Background

1. This joint working group of the COT and ACP on bystander risk assessment (BRAWG) first met in April 2010, following agreement between the committees to work together in this way in November 2009. This draft report has been prepared by members of the joint working group of the ACP and COT. The working group has held a total of four working meetings and an open meeting with stakeholders. Stakeholders were also invited to provide written comments following the open meeting.

2. The working group has considered the current UK approach to risk assessment for bystanders and reviewed approaches both in use and under development by a number of other regulatory authorities. They have considered some recent research in the field. The working group has examined and explained the exposures that need to be assessed for bystanders and residents adjacent to fields sprayed with plant protection products. They have also considered the toxicology data available to inform risk assessment for plant protection products.

3. The working group's conclusions and recommendations are presented in the draft report in Annex 1. Annex 2 contains a table comparing the BRAWG report proposals for risk assessment with the draft guidance of the European Food Safety Authority (EFSA), which might be a helpful tool when considering the draft report.

Questions for the Committees

(i) The ACP and COT are invited to consider the draft report and provide any comments they may have to the secretariat of the working group.

(ii) The ACP and COT are invited to consider whether this report should be passed to Ministers as the recommendations of both committees on a revised approach to assessing the risk from plant protection products to bystanders and residents adjacent to treated fields in the UK.
ADVISORY COMMITTEE ON PESTICIDES

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

MEETING DATES: ACP 13 MARCH 2012; COT 20 MARCH 2012

DRAFT REPORT OF THE JOINT WORKING GROUP ON BYSTANDER RISK ASSESSMENT

COT Secretariat
March 2012
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

THIS VERSION OF THE DRAFT REPORT IS FOR CONSIDERATION BY THE FULL COMMITTEES OF ACP AND COT.
REPORT by the BYSTANDER RISK ASSESSMENT WORKING GROUP (BRAWG)

Executive Summary

To follow.

1 Introduction

1.1 This short life working group was set up under the auspices of the Advisory Committee on Pesticides (ACP) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (CoT) as both had accepted that it was time for a formal review of the scientific evidence concerning bystanders and residents potentially exposed to pesticides. Membership of the group can be found at Appendix 1. The working group considered work recently undertaken by European Food Safety Authority (EFSA) in reviewing this area and a summary of EFSA’s work and their conclusions is included at Appendix 2. The group also considered the current Department for Environment Food and Rural Affairs (Defra) funded research which related to better assessment of the factors governing likely exposures in these settings (the BREAM project).

1.2 Four meetings of the working group were held which covered information on pathways of exposure, exposure measurement, exposure assessment, local toxicity, and systemic toxicity, all of which need to be considered in a regulatory risk assessment prior to approval of a plant protection product.

1.3 An advanced draft report was discussed in an open meeting on the 7th December giving all stakeholders and other interested individuals, industry, institutions and bodies the opportunity to respond. The final report will be submitted to Defra ministers by DATE TO BE DETERMINED.

Terms of Reference

1.4 The agreed terms of reference for this working group were:

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

1.5 The agreed aims of the working group were:

1. To agree a definition of operators, workers, bystanders and residents
2. To agree the nature of the exposures that require consideration
3. To review the current approach to modelling these exposures for bystanders and residents in the light of current knowledge
4. To review the approach to assessing the risk arising from these exposures in the light of current knowledge.
Background

1.6 The potential for an environmental exposure such as a pesticide to have an effect on health can be considered by using a simple, linear, source to outcome model – emission of the agent, the exposure of an individual (or population) to that agent, the effect (or lack of effect) seen in the individual or population (taking into consideration individual and population susceptibility) and the results of attempts to control either the emission or the exposure. To be able to work out this pathway certain information is necessary – the agent involved, the amount used, the duration of use, information about the people exposed and the time scale of development of symptoms or disease. In real life it is very rare indeed for all such information to be available, making assessment of a given exposure and its consequences difficult. An even greater challenge is whether the information available allows prediction of what might happen should a similar event occur in the future. Assumptions have to be made to estimate exposures, the first step in determining the extent of any potential impact on health. The assumptions made in assessing the risks from pesticides, while based on scientific information, have been criticised by a number of groups, scientists and other individuals.

1.7 A particular area of criticism has been the approach adopted in considering the potential for pesticides to impact on the health of individuals like residents and bystanders not involved in pesticide application. There has been much debate about the assumptions involved which were highlighted in the Royal Commission on Environmental Pollution report in 2005 [1]. The legal case pursued by Georgina Downs [2] also added weight to the concern about this area.

1.8 EFSA has recently considered this issue and has drafted guidance for the development of relevant exposure assessments [3]. The pathways and routes mentioned in the EFSA draft guidance are comparable to those currently used for bystander and residential exposure assessments in the UK, but some parameter values are different. The group noted that the German authorities have recently developed a similar approach and these documents were very helpful in its deliberations [4].

1.9 Ministers asked both ACP and CoT for specific advice about the issues raised in the judgement from Mr Justice Collins [2], any other issues that should be addressed in a review of policy in this area, and what additional information will be required to inform the review. CoT provided some initial written advice, and both committees requested some additional information to assist their consideration. This background to the issue contributed to the decision by ACP to suggest to CoT that the committees work together, leading to the establishment of this joint working group.

Definitions

1.10 A key factor in the work of the group was to agree on definitions of the individual groups possibly at risk from pesticide exposure. The working group agreed with the EFSA PPR Panel draft guidance [3] on pesticide exposure assessments that there should be separate consideration of exposure for operators, workers, bystanders and residents. The working group agreed that the EFSA definitions of exposed groups should be adopted subject to changing the phrase, for residents and bystanders, ‘who take no action’ to ‘who may take no action’ to more accurately
describe behaviour. In relation to this, the group noted that when operators and workers use products this must be in accordance with the conditions of approval which may include the use of personal protective equipment (PPE) by operators. Operators will have access to the pesticide product label giving directions for use in accordance with the approval and should be informed of any specific restrictions applying to them. At present UK assessments for workers, residents and bystanders assume they do not use PPE.

1.11 The agreed definitions are:

a. **Operators**: persons who are involved in activities relating to the application of a plant protection product (PPP); 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 take action to avoid or control exposure.

d. **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 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.

**Exposures**

1.12 A second important factor in the work of the group was to agree the nature of the exposures that require consideration. This includes not only the specific pesticide but also the route of exposure and any behaviour that may alter exposure. Operators, workers, bystanders and residents may be exposed to pesticides either directly through contact with spray drift (via dermal or inhalation routes) or indirectly through contact with drift deposits (dermal or ingestion) or vapour drift arising from volatisation 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. Whilst operators will be able to use PPE to reduce exposure, bystanders and
residents, by their nature, will not use PPE and may or may not be able to take action to reduce exposure.

1.13 The working group agree with the EFSA PPR Panel draft guidance [3] that suggests acute exposure assessments are required for bystanders and for residents and longer-term exposure assessments for residents. The same pathways of exposure and routes of exposure should be considered in both the bystander and resident exposure assessments but some parameters may use different values to reflect the differences between acute and prolonged exposure. The group also agree with the EFSA PPR Panel draft guidance [3] that acute risk assessments are required only where the plant protection product is concluded to pose risks from single (or acute) exposures, i.e. where it has been found appropriate to set acute reference doses for dietary risk assessment and an acute AOEL has been set.

1.14 Consequently, there was a need not only to review the approaches used to model exposures but also how to assess risk to those exposed in these scenarios.

2 Pathways of exposure for bystanders and residents

2.1 Both bystanders and residents have potential for short-term (acute) exposure to pesticides. This exposure is greatest during and immediately subsequent to spraying activity and can be divided into direct exposure to spray drift droplets and direct exposure to drift of pesticide vapour generated during spraying. Evidence demonstrates that dermal exposure to spray drift droplets are by far the dominant component of acute exposure [4], so exposure assessment focuses on estimating this component. Longer-term (chronic) exposure occurs in the hours and days following spraying activity and is most relevant to residents living close to agricultural fields. Residents may be directly exposed to pesticide vapour arising from 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 (young children) or dermal contact with surfaces that have been contaminated by deposition of spray drift. However 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, with each pesticide being applied at particular times of year. The exposures that could take place in the days following application will decrease with time.

Direct exposure to spray drift

2.2 The current UK approach estimates adult exposure from contact with spray drift and inhalation of spray droplets after a single spraying event (8m downwind from the edge of the treatment area after a single pass for boom sprayers and a whole orchard for broadcast air assisted sprayers). The estimates are based on UK measurements of spray drift data from the 1980s.

