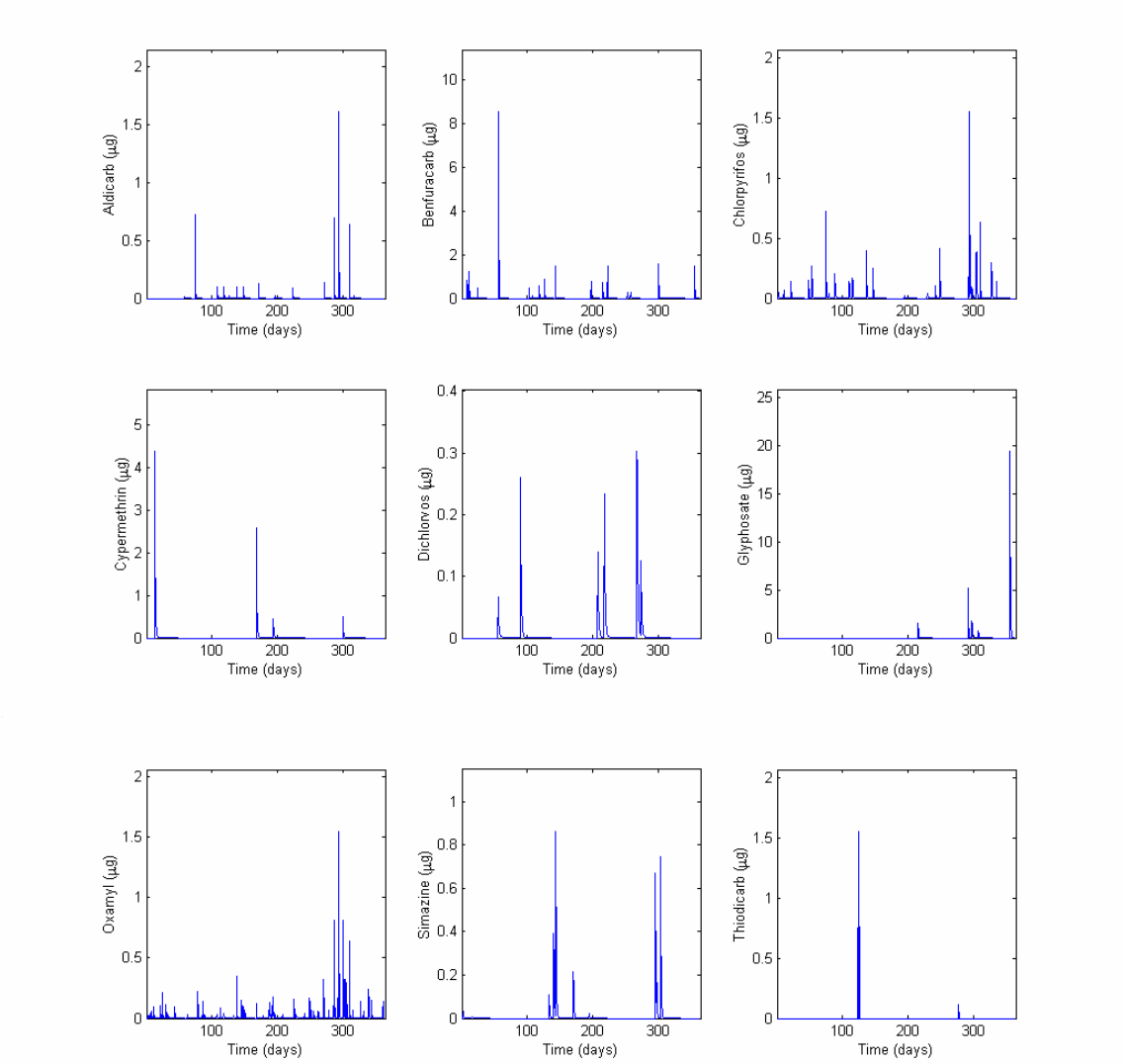


Figure 7.3 Time course of pesticide internal dose through consumption of food for an adult.

Figure 7.4 shows the corresponding graphs for daily internal dose for an infant. The most obvious difference between the two sets of graphs is the much lower internal doses in infant compared with the adult.

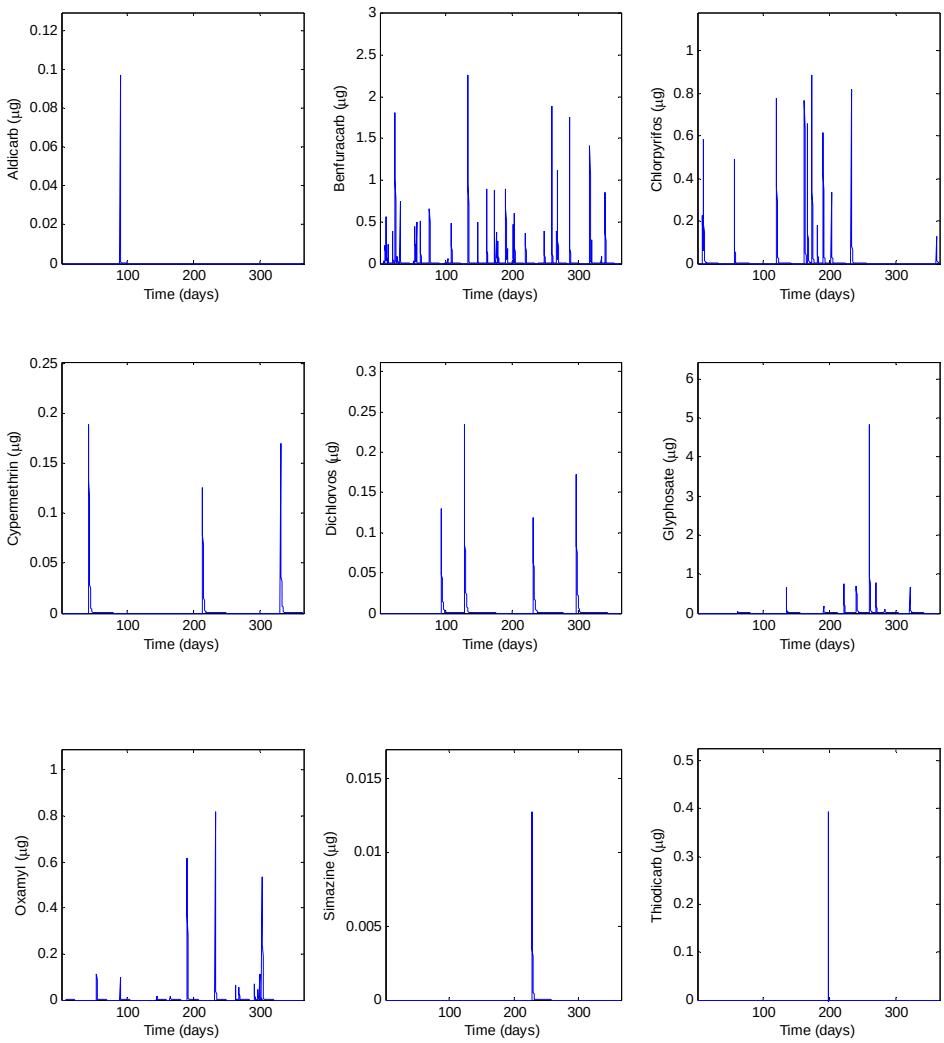


Figure 7.4 Time course of pesticide internal dose through consumption of food for an infant.

7.3 DEVELOPMENT OF THE CONCEPTUAL BASIS FOR DERMAL UPTAKE OF PESTICIDES IN OCCUPATIONAL AND NON-DIETARY CONSUMER SCENARIOS

7.3.1 Description of model for occupational exposure

Pesticide exposure was defined by the following formula:

$$U = A_{Spray} M_{Appl} k_f k_{Abs} \qquad (7.6)$$

where U is the uptake of the active ingredient (µg), A_{Spray} the area sprayed that day (ha), M_{Appl} the mass of pesticide applied per hectare (µg/ha), k_f is a dimensionless constant that related the quantity active applied to the field to the potential exposure of the applicator (skin, lung or gut)

and k_{Abs} is the fraction of active ingredient absorbed across the appropriate boundary membrane (skin, lung, gut). The parameters were obtained as described in Chapter 6.

In the model we define three types of individuals associated with occupational exposure to pesticides. They are: Farmers, Contractors and Bystanders. We will use a working definition for each type of individuals.

(i) Farmers
A farmer is someone involved in the usage of pesticides occupationally and is therefore exposed to these compounds. A farmer will work in a fixed holding throughout the year. Below (Figure 7.5) is the schematic description for the simulation of a farmer's pattern of exposure to pesticide. The distributions for the model parameters were derived from the data.

(ii) Contractors
A contractor is also a farm worker. However, he can work in more than one farm a year. The simulation scheme goes through the similar process as that of the farmer:

- Select the different farms (holding type), holding area, crop number and types grown and holding area reserved for each crop.
- Generate the number of spray days per year for the contractor
- Each spray day, the contractor can work in a different farm (note that the contractor can work in the same farm more than once)
- On a spray day, the contractor pesticide exposure is estimated as the daily pesticide exposure on that farm for that month.

(iii) Bystanders
The bystander is defined as someone who lives in the neighbourhood of a farm. The bystander's exposure follows the same pattern of exposure as that of a farmer. However, the bystander only receives a fraction of the farmer's exposure. We model the bystander's exposure according to the description in Chapter 6, using the information given in Table 6.10.

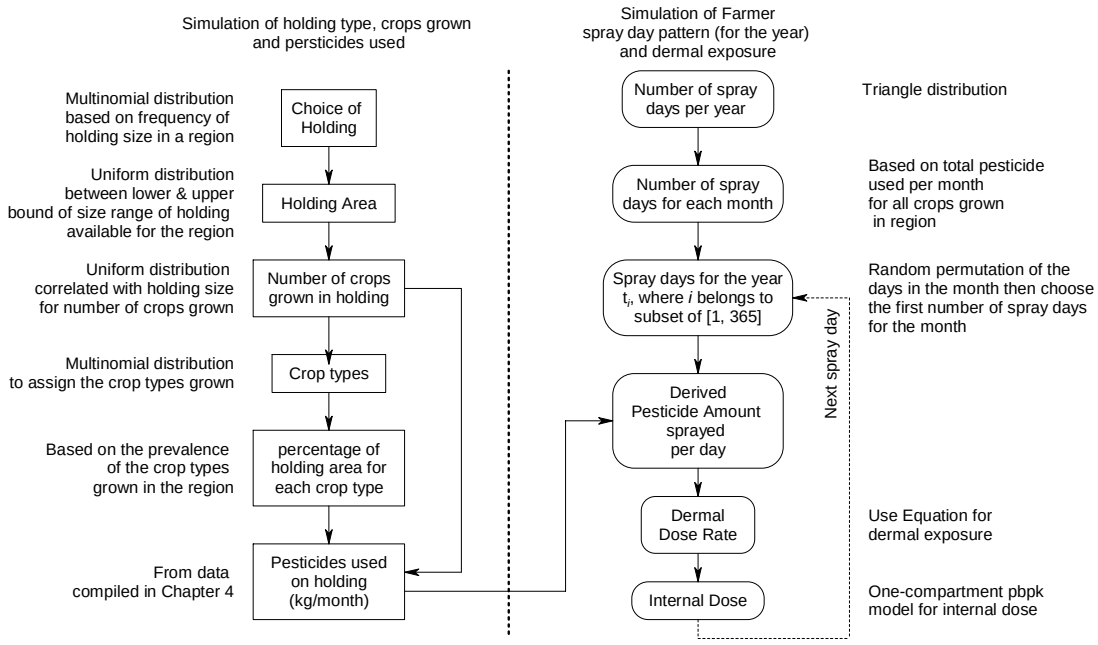


Figure 7.5 Simulation scheme of the pesticide exposure for a farmer.

7.3.2 Index of mixture

As a measure of the total mixture of the pesticide mixture, we also calculate the total pesticide internal dose. This measure is the sum of all the pesticides in the body for each day exposed divided by the Acceptable Daily Intake (ADI).

$$IDX = \sum_{k=1}^{N} C_k / ADI_k \tag{7.7}$$

Where the ADI_k is the Allowable Daily Intake for pesticide *k.*

The IDX is a dimensionless number that provides a representation of the aggregate exposure by normalising each internal dose estimate by the corresponding ADI. If the value of IDX is greater than unity it suggests that the aggregate dose is greater than the overall ADI. This equation assumes the effects of the individual compounds are additive and the ADI reflects the relative toxicity of the substances.

The values for ADI were obtained from the PSD Toxicological Endpoints database (https://secure.pesticides.gov.uk/TEAWeb/). ADIs were available for all of the compounds included in the study although AOELs were available for only 12 compounds. For the index it is necessary to choose a single reference value and because of the greater availability of the ADI data these were selected for use in this study. However, it is reassuring to note that there is a fairly good association between the two values.

It should be noted that the form of equation 7.7 assumes that the relative concentration of the different pesticides normalised to the ADI is unimportant in determining any risk. So for example, a high index may be attributed to high intake of a few pesticides or lower levels of a much wider range of compounds. The validity of this assumption is unclear.

7.4 RESULTS OF SIMULATIONS FOR FARMERS, CONTRACTORS AND BYSTANDERS

7.4.1 Daily internal dose estimates

Applying the simulation steps as describes above, we obtain the following results for Farmers, Contractors and Bystanders. In this example the bystander receives the exposure from the farmer. We present the results in the form of the internal dose of the pesticides for each occupational group respectively.

For the farmer, the pesticide internal doses for each day are shown in Figure 7.6, in this case for 11 pesticides that were applied during the course of the year.

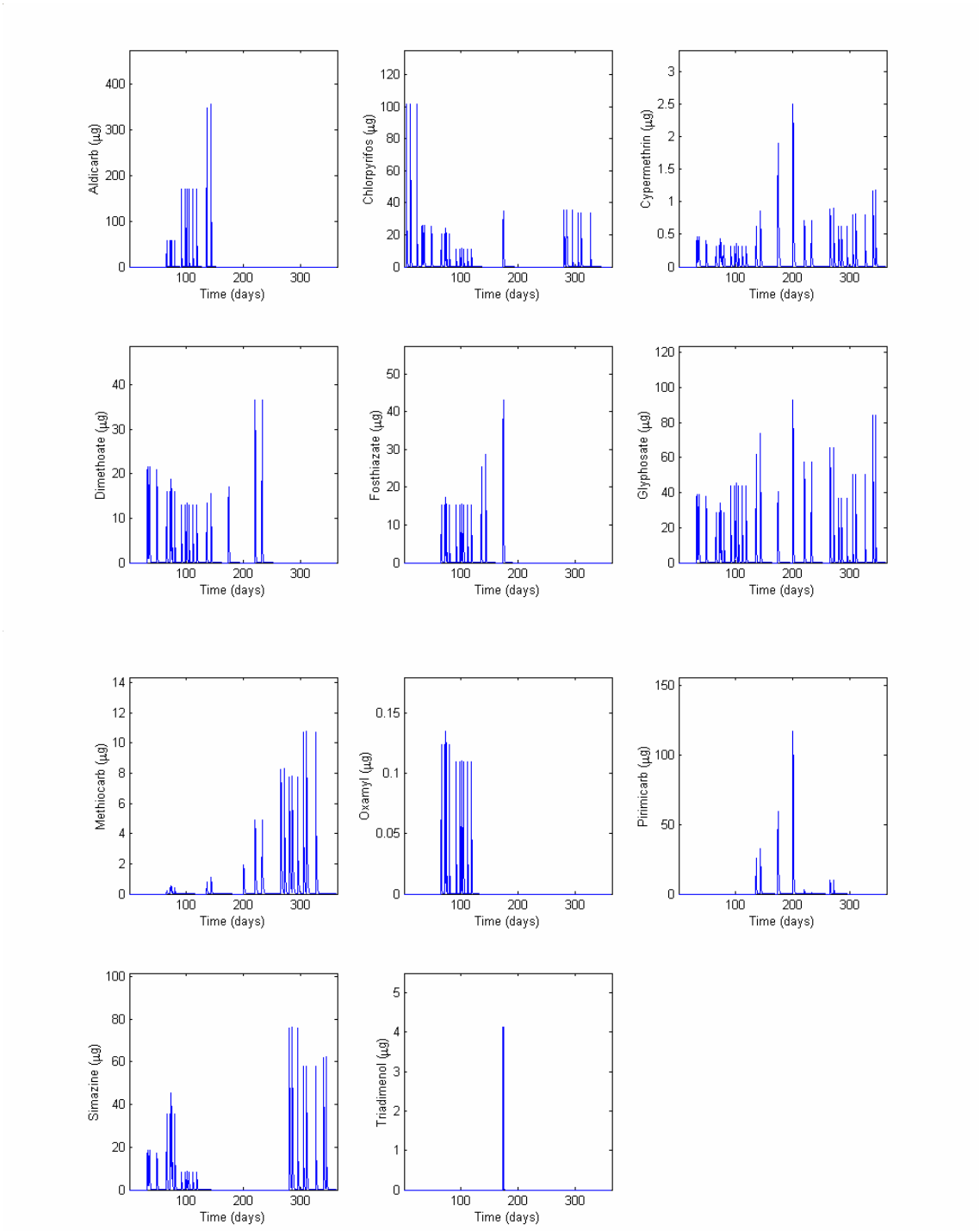


Figure 7.6 Daily internal dose for a farmer exposure.

