REPORT OF THE JOINT WORKING GROUP ON BYSTANDER RISK ASSESSMENT

Advisory Committee on Pesticides

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

REPORT by the BYSTANDER RISK ASSESSMENT WORKING GROUP (BRAWG)

1. Executive Summary

1.1 This report, from a joint working group of the Advisory Committee on Pesticides and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, considers the methods used in the regulatory assessment of potential health risks to bystanders and residents from the application of pesticides in plant protection products. The membership of the group is given in Appendix 1.

1.2 The terms of reference were to review the current approach to modelling bystander and resident exposure to plant protection products in the light of current scientific knowledge. The aims of the working group were then:
- To agree definitions of operators, workers, bystanders and residents
- To agree the nature of the exposures that require consideration
- To review the current approach to modelling these exposures for bystanders and residents in the light of current knowledge and
- To review the approach to assessing the risks arising from these exposures in the light of current knowledge.

1.3 The working group considered an opinion on pesticide exposure assessment for regulatory risk assessment that was published in 2010 by the Plant Protection Products and Residues (PPR) Panel of the European Food Safety Authority (EFSA) (a summary of which is included at Appendix 2). They also considered current research funded by the Department for Environment Food and Rural Affairs (Defra), aimed at better assessment of the factors influencing the exposures of bystanders and residents to pesticides (the BREAM project). A draft report was developed through a series of meetings and revised after consultation and comments at an open public meeting.

Structure of the report

1.4 The report consists of the following sections:
- Introduction (section 2),
- Pathways of exposure for bystanders and residents (section 3),
- Toxicology (Section 4),
- Summary (section 5), and
- Recommendations (section 6).

Conclusions of the working group

1.5 The working group considers that acute (short-term) exposure assessments are required for both bystanders and residents, and that for residents longer-term exposure assessments are also needed. The same pathways and routes of exposure should be considered in both categories of exposure assessment, but the group recognises that some of the parameters used in the respective exposure models may need to take different values, to reflect differences between acute and longer term exposure.

1.6 The working group considers it appropriate that estimates of potential exposure through each pathway and route should be aggregated (combined). However, some pathways and routes of exposure may make only a very minor contribution

to total potential exposure in comparison with others and can therefore be ignored as they will have no material impact on the risk assessment. Simple addition of individual (conservative) estimates is not appropriate as this will yield an unrealistic exposure estimate that is overly conservative. Rather the group recommends that, if possible, probabilistic modelling is the most appropriate approach to aggregation.

1.7 The working group agrees that short-term exposure to pesticides is greatest during and immediately subsequent to spraying activity and can be divided into direct exposure to spray drift droplets, direct exposure to drift of pesticide vapour and short-term indirect exposure through dermal contact with surfaces that have been contaminated by spray drift deposits generated during spraying. Longer-term (chronic) exposure can occur through repeated short-term exposures at the time of and shortly after spraying events, and also through exposures for longer intervals after spraying activity. The latter can arise through direct exposure to pesticide vapour produced by volatilisation from treated plant and soil surfaces; and through indirect exposure as a consequence of dermal contact with surfaces that have been contaminated by spray drift deposits, or through consumption of garden crops, inhalation of dusts, or (in young children) ingestion of soil/dirt, if these have been contaminated by spray drift deposits.

1.8 The group recommends that the approach proposed by EFSA in their draft guidance for estimation of potential bystander and resident exposure, augmented by the results of the most recent exposure studies, in particular the data from the Bystander and Resident Exposure Assessment Model, BREAM, should be followed by regulatory authorities, as it represents the most appropriate approach at the current time.

1.9 For risk assessment the working group concluded that:

1.9.1 for <u>direct exposure to spray drift</u> a suitable scenario is to assume that an individual is standing 2 metres from the edge of the spray boom. Exposure estimates should use the 95th percentile of exposure concentrations from the BREAM data for acute assessments, and the 75th percentile value for chronic assessments.

1.9.2 for <u>direct exposure to vapour drift</u> the current approach of using average concentrations measured in air during the 24 hours following application of representative compounds with low and high volatilities should be retained. The group noted that the trials from which measurements were taken for pesticides with high volatilities involved application at rates much higher than those used in the UK, often in environmental conditions conducive to high volatilisation.

1.9.3 for <u>indirect exposure to spray drift via dermal contact with contaminated surfaces</u> an approach based upon the current EPA model is appropriate, but consideration should be given to potential accumulation of pesticides on surfaces as a result of repeat sprayings. Members noted that this method is likely to be conservative as dermal

absorption is assumed to be 100% unless data are available to support a lower value[1].

1.9.4 for dermal exposures arising from spray drift deposits, behavioural differences between adults and children (and between children of different ages) should be taken into consideration .

1.9.5 for <u>indirect exposure via consumption of pesticides deposited on garden produce,</u> methodology should be developed consistent with that used in other assessments of dietary exposure to pesticides.

1.9.6 <u>for indirect exposure by entering treated crops</u>, potential exposure should be estimated using standard worker exposure models and with the assumption that a 30 minute exposure is likely to reflect a worst case scenario.

1.10 The working group notes that pesticides are extensively tested for toxicity prior to authorisation for use. Testing is as rigorous as for human medicines with the obvious exception that there are no clinical dosing studies of pesticides in humans. Applications for approval of a pesticide are supported by an extensive database of scientific studies designed to help regulators understand the effects of that pesticide on the target pest, its possible environmental effects and, most importantly, the possible adverse effects it might cause to human health and the doses at which these effects might occur.

1.11 The working group notes a concern that some individuals may become sensitised to pesticides and that, in general, risk factors for sensitisation are not well understood. The local lymph node assay can provide estimates of the potency of pesticides to induce skin sensitisation, but further work is required to understand the relationship between potency estimates of pesticide formulations in current use and human risk.

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[1] New EU guidance on dermal absorption will be adopted for all applications in Europe after 30 Nov 2012. This guidance changes the relevant default value for dermal absorption to 75%. Based on the available data this approach will continue to be protective. This footnote is relevant to each reference to the default dermal absorption in this report.

2   Introduction

2.1   The use of pesticides and their possible effects on human health have, for some time, given rise to public concern and discussion. Particular focus has been given to the approach adopted, and the assumptions made, when considering the potential for pesticides to impact on the health of residents and bystanders who may be inadvertently exposed as a consequence of pesticide application.

2.2   In 2005, The Royal Commission on Environmental Pollution (RCEP) published a report on "Crop Spraying and the Health of Residents and Bystanders" [1]. The report highlighted a number of issues and concerns related to this aspect of risk assessment. A legal case pursued by Ms Georgina Downs [2] further emphasised concerns in this area.

2.3   In 2009 Ministers asked both the Advisory Committee on Pesticides (ACP) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) for specific advice about:

- issues raised in a judgement in 2008 from Mr Justice Collins [2] (later overturned at appeal in July 2009) [3];
- their views on any other issues that should be addressed; and
- what additional information would be required to inform a review of policy in this area.

COT provided some initial written advice in May 2009 [4], and both committees requested further background information, at their meetings during 2009 [4,5].

2.4   ACP and COT both agreed a need for a formal review of the methods used in regulatory assessment of the potential risks to health of bystanders and residents from exposure to pesticides in plant protection products. The two committees therefore established a short-life working group (membership of which can be found at Appendix 1) to carry out the work that was required. This report presents the findings and recommendations of the working group.

2.5   As part of their task, the working group considered a recent opinion on the topic published by the Panel on Plant Protection Products and their Residues (PPR) of the European Food Safety Authority (EFSA), the summary of which is included at Appendix 2. The pathways and routes of exposure that are specified in the EFSA draft guidance [6] for the development of relevant exposure assessments are the same as those currently considered in UK risk assessments for bystanders and residents, but there are differences in some of the numerical values used in the exposure models. The group noted that the German authorities had recently developed similar guidance [7]. Both the EFSA and the German documents proved helpful in the group's deliberations.

2.6   The group also considered current research funded by the Department for Environment Food and Rural Affairs (Defra), aimed at better understanding of the factors influencing the exposures of bystanders and residents (The Bystander and Resident Exposure Model, the BREAM project) [8 - 14].

2.7   Seven meetings of the working group were held (including an open meeting and telephone conferences). An advanced draft report was discussed at an open

meeting of the working group on 7 December 2011, giving all stakeholders (interested individuals, industry, institutions and other bodies) an opportunity to comment. The final report will be submitted to Defra Ministers.

2.8 Terms of Reference

2.8.1 The agreed terms of reference for the working group were:

To review the current approach to modelling bystander and resident exposure to plant protection products (PPPs) in the light of current scientific knowledge

2.8.2 The agreed aims of the working group were:

a) to agree a definition of operators, workers, bystanders and residents
b) to agree the nature of the exposures that require consideration
c) to review the current approach to modelling these exposures for bystanders and residents in the light of current knowledge
d) to review the approach to assessing the risk arising from these exposures in the light of current knowledge.

2.8.3 The working group focused its attention on boom sprayers used on arable crops as this method of application is widely used to apply pesticides in the UK. It is also the method most frequently reported in health incidents associated with pesticide exposures. The working group did NOT consider other methods of application such as orchard application, vineyard application, glasshouse application, knapsack application, use of hand-held applicators, home-garden application methods, methods used in applying solid formulations such as granules, or specialist application techniques such as controlled droplet applicators. Defra/CRD have commissioned research on some of these methods [15,16,17].

2.9 Definitions

2.9.1 The working group agreed with the EFSA PPR Panel draft guidance [6] on pesticide exposure assessments that there should be separate consideration of exposure for operators, workers, bystanders and residents.

2.9.2 The working group agreed that the EFSA definitions [6] of exposed groups were, in general, appropriate and could be adopted. However, the definitions of both bystanders and residents were modified by changing the phrase, 'who take no action' to 'who may not choose or be able to take action'. The working group considered this to be a more accurate description of their behaviour. The definitions agreed by the working group were:

a. **Operators**: persons who are involved in activities relating to the application of a plant protection product; such activities include mixing/loading the product into the application machinery, operation of the application machinery, repair of the application machinery whilst it contains the plant protection product, and emptying/cleaning the machinery/containers after use. Operators may be either professional (e.g. farmers or contract applicators engaged in commercial crop production) or amateur users (e.g. home garden users).

b. **Workers**: persons who, as part of their employment, enter an area that has been treated previously with a PPP, or who handle a crop (up to and including workers involved in harvesting and storage activities) that has been treated with a PPP.

c. **Bystanders**: persons who are located within or directly adjacent to the area where PPP application or treatment is in process or has recently been completed; whose presence is quite incidental and unrelated to work involving PPPs, but whose position might lead them to be exposed; and who may not choose or be able to take action to avoid or control exposure.

d. **Residents**: persons who live, work or attend a school or other institution adjacent to an area that is or has been treated with a PPP; whose presence is quite incidental and unrelated to work involving PPPs but whose position might lead them to be exposed; who may not choose or be able to take action to avoid or control exposure; and who might be in the location for 24 hours per day.

The working group noted that there can be overlap between these exposure groups e.g. a resident might also be a worker and a bystander.

2.9.3   In relation to this, the working group noted that when operators and workers use products, this must be in accordance with the legal conditions of authorisation that are set for each product and specified on the product label. These may require the use of personal protective equipment (PPE) by professional operators. Operators will have access to the pesticide product label giving directions for use in accordance with the approval, and should be aware of any specific restrictions applying to them. At present regulatory risk assessments in the UK for workers, residents and bystanders assume that they do not use PPE.

2.9.4   The regulation on the Placing of Plant Protection Products on the Market (EC 1107/2009) considers 'residents subject to high pesticides exposure over the long term' as a vulnerable group, and the EU Directive on Sustainable Use of Pesticides (Directive 2009/128/EC) has provisions for reduction of pesticide use or risks in specific areas, including those used by vulnerable groups.

2.10   Framework for regulatory risk assessment

2.10.1 The potential for exposure to a pesticide to have an effect on human health will depend upon:

a)   the extent to which individuals are exposed to the pesticide by different routes (skin contact, inhalation, ingestion); and
b)   the toxicity of the chemical and its potential to affect human health according to the routes and levels of exposure.

2.10.2 For regulatory assessment of a new pesticide, there are no direct empirical data on the levels of human exposure which will occur. Assumptions therefore have to be made to estimate the exposures that could occur, and these assumptions are the first step in determining the potential for any impact on health. Available data on the measured distributions of *actual* exposures to other substances are used to

inform realistic upper estimates of *potential* exposures to the new pesticide, derived through an exposure model.

2.10.3 In regulatory risk assessment, the aim is to identify:

  a) the types of toxicity that might occur in particular circumstances of exposure (short-term/acute, long-term/chronic, local effects such as irritation),
  b) the maximum levels of exposure at which there is practical certainty, on the basis of all known facts at the time of evaluation, that there will be no appreciable health risk to the people exposed; such levels are known as 'toxicological reference values'[2] - and
  c) realistic upper estimates of the exposures that could occur in each relevant set of circumstances for comparison with the appropriate toxicological reference values.

2.10.4 The term 'pesticides' covers a wide range of different chemicals, each with different properties and effects. Regulatory risk assessments need to take into account the specific properties and effects of individual substances.   In some parts of the risk assessment process it is appropriate to assume a standard value for a parameter as a pre-set or 'default value' in the absence of substance-specific data. These 'default values' are deliberately selected to be protective in an initial tier of risk assessment. For example, estimates of exposure to vapour are often based on field experiments in California, in which a relatively volatile pesticide (chlorpyrifos) was applied at high rate under conditions highly conducive to volatilisation (temperatures up to 42°C). This study will tend to provide values at the higher end of the range of possibilities for a volatile pesticide, and thus its use in risk assessment is likely to be protective for weather conditions and application rates relevant to the UK. Refinement of the risk assessment can then be undertaken where necessary, by requiring additional substance-specific data to improve the estimate so that it more closely reflects reality.

2.11   Exposures

2.11.1 The working group considered which aspects of exposure would require consideration in risk assessments for bystanders and residents. These include the identity of the pesticide, the routes of possible exposure, and any behaviour that might alter exposure. Bystanders and residents may be exposed to pesticides either directly through contact with spray drift (via the dermal or inhalation routes); and/or indirectly through contact with drift deposits (dermal or ingestion), and/or vapour drift arising from volatilisation of deposits (dermal or inhalation). The group also noted that exposures usually decline over time from the initial value at, or close to, the time of application. Operators will be able to use PPE to reduce exposure, whereas bystanders and residents, by their nature, will not use PPE, and are considered as groups who may not choose or be able to take action to avoid or control exposure.

2.12   Risk assessments required

2.12.1. The working group were in agreement with the proposal in the EFSA PPR Panel draft guidance [6] that acute/short-term exposure assessments are required for bystanders and residents, and that for residents, longer-term exposure assessments are also needed. The same pathways (e.g. vapour, drift deposits) and routes (e.g.

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[2] Also known as 'health based guidance values'

dermal, inhalation) of exposure should be considered in both the bystander and the resident exposure assessments, but some of the parameters used in the models may need to take different values to reflect the differences between acute/short-term and longer term exposure. The current approach to exposure assessment for pesticide spraying is summarised in Table 1

2.12.2 The working group also agreed with the EFSA PPR Panel draft guidance [6] that acute risk assessments are required only where the PPP is judged to pose potential health risks from single (or acute) exposures – i.e. where the toxicology is such that it has been found necessary to establish an acute reference dose (ARfD) for dietary risk assessment or an acute acceptable operator exposure level (AAOEL).

3   Pathways of exposure for bystanders and residents

3.1   Both bystanders and residents are potentially exposed to pesticides short-term (acutely). This exposure is greatest during and immediately subsequent to spraying activity and can be divided into direct exposure to spray drift droplets, direct exposure to drift of pesticide vapour, and short-term indirect exposure by dermal contact with surfaces that have been contaminated by deposition of spray generated during spraying. The evidence shows that dermal exposure to spray drift droplets contributes by far the most to the maximum acute exposures that can realistically occur [7], so assessment focuses on estimating this component of exposure. Longer-term (chronic) exposure can occur not only through repeated short-term exposures at the time of and shortly after spraying events, but also through exposures for longer intervals after spraying activity, and is most relevant to residents living close to agricultural fields. In the days following a spray event, residents may be directly exposed to pesticide vapour arising through volatilisation from treated plant and soil surfaces; they may also be indirectly exposed to spray drift by consumption of garden crops, inhalation of dusts, ingestion of dirt/soil (young children) or dermal contact with surfaces that have been contaminated by deposition of spray drift. Although a resident might be living next to a field over very long periods or even a lifetime, they will not be exposed to the same pesticide every day throughout that period as pesticide use is seasonal, each pesticide being applied at particular times of year. The exposures that could take place in the days following application will decrease with time elapsed since the application.

3.2   In estimating potential exposures and risks there are always uncertainties. For exposures of bystanders and residents, uncertainty can arise from variability in methods of spraying, changeable weather conditions, differences in human behaviour, unknown extent of dermal penetration, unexpected human toxicity and lack of information on individual absorption, metabolism and excretion. Regulatory risk assessments account for these uncertainties by erring on the side of caution in the selection of parameters for use in exposure models, and by application of assessment factors to ensure a large margin between the doses at which there are no observed adverse effects in animals and the maximum possible exposures of people. Thus, whilst the results of such risk assessments are often reported using apparently precise numerical values, these include substantial allowance for uncertainty about the true risk.