2.3 There have been significant changes in application practices for plant protection products since that time 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 and now provides up to date data and models to estimate direct exposure to spray drift. [5-9]
2.4 BREAM is a development of a mechanistic particle tracking spray drift model. It allows greater flexibility than the previous empirical model by estimating 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 modelling to sample the distributions of the input parameters. The model outputs are predictions of spray droplet concentrations in breathing zones, potential dermal exposure, and ground deposits at varying distances up to 15m from the spray boom.

2.5 The scenarios covered in the BREAM study include estimates for adults and children positioned at a range of distances from the sprayer (up to as close as 2 m) and show 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 show that the amount of spray contamination falls away quite rapidly a matter of a few metres from the edge of the spray boom. However, the decline in airborne spray drift suggests low-level exposure continues over a greater distance from the boom. BREAM and the current model produce exposure estimates that agree well at 8m from the boom but BREAM predicts exposure (principally dermal) up to an order of magnitude greater closer to the boom for the larger, faster machinery in current use.

2.6 The EFSA group has been informed of these critical findings from BREAM and have as a consequence included an additional 10-fold factor to adjust for estimated exposure near the spray boom [3]. The working group agreed that the BREAM calculator probably over estimates exposure as it assumes limited dispersion but it is more relevant for bystander and resident risk assessments as 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). It could also incorporate better information on buffer zones and crop-type as data become available.

2.7 The group considered the current assumptions for proximity of bystanders and residents to the spray boom and duration of exposure. With a spray vehicle typically travelling at 2.5 – 3.5 m/sec and data that show that spray droplets fall to the ground in seconds the current assumption of 5 minutes exposure is conservative. Indeed a sprayer travelling at these speeds could have covered about a kilometre in five minutes. There are difficulties controlling long booms and a high risk of damage from collisions with field boundary features such as fences, hedges, trees etc It is also likely that normal bystander behaviour would be to move away from the boom, so the group considers a distance of 2m is a close distance in practice. This value is the minimum distance measured from the centre of the hedge line that is permitted for spray operations under cross compliance regulations. In addition, spray operators must be trained and the Code of Practice for using plant protection products requires them to protect the public and prevent overspray on adjacent properties. [10] The group felt that 2m was an appropriate minimum distance for acute estimates of exposure and that a suitable scenario for short term risk assessment would be someone standing 2m from the edge of the spray boom using the 95th percentile of exposure concentrations during a single pass (or about 5 min).
2.8 The group also considered exposures from repeated spraying events in the same or adjacent fields. A worst case might be a spray programme used to control potato blight. Under conditions of very high disease pressure application intervals can be as frequent as every three days, but such conditions are unlikely to persist for more than a ten day interval. Potatoes are usually grown on a wide rotation of typically one year in five. Wheat however can be grown continuously and a susceptible cultivar under conditions of high disease pressure could be sprayed three times on a ten day interval during May and June, with up to a total number of seven spray applications through the life of the crop, October through to July.

2.9 Thus a risk assessment for residents should include both a short term risk assessment for exposure to the spray and to volatiles (exactly as the bystander risk assessment) and a longer term risk assessment for exposure to spray, vapour and dislodgeable residues. The group noted that the current estimates make no differentiation 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. It was also noted that children have a lower breathing rate, smaller surface area and the differences in estimated exposures reduce as the distance away from the boom increases so adult exposure values may be appropriate. However, a separate assessment for children and adults should be considered.

**Direct exposure to vapour drift**

*Volatilisation from soil and plant surfaces*

2.10 The vapour pressure\(^1\) of a chemical defines the inherent tendency of the chemical to move from the liquid or solid phase into the gas phase. Plant surfaces are generally considered to be relatively inert and it has been demonstrated that vapour pressure acts as a primary control on volatilisation under controlled conditions [11]. The interactions between pesticides and water/solid particles within soil mean that sorption capacity of the pesticide and water solubility are additional controls on volatilisation from soil surfaces [11]. However, the working group noted that many of the data available in the literature on these issues are for older chemicals that tended to have relatively large potentials for volatilisation.

2.11 Under field conditions, volatilisation from soil and plant surfaces is also mediated 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 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. Equally there is no scientific consensus on whether there is a lower threshold of vapour pressure below which volatilisation becomes an insignificant pathway of entry into the environment. More information can be found at Appendix 3.

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\(^1\) The vapour pressure of a chemical is a measure of its tendency 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 solubility, by formulation, and by weather variables including temperature, wind speed and relative humidity.
2.12 The current approach in UK risk assessment is to use vapour pressure to separate compounds with low inherent volatility (<0.005 Pa) from those with moderate inherent volatility (0.005-0.01 Pa) and then to assume conservative values for average concentrations in air during the 24 hours following application of 1 and 15 μg m\(^{-3}\), respectively [12]. These values were set as protective of volatile emissions 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 [9, 13-14] concluded that these 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 use conditions; 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 the regulatory approach assumes that there is no decrease in this daily exposure on successive days.

2.13 Data on volatile emissions from field experiments are sparse. Butler-Ellis et al., [13] have suggested that the expected relationship between vapour pressure and volatile emissions may not hold under field conditions. However, a repeat of their experiments with epoxiconazole and fenpropidin yielded behaviour in line with that expected from the respective vapour pressures [15]. In the absence of robust alternatives, the working group believes that the current approach of using conservative values for average concentration in air during the 24 hours following application of low and medium volatilities as in para 2.12 should be retained. These values will be very conservative for the vast majority of situations in the UK and greater transparency is required in communicating this conservatism 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 smaller 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 of the order of 0.015 μg m\(^{-3}\) in Canada and 0.12 μg m\(^{-3}\) in France [16, 17]. 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 the potential to revise the first-tier estimate of concentrations in air (para 2.12) using 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.

2.14 While this approach is the most appropriate for current conditions and given the most recent scientific evidence, the working group feels that further research should be undertaken to develop approaches able to calculate volatilisation losses for individual active substances. Regression approaches [11] 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 current-use pesticides. Mechanistic models such as the Pesticide Emission Model [18] offer a further opportunity, but will require work to demonstrate validity for agricultural conditions in Europe.

**Indirect exposure to spray drift**

*Estimating the level of drift fallout*

2.15 This pathway covers a number of routes, but exposure to 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, although it is recognised that in practice boundary structures can affect the level of drift deposited. The current UK approach uses the same spray drift data as used for the assessment of aquatic risks. These data were generated in Germany and are widely used throughout the EU. However, the BREAM project has provided updated data for modern boom sprayer applications in the UK and use of these data would be more protective.

2.16 The level of deposited pesticide is expected to decline rapidly with distance from the end of the spray boom. In some circumstances (e.g. wire fencing) there are only good practice guidelines but no restrictions are placed on spray operators as to how close to boundaries they can spray. However most field boundaries have separation provided by either hedges or ditches and greater separation is provided over and above this through field margin Entry Level Stewardship options. Two thirds of farmers participate in Stewardship schemes and over 30% of agreement holders have included additional field margin buffers of 2.0, 4.0 or 6.0 metres in their agreements. 82% 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.

2.17 The group concluded that it was unreasonable to assume no separation between the sprayer and the fallout zone and that a value of 2m was an appropriate worst case scenario for acute risk assessments and 5m for longer term sub chronic risk assessments. It is important to note that these are assumptions made about the data selected for use in risk assessment. They do not imply that we assume a buffer zone of this size is present.

**Dermal exposure and ingestion**

2.18 Having established an estimated level of drift fall out, 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 for estimating point estimates of exposure to lawn treatments. In 2009 the US EPA reviewed this approach and until a revised model is available the group believes it is reasonable to continue with the current EPA model [19]. This is in accordance with the conclusions of the EFSA PPR Panel. However, the working group feels that consideration should also be given to repeated as well as single exposures to determine the levels of potential
accumulation of product. More details of the calculations underlying calculation of dermal exposures can be found at Appendix 4.

2.19 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 although the 2 hour limit used for exposure to grass residues is likely sufficient to deal with this. However, the group feel that further information on such other animal related exposures are needed to improve estimates.

*Exposures to residues on garden crops*

2.20 A source of indirect exposure to pesticide residues following spray drift is through garden produce. Such produce may be grown right up to a 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 considered should be 2m for an acute risk assessment and 5m for a sub-chronic risk assessment.

*Exposure to residues on treated crops*

2.21 The EFSA draft guidance considers that bystanders and residents may also be potentially 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 estimate dermal exposure as a product of the measured or estimated dislodgeable foliar residue, DFR, and a task specific transfer coefficient (TC)\(^2\) which reflects the degree of contact with the treated foliage. There are only a limited number of TC values available to use in the EU and these are set out in the EFSA draft guidance [3]. In the absence of specific data on dermal absorption a default value of 100% absorption is used to convert dermal exposure to systemic exposure. Overall this approach is likely to overestimate exposure and to be protective.