In this case the pattern is determined by the pattern of spraying of different products throughout the year. The internal doses arising from farm work are much higher than was seen from food consumption; maximum internal daily doses were more typically in the range of 10 to 100 µg.

For a bystander, we derive the internal doses from the farmer's exposure, i.e. based on the modelled pattern of use using the EUROPOEM model for the estimated bystander exposure

level, although the internal dose is generally lower than farmers. The results from a single bystander are shown in Figure 7.7.

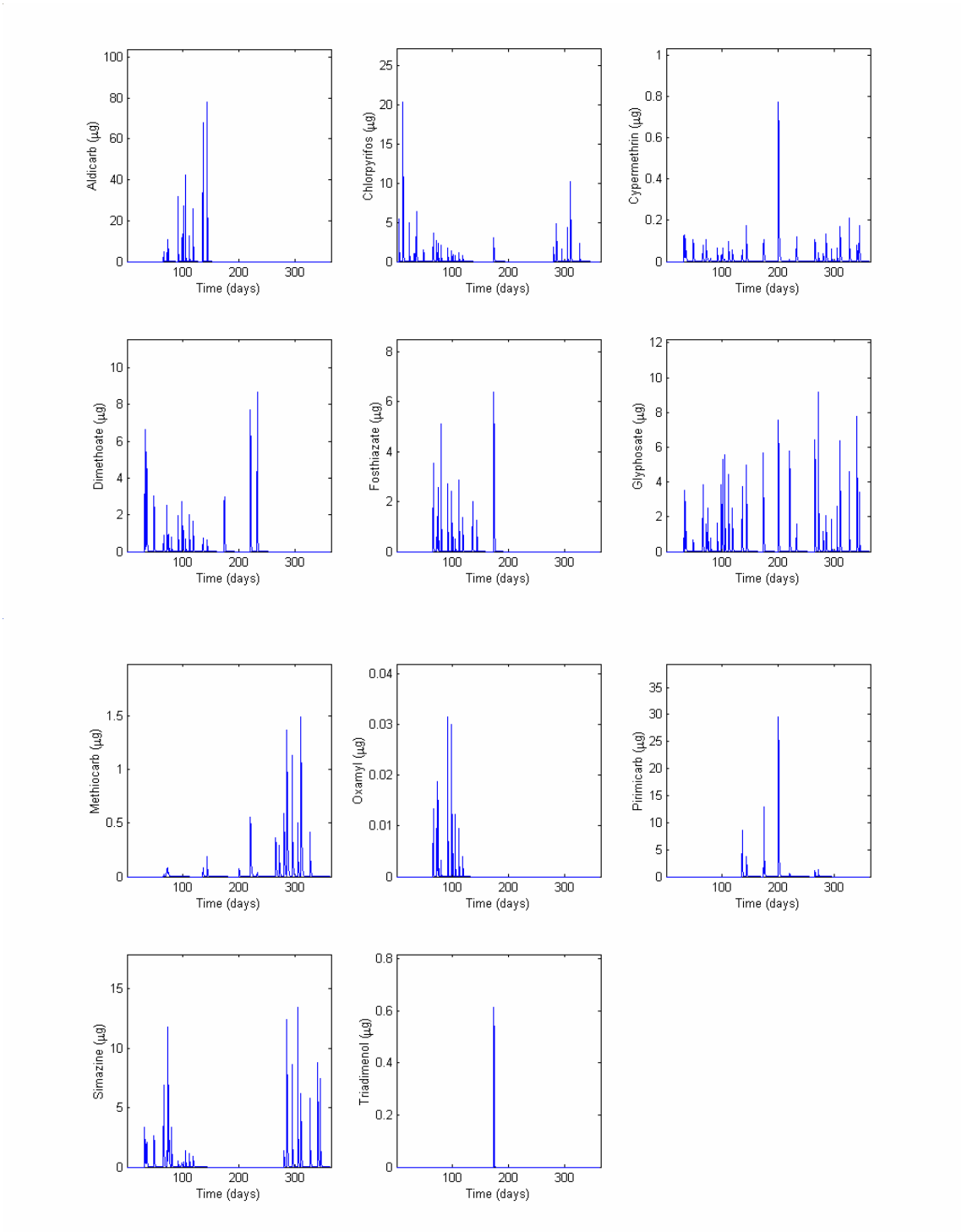


Figure 7.7 Daily internal dose for a bystander exposure

For a contractor, we apply the simulation scheme in section 7.2.1. The results from a simulation for a contractor are shown in Figure 7.8.

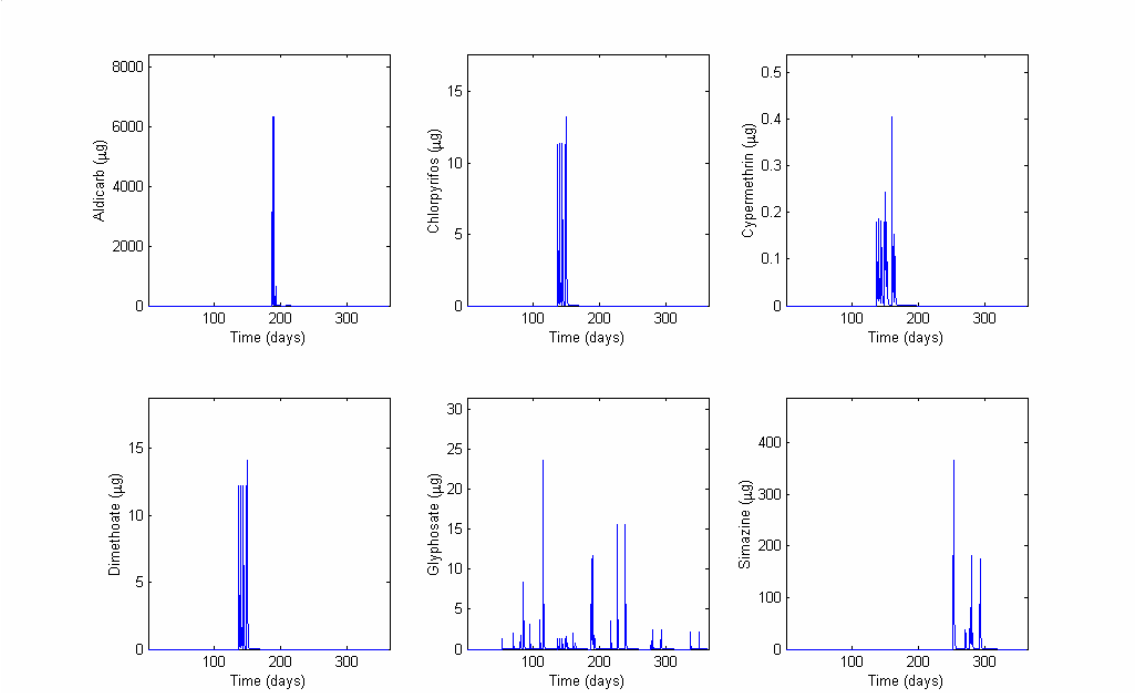


Figure 7.8 Daily pesticide internal doses for a contractor exposure

7.4.2 Cumulative dose estimates for adult dietary exposure

Figure 7.9 shows the average annual simulated dose for 1000 adults in the population for Aldicarb. 1000 iterations of the model were used to obtain a prediction that had acceptable convergence while keeping the computing effort within a reasonable bound. Note, the dose is shown on a log-scale so that "-1" corresponds to 10^{-1} or 0.1 µg/kg body weight. The solid line represents the median daily dose for an individual over the year and the dotted line the maximum daily dose during the year, i.e. the highest daily dose for any "individual" in the simulation.

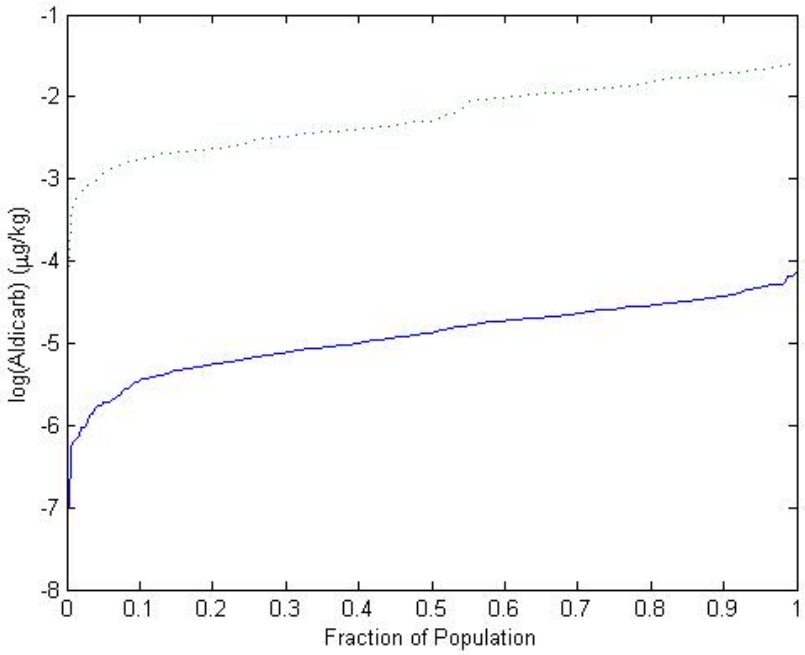


Figure 7.9 The total 'average internal dose' for Aldicarb for the population of adults.

The population median dose over a year is about 10^{-5} µg/kg and 90% of these doses were less than about 4 x 10^{-5} µg/kg. The median maximum daily dose for individuals is about 5 x 10^{-3} µg/kg and 90% of these doses were less than about 2 x 10^{-2} µg/kg. For comparison the ADI for Aldicarb is 3 µg/kg/day, which is 10.4 µg/kg adjusted to represent internal dose.

The corresponding data for Glyphosate is shown in Figure 7.10. The population median dose is about 8 x 10^{-5} µg/kg and 90% of these were less than about 3 x 10^{-4} µg/kg. The maximum daily dose has a median value of 2.7 x 10^{-2} and 90% are less than 1.2 x 10^{-1} µg/kg. The ADI for Glyphosate is 300 µg/kg/day, which is 580 µg/kg adjusted to represent internal dose.

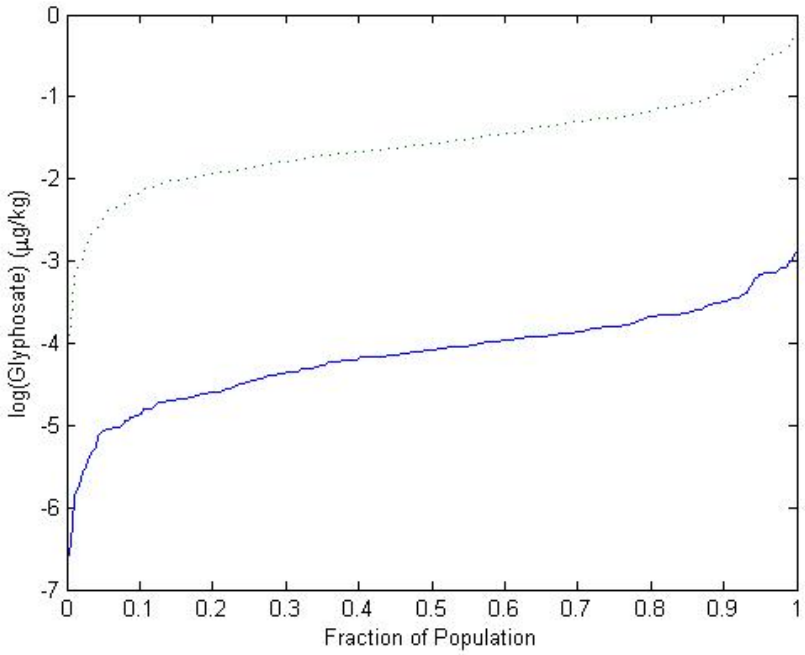


Figure 7.10 The total 'average internal dose' for Glyphosate for the population of adults.

Data from all pesticides for the adult simulation runs are summarised in Table 7.1

Table 7.1 Summary statistics for internal dose of pesticides for adults exposed from food consumption (μg/kg).

	Adjusted ADI dose	Average dose		Maximum dose	
		50th	90th	50th	90th
Aldicarb	10.4	0.00001	0.00004	0.0051	0.0193
Benfuracarb	20.1	0.00024	0.00040	0.0449	0.0821
Beta-cyfluthrin	3.3	0.00002	0.00003	0.0048	0.0073
Chlorpyrifos	20.4	0.00008	0.00016	0.0133	0.0258
Cypermethrin	64.8	0.00003	0.00014	0.0082	0.0374
Dichlorvos	5.1	0.00002	0.00005	0.0032	0.0069
Glyphosate	585.0	0.00008	0.00032	0.0267	0.1163
Malathion	745.0	0.00001	0.00001	0.0036	0.0080
Methiocarb	15.2	0.00001	0.00002	0.0028	0.0040
Oxamyl	2.6	0.00008	0.00014	0.0130	0.0248
Pirimicarb	57.0	0.00001	0.00012	0.0022	0.0497
Simazine	7.8	0.00008	0.00025	0.0104	0.0674
Thiodicarb	164.0	0.00001	0.00002	0.0144	0.0345

7.4.3 Cumulative internal dose estimates for infant dietary exposure

Corresponding data for infants from food consumption are shown in Figures 7.11 and 7.12, and Table 7.2. The dose estimates are lower than for the adults when expressed in terms of the mass of pesticide but were greater when the data are normalised to body mass. For Aldicarb the median population dose was 1.6 x 10^{-5} μg/kg and the median maximum individual dose was 9 x 10^{-3} μg/kg, which are two to three times the corresponding data for adults. For Glyphosate the median population exposure is 5 x 10^{-4} μg/kg and the median maximum individual exposure is 1.5 x 10^{-1} μg/kg. These data are about five times the corresponding adult dose estimates. However, these dose estimates were again much less than the relevant ADIs.

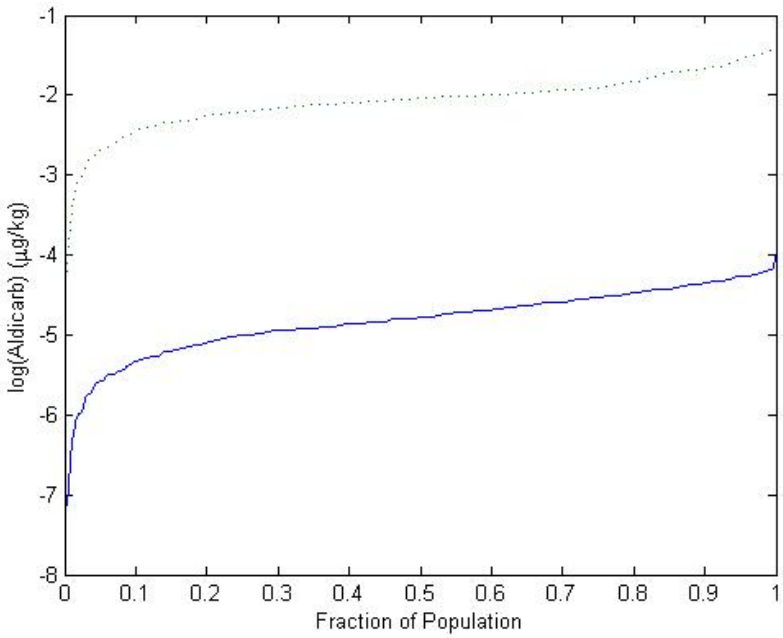


Figure 7.11 The 'average internal dose' for Aldicarb for the population of infants.

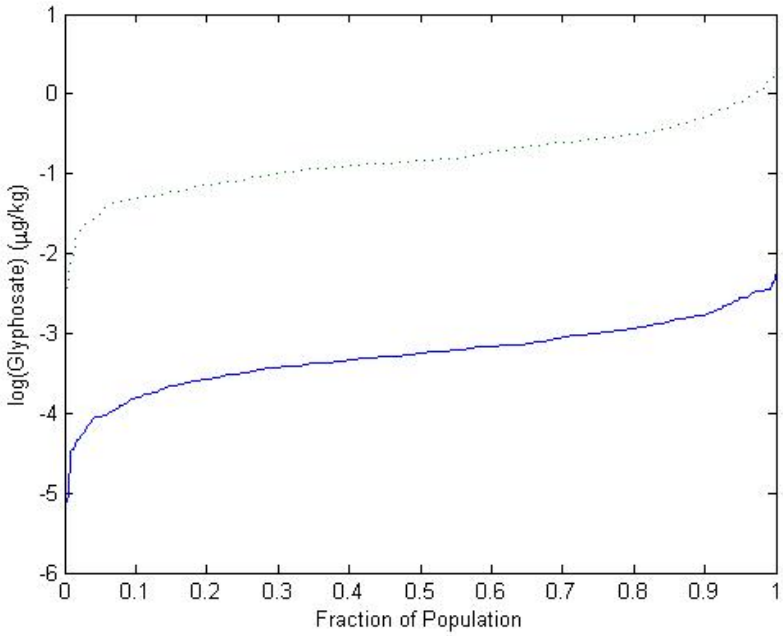


Figure 7.12 The 'average internal dose' for Glyphosate for the population of infants.