Direct exposure to spray drift

3.3	Currently the UK method of assessing direct exposure to spray drift is to estimate exposure of an adult through contact with spray drift and inhalation of spray droplets 8 metres downwind from a boom sprayer that made a single pass. This was based on UK measurements of spray drift from the 1980s.

3.4	There have been significant changes in application practices for plant protection products since the 1980s (e.g. use of larger, faster machinery, different spray nozzles) and the Royal Commission on Environmental Pollution (RCEP) report in 2005 suggested further research to develop a more sophisticated approach [1]. The Bystander and Resident Exposure Assessment Model (BREAM) project was commissioned by Defra to provide up-to-date measurements and models by which to estimate direct exposure to spray drift. [8-14]

3.5	The BREAM project has developed a computational model to describe the dispersion of droplets and vapours arising from the application of pesticide sprays. It provides greater flexibility than the previous deterministic model, enabling estimation of exposures under a wider range of conditions by allowing variation in the model input parameters (e.g. nozzle types, application rates, wind speed, boom height). To prevent combinations of worst-case input parameters leading to unrealistic results, the model uses probabilistic modeling to sample the distributions of the input parameters. The model outputs are predictions of spray droplet concentrations in breathing zones, potential dermal exposures, and ground deposits at varying distances up to 15 metres from the spray boom. Estimates are provided for the mean, 75th percentile and 95th percentile of each distribution[3].

3.6	The scenarios covered in the BREAM study included adults and children positioned at a range of distances from the sprayer (up to as close as 2 metres); this showed that exposure to spray 'plumes' is probably more relevant to most bystander and acute resident exposures than ground deposition of spray drift. Data on drift depositing on the ground showed that the amount of spray contamination falls away quite rapidly a matter of a few metres from the edge of the spray boom. However, data on airborne spray drift suggested that low-level exposure can also occur at a greater distance from the boom. BREAM and the model that is currently used in UK risk assessments produce exposure estimates that are of similar magnitude at 8 metres from the boom, but BREAM predicts exposure (principally dermal) up to an order of magnitude higher for people who are closer to the booms of the larger and faster machinery that is now in use.

3.7	The EFSA group was informed of these critical findings from BREAM and, as a consequence, included an additional 10-fold factor to account for higher estimated exposures close to the spray boom [6]. The working group considered that the BREAM approach probably overestimates exposure as it assumes limited dispersion, but it supersedes earlier data used in the EFSA draft guidance. In addition it reflects modern spray practice, and allows modelling of a number of variables (e.g. nozzle type and number, boom and crop height, wind speed and direction). As further data become available, it could also incorporate better information on buffer zones and crop-type.

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[3] The basis of these percentiles is exposure per 'bystander event' rather than being averaged over e.g. a 24 hour period.

3.8   The working group considered current assumptions about the distance between the spray boom and a bystander or resident. Although it may be possible to spray right up to a field boundary, this is unlikely to be common in practice because:

- there are difficulties in controlling the movement of long booms, and as there is a high risk of damage from collisions with field boundary features such as fences, hedges and trees, operators will usually not spray right up to a field margin with such a feature.
- cross compliance rules do not allow pesticide application within 2 metres of the centre of a hedgerow, watercourse or field ditch [18].
- spray operators must be trained, and the Code of Practice for use of plant protection products requires them to protect the public and prevent overspray of adjacent properties [19].

The working group felt that 2 metres was an appropriate minimum distance to assume in estimates of potential acute exposure, and that this was protective as it is likely that the normal behaviour of a bystander or resident would be to move away from a boom.

3.9   The working group also considered current assumptions regarding the duration of exposure. With a spray vehicle typically travelling at 2.5 – 3.5 metres/sec and data which show that spray droplets fall to the ground in a few seconds, the current assumption of 5 minutes inhalation exposure is protective. Indeed a sprayer travelling at these speeds could have covered about a kilometre in five minutes. The working group thus agreed that a suitable scenario for short-term risk assessment would be an individual standing 2 metres from the edge of the spray boom, and to use the 95th percentile of exposure concentrations during a single pass (or about 5 minutes).

3.10   The group considered exposures from repeated spraying events. This could be from repeat passes of a spray boom in the same field on a single day, or from repeat events on different days in the same or adjacent fields. For repeat events in the same field, BREAM predicts a mean increase of <3% over the 95th percentile value from the first pass, which the working group considered would be covered by the allowance for uncertainty elsewhere in estimates of potential exposure. For repeat events on different days a worst case might be a spray programme used to control potato blight. The nature of this disease means that at certain times application intervals can be as frequent as every three days, but such conditions are unlikely to persist for more than a ten day period. Potatoes are usually grown on a wide rotation of typically one year in five. Wheat can be grown continuously and when disease levels are high a susceptible variety could be sprayed three times at ten-day intervals during May and June, with about seven spray applications during the life of the crop from October through to July. The assumption in regulatory risk assessment that exposure takes place on a daily basis throughout the spraying season is thus protective.

3.11   A risk assessment for residents should include an assessment for short-term exposure to spray and to volatilised pesticide (vapour), and to dislodgeable residues, whether following entry to recently treated crops or through playing on grass adjacent to treated areas (exactly as in bystander risk assessment). There should also be an assessment of longer term exposure to spray, vapour and dislodgeable residues. The group noted that current methods make no distinction between adult and child exposures to spray drift. BREAM data showed there was only a marginal difference,

but child exposures to airborne spray were predicted to be higher near the boom because the boom is about child height. However, the group also noted that although children have a higher breathing rate than adults, they have smaller lungs and a smaller body surface area, and that the differences in estimated exposures reduce as the distance from the boom increases. Thus, it may be appropriate to use adult exposure values in risk assessments for children. Nevertheless, a separate assessment for children and adults should be considered.

Direct exposure to vapour drift

Volatilisation from soil and plant surfaces

3.12   The vapour pressure of a pesticide is a measure of its tendency to move into the gas phase from either the liquid or solid form. Pesticides with a higher vapour pressure have greater potential for volatilisation from treated soil and plant surfaces. Plant surfaces are generally considered to be relatively inert, and it has been shown that vapour pressure is the primary determinant of volatilisation under experimentally controlled conditions [20]. Interactions between pesticides and water/solid particles within soil mean that sorption capacity for the pesticide and water solubility are additional factors that can influence volatilisation from soil surfaces [20]. However, the working group noted that many of the data available in the literature on this topic are for older chemicals some of which had relatively high potential for volatilisation and hence would overestimate the gas phase concentration of many pesticides in current use.

3.13   Under field conditions, volatilisation from soil and plant surfaces is also influenced by a range of environmental factors including temperature, wind speed and humidity, as well as by pesticide formulation and extent of dilution by water within the spray mix. This makes prediction of volatilisation from soil and plant surfaces under field conditions highly complex, and to date there is no agreed approach for quantitative estimation of the loss. Equally there is no scientific consensus on whether there is a threshold of vapour pressure below which volatilisation becomes an insignificant pathway of entry into the environment. More information can be found at Appendix 3.

3.14   The current approach in UK risk assessment is to distinguish compounds with low inherent volatility (vapour pressure <0.005 Pa) from those with moderate inherent volatility (vapour pressure 0.005-0.01 Pa), and then to assume relatively high values for average concentrations in air of 1 and 15 µg/m^3, respectively during the 24 hours following application [21]. These values are based on field data for a low volatility chemical (parathion) applied at high rate in Germany and a moderate volatility chemical (chlorpyrifos) applied at high rate under conditions highly conducive to volatilisation in California (temperatures up to 42°C). The BREAM project [12 - 14] concluded that the values were conservative: '24-hour mean vapour concentrations very close to a treated plot did not exceed the current value used in regulatory exposure assessment, even when stable concentrations and high temperatures were recorded'. The BREAM report suggested that an alternative might be to assume 95% loss of pesticide via volatilisation within 24 hours of application, independent of pesticide properties and conditions of use; this approach is considered excessively conservative, given that such large volatile emissions have only been recorded for pesticides no longer approved for use, and that for regulatory purposes it is assumed that there is no decrease in this daily exposure on successive days.

3.15   Data on volatile emissions from field experiments are sparse and contradictory. Butler-Ellis et al [13] have suggested that the expected relationship between vapour pressure and volatile emissions may not hold under field conditions, although further work has yielded results in line with those expected from vapour pressures [22]. In the absence of robust data, the working group believes that the current approach of using relatively high values for average concentration in air during the 24 hours following application of compounds with low and medium volatilities, as described in paragraph 3.14, should be retained. These values will be very protective for the vast majority of situations in the UK, and greater transparency is required in communicating this protection to users and other stakeholders. In particular, the approach ignores the fact that pesticide concentrations in air arising from volatilisation will be related to dose, and that many chemicals are used at very much lower doses than those of parathion and chlorpyrifos in the original German and Californian trials. Monitoring of ambient air in Canada and France for a wide range of pesticides showed maximum concentrations at rural, agricultural locations to be in the order of 0.015 $\mu g/m^3$ in Canada and 0.12 $\mu g/m^3$ in France [23, 24] (compared to the assumptions in current risk assessments of 1 or 15 $\mu g/m^3$). A recent Californian report stated that 'air monitoring of nearly three dozen pesticides in California for the past year (2011) shows residues well below levels established to protect human health and the environment' [25]. The BREAM model can use a specific measure of loss via volatilisation as an input to drive exposure estimates. Risk assessment would be better able to identify issues of concern by including an option to revise the first-tier estimate of concentrations in air (paragraph 3.14) using more reliable measurements from field monitoring. For foliar applications, field data would need to measure volatilisation from foliar surfaces as these generally exceed those from soil, and data would need to be representative of the range of weather, cropping and use conditions for the compound being assessed.

3.16   While this approach is the most appropriate for current conditions, given the most recent scientific evidence, the working group feels that further research should be undertaken to develop methods of calculating losses through volatilisation for individual pesticides. Methods that predict volatilisation from the properties of existing pesticides [20] require work to reduce uncertainties by including more recent data (particularly studies undertaken under European conditions), and compounds with lower vapour pressures and lower application rates that are typical of many pesticides in current use. Mechanistic models such as the Pesticide Emission Model [26] offer a further opportunity for improvement, but will require work to demonstrate their validity for agricultural conditions in Europe.

Indirect exposure to spray drift

Estimating the level of drift fallout

3.17   This pathway involves various routes of exposure, but origin from spray drift deposits is the common factor. Therefore, the starting point is the level of drift that may be deposited adjacent to a treated area, for example on a neighbouring lawn. As a worst case it is assumed that any boundary structure has a negligible impact on the level of drift that passes over the boundary and is then deposited; in practice, it is recognised that boundary structures can affect the level of drift deposited. The current UK approach uses the same spray drift data for estimating deposition on horizontal surfaces as are used for the assessment of risks to aquatic wildlife. These data were generated in Germany and are widely used throughout the EU. However,

the BREAM project has provided updated measurements for modern boom sprayer applications in the UK, and use of these data would be more protective.

3.18   The amount of deposited pesticide is expected to decline rapidly with distance from the end of the spray boom. Most field boundaries have separation provided by either hedges or ditches that are subject to legal cross compliance buffer zones (2 metres from the centre of a hedge and 1 metre from the top of a ditch bank) and additional separation can be provided through field margin Entry Level Stewardship options. Two thirds of farmers participate in stewardship schemes and 33% of agreement holders have included additional field margin buffers of 2.0, 4.0, 6.0 or 12 metres in their agreements, covering a total of 50 904 Ha. 85% of these strips are located on arable land.   Buffer zones and non-cultivated zones also contribute to such a separation and many farmers will have areas like this which are not recorded as environmental stewardship, but are nevertheless part of the voluntary Campaign for the Farmed Environment [27]. However in some circumstances (e.g. wire fencing), whilst there no specific restrictions placed on spray operators as to how close to such boundaries they can spray, there are good practice guidelines (e.g. guidance in the Code of Practice for using plant protection products [19]) to minimise risks.

3.19   As with direct exposure to spray drift (paragraph 3.8) the working group concluded that 2 metres from the boom end and the 95th centile of estimated exposure concentrations was an appropriate worst case scenario for acute risk assessments.   For assessments of longer term risk, the working group agreed that 2 metres was the appropriate distance, but that a lower percentile (the 75th percentile as provided by BREAM) was appropriate because it was very unlikely that repeated exposures would all occur at the higher levels, but rather they would be mixed with lower values on a number of occasions. The working group noted that these are choices of the data for use in risk assessment and reflect assumptions about the continuous location of an exposed individual relative to the end of the boom. They do not imply an assumption that a 2 metre buffer zone is present.

Dermal exposure and ingestion

3.20   Having established an estimated level of drift fall out (e.g. paragraphs 3.17-3.19), both the draft EFSA and the current UK approach estimate exposures of children playing on grass, assuming exposure through dermal contact, hand-to-mouth and object-to-mouth transfer. This is done using an approach developed by the US EPA to derive point estimates of exposure to lawn treatments [28]. The US EPA recently updated their approach [29], and the working group agreed that the figures used in these calculations should be modified as necessary, in line with the most recent recommendations of the US EPA. However, the working group feels that consideration should also be given to repeated applications as well as single exposures to determine the levels of potential accumulation of product. More details of the calculations underlying estimation of dermal exposures can be found at Appendix 4.

3.21   Exposure from contact with companion animals was considered to be adequately covered by the assessment of more direct exposure to residues on grass. It is possible that situations such as stroking contaminated animals may increase exposures, but the 2 hours of contact assumed for exposure to grass residues should

allow for this. Nevertheless, the working group feel that further information on animal-related exposures is needed to check these assumptions.

Exposures to residues on garden crops

3.22   Another possible source of indirect exposure following spray drift is to pesticide residues through consumption of contaminated garden produce. Such produce may be grown right up to a field boundary. The group considers that assessments should include this route of exposure. Methodology would need to be developed to do so and, for consistency with other assessments, the distances from the sprayer that are assumed should be 2 metres for both acute and longer term risk assessment.

Exposure to residues on treated crops

3.23   The EFSA draft guidance [6] considers that bystanders and residents could also be exposed to residues by entering treated crops (e.g. walking across a recently sprayed field) and proposes that these exposures should be estimated by application of the standard worker exposure models. These models estimate dermal exposure as a product of the measured or estimated dislodgeable foliar residue (DFR), and a task specific transfer coefficient (TC) which reflects the degree of contact with the treated foliage. Only a limited number of TC values are available for use in the EU and these are set out in the EFSA draft guidance [6]. In the absence of specific data on dermal absorption, a default value of 100% is used to convert dermal exposure to systemic exposure. Overall this approach is likely to overestimate exposure and to be protective.

3.24   The worker exposure model assumes relatively intimate contact with the treated crop – such as that occurring when hand-harvesting crops. Contact is likely to be less intimate when walking through a treated field, but there is uncertainty as to the real extent of dermal exposure from dislodgeable residues through this lower level of contact. It is unclear how long someone might walk continuously through a recently treated crop, but the increasing practice of block cropping means they could be crossing several fields treated with the same pesticide on the same day. Further, a local resident might walk through the same field more than once in a single day – for example whilst exercising a dog. Taking these considerations into account, the group concluded that a time period of 30 minutes might be an appropriate assumption, recognising that the resultant modelling of dermal exposure over a 30 minute period is likely to represent very much a worst-case scenario.

Total systemic exposure

3.25   The working group considered that it is appropriate to cover the possibility that exposure might occur by more than one pathway and therefore the individual exposure estimates for each pathway should be aggregated (combined). As the estimate for each exposure pathway is based on conservative assumptions, it is very unlikely that a person would be in the highest percentile estimates for every exposure pathway; hence, simple summing of the various estimates is inappropriate as it would result in an overall exposure scenario that was very unrealistic. Instead, a probabilistic modelling approach could be used if appropriate data were available. This requirement is being addressed by the EU ACROPOLIS project, the results of which will reduce uncertainty in this area [30].

3.26   The working group considered a range of other possible exposures and felt that if potential intake by a particular route was sufficiently low it might be considered within the range of uncertainties of other routes and could be ignored. An example is exposure through the eyes. The group considered that as the eyes represent only a very small proportion of the total surface area of the body that could be exposed, this route was unlikely to contribute significantly to total potential systemic exposure and would not require specific assessment.

3.27   Biological monitoring is based on the analysis of substances in urine or blood and is often used in occupational and environmental studies to assess total systemic exposure by inhalation, ingestion and dermal absorption. The chemicals measured are sometimes referred to as biomarkers. As such markers reflect exposure by all pathways and routes, they can be used to assess the effectiveness of exposure controls (like gloves and masks) and their use (behavioural aspects of control). Levels of pesticides or their metabolites can be used to estimate systemic dose by comparison with data from volunteer studies or values derived from toxicokinetic models [31].   An example of the usefulness of this approach is a small biological monitoring study of pesticide exposure in the UK [32] in which cypermethrin metabolites were detected in the urine of spray operators more frequently than in that of post-application workers, bystanders or consumers. Similarly, a metabolite of mancozeb was found more frequently in urine from spray operators than bystanders. In all cases, the levels of metabolites found were lower than those predicted by a toxicokinetic model (indicating that the model was conservative), and the metabolite levels found would have arisen from exposures that were well below the Acceptable Operator Exposure Level (AOEL) or the Acceptable Daily Intake (ADI) (suggesting that exposures were unlikely to be high enough to cause harm).