2.22 When undertaking risk assessment the EFSA default value for the time a bystander may spend in a treated crop is 15 minutes (e.g., on a footpath or right of way crossing a crop). The working group consider that this is too short for current practice with large crop blocks of the same variety and recommend that this value should be 30 minutes.

*Total systemic exposure*

2.23 The group considered that it is appropriate to include the possibility that exposure by different pathways might occur and therefore the individual exposure estimates for each pathway should be aggregated. This might include exposures via the eyes, although this represents only a very small surface area of the total potentially exposed. Because each estimate of exposure is based on conservative assumptions it would be inappropriate to simply add them together as this would

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\(^2\) The TC value is derived from the ratio of measured exposures to the DFR values from other cases. It is assumed that the TC reflects the scale of transfer of the dislodgeable residues and exposure can then be estimated for a new example with a different DFR.
result in a super-conservative exposure estimate that was unrealistic. Instead a probabilistic modelling approach could be used if data were available.

2.24 One of the routes to systemic exposure not currently part of a bystander and resident exposure assessment is dietary exposure, whether from dietary exposure to residues arising from specific crop treatments or from spray drift onto garden crops. This may require the development of appropriate tools. Alternatively if estimates of consumer intake were sufficiently low (<10% of the estimated total) it might be considered within the range of uncertainties of other routes and could be ignored.

2.25 Biological monitoring is based on the analysis of substances in urine or blood and is often used in occupational and environmental studies to assess systemic exposure by inhalation, ingestion and dermal absorption. Such measurements are sometimes referred to as biomarkers. Because such markers reflect exposure by all routes, in theory 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 guidance values derived from toxicokinetic models [20]. An example of the utility of the approach is a small biological monitoring study of pesticide exposure in the UK [21] where cypermethrin metabolites were detected in the urine of spray operators more frequently than in that of post-application workers, bystanders or consumers. A metabolite of mancozeb was found more frequently in urine from spray operators than bystanders and in all cases the levels of metabolites found were lower than those predicted by a toxicokinetic model and such measured exposures were below the Acceptable Operator Exposure level (AOEL) or the Acceptable Daily Intake (ADI).

2.26 The likelihood of co-exposure of residents to simultaneous multiple pesticides other than as tank mixes from agricultural use was also assessed. This would depend on the number of fields around a residence, the types of crop and the prevailing wind conditions. It was concluded that some of these factors, together with the practice of block cropping would make simultaneous co-exposure uncommon.

2.27 Repeat passes of a spray boom might be a factor in increasing dose to bystanders or residents; in practice, increases in exposures from spray deposits with additional passes are likely to be very small as the major exposure comes from spray deposits in the pass which is closest to the bystander or resident. The BREAM calculator predicts the major contribution to dermal deposits will be greatest on the closest first pass and subsequent upwind passes (at least 24m away) might increase total deposits by around 3%. Vapour may travel further and could also contribute to exposure. There are greater uncertainties in model predictions of vapour concentrations at a distance, but it is reasonable to assume that although multiple passes (or greater crop areas) could result in higher values for exposure to vapour their combined contribution to total exposure will be small.

2.28 The question of secondary exposure to re-distributed residues (by which we mean exposure arising as a secondary release of pesticide from its first settling point at first 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. Dust raised during harvesting can cause significant health impacts through allergic
responses to allergens from plants themselves or to fungal spores or other microbes and the group felt that these were better characterised and likely more important than reactions to pesticide residues in the dust.

2.29 There is also a possible risk of secondary exposure for instance by subsequent re-volatilisation and uplift from foliage. Limited research into this possibility following the application of sulphuric acid to potatoes indicated that none of the substances produced by the action of sulphuric acid on potato haulms would be present at concentrations likely to pose a significant health risk to bystanders. [22]

2.30 There is evidence of long-range transport of current-use pesticides, and of both wet and dry deposition of them. The concentrations in air and rates of deposition are very small compared to the near-field concentrations and rates recommended to be included within the risk assessment. Hence as the group recommend that it is not appropriate to simply add up all possible routes of exposure, there is no scientific justification to be concerned explicitly about long-range transport within the bystander and resident risk assessment scheme.

3 Toxicology

3.1 One of the aims of this group was to review the approach to assessing the risk arising from these exposures in the light of current knowledge. We therefore describe the current approach to the role that toxicology plays in the regulation of pesticides to provide background for the main issues in this report.

3.2 Each application for approval of a pesticide is accompanied by an extensive data base of scientific studies designed to help regulators understand the effects of that pesticide on the target pest, the possible environmental effects and, most importantly, the possible adverse effects it might cause to health and the dose at which these effects might occur. The toxicology studies considered for a pesticide 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. The only data directly relating to effects on humans comes from health monitoring of manufacturing personnel and reports of any poisonings that may have occurred (usually as a result of deliberate self harm).

3.3 Understanding of the potential for exposure to a pesticide to cause harm to human health depends not just on the level of exposure to a specific agent but also to the degree of toxicity of the agent. Evidence to inform this 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 received by humans in 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 allows the development of indices of allowable exposure for that active substance such as the AOEL, ADI, ARfD (see paragraphs 3.4 onwards) which in turn will be considered for readjustment in the face of new scientific evidence.

**Current registration package**

*Reference doses including acute reference dose (ARfD), AOEL, ADI*
3.4 The current UK and EU package for registration of a pesticide requires data to derive these health based guidance values (e.g. AOEL, ADI, ARfD) for the active ingredient. The regulatory framework underpinning these requirements are the EU Directive 91/414/EEC and it’s replacement, Regulation (EC) 1107/2009, and information on co-formulants as mandated by REACH (Registration, Evaluation, Authorisation and Restriction of Chemical substances: EC 1907/2006).

3.5 In addition, information on the physicochemical characteristics of the substance such as molecular mass, pH, water solubility, octanol:water partition coefficient and pKa is required. These data are useful in guiding and interpreting the design of toxicokinetic and toxicological studies and in helping to estimate exposure.

3.6 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, such as oral, inhalation and topical. 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 [23].

3.7 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, 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, in the draft OECD Guidance No. 116 (recently approved by the Working Group of National Coordinators of the Test Guidelines. Program) [24].

3.8 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 lifestage, known as the “critical effects”; 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.

3.9 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 2 generations;
- developmental toxicity, in two species;
- additional special studies, as necessary,
3.10 Data should be generated without using animals where suitable methods are available. In practice, this applies to only a few endpoints at present, such as skin and eye irritation. All studies are performed according to agreed protocols and standards of design and conduct. This includes issues such as quality assurance and data retention.

3.11 Where animals are used in toxicity testing they are examined regularly for general condition, signs and behaviour. The early appearance of tumours is assessed by physical observation and palpation. Animals are terminated early if there any indications that this is necessary on humane grounds. At the end of the study, surviving animals are terminated and subject to a comprehensive 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 terminated early or that die prematurely are also subject to detailed examination.

**Acute toxicity studies**

3.12 In studies of acute toxicity, the emphasis is on identifying the toxicity class, rather than on obtaining a numerically precise estimate of acute lethality, on 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.

3.13 Whilst current acute toxicity studies place more emphasis on the observation of non-lethal effects than the LD50 test, it is recognised that there are a number of acute effects, for example on 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 the increasing emphasis on the acute reference data for dietary exposure and now the acute AOEL (see below), the 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). [25]

3.14 In studies involving more than one exposure, a wide range of end-points (effects) is 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; histopathology (of more than 30 tissues).

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3 LD50: The theoretical lethal dose for 50 per cent of a group of organisms
3.15 Studies are performed for progressively longer periods, using the results of 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 studies to help in dose selection and may not be sufficiently extensive to help in the evaluation of the compound per se. In such cases, there should always be a more comprehensive, longer-term study available.

3.16 Typical study durations would be 7 days (almost always only for range finding), 28 days (increasingly this is more than just range finding), 90 days and possibly 1 year (in dogs) or as the chronic toxicity component of a 2 year 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.

3.17 These studies are designed to identify systemic effects, that is an effect 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 on repeated exposures).

Genotoxicity, carcinogenicity and mutagenicity

3.18 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.

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

3.20 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.

3.21 Additional studies may be undertaken on the mode of action of a compound in causing carcinogenic effects. Such studies are case-by-case 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.

3.22 Compounds that are classified as category 1A or 1B carcinogens will not normally be approved for use as pesticides in Europe, unless exposure is such that it is considered negligible.

Reproductive studies
3.23 Compounds are investigated for possible effects on reproduction, over two generations, in rats. The so-called multi-generation study involves exposure of both 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, 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.

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

3.25 All stages of reproduction are covered 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.

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

Developmental studies

3.27 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.