Table 7.2 Summary statistics for internal dose of pesticides for children exposed from food consumption (µg/kg).

	Adjusted ADI dose	Average dose		Maximum dose	
		50th	90th	50th	90th
Aldicarb	10.4	0.00002	0.00004	0.0091	0.0214
Benfuracarb	20.1	0.00150	0.00230	0.2044	0.4457
Beta-cyfluthrin	3.3	0.00005	0.00010	0.0139	0.0279
Chlorpyrifos	20.4	0.00026	0.00048	0.0525	0.0905
Cypermethrin	64.8	0.00012	0.00055	0.0287	0.1172
Dichlorvos	5.1	0.00004	0.00012	0.0096	0.0229
Glyphosate	585.0	0.00057	0.00170	0.1450	0.4867
Malathion	745.0	0.00001	0.00003	0.0120	0.0245
Methiocarb	15.2	0.00003	0.00004	0.0093	0.0126
Oxamyl	2.6	0.00018	0.00036	0.0463	0.0795
Pirimicarb	57.0	0.00010	0.00038	0.0426	0.1552
Simazine	7.8	0.00002	0.00008	0.0075	0.0278
Thiodicarb	164.0	0.00001	0.00003	0.0233	0.0622

7.4.4 Internal dose estimates for farmers from occupational and dietary exposure

The corresponding data for the population simulation of farmers, for pesticide exposure from spraying only is shown in Figures 7.13, 7.14 and Table 7.3. As expected, the exposures for farmers, principally from their occupational exposures, were much higher than for the exposure of the general population from non occupational sources. The median population dose estimates for Aldicarb and Glyphosate were 0.09 µg/kg and 0.02 µg/kg, respectively. The median individual maximum dose estimates were 11 and 0.7 µg/kg, respectively. For both of these

pesticides some of the simulations produced high individual dose estimates comparable to the ADI adjusted to represent internal dose, i.e. 10.4 and 580 µg/kg for Aldicarb and Glyphosate, respectively.

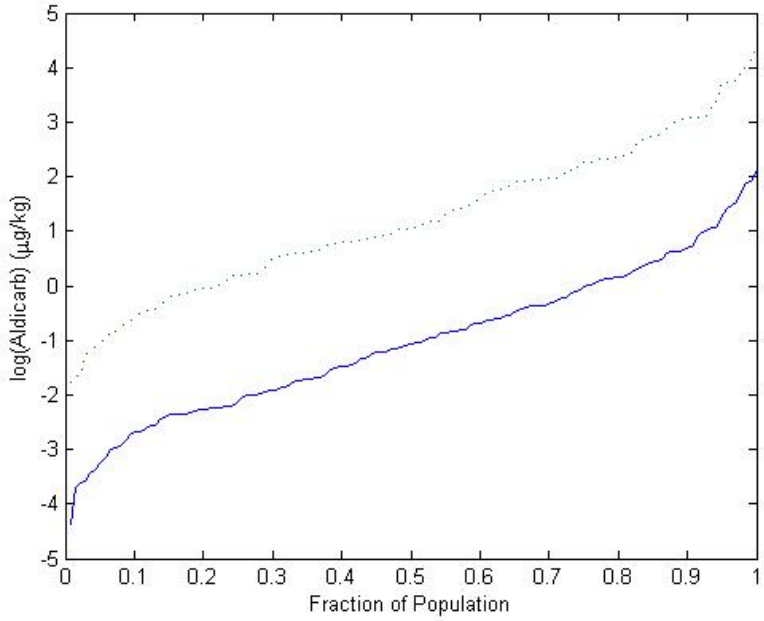


Figure 7.13 The 'average internal dose' for Aldicarb the population of farmers.

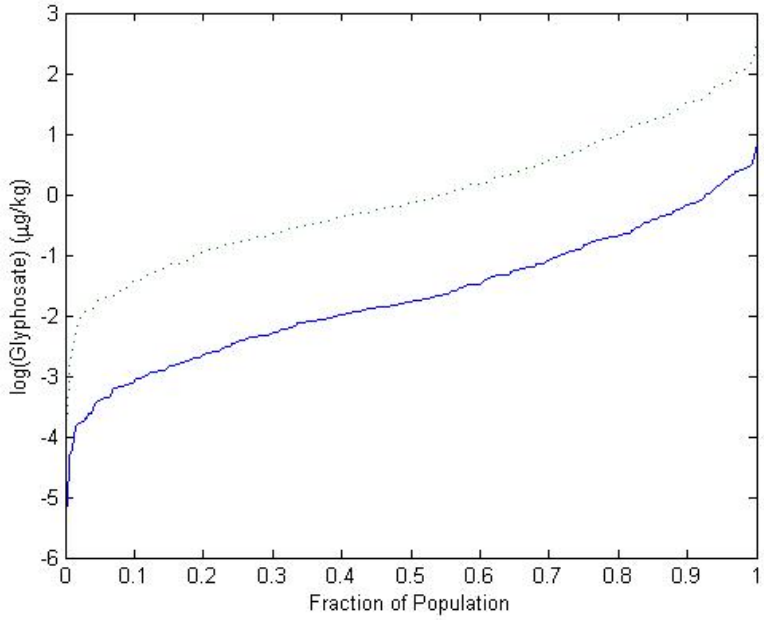


Figure 7.14 The 'average internal dose' for Glyphosate the population of farmers.

Table 7.3 Summary statistics for internal dose of pesticides for farmers from occupational exposure (μg/kg).

	Adjusted ADI dose	Average dose		Maximum dose	
		50th	90th	50th	90th
Aldicarb	10.4	0.087	4.335	11.158	113.100
Chlorpyrifos	20.4	0.022	0.836	1.076	46.591
Cypermethrin	64.8	0.012	0.328	0.571	16.022
Dimethoate	2.1	0.010	0.348	0.775	29.185
Fosthiazate	9.2	0.010	0.450	1.282	56.621
Glyphosate	585.0	0.017	0.660	0.725	31.656
Methiocarb	15.2	0.021	0.832	1.367	44.036
Oxamyl	2.6	0.00001	0.0006	0.001	0.065
Pirimicarb	57.0	0.117	3.220	7.300	242.900
Simazine	7.8	0.179	5.710	8.395	241.000
Triadimenol	164.0	0.0001	0.006	0.087	4.051

7.4.5 Internal cumulative dose estimates for bystanders from dietary and non-dietary exposure pathways

Figures 7.15 and 7.16 show the estimated distribution of doses for bystanders. These data are very similar in pattern to farmers because the simulation is based on the assumption that bystander exposure is closely linked to spraying. However, the dose estimates are all lower with the median population estimates being about 10^{-2} μg/kg for Aldicarb and 2 x 10^{-3} μg/kg for Gyphosate, which are about one tenth of the corresponding values for farmers. Note we do not take account of the physical form of the pesticide and so although aldicarb is a solid we still assume the EUROPOEM model is valid.

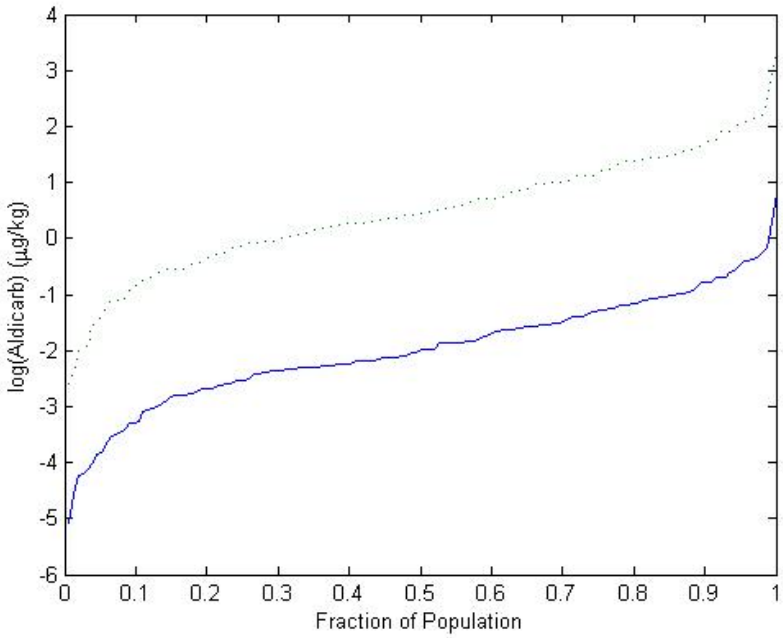


Figure 7.15 The total 'average internal dose' for Aldicarb for the population of bystanders.

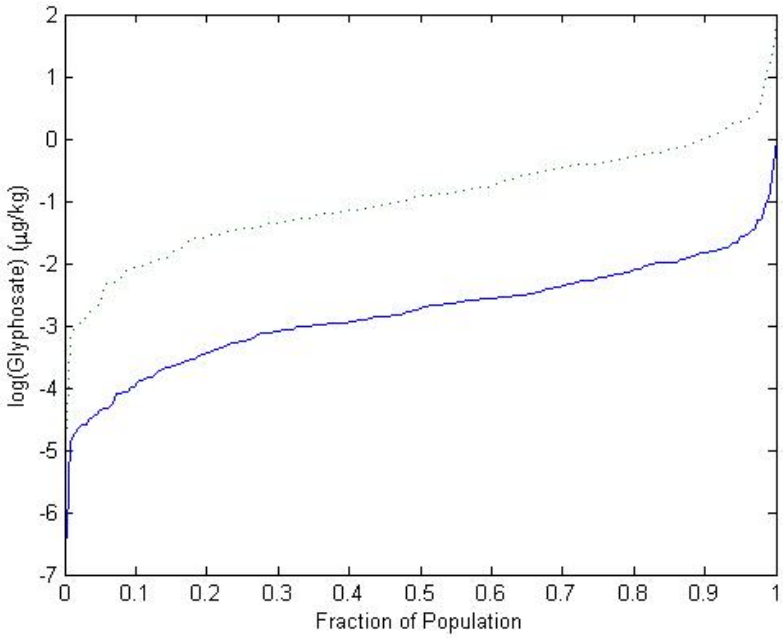


Figure 7.16 The total 'average internal dose' for Glyphosate for the population of bystanders.

Table 7.4 Summary statistics for internal dose of pesticides for bystanders from exposure as a bystander (µg/kg).

	Adjusted ADI dose	Average dose		Maximum dose	
		50th	90th	50th	90th
Aldicarb	10.4	0.01040	0.16160	2.57920	47.4874
Chlorpyrifos	20.4	0.00150	0.01750	0.14390	1.2367
Cypermethrin	64.8	0.00066	0.01070	0.04520	0.6926
Dimethoate	2.1	0.00097	0.00800	0.11710	0.9282
Fosthiazate	9.2	0.00170	0.03250	0.30360	5.7407
Glyphosate	585.0	0.00190	0.01440	0.11840	0.9847
Methiocarb	15.2	0.00170	0.02540	0.12770	1.9441
Oxamyl	2.6	<0.00001	0.00001	0.00034	0.0021
Pirimicarb	57.0	0.00620	0.10230	0.68470	9.8784
Simazine	7.8	0.01060	0.14900	0.76580	9.1170
Triadimenol	164.0	0.00001	0.00120	0.00590	0.3284

7.4.6 Internal dose estimates for adult vegetarians from dietary exposure

Figures 7.17 and 7.18 show data for adult vegetarians for Aldicarb and Glyphosate. For Aldicarb the median dose estimate for the population was 4×10^{-6} µg/kg and the median maximum dose for individuals was 2×10^{-3} µg/kg. The 90th percentile of the population dose is 8×10^{-6} µg/kg and the 90th percentile of their maximum exposure was about 2×10^{-3} µg/kg. For Glyphosate the median dose estimate was 8×10^{-5} µg/kg and the 90th percentile of the 90th percentile of the maximum dose was 8×10^{-2} µg/kg. These figures are broadly similar to the

data for other adults, i.e. being a vegetarian does not importantly alter the likelihood of exposure to pesticide residues from food consumption.

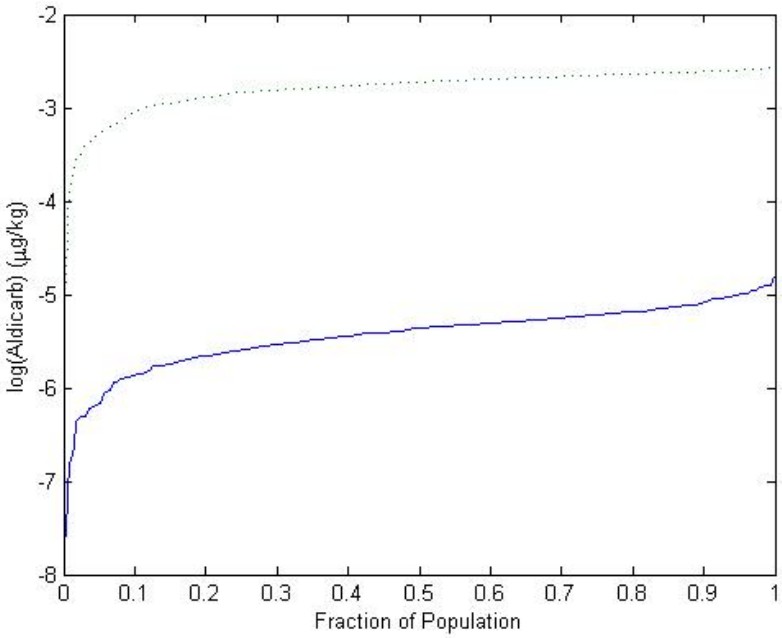


Figure 7.17 The 'average internal dose' for Aldicarb for vegetarians.

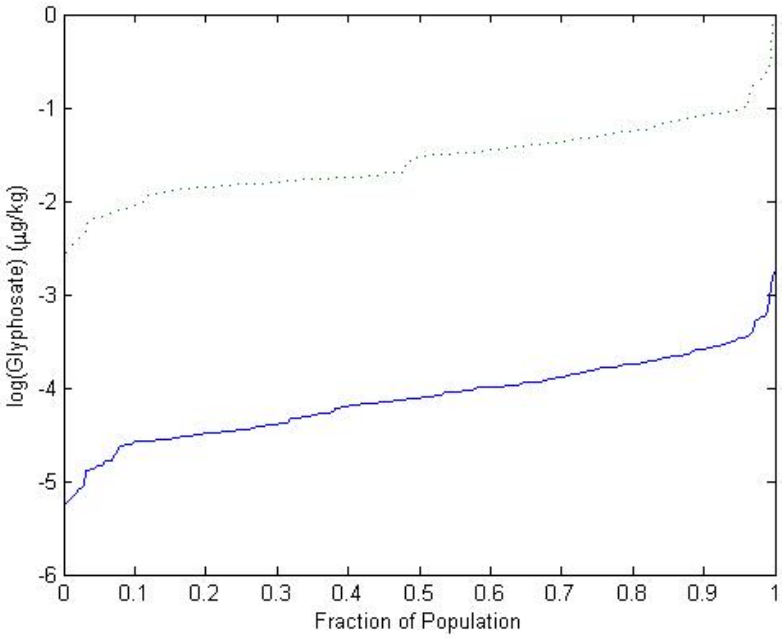


Figure 7.18 The 'average internal dose' for Glyphosate for vegetarians.

Table 7.5 shows the dose estimates for adult vegetarians.

Table 7.5 Summary statistics for internal dose of pesticides for vegetarians from food consumption (μg/kg).

		Average dose		Maximum dose	
		50th	90th	50th	90th
Aldicarb	10.4	0.00001	0.00001	0.0019	0.0024
Benfuracarb	20.1	0.00036	0.00057	0.0520	0.1162
Beta-cyfluthrin	3.3	0.00001	0.00001	0.0034	0.0041
Chlorpyrifos	20.4	0.00005	0.00011	0.0118	0.0239
Cypermethrin	64.8	0.00004	0.00011	0.0091	0.0245
Dichlorvos	5.1	0.00002	0.00005	0.0054	0.0070
Glyphosate	585.0	0.00008	0.00026	0.0293	0.0829
Malathion	745.0	0.00001	0.00001	0.0036	0.0042
Oxamyl	2.6	0.00004	0.00009	0.0088	0.0298
Pirimicarb	57.0	0.00002	0.00002	0.0067	0.0073
Simazine	7.8	0.00003	0.00013	0.0090	0.0340
Thiodicarb	164.0	0.00001	0.00001	0.0099	0.0217

7.4.7 Aggregate cumulative dose estimates for each population group

The data for each of the population groups are presented in the following graphs for the aggregate exposure obtained by dividing the dose estimates by the adjusted ADI and summing over all pesticides. In these graphs any predicted exposure above unity indicates that the effect of the mixture is greater than the combined "ADI". Figure 7.19 shows these data for anti-cholinesterase pesticides for adult non-vegetarians from food consumption. The median exposures are all much less than one and the maximum individual exposures were all less than one tenth of the dose equivalent to the combined ADI.