3.28   The group also considered the likelihood of simultaneous co-exposure of residents to multiple pesticides other than from tank mixes. This would depend on the number of fields around a residence, the types of crop and the prevailing wind conditions. It was concluded that the potential effects of such co-exposures could be addressed by existing methodology (see 4.57 and 4.58).   The possibility of exposure to the same substance on multiple days throughout the spraying season was also considered. It was concluded that this is already covered by the risk assessment.   In the future, the EU ACROPOLIS project [30] may provide additional information on the assessment of combined exposures to pesticides.

3.29   The question of secondary exposure to re-distributed residues (by which is meant exposure arising as a secondary release of pesticide from its first settling point after use, for example in dust at harvesting) was also considered by the group. All farmers have to abide by a pre-harvest interval between application of pesticides and harvesting, which will reduce such secondary exposure by natural degradation. A substantial quantity of dust would have to be inhaled to reach reference doses, such as the AOEL. The working group concluded that this pathway would not add significantly to total potential exposure.

3.30   There is also a possible risk of secondary exposure by subsequent re-volatilisation and uplift from foliage (of either the pesticide or degradation products). Limited research into this possibility following the application of sulphuric acid to potatoes indicated that neither sulphuric acid nor any of the substances produced by its action on potato tops would be present in air at concentrations likely to pose a significant health risk to bystanders [33].

3.31   There is some evidence of long-range transport of pesticides currently in use, and of both their wet and dry deposition. However, the concentrations in air and rates of deposition are small [23, 24 and 34] compared to the near-field concentrations and to the rates of deposition that the working group has recommended be assumed in risk assessment. The working group therefore considers that the contribution of such exposures will be within the range of uncertainties of potential exposures from other pathways and that they can be ignored for the purposes of risk assessment (see para 3.26).

4   Toxicology

4.1   As well as considering the methods for modelling the potential exposures of bystanders and residents, the group reviewed the regulatory approach to assessing risks to health that might arise from such exposures.

4.2   Each application for approval of a pesticide is accompanied by an extensive database of scientific studies designed to help regulators understand:

a)   its effects on the target pest,
b)   its possible environmental effects and, most importantly,
c)   the adverse effects it might cause to health and,
d)   the doses at which these effects might occur.

The toxicology studies considered in regulation of pesticides are similar to those undertaken for pharmaceuticals before they are licensed, with the obvious exception that there are no clinical dosing studies of pesticides in humans. Normally, the only data directly relating to effects on humans come from health monitoring of manufacturing personnel, epidemiological data on people exposed in the use of pesticides and reports of any poisonings that may have occurred (usually as a result of deliberate self-harm).

4.3   The potential for exposure to a pesticide to cause harm to human health depends not only on the level of exposure to the chemical but also on the degree to which it is toxic. Evidence on the latter comes from studies of animals exposed by different routes and at different doses. The highest doses tested are always much higher than the doses likely to be incurred by humans through normal use of the pesticide. Specific studies are required on both the active substance alone and the product formulation containing the active substance.   The data on the active substance allow the establishment of indices of acceptable exposure (toxicological reference values or reference doses) for that active substance such as the AOEL, ADI, ARfD (see paragraphs 4.4 onwards), which are reconsidered periodically in the light of any new scientific evidence.

Current registration package

Reference doses including acute reference dose (ARfD), AOEL, ADI

4.4   The current UK and EU package for registration of a pesticide requires data to enable the establishment of reference values (e.g. AOEL, ADI, ARfD) for the active substance. The regulatory framework underpinning these requirements is the EU Directive 91/414/EEC and its replacement, Regulation EC 1107/2009. In addition,

information on co-formulants is mandated by REACH (Registration, Evaluation, Authorisation and Restriction of Chemical substances: EC 1907/2006).

4.5   Information on the physicochemical characteristics of the substance such as molecular mass, pH, water solubility, octanol:water partition coefficient and pKa is also required. These data are useful in guiding and interpreting the design of toxicokinetic and toxicological studies and in helping to estimate potential exposures.

4.6   The metabolism and toxicokinetics of the substance should be characterised in at least one experimental species, with information on absorption by potentially relevant routes of exposure (e.g. oral, by inhalation and dermal). The importance of information on metabolism and toxicokinetics in the design, interpretation and extrapolation of data from toxicity studies is further emphasised in the proposed revised data requirements for active substances [35].

4.7   In recent years there has been increasing emphasis on issues such as systemic exposure, plasma elimination half-life and the use of *in vitro* systems, including human derived systems, to obtain comparative data on metabolism in studies on toxicokinetics. The use of toxicokinetic data to help interpret the results of long-term studies of toxicity has been enhanced by the option of obtaining such data during the conduct of these studies, as provided for in the draft OECD Guidance No. 116 (recently approved by the Working Group of National Coordinators of the Test Guidelines Program) [36].

4.8   Toxicity testing is undertaken *in vitro* and in experimental animals to characterise the toxicological profile of the substance, including hazard identification, i.e. the organs and body systems adversely affected on exposure; identification of the most sensitive, relevant effects, taking account of species and life stage (known as the "critical effects"); and dose-response evaluation, including consideration of the shape of the dose-response curve and identification of reference points (points of departure), such as the NOAEL (no-observed-adverse-effect level) or the BMDL10 (lower 95% confidence limit of the benchmark dose for a 10% response) for the critical effects.

4.9   Toxicity data required comprise the following:
- acute toxicity (effects of single dose via oral, dermal and inhalation routes);
- skin and eye irritancy;
- dermal sensitisation;
- repeat oral dose toxicity (up to 3 months repeated exposure in at least two species);
- sometimes repeat dose studies via the dermal and/or inhalation routes;
- genotoxicity (effects on DNA and chromosomes *in vitro*, and *in vivo* as necessary);
- chronic toxicity/carcinogenicity (or "lifetime" exposure) in two species;
- reproductive toxicity, over two generations;
- developmental toxicity, in two species;
- additional special studies, as necessary,
  - e.g. neurotoxicity, or toxicity studies on metabolites and supplementary studies on the active substance to elucidate mode of action for observed effects, e.g. tumourigenicity.

4.10   Data should be generated without using animals where suitable methods are available. In practice, this applies to only a few endpoints (effects) at present, such

as skin and eye irritation. All studies are performed according to agreed protocols and standards of design and conduct. This includes requirements for quality assurance and data retention.

4.11   Where animals are used in toxicity testing, they are examined regularly for general condition, clinical signs and behaviour. The early appearance of tumours is assessed by physical observation and palpation. Tests are stopped early if there any indications that this is necessary on humane grounds. At the end of a study, surviving animals are subject to a comprehensive post-mortem examination, both macroscopically, looking for any abnormalities of appearance or structure of the tissues, and microscopically, by histopathological study of sections from over 30 different tissues, together with any region of an organ or tissue that appears abnormal by visual inspection. Any animals that are euthanized or that die prematurely are also subject to detailed examination.

4.12   Not all effects produced in toxicity studies are adverse. They may be adaptive or reflect homeostatic regulation. In a few instances, there is agreement that such an effect should not be used as a basis for risk assessment. An example of this is benign adaptive hepatic hypertrophy, where the liver weight increases to adapt to the need to increase the elimination of a foreign compound. This is a reversible process with no adverse effects on the health of the organism.

4.13   The working group also recognised that some health outcomes (e.g. psychological effects) are not amenable to study in animals.

Acute toxicity studies

4.14   In studies of acute toxicity, the emphasis is on identifying the toxicity class, (rather than on obtaining a numerically precise estimate of acute lethality), the time to onset and duration of effects, reversibility, behavioural effects and other clinical signs, and pathological changes occurring either immediately or in the days following exposure.

4.15   Current acute toxicity studies place more emphasis on the observation of non-lethal effects. It is recognised that there are a number of acute effects, for example on specific target organs, that will not be detected using the current protocols. These effects will be detected in longer term studies, such as a 28-day study, often at lower doses. With increasing emphasis on the acute reference dose for dietary exposure, and now the acute AOEL (see below), a possible need to refine acute toxicity assessment has been recognised and the option of conducting a non-lethal test to determine whether effects observed in longer term studies do occur acutely is now available in the OECD Guidance No. 124 for The Derivation of an Acute Reference Dose (ENV/JM/MONO(2010)15) [37].

4.16   In studies involving repeated exposure, a wide range of end-points are investigated, including: mortality, clinical signs and behaviour, ophthalmoscopy (visual examination of the eye, including retina and optic disc), water and food consumption, food efficiency (body weight compared to calorie intake), body weight (absolute and rate of change); clinical chemistry (serum, blood, and urine); haematology; organ weights; gross pathology; and histopathology (of more than 30 tissues).

4.17   Studies are performed for progressively longer periods, using the results from each exposure duration to help select the doses for the next (longer) duration study. Some of the shorter range-finding studies are very much preliminary investigations to help in dose selection and may not be sufficiently extensive to help directly in the evaluation of the compound. In such cases, there should always be a more comprehensive, longer-term study available.

4.18   Typical study durations would be 7 days (almost always only for dose-range finding), 28 days (increasingly this is more than just range finding), 90 days and possibly 1 year (in dogs), and 2 years (as the chronic toxicity component of a 2-year carcinogenicity study – see below). In many studies, interim measurements are made, including observations of behaviour, ophthalmoscopy, clinical signs, clinical chemistry, haematology, urinalysis, body weight, food and water consumption. The number and nature of these measurements is influenced by the size of the experimental animal. For example, the range possible in dogs is much greater than in mice.

4.19   These studies are designed to identify systemic effects – that is effects on any tissue or organ system or on the animal as a whole. Examples of the latter include changes in body weight, unexplained clinical signs, and increased mortality (although this would not be anticipated from the doses selected, there may be unexpected effects on mortality from repeated exposures).

Genotoxicity, carcinogenicity and mutagenicity

4.20   Genotoxicity testing involves assessment of chemical structure for characteristic features of mutagenic compounds (structural alerts), and tests *in vitro* for mutation and chromosomal damage (numerical and structural). Depending on the outcome of these tests, additional studies *in vivo* may be required.

4.21   Compounds that are classified as mutagens will not normally be approved for use as pesticides in Europe.

4.22   Carcinogenicity testing involves studies for 2 years in rats and for 18 months in mice (in both sexes in each case). The study in rats is often combined with an investigation of chronic toxicity (see above). Animals are exposed daily, most often via the diet, to doses up to a level that induces some minor effects on the animals (e.g. slight weight loss), to ensure that the compound has been tested for possible carcinogenic effects to the maximum dose possible.

4.23   Additional studies may be undertaken on the mode of action of a compound (how it works) in causing carcinogenic effects. Such studies are undertaken on a case-by-case basis and their nature is dictated by the findings in the carcinogenicity studies together with all other relevant information on the compound and on structurally similar compounds.

4.24   Compounds that are classified as category 1A or 1B carcinogens (i.e. compounds that are known or presumed to have carcinogenic potential for humans based on evidence derived from human or animal studies) will not normally be approved for use as pesticides in Europe, unless exposure can be considered negligible in accordance with Regulation EC 1107/2009.

Reproductive studies

4.25   Compounds are investigated for possible effects on reproduction, over two generations, in rats. The so-called multi-generation study involves exposure of males for at least one spermatogenic cycle (unless data on spermatogenesis are available from a 90-day study), and females for several oestrus cycles before mating, during the mating period, and females during gestation and until weaning of the F1 offspring.   At weaning, offspring are administered the compound until sexually mature, during mating, and in females during gestation and until weaning of the F2 generation.

4.26   A wide range of parameters that could reflect effects on reproduction is assessed in this test, including effects on male and female gametes, mating behaviour, fertilisation, implantation and survival of embryos and foetuses, post-natal survival, and development and reproductive performance of offspring.

4.27   All stages of reproduction are investigated and testing covers more than one generation. The one exception is the health consequences in later life of early life (*in utero* or early postnatal) exposure because current multi-generation test protocols do not follow the animals into old age. However, there is little evidence that effects would be observed using such a protocol that are not otherwise detected in current toxicity testing procedures and there are a number of practical difficulties in conducting studies of this nature [38, 39].

4.28   The OECD has recently adopted a test guideline (Test Guideline 443) for an extended one-generation study, to reduce the number of animals used whilst improving the efficiency of testing.

Developmental studies

4.29   The possible effects of compounds on development are assessed in rats and rabbits. Pregnant animals are dosed from the time of implantation until the day before expected normal delivery. Animals are delivered by Caesarean section, to avoid possible cannibalisation of the offspring, a particular problem when there are any abnormalities.

4.30   Females are examined throughout pregnancy for signs of toxicity, such as appearance, clinical signs, body weight, and food and water intake. At termination, the dams are examined macroscopically. Uterine weights are recorded and the uterine contents examined for embryonic or fetal loss. The fetuses are examined macroscopically, weighed and sexed. Some are examined for skeletal effects and others for effects on soft tissues. This requires different processing and stains.

4.31   Compounds that are classified as toxic for reproduction category 1A or 1B (known or presumed to produce an adverse effect on reproductive ability or capacity or on development in humans on the basis of either reproductive or developmental toxicity studies) will not normally be approved for use as pesticides in Europe, unless exposure can be considered negligible in accordance with Regulation EC 1107/2009.

Neurotoxicity studies

4.32   In the repeat dose toxicity studies described above, animals are regularly assessed for clinical or behavioural signs that might indicate neurotoxicity. At termination, tissues from the nervous system are examined for any evidence of histopathological damage. If necessary, based on structural similarity to other compounds with effects of concern, or because of indications of neurotoxicity during testing for systemic effects as above, specific studies on acute and repeat dose neurotoxicity are required.

4.33   Animals are observed for their general behaviour, for specific aspects of behaviour using simple intervention tests (for example for balance), and for macroscopic or microscopic evidence of damage to nervous tissue in the periphery and the central nervous system.

Immunotoxicity and endocrinological studies

4.34   Similarly, in the repeat dose toxicity studies described above, tissues from the immune and endocrine systems are examined on termination for any evidence of histopathological damage. Additional specific studies on the immunotoxicological potential or on potential effects on the endocrine system may be required on the basis of chemical structure or findings in the above studies.

Studies on metabolites of the primary agent

4.35   On a case by case basis, studies on metabolites may be necessary. This might be the case where metabolites or degradates are found in plants or animal products, soil, groundwater or the air, which differ from those found in the animal species used for the toxicology studies, or are formed in only low amounts in such animals. The need for further testing is based on the amount of metabolite found in various media and the chemical structure of the metabolite compared to that of the parent compound.

4.36   The EFSA Panel on Plant Protection Products and their Residues (PPR) has recently published guidance on this issue [40].

Main objectives of testing and aspects of study design

4.37   In almost all of the above tests, there are two objectives.
• to assess the possible hazard of the compound, i.e. is it capable of causing effect(s) in the test system.
• to characterise the dose-response relationship for any effects observed.

4.38   These two objectives have an effect on study design. Generally, there should be sufficient numbers of animals to ensure statistical confidence in the outcome. This, together with practical and ethical considerations, is the basis for the numbers of animals per dose group in the test guidelines. For larger species, such as dogs, dose groups are smaller.

4.39   The number of dose groups is similarly based on study objectives, practicality, and ethics of animal experimentation. As a result, most guidelines recommend a minimum of three dose groups plus a suitable control group. Doses are selected on the basis of range-finding studies. The maximum dose should be such that some effect is produced, but not such that the lifespan of the animals is reduced. The

minimum dose should be one that produces no observable effect. The other dose(s) should be spaced appropriately between the top dose and the lowest dose.

4.40   The RCEP in its report on crop spraying [1] suggested that human cell culture models might help overcome some of the perceived limitations of current toxicity testing methods. There is currently much effort to develop alternatives to animal models for toxicity testing, including computer-based quantitative or semi-quantitative modelling and simulation, use of information from structural analogues, and *in vitro* test systems, preferably using human-derived cells, either primary cells or continuous cell lines. Whilst holding much promise, this work is still at a relatively early stage, and at present the majority of the tests are unable on their own to provide sufficient reassurance of protection of human health for regulatory purposes [41].

4.41   Revised toxicology data requirements are being prepared at present in Europe. These are expected to be published in 2013, to come into full effect from 2014 [35].   These requirements include specific prohibitions on animal testing unless there is no other validated and/or acceptable alternative. There is also a prohibition on testing in humans and non-human primates.

4.42   These requirements are as follows in the draft document:

> '*7.1   Where new tests are carried out for the purpose of Regulation EC No 1107/2009, tests on vertebrate animals described in this Regulation and within the meaning of Directive 2010/63/EU shall be undertaken only where no other validated and/or acceptable alternative is possible.*
>
> *Alternatives include in vitro methods and in silico methods. Reduction and refinement methods for in vivo testing shall also be considered to keep the number of animals used in testing to a minimum.*
>
> *7.2 The principles of replacement, reduction and refinement of the use of animals should be fully taken into account in the design of the test methods, in particular when appropriate validated methods become available to replace, reduce or refine animal testing.*
>
> *7.3 Tests on humans and non-human primates shall not be performed for the purpose of this Regulation.*'

4.43   All toxicity testing should be conducted with reduction, refinement and replacement of animal tests in mind (the 3Rs). As soon as scientifically acceptable methods meeting one or more of the objectives of the 3Rs are available, these must be used in preference to the existing methods.