3.28 Dams are examined throughout pregnancy for signs of toxicity, such as appearance, clinical signs, body weight, 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 foetuses 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.

3.29 Compounds that are classified as toxic for reproduction category 1A or 1B (on the basis of either reproductive or developmental toxicity studies) will not normally be approved for use as pesticides in Europe, unless exposure is such that it is considered negligible.

Neurotoxicity studies

3.30 If necessary, based on structural similarity to other compounds with effects of concern, or because of indications during testing for systemic effects as above, studies on acute and repeat dose neurotoxicity are required.
3.31 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*

3.32 Similarly, additional 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*

3.33 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 in animal products, soil, groundwater, or in the air that differ from those found in the animal species used for the toxicology studies or that 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.

3.34 This is an issue currently subject to active discussion by EFSA.

*Main objectives of testing and study design aspects*

3.35 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 the effects observed.

3.36 These two objectives impact 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 of the numbers of animals per dose group in the test guidelines. For larger species, such as dogs, dose groups are smaller.

3.37 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.

3.38 The Royal Commission on Environmental Pollution 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. Whist holding much promise, this work is still at a relatively early stage and at present the majority of the tests are unable to provide sufficient reassurance as to the protection of human health to enable reliance solely on them for regulatory purposes [26].

3.39 Revised toxicology data requirements are being prepared at present in Europe. These are expected to be published in 2012, to come into full effect from 2014 [23]. These requirements include specific prohibitions on animal testing unless there is no other validated and/or acceptable alternative. There is also a prohibition on human or non-human primate testing.

3.40 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.’

3.41 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

3.42 In evaluating a compound, any available human data should be considered. It is no longer possible to study pesticides 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.

3.43 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 events. 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.

3.44 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 the 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.
The No Observable Adverse Effect Level (NOAEL)

3.45 For endpoints other than for carcinogenicity 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), the highest dose for which the effect is not statistically different from that in the controls.

3.46 An alternative approach is to fit a mathematical relationship to the dose-response data and to determine 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. bodyweight). This is known as the benchmark dose (BMD). The lower 95% confidence limit on the BMD can be determined mathematically to give the BMDL.

3.47 The NOAEL is not a true threshold. It may be above or below the true threshold since it is dependent on the doses chosen for the study. 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 [27].

3.48 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 often known as the critical NOAEL, and the associated effect as the critical effect, i.e. the one that underlies the AOEL.

Uncertainty factors

3.49 In order to extrapolate the critical NOAEL to humans, uncertainty factors (also known as safety or assessment factors) are used, to account for possible species differences in sensitivity and for interindividual variability in humans. The values normally used are 10x for each of these factors, resulting in an overall uncertainty factor of 100.

3.50 Additional uncertainty factors may be used for a variety of reasons. These include the absence of a NOAEL, with extrapolation from the lowest observed adverse effect level (LOAEL), provided that the effect at the LOAEL is of relatively low magnitude, 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 compound specific assessment factors e.g. where good specific toxicokinetic and toxicodynamic data are available that enable changes to the default assumptions to be made [28]. The overall uncertainty factor is obtained from the product of all of the uncertainty factors used.

3.51 The acceptable operator exposure level (AOEL) is established by dividing the critical NOAEL by the overall uncertainty factor. Where there is incomplete absorption by the oral route, the AOEL is adjusted for the fraction of the absorbed dose, 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 of this duration, whatever the route of exposure. (NB this
differs from ADI and ARfD that are derived from oral studies and are used to estimate risk from oral exposures and thus do not need to be adjusted in this way. This allows exposure by routes where absorption is incomplete to be adjusted, so that it can be expressed as equivalent systemic exposure for comparison with this AOEL.

3.52 AOELs are based on the appropriate exposure scenario, in which, for most pesticides, it is 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.

3.53 Where estimated exposure exceeds the AOEL (or other relevant health based guidance value), this does not necessarily mean that there is a potential health concern. 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 potential concern. The group note that there are specific requirements in legislation governing estimates of exposure and comparison with the AOEL.

3.54 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 [25]. In general, when extrapolating from studies in rodents to human exposure scenarios, proportionality of lifespan is used. 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 health based guidance value.

3.55 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 impact on exposed subjects is considered further.

Additivity

3.56 Several groups have recently reviewed the evidence for departures from additivity at human relevant exposures to multiple environmental chemicals [29, 30]. Exposures to mixtures would usually be from tank mixes or, very rarely, from different
sprays being applied to different crops in neighbouring fields. In general, it has been concluded that approaches other than simply adding exposures are not more predictive of impact if exposure to individual compounds is below the respective health based guidance value. 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 group to be appropriate.

3.57 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 [31, 32]. 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**

3.58 Pesticides are extensively tested for toxicity prior to authorisation. Testing is as rigorous, if not more so, than for human medicines. A comprehensive series of both morphological and functional endpoints is investigated, in exposures spanning from a single occasion to a lifetime. Possible effects during potential 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 [33].

**Local effects: irritation and skin sensitisation**

**Skin sensitisation and pesticides**

3.59 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 sets out general 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). If an in use dilution as specified on the label of the product was 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.

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4 Although lifetime in rodents is appreciable less than in humans (e.g. 2 years in rats cf ~80 years in humans) there is good evidence that effects scale with fraction of lifetime over which exposure occurs. This is because of the proportionally higher metabolic rate in rodents compared to humans.
3.60 Bystander and resident exposure to pesticides is most likely to occur via the skin, the mouth, the respiratory tract and the eyes to diluted products. Acute effects such as skin or eye irritation, cough or sore throats localised to the exposed tissue, can then occur if the exposure is at a sufficiently high concentration for a sufficient period of time. Whilst these effects have been considered nuisance effects, they nonetheless are clinically relevant and can impact on quality of life.

3.61 As well as these acute effects, there is concern that pesticide exposure may result in sensitisation potentially 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 can react to considerably 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).

3.62 In the skin, the dose per unit area is the key exposure parameter that determines sensitisation. A dose that can elicit sensitisation may not necessarily cause sensitisation if administered over a larger area of the skin. The dose required to sensitise an individual may also be different from that required to subsequently elicit symptoms 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 and so exposure to doses below the induction threshold may not induce sensitisation. Doses below the elicitation threshold will not induce a clinical response in sensitised individuals. Conversely, for some sensitisers all individuals appear to be susceptible when exposed at a sufficiently high level.

3.63 The local lymph node assay (LLNA) is one of the tests (OECD 429) used to examine whether a chemical is a skin sensitiser [34]. This assay studies the induction phase of skin sensitisation and provides quantitative data for assessing the sensitisation potency of a chemical. Chemicals that induce a three-fold increase over background activity are considered sensitisers and the concentration of the chemical (known as the EC3) required to cause such an increase can be used to assess the potency of that chemical. Chemicals that when diluted 50 times or more (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.

3.64 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) may represent a low risk to humans. However, even chemicals with high EC3 values (>50%) have been reported to cause skin sensitisation in some humans so that it is not currently possible to identify an EC3 value below 100% suitable for categorising chemicals as having low sensitising potential.

3.65 The largest publically available database of LLNA results of pesticide formulations was published in 2010 by ICCVAM [35]. 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 are actually approved in the UK.

3.66 Given these caveats, twenty formulations that were identified as sensitisers appear to be similar to products approved in the UK, although 7 of these contain higher active substance concentrations than actually approved. The EC3 values of these products ranged from 1-56%.

3.67 Where pesticides are used in spraying, bystanders and residents are exposed to the diluted formulation, typically diluted so that the concentration is less than 1%. To what extent this is associated with an increased risk of sensitisation is understood for few agents. For risk assessment a semi quantitative approach, such as in the REACH guidance could be considered as an approach to defining the risk more clearly.
Summary of main issues identified (Table 1)

Exposures

4.1 The group was very aware of the limitations of the evidence base when considering the effects of pesticide exposure in this setting on human health, largely because of the issue of inadequate measures of exposure, although the group had more confidence when considering short term effects. The use of general group terms such as ‘pesticides’ or ‘insecticides’, which include compounds with different chemistries, add to the uncertainty in this regard.

4.2 In most cases exposure assessments are based on a worst case scenario which is very unlikely to occur except in most unusual circumstances. The group believes that this approach is sufficiently precautionary to minimise significant risk to health.

4.3 The group found that information relating to estimation of bystander and resident exposures to pesticide spray would be significantly improved with the BREAM dataset but that there remain unanswered questions. These include the issues around volatility as vapours can carry often considerable distances even though levels measured distant from a spray source have been measured as very low. The group noted that the data available to assess this issue relates solely to chlorpyrifos and accept that data might differ for other actives. However, the group believe that these differences are very unlikely to have an impact on health outcomes in the UK setting because chlorpyrifos is a pesticide with a higher volatility than most pesticides and these data were obtained in California where the climate is generally rather warmer than that of the UK [36]. The warmer temperatures encourage volatilisation and so these data represent potential exposures at the higher end of what is likely in the UK. Where vapour pressure is significantly higher than that of chlorpyrifos, the BREAM air dispersion modelling for the unit flux is used and adjusted by either a measured flux or an estimated flux.

