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Opinion of the Scientific Panel on Plant protection products and their Residues on a request from the Commission on acute dietary intake assessment of pesticide residues in fruit and vegetables

(Question N° EFSA-Q-2006-114)

adopted on 19 April 2007

This opinion supersedes the statement of the PPR Panel adopted on 8 March 2007 on the same subject

SUMMARY OF OPINION

Acute dietary intake is one of the factors considered by Member States, the European Commission and international authorities when setting Maximum Residue Levels (MRLs) for pesticides. The MRL is the maximum concentration of a pesticide residue (expressed as mg/kg) that is legally permitted in or on a food or agricultural commodity or animal feedstuff.

The measure of acute dietary exposure that is used in MRL-setting is the International Estimate of Short Term Intake (IESTI). The IESTI is calculated using one of 4 standard equations, depending on the type of commodity involved. An MRL above the limit of detection is set for a commodity only if its IESTI does not exceed the Acute Reference Dose (ARfD) of the pesticide concerned.

There are discussions at international level about whether to change the way that IESTI equations are calculated. Therefore the European Commission asked the EFSA Scientific Panel on Plant protection products and their Residues (PPR Panel) for an Opinion on how conservative the IESTI equation is, with respect to the percentage of the total European population protected from intakes above the ARfD, and how much this would be altered by changes to the way the IESTI is calculated. However, the Panel is aware that risk managers are also interested in the special case of people who consume a commodity containing residues at the MRL. Therefore the Panel undertook two types of assessment: “total population assessments”, estimating the level of protection for the total population based on the levels of pesticides observed in monitoring programs, and “MRL-level assessments” for the special case of people who consume one commodity containing residues at the MRL and other commodities at monitoring levels.

The Panel estimated acute dietary intakes by probabilistic modelling. This used data on food consumption and body weight from national surveys, and took account of unit-to-unit variability of residues using variability factors. The probabilistic estimates of intakes were higher than measured intakes from a duplicate diet study, suggesting the Panel’s results are conservative (*i.e.* overestimating intakes and underestimating levels of protection). However, this comparison was possible for only 6 pesticides in one country and one age group, and extrapolation to others countries and age groups is uncertain.

It was not possible to conduct probabilistic modelling for the entire population of the EU, or for all pesticides. The Panel conducted total population assessments for a number of scenarios representing different combinations of 13 pesticides, 8 countries and a range of age groups from babies to seniors. For practical reasons, the MRL–level assessments were based on a reduced range of scenarios, representing only two countries (Germany and The Netherlands) and 11 pesticides.

For the total population, the Panel’s estimates suggested that the level of protection (LoP) provided by the IESTI equation as currently used in the EU (including variability factors of 5 & 7) varies quite widely between different countries, age groups and pesticides. For some pesticide/country/age group scenarios the estimated LoP was between 99 and 99.9%, *i.e.*

between 99% and 99.9% of person-days had estimated intakes below the ARfD. None of the estimated LoPs for the total population were below 99%, and for most scenarios they were above 99.9% and often above 99.99%. The estimates are very uncertain but probably conservative, *i.e.* more likely to underestimate than overestimate the true LoPs.

Changing the variability factors of 5 & 7 to 3 would decrease the calculated IESTIs for some commodities. This would result in additional MRLs being set, potentially increasing intakes and decreasing LoPs. Changing the variability factor to 3 increased the number of commodities qualifying for MRLs in 25 of 78 pesticide/country/age group scenarios in the Panel's total population assessments. The resulting reductions in LoPs were: generally much smaller than the existing range of variation in LoPs between the pesticide/country scenarios modelled by the Panel; smaller than the effect on LoPs of reducing the margin between maximum IESTI and the ARfD in the scenarios modelled by the Panel; and for most but not all scenarios, within the range of quantified and unquantified uncertainties affecting the assessment.

Changing the way the variability factor was represented in the probabilistic models used by the Panel (fixed factors of 1, 5 and 7 versus distribution) had little effect on the distribution and uncertainty of estimated intakes for the total population. This implies that estimated intakes and LoPs for the total population were more strongly influenced by other factors (*e.g.* extreme values in the consumption and residue monitoring data).

The Panel's results suggest that the IESTI is a poor indicator of the LoP for the total population (a purpose for which it was not designed), and of the contribution of individual commodities to the aggregate intake of a pesticide. This is because it considers each commodity separately, and does not take account of key factors such as the frequency of consumption and residues.

For consumers of a single commodity at the MRL and others at monitoring levels (MRL-level assessments), the LoP provided by the current IESTI equation again varied widely between different countries and pesticides, and also between commodities. The Panel estimated LoPs for a total of 92 pesticide/country/commodity scenarios relating to The Netherlands and Germany, mainly for young children. Eighty-one of these scenarios would qualify for MRLs with the current IESTI equations. For some of these scenarios, the estimated LoP was between 90 and 99%, but most scenarios were above 99% and many above 99.9%. Again, the estimates are very uncertain but probably conservative, *i.e.* probably underestimate the true LoPs.

The Panel's results suggest that the IESTI is a much better indicator of the LoP for consumers of commodities at the MRL (the purpose for which it was designed) than for the total population. On average, the commodity at the MRL contributed over 90% of the intake in these scenarios.

Changing the variability factor in the IESTI equation from 5 and 7 to 3 increased the number of pesticide/country/commodities qualifying for MRLs from 81 to 86. Because the proportion of scenarios added was small it did not markedly change the overall distribution of LoPs in the MRL-level assessments, although 4 of the 5 added scenarios had estimated LoPs at or below 99%.

Replacing the highest residue (HR) in the IESTI equation with the MRL decreased the number of pesticide/country/commodities qualifying for MRLs from 81 to 73. This had a slightly larger effect on the overall distribution of LoPs for MRL-level assessments than changing the variability factor. Again, the changes occurred at the lower end of the distribution: 7 of the 8 deleted commodities had estimated LoPs around 99%. However, it must be remembered that the estimated LoPs are very uncertain and probably conservative (*i.e.* probably underestimate the true LoPs).

There is a need for risk managers to decide which measure(s) of the level of protection they consider relevant for which purposes (*e.g.* in MRL-setting versus post-authorisation assessment of monitoring data). The Panel's results suggest that the current IESTI equations are better indicators of the LoP for consumers of commodities at the MRL, for which they were designed, than of the LoP for the total population at monitoring levels. If measures of the LoP for the total population are required, then consideration should be given to modifying the IESTI equations or developing alternatives for this purpose. Based on the Panel's experience, this would require substantial research.

The high levels of uncertainty encountered in this Opinion are an inevitable consequence of limitations in the data currently available. Most of the uncertainties could be reduced in the future if desired, by collecting further data (*e.g.* larger monitoring programmes, to provide better estimates of the frequency of high concentrations). Some of the uncertainties could also be reduced, or at least better characterised, by further modelling with existing data. Consideration could also be given to conducting more duplicate diet studies covering a wider range of countries and age groups, to provide a better basis for calibrating intake assessment methods (both deterministic and probabilistic) and for evaluating actual levels of protection.

Key words: Pesticide, MRL, acute dietary intake, IESTI equations, variability factors, Acute Reference Dose, level of protection, probabilistic modelling.

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BACKGROUND[1]

On March 2005 the EFSA PPR Panel gave, at the request of the Commission, an opinion on a variability factor to be used for acute dietary intake assessment of pesticide residues in fruit and vegetables. The opinion made clear that the choice of a variability factor had consequences for the level of protection of European consumers, but that such a choice was in the remit of the risk managers. When discussing the implications of the risk management options given by EFSA in its opinion, Commission and Member States experts recognised that the variability factor was only one of several variables that could influence the level of protection of the IESTI (international estimated short term intake) equation as presented by JMPR (2002).

Other factors are the highest residue (HR), the unit weight (U), the large portion size (LP) and the percentile of consumers associated with this portion size, the body weight (bw) of the consumers. It was also realised that some parameters were crucial for the outcome of the equation, while the influence of others was negligible.

In subsequent discussions the Member States and the Commission agreed that it was better to evaluate the options in relation to the full IESTI equation rather than to look at some factors in isolation.

Therefore the Commission submits a question to EFSA concerning the relative contribution of the variables to the total of the IESTI equation.

The intention is to use the outcome of the opinion for deciding about an IESTI equation to be used for future fixing of MRLs for pesticide residues under Regulation (EC) No 396/2005.

[1] Provided by the European Commission

Terms of reference

- How conservative is the IESTI equation with respect to the percentage of the total European population protected?
- What is the sensitivity - in terms of probability of exceeding the ARfD - to variation and uncertainty in each of the parameters of the IESTI model?
- How does replacing the HR with other estimates of highest residues *e.g.* the MRL (determined either using the EU method –Rber, Rmax-, or an alternative statistical method as the lognormal distribution recently proposed by NAFTA) affect the outcome of the equation?

ASSESSMENT

1 Introduction & approach

The Commission states that it intends to use this opinion to decide about an IESTI equation to be used for future fixing of MRLs (Maximum Residue Limits) under Regulation (EC) No 396/2005 (see Background). This section therefore begins by introducing the IESTI equations and describing how they are used in fixing MRLs. It then proceeds to interpret the questions posed to the Panel and explains the approaches used to address them.

The IESTI equations are used by authorities to make decisions that affect public health. It is therefore important to understand how intakes estimated using the IESTI equations relate to real intakes. The request to the Panel addresses this important but very challenging question. The Panel expected that it would be able to give a clear answer, but discovered that in fact it is not possible to draw firm general conclusions about the performance of the IESTI equations. This is partly because of unavoidable uncertainties caused by limitations of existing data, and partly because real intakes could change in future in ways that would not be reflected by the IESTI equations. However, it is important to give decision-makers the best indication that science can currently provide of how the current procedure performs, and in particular how changes in the inputs (*e.g.* changing the variability factor to 3) might affect it. This requires complex calculations and concepts, which the Panel presents in the Opinion. The presentation is further complicated by the need to consider two different measures for the performance of the IESTI equations (protection of the total population versus protection of those people who consume commodities at the MRL). More detail for specialists is provided in the Appendix. Policy-makers and non-specialists may prefer to concentrate on the conclusions section, which repeats key results and discusses their interpretation.

1.1 THE IESTI EQUATIONS

The procedures for calculating short-term intake using the IESTI equations were originally developed by the FAO/WHO Geneva Consultation in 1997 (Anon., 1998), and refined at the International Conference on Pesticide Residues Variability and Acute Dietary Risk Assessment (Harris *et al*., 1998) and at subsequent meetings of the JMPR (FAO/WHO Joint Meeting on Pesticide Residues). Short term intakes relate to intake over a period of 24 hours, to be compatible with the Acute Reference Dose (ARfD) which also relates to an intake over 24 hours or less.

A key feature of the IESTI equations is that they are calculated for one commodity at a time, and do not estimate combined intake from multiple commodities. The Geneva Consultation justified this by stating that the consumption of two different commodities in large portion weights by an individual consumer in a short period of time is not likely and, furthermore, the presence on those commodities of the same pesticide at its MRLs was considered even less likely (Anon., 1998). It can be inferred from this that the Geneva Consultation considered the IESTI calculation for a single commodity to be sufficiently conservative to provide an appropriate degree of protection for consumers exposed via multiple commodities.

The IESTI equations are presented in detail in the Appendix (Section 8.1.1). Different versions of the equation are used for different types of commodities. An example of an IESTI equation is case 2a. This is used for commodities where the unit weight of individual items is greater than 25g but a large portion contains more than one item. For example, a single apple might weigh 100g but a "high consumer" might eat several apples in one day. For an unprocessed commodity, the equation for case 2a takes the following form:

$$IESTI = \frac{U \times HR \times v \quad + \quad (LP - U) \times HR}{bw}$$

where:

U unit weight of individual items of the commodity, in kg (edible portion only).

HR highest residue in composite sample of edible portion found in supervised trials from which the MRL or STMR was derived, in mg/kg.

v variability factor - the factor applied to the composite residue to approximate the residue level in a high-residue single unit, generally set to default values of 1, 3, 5 or 7 depending on the commodity (see Appendix section 8.1.2). Intended to represent the residue level in the 97.5th percentile unit divided by the mean residue level for the lot.

LP the 97.5th percentile of portion sizes taken by people consuming the commodity, in kg of food per day.

bw mean body weight for the target population subgroup, in kg.