Use of studies in humans

4.44   In evaluating a compound, any available human data should be considered. It is no longer possible to study pesticides experimentally in human volunteers, even at very low doses, under the current EU Regulation. However, relevant information may be available from observational studies of those involved in manufacture of the compound, from epidemiological studies of compounds already in use, or from clinical studies of compounds with potentially therapeutic applications.

4.45   Some effects observed in animal studies are not relevant to humans, because of fundamental differences in biochemistry or physiology or because of profound quantitative differences in key processes. However, it is often not possible to determine whether an effect observed in a toxicity study is relevant to humans. In the absence of sound evidence to the contrary, any effect observed in such a study is assumed to be relevant to humans.

The No Observable Adverse Effect Level (NOAEL)

4.46   For endpoints other than cancer caused by genotoxic compounds, it is generally agreed that there is a biological threshold in the dose-response relationship, below which there is no effect. For such substances, a reference point (also known as a point of departure) is identified for the most sensitive effect(s) in each study. Most typically, this is the no observed adverse effect level (NOAEL) – usually the highest dose for which the effect is not statistically different from that in the controls.

4.47   An alternative approach is to fit a mathematical relationship to the dose-response data and to estimate the dose producing a pre-defined response, usually 10% for incidence data (e.g. number of foetuses with skeletal variations) and 5% for continuous data (e.g. change in bodyweight). This is known as the benchmark dose (BMD). The lower 95% confidence limit for the estimated BMD (known as the BMDL) is then determined mathematically to account for experimental uncertainty, and used as a reference point.

4.48   The NOAEL in a given study is not necessarily a zero effect level. It may be above or below the true threshold since it is dependent on the doses chosen for the study as well as chance variation between samples. However, there is sufficient conservatism in the risk assessment process that any residual effect at the NOAEL is taken into account in the derivation of health based guidance values [42].

4.49   Those studies considered relevant to the pattern of exposure of operators, workers, residents and bystanders, based on study duration, are assessed for the lowest relevant NOAEL in any species. This is known as the critical NOAEL, and the associated effect as the critical effect, i.e. the one that underlies the AOEL.

Uncertainty factors

4.50   In order to extrapolate the critical NOAEL (or other reference point) to a reference dose for humans, uncertainty factors (also known as safety or assessment factors) are used, to account for possible species differences in sensitivity and for inter-individual variability in humans. Values of 10 are normally used for each of these factors, resulting in an overall uncertainty factor of 100, on the assumption that they act independently. This is not always the case. For example, the critical effect may be observed in neonatal animals, yet part of the factor of 10 for inter-individual variability is to account for possible age-related differences. This contributes to the conservatism of the risk assessment.

4.51   Additional uncertainty factors may be used for a variety of reasons. These include: the absence of a NOAEL, with extrapolation instead from the lowest observed adverse effect level (LOAEL) (provided that the effect at the LOAEL is of relatively low magnitude or frequency); deficiencies in the database; and severity of

effects. Each additional factor is given a value from 2-10, the magnitude being determined by expert judgement. It is also possible to use chemical specific adjustment factors (CSAFs) e.g. where adequate specific toxicokinetic or toxicodynamic data are available to enable a default factor to be replaced by a data-derived factor [43]. The overall uncertainty factor is obtained from the product of all of the uncertainty factors used.

4.52   The Acceptable Operator Exposure Level (AOEL) is established by dividing the critical NOAEL by the overall uncertainty factor. Where the critical NOAEL comes from a study using oral administration of a pesticide and there is incomplete absorption by the oral route, the AOEL is adjusted for the fraction of the dose that is absorbed, as determined from toxicokinetic studies. The resulting AOEL thus reflects the effects of systemic exposure following 100% absorption and can be used as the relevant comparator for exposures by whatever route. (NB this differs from the ADI and ARfD which are derived from oral studies and are used to assess risk from oral exposures and thus do not need to be adjusted in this way). To do this, allowance must also be made for the completeness of absorption from the routes of exposure under consideration, with derivation of an equivalent systemic exposure for comparison with the AOEL.

4.53   AOELs are based on the most appropriate exposure scenario, in which, for most pesticides, it is currently assumed that a person is exposed every day over the course of a spraying season, year on year. For some products, exposure may be for a very short period, or may be subject to short "spikes". To date this has been dealt with by comparison with the conventional AOEL, often based on a 90-day study. However, according to a proposal from EFSA, currently under consultation, an approach for establishing acute AOELs is being developed for this purpose. This would also be of value for assessing bystander and acute resident exposures.

4.54   Where estimated exposure exceeds the AOEL (or other relevant reference value), this does not necessarily mean that adverse health effects will occur. This will depend on the nature of the endpoint on which the AOEL is based, the magnitude of exceedance of the AOEL and the duration of such exceedance. Scientifically, short term exceedances by a modest amount are very unlikely to be a cause for concern. The development of acute AOELs in the future will help in assessing whether there is concern from short-term higher exposures. The working group note that there are specific requirements in legislation governing estimates of exposure and comparison with the AOEL.

4.55   Although guidance on the establishment of acute AOELs would need to be prepared, the principle is well established and guidance exists for establishing acute reference doses (ARfDs) for dietary risk assessment [37]. In general, when extrapolating from studies in rodents to human exposure scenarios, proportionality of lifespan is assumed. Although lifetime in rodents is appreciably less than in humans (e.g. 2 years in rats c.f. ~80 years in humans) there is good evidence that effects scale with fraction of lifetime over which exposure occurs [44, 45]). Hence, a study of 3 months duration in rodents would be considered to cover 10% of the lifespan, i.e. equivalent to 7 years in humans. Exposure is assumed to occur at the same, maximal, level every day throughout this period. Where anticipated exposure in humans is longer than this, for example for a substantial proportion of a lifetime, or because of long persistence of the compound in the body (uncommon with modern pesticides), health based guidance values based on chronic exposure should be

used, such as the ADI. Appropriate consideration would need to be given to absorption by the different routes of exposure for comparison with the reference value.

4.56   In addition to studies on the active ingredient, data are required on the product as intended for supply to users. Necessary information includes data on acute toxicity by the oral, dermal and, if appropriate, inhalation routes, skin and eye irritancy and skin sensitisation. These data are assessed for any evidence of route-specific effects or additive effects of the mixture components. If results different from those anticipated are observed, their potential implications for exposed people is considered further.

Additivity

4.57   Several groups have recently reviewed the evidence for departures from additivity of toxicity when there is exposure close in time to multiple environmental chemicals at the levels which occur in humans [46, 47]. Exposures of bystanders and residents to combinations of pesticides would usually be from tank mixes or from different sprays being applied to different crops in neighbouring fields. In general, it has been concluded that, for compounds with a similar mode of toxic action, approaches based on simple addition of exposures, adjusted for potency, are predictive of impact. Consequently, the strategy of grouping compounds with a similar mode of action, e.g. acetylcholine esterase inhibitors (organophosphates and N-methylcarbamates), and using dose addition in their assessment is believed by the working group to be appropriate.

4.58   For other co-exposures, the possibility of synergy should be considered on a case-by-case basis. For example, potent inhibition of metabolic elimination of one compound by another would require specific information on the degree of that inhibition and the shape of the dose-response function. However, for most co-exposures to dissimilarly acting compounds, the assumption is that they would act independently [48, 49]. Hence, no consideration additional to that for the individual compounds would be required in the assessment of their co-exposure. It is expected that on-going work by EFSA on which combinations of pesticides should be assessed together, will be of value here.

Summary of approaches to toxicity testing of pesticides

4.59   Pesticides are extensively tested for toxicity prior to authorisation. Testing is as rigorous, if not more so, than for human medicines with the obvious exception that there are no clinical dosing studies of pesticides in humans. A comprehensive series of both morphological and functional endpoints is investigated, in exposures spanning from a single occasion to a lifetime. Possible effects during potentially vulnerable life stages are investigated, including throughout the period of reproduction, *in utero* and in early life. Because testing is in whole organisms, unanticipated effects can be detected, and these are further investigated as necessary. The behaviour of animals is regularly monitored in all studies, and any indications of altered behaviour would trigger further investigation. Suggestions that current testing is not sufficiently sensitive to detect certain endpoints such as altered developmental neurotoxicity have not been substantiated. In general, reproductive studies (such as the two-generation study) appear to be sufficiently protective [50].

Local effects: irritation and skin sensitisation

Skin sensitisation and pesticides

4.60   The current approach to assessing local effects of chemicals is to use dilutions based upon trigger concentrations set out in the Dangerous Preparations Directive (1999/45/EC). This gives concentrations at which the classifications of dangerous substances are carried over to products containing them, unless the product itself has been tested for the end-point(s) of concern. The generic trigger concentrations for irritancy and sensitisation are 20% and 1% (w/w) respectively. If an in-use dilution as specified on the label of a product is above the trigger value for classification then a specific assessment of the dilution should be performed. The derivation of these trigger concentrations is based upon expert opinion.

4.61   Bystander and resident exposure to pesticides is most likely to be to diluted products and can occur either *via* the skin, the mouth, the respiratory tract or the eyes. Acute effects such as skin or eye irritation, cough and sore throats, localised to directly exposed tissues, can then occur if the exposure is at a sufficiently high concentration for a sufficient period of time. Whilst these have been considered nuisance effects, they nonetheless are clinically relevant and can impact on quality of life.

4.62   As well as these acute effects, there is concern that pesticide exposure may result in allergic sensitisation, possibly with longer term consequences.   An individual can become sensitised as a result of exposure to a substance that can induce a specific immunological reaction ("induction"), such that the individual then reacts to much lower concentrations on further exposure ("elicitation"). On initial contact with a skin sensitiser, the exposed person may experience no obvious symptoms, yet further contact with the same substance may result in clinical manifestations (either skin or respiratory). A background document on the mechanisms of skin sensitisation to chemicals is provided in Appendix 5.

4.63   In the skin, the dose per unit area is the key exposure parameter that determines sensitisation. A dose that can cause sensitisation may not necessarily do so if administered over a larger area of the skin. The dose required to sensitise an individual may also be different from that required to elicit symptoms subsequently in a sensitised individual. The induction and elicitation phases both exhibit dose thresholds and a dose-response relationship. The more potent a sensitiser, the lower the threshold dose for induction. Exposure to doses below the induction threshold will not induce sensitisation. Doses below the elicitation threshold will not induce a clinical response in sensitised individuals. For some sensitisers all individuals appear to be susceptible when exposed at a sufficiently high level, whereas for other chemicals, regardless of dose, only certain individuals appear to be susceptible.

4.64   The mouse local lymph node assay (LLNA) is one of the tests (OECD 429) used to examine whether a chemical might be a skin sensitiser [51]. This studies the initial phase of skin sensitisation and provides quantitative data for assessing the sensitising potency of a chemical. Chemicals that induce a three-fold increase in activity over background (known as a "stimulation index" of 3) are considered sensitisers and the concentration of the chemical (known as the EC3) required to cause such an increase can be used to quantify the potency of that chemical. Chemicals which when diluted 50 or more times (to a concentration of 2% or less)

give a positive response in the assay (*i.e.* an EC3 value of <2%) have been classified as having strong or extreme potency and are likely to pose the greatest risk of sensitisation to humans

4.65   At the other end of the scale, chemicals with high EC3 values (*i.e.* they give a positive result only when tested at high concentrations) are likely to present a low risk to humans. However, even chemicals with high EC3 values (>50%) have been reported to cause skin sensitisation in some humans, and therefore it is not currently possible to identify an EC3 value below 100% suitable for categorising chemicals as having no sensitising potential in any individual.

4.66   The largest publicly available database of LLNA results for pesticide formulations was published in 2010 by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) [52]. Of the 104 tested products, 54% were classified as sensitisers. Some of the formulations were identified by the name of the active substance but for other formulations only limited details were available. Hence it is difficult to ascertain whether the tested formulations are representative of those in use generally, or more specifically those that are actually approved in the UK.

4.67   With these caveats, twenty formulations that were identified as sensitisers appear to be similar to products approved in the UK, although seven of them contained higher concentrations of active substance than are approved. The EC3 values of these products ranged from 1-56% and as outlined in paragraph 4.65, they thus have the potential to be human sensitisers.

4.68   When pesticides are sprayed, the exposure of bystanders and residents is to the diluted formulation, typically diluted so that the concentration is less than 1%. The extent to which such exposure carries a risk of sensitisation is not fully established, but there are few reports of apparent sensitisation from such exposure. For risk assessment, an approach such as that set out in the REACH guidance could be considered as a method of defining the risk more clearly.

5   Conclusions and recommendations

Exposures

5.1   The working group recognises the limitations of the evidence base concerning the effects of pesticides on human health, largely because of uncertainties about levels of exposure in published studies, although this was less of a problem in studies of short-term effects. A further limitation is that many epidemiological studies have explored health risks only in relation to broad classes of exposure such as 'pesticides' or 'insecticides'. They thus group together compounds with different chemistries and toxic potential, making interpretation difficult. The group notes that there are also important problems in the ascertainment of health outcomes (symptoms reported are often non-specific, tests to confirm diagnoses are often lacking and there is a possibility that minor effects are under-reported). A separate working group of the ACP, the Pesticides Adverse Health Effect Surveillance Scheme working group (PAHES) is considering these specific difficulties.

5.2   In most cases the modelled exposures that are used in regulatory risk assessments are based on a worst-case scenario which is unlikely to occur other

than in the most unusual circumstances. The group concludes that this approach is sufficiently conservative to minimise risk to health. It is important to note that the approach to exposure assessment for regulatory approval of pesticides is to obtain a realistic upper estimate for exposure in a specified group (e.g. residents) over a relevant time period. This does not mean that each risk assessment must include calculations of potential exposure from every possible pathway and route of exposure. If a generic evaluation indicates that some pathways/routes make no material contribution to total potential systemic exposure in comparison with others, they can be omitted from the calculations without compromising safety. However, this does not mean that they have not been considered or taken into account. Furthermore, where the duration of exposure that leads to a toxic effect is several months, exceedance of the reference value on a single day is not of concern as it is the longer-term average exposure that matters. Of course, if the substance were acutely toxic, it would also have an acute toxicological reference value, but this would often be higher than the longer-term reference value.

5.3   The working group concludes that estimation of potential bystander and resident exposures to pesticide spray would be significantly improved by use of the BREAM dataset on spray deposits. There are still uncertainties around the factors governing volatility and predicting vapour concentrations. However, although vapours can carry considerable distances, the levels measured distant from a spray source are very low. The group concludes that further research is needed to refine the models used. The group notes that the data used to estimate exposure to vapour in risk assessments relate solely to chlorpyrifos (and parathion for low volatility substances) and recognises that levels might differ for other active substances. However, the group believes that these differences are very unlikely to compromise safety in the UK setting since chlorpyrifos has a higher volatility than most pesticides, and the data on it were obtained in California where the climate is generally rather warmer than that of the UK [53]. Warmer temperatures encourage volatilisation, and therefore the levels measured in the California study are likely to be at the higher end of those that occur in the UK.

5.4   The group notes that currently, estimates of potential exposure are based on mean data, but that the BREAM data provide other values that could be used in risk assessment. Members consider that different percentiles could be used for acute (95%) and longer term (75%) risk assessments. Lower values could be used in longer-term assessments because it is very unlikely that repeated exposures would all occur at the higher levels, but rather they would be mixed with lower values on a number of occasions.

5.5   The group notes that the measurements on spray drift proposed for use in risk assessment relate to wind speeds at the upper end of the range in which spraying is legally permitted. Whilst it is possible that some specific nozzles could produce higher drift, this is likely to fall within the range of uncertainties for which allowance is made in the overall assessment.

5.6   The group notes that conversion of information on dermal deposition to systemic exposure estimates is difficult, and that where no data are available, current guidance is to assume, as a default, that dermal absorption could be as high as 100%. However, where data are available, the range of measured dermal absorption has usually been between 1 and 10% [54].

5.7   In addition, the behaviour, body size and potential for dermal contact with contaminated surfaces differ between adults and children. The group concludes that behavioural differences between adults and children (and between children of different ages) should continue to be taken into consideration in assessing dermal exposures to dislodgeable residues arising from spray drift deposits. For instance, children are assumed to play in direct contact with the ground. During this play they may be exposed to dislodgeable residues over a substantial proportion of their body. In addition they are likely to transfer some of these residues from hands or objects they play with to their mouths, resulting in an additional route of exposure. The working group considers that these behaviours are appropriately captured in the US EPA turf model. This model represents a behaviour pattern that is likely to result in greater exposure to dislodgeable residues than adult behaviours, a difference that will be even greater when exposures are adjusted for body weight.   Adult exposure estimates for dislodgeable residues should therefore focus on the 're-entry' scenario of walking across a treated field. The group agrees that in this way, separate scenarios should be considered for adults and children in risk assessment.

5.8   The group concludes that estimates of potential exposure by different routes are each based on conservative assumptions, and it would be inappropriate simply to add them up as this would result in a very conservative estimate of total potential exposure based on unrealistic assumptions. The USA EPA has made some probabilistic estimates of total exposures, but these require suitable input data.   The group believes that tools to generate more realistic estimates of total potential exposure should be developed.