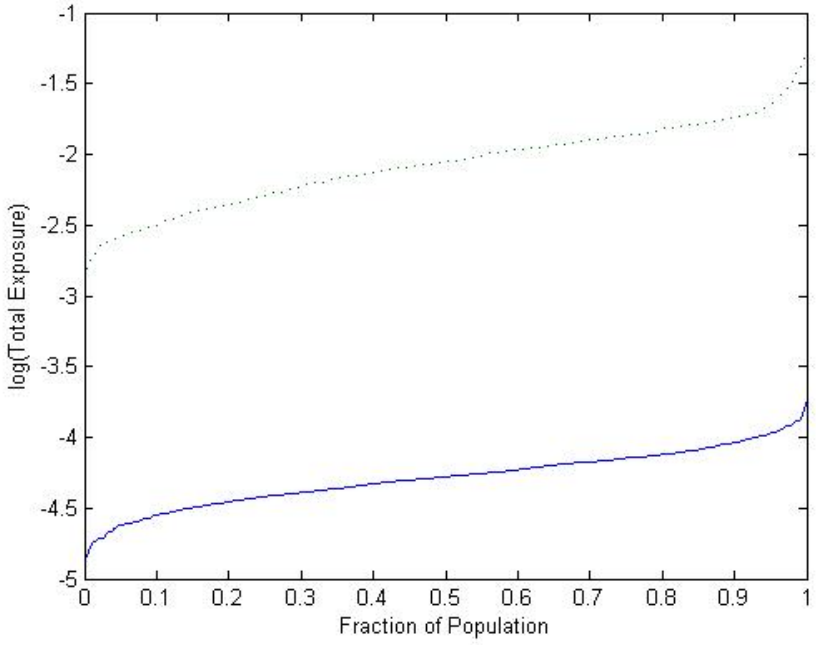


Figure 7.19 The total pesticide doses for anti-cholinesterase pesticides for adult non-vegetarians.

Figure 7.20 shows the corresponding graph for pesticides classified as possible oestrogen agonists, which shows a similar pattern to that for anti-cholinesterase pesticides.

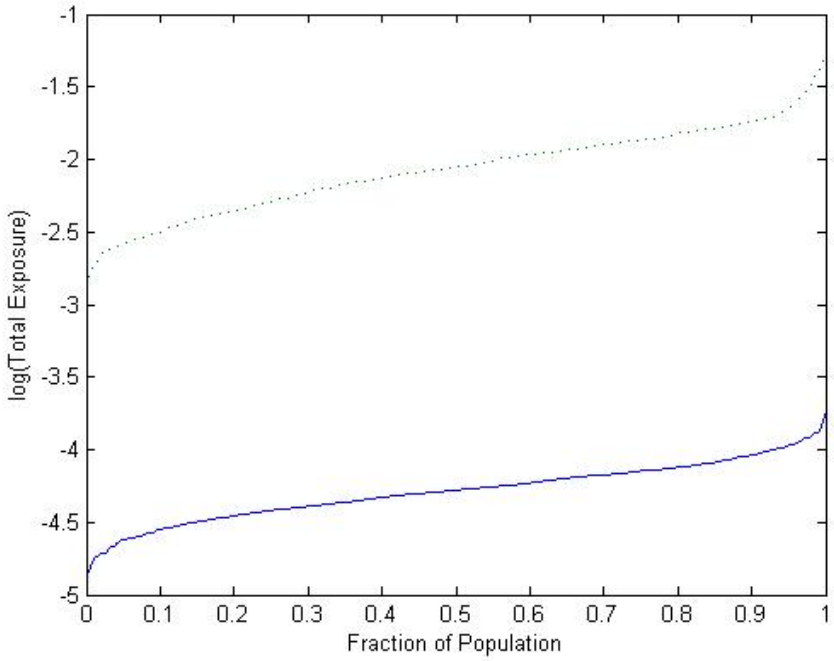


Figure 7.20 The total pesticide doses for oestrogen agonist pesticides for adult non-vegetarians.

Figures 7.21 and 7.22 show the corresponding data for adult vegetarians and children for anti-cholinesterase pesticides. The data for oestrogen agonists are similar.

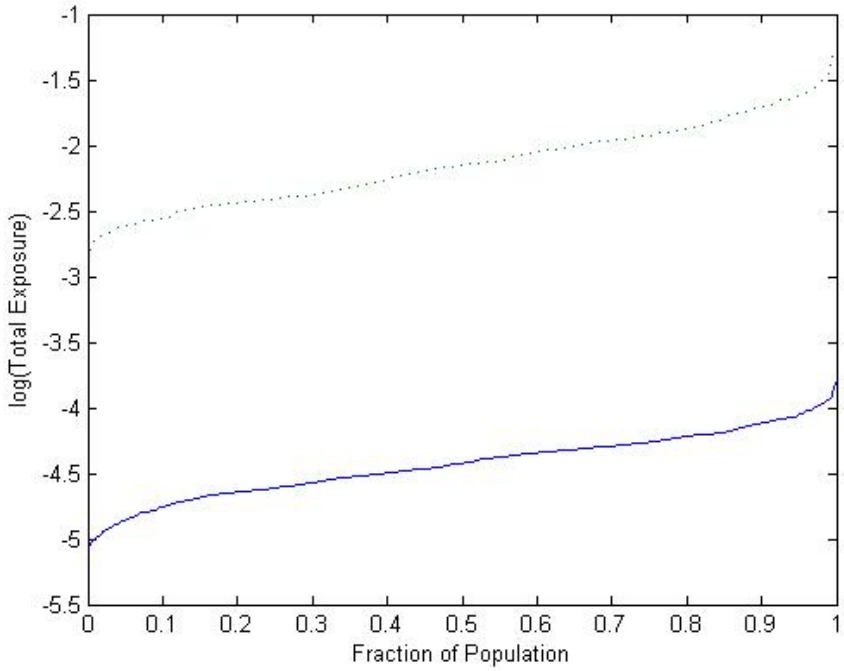


Figure 7.21 The total pesticide doses for anti- cholinesterase pesticides for adult vegetarians.

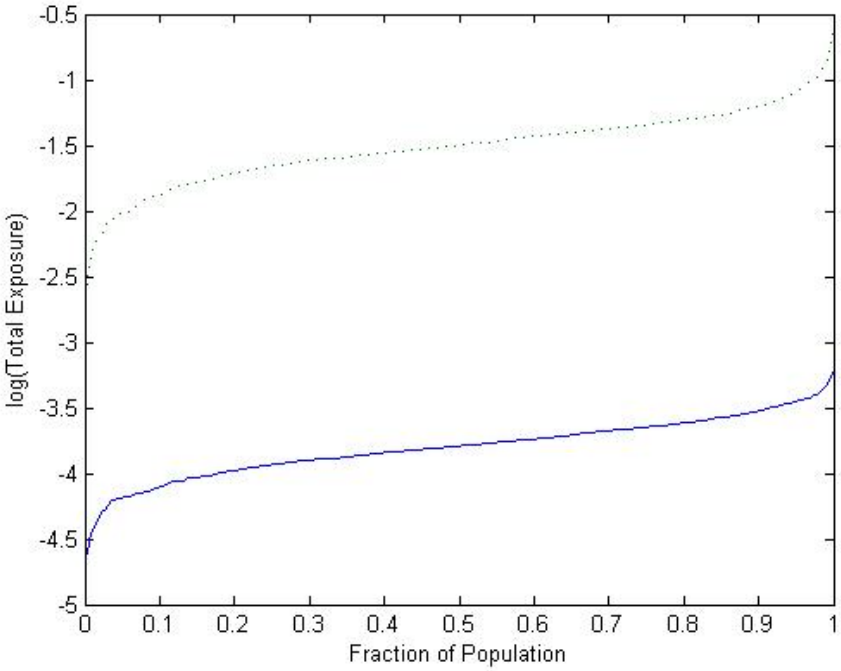


Figure 7.22. The total pesticide doses for anti- cholinesterase pesticides for children.

The data from the modelling of child exposure show that the distribution of aggregate dose are higher than for adults, as noted earlier, but that all of the estimates are lower than unity.

Figure 7.23 shows data for the population of bystanders in Great Britain. As expected the aggregate exposures for anti-cholinesterase compounds was higher than from food consumption and for about 10% of bystanders the aggregate exposure exceeded the dose equivalent to the combined ADI. None of the median estimates exceeded the combined ADI dose.

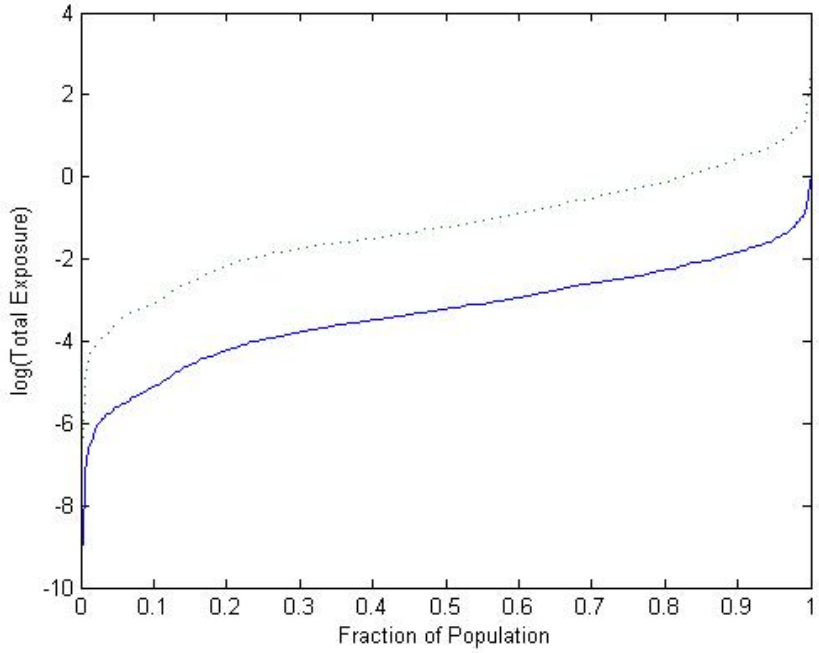


Figure 7.23 The total pesticide doses for anti-cholinesterase pesticides for bystanders.

The estimated internal dose estimates for the population of farmers for anti-cholinesterase pesticides is shown in Figure 7.24. In this scenario about 20% of individuals had a maximum estimated dose higher than the combined ADI dose and about 3% had median dose estimates above the combined ADI dose. However, the median dose for the population was well below the combined ADI dose.

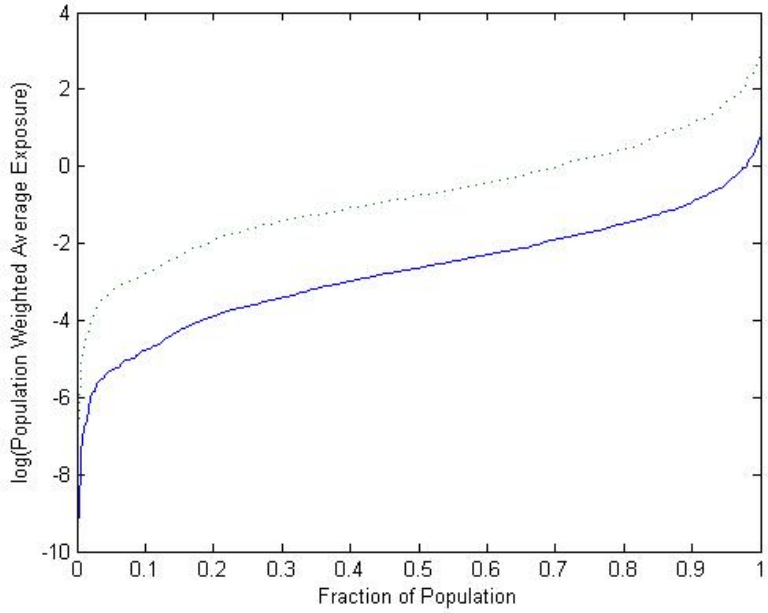


Figure 7.24 The total pesticide doses for anti-cholinesterase pesticides for farmers.

Figure 7.25 shows the population dose estimates for contractors for anti-cholinesterase pesticides.

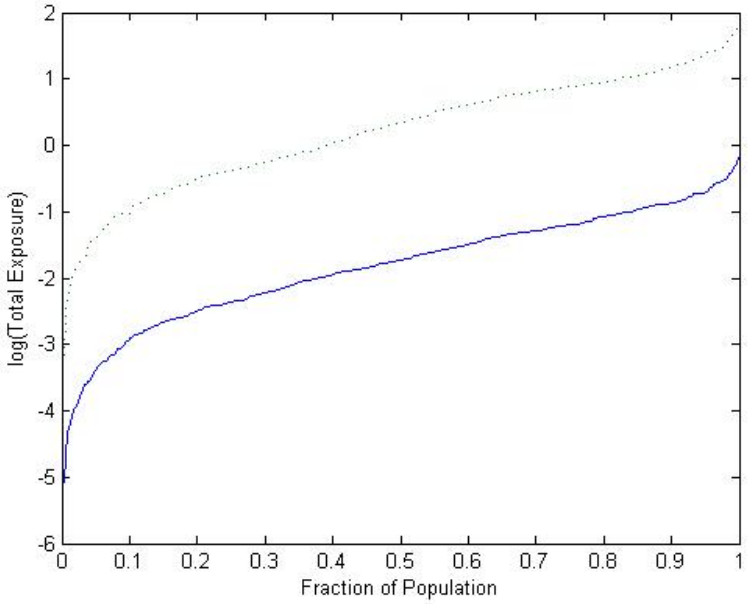


Figure 7.25 The total pesticide doses for anti-cholinesterase pesticides for Contractors.

In this case about 60% of the maximum individual dose estimates exceeded the dose equivalent to the combined ADI, although the median exposures for all contractors were below this value. For contractors, both the average aggregate dose estimates and the variability in the dose estimates were greater than for farmers.

The pattern of dose estimates is different for contractors and farmers for oestrogen agonist compounds (Figures 7.26 and 7.27). In this case the farmers had higher estimated aggregate doses and higher maximum doses compared to the contractors, which is because of differences in the pattern of usage of pesticide products. In this case about 50% of the farmers had maximum dose estimates above the combined ADI dose and only about 20% of the contractors had similarly high dose estimates.

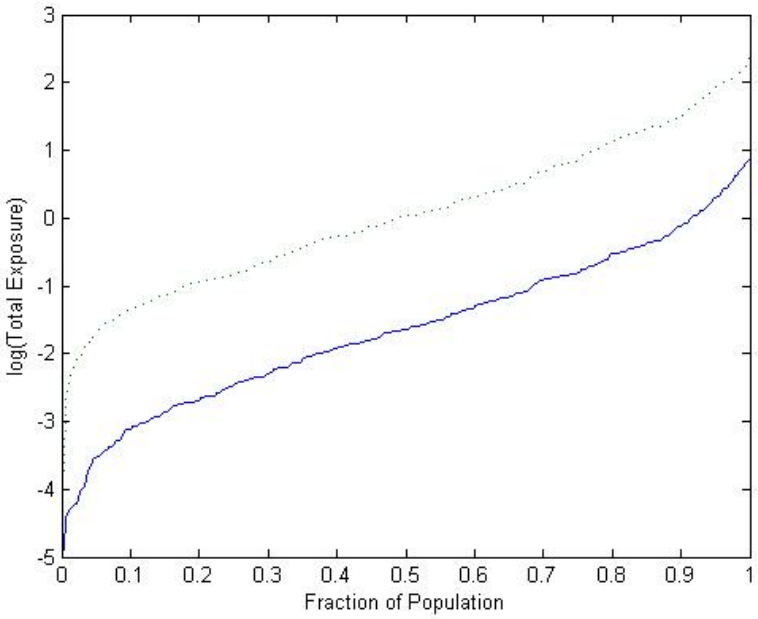


Figure 7.26 The total pesticide dose estimates for oestrogen agonist pesticides for farmers.

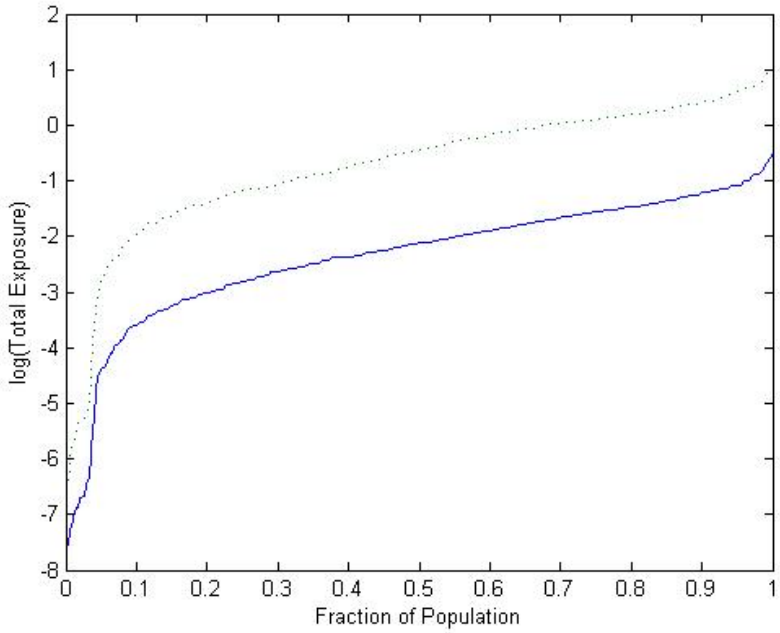


Figure 7.27 The total pesticide dose estimates for oestrogen agonist pesticides for contractors.