The first part of the equation (before the "+" sign) estimates the intake resulting from a single unit U of the commodity containing high residues (HR x v), and the second part of the equation estimates the intake resulting from the remainder of the large portion (LP-U) assuming that this contains residues at the HR.

It is important to recognise what the IESTI equation does and does not do:

- The IESTI equation provides an estimate of the level of intake (in mg/kg bw), which is intended to be conservative (*i.e.* higher than most actual intakes).
- The IESTI equation does not estimate the proportion of the population experiencing that level of intake. This is an important point in the context of this Opinion, because the Question to the Panel concerns the proportion of population protected. The implications of this are considered in section 1.3.
- The IESTI equation estimates intake from a single commodity, not multiple commodities. There is an implied assumption that the calculation is conservative enough to cover contributions from other commodities.

1.2 HOW THE IESTI EQUATIONS ARE USED

The original purpose of the IESTI equations was for use in MRL-setting (Anon., 1998). The MRL is the maximum concentration of a pesticide residue (expressed as mg/kg) that is legally permitted in or on a food or agricultural commodity or animal feedstuff. Consignments of individual commodities that are found to contain residues above the MRL may be removed from the market.

MRL-setting is done for one commodity and pesticide at a time and involves several steps:

1. The mode of use of the pesticide that gives rise to the highest residues in supervised trials is identified: this is referred to as the "critical GAP" (Good Agricultural Practice).
2. Residue data from supervised trials for the critical GAP are used to derive a proposed MRL. The MRL is usually chosen from a fixed scale of values and must equal or exceed the highest residue (HR) from the supervised trials.
3. The short-term dietary intake is estimated for the critical GAP, using the relevant IESTI equation.
4. The IESTI is compared to the Acute Reference Dose (ARfD) for the pesticide.
   - If the IESTI is less than the ARfD, the risk is considered acceptable and the proposed MRL is confirmed.
   - If the IESTI is greater than the ARfD, the risk is considered unacceptable and the proposed MRL is rejected: as a consequence, the pesticide use that gave rise to the critical GAP will not be permitted.
5. In cases where a proposed MRL is rejected, consideration may be given to setting an MRL for other uses of the pesticide on the same commodity, if they give rise to lower residues (*e.g.* due to lower application rates) and hence to an IESTI below the ARfD.

This procedure is conducted at several different levels: at international level for setting of MRLs through JMPR and CCPR (Codex Committee on Pesticide Residues), at EU level for setting MRLs within the EU and for deciding on the EU position for CCPR meetings, and by Member States if they wish to propose new or modified EU MRLs[2].

It is important to note that, although MRL-setting is conducted for each commodity separately, the overall effect of the procedure is to determine the number and nature of internationally-traded commodities on which use of each pesticide will be permitted.

Some countries use the IESTI equation for an additional (though related) purpose: to assess the safety of residues found in monitoring and enforcement programs. In these cases the IESTI equations might be calculated replacing the HR with residue values found in consignments of commodities monitored in international trade, or with residue values measured in samples taken from the market place. The JMPR has recently stated that the adequacy of the IESTI equation for this purpose needs to be discussed further (JMPR, 2006). This use of the IESTI equation is outside the remit set by the European Commission for this opinion, which refers specifically to MRL setting.

1.3 Interpretation of the terms of reference, and approaches for fulfilling them

1.3.1 Percentage of the total European population protected

The first bullet of the Terms of Reference requests that the conservatism of the IESTI equation should be assessed in terms of the percentage of the total European population that is "protected". The second bullet implies that the criterion for protection is not exceeding the ARfD, so the measure requested is the proportion of the population whose intakes are at or below the ARfD. This is consistent with Article 10 of Regulation (EC) No 396/2005 which states that, when assessing applications concerning MRLs, The Authority (EFSA) should assess the risks of the ARfD being exceeded.

[2] This paragraph describes the situation that will apply when Regulation (EC) No. 396/2005 comes into force.

It is not feasible to carry out evaluations for the whole of the European population, as the necessary data on consumption patterns are not available for all Member States. Therefore, the Panel assessed intake for countries for which data were available. To provide a comprehensive evaluation of the IESTI equation, it would also be necessary to evaluate the proportion of the population that is protected for all pesticides. This was also not feasible within the time and resources available, so the Panel attempted to select a representative subset of pesticides for analysis. The extent to which the Panel's results can be extrapolated to other countries and other pesticides is discussed in Section 7.

Food containing residues at the level of the adopted Codex MRL must be safe for consumers (CCPR, 2005). Consistent with this, evaluation of a proposed MRL is generally focussed on the commodity containing residues at the level of the MRL. However, the Question to the Panel refers specifically to the "total population". This implies that the assessment of intake for this Opinion should include the full range of variation in consumption (including both non-consumers and high consumers) and the full range of residues (not just at the MRL). Since there is interest in both types of assessment, the Panel decided to undertake both. This section (1.3.1) considers intake assessment for the total population, while the following section considers assessment of intake at the MRL.

When assessing whether a person is protected from exceeding the ARfD for a particular pesticide, it is logical to consider their overall intake of the pesticide, which may include contributions from more than one commodity. This is implied by Article 10 of Regulation (EC) No 396/2005, which requires an assessment of the risk of the ARfD being exceeded "as a result of the modification of the MRL", because this risk must depend in part on the level of any pre-existing intake of residues on other commodities[3].

The Panel concluded that the first bullet of the Terms of Reference requires assessing the distribution of intake in the total population to residues from all commodities, and using this to estimate the percentage of the population that will experience acute intakes at or below the ARfD (*i.e.* the proportion of the total population that is protected).

The PPR Panel was able to quantify distributions of intakes in two different ways:

- with data from a duplicate diet study (Boon *et al*., 2003), in which intake was measured directly for a group of consumers by taking duplicate portions of each meal they eat and analyzing these samples for pesticide residues; and
- with estimates from probabilistic modelling, where data on food consumption, pesticide residues in food and body weight are used to estimate the distribution of intake within the population.

Although duplicate diet studies may be expected to provide more accurate estimates of intake, they were available to the Panel for only 6 pesticides, in one country and one age group. Furthermore, the limited size of these studies (ca. 250 infants) means that they provide only a limited picture of the distribution of intake (see Section 6 and Figure 31). Therefore most of the results in the Opinion had to be produced by probabilistic modelling, in order to cover a reasonable range of pesticides, countries and age groups. In order to interpret the results, it is essential to evaluate the reliability and realism of modelled intakes. Therefore Section 6 assesses the degree of agreement between modelled intakes and direct measurements of

[3] The Regulation also states that cumulative and synergistic effects (resulting from combined intake of different pesticides) should be considered, when methods to assess them are available. Such effects are not considered here because methods for their assessment are currently the subject of a self-tasking question by the PPR Panel.

intake from the duplicate diet study. In addition, uncertainties associated with the modelled intakes are discussed in Section 7.

1.3.2 Intake of residues at the MRL

As stated above, intake of the total population is not the only relevant consideration in relation to MRL-setting. As foods containing residues at the level of the MRL are permitted in international trade, such foods must be "safe" for consumers (CCPR, 2005). On this basis, a discussion paper (CX/PR 05/37/4) presented to the 2005 meeting of the CCPR suggested that intake assessment in MRL-setting for a particular commodity should include only persons who consume that commodity, and should consider residues at the level of the MRL. Such an assessment is not explicitly requested in the Question to the Panel. However, in recognition that this perspective on intake is also important, the PPR Panel conducted probabilistic assessments of intake at the MRL for consumers only, as well those described in the preceding section.

When assessing the intake of persons consuming one commodity containing residues at the MRL, it is again logical to consider contributions from other commodities in addition to the one containing residues at the level of the MRL, because they contribute to the risk of exceeding the ARfD. However, in such an assessment, residues in the additional commodities should be allowed to vary over the range found in the market place, as indicated by monitoring data.

1.3.3 Magnitude by which the ARfD is exceeded

Exceeding the ARfD does not necessarily mean that toxic effects will occur, because of the safety factors that are incorporated in the ARfD. Therefore, where possible the Panel examined the magnitude by which the ARfD is exceeded, as well as the proportion of the population who do so.

1.3.4 Effect of changing IESTI inputs

The Background for the Opinion together with the second and third bullets of the Terms of Reference make clear that the Commission's primary interest is in the choice of inputs for the IESTI equation, especially the values used for the variability factor and the high residue HR. This topic has received considerable attention in recent years, including a previous Opinion of the PPR Panel (EFSA, 2005) and publications in the scientific literature (*e.g.* Hamilton *et al*., 2004; Ambrus, 2006; Rawn *et al*., 2006), and at an international level the JMPR has decided to change the variability factors for some commodities from 5 and 7 to 3. Therefore the Panel's analysis focused on evaluating changes to the inputs of the IESTI equations, not changes to their structure (the potential need for structural change is briefly considered in the Conclusion of the Opinion).

At first sight, it might be thought that the effects of changing the inputs to the IESTI equations could be evaluated through a conventional sensitivity analysis, where each input is varied over some reasonable range and its impact on the output is quantified. However, this would be insufficient in this case, because the Question to the Panel concerns not the output of the IESTI equations per se (estimates of intake), but in the consequences for the protection of consumers (percentage of people exceeding the ARfD). This is explicitly stated in the second bullet of the Terms of Reference.

Changes to the IESTI equations only affect levels of protection for a pesticide if they result in changes to the list of uses for which that pesticide is authorised. For example, changing the variability factor from the current default values of 5 or 7 to 3 would result in more uses being permitted to continue when MRLs are reviewed. Therefore the Panel estimated the effect of changes to the IESTI equations for each pesticide by the following procedure:

- Recalculate the IESTIs for all commodities with the alternative IESTI inputs (*e.g.* variability factor of 3).

- Re-run the probabilistic models, including only those commodities for which the new IESTI does not exceed the ARfD for the corresponding pesticide.
- Compare the resulting levels of protection with those obtained using the current IESTI inputs (including variability factors of 5 and 7).

Unfortunately, this procedure requires dozens of new probabilistic model runs for each change in the IESTI inputs. This severely limited the range of changes that the Panel was able to examine in the time available. The Panel expended significant effort exploring ways of analysing the effect of changing IESTI inputs without rerunning the probabilistic models, but did not find any satisfactory alternative.

1.3.5 Limits to the predictability of the general performance of the IESTI equations

The Background to the question states that the Commission intends to use this Opinion to decide about an IESTI equation to be used for future fixing of MRLs. This implies that the interest is in how use of the IESTI equation performs as a procedure over many pesticides, and over a number of years. Three important factors limit the reliability with which general performance of the procedure can be assessed.

1. <u>The sample of pesticides analysed by the Panel, may not be representative of those that will be encountered in the future.</u> Changes in performance could be caused by differences in the number of commodities pesticides are used on, the manner in which they are applied, the behaviour of their residues (*e.g.* variation in persistence between pesticides, or annual variation in weather and pest levels), and the resulting intakes.
2. <u>The IESTI equation takes no account of two key drivers of overall intake: the number of commodities in which the pesticide occurs (more commodities = more intake), and the frequency of consumption of each commodity.</u> This is because historically the intent was to obtain a conservative estimate of the <u>level</u> of intake that might occur amongst consumers of a single commodity, and it was assumed that the contribution of other commodities would be small (see Section 1.1). However, the Terms of Reference and Regulation (EC) No 396/2005 show that there is also interest in the <u>proportion</u> of intakes that exceed the ARfD, which will increase with both the number of commodities affected and the frequency of consumption. These two variables change from pesticide to pesticide, and they will also change over time, and they will alter intake, but their effect cannot be reflected by the IESTI equations.
3. <u>Changing the IESTI equation is itself likely to change the pattern of pesticide use and intake.</u> For example, as already mentioned, if a change in the method of calculation causes the IESTI for a commodity to exceed the ARfD, the GAP for that commodity might be modified in various ways to gain authorisation, and it is difficult to predict how this would alter intake and hence the proportion of people protected.

These three factors limit the Panel's ability to predict general performance of the IESTI equation, and need to be considered carefully when interpreting the Panel's findings (see Sections 7 and 8).

Note that the second limitation mentioned above is less severe for the assessment considering intake at the MRL, because in this case the analysis is limited to consumers of the commodity which is at the MRL, and the contribution to intake of other commodities is likely to be smaller. However, the first and third limitations still apply.