5.9   The group agrees that to take account of spray drift residues on garden produce, empirical data should be obtained on the range of exposures that could result. This would aid understanding of the relative importance of this pathway of exposure in risk assessment.

5.10   The group notes that there is a paucity of information on biomarkers, either of exposure or biological effects, in published, population-based studies, although some small studies suggest that approaches to risk assessment using biomarkers can be very helpful. Given this limited evidence base, the group considers that no recommendations can be made at this time with respect to the use of biomarkers in risk assessment. The group notes that a sub-group of the ACP, (PAHES) is considering this aspect of exposure assessment in more detail.

5.11   The group concludes that while measurement of, say, airborne levels of a pesticide is helpful as an index of exposure, what matters in terms of health effects is the dose that reaches a target organ within the body. Where exposure to more than one pesticide (or its co-formulant(s)) occurs, the question arises as to whether the effects of such multiple exposures should be regarded as additive, synergistic or neither. For pesticides with a similar mode of toxic action, approaches based on simple addition of exposures, adjusted for potency, should be predictive of impact. For other co-exposures, the possibility of synergy should be considered on a case-by-case basis. However, for most co-exposures to dissimilarly acting compounds, the assumption is that they would act independently and no consideration additional to that for the individual compounds would be required.

5.12   While it considers that the approach proposed by EFSA in their draft guidance on exposure assessment of residents and bystanders is sufficiently conservative, the

group concludes that there remains a need to address some specific questions relating to dosimetry. The key drivers of potential exposure under different circumstances need to be determined and at present there are few data to address this. This work is important because understanding which factors may have most influence will determine how current practice could be modified to reduce exposures.

Toxicity

5.13   The group agrees that current toxicity testing of pesticides is comprehensive, given the constraint that it cannot be conducted in humans; the testing covers potentially vulnerable life stages. There has been some discussion about the possible impact of *in utero* exposure on disease in later life. However, the group notes that there are practical difficulties in implementing a routine testing protocol for this. The revised OECD test guideline for chronic toxicity testing (TG 452) [55] does not envisage use of such a testing protocol. The group agrees that the key issue is whether effects that would not otherwise be detected would be observed using such a protocol. Available evidence suggests that the current regime of tests, including chronic toxicity, carcinogenicity and reproductive toxicity testing, would identify any potential adverse effects regardless of the mechanism [39].

Dose and sensitisation

5.14   The group notes a concern that some individuals may become sensitised to pesticides (or indeed other substances), possibly following apparently low exposures relative to the sensitising dose in animals, and that risk factors for sensitisation are not well understood, either for pesticides or for other substances. The group considers that it is important to identify the extent to which current or new formulations may change the ability of chemicals to act as sensitisers.

5.15   The group recognises the utility of the LLNA in providing potency estimates for different pesticides with regard to the induction of skin sensitisation, but that there are difficulties in estimating potency for elicitation. Further work is required to characterise better the LLNA potency of current formulations used in the UK.   The relationship between such potency estimates and human risk is unclear and further work is required to define this relationship.

Recommendations

5.16   The working group **recommends** that the approach proposed by EFSA in their draft guidance on estimation of potential bystander and resident exposures, augmented by the results of the most recent exposure studies, in particular the data from the Bystander and Resident Exposure Assessment Model, BREAM, should be followed by regulatory authorities, as it represents the most appropriate approach at the current time. The proposed approaches are outlined in Table 2, with a comparison between the BRAWG and EFSA recommendations shown in Appendix 6.

5.17   The working group **recommends** that the models used to estimate potential exposures in regulatory risk assessment should be continually refined by more data as these become available (e.g. for a wider range of application techniques and on impacts of various drift mitigation measures).

5.18   The working group has considered the potential distance of a sprayer from the field boundary and the position of the bystander or resident assumed in regulatory risk assessments. The group **recommends** that a 2 metre distance between the sprayer and the bystander or resident should be assumed. In addition the working group **recommends** that models to estimate the potential exposures of bystanders and residents should use different percentiles of spray drift measurements according to the time period of exposure that is relevant. The 95th percentile should be used for acute exposures and the 75th percentile for longer term exposures. Risk managers may wish to consider whether the risk assessment assumption needs to be supported by any further risk management options, such as statutory restrictions or other guidance.

5.19   The working group considered the extent of exposure arising from volatilisation of pesticides, and **recommends** that the current approach of using generic values should be retained, but that further research should be undertaken to develop methods of calculating volatilisation losses for individual active substances. The recommendation from BREAM to assume that 95% of applied pesticide is lost via volatilisation over the first 24 hours from application is unrealistic and too conservative, and should not be built into the risk assessment. Approaches that assess volatilisation losses based on pesticides' physico-chemical properties may be of use for application in lower tiers of assessment. Additional work is required to refine exposure assessments by including more recent data, particularly from studies undertaken under European conditions, and on compounds with lower vapour pressures and lower application rates that are more typical of current-use pesticides. The working group **recommends** that further work be undertaken to determine whether models such as the Pesticide Emission Model [26] are appropriate for use given the agricultural conditions in Europe.

5.20   The working group recognises that currently, in the absence of specific data, a default value of 100% dermal absorption is used to convert dermal exposure to systemic exposure. Whilst this approach is likely to overestimate exposure and to be protective, the working group **recommends** that further work should be undertaken to better characterise dermal absorption of pesticides.

5.21   The working group **recommends** that in estimating potential dermal exposures, consideration should be given to the possibility that surface deposits of a pesticide may accumulate following repeated applications.

5.22   The working group **recommends** that further information on exposures from contact with companion animals are needed to confirm assumptions that the approach proposed for indirect exposures adequately accounts for this exposure pathway.

5.23   For regulatory risk assessment, the default value proposed by EFSA for the time it is assumed that a bystander (or resident) may spend in a treated crop (e.g. on a footpath or right of way crossing a crop) is 15 minutes. The working group believes that this may not represent a realistic worst case, and thus **recommends** that a value of 30 minutes should be used.

5.24   The working group **recommends** that given the lack of available information, research should be undertaken to quantify exposure from residues on garden crops arising from spray drift.

5.25   For assessment of total potential systemic exposure, the group **recommends** that estimates of potential exposure from different sources and by different routes should not simply be summed as a matter of routine. In some cases where the exposures are linked to the same spraying event (e.g. direct inhalation and dermal exposure to spray drift) it would be appropriate to use a high percentile for both. In other cases, where possible, a probabilistic approach should be used. The working group **recommends** that tools to obtain a more realistic estimate be developed.

5.26   The working group **recommends** that given their physiological and behavioural differences, separate risk assessments should be considered for children and adults exposed as bystanders or residents.

5.27   The group **recommends** that research be conducted on the extent to which current or new formulations may change the ability of chemicals to act as sensitisers.

5.28   The group recognises the importance of the local lymph node assay (LLNA) in providing more quantitative estimates of sensitising potency, but **recommends** that further work be undertaken to characterise better the LLNA potency of formulations currently used, and the influence of co-formulants on sensitisation. The relationship between such potency estimates and human risk is unclear and the group **recommends** that further work be undertaken to define this relationship**.**

5.29   The group considered the expressed concern that the current regulatory package does not test specifically for fetal origins of diseases of old age such as cancers and diabetes, for which studies in epigenetics have suggested possible mechanisms. As yet, there are no clear data indicating that the standard test package fails to protect against such effects, but there is concern that it might. Overall the group agreed that this area of science was not yet at a point where a valid test for such effects could be introduced, but **recommends** that new work in this area should be carefully evaluated as it emerges.

TABLE 1 Current approaches to risk assessment for pesticide spraying

EXPOSURE	SOURCE	ROUTE	BYSTANDERS	RESIDENTS ADULTS	RESIDENTS CHILDREN	COMMENTS
During spraying (acute)	Spray drift	Inhalation	8 metres down wind, single pass of 12 metre boom sprayer, 0.006ml spray (5 min inhalation), estimates based on mean data from highest exposure data set. Assessment for adult assumed to cover children	Assume exposure is covered by bystander assessment	Assume exposure is covered by bystander assessment	5 mins is longer than it takes for the spray plume to pass. Total acute exposure is sum of inhalation and dermal and is compared to AOEL used for repeated exposures.
		Dermal	8 metres, downwind 0.1ml spray, no reduction from clothing, 60Kg adult, default 100% absorption	Assume exposure is covered by bystander assessment	Assume exposure is covered by bystander assessment	
		Ingestion	Not considered			
Post spraying longer term	Volatilisation from deposits	Inhalation	Not separately considered – covered by adult resident assessment	24h exposure to 1 or 15µg/m^3 (taken from German data and from California EPA chlorpyrifos monitoring [53], 60kg adult, respiring 15.2 m^3/day	24h exposure to 1 or 15µg/m^3 (German data and from California EPA chlorpyrifos monitoring [53]), 15Kg child , respiring 8.3 m^3/day	For any substance more volatile than chlorpyrifos an estimate of flux and the BREAM air dispersion model is used.
	Spray fallout/deposition	Dermal	Assumed covered by re-entry worker exposure – (adult assessment 2 hours intimate contact with treated crop and no PPE)	Assumed covered by re-entry worker exposure – (adult assessment 2 hours intimate contact with treated crop and no PPE)	Uses US EPA lawn re-entry model. Calculates dermal exposure using drift fall out, turf transferable residue, transfer co-efficient from grass to skin and duration of contact with contaminated turf. Assumes 2 hour contact period and 15kg child	US EPA model has recently been updated.

EXPOSURE	SOURCE	ROUTE	BYSTANDERS	RESIDENTS ADULTS	RESIDENTS CHILDREN	COMMENTS
		Ingestion	Not separately considered but assumes that child ingestion exposure is likely to cover adult	Not separately considered but assumes that child ingestion exposure is likely to cover adult	US EPA lawn re-entry model. Assumes a proportion of residue picked up on the hand is transfered to the mouth (eg by child sucking thumb, licking hand etc) Allows for repeated exposure and re-contamination of hand. PLUS direct consumption/mouthing of contaminated grass. Assumes grass from 25cm^2 area is 'consumed' .	Children's exposure is assumed to be the sum of those from dermal, ingested and inhaled routes. US EPA model has recently been updated
During and post spraying		Local effects (sensitisation and irritation)	Consider dilution and classification criteria to understand likelihood of effect.	Consider dilution/dispersion and classification criteria to understand likelihood of effect.	Consider dilution/dispersion and classification criteria to understand likelihood of effect.	Based on limited data. Dilution of concentrates in line with directions for use and the code of practice suggests the criteria for classification for these effects would not be merited.

TABLE 2 Proposed approaches to risk assessment for pesticide spraying

EXPOSURE	SOURCE	ROUTE	BYSTANDERS	RESIDENTS ADULTS	RESIDENTS CHILDREN	COMMENTS
Acute/during spraying	Spray drift	Inhalation	2 metres down wind, single pass, 24 metre boom sprayer total spray cloud estimates based on 95 percentile data. Evaluation for adults and children.	As bystander	As bystander	Total acute exposure is sum of inhalation and dermal and is compared to an acute AOEL
		Dermal	2 metres down wind, single pass, 24 metre boom sprayer total spray cloud estimates based on 95 percentile data. Evaluation for adults and children. No reduction from clothing, 60Kg Adult, default 100% absorption.	As bystander	Uses US EPA lawn re-entry model. Calculates dermal exposure using 95 percentile drift fall out at 2 metres, turf transferable residue, a higher transfer co-efficient from grass to skin and duration of contact with contaminated turf. Assumes 2 hour contact period and 15kg child	
	Entry to treated areas		EUROPOEM worker re-entry model with 30 min exposure to reflect walking across a freshly treated field.	As bystander	Assumed covered by child lawn exposure estimate as above	
		Ingestion	Not considered			
longer term/ post spraying	Volatilisation from deposits	Inhalation	Not separately considered – covered by adult resident assessment	24h exposure to 1or 15µg/m^3 (as above), or estimate of flux and BREAM air dispersion model, 60kg female, respiring 15.2m^3/day	24h exposure to 1 or 15µg/m^3 or estimate of flux and BREAM air dispersion model (as above) 15Kg child , respiring 8.3 m^3/day	Compare to repeat dose AOEL Consider aggregating acute and sub chronic resident exposure
	Spray fallout/deposition	Dermal		Assume covered by bystander entry to treated areas (EUROPOEM worker re-entry model 30 min exposure).	Uses US EPA lawn re-entry model, Calculates dermal exposure using 75th percentile drift fall out at 2 metres, turf transferable residue, average transfer co-efficient from grass to skin and duration of contact with contaminated turf. Assumes 2 hour contact period and 15kg child	

EXPOSURE	SOURCE	ROUTE	BYSTANDERS	RESIDENTS ADULTS	RESIDENTS CHILDREN	COMMENTS
		Ingestion	Not separately considered but assumes that child ingestion exposure is likely to cover adult	Not separately considered but assumes that child ingestion exposure is likely to cover adult	US EPA lawn re-entry model. Assumes a proportion of residue picked up on the hand is transfered to the mouth (eg by child sucking thumb, licking hand etc) Allows for repeated exposure and re-contamination of hand. PLUS direct consumption/mouthing of contaminated grass. Assumes grass from 25cm^2 area is 'consumed'.	Children's exposure is the sum of dermal and inhalation. Consider ingestion of garden produce and other dietary sources? Use probabilistic modelling for aggregated exposures. US EPA model has recently been updated
	Repeated spray exposures	inhalation		Consider weekly repeated exposures with values for 2 metres downwind from 24 metre boom sprayer. Use 75 percentile data for spray drift	Consider weekly repeated exposures with values for 2 metres downwind from 24 metre boom sprayer Use 75 percentile data for spray drift	
		dermal		Consider weekly repeated exposures with values for 2 metres downwind from 24 metre boom sprayer. Use 75 percentile data for spray drift	Consider weekly repeated exposures with values for 2 metres downwind from 24 metre boom sprayer Use 75 percentile data for spray drift	
		Via eyes				Considered covered by the dermal exposure estimate taking into account the small surface area of the eyes compared to the rest of the exposed skin and the efficiency of the blink reflex resulting in dermal coverage of the cornea

EXPOSURE	SOURCE	ROUTE	BYSTANDERS	RESIDENTS ADULTS	RESIDENTS CHILDREN	COMMENTS
		Ingestion via home grown fruit and veg		This may require the development of appropriate tools. Alternatively if estimates of consumer intake was sufficiently low (<10% of the estimated total) it might be considered within the range of uncertainties of other routes and could be ignored.	This may require the development of appropriate tools. Alternatively if estimates of consumer intake was sufficiently low (<10% of the estimated total) it might be considered within the range of uncertainties of other routes and could be ignored.	
During and post spraying		Local effects (sensitisation and irritation)	Consider dilution and classification criteria to understand likelihood of effect.	Consider dilution/dispersion and classification criteria to understand likelihood of effect.	Consider dilution/dispersion and classification criteria to understand likelihood of effect.	Consider semi quantitative approach as in REACH guidance.
Other exposures		Exposure via pollens dusts etc				Concluded a minimal contributor to the exposures being considered here.
		Transfer of residues indoors from treated areas				Covered by assessment of direct exposure of child playing on treated lawn
		Exposure in precipitation and reactivation				Unlikely to be at levels of concern for human health.
		Exposure from long range transport				Unlikely to be at levels of concern for human health

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Appendix 1

Members of the Bystander Risk Assessment Working Group

Chairman	
Professor J G Ayres	ACP
Members	
Prof A Boobis	COT
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Prof I D Morris	COT
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*The Working Group was sad to record the death of Dr D Ray during 2010.

Prof Ayres was 'hors de combat' from December 2011 but has seen and agreed the final report.

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Appendix 2

Executive Summary of EFSA document published 18 Feb 2010
from http://www.efsa.europa.eu/en/efsajournal/pub/1501.htm (accessed 11/11/11)

The European Food Safety Authority (EFSA) asked its Panel on Plant Protection products and their Residues to prepare a Guidance Document on pesticide exposure assessment for workers, operators, bystanders and residents. The Guidance Document would be for use in regulatory risk assessment for plant protection products, both to determine eligibility for inclusion in Annex 1 of Council Directive 91/414/EEC, and also to underpin the authorisation of products by individual Member States.

The starting point for the opinion was an outsourced project carried out jointly by the UK Pesticides Safety Directorate (PSD) and the University of Ghent (UG), who systematically reviewed and evaluated relevant sources of information. In addition, as a check that important data had not been overlooked, a draft of the opinion was made available via a public consultation in August 2009. In response to the comments received, various clarifications and amendments were made.

Council Directive 91/414/EEC requires that the residues of plant protection products (PPPs) applied in accordance with good plant protection practice must not have "any harmful effects on human or animal health". Currently, risk assessment for operators, workers, bystanders and residents uses a deterministic method, in which a check is made that reasonable upper estimates for daily systemic exposure are below a relevant toxicological reference value, the Acceptable Operator Exposure Level (AOEL). Available data do not indicate any major flaws in the current methods of risk assessment for operators, workers, bystanders and residents.