4.4 Members noted that current estimates of exposure are based on mean data, but that the BREAM data provide other percentiles that could be used in risk assessment. Members agreed that different percentiles could be used for acute and longer term risk assessments.

4.5 Members also noted that the data gathered on the high drift scenario used wind speeds at the top end of legal spraying practice. It might be possible that some specific nozzles could produce higher drift.

4.6 Members noted that conversion of dermal deposition to systemic exposure estimates is difficult. The group noted that that where no data are available it is assumed, as a default, that dermal absorption could be up to 100%. This is in line with current guidance. Where data were available the range was usually found to be between 1 and 10%. Thus the dermal absorption can be a critical factor in the risk assessment [37]. In addition, the behaviour, body size and potential for dermal contact with contaminated surfaces are different for adults and children.

4.7 The group agreed that behavioural differences between adults and children (and by children at different ages) should be taken into consideration in assessing
dermal exposures to dislodgeable residues arising from spray drift deposit on the ground. 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 reasonable proportion of their body. In addition they are likely to transfer some of these residues from hands or objects they play with to mouths resulting in an additional route of exposure. Members agreed that these behaviours were appropriately captured in the US EPA turf model. This would represent a behaviour pattern likely to result in greater exposure to dislodgeable residues than adult behaviour patterns. Exposure per unit body weight also suggests the adult exposure can be considered to be covered by the model for children. Adult exposure estimates for dislodgeable residues should therefore focus on the ‘re-entry’ scenario of walking across a treated field. Taking these aspects into consideration, members agreed separate scenarios for adult and child should be considered in risk assessment.

4.8 The group noted that estimates of exposure are based on conservative assumptions and so it would be inappropriate to simply add them up as this would result in a very conservative estimate of exposure based on overall unrealistic assumptions. The USA had completed some probabilistic estimates, but these required suitable input data. Members considered whether to recommend a very worst case conservative approach or to recommend that tools to complete a more realistic estimate be developed.

4.9 The group agreed that ideally data on a range of exposures from consumer intakes to take account of spray drift residues on garden produce could be obtained. If these contributed say 10% or less to the estimated exposures they would be well within the range of other exposure estimates anyway and hence could be ignored for these purposes.

4.10 Members noted that there was a paucity of information on biomarkers, either of exposure or outcomes, in published, population-based studies although some small studies suggest that approaches to risk assessment using biomarkers can be very helpful. However, given this limited evidence base the group felt that no recommendations with respect to the use of biomarkers in risk assessment could be made. The group noted that a sub-group of ACP (the pesticides adverse health effect surveillance scheme working group, PAHES) was considering this aspect of exposure assessment in more detail.

*Dosing*

4.11 While measurement of, say, airborne levels of a pesticide as a measure of exposure is helpful what matters in terms of health effects is what dose actually reaches a target organ within the body. Where exposure to more than one agent (or its co-formulant(s)) occurs the issue of whether such multiple exposures can be regarded as additive, synergistic or neither is raised. Equally, total exposure to one compound through different routes (inhalation, dermal or by ingestion) may not be best achieved simply by adding up all routes, which would be very conservative.

4.12 While it can be considered that the approach taken by EFSA seems to be sufficiently precautionary there remains a need to attend to some specific issues relating to dosimetry. The key drivers of exposure under different exposures needs to be determined and at present there are few data to aid assessment. This is
important as understanding which aspects may have little influence will influence how current practice could be modified to reduce exposures.

**Toxicity**

4.13 Current toxicity testing of pesticides is comprehensive and covers potentially vulnerable life stages. There has been some discussion about the possible impact of *in utero* exposure on disease in later life. However, there are practical difficulties in implementing such a testing protocol routinely. The revised OECD test guideline for chronic toxicity testing (TG 452) [38] does not envisage use of this protocol. The key issue is whether effects that would not otherwise be detected would be observed using such a protocol. There is little evidence that this would be the case using the current test series, including chronic toxicity, carcinogenicity and reproductive toxicity testing.

**Dose and sensitisation**

4.14 The group noted that there is concern that some individuals may become sensitised to pesticides, and that risk factors for sensitisation are not well understood. In addition the group felt it was important to identify the extent to which current or new formulations may change the ability of chemicals to act as sensitisers.

4.15 Members recognised the usefulness of the LLNA in providing potency estimates for different pesticides with regard to the induction of skin sensitisation but that there are difficulties in providing potency estimates for elicitation. Further work is required to better characterise 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.

**5 Recommendations**

5.1 The group recommends that the approach taken by EFSA in their draft guidance for estimation of bystander and resident exposure, being supported by the latest science, in particular the data from BREAM, should be followed by the regulatory authorities as representing the most appropriate approach at the current time.

5.2 The models used should be continuously refined by more data as these become available (e.g. range of application techniques and impacts of various drift mitigation measures).

5.3 The group considered the issue around the distance between a field boundary edge and the sprayer and the position of the bystander or resident assumed in the risk assessments and recommend that for acute exposures a 2m distance between the sprayer and the bystander or resident is most appropriate while for potential longer term exposure a 5m distance should be used.

5.4 When considering risk assessment, the EFSA default value for the time it is assumed a bystander may spend in a treated crop is 15 minutes (e.g. on a footpath or right of way crossing a crop). The working group consider that this is too short for
large crop blocks of the same variety and **recommend** this value should be 30 minutes.

5.5 For total exposure assessment the group **recommend** that estimates are not simply added up because the likelihood of a naked individual receiving all the combined high exposures with absorption across all the routes being as high as assumed is vanishingly small. In some cases where the exposures are linked to the same spraying event (e.g. direct inhalation and dermal exposure to spray drift and indirect exposure to ground deposits) it would be appropriate to use a high percentile for all three. In other cases, where possible, a probabilistic approach should be used. This issue is being addressed by the EU ACROPOLIS project which will reduce uncertainty in this area [39].

5.6 In addition the group **recommend** that research be conducted into the extent to which current or new formulations may change the ability of chemicals to act as sensitisers.

5.7 The group recognises the importance of the LLNA in providing more quantitative estimates of potency. However the group recommends that further work is required to better characterise the LLNA potency of current formulations 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 is required to define this relationship.

5.8 Some concern has been expressed that the current regulatory package does not test specifically for foetal origins of diseases of old age such as cancers and diabetes for which studies in epigenetics have suggested possible mechanisms. There are as yet no good data confirming that the standard test package is missing information, but the concern is that it might be. Overall the group agreed that this was not yet a mature field for the working group to be able to suggest a valid way forward but **recommend** that new work in this area should be carefully evaluated as it appears.
TABLE 1 Summary of current and proposed approaches to risk assessment for pesticide spraying