1.3.6 Contribution of different commodities to aggregate intake

As noted in the preceding sections, the proportion of intakes exceeding the ARfD for a particular pesticide will accumulate as the number of commodities is found in increases, so aggregate intake is of interest to risk managers. Furthermore, while it is true that it will be very rare that a consumer eats large portions of different commodities on the same day, both containing residues of the same pesticide at the MRLs, less rare events may contribute significantly to increasing intake. For example, a consumer might eat a large portion of one commodity at the MRL, which may result in an intake just below the ARfD, and on the same day a medium-sized portion of another commodity at 10% of the MRL, which might increase intake enough to result in exceedance of the ARfD.

For these reasons, the Panel believes that a more quantitative examination of the contribution of multiple commodities to intake would be useful. However, as this is not a primary focus of the question and time was limited, the Panel decided to carry out only a limited analysis of this issue (see Section 5).

2 Selection of countries and pesticides considered in the opinion

2.1 SELECTION OF PESTICIDES

The number of pesticides that could be addressed in this opinion was restricted by the time available to do the work. The following selection criteria were applied:

- The compound is an EAS (existing active substance)
- The substance is already on Annex I of Directive 91/414/EEC or in SANCO doc 3010
- The compound has an ARfD
- The compound has at least one notified use evaluated in the DAR (Draft Assessment Report) that is relevant to consumer intake and that generates residues above the LOQ
- Only List[4] 2 compounds were selected, since for List 1 compounds the evaluation was done long ago and List 3 and 4 evaluations are not yet completed.

In addition, carbendazim was selected because one of the available models is targeted to this compound, and thiacloprid was selected because it is an example of a new compound with already a wide use. This resulted in selection of 13 pesticides, as listed in Table 1.

Other factors that were considered by the Panel in making its selection were:

- Compound is used on a broad range of commodities
- Include a range of categories (fungicide, insecticide, herbicide)
- Include a range of compound classes (*e.g.* OP ester, thiol reagent)

Factors that may have been important but that were not systematically checked:

- Cover commodities important in EU diets (apple, potato, orange, ….)
- Cover commodities important in trade
- Include example(s) of post-harvest use.

[4] The European Community has prioritised and timetables reviews of exisiting active substances under Directive 91/414/EEC allotting individual compounds to 4 lists, see Regulations No. (EEC) 3600/92, (EC) 933/94, (EC) 451/2000, (EC) 703/2001 & (EC) 1112/2002.

Table 1: Pesticides selected by applying the criteria described in the text.

	Compound	Category	Class	Mechanism of pesticidal action
1	Captan	fungicide	phthalimide	Non-specific thiol reactant
2	Carbendazim	fungicide	benzimidazole	Inhibits beta-tubulin synthesis
3	Dimethoate	Insecticide, acaricide	organophosphorus	Cholinesterase inhibitor
4	Dimethomorph	fungicide	cinnamic acid	Inhibits the formation of the oomycete fungal cell wall
5	Folpet[5]	fungicide	phthalimide	Non-specific thiol reactant
6	Haloxyfop	herbicide	aryloxyphenoxypro-pionate	Fatty acid synthesis inhibitor
7	Metconazole	fungicide	triazole	Steroid demethylation (ergosterol biosynthesis) inhibitor
8	Methomyl	Insecticide, acaricide	carbamate	Cholinesterase inhibitor
9	Phosmet	Insecticide, acaricide	organophosphorus	Cholinesterase inhibitor
10	Pirimiphos-methyl	Insecticide, acaricide	organophosphorus	Cholinesterase inhibitor
11	Propamocarb	fungicide	carbamate (but not a methyl-carbamate)	Multi-site inhibitor
12	Thiacloprid	insecticide	neonicotinoid	Agonist of the nicotinic acetylcholine receptor
13	Tolylfluanid	fungicide	sulphamide	Non-specific thiol reactant

In addition, six compounds were included for which direct measurements of intake are available, from the duplicate diet study of Boon *et al*., (2003). These are listed in Table 2.

Table 2: Pesticides for which duplicate diet study data were available.

	Compound	Category	Class	Mechanism of pesticidal action
1	Chlorfenvinphos	Insecticide, acaricide	organophosphorus	Cholinesterase inhibitor
2	Chlorpyrifos	Insecticide	organophosphorus	Cholinesterase inhibitor
3	Iprodione	fungicide	dicarboximide	Inhibits germination of spores and growth of fungal mycelium
4	Methamidophos	Insecticide, acaricide	organophosphorus	Cholinesterase inhibitor
5	Pirimicarb	Insecticide	carbamate	Cholinesterase inhibitor
6	Pirimiphos-methyl	Insecticide, acaricide	organophosphorus	Cholinesterase inhibitor

The PPR Panel referred the selection of pesticides in Tables 1 and 2 to all Member States at the meeting of the Standing Committee on the Food Chain and Animal Health-Residues on 7-8 December 2006 for comments. No suggestions for addition or deletion were received, and therefore the Panel proceeded with this selection.

The PPR Panel recognised that 9 out of the 19 compounds in the two lists were cholinesterase inhibitors. This was necessary to meet as many of the criteria for selection as possible, but

[5] Residue definition for captan: captan + folpet or captan alone; residue definition for folpet: captan + folper or folpet alone.

reinforces the need for care when considering the implications of the Panel's results for pesticides in general.

2.2 SELECTION OF COUNTRIES AND AGE GROUPS

Although the PPR Panel realised that it would be preferable to include in the analysis a representative selection of countries from the different European regions (North, South, East, West), and a range of different age groups, the PPR Panel was restricted by the availability of necessary data on consumption and residues, and by limitations of time.

The countries and age groups for which analyses were conducted are listed in Table 3. Data used in IESTI calculations and probabilistic modelling for each country are summarised in the Appendix to the Opinion. The selected countries cover 3 of the 4 regional diets within Europe, as defined by the WHO GEMS cluster diets (WHO, 2005). Specifically, they include representatives of GEMS diets F (Scandanavian), E (central European) and B (Mediterranean) but not D, which includes 2 EU Member States (Bulgaria and Romania).

Table 3: Countries and age groups for which analyses are presented in this Opinion, together with the country abbreviations used in the remainder of this Opinion.

Country		Group	Age (Years)	Pesticides[1]
Czech Republic	CZ	Children	4-9	cap, dim[3], met[3], tol
Czech Republic	CZ	Over 10 years	10-90	cap, dim[3], met[3], tol
Denmark	DK	Children	4-6	cap, dim[3], met[3], tol
Denmark	DK	Adults	18-75	cap, dim[3], met[3], tol
France	FR	3-6 years	3-6	cap, car, dim[3], dio, met, tol
France	FR	Over 7 years	7-92	cap, car, dim[3], dio, met, tol
Germany	DE	Children	2-<5	cap, car, dim, fol, hal, met, mtc, pho. pir, pro, thi, tol
Ireland	IE	Children	5-12	cap, car, dio, ipr, pho, pim, pir, prc, tol
Italy	IT	Children	1-17	cap, dim, met, tol[3]
Italy	IT	Adults	18-64	cap, dim, met, tol[3]
Sweden	SE	Children	3-13	cap, dim[3], met, tol
Sweden	SE	Adults	17-79	cap, dim[3], met, tol
The Netherlands	NL	Babies	0.6-1	cap, car, clf[2], clp[2], dim, dio, ipr[2], fol, hal, met, mtc, mth[2], pho, pim[2], pir, pro, thi, tol
The Netherlands	NL	Children	1-6	cap, car, dim, dio, fol, hal, met, mtc, pho, pir, pro, thi, tol
The Netherlands	NL	All ages	1-97	cap, car, dim, dio, fol, hal, met, mtc, pho, pir, pro, thi, tol
United Kingdom	UK	Toddler	1.5-4.5	car[4]

[1] cap=captan, car=carbendazim, clf=chlorfenvinphos, clp=chlorpyrifos, dim=dimethomorph, dio=dimethoate, ipr=iprodione, fol=folpet, hal=haloxyfop, met=methomyl, mtc=metconazole, mth=methamidophos, pho=phosmet,, pim=pirimicarb, pir=pirimiphos-methyl, prc=procymidone, pro=propamocarb, thi=thiacloprid,, tol=tolylfluanid
[2] pesticides only considered in the duplicate diet study
[3] only using field trial data (monitoring data not available)
[4] only considered in the model comparison study and the uncertainty analysis.

3 What is the current level of protection (LoP)?

This section addresses the first bullet of the Terms of Reference: how conservative is the IESTI equation with respect to the percentage of the total European population protected? As noted in Section 1, the second bullet of the Terms of Reference implies that the level of protection (LoP) should be evaluated in terms of the proportion of the population whose acute dietary intakes are at or below the ARfD. This requires estimation of the distribution of intakes in the population, so that the proportion at or below the ARfD can be determined. The result represents the level of protection achieved for the regulatory conditions under which the distributions of intakes occurred. Thus the performance of the IESTI equations is assessed not directly, but through their impact via MRL-setting on the distribution of intakes.

As explained in Section 1, the Panel estimated the distribution of intakes in the population primarily by using probabilistic modelling. This was repeated for different pesticides, age groups and countries, to provide as broad a picture as possible given the time and data available.

The basic approach for the probabilistic models used in the Opinion is described in Box 1. More details are given in the Appendix (Section 8.8) [6].

Note that the models used for this Opinion estimate the distribution of intakes in terms of "person-days", combining variation between people and over time in a single measure. This is currently the most common approach for probabilistic modelling of dietary intake and is used as standard by the CREMe and MCRA models (see below).

<u>Thus the primary measure of level of protection (LoP) used in this Opinion is the percentage of person-days with intakes at or below the Acute Reference Dose.</u>

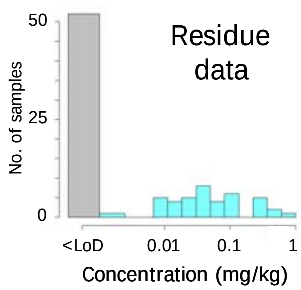
[6] A more detailed introduction to probabilistic modelling of dietary intakes may be found in documents provided to Codex by the US Environmental Protection Agency (documents pr0203ae.pdf and pr0203be.pdf, available on the internet at ftp://ftp.fao.org/codex/ccpr34/).

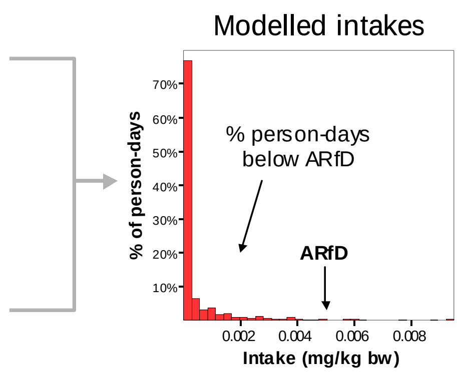
Box 1: Introduction to probabilistic modelling approach used in the Opinion.

Estimating intake from one commodity for one person on one day requires multiplying the amount of commodity they consume by the concentration of pesticide it contains, and then dividing by body weight. However, risk managers need to know how often intakes exceed the ARfD, when considered for multiple persons and multiple days. The probabilistic approach estimates this by taking consumption and body weights for multiple persons and multiple days and combining it with different concentrations, selected at random. This process is illustrated diagrammatically below.

Dietary survey data

Person no.	body wt (kg)	day	Consumption (g)
01	65	1	210
01	65	2	80
02	72	1	25
02	72	2	190
Etc.			





Consumption and body weight data are derived from national dietary surveys, and the concentrations are derived from monitoring or field trial data.

In more detail, the basic procedure is as follows:

1. Select one "person-day" record from the dietary survey, comprising consumption and body weight.
2. Sample a single concentration at random from a distribution estimated from the residue data.
3. Calculate the modelled intake for this person-day by multiplying consumption with concentration and dividing by body weight.
4. Repeat steps 1-3 for a large number of person-days, calculating a modelled intake for each.
5. Determine the percentage of modelled intakes for all the person-days that are below the ARfD for the pesticide. This is the measure of level of protection used by the Panel for this Opinion. The modelled intakes can also be presented as a histogram (as above) or in other graphical formats (*e.g.* Figure 1, see later).

In practice, additional steps are needed, *e.g.* to take account of multiple commodities. More details are given in following sections, and at more length in the Appendix (Section 8.8).

The results in Sections 3-5 were generated by 3 different probabilistic models: one for Ireland (CREMe), one for Germany (Uni-HB) and one for the other countries (MCRA). This was necessary because consumption data for the countries considered was not all available within one model.