Combining together all of the dose estimates for anti-cholinesterase pesticides for the adults and children in the population from food consumption gives the data shown in Figure 7.28. This shows that from our simulations, which confirms that none of the aggregate daily dose estimates for anti-cholinesterase pesticides exceeded the dose equivalent to the combined ADI for these compounds. The maximum dose estimate was about one tenth of the dose estimate for the combined ADI. There is considerable day-to-day variability in predicted consumption of pesticide residues and a smaller variation within the population.

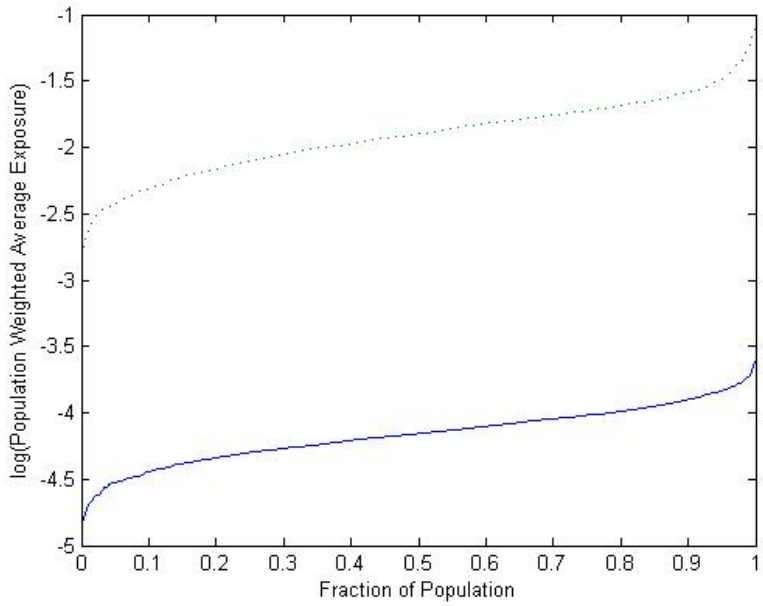


Figure 7.28 The total pesticide dose estimates for anti-cholinesterase pesticides from food consumption for the British population.

It is inappropriate to combine the exposures associated with occupations into the general population because they affect only a relatively small proportion of people (less than 1%). However, these are the most highly exposed section of the population. We have summarised data for bystanders, contractors and farmers as a group in Figure 7.29 for ant-cholinesterase compounds. This confirms that more than a quarter of people in this group have a predicted maximum dose in excess of the dose associated with the combined ADI, and most of these would be farmers or contractors, although some will be bystanders. A very small number of people, probably less than 10,000 in the whole of Great Britain, are estimated to have median exposures in excess of the dose equivalent to the combined ADI.

The situation is similar for oestrogen agonist compounds in terms of the proportion of the population and the work-related exposed population with higher predicted internal doses.

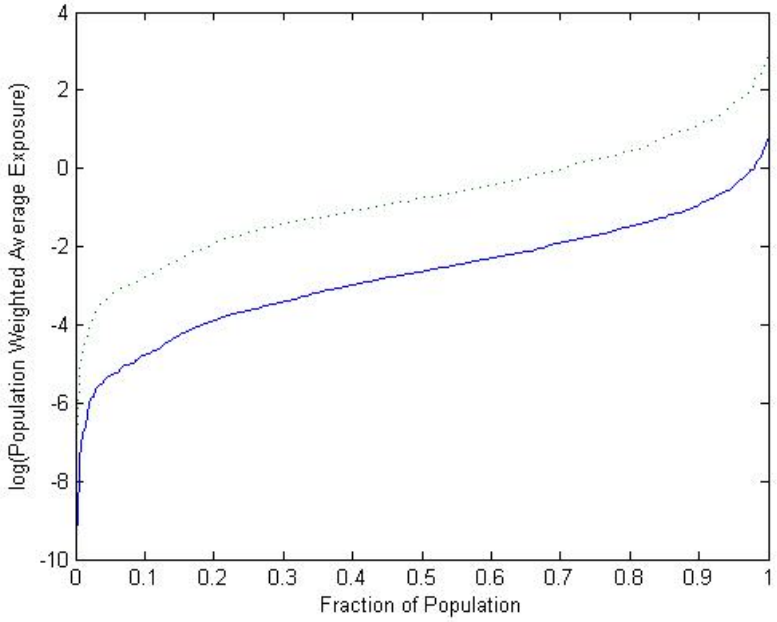


Figure 7.29 The total pesticide dose estimates for anti-cholinesterase pesticides from agricultural use for the British population.

7.5 UNCERTAINTY ANALYSIS

7.5.1 Introduction

Uncertainty in the simulations that we have carried out may arise either because the models used to estimate exposure were unreliable or because the parameters used in the models are not known with certainty. To attempt to counter both of these sources of uncertainty we have selected accepted scientific models, or example the EUROPOEM model for applicators and bystanders, and have relied on the available date related to exposure, for example the pesticide residue data.

To demonstrate the model behaviour in relation to the uncertainty in the values of key model parameters, we have selected two cases for further investigation: bystander and vegetarian. In each of these models, we varied one (or two correlated) parameter(s) and simulated the model with the changed parameter(s). The result is then compared graphically with the original data (the baseline).

A complete sensitivity/uncertainty analysis is out of the scope of this current study, although, this limited exercise can demonstrate to some extent the robustness of the model arising from large variation in some key parameters.

7.5.2 Uncertainty analysis for the bystander model

In the main simulations the bystander's exposure is modelled a fraction of the farmer's exposure. This fraction is described as:

$$F = R/10^4 \qquad (7.8)$$

where R is a random variable following a triangular distribution, for example (3, 35, 227).

In this simulation we set F = 1, which is equivalent to assuming that the bystander receives the maximum possible amount of exposure from the pesticide application. The results are shown in Figures 7.30 and 7.31 for anti-cholinesterase and oestrogen agonist pesticides for total pesticide dose. Note that the plots are: baseline (blue) and new data (green).

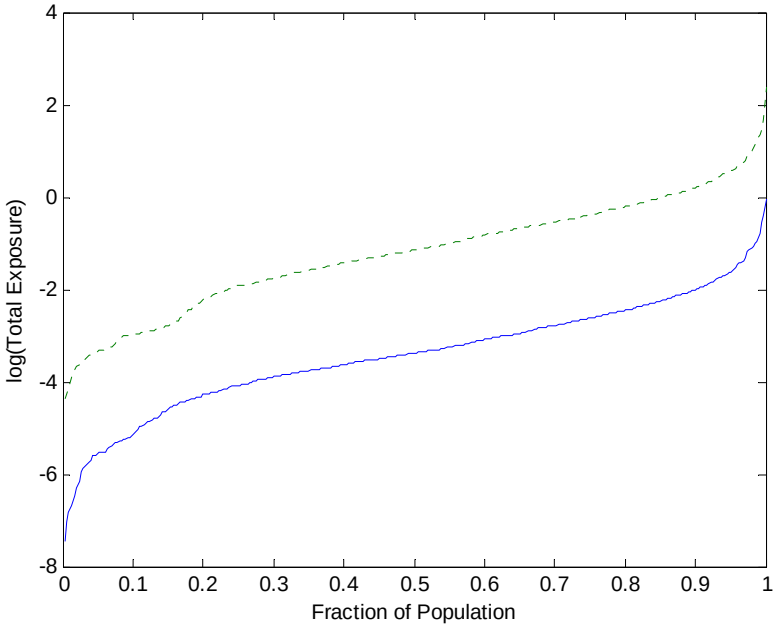


Figure 7.30 Result of uncertainty analysis for anti-cholinesterase pesticides

In this plot the new data are about two orders of magnitude higher than in the original simulation. So for anti-cholinesterase pesticides in this very extreme situation there would have been about 10% of the population whose median combined dose would exceed the combined ADI, compared with 3% in the original simulations.

The corresponding data for oestrogen agonist pesticide compounds are shown in Figure 7.31. These data show a similar change in the median dose estimates and a corresponding increase in the proportion who could have a dose in excess of the combined ADI dose.

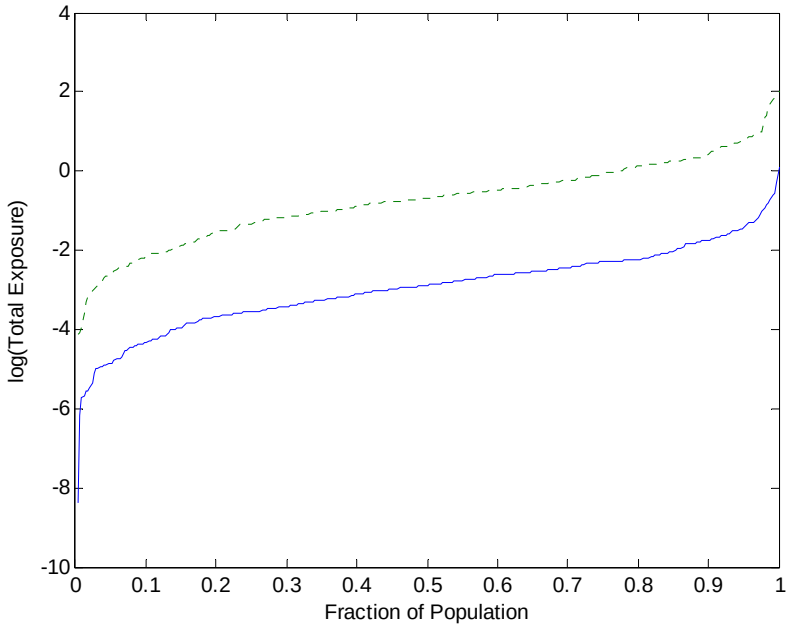


Figure 7.31 Result of uncertainty analysis for oestrogen pesticides

7.5.3 Uncertainty analysis for the vegetarian model

Vegetarians were selected for the uncertainty analysis because any changes in the assumptions about consumption would preferentially have impacted on this group. For the vegetarian model we change the following parameters:

1. the probability for eating a fresh (i.e. unprocessed) fruit (per day) is changed from 0.5 to 1, i.e. the reduction ins residues from processing was removed; and

2. the maximum number of fruit portions eaten per day was set to 10 (from 5).

The results of the simulation are shown in Figures 7.32 and 7.33, where again the blue line represents the original distribution of median combined dose estimates and the green line the new distribution of median dose estimates.

The magnitude of the change in the median dose estimates was much smaller than of the bystander model and neither for the anti-cholinesterase nor the oestrogen agonist compounds was there any median dose estimates that were above the ADI dose.

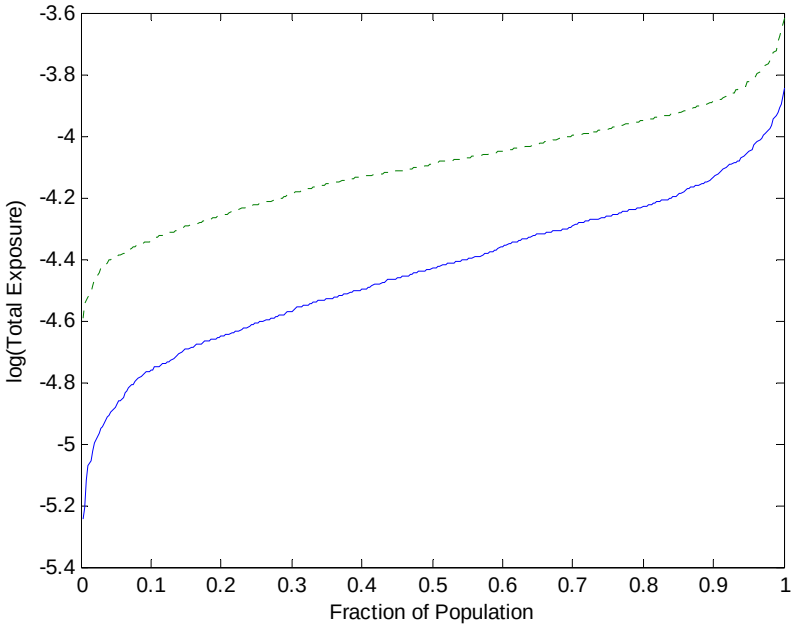


Figure 7.32 Result of uncertainty analysis for anti-cholinesterase pesticides

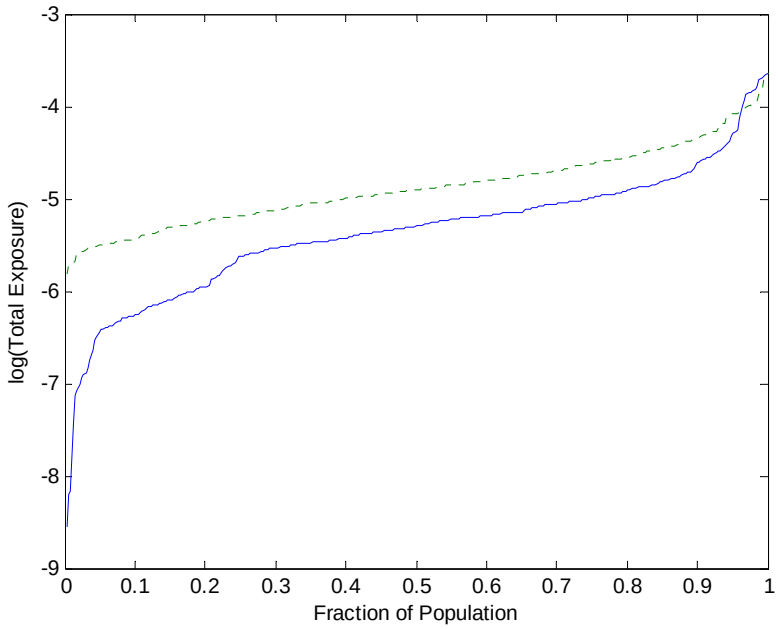


Figure 7.34 Result of uncertainty analysis for oestrogen pesticides

7.5.4 Conclusion

This exercise to define the uncertainty is by no mean a complete sensitivity/uncertainty analysis. However, the results shown here have demonstrated that an increase in exposure results in an increase in the internal dose estimate of the pesticide mixture. Most importantly, the increase is not proportional to the change in exposure. This is due to the non-linearity of the relationships between the model variables and also the dependence of the model on many parameters.

In a comprehensive sensitivity analysis, we need to identify the key model parameters that the model is most sensitive too and vary these parameters according to some prescribed probability distribution. This is however beyond the scope of the present study.

However, despite these limitations the analysis shows that the food consumption simulations are particularly robust and that choosing quite extreme parameters for the pattern of fruit and vegetable consumption does not materially affect the conclusions. For the bystanders the extreme assumption of assuming their exposure was comparable to the farmer produced higher combined dose estimates, with corresponding increases in the proportion of the group exposed above the combined ADI dose. However, this was still only a small proportion of the total exposed population.

8 THE RISK ASSESSMENT FRAMEWORK

Objective 13	Scoping study to determine information required for risk assessment framework incorporating current COT recommendations on assessment of mixtures. Proposed requirements compared with existing regulatory framework.
Objective 14	Estimate of extent of additional requirements and associated additional cost for approvals and authorisations if COT recommendations were to be adopted. Basic analysis and discussion of impact at policy level.
Objective 15	Development of a proposed outline for a prioritisation scheme. Selection of a group of chemicals of concern for development of a case study comparing risk assessments under existing and proposed frameworks using data generated during other phases of this project.

Earlier Chapters have used the available data to assess cumulative and aggregate exposure to mixtures of particular compounds of interest. However there is a lack of information to be able to adequately assess the consequent risk, due in part to the nature of the current regulatory framework, and data being generated for data packages required for the Directive 91/414/EEC. An evaluation of the extra data requirements for the assessment of risk of exposure to mixtures is required. A summary of the existing regulatory framework in the UK will identify gaps in data requirements and knowledge needed.

8.1 BRIEF OVERVIEW OF THE REGULATION OF PESTICIDES AND VETERINARY MEDICINES IN THE UK

The general principles whereby pesticides, biocides and veterinary medicines are regulated are broadly similar. The regulations relating to pesticides will be focussed on in more detail in this section, as this has been the main focus of earlier sections of the report.

The term pesticide is considered to include plant protection products, rodenticides, animal and bird repellents. Food storage treatments, plant growth regulators, anti-fouling products for boats and wood preservatives all also fall within the definition of pesticides. Agricultural pesticides include those used in agriculture, horticulture, private gardens and forestry as well as weed killers for use in and around watercourses, lakes and for use on non-crop land such as roads and railways. The Pesticides Safety Directorate (PSD), an agency of the Department for Food and Rural Affairs (DEFRA) is responsible for regulating agricultural pesticides at a national level. Non-agricultural pesticides (biocides) include those used in wood preservation, as masonry biocides, as public hygiene/nuisance insecticides and as anti-fouling products on boats. The Health and Safety Executive (HSE) is responsible for non-agricultural pesticides at the national level.

As the regulation of agricultural and non-agricultural pesticides and veterinary medicinal products is governed by EC legislation, the UK cannot unilaterally add requirements to the authorisation process of these substances.

Active ingredients are evaluated at the EU level, with the task of rapporteur for specific compounds being delegated to a particular member state. Each member state is responsible for

regulation at a national level. Only active ingredients on the Annex I listing can be approved for use by national authorities.

The Plant Protection Products Directive (91/414/EEC) came into force on 26 July 1993 and is implemented in the UK by the Plant Protection Products Regulations 2003.