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Source</th>
<th>Route</th>
<th>Bystanders</th>
<th>Residents Adults</th>
<th>Residents Children</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current approach</td>
<td></td>
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<td></td>
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<tr>
<td>During spraying (acute)</td>
<td>Spray drift</td>
<td>Inhalation</td>
<td>8m down wind, single pass of 12m 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</td>
<td>Assume exposure is covered by bystander assessment</td>
<td>Assume exposure is covered by bystander assessment</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermal</td>
<td>8m, downwind 0.1ml spray, no reduction from clothing, 60Kg adult, default 100% absorption</td>
<td>Assume exposure is covered by bystander assessment</td>
<td>Assume exposure is covered by bystander assessment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ingestion</td>
<td>Not considered</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Post spraying Sub Chronic/</td>
<td>Volatilisation from deposits</td>
<td>Inhalation</td>
<td>Not separately considered – covered by adult resident assessment</td>
<td>24h exposure to 1 or 15µg/m³ (taken from German data and from California EPA chlorpyrifos monitoring[^36^], 60kg adult, respiring 15.2 m³/day)</td>
<td>24h exposure to 1 or 15µg/m³ (German data and from California EPA chlorpyrifos monitoring[^36^]), 15Kg child, respiring 8.3 m³/day</td>
<td>For any substance more volatile than chlorpyrifos an estimate of flux and the BREAM air dispersion model is used.</td>
</tr>
<tr>
<td>Spray fallout/deposition</td>
<td>Dermal</td>
<td>Ingestion</td>
<td>During and post spraying</td>
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<tr>
<td>Assumed covered by re-entry worker exposure – (adult assessment 2 hours intimate contact with treated crop and no PPE)</td>
<td>Assumed covered by re-entry worker exposure – (adult assessment 2 hours intimate contact with treated crop and no PPE)</td>
<td>Not separately considered but assumes that child ingestion exposure is likely to cover adult</td>
<td>Children’s exposure is assumed to be the sum of those from dermal, ingested and inhaled routes.</td>
<td></td>
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<tr>
<td>Uses US EPA lawn re-entry model. Calculates dermal exposure using drift fall out, turf transferable residue, transfer coefficient from grass to skin and duration of contact with contaminated turf. Assumes 2 hour contact period and 15kg child</td>
<td>US EPA lawn re-entry model. Assumes a proportion of residue picked up on the hand is transferred 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 25cm² area is ‘consumed’.</td>
<td>Consider dilution and classification criteria to understand likelihood of effect.</td>
<td>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.</td>
<td></td>
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<tr>
<td>Ingestion Not separately considered but assumes that child ingestion exposure is likely to cover adult</td>
<td>Not separately considered but assumes that child ingestion exposure is likely to cover adult</td>
<td>Consider dilution/dispersion and classification criteria to understand likelihood of effect.</td>
<td>Consider dilution/dispersion and classification criteria to understand likelihood of effect.</td>
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</tr>
<tr>
<td>Proposed approach</td>
<td>Source</td>
<td>Route</td>
<td>Bystanders</td>
<td>Residents Adults</td>
<td>Residents Children</td>
<td>Comments</td>
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<tr>
<td>Acute/during spraying</td>
<td>Spray drift</td>
<td>Inhalation</td>
<td>2m down wind, single pass, 24 m boom sprayer total spray cloud (approx equivalent to 0.002 and 0.0015 ml for adults and children, respectively) estimates based on 95 percentile data. Evaluation for adults and children.</td>
<td>As bystander</td>
<td>As bystander</td>
<td>Total acute exposure is sum of inhalation and dermal and is compared to an acute AOEL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermal</td>
<td>2m down wind, single pass, 24 m boom sprayer total spray cloud (approx. equivalent 3 ml adults and 1 ml children) estimates based on 95 percentile data. Evaluation for adults and children, no reduction from clothing, 60Kg adult, default 100% absorption.</td>
<td>As bystander</td>
<td>Uses US EPA lawn re-entry model. Calculates dermal exposure using drift fall out, turf transferable residue, a higher transfer coefficient from grass to skin and duration of contact with contaminated turf. Assumes 2 hour contact period and 15Kg child</td>
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<tr>
<td></td>
<td></td>
<td>Entry to treated areas</td>
<td>EuroPOEM worker re-entry model with 30 min exposure to reflect walking across a freshly treated field.</td>
<td>As bystander</td>
<td>Assumed covered by child lawn exposure estimate as above</td>
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<tr>
<td></td>
<td></td>
<td>Ingestion</td>
<td>Not considered</td>
<td>24h exposure to 1 or 15µg/m³ (as above), or estimate of flux and BREAM air dispersion model, 60Kg female, respiring 15.2 m³/day</td>
<td>24h exposure to 1 or 15µg/m³ or estimate of flux and BREAM air dispersion model (as above) 15Kg child, respiring 8.3 m³/day</td>
<td>Compare to repeat dose AOEL. Consider aggregating acute and sub chronic resident exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Volatilisation from deposits</td>
<td>Inhalation</td>
<td>Not separately considered – covered by adult resident assessment</td>
<td>24h exposure to 1 or 15µg/m³ (as above), or estimate of flux and BREAM air dispersion model, 60Kg female, respiring 15.2 m³/day</td>
<td></td>
</tr>
<tr>
<td>Spray fallout/deposition</td>
<td>Dermal</td>
<td>Assume covered by bystander entry to treated areas (EuroPOEM worker re-entry model 30 min exposure).</td>
<td>Uses US EPA lawn re-entry model. Calculates dermal exposure using drift fall out at 5m, turf transferable residue, average transfer coefficient from grass to skin and duration of contact with contaminated turf. Assumes 2 hour contact period and 15kg child exposure. Not separately considered but assumes that child ingestion exposure is likely to cover adult.</td>
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<tr>
<td>Ingestion</td>
<td></td>
<td>Not separately considered but assumes that child ingestion exposure is likely to cover adult.</td>
<td>US EPA lawn re-entry model. Assumes a proportion of residue picked up on the hand is transferred 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 25cm² area is 'consumed'.</td>
<td>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.</td>
<td></td>
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<tr>
<td>Repeated spray exposures</td>
<td>inhalation</td>
<td>Consider weekly repeated exposures with values for 5m downwind from 24m boom sprayer. Use 75 percentile data for spray drift</td>
<td>Consider weekly repeated exposures with values for 5m downwind from 24m boom sprayer. Use 75 percentile data for spray drift</td>
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<tr>
<td>Route</td>
<td>Consider weekly repeated exposures with values for 5m downwind from 24m boom sprayer. Use 75 percentile data for spray drift</td>
<td>Consider weekly repeated exposures with values for 5m downwind from 24m boom sprayer. Use 75 percentile data for spray drift</td>
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<tr>
<td>Dermal</td>
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<tr>
<td>Ingestion via home grown fruit and veg</td>
<td>This may require the development of appropriate tools. Alternatively if estimates of consumer intake was sufficiently low (&lt;10% of the estimated total) it might be considered within the range of uncertainties of other routes and could be ignored.</td>
<td>This may require the development of appropriate tools. Alternatively if estimates of consumer intake was sufficiently low (&lt;10% of the estimated total) it might be considered within the range of uncertainties of other routes and could be ignored.</td>
<td></td>
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<tr>
<td>During and post spraying</td>
<td>Consider dilution and classification criteria to understand likelihood of effect.</td>
<td>Consider dilution/dispersion and classification criteria to understand likelihood of effect.</td>
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<tr>
<td>Local effects (sensitisation and irritation)</td>
<td></td>
<td></td>
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<tr>
<td>Other exposures</td>
<td>Consider semi quantitative approach as in REACH guidance.</td>
<td>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</td>
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<tr>
<td>Via eyes</td>
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</tbody>
</table>
Exposure via pollens dusts etc

Conclusion: minimal

Risks from dusts, pollens, fungal spores etc likely more important than reactions to pesticide residues

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

SE(d) = Systemic exposure via the dermal route, SE(h) = Systemic exposure via the hand-to-mouth route, SE(o) = Systemic exposure via mouthing activity
AR = total application rate of a.s. in µg/cm² (= 10x rate in kg a.s./ha)
DF = drift fallout value of 5.4% of the applied dose for vineyard sprayers
TTR = turf transferable residue value of 5% (EPA default value)
TC = transfer coefficient of 5200 cm²/h (standard EPA value for this situation)
H = duration of exposure of 2 hours per day (standard EPA 90th percentile value)
DA = dermal absorption of the a.s. in the spray solution
BW = body weight of 15 kg
SE = saliva extraction factor of 50% (EPA default value)
SA = surface area of the hands in contact with the mouth (the value of 20 cm²/event represents the palmar surface of three fingers)
Freq = frequency of hand to mouth events/hour (the value of 20 events/hour is the 90th percentile of observations ranging from 0 to 70 events/hour)
IgR = ingestion rate for mouthing of 25 cm² grass/day (EPA default value)
References

1. Royal Commission on Environmental Pollution Sept 2005. Crop Spraying and the Health of Residents and Bystanders.
2. Georgina Downs and the Secretary of State for Environment Food and Rural Affairs Case No: CO/4483/2004
assessment of resident and bystander exposure. Biosystems Engineering 107, 149-154
22. ACP 6 (305/04) Risks to bystanders from the desiccation of potato haulms with 77% sulphuric acid. (ACP minutes, January 2004)
23. SANCO/11802/2010 proposed data requirements for active substances under regulation 1107/2009


47. OECD 2002 Test guideline 404. Acute Dermal Irritation/Corrosion

48. OECD 2002 Test guideline 405 Acute Eye Irritation/Corrosion

49. OECD 2010 Test guideline 439 In vitro skin irritation: Reconstructed human epidermis test method

50. OECD 1992 Test guideline 406 Skin Sensitisation


Appendix 1

Members of the Bystander Risk Assessment Working Group

<table>
<thead>
<tr>
<th>Chairman</th>
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<tbody>
<tr>
<td>Professor J G Ayres</td>
<td>ACP</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Members</th>
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<tbody>
<tr>
<td>Prof A Boobis</td>
<td>COT</td>
</tr>
<tr>
<td>Prof C Brown</td>
<td>ACP</td>
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<tr>
<td>Dr J Cocker</td>
<td>ACP</td>
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<tr>
<td>Dr A Leake</td>
<td>ACP</td>
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<tr>
<td>Prof I Morris</td>
<td>COT</td>
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<tr>
<td>Dr A Povey</td>
<td>ACP</td>
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<tr>
<td>Dr D Ray*</td>
<td>ACP and COT</td>
</tr>
<tr>
<td>Ms A Ward</td>
<td>COT</td>
</tr>
</tbody>
</table>

*The Working Group was sad to record the death of Dr D Ray during 2010.
Appendix 2

Executive Summary of EFSA document published 18 Feb 2010


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.\textsuperscript{5}

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 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.