All three models modelled variability in consumption using dietary surveys, which are summarised in the Appendix (Section 8.7). Each survey provided data on a number of individuals (range 341-6250) over a number of days (2-7)[7]. CREMe and MCRA were developed previously (McNamara *et al*., 2003, van der Voet *et al*., 1999, de Boer and van der Voet, 2006), but Uni-HB was developed specifically for use in this Opinion. Details of the three models are described in the Appendix (Section 8.8). The performance of the three models is compared using a common dataset for one country (UK) in Section 7.

The following sub-sections present results from applying the above approach in different ways:

- Section 3.1 estimates the level of protection for the total population, in 4 ways:
    - Modelling in Section 3.1.1 used concentration data from monitoring and included all the commodities on which each pesticide was found.
    - Modelling in Section 3.1.2 used supervised field trials for commodities where data were available, and monitoring data for other commodities.
    - Modelling in Section 3.1.3 used concentration data from monitoring, but excluded those commodities for which the IESTI exceeds the ARfD.
    - Section 3.1.4 models how the LoP would change in situations where the highest IESTI is closer to the ARfD.
- Section 3.2 estimates the level of protection for people consuming one commodity at the MRL and other commodities at monitoring levels.

The rationale for each approach, and how it relates to the Question put to the Panel, are explained at the beginning of each sub-section.

It is important to note that monitoring data and field trials have significant limitations as indicators of concentrations in the market place. No country surveys all commodities and some countries survey only a few, which might cause monitoring data to under-estimate the concentrations actually occurring. This might lead to under-estimation of intakes, but other factors act in the opposite direction and tend towards over-estimation (*e.g.* some monitoring is deliberately targeted on situations where unusually high residues are expected, and monitoring data do not reflect the effects of processing, which may decrease residues). It is uncertain whether, overall, modelling based on monitoring data is more likely to under- or over-estimate intakes. Modelled intakes for 6 pesticides were higher than measured intakes from duplicate diet studies with Dutch babies, but it is uncertain whether this would apply generally to other age groups, pesticides and countries (see Section 6).

Modelling based on field trial data is likely to over-estimate intakes, because field trial conditions are supposed to tend towards a worst case, and because it was assumed that these concentrations occur in all relevant commodity lots in the market place (*i.e.* 100% of the relevant crops are treated: an extreme worst case).

The implications of these and other uncertainties for interpretation of the Panel's findings are discussed in Section 7.3.

[7] An exception to this is the consumption data for the duplicate diet study used in Section 6, which comprised data for a single day.

3.1 LEVEL OF PROTECTION FOR WHOLE POPULATION

3.1.1 Percent exceedance of ARfD based on monitoring data, including all commodities

In this section, the concentration data used in the probabilistic models are taken from monitoring studies (these data are summarised in the Appendix, Section 8.5). All of the commodities in which the pesticide has been found are included in the analysis.

The most recent monitoring data that were available are from around 2003. However, at that time, many pesticides had not yet been evaluated with the IESTI equation, because acute intake assessment was only just starting to be used within MRL-setting (previously MRL-setting had considered only chronic intake, Anon., 1998). Therefore, <u>the results in this section should be interpreted as estimating the level of protection that existed during the period up to about 2003, prior to full introduction of the IESTI equations in MRL-setting</u>.

This means that the <u>results in this section do not reflect the level of protection provided by the IESTI equations when fully introduced into MRL-setting</u>: this is addressed in the section 3.1.3, where commodities with IESTI values above the ARfD were omitted[8].

Note that only those commodities for which monitoring data were available were included in modelling. As already stated, due to the influence of other factors, it is uncertain whether this will cause under-estimation of intakes.

Note also that the results reflect the levels of usage (proportion of crop treated) of the period when the monitoring data were collected, which may since have changed for a number of reasons (*e.g.* weather, pest/disease pressure, introduction/withdrawal of alternative products, changes in farmer purchasing habits).

Monitoring data comprise measurements of pesticide concentration in pooled samples of commodity (*e.g.* 10 apples taken from a single lot in the marketplace and homogenised together before analysis). The Panel's analyses with monitoring data (here and subsequently) included the following assumptions:

- Unit-to-unit variability within commodity lots (*e.g.* between individual apples) was modelled using fixed variability factors of 1, 3, 5 and 6.83 according to the commodity (as in the current use of the IESTI equation, but replacing 7 with 6.83[9]). Variability of this magnitude is reported in at least some market samples (EFSA, 2005). Applying it to every lot probably over-estimates the frequency of higher concentrations. Limited modelling with an alternative assumption (a distribution of variability factors derived from EFSA, 2005) indicated that this had little impact on intakes modelled with monitoring data (Sections 7.1 and 8.8.5).

[8] Although the results in Section 3.1.1 do not address the Question to the Panel (because they do not reflect the full effect of the IESTI equations), the Panel decided to include them because (a) it anticipated that some readers would wish to see estimates of the full intake implied by the monitoring data, and (b) they contribute to developing a picture of the effect of introducing the IESTI equations.

[9] Unit-to-unit variability in positive samples was assumed to follow a lognormal distribution with mean equal to the batch mean and standard deviation estimated using the relevant variability factor. A variability factor of 6.83 rather than 7 was used for commodities with unit weights between 25g and 250g, because 6.83 is the largest variability factor that is compatible with a lognormal distribution. Further details are given in the Appendix (Section 8.8, probabilistic modelling).

- Measurements that were reported as being unquantified were assumed to be zero[10]. This will underestimate a proportion of the smaller concentrations actually occurring. (A more refined treatment of non-detects is explored for one commodity in Section 7.1.)

Uncertainties concerning these and other aspects of the analysis are discussed further in Section 7.3, where their combined influence on the assessment outcome is evaluated.

A separate modelling run was performed for each combination of pesticide, country and age group. Figure 1(a) and (b) shows an example of the results, for intake of The Netherlands total population (age range 1-97) to the pesticide captan. Each graph contains four things:

- A dotted curve showing the distribution of estimated intakes. The distribution is plotted in cumulative form, so that the vertical axis shows the percentage of intakes that are equal or below any given point on the horizontal axis[11]. This is intended to make it easier to read off the key results needed for the opinion, *e.g.* the percentage of intakes equal or below the ARfD.
- A solid vertical line marking the position on the horizontal axis of the ARfD for captan (0.1 mg/kg bw/day). Note that the horizontal axis is plotted on a logarithmic scale.
- A horizontal arrow showing how to find the level of protection. Find the place where the intake distribution (dotted curve) crosses the ARfD line, and follow the arrow to the vertical axis to read off the proportion of intakes equal or below this level. In Figure 1(a), the arrow is very close to 100% on the vertical axis. Figure 1(b) shows exactly the same results with the vertical axis replotted on a modified logarithmic scale, to allow finer discrimination of the high percentiles. The arrow in Figure 1(b) shows that, in this example, between 99 and 99.9% of person-days are at or below the ARfD. As the ARfD is generally in the upper part of the intake distribution, logarithmic axes will be used in many of the graphs in this opinion[12].
- A set of broken vertical lines showing the positions on the horizontal axis of the IESTIs for each of the commodities for which the inputs for the IESTI equation were available[13]. In this case, three commodities (pears, apples and peaches) have IESTIs exceeding the ARfD. Therefore, one would expect that, when captan is re-evaluated using the IESTI equation, MRLs would not be set for these commodities. This might lead to use of captan on these commodities being completely withdrawn: the consequence of this for intake is shown later in Section 3.1.3.

[10] An exception is the German residue data which were only available in summary form (number of analyses, some percentiles, maximum, number of non-detects and number of unquantified detects). Non-detects were set to zero, the number of unquantified detects was used together with the percentiles to estimate a parametric distribution of pesticide concentrations in pooled samples.

[11] The cumulative distribution (as in Figure 1) is an alternative way of plotting the same data that could shown in the more familiar format of a histogram (*e.g.* the histogram of intakes in Box 1). Whereas each bar in a histogram shows the frequency of intakes within the range covered by that bar, each point on the cumulative distribution curve shows the proportion of intakes that are below or equal to the corresponding level on the horizontal axis.

[12] As a consequence of this scaling, estimates of the LoP in this Opinion are generally (and arbitrarily) expressed in relation to the values 90%, 99%, 99.9% and 99.99%.

[13] Note that monitoring data was not necessarily available for all of the commodities for which an IESTI could be calculated, although generally monitoring would be available for the major commodities.

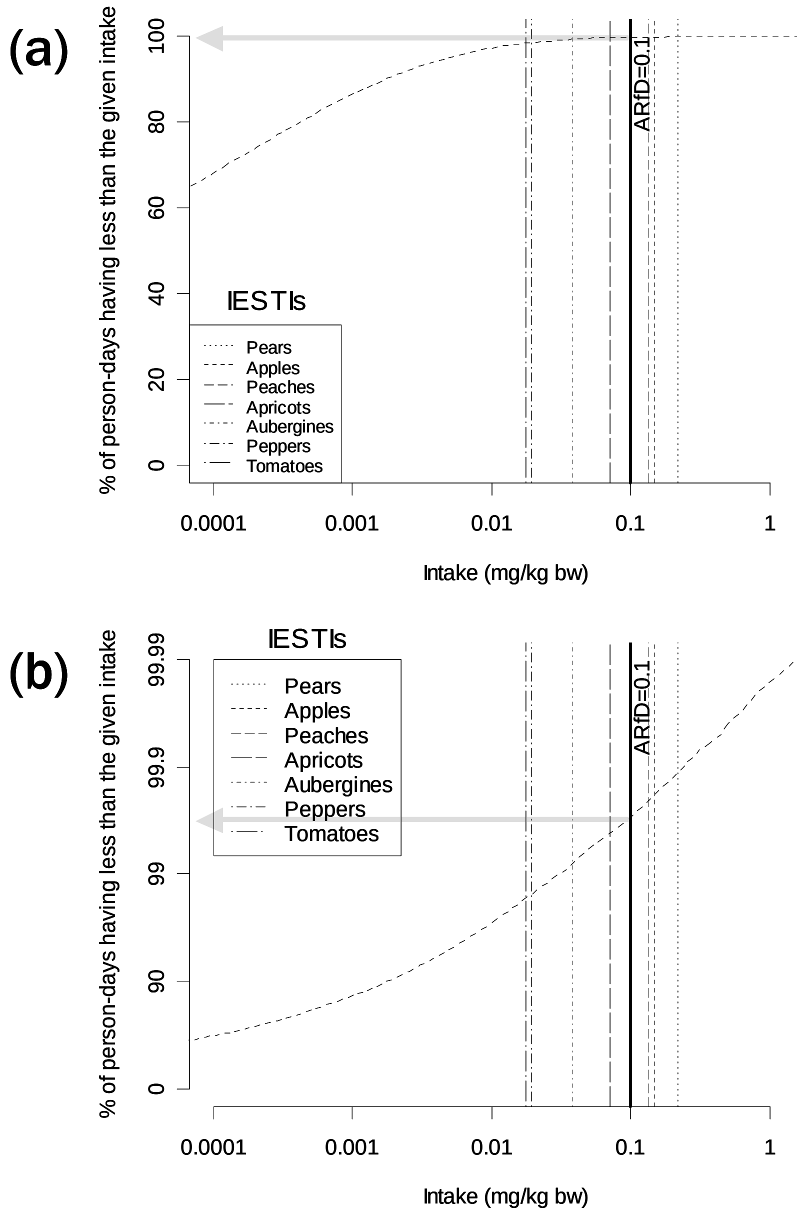


Figure 1 (a): Example of results for a single pesticide, country and age group (captan, The Netherlands, total population). Dotted curve shows distribution of intake estimated by probabilistic modelling, solid vertical line shows Acute Reference Dose (ARfD), broken vertical lines show captan IESTIs for various commodities (listed in descending order in the legend). The horizontal gray arrow illustrates how to read off the percentage of person-days with intakes at or below the ARfD. (b): The same results, replotted with the vertical axis on a modified logarithmic scale[14] to allow finer discrimination of high percentiles.

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[14] Normally, percentages plotted on a logarithmic scale would have tick marks at 0.01, 0.1, 1, 10, 100%, but this would not achieve the desired effect of increasing discrimination at percentages close to 100%. Therefore the Panel used a modified scale in which each percentage is subtracted from 100 before taking

The Panel wishes to emphasise that readers should interpret all the results with caution. The intake distribution shown in Figure 1 is an estimate of intake, not a measurement. The model is restricted to commodities included in The Netherlands' monitoring program, whereas in reality some other commodities may contain captan. Despite this, comparison with results from duplicate diet studies suggests that probabilistic models using monitoring data may over-estimate actual intakes, although this is not certain (Section 6). A summary of uncertainties affecting the calculations and an evaluation of their overall impact on the Panel's findings are presented in Section 7.3.