The main elements of the Directive are as follows:

- To harmonise the overall arrangements for authorisation of plant protection products within the European Union. This is achieved by harmonising the process for considering the safety of active substances at a European Community level by establishing agreed criteria for considering the safety of those products. Product authorisation remains the responsibility of individual Member States.

- The Directive provides for the establishment of a positive list of active substances (the Annex I list) that have been shown to be without unacceptable risk to people or the environment.

- Active substances are added to Annex I of the Directive as existing active substances are reviewed (under the European Commission (EC) Review Programme) and new ones authorised.

- Member States can only authorise the marketing and use of plant protection products after an active substance is listed in Annex I, except where transitional arrangements apply.

Before an active substance can be considered for inclusion in Annex I of Directive 91/414/EEC, companies must submit a complete data package (dossier) on both the active substance and at least one plant protection product containing that active substance. The data required:

- identify an active substance and plant protection product;
- describe their physical and chemical properties;
- their effects on target pests, and;
- allow for a risk assessment to be made of any possible effects on workers, consumers, the environment and non-target plants and animals.

Comprehensive lists of the data required to be evaluated to satisfy inclusion in Annex I of the Directive, or the authorisation of a plant protection product are set out in the Directive, (Annexes II and III). Annex II data relate to the active substance and Annex III to the plant protection product. These data are submitted to one or more Member States for evaluation. A report of the evaluation is submitted to the European Food Safety Authority (EFSA). Following peer review of the report EFSA makes a recommendation to the European Commission on whether Annex I inclusion is acceptable. This recommendation is then discussed by all Member States in the framework of the Standing Committee on the Food Chain and Animal Health (SCFA), previously the Standing Committee on Plant Health (SCPH). Where necessary, the Scientific Panel is consulted before the SCFA can deliver an opinion on whether an active substance should be included in Annex I of 91/414/EEC.

The Pesticides Safety Directorate is the responsible authority in the UK for product authorisations under this Directive. The Advisory Committee on Pesticides (ACP) is an independent body of experts that advises Ministers on all major pesticide issues. The ACP is supported by a number of panels as well as other Committees such as:

- Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (COT);
- Committee on Mutagenicity (COM);
- Committee on Carcinogenicity (COC).

Therefore once an active ingredient has been listed on Annex I following evaluation by EFSA, applications can be made to have products that contain the active ingredient approved in individual Member States for specified uses. The data required relating to toxicological studies is summarised below.

8.2 TOXICOLOGICLA DATA REQUIREMENTS OF THE DIRECTIVE 91/414/EEC

a) Acute toxicity

- Oral
- Percutaneous
- Inhalation
- Intraperitoneal
- Skin and where appropriate eye irritation
- Skin sensitisation

b) Short-term toxicity

- Oral cumulative toxicity (28-day study)
- Oral administration - two species, one rodent (preferably rat) and one non-rodent, usually 90-day study
- Other routes (inhalation, percutaneous as appropriate)

c) Chronic toxicity

- Oral long-term toxicity and carcinogenicity (rat and other mammalian species) - other routes as appropriate

d) Mutagenicity - test battery to assess gene mutations, chromosomal aberrations and DNA perturbations

e) Reproductive toxicity

- Teratogenicity studies - rabbit and one rodent species, oral and when appropriate percutaneous
- Multigeneration studies in mammals (at least two generations)

f) Metabolism studies in mammals

- Absorption, distribution and excretion studies - following both oral and percutaneous administration
- Elucidation of metabolic pathways

g) Neurotoxicity studies - including where appropriate delayed neurotoxicity tests in adult hens

h) Supplementary studies

- Toxic effects of metabolites from treated plants in cases where different from those identified in animal studies
- Any mechanistic studies needed to clarify effects reported in toxicity studies

i) Toxic effects on livestock and pets

j) Medical data
- Medical surveillance on manufacturing plant personnel
- Direct observation, e.g. clinical cases and poisoning incidents
- Health records, both from industry and agriculture
- Observations on exposure of the general population and epidemiological studies if appropriate
- Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests
- Sensitisation/allergenicity observations
- Proposed treatment: first aid measures, antidotes, medical treatment
- Prognosis of expected effects of poisoning

k) Summary of mammalian toxicology and conclusions (including no observable adverse effect level (NOAEL), no observable effect level (NOEL), acceptable daily intake (ADI). Overall evaluation with regard to all toxicological data, and other information concerning the active substance. Data on potential human toxicity are required for the active ingredient, the formulated product and important metabolites of the active ingredient. These data are generated with laboratory animals in facilities compliant with the principles of Good Laboratory Practice (GLP).

Extra information may be required for specific effects such as those that may affect the nervous system, immune, or endocrine systems. Acceptable levels of exposure can be derived from the no observed adverse effect levels (NOAELs). Three key acceptable exposure levels are normally established for an agricultural pesticide:

Acceptable daily intake (ADI)

This is the mean amount of a compound (mg/kg body weight) which can be consumed on a daily basis, from which no harm will result (based on the interpretation of toxicology data). The starting point for the derivation of the ADI is usually the lowest relevant NOAEL that has been observed in toxicity studies. This is then normally divided by 100, a factor of 10 for animal to human sensitivity and a factor of 10 for variation within the human population. A factor of less than 100 may be used when there are appropriate human data or a larger factor may be used for compounds producing severe effects or as an interim measure when there is additional uncertainty surrounding an aspect of the data package. The studies from which NOAELs and hence ADIs are derived take into account any impurities in the pesticide active ingredient as manufactured, and also any toxic metabolites formed in the body.

Acute reference dose (ARfD)

The ARfD relates to the amount of a chemical that can be taken in at one meal or on one day. It is usually derived from the lowest relevant NOAEL in studies that have assessed effects following short-term exposure or end-points such as developmental toxicity that may be affected by a single dose at a critical time.

Acceptable operator exposure level (AOEL)

This relates to a level of daily exposure that would not cause adverse effects in operators (workers) who work with a pesticide regularly defined by the pattern of usage of the pesticide. This can be either a short-term or a long-term AOEL. AOELs are derived in a similar way to the ADI, although they are often based on an appropriate study that used dermal exposures.

8.3 PROCEDURES FOR ESTIMATING EXPOSURES

8.3.1 Dietary Intakes

For chronic intakes this takes into account all foodstuffs in which residues might occur, including those resulting from the use of other products that contain the same active ingredient. If the use of a pesticide produces significant concentrations of toxic metabolites in food the acceptability of exposure to each of these metabolites is also assessed. To check whether the proposed use of a pesticide might cause unacceptable dietary exposures, an estimate is made of a high level intake that an individual might incur over a prolonged period.

If the pesticide has toxic effects that could arise from a single dose, an estimate is made of the high dietary exposure that could occur in a single day or from a large portion of that food. These estimates are based on the distribution of measured residues of the pesticide in foods derived (directly or indirectly) from treated crops, and data on the national patterns of consumption for different foods from surveys.

Separate calculations are carried out for dietary exposures in a number of different consumer groups, including infants, toddlers, children and adults to check that the particular dietary characteristics of all age groups are covered. Initial estimates are currently performed using a set of conservative assumptions and produce point (deterministic) estimates representing a realistic approximate worst case.

In determining the likely long-term exposure, the median residue level from trials performed following application of the pesticide according to the highest approved application rate and shortest pre-harvest interval, is used. The total intake for all foods from crops treated with the pesticide is estimated as follows: the sum of the two highest 97.5th percentile intakes plus the mean population intakes for other foods. The results are summed to give a value in mg/kg body-weight, which can be compared with the ADI.

For the acute intake estimate the highest residue found in trials is multiplied by a variability factor of (1 – 10) and by the daily consumption for a high level consumer (97.5 centile) and corrected for body weight. This also gives a value in mg/kg body-weight and is compared with the ARfD.

8.3.2 Maximum Residue Levels (MRLs)

Although MRLs for pesticides and veterinary medicines are statutory limits, MRLs for pesticides are not safety based, whereas those for veterinary medicines are.

MRLs are defined as the maximum concentration of pesticide residue (expressed as milligrams of residue per kilogram of food/feeding stuff) legally permitted in or on food commodities and animal feeds. These are based on Good Agricultural Practice (GAP) and are intended primarily as a check that GAP is being followed and to assist international trade in treated produce. Formerly MRLs were set domestically under the Pesticides (Maximum Residue Levels in Food)

Regulations. Currently most MRLs in the UK legislation are those that have been agreed at the EU level.

8.4 ASSESSMENT OF EXPOSURES TO COMBINATIONS OF PESTICIDES

The current assessment of a pesticide is mostly focussed on the acceptability of an individual active substance in isolation. The potential for the toxicity of an active substance to be altered by other components of the formulation or other residues on a crop is not investigated in as much detail as the properties of the individual active substance.

The acute toxicity of the formulation as sold must be addressed. This may be done either by testing the formulation or by a calculation based on the properties of its constituents. If data show the acute toxicity of the formulation to be significantly different from that expected based on its individual constituents this would be investigated further.

It is unusual for repeat dose oral studies to be performed on a formulation therefore any interactions that alter the toxicity profile of the active ingredient following repeated exposure are unlikely to be identified.

Formulations may contain more than one active substance. When assessing formulations containing two or more active substances with a common mechanism of action or similar toxicity profiles the potential for interaction is currently considered.

Current UK and international assessments of pesticides do not routinely take any specific account of the risk to consumers from the potential for interaction of residues of different pesticides or to operators from the potential effects of simultaneous or sequential exposure to different active substances.

In specific cases, where a range of compounds degrade to a common toxic metabolite and residue, a group ADI has been set – e.g. ethylene*bis*dithiocarbamates (EBDCs) are assessed in terms of ethylene thiourea (ETU). It is generally assumed that exposures will be significantly below the NOAELs in animals, therefore significant interactions are unlikely. The potential for simple interaction is addressed based on these assumptions.

8.5 EVIDENCE OF EXPOSURE TO MULTIPLE PESTICIDE RESIDUES IN THE DIET

There is existing information on the potential for multiple exposures to pesticides. These data have been used in this study, and come from four main sources:

- The pesticides residue surveillance programme, where food commodities are screened for a range of pesticides in each year;
- Analyses of pesticides in the Total Diet Survey which measure levels in the main components of the diet;
- The National Diet and Nutrition Survey, which provides information on the food and drink consumption habits of individuals in the UK;
- The pesticide surveillance programme, which provides details of the use of pesticides in the UK, and can be used to identify the occurrence of tank mixes of pesticides on particular crops.

The pesticide surveillance programme, which is funded by DEFRA and carried out the Central Science Laboratory provides detailed usage patterns for pesticides, but is only relevant for UK produce. There is a wide range of food types available to UK consumers, and detailed pesticide usage information on such produce can be scarce, or as is often the case non-existent.

The Pesticide Residue Committee (PRC) surveillance monitoring programme has what are known as rolling programmes, focussing on particular food commodities each season. There are also specially targeted surveys to look at known problems of excessive residue or illegal residues. Surveys of three dietary staples, bread, milk and potatoes, are undertaken each year.

There is a list of pesticides that are sought in the samples, and the choice of pesticides is primarily influenced by:

- Pesticide usage data;
- Potential for residues occurring (usage pattern or physico-chemical properties);
- Analytical capabilities of laboratories;
- Toxicological profile of the pesticide;
- Evidence of problematical residues from earlier surveys.

Some information on pesticide use in a large range of countries across the world is available commercially, which could be used to allow greater targeting of the pesticides sought, particularly for crops imported from outside the EU. Post harvest treatments have the greatest potential for producing residues due to the short time between use and marketing of the produce. Insecticides and fungicides tend to be targeted more than herbicides, which again often relates to timing of use. Notable exceptions include the use of desiccants on potatoes and oilseed rape and glyphosate in cereals.

A range of 200-300 pesticides can be quantified, depending on the multi-residue method employed. Analysis of pesticides not part of the multi-residue method needs to be carried out separately, which adds cost to the programme. At the moment quantification of residues is only carried out at or above the reporting limit (RL), which is a problem identified in earlier chapters of this report.

In addition to the national monitoring programme, the UK participates in an EU-wide co-ordinated monitoring programme. The aim of the community programmes is to ensure compliance with residues legislation and to enable estimation of the actual exposure to pesticides from the diet.

8.6 RECOMMENDATIONS BY THE COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT) AND CONSEQUENCES FOR THEIR ADOPTION

This section of the report discusses the recommendations made by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) on pesticide mixtures and health.

It is considered by the COT that certain groups of the population are more vulnerable to possible effects of combined exposures, with the developing brain and endocrine systems of the foetus and of young children of particular concern. The wide variety of sources of human exposure to pesticides and veterinary medicines, including food, is the central theme to this report.

The COT report concludes that "the impact of combined exposure to multiple pesticides of either toxicologically different or similar groups is only rarely addressed by European regulatory authorities and combined exposure has only recently been considered in the USA". As already mentioned the regulation of pesticides and veterinary medicines in EU member states has already been harmonised to a great extent. The conclusions reported by the COT, although relating to the UK position, would have an impact beyond the national level.

Principal COT recommendations related to regulation are listed below with a brief comment relating to the consequences for their adoption.

a) The approval system for pesticides (including veterinary medicines) should consider all sources of exposure.

Our report has highlighted gaps in data relating to exposure to pesticides and veterinary medicines. One of the areas where data are importantly lacking is in relation to the use of veterinary products and biocides. The Pesticide Usage Survey provides data for agricultural pesticide use. Similar data for other compounds would be needed for other uses.

b) Establish a framework to decide when it is appropriate to carry out combined risk assessments of exposures to more than one pesticide and/or veterinary medicine.

This would require a cross departmental approach by UK regulatory authorities to consider agricultural pesticides, non-agricultural pesticides and veterinary medicines. This co-ordinated approach would have to identify which compounds would need to have additional toxicological data to support their authorisation for use or sale.

c) For assessment of combined exposures, chemicals with different toxic actions will act independently (simple dissimilar action), and those with the same toxic action will act additively (simple similar action).

This statement by COT, indicating that when it deemed necessary to carry out risk assessment of combined exposure, the default assumptions should be that compounds with different toxic actions would act independently, and those with the same toxic action would act additively.

d) A toxic equivalency approach might be considered. In specific instances the possibility of interaction, particularly potentiation, may have to be considered. In such circumstances adequate dose-response data will be essential in the interpretation of findings in relation to dietary intakes and other human exposures.

This has implications for the way toxicological studies are currently done to generate data packages for regulatory submissions, requiring an investigation of the possible interaction of compounds and the generation of dose response data. Although the COT recommendations focus on the additive effects of pesticides, other types of interaction should be borne in mind.

e) The approval of pesticides and authorization of compounds used in veterinary medicine should include more formal analysis, and possibly experimental investigation, of the potential for combined toxic action or interaction due to the addition of other substances to the formulations employed. This consideration should also include tank mixes of pesticides.

This also has implications for the way toxicological and exposure studies are currently done to generate data packages for regulatory submissions, requiring an investigation of the possible

interaction of coformulants with active ingredients. Tank mixes are relevant for exposure at the time of application, such as operators and bystanders, but not considered necessary for dietary exposure.

Further work should be undertaken, in suitable experimental systems, to characterise both the nature of, and dose-response relationships for, combined actions of pesticides, veterinary medicines and similar substances. Such studies should be performed at doses that include those potentially ingested by humans in the diet. Groups of pesticides having common targets of toxicological action should be identified. Such work might include the identification of sites of action at a molecular level, to identify those groups of compounds that would be expected to show simple similar action. Studies of protein and/or RNA expression, using modern array technology, in relevant systems may be appropriate in some cases. These may be followed up by more detailed mechanistic studies of gene expression and/or enzyme or hormonal activity as necessary. Array technology (RNA and protein) may be appropriate in some cases, or enzyme or hormonal activity in others.

f) Analysis of all sources of exposure to pesticides and of concurrent exposure to more than one pesticide will require changes in the methods used for risk assessment, including, in some cases, the use of probabilistic exposure assessment. This will be contingent on changes in residue surveillance.

As indicated there would be a need to modify the way the surveillance programmes are carried out to generate data for the residues in food. A statistical distribution of the residues would be needed for probabilistic modelling, which means values for residues which are between the Limits of Quantification (LOQ) and the Reporting Limit (RL). Currently values below the RL are reported as such, i.e.<RL.

There would also be a need to ensure that significant residues were identified in the surveillance programmes, and that the occurrence of unusual or unexpected compounds could be identified.

There are also COT recommendations for surveillance, research and public information, which are listed below. These recommendations are self explanatory, and will be considered further later in this report.

g) Dietary and food consumption surveys in the UK should continue to cover all social, age, and ethnic groups within the population. Consideration should be given as to whether additional groups need to be covered.

Feedback from the dietary and food consumption surveys and residue monitoring could be used to identify where food items with a potentially higher risk of dietary exposure are being consumed by groups of the population. Trends and changes need to be monitored.

h) Aggregate exposure assessment will require acquisition of robust data on all pathways of exposure to pesticides and veterinary medicines and on sources of variation in such exposure.

Data on exposure from sources other than food and water seem to be extremely poor or non-existent. With a few exceptions, biomarkers and markers of effect, which would help enable the estimation of exposure are not available; nor are adequate intake data available.

i) Residue surveillance programmes should be modified in the light of the need for representative data for probabilistic exposure assessment. The effect of food processing

and preparation on the bioavailability and chemical nature of residues should be further investigated.