Nevertheless, the current method of risk assessment is not completely satisfactory. For some exposure scenarios, the empirical data underpinning exposure estimates are sparse, making the estimates less reliable statistically. For others, more than one model may be available with which to estimate exposures, and where this occurs, there can be inconsistency between the approaches adopted by regulatory authorities. Furthermore, exposure values based on 50th or 75th centiles of empirical datasets may substantially underestimate the maximum exposures that could reasonably occur in a single day, compromising margins of safety for PPPs that are acutely toxic.

Therefore, in developing the Guidance Document, the PPR Panel has proposed a number of changes to current practice. It is suggested that routine risk assessment for individual PPPs should continue to use deterministic methods, and that a tiered approach to exposure assessment remains appropriate. However, there are strong arguments for introducing an additional acute risk assessment for operators, workers and bystanders, where PPPs are acutely toxic. This will require the specification of a separate toxicological reference value, an "acute AOEL" ("AAOEL"), analogous to the Acute Reference Dose that is used in dietary risk assessment for acutely toxic PPPs. For acute risk assessments, exposure estimates should normally be based on 95th centiles of relevant data sets, whereas for longer term risk assessments, the starting

point should be a 75th centile[4].

Furthermore, to allow for the statistical uncertainty in centiles of small datasets, it is proposed that as a default, the exposure value used for risk assessment should be the higher of: a) the appropriate centile in the relevant dataset; and b) a parametric estimate of the corresponding centile in the theoretical population of measurements from which the dataset was derived, under that the assumption that the overall distribution of measurements is log-normal. However, where there is convincing evidence that this assumption of log-normality is unreasonable, it should be open to the regulator to adopt an alternative approach on a case-by-case basis.

Applying the recommended approach, proposals are set out for standardised estimation of exposures in first tier risk assessments for each of the exposure scenarios most commonly encountered in regulatory practice. An element of risk management is implicit in any scheme of this sort. In framing its proposals, the PPR Panel has aimed for a level of precaution similar to or slightly greater than that currently applied. However, it is open to risk managers in the European Commission to modify the level of precaution if they wish (e.g. by changing the centiles on which exposure estimates are based).

The opinion also identifies those scenarios for which exposure estimates are least satisfactory, and makes recommendations for further research that would reduce current uncertainties.

Finally, in an appendix, the Panel has set out a draft format for a Guidance Document. It is suggested that once the final form of this Guidance Document has been agreed by risk managers, a paper should be produced showing how each parameter in the Guidance Document was derived, and a spreadsheet should be developed to facilitate the calculations that it requires.
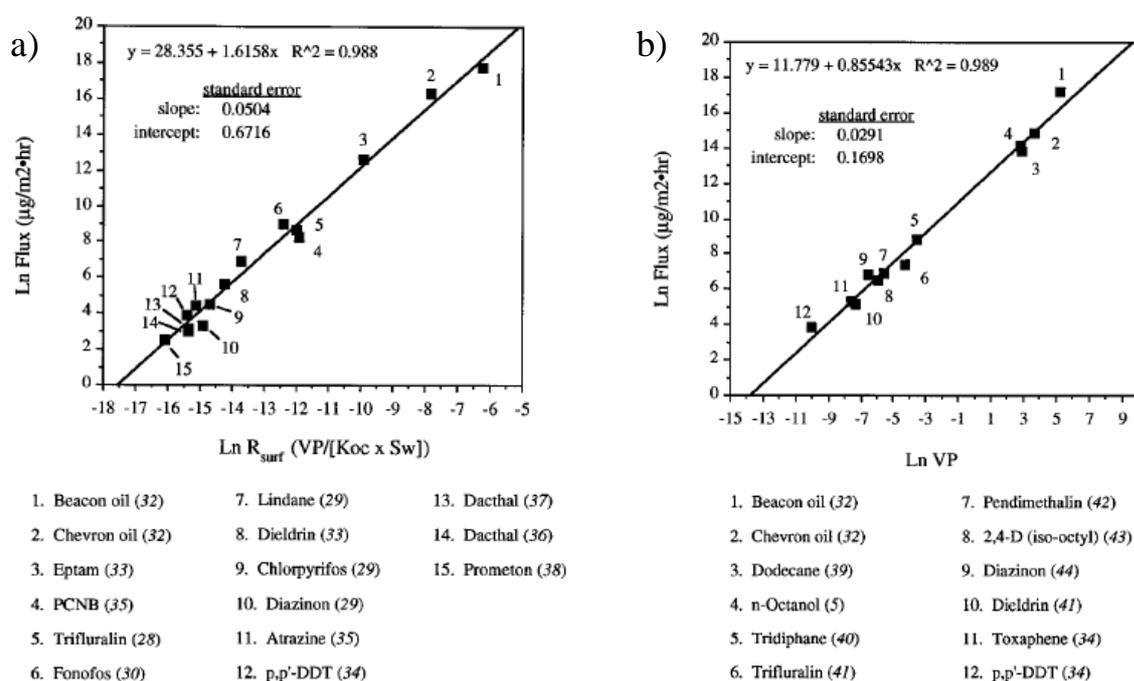
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[4] Clarification from BRAWG: The lower percentile for each individual event is used in long-term risk assessment because probabilities of successive events multiply through. Thus the probability of two successive exposures at the 75th percentile equates to a 94th percentile overall; that for three successive 75th percentile exposures, equates to a 98.5th percentile overall and so on.

Appendix 3

Volatilisation from soil and plant surfaces

The vapour pressure of a chemical defines its inherent tendency to partition from the liquid phase (or solid where sublimation occurs) into the gas phase. It is measured at a defined temperature by isolating the pure liquid (or solid) inside an evacuated container and measuring the equilibrium pressure of the gas phase. Plant surfaces are generally considered to be relatively inert and review has demonstrated that vapour pressure is the primary determinant of volatilisation under controlled conditions [20] (Figure 1b). The interactions between pesticides and water/solid particles within soil mean that sorption capacity for the pesticide and water solubility are additional determinants of volatilisation from soil surfaces [20] (Figure 1a).

a)
$y = 28.355 + 1.6158x$ $R^2 = 0.988$
standard error
slope: 0.0504
intercept: 0.6716

Ln Flux ($\mu g/m2 \cdot hr$)

Ln R$_{surf}$ (VP/[Koc x Sw])

b)
$y = 11.779 + 0.85543x$ $R^2 = 0.989$
standard error
slope: 0.0291
intercept: 0.1698

Ln Flux ($\mu g/m2 \cdot hr$)

Ln VP

1. Beacon oil (32)	7. Lindane (29)	13. Dacthal (37)
2. Chevron oil (32)	8. Dieldrin (33)	14. Dacthal (36)
3. Eptam (33)	9. Chlorpyrifos (29)	15. Prometon (38)
4. PCNB (35)	10. Diazinon (29)	
5. Trifluralin (28)	11. Atrazine (35)	
6. Fonofos (30)	12. p,p'-DDT (34)	

|	
1. Beacon oil (32)	7. Pendimethalin (42)
2. Chevron oil (32)	8. 2,4-D (iso-octyl) (43)
3. Dodecane (39)	9. Diazinon (44)
4. n-Octanol (5)	10. Dieldrin (41)
5. Tridiphane (40)	11. Toxaphene (34)
6. Trifluralin (41)	12. p,p'-DDT (34)

Figure 1. Relationship between volatilisation of pesticides from a) soil and b) inert surfaces (plants, glass, plastic) and pesticide properties (vapour pressure/organic carbon partition coefficient/water solubility, and vapour pressure, respectively). Source: Woodrow et al. (1997) [20].

Under field conditions, the relatively simple relationships with pesticide properties identified by Woodrow et al. (1997) are modified by a range of environmental factors including temperature, wind speed, humidity, pesticide formulation and extent of dilution by water within the spray mix [20]. This makes prediction of losses from soil and plant surfaces under field conditions highly complex, and to date there is no agreed approach for quantitative estimation of the loss. The current approach in UK risk assessment is to use vapour pressure to distinguish compounds with low volatility (<0.005 Pa) and moderate volatility (0.005-0.01 Pa), and then to assume conservative values for average concentration in air during the 24 hours following application of 1 and 15 $\mu g/m^3$, respectively [21] .

An expert group convened by the European Commission's DG Sanco worked between 2002 and 2005 to review and recommend approaches for inclusion of aerial transport of pesticides into ecological risk assessment [56]. The group considered

vapour pressure to be a primary determinant of volatilisation from soil and plant surfaces. On the basis of reviews of field and wind tunnel data (Figure 2), they recommended cut-off criteria for deciding on whether volatilisation should be considered as a route of entry to the environment within regulatory risk assessment; these criteria were 1×10^{-4} Pa for application to soil and 1×10^{-5} Pa for application to plant surfaces. The criteria proposed by FOCUS (2008) were rejected during review by the PPR panel of EFSA (2007) as being too simplistic [57]; one reason for this is that the vapour pressure of the pure substance is only loosely related to the effective vapour pressure of the product under conditions of use due to the influence of surfactants and other co-formulants and diluting carrier (normally water); a further objection was that volatile emission itself is not a risk assessment endpoint and is thus unsuitable to screen substances out of the risk assessment. German regulatory procedures also recognise vapour pressure $<1\times10^{-5}$ Pa as an index of non-volatile compounds for which losses to air are insignificant [7], but this threshold was similarly dismissed as too simplistic within a subsequent EFSA opinion [6].

a)   b)
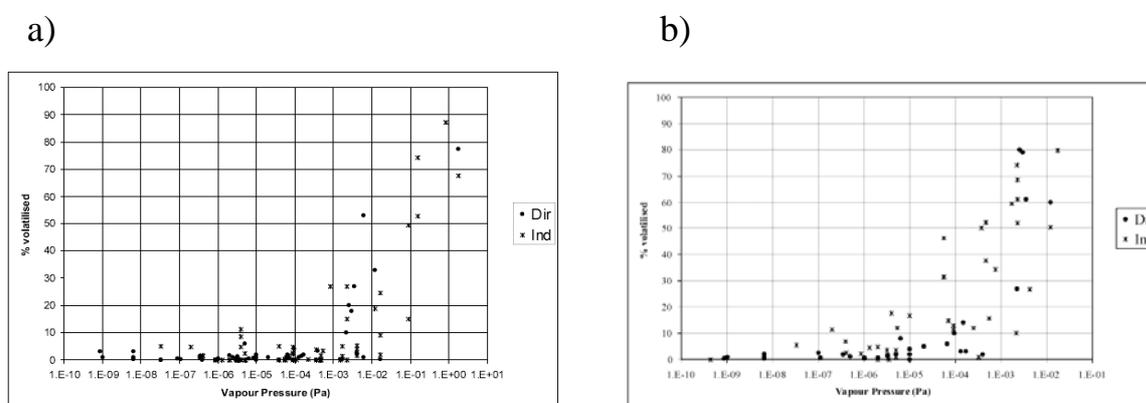
Figure 2. Volatilisation of pesticides from a) soil and b) plant surfaces as a function of vapour pressure. Data are divided into those arising from direct experimental measurement and those estimated from indirect measurement. Source: FOCUS (2008).

The relevant scientific literature was reviewed as part of the BREAM project [12]. The researchers cite a review of available literature by Smit et al. (1998) as evidence that losses from plant surfaces via volatilisation can range between 0 and 100% with a near uniform distribution in values [58]. It was considered that current defaults used within risk assessment (1 and 15 $\mu g/m^3$) were broadly conservative, but it was suggested that an alternative might be to assume 95% loss of pesticide via volatilisation within 24 hours of application, independent of pesticide properties and use conditions. Smit et al. (1998) collated information from a range of studies reported from 1977 to 1997 [58]. More than half the data were for organochlorine and organophosphorus compounds no longer permitted on the market; many of these compounds (e.g. lindane) are particularly prone to volatilisation, so the assertion by TAG, 2010 is considered over-simplistic and unrepresentative for the range of chemistries currently in use.

A major review of the literature reported recently by the US EPA (2010) aimed to make recommendations on regulatory approaches [59]. The report rejected a tier-1 screening tool based on vapour pressure because of a lack of connection to how a pesticide is actually used and a lack of confidence in the conservatism in resulting concentration predictions. In its place, US EPA (2010) suggested that the approach of Woodrow et al. (1997) should be refined to provide a first screen. The overall

approach of correlating loss with pesticide properties (Figure 1) was accepted, but it was felt that the database underlying the correlations would need to be extended and updated [59]. The report also reviewed approaches with potential for use at higher tiers. It was considered that the main generalised fate models such as PRZM and PEARL were not acceptable for use because (i) the descriptions of pesticide volatilisation had not been validated for low- to moderately-volatile compounds, and (ii) volatilisation was a loss term within a leaching simulation rather than the primary prediction target. Instead, it was decided that the Pesticide Emission Model originally reported by Scholtz et al. (2002a;b) should be investigated for potential application[26, 60]. This model describes the advection and diffusion of heat, moisture and pesticide within the soil column and exchange with the atmosphere through heat transfer, evapotranspiration and volatilization; exchanges of foliar-applied pesticide with both soil and atmosphere are also included.

Appendix 4

Calculations relating to dermal exposure

The EFSA draft Guidance document [6] includes an approach similar to that proposed in this document, based on the original EPA approach, supported by Dutch data. If necessary, these figures will be amended, taking account of the updated US EPA guidance.

The current model for exposure via the dermal route takes the form:

$$DE = AR \times DF \times TTR_d \times TC \times H/BW$$

Where:
DE = Dermal exposure
AR = field application rate
DF = drift fallout value,
TTR_d = turf transferable residue
TC = transfer coefficient
H = Exposure duration for a typical day (hours)
BW = Bodyweight

To estimate systemic exposure the dermal exposure is multiplied by a default or compound specific dermal absorption value. The AR value is the application rate recommended on the product label, and the drift value is expected fallout expressed as a percentage of the full application rate discussed above.

Issues to consider are the child age, which will determine behaviours and body weight; TTR_d; the TC; and the duration of exposure.

The EFSA guidance [6] recommends that for reasons of transparency exposure estimates should be performed for children aged <1, 1 to <3, 3 to <6, 6 to <11, 11 to 16 years old, and adults. Body weights for these groups are also recommended.

The TTR_d value represents the percentage of pesticide residue that remains on the turf surface available for removal by skin contact. Product specific data might be available, but in most cases they are not. In such cases the EFSA proposal is to use a value of 5% for sprays, based on the higher values observed for a range of products applied as sprays to lawns (actual range <0.001 to 6.1%) see EPA draft SOP Table 3-4 [28]. For Granules the proposed TTR_d value is 1%.

The TC value is derived as the ratio of measured exposure per unit to a measured TTR_d and by simple multiplication is used to estimate the unit time exposure for a new situation. Note that while exposure measurements are standardised, measurements of TTR_ds have employed different methods involving for example rollers or sledges, and these different methods give rise to different TTR_d values. It is therefore important to ensure the TC and TTR_d values reflect the same method, else the exposure estimate will not be valid. The EFSA proposal is to use TC values based on data from measurements in scripted activity scenarios with adults that are adjusted by the ratio of body surface areas for the different groups. This is similar to the approach used by the US EPA. In should also be noted there are a number of studies that have measured TCs and the issue of appropriate values is not

straightforward, see the RIVM report [61] for further evaluation. The EFSA draft guidance takes as the starting point TC values for acute exposure of 14,500 cm^2/hour and for repeated exposures 7,300 cm^2/hour. The Draft EPA SOP proposed higher values but that assessment did not include all of the data from the study under consideration and comment was made that lower values were excluded by the EPA due to a misunderstanding (it was claimed a helicopter was used in the study to dry the grass <u>before</u> and not as had been assumed by the EPA <u>after</u> the application). See EPA draft SOP Table 3-5.

The duration of exposure time on the lawn is taken as 2 hours. See RIVM report Table 4, based on EPA data, and also EPA draft SOP Table 3-6.

  i) Hand-to-mouth exposure

The current model for hand-to-mouth exposure takes the form:

$SE(h) = (AR \times DF \times TTR_d \times SE \times SA \times Freq \times H)/BW$

Where:
SE(h) = Systemic exposure via the hand-to-mouth route
AR = field application rate
DF = drift fallout value,
TTR_d = turf transferable residue
SE = saliva extraction factor
SA = surface area of the hands
Freq = frequency of hand to mouth events/hour
H = exposure duration (hours)
BW = body weight

The values for AR, DF, TTR_d and H are as discussed above. Issues to consider are the values for SE, SA, and Freq.

The saliva extraction value SE is an estimate of the efficiency of mouthing in removing residues from the surface of the hands, expressed as a percentage. The EFSA guidance and the current UK approach [21] propose the mean value measured in a study using three active substances see – EPA draft SOP Section 2.6 and Appendix A.3 [28].

The assumption regarding the surface area of hands mouthed, SA, is based on the previous EPA SOP (see RIVM report page 61) where the value taken is 20 cm^2 skin area contacted each time a child puts a hand in his or her mouth (this is equivalent to the palmar surface of three fingers and is approximately 10% of the hand surface for a 3 to < 6 year old). More information on the fraction of the hand mouthed is presented in EPA draft SOP Section 2.4 [28].