Figure 2 shows results for all the countries and age groups modelled for captan. There are 15 curves, each representing the estimated intake distribution for a different combination of country and age group, as indicated in the legend on the figure. The curves cross the ARfD at different heights: by reading across from these crossing points to the vertical axis it can be seen that the estimated percentage of person-days at or below the ARfD varies between about 99% (for the lowest curve, baby age group in The Netherlands) to well above 99.99% (top curve, Ireland 5-12 age group).

It must be remembered that the modelling results are influenced by the extent of monitoring programs in different countries. Captan intakes appear higher for The Netherlands than other countries in Figure 2, but this is due at least partly to the wider range of commodities which are monitored in that country. Another factor which may cause differences between estimated intakes for different countries is the completeness of food composition tables for each country: if they do not identify all of the prepared foods that contain each commodity, intake of the pesticide may be under-estimated. Differences in residues and intakes could also occur due to variation in the number of commodities a pesticide is authorised for in different countries.

One can get an impression of the way the level of protection for captan varies between countries and age groups by looking at the range of points where the curves cross the ARfD line in Figure 2. Another way of summarizing the variation in levels of protection is shown in Figure 3. This was produced by reading of the percentage of person-days at or below the ARfD for each country/age group curve in Figure 2, and plotting them as a distribution in Figure 3. This distribution is plotted in complementary cumulative[15] form, so that one can read off the vertical axis the proportion of scenarios (country/age combinations) for which a given level of protection is achieved or exceeded. As an example, the arrow in Figure 3 shows that 99.9% or more of person-days are protected in about 0.7 (70%) of the captan scenarios that were modelled.

logarithms, so that the tick marks appear at 99.99, 99.9, 99, 90 and 0% and maximum discrimination occurs close to 100%. The value 100% cannot appear on this scale because the log of zero is minus infinity.

[15] A complementary cumulative distribution shows the proportion of scenarios that exceed any given value on the horizontal axis, in contrast to the cumulative distribution, which shows the proportion equal or below any given value. A complementary cumulative distribution can be obtained from a cumulative distribution by subtracting the vertical axis value from each point from 1. In effect, this inverts the distribution.

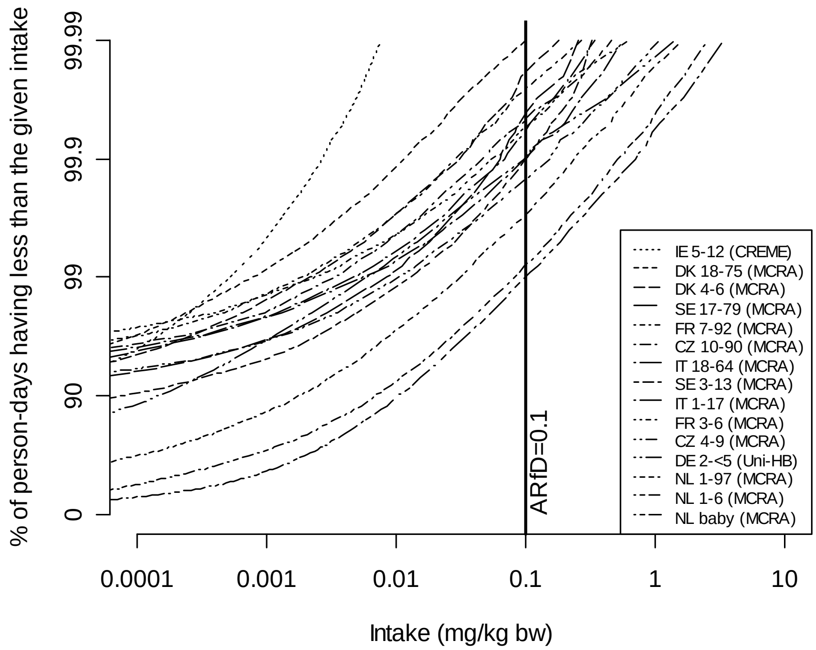

Figure 2: Example of results for a single pesticide (captan) in multiple countries and age groups. Broken curves show distributions of intake for different countries and age groups, estimated by probabilistic modelling, solid vertical line shows Acute Reference Dose (ARfD). Legend shows country, age group and model name (MCRA, Uni-HB or CRÈMe) for each curve (listed in the order they appear left to right at the top of the graph, *e.g.* Ireland ages 5-12 is the leftmost curve).

Figure 4 summarises the estimated level of protection achieved in all the scenarios for all the pesticides modelled by the Panel, using the same format as Figure 3.

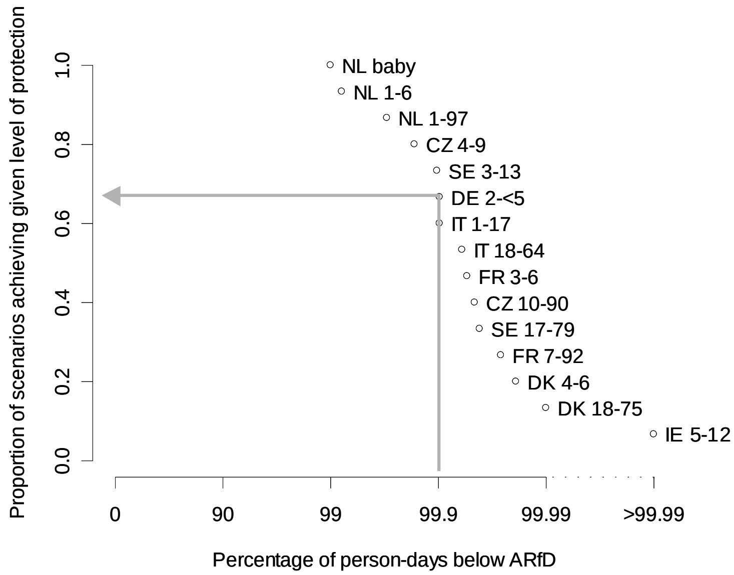

Figure 3: Example of results for a single pesticide (captan) in multiple countries and age groups. Points show the estimated levels of protection achieved for the different country/age group scenarios, taken from the curves in Figure 2. Arrow shows how to read off (on the vertical axis) the proportion of scenarios that achieve a given level of protection (on the horizontal axis).

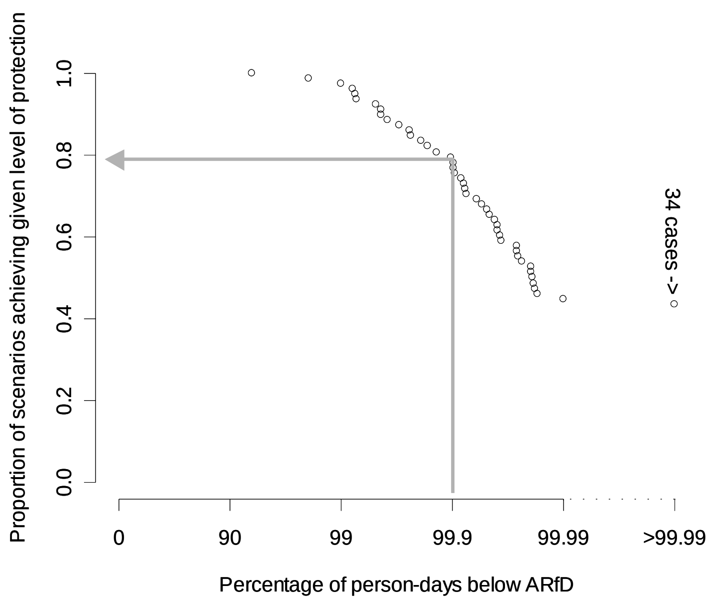

Figure 4: Summary of results for all pesticides, countries and age groups, obtained by probabilistic modelling with monitoring data and all commodities included.

Points show the distribution of levels of protection achieved for the different pesticide/country/age group scenarios. The total number of scenarios shown is 78. The arrow shows how to read off the proportion of scenarios that achieve a given level of protection: for example, 99.9% of person-days are below the ARfD in about 4 out of 5 (0.8) scenarios. Thirty-four scenarios with levels of protection >99.99% are represented by a single symbol at the right side of the graph.

Figure 4 provides the main result for this section: an indication of how the level of protection for acute dietary intake varied between the modelled pesticides during the period from which monitoring data were available. The Panel wishes to emphasise that these results must be interpreted with care. First, the probabilistic estimates of intake are uncertain, *e.g.* due to incomplete coverage of monitoring data, although comparison with duplicate diet studies suggests they may be conservative (see Section 6). Second, for some pesticides the ARfD was agreed after the period represented by the monitoring data, and for some the ARfD is not yet fully agreed (see Appendix Section 8.4 for details). Third, although the results in Figure 4 cover a range of pesticides, countries and age groups, they are only approximately representative of the wider European population. The combined effect of these and other uncertainties on the Panel's findings is evaluated in Section 7.3.

Finally, it must be remembered that the results in Figure 4 reflect the situation in the period from which monitoring data were available, *i.e.* up to around 2003, before the IESTI equations were fully introduced. The potential effect of the IESTI equations when fully introduced is examined in Section 3.1.3.

3.1.2 Percent exceedance of ARfD using field trial data for some commodities

Results in the preceding section were obtained using residue data from monitoring studies conducted up to around 2003. As has been mentioned several times, this may tend to under-estimate intakes because it ignores the potential contribution from residues in commodities that were not included in monitoring programs. It might have been possible to correct for this by assuming that unmonitored commodities contained residues at similar levels to monitored commodities, perhaps excluding any commodities that would never be treated with the pesticide in question. The Panel did not do this, due to lack of time.

However, the Panel did explore another way of making the estimated intakes more conservative. This involved modelling concentrations for some commodities using data from supervised field trials, rather than monitoring programs. This is expected to be more conservative because in general, residues in field trials are higher than those found in monitoring, because the conditions are intended to approach worst case and samples are taken and analysed sooner after harvest. However, the highest residues for individual samples in monitoring programs are sometimes higher than those from supervised trials.

For the models in this section, field trial data were used for those pesticide/commodity combinations for which they were available. It was assumed that these concentrations applied to 100% of the commodity on the market: this is an extreme worst case, because in practice part of the commodity would have been untreated or treated with different pesticides. Furthermore, some of the commodities for which supervised trials were available may in fact not have authorised uses in the EU. The contribution to intake of other commodities (without supervised trials) was modelled using monitoring data, if available.

The results in this section might therefore be interpreted as representing a hypothetical situation where the pesticide under consideration is used on 100% of all the crops for which it has supervised trials data. This is clearly an extreme worst case that is much more severe than most real situations, although high market shares might sometimes be achieved for a small number of uses, *e.g.* by a successful new pesticide in its first few years on the market. It would be possible to make these models more realistic using information on actual market shares, but due to lack of time, and lack of market share information, the Panel did not do this.[16]

The methodology for probabilistic modelling in this section was similar to that for the preceding section. The only difference was that where residue data from field trials were used, the variability factor describing unit-to-unit variation was not fixed (as before) but varied between lots according to a lognormal distribution with mean 0.423 and standard deviation 0.125 on the logarithmic scale (base 10): on the natural scale this distribution has a median of 2.65, and 95th percentile of 4.25. This distribution was derived from analyses done for the earlier EFSA Opinion on variability factors (EFSA, 2005) and was truncated at 6.83, as this is the highest variability factor that is compatible with the assumption of lognormality.

Figure 5 shows one example of the effect of replacing monitoring data for some commodities with field trial data, using the same scenario as in Figure 1: captan and the Dutch age group 1-97. Note that the dotted curve in Figure 5 starts lower on the vertical axis on the left of the graph than does the solid curve: as expected, a much larger proportion of the population is exposed when it is assumed that 100% of the crop is treated for those commodities with field trial data. However, the two curves cross to the right of the graph, so that the estimated level of protection is higher when modelled with field trial data than with monitoring data only (the dotted curve in Figure 5 crosses the ARfD line at a higher point than the solid curve).