The surveillance is not random but is targeted on products where previous experience or other information suggests that there are likely to be problems. Therefore, it is extremely difficult to assess the frequency with which residues, below or above legally enforceable MRLs occur. It is even more difficult to assess the frequency of multiple residues occurring in the same product. There are further difficulties with limits of detection and reporting limits for assays, and the MRLs for pesticides in crops exist primarily to assess good agricultural practice (GAP).

It was concluded that a representative program of surveillance would be necessary to assess the frequency of residues, including multiple residues. The Committee recognised that sources of information about the usage of pesticides, veterinary medicines and growth promoters outside the UK are limited.

8.7 PROPOSED REQUIREMENTS COMPARED WITH EXISTING REGULATORY FRAMEWORK.

The COT report recommendations have implications for the way pesticides and veterinary medicines are regulated in the UK. This in turn has implications at the EU level, as much of the toxicology data evaluated for a particular active ingredient is carried out prior to the Annex I listing.

There are six COT recommendations relating to the regulatory framework. There are consequences for the surveillance activities and supporting research required to provide the data and information for the regulatory framework to function. The six regulatory recommendations have therefore been considered in this way.

8.7.1 All sources of exposure should be considered

Non-dietary exposure

The gaps in data relating to exposure to pesticides and veterinary medicines would be addressed by following the recommendations listed earlier under surveillance. The types of data required relate to both dietary and non-dietary exposure. Surveillance programmes would need to be modified to generate such data, which has potentially large cost implications.

Exposure data for agricultural pesticides is well established for the principal application scenarios in the UK. The development of the EUROPOEM database and the North American Pesticide Handlers Exposure Database (PHED) is expected to result in a more comprehensive model, the Agricultural Handlers Exposure Database (AHED). Recent DEFRA funded research carried out by CSL has also investigated the exposure to pesticides from amateur uses. DEFRA funded research is currently taking place to evaluate bystander exposure to agricultural pesticides. These databases are based on conventional sampling methodology using interception sampling protocols, i.e. cotton patches on the skin or clothing, but it is likely that they provide an overestimate of actual exposure to the skin because of the greater retention of the sampling media compared with human skin. Further work is needed to improve the sampling methods to give a more accurate assessment of exposure.

As databases are established and developed information on the pathways and sources of variation in exposure will improve. However data are lacking for the use of biocides and certain veterinary medicines.

Other sources of exposure that need to be considered are human medicines such as antibiotics and head lice treatments which could contribute to the exposure to mixtures of compounds used as pesticides or veterinary products.

Dietary exposure

The FSA programme of consumption surveys needs to be constantly reviewed to ensure that all social, age and ethnic groups are covered. These data provide the basis for estimating dietary exposure as shown in the earlier work packages. The residue surveillance for pesticides and veterinary residues in food carried out in the UK is not intended to provide data for dietary exposure. The Pesticide Residues Committee (PRC) are responsible for the annual monitoring of pesticide residues in food and drink to ensure that no residues are occurring in food and where residues are found that they are: either within the MRL, or if they are above the MRL that they are below the separate safety limits set for residue consumption (and which are always significantly above the MRL). The programmes are often targeted on compounds and food products where there is some history or new information that suggests that there are likely to be problems. The setting of the MRLs for pesticides is not related to toxicological data or possible health implications, but exist as a post regulatory control to demonstrate that good agricultural practice (GAP) is being followed.

Therefore the main objectives of residue surveillance programmes need to be addressed. As only data for residue levels above the reporting limit (RL) are reported (or recorded) it is very difficult to obtain information on the true distribution of residues between the LOQ and the MRL.

To achieve the COT recommendations a representative programme of surveillance would be necessary to assess the frequency of all residues. This would include information relating to distribution of residue values above the LOQ that could be used in probabilistic models. Knowledge of products being used is required to focus the surveillance programmes, which relates back to data on usage patterns in other member states and non-EU countries. It is recognised that sources of information about the usage of pesticides, veterinary medicines and growth promoters outside the UK are limited, and any UK-based data collection would be very difficult.

The Pesticide Usage Survey data for the UK provides a useful source of information to assess when exposure to mixtures could occur either during application or as residues in food for UK produce. Similar information would be needed for other EU member states and non-EU countries. This is beyond the control of the UK, but lack of this type of information has implications for the uncertainty involved with risk assessments.

The development of sensitive biological monitoring methods would provide data on the incidence of exposure to mixtures of pesticides from all sources of exposure. In addition the use of biological effect monitoring could provide an indication of the possible health effects of exposure to mixtures.

8.7.2 Framework for decisions on which compounds require combined risk assessments of exposures

This is discussed in greater detail in Section 8.9, and involves a cross departmental approach by UK regulatory authorities for pesticides, biocides and veterinary medicines. This co-ordinated approach would need to identify, and prioritise, groups of compounds with a common mechanism of action. This is beyond what is required by the current regulatory framework.

It is important to realise that aggregate and cumulative exposure to a class of pesticide compounds can only be carried out as a whole and it is probably not possible to assess the impact of a single compound in a regulatory context, i.e. it is the sum of all exposures that is important. It may be possible to assess the incremental effect of approving or restricting the use of a single compound in relation to a larger group of compounds that act in a similar way, but the evaluation would be based on a large number of assumptions about the behaviour of the market in relation to the change, e.g. whether approving one compound would result in loss of market share for another.

8.7.3 Independent and additive action

Although the COT concluded that in most cases the outcome of combined exposures would be simple additivity of effect (two compounds with the same toxic end-point and same mechanism) the possibility exists that that enhanced toxicity might occur where two pesticides acted on the same toxic end-point but by different mechanisms.

8.7.4 Toxic equivalency and dose-response data

Toxicological studies are currently done on the single active ingredient or formulated product. A framework established in response to the COT recommendation in Section 8.7.2 would identify the priority compounds for which a combined risk assessment should be done. The implication of this are potentially immense in terms of generating data packages for regulatory submissions, as this would require an investigation of the possible interaction of many compounds and the generation of dose response data.

Toxic Equivalency Factors (TEF) are used to determe the human health risk from exposure to dioxins, by characterising the toxicities of individual dioxin compounds. The COT report suggests that this may be a way to assess exposure to a range of pesticides in a mixture. This approach used for dioxins could be used in much the same way for pesticides with similar toxicity mechanisms or toxic end points, but with widely ranging toxicity. In considering the TEF approach for pesticide mixtures the use of TEFs for dioxins can provide a useful insight into potential advantages and disadvantages.

With the ability to assign TEFs to individual pesticide compounds, it is possible to determine a number that represents the total toxicity of any given absorbed dose of the pesticides in question. In the case of dioxins the mass of each compound is multiplied by the appropriate TEF. When this is done for each of the compounds in a mixture, the products are summed to obtain a toxicity-weighted mass quantity, known as the Toxic Equivalents (TEQ). This use of toxic equivalency could be developed in the case the pesticides in a mixture are considered to have an additive effect.

In our modelling work we have selected groups of compounds where we consider there is a similar mode of toxic action and we have assumed additivity of dose.

Running probabilistic models with different scenarios (i.e. additive, synergistic, antagonistic) and evaluating the outcome would provide an indication of how close the exposure would be to the harmful dose. This is discussed further in Section 8.9.

The regulatory framework already considers the possibility of toxic interactions where two or more pesticides are co-formulated in the same product. Work has started with a DEFRA funded pilot study to investigate possible interactions with products that are commonly tank mixed. Although PSD reports that it is working towards a combined risk assessment for dietary

exposure to residues of organophosphate and carbamates pesticides it acknowledges that the approach being adopted will have scientific limitations.

The assessment of toxicity described in Section 8.6 takes into account the uncertainties in extrapolating from animals to humans, and also the variability within the human population for possible sensitivity to the toxic effects of the pesticide. There is never a situation of zero risk, as at the extreme ends of the spectrum an unusually sensitive individual might also be an extremely high consumer of foods containing residues of a pesticide at or close to the MRL. The probability of this occurring is very low, but still possible.

The majority of existing information relating to the effects of combinations of pesticides comes from studies with experimental animals or as part of in vitro studies. Such studies tend to be focussed at the effects due to combined actions on the same toxic end point, and tend to use levels of exposure that are much higher than those likely to occur as a result of ingestion of pesticide residues in food.

Direct interactions can also occur between the components of a mixture. Some studies have found both synergistic and antagonistic interactions, as well as additive effects in mixtures, again usually at higher exposure values than would occur via dietary exposure. The underlying mechanisms for most interactions is not known, although with increasing knowledge from a range of animal studies providing key information from pharmacokinetics through to toxicology for single compounds, it is increasingly feasible to predict some interactions, for example using QSAR (Quantitative Structure-Activity Relationships) or with PBPK (Physiologically Based Pharmacokinetic) modelling.

8.7.5 Combined toxic action

The approval of pesticides and authorization of compounds used in veterinary medicine should include more formal analysis, and possibly experimental investigation, of the potential for combined toxic action or interaction due to the addition of other substances to the formulations employed. This consideration should also include tank mixes of pesticides.

This has implications for the way toxicological studies are currently done to generate data packages for regulatory submissions, requiring an investigation of the possible interaction of co-formulants with active ingredients. This mainly applies to when pesticides are used together, such as with tank mixing. Although the pesticide risk assessment currently considers the formulated product, consequences of possible combined toxic action or interaction needs to consider interactions with other compounds. This relates principally to occupational and bystander exposure, where exposure to the active ingredients and co-formulants in tank mixes would occur.

8.7.6 Probabilistic modelling

Analysis of all sources of exposure to pesticides and of concurrent exposure to more than one pesticide will require changes in the methods used for risk assessment, including, in some cases, the use of probabilistic exposure assessment. This will be contingent on changes in residue surveillance.

Modifications of the way the surveillance programmes are carried to provide data on the distribution and variation of the residues could be fed into probabilistic models. In the present work we have explored the use of existing residue surveillance data but are concerned that the limitations make it not an ideal source for modelling. Risk assessment with deterministic methods are considered to be conservative, not using the full array of information of multiple

sources of exposure and variation in routes of exposure to more than one compound. Probabilistic methods are being used for exposure to compounds in a number of fields, particularly where there are multiple sources of exposure with a wide variation in exposure levels.

The use of probabilistic models does have some drawbacks, such as the large volume of data required as input parameters and the computing time required to run simulations.

8.8 ESTIMATE OF EXTENT OF ADDITIONAL REQUIREMENTS AND ASSOCIATED ADDITIONAL COST FOR APPROVALS AND AUTHORISATIONS IF COT RECOMMENDATIONS WERE TO BE ADOPTED

8.8.1 Sources and quantification of exposure

- Pesticide usage for non agricultural pesticides (HSE) and veterinary medicines (VMD)
- Food consumption surveys structure
- Residue surveillance surveys structure
- Lower reporting limit for residues
- Duplicate Diet Surveys to validate models
- Biological monitoring for surveillance of exposure

Non-agricultural pesticides and veterinary medicines would need to have more detailed information available on usage, similar to the data gathered by CSL for the Pesticide Usage Survey. The cost of this exercise is not likely to be exceed that of Pesticide Usage Survey given the usage of these products compared to agricultural pesticides.

The principal costs are associated with the surveillance of pesticide residues in food. Current surveillance for agricultural pesticides and veterinary medicines is in the region of £5 million per annum. The broadening of the scope for food commodities samples has cost implications which can be estimated in relation to the number of samples collected and analysed.

The consequences of setting of lower RL values for the surveillance programmes have greater implications, that are more difficult to estimate. Most pesticides have a RL currently set at 10ppb (0.01 mg/kg), and laboratories carrying out the analysis have analytical methods that can detect for up to 200 pesticides. As the number of pesticides being sought increases, the cost increases. There is a consequent increase in the number of samples required for method validation (e.g. matrix matching and recoveries). However quantifying pesticide residues below 0.01 mg/kg has cost implications that are determined by various factors such as the properties of the compound being analysed. Analytical methods would need to be modified, and include extra steps such as extract clean-up and concentration. The cost implications would have to be evaluated based on the pesticide in question and the RL required for the residue in particular matrices.

Biological monitoring for surveillance of exposure is not done on any scale, although some research projects in the past have attempted to measure parent compounds and metabolites of groups of pesticides. Any programme set up to monitor pesticides in body fluids such as urine is

likely to aimed at validating the modelling of exposure, for example in combination with a total diet survey approach.

The costs associated with surveillance are likely to have to be met by Government regulators and policy makers.

8.8.2 Framework for decisions on which compounds require combined risk assessments of exposures

- Considered to require the setting up of a cross departmental committee to identify, and prioritise, groups of compounds with a common mechanism of action.

The cost of such a cross departmental approach would again be met by Government regulators and policy makers, requiring decisions on the use of pesticides to be made using a common approach.

8.8.3 Toxic equivalency and dose-response data

In cases where combined exposures to compounds occurs COT indicate that the action would be independent or additive. In these cases it is not necessary to carry out comprehensive toxicological studies evaluating the effect of combined exposures. However COT also indicate that the possibility exists that that enhanced toxicity might occur where two pesticides act on the same toxic end-point but by different mechanisms. Extra toxicological information is likely to be requested by the regulatory authorities in support of cases where a compound is suspected of exhibiting potentiation. This cost would have to be met by the industry in compiling the dossier for the new (or reviewed) compound to the regulatory authority.

In considering toxic equivalency, then this could be done by regulators using toxicological data already supplied by industry as part of regulatory packages. However there may be a need for the industry to supply supplementary data from further toxicological studies.

8.8.4 The approval of pesticides and authorization of compounds used in veterinary medicine should include more formal analysis, and possibly experimental investigation, of the potential for combined toxic action or interaction due to the addition of other substances to the formulations employed. This consideration should also include tank mixes of pesticides

This relates principally to the exposure to the formulations of the pesticides and veterinary medicines, where co-formulants need to be assessed for possible effect on the action of other compounds.

- Identify where tank mixes could occur
- Identify co-formulants of greatest consequence
- Generate data for possible interaction of compounds for factors such as toxicological effect and rates of dermal penetration

Data identified as being required as part of the surveillance for usage would provide information on which products were being used in tank mixes. Further data from industry is likely to be required by regulatory authorities in support of formulations containing co-formulants considered to be of greatest concern.

8.8.5 Analysis of all sources of exposure to pesticides and of concurrent exposure to more than one pesticide will require changes in the methods used for risk assessment, including, in some cases, the use of probabilistic exposure assessment. This will be contingent on changes in residue surveillance

- Probabilistic models need to be developed, validated and used for risk assessment in the regulatory process

Development and validation of probabilistic models for risk assessment is likely to be done by regulatory authorities, although industry could be required to provide an assessment of the analysis of exposure to pesticide mixtures from all routes.

8.9 BASIC ANALYSIS AND DISCUSSION OF IMPACT AT POLICY LEVEL

To respond to the issues of possible human health effects of exposure to a mixture of pesticides the regulatory framework would need greater co-ordination between regulatory authorities. There is a need to prioritise scenarios where risk assessments should be carried out for exposure to mixtures of pesticides, considering all sources, pathways and routes of exposure. In cases where exposure to a mixture of compounds was considered to result in a potentially harmful dose there would be a need to regulate for this. In some cases this may require regulatory authorities to consider the removal of a pesticide or pesticides from the authorised list. In such cases some conflict would occur, particularly when compounds with very different uses were being evaluated.

The information currently available to regulators is not adequate to allow the risk assessment to be carried out without some degree of associated uncertainty. To assess the risk of exposure to mixtures, more detailed information would be required on the sources and pathways of exposure, particularly for dietary exposure, as this route of exposure affects the majority of the UK population. This has consequences for the way residue surveillance programmes are organised, together with a need to reduce the reporting limits for residues in food products. Data would be needed on the patterns for non-agricultural use of pesticides, biocides and veterinary medicines comparable to that that exists for agricultural use of pesticides in the UK.

Impacts on the UK policy for pesticides are likely to result from further scrutiny of the way pesticides are used. Instances where pesticides have been assessed as being a priority by the co-ordinated assessment framework would require measures to be taken to reduce the levels of human exposure. In cases where exposure is from use of pesticides in the UK, policy can influence the use of particular pesticides, for example through substitution of those of greatest concern. This is also true to some extent at the EU level, where UK Government Departments contribute to EU policy. However in cases where dietary exposure to pesticides is from consumption of food commodities imported from outside the EU, there is less control on residue from UK Government policy. Pesticide residue surveillance programmes need to be more vigilant in identifying where residues of concern are arising, and international agreement would be required to lower MRL values for priority pesticide and crop combinations. As analytical capabilities advance the possibility of further reducing the MRL is feasible. This places the responsibility on exporting countries to conform with the MRL values. In some cases the MRL can be reduced to such a level in certain food commodities that the use of the pesticide is not possible. This recently occurred for the MRL for carbendazim in apples.

Dealing with the issues of human exposure to mixtures of pesticides will therefore require UK policy intervention at national, EU and international (non EU) levels. In considering dietary exposure to pesticides as incurred from residues in food commodities imported from beyond the EU, there are other policy interventions possible, which do not relate to pesticide usage, but more to the wider question of the balance between UK or EU produced food and food imported from outside the EU.

8.9.1 Development of a proposed outline for a prioritisation scheme

Any prioritisation scheme needs to consider the major routes and sources of exposure for the UK population. Therefore the dietary exposure of the population would be of primary interest to regulators, as this affects virtually all of the population, although at lower levels than occupational exposure.