\textsuperscript{5} Clarification from BRAWG: The lower centile 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 75\textsuperscript{th} centile equates to a 94\textsuperscript{th} percentile overall; that for three successive 75\textsuperscript{th} percentile exposures, equates to a 98.5\textsuperscript{th} percentile overall and so on.
Appendix 3

Volatilisation from soil and plant surfaces

The vapour pressure of a chemical defines the inherent tendency of the chemical 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 a primary control on volatilisation under controlled conditions [11] (Figure 1b). The interactions between pesticides and water/solid particles within soil mean that sorption capacity of the pesticide and water solubility are additional controls on volatilisation from soil surfaces [11] (Figure 1a).

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).

Under field conditions, the relatively simple relationships with pesticide properties identified by Woodrow et al. (1997) are mediated by a range of environmental factors including temperature, wind speed, humidity, pesticide formulation and extent of dilution by water within the spray mix [11]. 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 separate 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 µg m⁻³, respectively [40].
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 [41]. The group considered vapour pressure to be a primary control on volatilisation from soil and plant surfaces. On the basis of reviews of field and wind tunnel data (Figure 2), they recommended cutoff criteria for deciding on whether volatilisation should be considered as a route of entry to the environment within regulatory risk assessment; these criteria were $1 \times 10^{-4}$ Pa for application to soil and $1 \times 10^{-5}$ 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 [42]; 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 use conditions 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 $VP < 1 \times 10^{-5}$ Pa as a threshold for non-volatile compounds where losses to air are insignificant [4], but this threshold was similarly dismissed as too simplistic within a subsequent EFSA opinion[3].

![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).](image)

The scientific literature was also reviewed within the BREAM project [9]. 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 [43]. It was considered that current defaults used within risk assessment (1 and 15 µg 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 [43]. 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 [44]. 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 [44]. 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[18, 45]. 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.

Recommendations:

1. In the absence of robust alternatives, the current approach should be maintained of using conservative values for average concentration in air during the 24 hours following application of 1 and 15 µg m⁻³ for compounds with low (VP <0.005 Pa) and moderate (VP 0.005-0.01 Pa) volatility, respectively. These values will be very conservative for the vast majority of situations in the UK and greater transparency is required in communicating this conservatism.

2. 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 overly precautionary and should not be built into the risk assessment.

3. The regressions of volatilisation losses with pesticide properties that were presented by Woodrow et al. (1997) offer a potential approach to calculate losses for individual active substances. Provided that sufficient conservatism was built into the approach, these regressions would have potential for application at lower-tiers of assessment. Additional work would be required 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 more typical of current-use pesticides.

4. The PEM model (Scholtz et al., 2002a;b) was considered most appropriate for potential application at higher-tiers of risk assessment in the USA [44] . The model was developed for conditions in the USA and validation status is relatively low, so significant further research would be required before any use in European risk assessment could be considered.
Appendix 4

Calculations relating to dermal exposure

The EFSA draft Guidance document [3] also includes a similar approach based on the original EPA approach, supported by Dutch data.

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)

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 [3] recommends that for reasons of transparency exposure estimates should be done 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 working group considered that although the behaviours of 3 year olds were clearly different to 6 year olds, there was a lack of information on differences in exposure verses differences in behaviour.

The \( TTR_d \) value represents the pesticide residue that remains on the turf surface available for removal by skin contact. Product specific data might be available, but in most cases it is not. In which case the EFSA proposal is to use a value of 5% for sprays based on the higher values observed for a range of product applied as sprays to lawns (actual range <0.001 to 6.1%) see EPA draft SOP Table 3-4 [19]. For Granules the value proposed is a \( TTR_d \) of 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 \( TTR_d \)s 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. It should also be noted that there are a number of studies which have measured TCs and issue of appropriate values is not straightforward, see the RIVM report [46] 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 before and not as had been assumed by the EPA after 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 takes the form:

$$SE(h) = \frac{(AR \times DF \times TTR_d \times SE \times SA \times Freq \times H)}{BW}$$

Where:

- $SE(h)$ = Systemic exposure via the hand-to-mouth route
- $AR$ = field application rate
- $DF$ = drift fallout value,
- $TTR_d$ = turf transferable residue
- $SE$ = salvia 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 [12] propose the mean value measured in study using three active substances see – EPA draft SOP Section 2.6 and Appendix A.3 [19].

The assumption regarding the surface area of hands mouthed, $SA$, is based on the previous EPA SOP (see RIVM report page 61) where the surface area of the hands mouthed is taken as 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 figures 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 [19].

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) [19]. 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:

$SE(o) = \frac{AR \times DF \times TTR_s \times IgR}{BW}$

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 compared to the 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 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 provokes an immune response sufficient to cause specific priming of the immune system. No visible changes occur in the skin until upon 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 disease. As the individual is immunologically primed, then 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 repeat contact. The dose per unit area is the key exposure parameter: a dose that elicits sensitisation may not necessarily cause sensitisation if administered over a larger area of the skin.

5 Evidence from both human and animal studies confirm that dose thresholds exist for both the induction and elicitation phases. This indicates that exposure to low subthreshold concentrations may not induce skin sensitisation. Conversely, 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 [47] 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 [48] 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) [49] 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) [50] and the other uses mice (OECD 429) [34]. The guinea pig tests seek to model the elicitation phase of the contact allergic reaction and so involve both induction and elicitation phases. Two types of assays have been developed that either use 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.

8 In the guinea-pig assays the animal is initially exposed to the test compound either topically or by intradermal injection (induction). The doses used are either 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 with the highest non-irritant dose of the test chemical (elicitation). The extent and degree of skin reaction is compared to those guinea-pigs who received the challenge but not the induction dose (irritant control group). The design of these tests limits the ability to provide 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 sacrificed 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 sensitiser. 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 and takes less time to complete.
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 [35]. 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 over the background radioactivity. 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.

<table>
<thead>
<tr>
<th>EC3 (%)</th>
<th>Potency category</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>&lt;0.1</td>
<td>Extreme</td>
<td>Dinitrochlorobenzene</td>
</tr>
<tr>
<td>≥0.1-&lt;1</td>
<td>Strong</td>
<td>4-phenylenediamine</td>
</tr>
<tr>
<td>≥1-&lt;10</td>
<td>Moderate</td>
<td>Dinocap</td>
</tr>
<tr>
<td>≥10-≤100</td>
<td>Weak</td>
<td>Trifuralin</td>
</tr>
</tbody>
</table>

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.” [52] In other words, it cannot be concluded reliably that a more dilute formulation of a classified product would not elicit a sensitisation response.
Glossary

**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 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).

**Actual dermal exposure:** Exposure to the skin that would occur in the presence of clothing and/or personal protective equipment.

**Acute exposure:** Exposure 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 significant toxicity.

**ADI:** 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 intended to define (on the basis of all known facts at the time of the evaluation) an estimate 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 [JMPR].

**Benchmark dose:** 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. bodyweight) when obtained from studies in laboratory animals. The lower 95% confidence limit on the BMD can be determined mathematically to give the BMDL.

**BREAM:** The bystander and resident exposure assessment model. A research project commissioned by Defra.

**Campaign for the farmed environment:** A voluntary campaign with the objective being to retain and exceed the environmental benefits that used to be provided by set-aside.
Carcinogens: the causal agents which induce 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.

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’.

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

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

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.

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).

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

Epigenetics: the study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence

Formulation: The composition of a pesticide product as supplied.

Gametes: eggs or sperm.

Genotoxic: shown to affect DNA, either through a direct reaction with DNA or through an effect on the number or integrity of the chromosomes

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

**Homeostatic regulation:** regulation of the internal environment, tending to maintain a stable, constant condition of properties like temperature or pH.

**In silico:** performed on computer or via computer simulation.

**In-use preparation:** The form in which a pesticide is applied after any dissolution, dilution or mixing of the product as supplied.

**In utero:** in the womb

**In vitro:** Term used to describe effects in biological material outside the living organism (animals, plants, etc)

**In vivo:** Term used to describe effects in living organisms (animal plants etc)

**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.

**Longer term exposure:** Exposure that takes place over the entire spraying period, potentially repeated every year.

**Molecular mass:** The molecular mass of a substance is the mass of one molecule of that 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 the effect is not statistically different from that in the controls

**Non-professional operators:** People who apply plant protection products non-occupationally – for example, in their gardens.