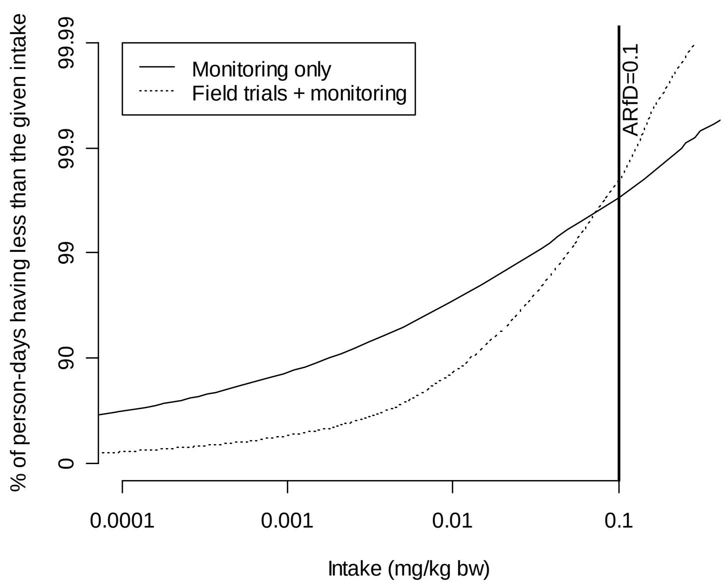

Figure 5: Example of results for a single pesticide, country and age group (captan, The Netherlands, total population). Solid curve shows distribution of intake estimated by probabilistic modelling, using monitoring data (copied from Figure 1). Dotted curve shows the distribution of intake for the same set of commodities, but using field trial data for those commodities where trials were available, and monitoring data for the remainder.

Similar results to Figure 5 (level of protection higher when estimated with field trial data) were seen for 11 out of 73 scenarios. This is contrary to the Panel's expectation, expressed above.

[16] Note that if probabilistic modelling were used to estimate intakes for new pesticide uses, no monitoring data would exist so modelling with field trial data would be the only option.

The Panel identified two possible explanations. First, it could result from monitoring data having lower means but higher variances than the field trial data for the same pesticide and commodity. Second, it could result from the fact that the Panel used a distribution of variability factors with field trial data (ranging up to 6.83, as described in the preceding paragraph) whereas for monitoring data the Panel fixed the variability factor at the maximum value of 6.83 (as explained in section 3.1.1). Both these factors may be contributing to the unexpected result, but the Panel had insufficient time to investigate them further. The second explanation contrasts with other findings of the Panel (sections 7.1 and 8.8.5), which indicated that intakes modelled with monitoring data were little affected by whether the variability factor was distributed or fixed at 6.83. A speculative explanation for this is that intakes estimated from monitoring data are more strongly driven by variation between lots of commodities (which is much higher for monitoring than field trials) than by unit-to-unit variation within lots. Again, the Panel lacked time to investigate further. Comparing the dotted curve to the ARfD in Figure 5 provides an estimate of the level of protection that would be achieved when assuming residues at field trial levels for a single pesticide/country/age group scenario (captan, The Netherlands, total population). This was repeated for each of the other pesticide/country/age group scenarios modelled by the Panel. The triangles in Figure 6 summarise the levels of protection achieved for all the scenarios, using the same format as in Figure 3. The results from Figure 3 are also shown as circles, for comparison.

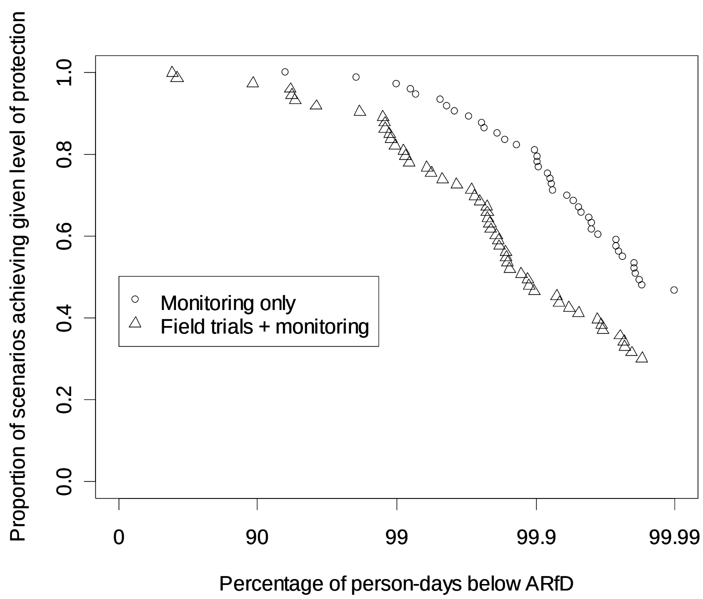

Figure 6: Levels of protection achieved for a range of pesticide/country/age group scenarios when estimating intakes using field trial data for some commodities (triangles), compared with estimates for the same scenarios using only monitoring data (circles, copied from Figure 4).

Overall, the estimated level of protection tends to be lower when intakes are modelled using residues from field studies instead of monitoring programs. For example, the proportion of scenarios achieving 99.9% protection is about 0.5 (triangles), compared to about 0.8 when using only monitoring data (Figure 6). However it must be remembered that, in some scenarios (such as that in Figure 5), the level of protection is higher when estimated with field trial data.

The Panel believes that models based on monitoring data are probably closer to real intakes than models based on field trial data, especially for those countries with the most complete monitoring programs. This view is supported by comparisons with duplicate diet studies, although these comparisons are also uncertain (see Section 6). However, for countries that monitor only a few commodities, using only monitoring data may be more likely to under-estimate intake. Modelling with field trial data and assuming 100% of the crop is treated is not realistic, but may provide a useful conservative estimate when monitoring data are limited or absent (*e.g.* for new pesticides).

Based on these considerations and the limited time available, the Panel decided to rely on modelling using only monitoring data in the remainder of this opinion. However, it must be remembered that this will cause some degree of under-estimation of intakes, especially for countries with less comprehensive monitoring programs, although other factors will tend to cause over-estimation. The effect of these and other uncertainties on the Panel's findings is evaluated in Section 7.

3.1.3 Percent exceedance of ARfD based on monitoring data, excluding commodities with IESTIs above the ARfD

In the period from which monitoring data were available, up to about 2003, most of the pesticides represented in the Panel's analysis had not yet had their MRLs reviewed using the IESTI equations. Some uses of these pesticides have IESTIs above the ARfD and will presumably be modified or withdrawn when they are reviewed[17]. Consequently, the results in two preceding sections do not represent the levels of protection that will be achieved when the IESTI equations are applied to all pesticides. Therefore, in the present section, the Panel repeats the analysis of Figures 1-4 but omitting those commodities with IESTIs above the ARfD.

It is important to recognise that simply omitting such commodities will underestimate intake in at least some scenarios. This is because omitting a commodity implies an assumption that its contribution to intake falls to zero, whereas in practice some intake may remain. This happens in several ways. First, instead of being withdrawn, the GAP for the affected commodity might be modified so as to produce lower residues in field trials, decreasing the IESTI so that it fell below the ARfD. Second, there may already exist other uses of the same pesticide on the same commodity but with a different GAP (*e.g.* to control a different pest), which results in a lower IESTI. Third, the pesticide may continue to have approved uses where it is applied at a lower rate to the same commodity as part of a mixed formulation, again resulting in a lower IESTI. Overall, approved uses of the pesticide might continue in about 10-20% (approximate estimate[18]) of those cases where the original critical GAP leads to an IESTI greater than the ARfD. It was not practical for the Panel to allow for this in its modelling, so this will tend to cause under-estimation of intakes in a proportion of scenarios. The implications of this for the Panel's conclusions are considered in section 7.3, together with other uncertainties.

This and subsequent sections use the same graphing formats as were introduced in the previous sections. Graphs with curves ascending left to right show cumulative distributions for intake of individual pesticide/country/age group scenarios. Graphs with a curve of points descending left to right are summary plots for multiple scenarios: showing the distribution of the levels of protection achieved.

Figure 7 shows the effect of excluding commodities with IESTIs above the ARfD for the same example as was used in Figure 1: captan and the Dutch age group 1-97. Three commodities have IESTIs above the ARfD when calculated for The Netherlands: pears, peaches and apples

[17] In addition, some of the pesticides included in the Panel's analysis may be withdrawn when their regulatory review under Directive 91/414/EC is completed.

[18] Approximate estimate based on the experience of some members of the Panel and Working Group who have been involved in the MRL-setting process.

(the IESTIs for these are shown by the vertical lines to the right of the ARfD in Figure 7. The curves in Figure 7 show the effect of excluding these commodities: the dotted curve shows the distribution of intake when they are included, and the solid curve shows the distribution when they are excluded. In general, removing some sources of intake should reduce intake and that is seen in this example: the solid curve is further to the left than the dotted curve. The effect of this on the level of protection can be seen by comparing the curves to the solid vertical line representing the ARfD: between 99 and 99.9% of person-days were at or below the ARfD when including all commodities, but this rises to greater than 99.99% when the pears, peaches and apples are excluded.

It is important to note that this procedure, of excluding the commodities with IESTIs above the ARfD, is only one of the possible outcomes when their MRLs are reviewed. Another possible outcome is that the notifiers might modify the use of captan on these commodities in order to retain them with lower MRLs, *e.g.* by reducing the application rate, decreasing the number of applications permitted, or increasing the interval between application and harvest. The Panel cannot model this situation because it is not possible to anticipate in what ways notifiers would choose to modify their uses. However, if uses were modified these commodities would continue to contribute to intake, but presumably at a lower level , so the intake distribution would then fall somewhere between the two curves shown in Figure 7.

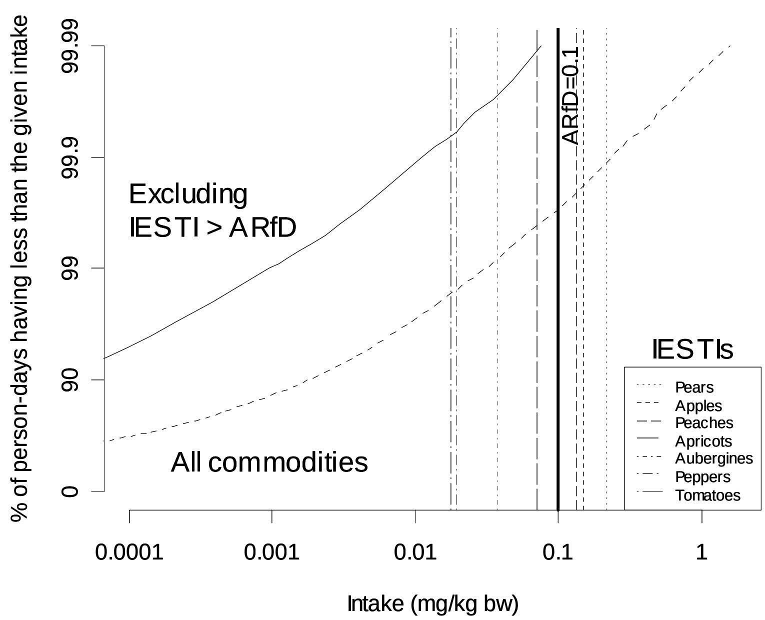

Figure 7: Example of results for a single pesticide, country and age group (captan, The Netherlands, total population). Dotted curve shows distribution of intake estimated by probabilistic modelling, using monitoring data for all commodities (copied from Figure 1). Solid curve shows the distribution of intake estimated by probabilistic modelling, after excluding those commodities for which the IESTI exceeds the ARfD (pears, peaches and apples).

Comparing the solid curve to the ARfD in Figure 7 provides an estimate of the level of protection that would be achieved by full introduction of the IESTI equations[19] for a single

[19] with their current default inputs (including variability factors of 5 and 7)

pesticide/country/age group scenario (captan, The Netherlands, total population). This addresses the first bullet of the Terms of Reference but only for that one scenario. Therefore, Figure 8 summarises the levels of protection achieved for all pesticide/country/age group scenarios modelled by the Panel. Again, these results refer to full introduction of the IESTI equations, *i.e.* all pesticide/commodity combinations with IESTIs exceeding their ARfDs have been excluded (a full list of these excluded pesticide/commodity combinations is provided in the Appendix, section 8.10).