For particular exposure scenarios the basic information and data to be considered are the inherent properties of the compound in question (toxicology) and its abundance (sources of human exposure). Bearing this in mind, the key data have been identified which are needed for the assessment of risks of exposure to mixtures.

In the absence of comprehensive toxicological data on the interaction of all possible combinations of exposure to compounds in use regulators require a mechanism to identify the priority compounds and mixtures. Initially this will have to use existing knowledge and data, together with probabilistic methods of risk assessment.

The scheme as outlined below is considered to be a starting point for assessing potential risks of exposure to mixtures of compounds for dietary exposure, using the following data.

Toxicology of a single compound

These data exist for all compounds registered for use as pesticides or veterinary medicines

Nature of interaction

This is not always known, but in many cases can be estimated based on the known toxicological properties of the compounds such as the mechanisms of action and the toxic end point.

Usage

Data from the Pesticide Usage Survey provides comprehensive information for agricultural pesticides. Similar data for biocides, amateur/amenity pesticides and veterinary medicines needs to be generated.

Occurrence in food residues using probabilistic models

As discussed earlier, some information is already generated as part of the residue surveillance programme, although this does have some shortcomings which would need to be addressed, such as the scope of the food commodities sampled and providing values for residues of compounds below the current reporting limits and the LOQ.

Occurrence in mixtures

Data from the modified residue surveillance programmes would provide a better indication of the occurrence of mixtures of compound as residues in single food items. In addition, the occurrence of mixtures of compounds in the diet of individuals can be used.

The scheme below could be used for an assessment of a mixture of two compounds. At this stage no weighting has been given to the factors. This could be considered for particular groups, such as occupationally exposed or bystanders, where the usage of the pesticide would contribute more to the total exposure than for urban dwellers not involved with pesticide use for example. In the example below the worst case scenario data have been entered, and no weighting of factors has been used.

Matrix to identify priority compounds for assessment of risks of exposure to mixtures

	Toxicology of single compounds A and B H 3 M 2 L 1	**Nature of interaction between A and B** Synergistic 4 Additive 3 Independent 2 Antagonistic 1
Usage H 3 M 2 L 1	**A B** **9 9**	**12**
Occurrence in food residues (Frequency as a residue) H 3 M 2 L 1	**A B** **9 9**	**12**
Occurrence in mixtures (Frequency of A and B in same food sample) H 3 M 2 L 1	**A B** **9 9**	**12**

PRIORITY SCORE: 54 + 36 = 90

8.9.2 Selection of a group of chemicals of concern for development of a case study comparing risk assessments under existing and proposed frameworks using data generated during other phases of this project

Results of simulations for exposure to pesticides, alone and in mixtures

When the pesticide is in the dilute or concentrated form occupational and bystander exposure are the principal types of exposure to be considered. Occupational exposure for agricultural pesticides can be considered to be for the pesticide handler, carrying out mixing and loading of the concentrate and/or application e.g. farmer, worker or contractor. This type of exposure is likely to result in the highest levels of exposure to single compounds, although is less likely to involve exposure to mixtures of several compounds, particularly in the case of cholinesterase inhibitors, where there are controls over tank mixing of compounds.

Earlier in the report we presented the results from simulation studies, with the results presented in the form of the absorbed (internal) dose of the pesticides for each occupational group and bystanders respectively. As expected the internal doses arising from occupational exposure were much higher than that from dietary exposure.

For a bystander, the internal doses have been derived from the farmer's exposure, i.e. in the model the farmer and bystanders exposure is assumed to result from the same source – the spraying of the field. However, the bystander exposure is lower because it is further assumed they are located further from the field being sprayed.

In Section 7 data have been presented for the average annual simulated dose for 1000 adults in the population for Aldicarb and Glyphosate. These have been shown to be below the ADI.

The corresponding data for the population simulation of farmers, for pesticide exposure from spraying only shows their occupational exposures were much higher than for the dietary exposure for the general population. For both of these pesticides some of the simulations produced high individual dose estimates comparable to the ADI adjusted to represent internal dose, i.e. 10.4 and 580 μg/kg for Aldicarb and Glyphosate, respectively.

The data for bystander exposure a similar in pattern to farmers occurs, due to the nature of the assumptions for exposure, but the dose estimates are all lower with the median population estimates being about 10^{-2} μg/kg for Aldicarb and 2 x 10^{-3} μg/kg for Gyphosate, which are about one tenth of the corresponding values for farmers.

The data for each of the population groups have been presented in Section 7 for the aggregate exposure of all the pesticides being considered. The median exposures are all much less than one and the maximum individual exposures were all less than one tenth of the dose equivalent to the combined ADI.

The data from the modelling of child exposure show that the distribution of aggregate dose are higher than for adults, as noted earlier, but that all of the estimates are lower than unity.

For bystanders the aggregate exposures to anti-cholinesterase compounds was higher than from food consumption and for about 10% of bystanders the aggregate exposure exceeded the dose equivalent to the combined ADI. None of the median estimates exceeded the combined ADI dose.

For farmers, the aggregate exposures to anti-cholinesterase pesticides showed around 20% of individuals had a maximum estimated dose higher than the combined ADI dose and about 3%

had median dose estimates above the combined ADI dose. However, the median dose for the population was well below the combined ADI dose.

Finally, in the case of contractors about 60% of the maximum individual dose estimates exceeded the dose equivalent to the combined ADI, although the median exposures for all contractors were below this value. For contractors, both the average aggregate dose estimates and the variability in the dose estimates were greater than for farmers.

Simulations for all of the dose estimates for anti-cholinesterase pesticides for the adults and children in the population from food consumption shows that none of the aggregate daily dose estimates for anti-cholinesterase pesticides exceeded the dose equivalent to the combined ADI for these compounds. The maximum dose estimate was about one tenth of the dose estimate for the combined ADI. There is considerable day-to-day variability in predicted consumption of pesticide residues and a smaller variation within the population.

Occupational exposure to pesticides represents a relatively small proportion of the UK population (<1%), although they represent an important area for risk assessment as they are the most highly exposed group of the UK population. Data for exposure of bystanders, contractors and farmers to anti-cholinesterase compounds confirms that more than a quarter of people in this group have a predicted maximum dose in excess of the dose associated with the combined ADI. This is principally made up from farmers or contractors, although the simulations show that some of them may be bystanders.

The scenarios chosen for bystander exposure represent a worst case, and are not representative of what could be considered to be typical bystander exposure scenarios. Experimental and surveillance data are lacking for bystander exposure. Existing data is EUROPOEM is from spray drift field studies where bystanders are close the sprayer (8m), where in practice only a small proportion of the bystanders will be as close to the sprayer.

The model simulations for exposure to cholinesterase inhibiting pesticides has shown the existing risk assessment and regulatory framework is protecting the general population from exposure via the dietary route.

9 DISCUSSION

Most risk assessments for pesticides and other chemicals focus on individual chemicals in a limited situation, for example a single pesticide product during application. However, in reality people may be exposed to the same active ingredient in a number of different products in a variety of situations, e.g. as a residue in food consumed, as a bystander during application of pesticides or in home or garden pesticide products. Thus there may be some aggregate exposure to the same compound from different uses that occur in reasonably close proximity in time because the compound will remain in the body for some time after exposure. In addition there are a range of pesticide active ingredients that may have the same effect on the body and so it is reasonable to expect that co-exposure to compounds with similar toxicological properties will have some cumulative effect on the body. It is the cumulative exposure that will be most clearly related to the risk of any adverse effects on pesticide users.

A clear understanding of the pattern of pesticide exposure at the population level is important in understanding likely cumulative levels of exposure. It is possible to measure aggregate exposure directly by using biological monitoring techniques and the cumulative exposure can be estimated by simultaneously measuring internal exposure to several different compounds and weighting these data to take account of the relative toxicity of each. However, there are many practical difficulties in undertaking this type of study. There may be issues around the sensitivity and specificity of the analytes for the compounds of interest, and it is expensive and time consuming to undertake this type of investigation. In addition, biological monitoring cannot easily identify the particular contributory source and would just provide an overall estimate of aggregate and cumulative exposure. It is possible to measure external exposure to evaluate the relative importance of different exposure circumstances using diet studies and by measuring skin and inhalation exposure of individuals, but this approach has even more practical problems than biomonitoring.

An alternative approach to provide some insight to the relative contributions to cumulative pesticide exposure of the population is by using modelling approaches, particularly Monte Carlo modelling. This approach relies on two important elements: firstly, there must be valid theoretical models available that describe the exposure circumstances and, secondly, there must be the underlying data available to parameterise the model to represent the particular circumstances that the population experiences. In any case before relying on any model it is necessary to compare the outputs from the model with data from real situations to ensure the validity of the approach.

In this project we have attempted to develop a practical theoretical model to describe population exposure to pesticide products. This has necessarily been based on already existing models and the available data. Whilst this is not ideal it is the only way that is available. In addition in an attempt to simulate exposure for the whole population of Great Britain we have had to remove a great deal of the complexity that exists in terms of the way work with pesticides is carried out and the way food is processed and eaten. In many situations we found that there was insufficient data available to sustain a reliable model of exposure and for this reason we have had to exclude some uses of pesticides and we have not included biocides or veterinary medicines, although there was little use of the compounds of interest in our study in the latter.

We have restricted the range of compounds to a subset of those that may inhibit cholinesterase production and a group of compounds that might act as oestrogen agonists. However, we believe that the results are suitable to demonstrate the important features of exposure to mixtures in the population for compounds with these types of effects.

An important practical difficulty is the limited amount of data available to undertake this type of exercise and the problems of combining different data collected for various purposes. Again, we have had to adopt some simplifications to achieve a coherent dataset for the modelling. We do not consider that these simplifications have introduced any bias into our predictions, but clearly there is some loss of specificity. Also, we have assumed that all of the exposures are independent of each other and that, for example, farmers who spray pesticides are no more or less likely to eat fruit than the general population.

Pesticide residues in food are very low and the measurement of these residues is focused on quantification when the residue exceeds the reporting limit (RL). This is a reasonable approach for regulating the intake of individual pesticides through food consumption but it has meant that we have poor information about residue levels below the RL, which for mixtures of several pesticides is an important limitation. We believe that the strategy we have adopted for inclusion of pesticide residues in food below the RL should not introduce any serious positive or negative bias. However, it is important that more information is obtained about pesticide residues in food below the RLs and this information is important for research into exposure to mixtures of pesticides. Also, there is little information available about the effect of processing on pesticide residues on food. We have chosen to assume that the effect is variable but will generally provide some reduction in the quantity of pesticide available for consumption. Further research to understand the effect of processing on pesticide residues would be valuable.

Overall we believe that the model that we have implemented provides a reasonable simulation of the British population exposure to pesticide mixtures and that it is sufficient to facilitate a discussion of the possible policy implications of exposure to pesticide mixtures. The pattern of exposure to all pesticide compounds is episodic, which might be expected for usage in agricultural situations where spraying is irregular and seasonal, but is also the case for food consumption. The irregular nature of the exposure means that the pattern of exposure changes for each simulation carried out, giving rise to a complex set of exposure situations, e.g. Figures 7.3 to 7.7.

The population dose estimates have been summarised graphically to show the median exposure for individuals in the population and their maximum exposure on any one day throughout the year. For most pesticides the median exposures in the population from food consumption vary over 2 to 3 orders of magnitude. However, the maximum dose estimates for individual pesticide compounds were all much less than the corresponding ADI. Internal dose estimates for children were generally less than or equal to those for adults when expressed as micro-grams per unit body mass. The main reason for this was the lower body mass distribution for children compared with adults and comparable or higher consumption of fruit and vegetables. Internal dose estimates for vegetarians were similar to those for other adults, which reflects the similar fruit and vegetable consumption for these two groups.

As expected the internal dose estimates for farmers and contractors were higher than for the general population. In some individual cases the maximum internal pesticide dose estimates were higher than the internal dose that would be expected from food consumption at the ADI, and for example for Aldicarb about 50% of the population had dose estimates higher than the ADI dose. However, about 90% of the median dose estimates for individual farmers for Aldicarb were less than the ADI dose. The dose estimates for bystanders were intermediate between farmers and the general population. For Aldicarb about 25% of dose estimates were greater than the ADI dose estimate, but all of the median estimates were less than the ADI dose.

We have chosen to use the ADI as the basis to aggregate different pesticide dose estimates. While for occupational exposure the AOEL may have been more appropriate we opted to use the ADI because of the greater completeness of the data. However, we also noted that there is a

fairly good association between ADI and AOEL values. The total dose estimates were then calculated for anti-cholinesterase pesticide compounds and oestrogen agonist compounds. These present a similar picture to the data for individual pesticides in terms of the relative differences between population groups and in terms of the relative levels of exposure. All of the daily aggregate dose estimates for food consumption were less than the dose equivalent to the combined ADI. This is reassuring and implies that there is no real risk from the combined exposure from pesticide residues in food. The day-to-day variation in internal dose estimates was very high and the maximum aggregate dose for an individual was generally about 300 times their median dose (Figures 7.18 to 7.21).

For those associated with occupational exposures the aggregate dose estimates were in many cases higher than the aggregate dose equivalent to the ADI, particularly for farmers and contractors. We realise that for occupational exposure comparison is normally made with the Acceptable Operator Exposure Level (AOEL) but there are not AOEL values for all of the compounds of interest here and so for practical reasons we have chosen to use the ADI. In many cases where there are both ADI and AOEL values they are the same or the AOEL is higher and so if there is any uncertainties in this respect we believe have erred towards overestimating rather than underestimating the possible risks to health. Our simulations suggest that there may be some people in the population living near to spraying activities who are bystanders and those who are occupationally exposed who may have unacceptably high exposures.

One major reservation we have concerning this finding is the assumption that the EUROPOEM database provides accurate estimates for occupational and bystander exposure. These data are based on the conventional measurement methods using interception samplers, e.g. cotton patches, attached to the skin or clothing. We believe that these samplers will overestimate the amount of pesticide residue that will be retained on the skin and may overestimate the actual material available for uptake into the body. If this is the case then while these data may be entirely appropriate for regulatory exposure assessments they may have positively biased our assessment of occupational and bystander exposure. Further work is necessary to confirm these findings. Also, we have inevitably had to simplify the exposure models because of limitations in the datasets and so, for example, we do not incorporate knapsack spraying into the Monte-Carlo models and we do not take account of the physical form of the pesticide. These simplifications with introduce some uncertainty into the predictions, in some cases resulting in underestimation of some exposures and in others, e.g. aldicarb, an overestimation of likely exposure. From a limited sensitivity analysis we were able to demonstrate that the conclusions from our simulations were not overly affected by the uncertainties in the choice of model parameters.

If cumulative and aggregate exposure of pesticides is to be integrated into a regulatory framework then there is an important need for better quality information about exposure and a more comprehensive dataset. For example, we have found that there is virtually no data available to assess the extent of exposure to biocides or veterinary medicines. Data on pesticide residues is only available for a selected range foods and the collection of these data is not ideally suited for probabilistic modelling.

The model that we have developed has demonstrated the potential benefits of this type of exercise. However, there are a number of limitations in the current implementation in terms of uses of pesticide active ingredients and in the reliability of the data input into the model. We suggest that it is worth considering how routine and non-routine data collection systems for pesticides could be adapted to make the overall dataset available for modelling more coherent and easier to integrate into this type of analysis. For food this would include getting consistency between the recording of food groups in surveys of food consumption, food recipes and in measurement of pesticide residue levels. Also, consideration should be given to improving the measurement and recording of residue levels below the reporting limit. In addition, data should

be obtained on the numbers of people using home and garden pesticides, biocides and who are exposed to pesticides as bystanders or neighbours. Further data and improved models for the levels of exposure of these groups would also be an advantage.

The model could be further refined to extend the scope of the simulation to include a wider range of exposure pathways. However, exposure models cannot be accepted as reliable unless they are validated against real exposure measurements. If the model that we have developed is to be used in the future to underpin the regulatory system then it is important to undertake studies to validate its reliability by comparing the model predictions with the results from a biomonitoring study within selected population groups.

However, it is our view that assessments of cumulative and aggregate exposure to pesticides cannot easily be integrated into the regulatory framework at the approval stage and it is probably better suited to be used as a tool for the regulators to periodically review the possible population risks for groups of pesticides of concern. To facilitate this process the regulators involved with pesticides, biocides and veterinary medicines should jointly plan the collection of routine exposure and toxicity data to provide a more suitable basis for probabilistic modelling of population exposure.

The impact of adopting the COT recommendations have been evaluated, in particular the extent to which changes to the UK regulatory framework may be required. It is clear that there are extra data and information that are needed to inform the regulatory processes. This information is both the responsibility of the regulator (e.g. pesticide usage surveys and residue surveillance) and the registrant (e.g. toxicological data). There is a need for a more co-ordinated approach to risk assessments to be carried out for exposure to more than one pesticide from all possible pathways. For example in considering the registration of a plant protection product, consideration would need to given to the potential for exposure to biocides, home and garden pesticides and veterinary medicines. Such as assessment would need to consider all sources and pathways of exposure and consider groups of compounds known to be of concern, and where exposure was considered to result in a potentially harmful dose there would be a need to regulate for this, which would inevitably lead to conflicts, particularly when compounds with very different uses were being evaluated.

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