The recommended frequency of hand mouthing events per hour, Freq, in the EFSA guidance is based on information (from a study by Reed et al) in an earlier EPA SOP, which appears to be based on a subset of the data in the EPA draft SOP (see appendix C) [28]. The values proposed are a mean value of 9.5 events per hour for repeated exposures and a 90th centile of 20 events per hour for acute exposures.

  ii) Object-to-mouth exposure

The current model for systemic exposure through mouthing or ingesting objects other than hands assumes that a child may place contaminated grass in their mouth and takes the form:

$$SE(o) = (AR \times DF \times TTR_s \times IgR)/BW$$

Where
SE(o) = Systemic exposure via mouthing activity
AR = field application rate
DF = drift fallout value
TTR_s = turf transferable residues
IgR = ingestion rate for mouthing of grass/day – this was assumed to be equivalent to 25 cm^2 of grass/day
BW = body weight

The values for AR and DF are as discussed above. The value for TTR_s is not the same TTR as before, because in this case an estimate is required to account for the extraction from turf by mouthing, as opposed to extraction by dermal contact. The EFSA proposal is to assume a value of 20% in this case based on the earlier EPA SOP.

The ingestion rate, IgR, is an assumption of the amount of grass that a child may put in their mouth in a day. Based on the earlier EPA SOP this has been recommended as equivalent to the amount of grass that covers 25 cm^2. The working group considered that exposure from contaminated objects may be more realistic, but the approach proposed was unlikely to underestimate exposure via this route.

Appendix 5

Background document on mechanisms of skin sensitisation to chemicals.

1   Topical exposure to chemical agents may result in an inflammation of the skin, defined as contact dermatitis. Two distinct processes may lead to contact dermatitis. Irritant contact dermatitis arises when the agent ("irritant") directly damages cells if applied to the skin in sufficient concentration and for a sufficient period of time. Allergic contact dermatitis arises as a result of exposure to a substance (sensitiser or allergen) that can induce a specific immunological reaction, such that the individual can react to considerably lower concentrations on challenge (also known as "hypersensitivity").

2   Allergic contact dermatitis arises from a series of complex cellular interactions with the skin sensitiser. In common with other forms of allergy, these interactions can be divided into an induction and an elicitation phase. In the induction phase, a susceptible individual is exposed to amounts of a sensitiser that provoke an immune response sufficient to cause specific priming of the immune system.   No visible changes occur in the skin until further contact (at the same or distant site) with the same chemical (or a cross-reacting chemical), when the clinical manifestations of allergic contact dermatitis (redness and swelling) are observed.

3   Thus, in the induction phase, the sensitiser penetrates the skin and must react either directly or indirectly with proteins to form a complex (or antigen) capable of stimulating a response from T lymphocytes. Langerhans cells and other dendritic cells in the skin transport the antigen to draining lymph nodes and during this transit mature so that they are able to present the transported complex to T lymphocytes. Responsive (allergen-specific) T lymphocytes are activated resulting in the proliferation (clonal expansion) and sustained release into the systemic circulation of those cells that have specifically recognised the antigen. The individual is now "primed" or "sensitised". Subsequent skin contact with the sensitiser activates the allergen-specific T cells leading to inflammation and the clinical manifestations of the response. As the individual is immunologically primed, the immune response in the elicitation phase is more rapid and more aggressive than that observed in the induction phase.

4   A sensitiser typically is a small molecule which must penetrate the skin barrier. The initiation of sensitisation may occur on the very first contact with the sensitiser or may occur upon repeated contact. The dose per unit area is the key exposure parameter: a dose (mass of substance) that can elicit sensitisation may not necessarily cause sensitisation if administered over a larger area of the skin.

5   Evidence from both human and animal studies confirms that dose thresholds exist for both the induction and elicitation phases. This indicates that exposure to low sub-threshold concentrations may not induce skin sensitisation. However, all individuals appear to be susceptible when exposed to a potent sensitiser at a sufficiently high level.

6   Testing procedures for identifying irritancy or sensitisation of chemicals have been developed for the protection of the public and guidelines are available through the OECD. For example OECD guideline 404 [62] is for a skin irritation test that involves treating the shaved skin of rabbits and observing whether redness or

swelling develops up to 14 days after application. OECD guideline 405 [63] is an eye irritation test that involves the application of a compound to the conjunctival sac of a rabbit and observing whether any redness, swelling, corneal opacity or iris lesions develop. A new guideline (OECD 439) [64] has also been developed for the use of human skin models to test skin irritation *in vitro* by measurement of cell viability after exposure to the test chemical.

7   For skin sensitisation there are three guidelines of which two use guinea pigs (OECD 406) [65] and the other uses mice (OECD 429) [51]. The guinea pig tests seek to model the elicitation phase of the contact allergic reaction and so involve both induction and elicitation phases. These tests use either an adjuvant (non-specific activator of the immune system) to potentiate sensitisation (Guinea Pig Maximisation Test:GPMT) or are adjuvant free (Buehler Test). The local lymph node assay (LLNA: OECD 429) studies the induction phase of skin sensitisation in mice.

8   In the guinea-pig assays the animals are initially exposed to the test compound either topically or by intradermal injection (induction). The doses used are the highest expected to cause mild to moderate skin irritation (GMPT) or mild irritation (Buehler). Following a period of 10-14 days to allow induction/priming and during which an immune response may develop, the animals are further challenged at a site different from that used for induction, with the highest non-irritant dose of the test chemical (elicitation). The extent and degree of skin reaction are compared with those in guinea-pigs that received the challenge but not the induction dose (irritant control group).   The design of these tests limits the ability to obtain information on potency of the chemical due to the requirement for non-irritant doses for challenge.

9   In the local lymph node assay (LLNA), concentrations of the test chemical that do not result in excessive local irritation or systemic toxicity are applied to the ears of CBA strain mice for three consecutive days. On the sixth day, the animals are injected typically with [^{3}H]-thymidine and are killed 5 hours later. The lymph nodes that drain the ears are excised and the radioactivity present in these lymph nodes, which has been incorporated into the activated immune cells, is quantified. For each concentration of the test chemical, a stimulation index (SI) is derived relative to concurrent vehicle-treated mice. If the SI at one or more of the test concentrations is 3 or more the chemical is classified as a skin sensiter. A lower level of stimulation is not classified.   The LLNA studies the induction phase of skin sensitisation and provides quantitative data suitable for dose-response assessment.

10   The guinea pig assays have largely been superseded by the LLNA. The performance of the LLNA has been widely validated and is reported to be similar to that of the guinea pig assays with respect to sensitivity and selectivity. The LLNA has advantages in reducing pain and distress to treated animals as well as being cheaper, taking less time to complete and in providing information on potency.

11   The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) recently evaluated whether the LLNA could be used to obtain accurate and reliable results on pesticide formulations [52]. Results indicated that the LLNA was more likely than a guinea pig test to yield a positive result. Of 104 pesticide formulations in the examined database, 54% were LLNA positive with a stimulation index of 3 or more. Of 23 formulations with both LLNA and guinea pig data, the LLNA identified 12 (53%) as sensitisers whereas the guinea pig tests identified 3 (13%). All three formulations positive in the guinea pig assays were

positive in the LLNA. It was concluded that the "accuracy performance of the LLNA supports its use for testing pesticide formulations".

12   From the results of a LLNA, it is possible to determine the concentration (known as the EC3) of test chemical that causes a reliable (i.e. where SI = 3) increase in level of thymidine incorporated. Rating systems based upon EC3 values have been developed to identify chemicals of different potency. One such classification is shown here and has been made largely on the basis of hazard identification assays for individual chemicals and not necessarily preparations and formulations. It has been suggested that if the LLNA data are reliable and of high quality then a preparation can be classified on the same basis as the individual ingredients.

EC3 (%)	Potency category[a]	Example	
		Pesticide	Non-pesticide[b]
<0.1	Extreme	-	Dinitroclorobenzene
≥0.1-<1	Strong	-	4-phenylenediamine
≥1-<10	Moderate	Dinocap	3,4-Dihydrocoumarin
≥10-≤100	Weak	Trifuralin	Cinnamic alcohol

[a] Categorisation from Gerberick *et al* 2007 [66]; [b] OECD-TG429-2010.pdf [51]; [c] ICCVAM Test Method Evaluation Report on Using the Murine Local Lymph Node Assay for Testing Pesticide Formulations, Metals and Substances in Aqueous Solutions, and Other products. NIH Publication Number 10-7512 [52].

13   There are significant positive correlations between EC3 values and the lowest concentrations of skin sensitisers that resulted in positive human repeat insult patch tests. Hence, chemicals with high EC3 values may represent a relatively low risk to humans. However a recent review concluded "it is currently not possible to define an EC3 value below 100% that would serve as an appropriate threshold for classification and labelling." [67]. In other words, it cannot be concluded reliably that a more dilute formulation of a classified product would not elicit a sensitisation response in at least some individuals.

Appendix 6

Table comparing EFSA and BRAWG recommendations for bystander and resident risk assessment
The text highlighted in yellow identifies the differences between the recommendations
BREAM: The bystander and resident exposure assessment model. A research project commissioned by Defra.
ACROPOLIS: Aggregate and Cumulative Risk of Pesticides: an on-line integrated Strategy. An EU research project.

	BRAWG	Draft EFSA
Definitions	**Bystanders**: persons who are located within or directly adjacent to the area where PPP application or treatment is in process or has recently been completed; whose presence is quite incidental and unrelated to work involving PPPs, but whose position might lead them to be exposed; and who may not choose or be able to take action to avoid or control exposure.	Bystanders are: persons who are located within or directly adjacent to the area where PPP application or treatment is in process or has recently been completed; whose presence is quite incidental and unrelated to work involving PPPs, but whose position might lead them to be exposed; and who take no action to avoid or control exposure.
	Residents: persons who live, work or attend school or other institution adjacent to an area that is or has been treated with a PPP; whose presence is quite incidental and unrelated to work involving PPPs but whose position might lead them to be exposed; who may not choose or be able to take action to avoid or control exposure; and who might be in the location for 24 hours per day. The regulation on the Placing of Plant Protection Products on the Market (EC 1107/2009) considers 'residents subject to high pesticides exposure over the long term' as a vulnerable group and the EU Directive on Sustainable Use of Pesticides (Directive 2009/128/EC) has provisions for reduction of pesticide use or risks in specific areas including those used by vulnerable groups.	Residents are: persons who live, work or attend school or any another institution adjacent to an area that is or has been treated with a PPP; whose presence is quite incidental and unrelated to work involving PPPs but whose position might lead them to be exposed; who take no action to avoid or control exposure; and who might be in the location for 24 hours per day.
'Coverage'	Bystander and resident exposure arising from ground based boom sprayers of low level crops. i.e. reduced coverage compared to EFSA draft guidance.	Operator, worker, bystander and resident exposure arising from application of solid and liquid pesticide formulations via large scale (eg tractor mounted) equipment; medium scale (eg professional hand held) equipment and small scale

	BRAWG	Draft EFSA
		(eg home garden) equipment covering the full range of crops and situations (eg field crops, orchards, vineyards, greenhouses, home gardens)
Body weights assumed	Adult 60kg Child 15kg	Adult 60 kg, Children aged 10 to <12 months, 8.7kg, 1 to <3 years, 12.3 kg, 3 to <6 years, 17.5 kg, 6 to <11years, 28.7 kg 11 to <16 years 50.2 kg (derived from data published by ECETOC (2001) and Prud'homme de Lodder (2006)).
Data used	Acute exposures: 95th percentile data from BREAM Longer term exposures 75th percentile data from BREAM Slightly simpler definition than EFSA.	For acute exposures (i.e. those that could occur in a single day), exposure estimates should be derived as the higher of: a) the 95th centile of the distribution of measurements in the sample; and b) a statistical estimate of the 95th centile for the theoretical population of measurements from which the sample was derived, under the assumption that this population has a log-normal distribution. For longer term exposures, exposures should be derived as the higher of: a) the 75th centile of the distribution of measurements in the sample; and b) a statistical estimate of the 75th centile for the theoretical population of measurements from which the sample was derived, under the assumption that this population has a log-normal distribution.
Risk assessments required	As EFSA	'Longer term' risk assessments (ie comparison with repeat dose based AOEL) required for residents in all cases. Residents acute risk is covered by the bystander scenario. Acute risk assessments (ie comparison with acute AOEL) required for bystanders only for PPPs with significant potential for toxicity in a single day. Bystanders do not require longer term risk

	BRAWG	Draft EFSA
		assessments.
Total exposure	Probabilistic methods should be used if data are available EU ACROPOLIS project may help in developing this approach.	Cumulative and aggregate risk assessments are often better undertaken using probabilistic methods (EFSA 2008)

Scenarios for residents

	BRAWG	EFSA <mark>(all 'longer term' risk assessments)</mark>
Spray drift	Evaluation for adults and children. Acute exposure to spray drift covered by bystander assessment. Repeated spray exposures; <mark>inhalation</mark> and dermal: Consider weekly repeated exposures with <mark>values from BREAM for 2 metres downwind</mark> from 24 metre boom sprayer. Use 75th percentile data for spray drift <mark>for adult and child resident</mark>	75th percentile for dermal and inhalational exposures with correction for incomplete dermal absorption of in-use dilution. For arable crops: Use Lloyd and Bell data standard nozzles applying 165l/ha. (Also recommended data sets for orchards). 8 metre data (x 10 to account for closer proximity to sprayer and multiple passes for dermal exposure – no need for adjustment for inhalational exposure) **1.16ml spray dilution/person Dermal exposure 0.00715ml spray dilution/person inhalational exposure.** Adult values protective for children if corrected for lower bodyweight.
Vapour	Acute exposure to vapour covered by bystander risk assessment. Adult longer term 24h exposure to 1or 15µg/m^3, or estimate of flux and BREAM air dispersion model, 60kg female, respiring <mark>15.2 m^3/day</mark> Child longer term inhalation: 24h exposure to 1 or 15µg/m^3 or estimate of flux and BREAM air dispersion model (as above) 15Kg child , respiring <mark>8.3 m^3/day</mark> Compare to repeat dose AOEL <mark>Consider aggregating acute and sub chronic resident exposure</mark>	UK and German approach based on highest time-weighted average for 24 hour period according to volatility of active substance. For **moderately volatile compounds** (vapour pressure ≥ 0.005 Pa and < 0.01 Pa), exposures should be calculated assuming a default concentration in air of 15 µg/m^3 and daily average breathing rates resulting in exposures of 3.5, 4.1, 6.6, 10.5, 16.1 and 17.1 µg/kg bw/day for adults, 11 to <16 year olds, 6 to <11 year olds, 3 to <6 year olds, 1 to <3 year olds, and <1 year olds, respectively. For compounds with **low volatility** (vapour pressure <0.005 Pa), exposures should be calculated assuming a default concentration in air of 1 µg/m3

	BRAWG	EFSA (all 'longer term' risk assessments)
		and daily average breathing rates resulting in exposures of 0.23, 0.27, 0.44, 0.70, 1.07 and 1.14 µg for adults 11 to <16 year olds, 6 to <11 year olds, 3 to <6 year olds, 1 to <3 year olds, and <1 year olds, respectively.
Surface deposits	Acute: Children assumed to cover risk for adult. Uses US EPA lawn re-entry model. Calculates dermal exposure using 95th percentile drift fall out at 2 metres from BREAM, turf transferable residue, a higher transfer co-efficient from grass to skin and duration of contact with contaminated turf. Assumes 2 hour contact period and 15kg child Adult longer term : Assume covered by child longer term and bystander entry to treated areas (EUROPOEM worker re-entry model 30 min exposure). Child longer term Uses US EPA lawn re-entry model. Calculates dermal exposure using 75th percentile drift fall out at 2 metres from BREAM, turf transferable residue, average transfer co-efficient from grass to skin and duration of contact with contaminated turf. Assumes 2 hour contact period and 15kg child Ingestion: assumes that child ingestion exposure is likely to cover adult Child ingestion (longer term) US EPA lawn re-entry model. Assumes a proportion of residue picked up on the hand is transfered to the mouth (eg by child sucking thumb, licking hand etc) Allows for repeated exposure and re-contamination of hand. PLUS direct consumption/mouthing of contaminated grass. Assumes grass from $25cm^2$ area is 'consumed'.	Uses US EPA lawn re-entry model. Exposure from surface deposits for children aged less than 1 year should be calculated as: Dermal exposure + Hand to mouth transfer + Object to mouth transfer Where for products applied in liquid sprays, Dermal exposure = 1.8 x Application rate (kg/ha) x Drift percentage x Dermal absorption percentage Hand to mouth transfer = 0.095 x Application rate (kg/ha) x Drift percentage x Oral absorption percentage and Object to mouth transfer = 0.05 x Application rate (kg/ha) x Drift percentage x Oral absorption percentage. Dermal and oral absorption percentages should be taken from the toxicological evaluation. For the dermal absorption percentage, use the higher of the values for the undiluted product and the in-use dilution. Drift percentage 90th centile at 10 metres (field crops) 2.9%. For children aged 1 to <3 years, dermal exposure should be calculated by replacing the coefficient of 1.8 in the above equation with 2.3. Hand to mouth and object to mouth exposure is the same as for less than 1 year olds. For older children and adults, exposure via hand to mouth and object to mouth transfer can be ignored. For products applied as sprays, dermal exposure for children aged 3 to <6, 6 to <11, and 11 to <16

	BRAWG	EFSA (all 'longer term' risk assessments)
		years and for adults should be calculated by replacing the coefficient 1.8 in the above equation with 3.1, 4.3, 6.4, and 7.3, respectively
Entry to treated crops	Adult EUROPOEM worker re-entry model with 30 min exposure to reflect walking across a freshly treated field. Children Assumed covered by child lawn exposure estimate as surface deposits (child)	Dermal exposure estimated based on EUROPOEM worker re-entry model with 15 min exposure period per day. Adults and children Exposure should be estimated as the product of the dislodgeable foliar residue (DFR, $\mu g/cm^2$), the transfer coefficient (TC, cm^2/h) (from Table 5 below), and the task duration (T, h/day) (EUROPOEM, 2002): Potential dermal exposure (PDE) $\mu g/day$ = DFR $\mu g/cm^2$ x TC cm^2/h x T h/day
Entry onto treated lawns	Covered by surface deposits and entry to treated crops	Calculated as surface deposit exposures with drift percentage assumed 100%. Adults and children
Eating home grown produce	This may require the development of appropriate tools. Alternatively if estimates of consumer intake was sufficiently low (<10% of the estimated total) it might be considered within the range of uncertainties of other routes and could be ignored.	Specific residues data from spray drift are not available so potential exposure cannot be reliably assessed. If required, further research would generate data
Local effects (sensitisation and irritation) during and post spraying	Consider dilution/dispersion and classification criteria to understand likelihood of effect. Consider semi quantitative approach as in REACH guidance.	