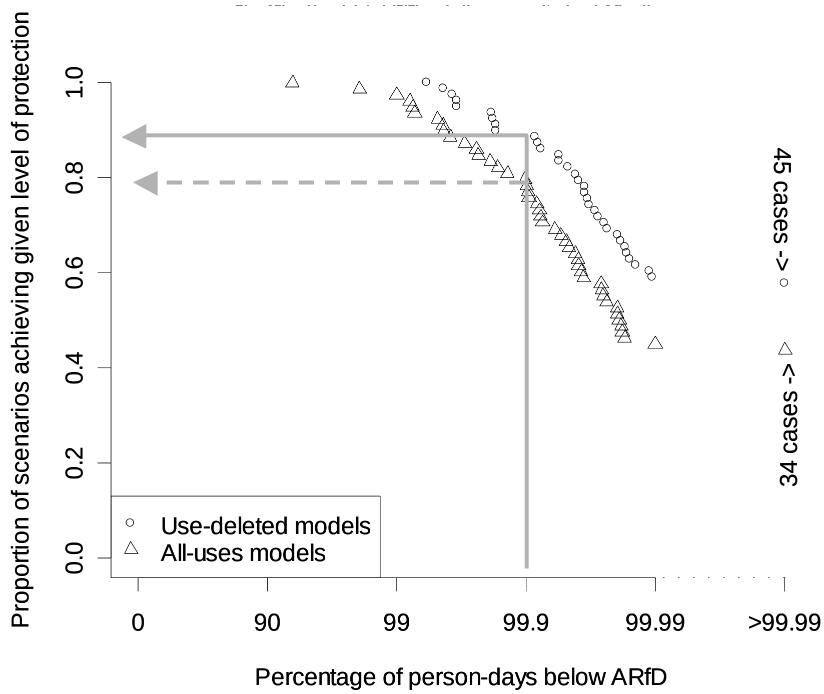

Figure 8: Summary of results for all pesticides, countries and age groups, obtained by probabilistic modelling with monitoring data after excluding all pesticide/commodity combinations for which the IESTI exceeds the ARfD. Circles ("use-deleted models") represent the distribution of levels of protection that would be achieved for the different pesticide/country/age group scenarios when the IESTI equations are fully implemented; triangles show the results including all commodities are included (copied from Figure 4). The total number of scenarios shown is 78. The arrows show that, when commodities with IESTIs above the ARfD are omitted, the proportion of scenarios achieving 99.9% protection rises from about 0.8 to about 0.9 (9 out of 10 scenarios).

Note that commodities were included or omitted for each scenario independently, based on the IESTIs for that scenario. Thus, for example, apples might be included for captan/NL/children but omitted for captan/NL/babies, whereas in reality if the MRL for apples was set to the LoD this would apply to both age groups. It would be difficult to represent this inter-dependence of scenarios in the modelling process, because it is uncertain which precise scenarios would actually be assessed in MRL-setting. Treating the scenarios independently will tend to overestimate intakes in some cases: this is considered together with other uncertainties affecting the results in section 7.3.

As expected, excluding commodities with IESTIs above the ARfD tends to increase the level of protection achieved: for example, the proportion of scenarios achieving 99.9% protection is about 0.9 or 9 out of 10, compared to about 0.8 when all commodities were included (as shown by the arrows in Figure 8). If the pesticide uses authorised for these commodities were modified rather than withdrawn, an intermediate result would be expected (*i.e.* lying between the two curves of points in Figure 8).

Figure 8 provides the main result for this section: an indication of how the level of protection for acute dietary intake would vary between the modelled pesticides if the IESTI equations with their current default inputs (including variability factors of 5 and 7) are fully introduced. Figure 8 therefore addresses the first bullet of the Terms of Reference: it provides an indication of how conservative the IESTI equation is with respect to the percentage of the total population protected. If risk managers can decide which level of protection they want, they can then read off the proportion of scenarios where this is achieved (bearing in mind the associated uncertainties, see below).

Another way of summarising the results for this section is shown in Table 4. This shows the number of pesticide/country/age group scenarios that achieve different levels of protection. For example, of the 78 scenarios modelled by the Panel, none had less than 99% protection and 9 scenarios had between 99% and 99.9% protection. These correspond to the numbers of points (circle symbols) falling in different segments of the distribution in Figure 8. If risk managers wish to consider other levels of protection not shown in Table 4, *e.g.* 95%, then these could be provided.

Table 4: Number of pesticide/country/age group scenarios that achieve different levels of protection, after excluding all commodities for which the IESTI exceeds the ARfD. Based on the same results as Figure 8. The second column from left shows the proportion of scenarios with different percentages of person-days below the ARfD. The third and fourth columns show the same for twice and ten times the ARfD, to give an indication of the magnitude of the intakes that are above the ARfD.

% of person-days below the given level of intake	Number of pesticide/country/age group scenarios (total=78)		
	1 x ARfD	2 x ARfD	10 x ARfD
0 – 90%	0	0	0
90 – 99%	0	0	0
99 – 99.9%	9	5	0
99.9 – 99.99%	24	20	9
> 99.99%	45	53	69

Note that although the analysis in this section is restricted to commodities with IESTIs that do not exceed the ARfD, a proportion of the population may do so. This might seem surprising at first sight, but happens because the IESTI equation considers only single commodities and does not take account of the full range of variation in residues, consumption and body weight.

The PPR Panel recognises that exceeding the ARfD does not necessarily mean that toxic effects will occur, because of the safety factors that are incorporated in the ARfD. Therefore, it is important to examine not only the proportion of intakes exceeding the ARfD, but also the magnitude by which the ARfD is exceeded. The Panel did this by showing in Table 4 results for exceeding 2x ARfD and 10x ARfD as well as 1x ARfD. This shows, for example, that all the 78 modelled scenarios had at least 99.9% of person-days below 10x ARfD (*i.e.* less than 0.1% or 1 in 1000 person-days exceeding the ARfD). Note that results of this type can be described in different ways and that the choice of description may influence risk perception, *e.g.* reporting the % person-days exceeding 10x ARfD may be perceived more negatively than reporting the same result in terms of % person-days below 10x ARfD.

The Panel wishes to emphasise that the results in Figure 8 and Table 4 must be interpreted with care:

- the probabilistic estimates of intake are uncertain and the true levels of intake could be either higher (*e.g.* due to limitations of monitoring data) or lower (*e.g.* as suggested by comparison with duplicate diet data, see Section 6),
- although the results cover a range of pesticides, countries and age groups, they are only approximately representative of the wider European population,
- the level of protection achieved for each pesticide depends in part on the number of commodities it is used on and the frequency of consumption, neither of which is taken into account by the IESTI equation: therefore the actual level of protection could change over time without being reflected in IESTI estimates.

The combined effect of these and other uncertainties on the Panel's findings is evaluated in Section 7.3.

Finally in this section, the Panel examined the results from Figure 8 in more detail to explore how the level of protection differs between pesticides and between countries. Results are shown in Figure 9. There is some indication of differences between pesticides, as would be expected, and perhaps also between countries. However, these patterns should be interpreted with great care; because the effects of pesticide, country and age-group are confounded (*e.g.* apparent differences between countries might actually be caused by differences in the age groups that were modelled for each country).

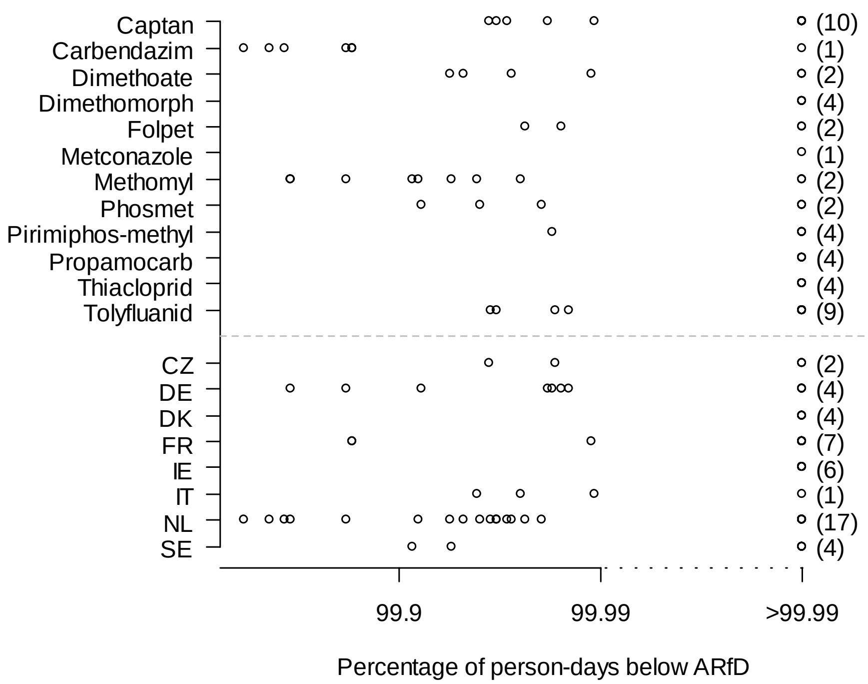

Figure 9: Levels of protection achieved in relation to pesticide and country. Results obtained using monitoring data and excluding commodities with IESTI>ARfD. The numbers in brackets at the right hand side indicate the number of overlying points at 100%.

3.1.4 Minimum level of protection if ARfDs were lower

Variation in the LoP is caused by various factors including differences in the number and type of commodities included, differences between age groups in intake relative to body weight, and different ARfDs for different pesticides. The results in the preceding section are an estimate of the LoPs for the scenarios modelled by the Panel, and can also be interpreted as an approximate indication of the LoPs that may be achieved for other pesticide/country/age group scenarios that are similar to those modelled by the Panel.

When the IESTI of a commodity is close or equal to the ARfD, the LoP may be lower than for the scenarios modelled by the Panel. To examine how much difference this might make to the LoPs, the Panel repeated the assessments, assuming that the ARfD is equal to the highest IESTI of the commodities included in each scenario[20]. The Panel refers to LoPs estimated in this way as "estimated minimum LoPs", because they represent the minimum LoP that could occur for a hypothetical scenario with the same pattern of uses and intakes as the real scenario but a lower ARfD.

An example of this approach is illustrated in Figure 10, for the scenario phosmet/The Netherlands/ages 1-97. The ARfD for phosmet is 0.045 mg/kg bw/day. The estimated distribution of dietary intakes for the 3 commodities considered does not reach the ARfD, which would imply a level of protection greater than 99.99%. However, if the ARfD were actually equal to the highest IESTI (for oranges), then the level of protection would be a little below 99.9%, as indicated by the gray arrow in Figure 10. This is a hypothetical scenario: it can be interpreted as the lowest level of protection that could occur for a pesticide with the same pattern of uses, residues and intake as phosmet but a different ARfD. It is an extreme worst case for this set of commodities, because if the ARfD were further reduced then use on the commodity with the highest IESTI would no longer be permissible.

[20] The highest IESTI is used because, if the ARfD were below this, use on that commodity would not be authorised and therefore the scenario including that use would not exist.

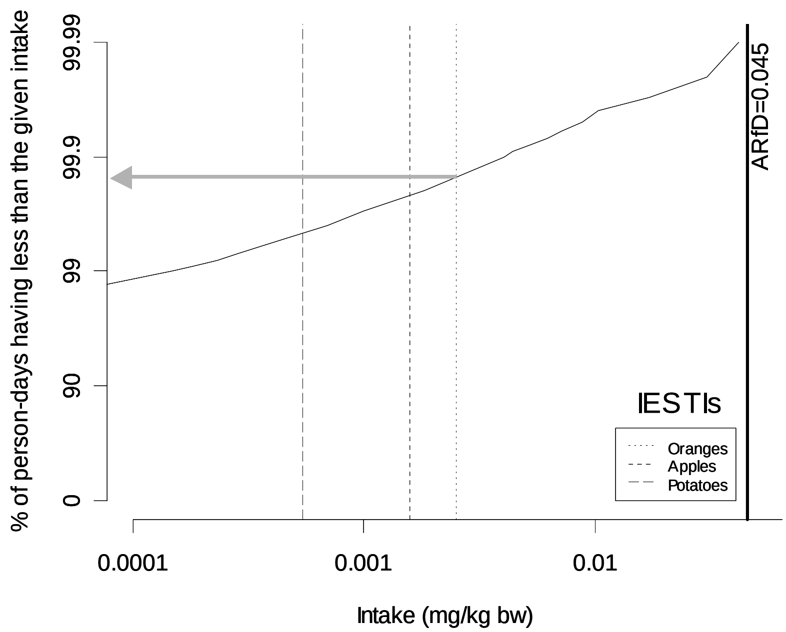

Figure 10: Estimation of minimum level of protection that would be obtained for a pesticide with the same pattern of uses, residues, and intakes as phosmet in The Netherlands but with a lower ARfD, equal to its highest IESTI (oranges). The level of protection with the true ARfD of phosmet is over 99.99%, but the minimum level of protection is under 99.9% as shown by the gray arrow.