**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:** is 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.

**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.

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

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

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

**pKa**: acid dissociation constant, is 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.

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

**Probabilistic model**: Statistical analysis tool that estimates, on the basis of past (historical) data, the probability of an event occurring again.

**Product**: A pesticide preparation as supplied. It includes not only the active substance(s), but also coformulants such as emulsifiers, solvents and safeners.

**Saliva extraction percentage**: 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 can react to considerably lower concentrations on further exposure (“elicitation”).

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

**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)**: A factor (with units ha/hr x 10-3) 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.

**Topical exposure**: Exposure to the skin
**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.

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

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

**Vapour pressure:** The vapour pressure of a chemical is a measure of its tendency 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 solubility, by formulation, and by weather variables including temperature, wind speed and relative humidity.
ADVISORY COMMITTEE ON PESTICIDES

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

A table comparing the BRAWG report proposals for risk assessment with the draft EFSA guidance.

Secretariat
March 2012
Table comparing EFSA and BRAWG recommendations for bystander and resident risk assessment

BREAM: The bystander and resident exposure assessment model. A research project commissioned by Defra.

<table>
<thead>
<tr>
<th>Definitions</th>
<th>BRAWG</th>
<th>Draft EFSA</th>
</tr>
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<tbody>
<tr>
<td><strong>Bystanders</strong>: 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 take action to avoid or control exposure.</td>
<td>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.</td>
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<tr>
<td><strong>Residents</strong>: persons who live, work or attend school or any 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 take action to avoid or control exposure; and who might be in the location for 24 hours per day.</td>
<td>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.</td>
<td>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</td>
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<tr>
<td></td>
<td>Reduction of pesticide use or risks in specific areas including those used by vulnerable groups.</td>
<td>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 (eg home garden) equipment covering the full range of crops and situations (eg field crops, orchards, vineyards, greenhouses, home gardens).</td>
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<tr>
<td>Coverage</td>
<td>Bystander and resident exposure arising from ground based boom sprayers of low level crops. <em>i.e. reduced coverage compared to EFSA draft guidance.</em></td>
<td></td>
</tr>
</tbody>
</table>
| 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 <11 years, 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 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

<table>
<thead>
<tr>
<th></th>
<th><strong>BRAWG</strong></th>
<th><strong>EFSA (all ‘longer term’ risk assessments)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spray drift</strong></td>
<td>Evaluation for adults and children.</td>
<td>75thile 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). 8m data (x 10 to account for closer proximity to sprayer and multiple passes for dermal exposure – no need for adjustment for inhalational exposure) <strong>1.16ml spray dilution/person Dermal exposure 0.00715ml spray dilution/person inhalational exposure.</strong> Adult values protective for children if corrected for lower bodyweight.</td>
</tr>
<tr>
<td></td>
<td>Acute exposure to spray drift covered by bystander assessment.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeated spray exposures; inhalation and dermal:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider weekly repeated exposures with values from BREAM for 5m downwind from 24m boom sprayer. Use 75th percentile data for spray drift for adult and child resident</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Vapour</strong></td>
<td>Acute exposure to vapour covered by bystander risk assessment.</td>
<td>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 &lt; 0.01 Pa), exposures should be calculated assuming a default concentration in air of 15 µg/m³ 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 &lt;16 year olds, 6 to &lt;11 year olds, 3 to &lt;6 year olds,</td>
</tr>
<tr>
<td></td>
<td>Adult longer term</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24h exposure to 1 or 15µg/m³, or estimate of flux and BREAM air dispersion model, 60kg female, respiring <strong>15.2 m³/day</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Child longer term inhalation: 24h exposure to 1 or 15µg/m³ or estimate of flux and BREAM air dispersion model (as above) 15Kg child, respiring <strong>8.3 m³/day</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Compare to repeat dose AOEL</td>
<td></td>
</tr>
<tr>
<td>Surface deposits</td>
<td>Consider aggregating acute and sub-chronic resident exposure</td>
<td></td>
</tr>
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<td>------------------</td>
<td>-------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Acute:</strong> Children assumed to cover risk for adult. Uses US EPA lawn re-entry model, Calculates dermal exposure using <strong>drift fall out at 2m from BREAM</strong>, 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</td>
<td></td>
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</tr>
<tr>
<td><strong>Adult longer term:</strong> Assume covered by child longer term and bystander entry to treated areas (EuroPOEM worker re-entry model 30 min exposure).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Child longer term</strong> Uses US EPA lawn re-entry model, Calculates dermal exposure using <strong>drift fall out at 5m from BREAM</strong>, turf transferable residue, average transfer co-efficient from grass to skin and duration of contact with</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exposure from surface deposits for children aged less than 1 year should be calculated as:</strong> Dermal exposure + Hand to mouth transfer + Object to mouth transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Where for products applied in liquid sprays, Dermal exposure = 1.8 x Application rate (kg/ha) x Drift percentage x Dermal absorption percentage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand to mouth transfer = 0.095 x Application rate (kg/ha) x Drift percentage x Oral absorption percentage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and Object to mouth transfer = 0.05 x Application rate (kg/ha) x Drift percentage x Oral absorption percentage.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal and oral absorption percentages</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 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.

TOX/2012/09 Annex 2
<table>
<thead>
<tr>
<th>Entry to treated crops</th>
<th>Adult</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>EuroPOEM worker re-entry model with 30 min exposure to reflect walking across a freshly treated field.</td>
<td>Dermal exposure estimated based on worker re-entry model with 15min exposure period per day. Adults and children Exposure should be estimated as the product of the dislodgeable foliar residue</td>
<td></td>
</tr>
</tbody>
</table>
TOX/2012/09 Annex 2

<table>
<thead>
<tr>
<th>Activity</th>
<th>Description</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry onto treated lawns</td>
<td>Covered by surface deposits and entry to treated crops</td>
<td>Calculated as surface deposit exposures with drift percentage assumed 100%. Adults and children</td>
</tr>
<tr>
<td>Eating home grown produce</td>
<td>This may require the development of appropriate tools. Alternatively if estimates of consumer intake was sufficiently low (&lt;10% of the estimated total) it might be considered within the range of uncertainties of other routes and could be ignored.</td>
<td>Specific residues data from spray drift are not available so potential exposure cannot be reliably assessed. If required, further research would generate data</td>
</tr>
<tr>
<td>Local effects (sensitisation and irritation) during and post spraying</td>
<td>Consider dilution/dispersion and classification criteria to understand likelihood of effect. Consider semi quantitative approach as in REACH guidance.</td>
<td></td>
</tr>
<tr>
<td>Scenarios for bystanders</td>
<td>BRAWG</td>
<td>EFSA</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Spray drift</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>Total acute exposure is sum of inhalation and dermal and is compared to an acute AOEL</td>
<td>Dermal and inhalational exposures as residents but using 95ile. Dermal 5.33ml spray dilution/person. Inhalation 0.022ml spray dilution/person</td>
</tr>
<tr>
<td></td>
<td>Dermal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2m down wind, single pass, 24 m boom sprayer total spray cloud (approx. equivalent 3 ml adults and 1 ml children) estimates based on 95 percentile data from BREAM. Evaluation for adults and children., no reduction from clothing, 60Kg adult, default 100% absorption.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhalational</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2m down wind, single pass, 24 m boom sprayer total spray cloud (approx equivalent to 0.002 and 0.0015 ml for adults and children, respectively) estimates based on 95 percentile data. Evaluation for adults and children.</td>
<td></td>
</tr>
<tr>
<td><strong>Vapour</strong></td>
<td>Not separately considered – covered by adult resident assessment</td>
<td>As residents</td>
</tr>
<tr>
<td><strong>Surface deposits</strong></td>
<td>EuroPOEM worker re-entry model with 30 min exposure to reflect walking across a freshly treated field.</td>
<td>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:</td>
</tr>
<tr>
<td></td>
<td>Ingestion: Not separately considered for bystanders but assumes that resident child ingestion exposure is likely to cover this.</td>
<td></td>
</tr>
</tbody>
</table>
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 10m (field crops) 2.9

For children aged 1 to <3 years, dermal exposure should be calculated by replacing the coefficient of 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.

<table>
<thead>
<tr>
<th>Entry to treated crops and lawns</th>
<th>As residents</th>
<th>As residents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local effects (sensitisation and irritation) during and post spraying</td>
<td>Consider dilution/dispersion and classification criteria to understand likelihood of effect. Consider semi quantitative approach as in REACH guidance.</td>
<td>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.</td>
</tr>
<tr>
<td>Other</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>