Scenarios for bystanders

	BRAWG	EFSA
Spray drift	Acute Total acute exposure is sum of inhalation and dermal and is compared to an acute AOEL Dermal 2 metres down wind, single pass, 24 metre boom sprayer total spray cloud estimates based on 95 percentile data from BREAM. Evaluation for adults and children, no reduction from clothing, 60Kg adult, default 100% absorption.	Dermal and inhalational exposures as residents but using 95th percentile. Dermal 5.33ml spray dilution/person. Inhalation 0.022ml spray dilution/person

	BRAWG	EFSA
	Inhalational ==2 metres== down wind, single pass, 24 metre boom sprayer total spray cloud estimates based on 95 percentile data. Evaluation for adults and children.	
Vapour	Not separately considered – covered by adult resident assessment	As residents
Surface deposits	EUROPOEM worker re-entry model with ==30 min exposure== to reflect walking across a freshly treated field. Ingestion: Not separately considered for bystanders but assumes that resident child ingestion exposure is likely to cover this.	Uses higher transfer coefficients than residents and increased frequency of infant hand to mouth activity than residents. Exposure from surface deposits for children aged less than 1 year should be calculated as: Dermal exposure + Hand to mouth transfer + Object to mouth transfer Where: Dermal exposure = 3.6 x Application rate (kg/ha) x Drift percentage x Dermal absorption percentage Hand to mouth transfer = 0.095 x Application rate (kg/ha) x Drift percentage x Oral absorption percentage Object to mouth transfer = 0.05 x Application rate (kg/ha) x Drift percentage x Oral absorption percentage. Dermal and oral percentages should be taken from the toxicological evaluation. For the dermal absorption percentage, use the higher of the values for the undiluted product and the in-use dilution. Drift percentage 90th centile at 10 metres (field crops) 2.9%. For children aged 1 to <3 years, dermal exposure should be calculated by replacing the coefficient of

	BRAWG	EFSA
		3.6 in the above equation with 4.6. Hand to mouth and object to mouth is the same as for less than 1 year olds.

For older children and adults, exposure via hand to mouth and object to mouth transfer can be ignored.

Dermal exposure for products applied as sprays for children aged 3 to <6, 6 to <11, and 11 to <16 years and for adults should be calculated by replacing the coefficient of 3.6 in the above equation with 6.1, 8.6, 12.6, and 14.5, respectively, |
Entry to treated crops and lawns	As residents	As residents
Local effects (sensitisation and irritation) during and post spraying	Consider dilution/dispersion and classification criteria to understand likelihood of effect. Consider semi quantitative approach as in REACH guidance.	The focus is on risk assessment for systemic toxicity and does not cover all the aspects of exposure that could be relevant to localised toxicity.
Other		When estimating the maximum exposure that a bystander might reasonably be expected to incur in a single day by higher tier methods, account must be taken of the possibility that a bystander could be a resident.

Glossary of Abbreviations, acronyms and definitions

Acceptable Operator Exposure Level (AOEL): The reference value against which non-dietary exposures to pesticides are currently assessed. It is intended to define a level of daily systemic exposure throughout a spraying season, year on year, below which no adverse systemic health effects would be expected. The AOEL is normally derived by applying an assessment factor (most often 100) to a No Observed Adverse Effect Level (NOAEL) (corrected if appropriate for incomplete absorption) from a toxicological study in which animals were dosed daily for 90 days or longer. Less often, the critical NOAEL comes from a study with a shorter dosing period (e.g. a developmental study).

Acute exposure: Exposure on a single day (e.g. that might occur on the day spraying takes place).

Acute Acceptable Operator Exposure Level (AAOEL): A term used in this report to describe a reference value against which acute non-dietary exposures (i.e. those that might be incurred in a single day) could be assessed. This would be relevant only to those plant protection products for which such exposures might produce acute toxicity. It would be an estimate of systemic exposure to a chemical substance, expressed on a bodyweight basis, that can be received over a short period of time, usually during one day, without appreciable health risk to the exposed individual.

ADI: Acceptable Daily Intake, the amount of a chemical which can be consumed every day for a lifetime in the practical certainty, on the basis of all known facts, that no harm will result. It is expressed in milligrams of the chemical per kilogram bodyweight of the consumer.

Aggregate risk assessment: Risk assessment that takes into account all pathways and routes of exposure to a single chemical.

ARfD: Acute reference dose, this is an estimate (on the basis of all known facts at the time of the evaluation) of the amount of a chemical substance in food (or drinking water), expressed on a bodyweight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer.

Benchmark dose (BMD): The dose of a substance that is estimated to carry a specified low incidence of a health effect, generally in the range of 1% to 10% above background, or the dose associated with a specified measure or change of a biological effect. The lower 95% confidence limit on the BMD can be determined mathematically, to take into account experimental uncertainty in the data, and is known as the BMDL.

Biomarker: A substance that can be used as an indicator or measure of exposure to, or of the biological effect of, a chemical or physical agent. Biomarkers of exposure to pesticides are often metabolites found in urine.

Biological monitoring: Measuring and assessing levels of chemicals or their 'metabolites' (substances into which the body converts the chemical) in the breath, urine or blood of exposed individuals. This monitoring may investigate either the

level of exposure to an active substance or look for chemical signs of a reaction to exposure.

BREAM: The Bystander and Resident Exposure Assessment Model. A research project commissioned by Defra.

Buffer Zone: An area left untreated between the area treated with a pesticide and adjacent land or water.

Campaign for the farmed environment: A voluntary campaign with the objective of retaining and exceeding the environmental benefits that used to be provided by set-aside.

Carcinogens: The causal agents that induce malignant tumours.

Centile: A value that partitions a distribution of measurements at a specific point when they are ranked in ascending order of magnitude. For example, the 75th centile from a sample of measurements is a value that is ≥ 75% of the measurements and ≤ 25% of the measurements. Also called percentile.

Code of Practice: The code of practice for using plant protection products.

Co-formulants: All of the ingredients in a pesticide product other than the active substance.

Computational model: A mathematical model in computational science to study the behaviour of a complex system by computer simulation.

COT: Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment.

Cross compliance: The Single Payment Scheme for farmers (SPS) requires farmers to demonstrate that they are keeping their land in good agricultural and environmental condition, and are complying with a number of legal requirements. Meeting these requirements is described in the legislation as 'cross compliance'.

CSAF: Chemical specific adjustment factor. A data-derived factor, based on specific toxicokinetic or toxicodynamic information, enabling part of the default uncertainty factor to be replaced by a factor specific for that chemical. The default uncertainty factor comprises a sub-factor of 4 for interspecies toxicokinetic differences, 2.5 for interspecies toxicodynamic differences (together comprising an interspecies factor of 10), and 3.2 (actually 3.16) for each of interindividual toxicokinetic and toxicodynamic differences (together comprising an intraspecies factor of 10). One or more of these sub-factors could be replaced by a chemical specific factor. The overall uncertainty factor is obtained from the product of all of the sub-factors.

Cumulative risk assessment: Risk assessment for combined exposure to two or more chemicals by all relevant pathways and routes.

Dermal: Relating to the skin.

Deterministic model: A deterministic model is one in which the relationship between parameters is fixed and a given input will always produce the same output.

Dislodgeable foliar residue: The residue of a pesticide following deposition on foliage or fruit, which can be transferred to a worker, bystander or resident through contact with the foliage or fruit.

Dosimetry: The measurement and calculation of the absorbed dose resulting from direct and indirect exposure.

EFSA: European Food Safety Authority

Endocrine system: The endocrine system is the system of glands, each of which secretes a type of hormone directly into the bloodstream to regulate the body by action on tissues at some distance from the site of release.

Entry level stewardship: One element of the Environmental Stewardship scheme open to all farmers, land managers and tenants. It is a voluntary scheme, designed to deliver significant environmental benefits in high priority areas. It requires a basic level of environmental management, and participants can choose from a wide range of more than 80 management options. Environmental Stewardship is a part of RDPE - the Rural Development Programme for England (2007–2013).

EPA: United States Environmental Protection Agency.

Epidemiology: The study of the distribution and patterns of health-events, health-characteristics and their causes or influences in well-defined populations.

Epigenetic: Relating to heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence.

Extrapolation: Extrapolation is the process of constructing new data points beyond the range of known and measured data.

Field conditions: The natural conditions in which a pesticide application may be made

Foliar applications: Applications of pesticide to the green parts (foliage) of plants

Formulation: The composition of a pesticide product as supplied.

FSA: Food Standards Agency.

Gametes: Eggs or sperm.

Genotoxic: Capable of damaging genetic material, either through a direct reaction with DNA or through an effect on the number or integrity of the chromosomes.

Guidance value: An alternative term for reference value: e.g. ADI, ARfD, AOEL.

Hand to mouth transfer: Transfer of pesticide residues from contaminated surfaces to the mouth via the hand – potentially a significant pathway of exposure, especially in infants.

Haematology: The study of blood, the blood-forming organs, and blood diseases.

Health Based Guidance Value: An alternative term for reference value: e.g. ADI, ARfD, AOEL.

Histopathology: The microscopic examination of tissue in order to study the manifestations of disease.

Homeostatic regulation: Regulation of the internal environment of a living organism, tending to maintain a stable, constant condition of properties such as temperature or pH.

Immunotoxicological: Relating to toxicity to the immune system.

In silico: Performed on computer or via computer simulation.

In utero: In the womb.

In vitro: In biological material outside the living organism (animals, plants, etc), such as cultured cells or tissue fractions.

In vivo: In living organisms (animals, plants, etc).

LOAEL: Lowest observed adverse effect level. The lowest dose for which an effect is statistically different from that in the controls.

Local lymph node assay (LLNA): A test in mice used to assess whether a chemical causes sensitisation. Details are in appendix 5 paragraph 9.

Log-normality: The nature of a statistical distribution in which the logarithms of individual measurements have a Gaussian or "normal" distribution. For a given scenario, measurements of individual exposures often have a log-normal distribution.

Mechanistic model: A mechanistic model is one in which the basic elements of the model have a direct correspondence to the underlying mechanisms in the system being modeled.

Metabolites: Substances into which the body converts a chemical.

Mutagen: A physical or chemical agent that changes the amount or structure of the genetic material in an organism or cell.

Molecular mass (M_r): The mass of one molecule of a substance, in unified atomic mass unit(s) u (equal to 1/12 the mass of one atom of the isotope carbon-12).

NOAEL: No observed adverse effect level. The highest dose for which an effect is not statistically different from that in the controls.

Object to mouth transfer: Transfer of pesticide residues to the mouth from contaminated objects through placement of the object in the mouth – a pathway of exposure of greatest importance in infants.

Octanol:water partition coefficient (KOW): The ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents (in this case octanol and water) at equilibrium. It provides a measure of how hydrophilic or lipophilic a substance is.

OECD: Organisation of Economic Co-operation and Development

Parametric: Relating to a summary characteristic of the (theoretically infinite) population from which a sample is derived. Population parameters can be estimated from corresponding sample statistics. For example, a sample mean may provide an estimate of the mean of the population from which the sample was derived.

Pathology: Is the precise study and diagnosis of disease, particularly changes in body tissues and organs that cause or are caused by disease.

Pathway of exposure: Source and type of exposure e.g. to spray drift or to vapour or to dislodgeable residues.

Percentile: An alternative word for centile.

Personal protective equipment: Equipment worn by an operator or worker that is designed to reduce hazardous exposures (e.g. gloves, coveralls, face masks).

Pesticide product: A pesticide preparation as supplied. It includes not only the active substance(s), but also co-formulants such as emulsifiers, solvents and safeners.

pH: A measure of the acidity or basicity of an aqueous solution.

Physicochemical: Relating to both physical and chemical properties

pKa: Acid dissociation constant, a quantitative measure of the strength of an acid in solution. A weak acid has a pK_a value in the approximate range −2 to 12 in water. Acids with a pK_a value of less than about −2 are said to be strong acids.

Plant protection product: Specifically defined in Regulation EC 1107/2009. Broadly a product used to protect plants or products derived from plants against harmful organisms. It includes insecticides, fungicides, herbicides, plant growth regulators, molluscicides, nematicides.

Point estimate: A single value (known as a statistic) calculated from sample data, which serves as a "best estimate" of an unknown population parameter.

Potential dermal exposure: Exposure to the skin that might occur in the absence of clothing or personal protective equipment.

PPE: Personal Protective Equipment

PPP: Plant Protection Product

PPR: European Food Safety Authority Panel on Plant Protection Products and their Residues.

Probabilistic model: Mathematical tool that estimates, on the basis of specified inputs (e.g. parameters estimated from empirical measurements), the probability of an event occurring.

RCEP: Royal Commission on Environmental Pollution (disbanded in 2011).

Reference point: Point on a dose-response curve (a dose) that is used as the starting point for the establishment of a health based guidance value. Examples of reference points are the No Observed Adverse Effect Level (NOAEL) and the BMDL10. Also known as a point of departure.

Regulatory Risk Assessment: Risk assessments used to inform the regulatory process

Risk: Possibility that a harmful event (death, injury or loss) arising from exposure to a chemical or physical agent may occur under specified conditions.

Route of exposure: The way people (or other living organisms) come into contact with a hazardous substance. Three routes of exposure are breathing (inhalation), eating or drinking (ingestion) and through contact with the skin (dermal).

Saliva extraction factor (SE): The fraction (expressed as a percentage) of pesticide extracted from a contaminated hand or object via saliva.

Sensitisation: An individual can become sensitised as a result of exposure to a substance that can induce a specific immunological reaction ("induction"), such that the individual then reacts to considerably lower concentrations on further exposure ("elicitation").

Sorption: a physical and chemical process by which one substance becomes attached to another, for example a pesticide to particles of soil.

Spray drift: Unintentional movement of pesticide away from the target area during spraying. Spray drift may include pesticide as spray droplets, vapour or small solid particles. It can leave residues as it settles onto adjacent ground or objects.

Stewardship scheme: Environmental Stewardship is an agri-environment scheme that provides funding to farmers and other land managers in England to deliver effective environmental management

Sub-chronic risk assessment: An assessment of the risk of adverse effects occurring as a result of the repeated daily exposure to a chemical for part of the life span.

Synergy: Two or more things functioning together to produce a result not independently obtainable and greater than that predicted on the basis of simple additivity.

Systemic exposure: Exposure of organs and tissues that occurs following absorption and distribution of a chemical in the body.

Task-specific factor (worker re-entry inhalation exposure): A factor relating to a specified task carried out by a re-entry worker (e.g. cutting ornamentals). It is multiplied by the rate at which a pesticide was applied to derive an estimate of potential exposures through inhalation.

Threshold: A threshold value is used to distinguish ranges of values where the behaviour predicted differs in some important way – for example, where there is zero effect for a dose below a critical or threshold value.

Topical exposure: Direct external exposure to a defined area of tissue (e.g. the skin of the hand or the eye).

Toxico-kinetic model: A mathematical model of the rate of absorption and elimination of a specific toxic substance, based on data taken (usually) from animal studies.

Toxicological Reference Values: Levels of exposure at which there is practical certainty on the basis of all known facts at the time of evaluation that there will be no appreciable health risk to the people exposed.

Transfer coefficient (TC): The rate at which dislodgeable foliar residues can be transferred to a worker, bystander or resident during a specified activity (expressed in terms of the area of contaminated foliage or fruit from which residues are transferred per hour).

Trigger concentration: Concentrations at which the classifications of dangerous substances are carried over to products containing them, unless the product itself has been tested for the end-point(s) of concern.

Turf transferable residue (TTR): Equivalent to a dislodgeable foliar residue for residues of plant protection products deposited on lawns.

US EPA: See EPA.

Vapour pressure: A measure of the tendency of a chemical to move into the gas phase from either the pure liquid or solid. The standard unit is the pascal (Pa). Pesticides with a higher vapour pressure will tend to have greater potential for volatilisation from treated soil and plant surfaces. However, volatilisation is also influenced by other properties of the chemical including its solubility, by formulation, and by weather variables including temperature, wind speed and relative humidity.

Volatility: A measure of the tendency of a substance to vaporise