The Panel repeated this procedure for all the scenarios it considered, setting the hypothetical ARfD equal to the highest IESTI in each case. Figure 11 shows the resulting minimum LoPs based on the same 78 scenarios as Figure 8. If a risk manager is considering a scenario which is generally similar to those modelled by the Panel but has an ARfD close to its highest IESTI, then Figure 11 is more relevant than Figure 8 as a guide to the LoP. The results for the actual and minimum levels of protection are compared in Table 5. The Panel emphasises that these results are affected by the same uncertainties that were listed in the preceding section, plus additional uncertainty associated with extrapolating to theoretical additional scenarios which are similar except for having lower ARfDs.

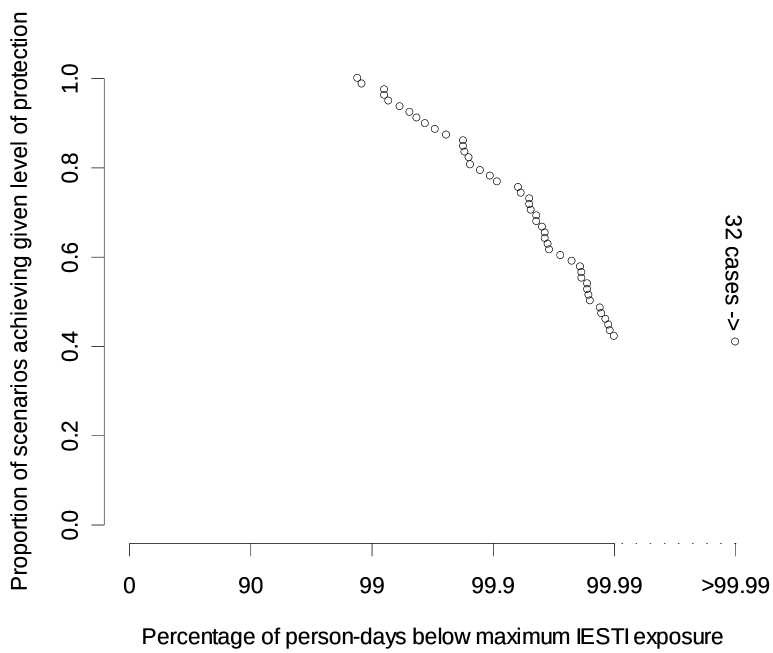

Figure 11: Results for the same set of pesticide/country/age group model runs as in Figure 8, but with levels of protection calculated assuming that the ARfD for each scenario was reduced to be equal to the highest IESTI for the commodities within that scenario. This is an estimate of the estimated minimum level of protection that could occur for hypothetical scenarios with the same pattern of uses and intakes as the real scenarios but smaller margins between the highest IESTIs and ARfDs.

Table 5: Comparison of the estimated actual levels of protection for the scenarios modelled by the Panel (from Figure 8) with the estimated minimum levels of protection for the same scenarios but smaller margins between the highest IESTIs and ARfDs (from Figure 11).

% of person-days below the given level of intake	Number of pesticide/country/age group scenarios (total=78)	
	Estimated actual level of protection	Estimated minimum level of protection
0 – 90%	0	0
90 – 99%	0	2
99 – 99.9%	9	16
99.9 – 99.99%	24	28
> 99.99%	45	32

3.2 Level of protection for consignments at the MRL

Sections 3.1.1 to 3.1.4 estimated the level of protection for all people in the selected age groups, including both consumers and non-consumers of the commodities considered. This was done because the question to the Panel specifically refers to "total population". However, as explained in section 1.3.2, there is also interest in the level of protection achieved for persons who consume a commodity containing residues at the level of the MRL. Therefore, in this section the Panel reports results for this type of assessment, even though it was not explicitly requested in the Terms of Reference.

Intakes for consumers of commodities at the MRL were modelled probabilistically using the same general approach as for the total population, with the following differences:

- Each assessment related to a focal commodity (*e.g.* apples), which was assumed to have a mean residue equal to the MRL for that commodity. Unit to unit variability of residues within that commodity was modelled in the same way as for the total population models (see section 3.1.1), *i.e.* using a fixed variability factor of 1, 3, 5, or 6.83 depending on commodity. As mentioned in section 3.1.1, there was evidence that assuming fixed or distributed variability factors gave similar results when modelling intakes for the total population. There was insufficient time to make this comparison for models of intake at the MRL. However, the higher variability factors may be less realistic for commodity lots where the measured composite residue is at the MRL[21]. This may lead to overestimation of intakes and hence underestimation of LoPs for consumers at the MRL, perhaps by a substantial amount. The effect of this and other uncertainties on the Panel's conclusions is considered in section 7.
- Modelling was limited to those person-days on which the focal commodity was consumed: this was done by excluding from the consumption data those person-day records with zero consumption of that commodity. Consequently the measure of level of protection for these "MRL scenarios" is expressed as the proportion of consumption-days (not person-days) on which the intake is at or below the ARfD.
- The contributions of other commodities consumed by the same individuals to their overall intake of the pesticide were modelled using distributions of concentrations derived from monitoring data. This makes the reasonable assumption that individuals who happen to consume one commodity at the MRL, take the other commodities they consume at random from the market place.[22]

Figure 12 shows the result of one example of such an assessment, for the scenario tolylfluanid/apples/The Netherlands/all ages (1-97). Note that because one commodity is selected to be at the MRL, multiple scenarios focusing on different commodities can be examined for the same combination of pesticide, country and age group. Therefore scenarios in this section are defined by commodity as well as pesticide, country and age group.

[21] This is because composite samples at the MRL may arise due to chance sampling of units with above-average residues, in which case applying the standard variability factors would over-estimate the upper percentile unit residues. However, if such an effect occurs it may not be strong, as Hill and Reynolds (2002) found no relationship between variability and mean concentration in market survey samples.

[22] It might be thought that assessments for consumers of commodities at the MRL should exclude intake of residues in other commodities, in the same way that the IESTI equation considers only one commodity at a time. However, this would under-estimate the actual intakes of such individuals. Although the contribution of other commodities may expected to be small relative to the commodity at the MRL in most cases, it will sometimes be sufficient to raise total intake above the ARfD. Therefore an assessment excluding other commodities would not be appropriate for estimating the true level of protection.

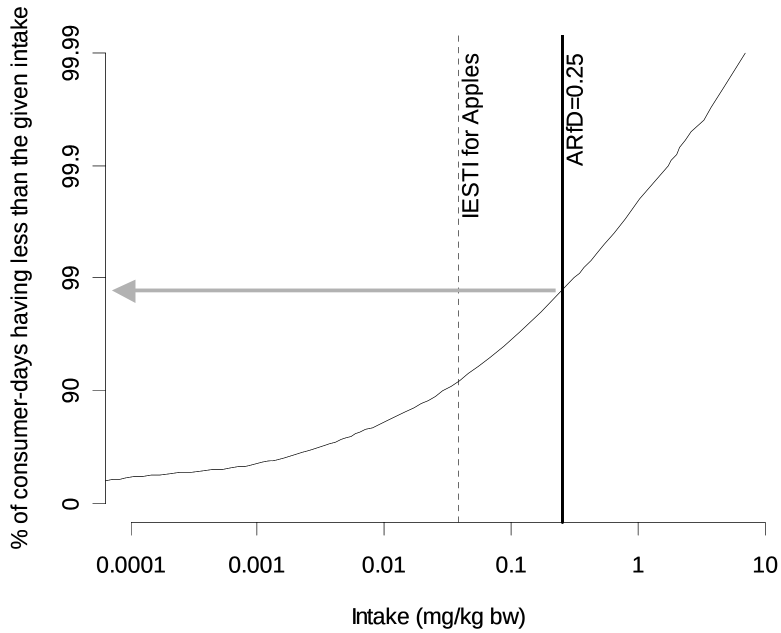

Figure 12: Cumulative distribution of intakes for consumers of apples containing mean residues at the MRL and other commodities at monitoring levels, for a single scenario (tolylfluanid, apples, The Netherlands, ages 1-97), estimated by probabilistic modelling. The gray arrow shows how to read off the % of consumption-days with intakes below the ARfD. The dotted line shows the IESTI for apples, calculated for this group of consumers.

Figure 12 estimates the level of protection for a single scenario (tolylfluanid, apples at MRL, other commodities at monitoring levels, The Netherlands, ages 1-97). In order to examine how the level of protection varies for a range of scenarios, similar models were run for 23 different commodity/age group combinations in The Netherlands, all for tolylfluanid; and also for 69 different pesticide/commodity combinations for age group 2-<5 in Germany. Note that due to limitations of time, this is a more limited selection of pesticide/country/age group scenarios than was considered for the total population assessments in section 3.1.

All the IESTIs for the scenario shown in Figure 12 are below the ARfD (the IESTI for apple is shown on the graph, but the commodities at monitoring levels in this scenario also had IESTIs below the ARfD). Therefore this scenario would be permitted to continue under Regulation (EC) No. 396/2005. However, some of the other scenarios modelled at the MRL had one or more commodities with IESTIs above the ARfD, so these commodities were excluded from modelling (both at the MRL and monitoring levels) in order to reflect the situation after full introduction of the IESTI equations. A full list of the excluded commodities is provided in the Appendix, section 8.10.

Results for tolylfluanid in The Netherlands are summarised in Figure 13. Each point in this graph is obtained by the method shown by the gray arrow in Figure 12, and represents the level of protection estimated for consumers of one commodity at the MRL and other commodities at monitoring levels.

Figure 13 has the same format (complementary cumulative distribution) as the earlier summary Figures 3, 4, 6 and 8 it shows the proportion of scenarios for which a given level of protection is achieved or exceeded. However, Figure 13 differs from the earlier figures in several respects.

First, all the results relate to one pesticide, tolylfluanid, which is the only pesticide modelled in MRL runs for The Netherlands. Second, results for different age groups are not combined in a single distribution, but plotted as three separate distributions (babies, 1-6 years and 1-97 years). This was done because, unlike the earlier figures where there was only one model run per age group (with all commodities at monitoring levels), in Figure 13 there are multiple models per age group (each with a different commodity modelled at the MRL). By examining the three distributions in Figure 13 it can be seen that:

- The level of protection (% consumption-days below the ARfD) varies widely, from about 94% to over 99.99%, depending on age group and commodity
- Levels of protection tend to be lower for babies than other age groups (the curve for babies is further to the left).

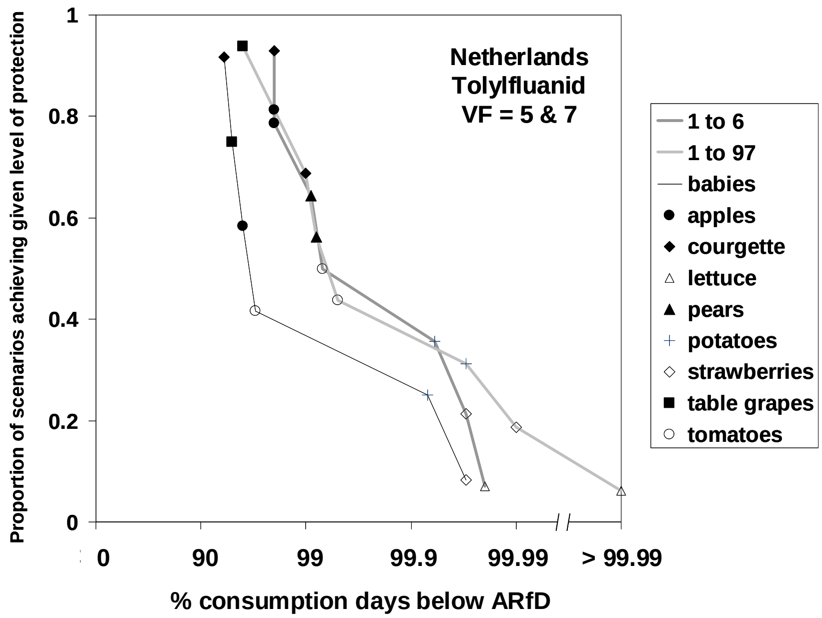

Figure 13: Estimates of the level of protection for people in The Netherlands consuming one commodity containing residues of tolylfluanid at the MRL and other commodities containing residues of tolylfluanid at monitoring levels. The symbol for each point identifies the commodity which is at the MRL and the line styles indicate the age group, as shown in the legend (the line to the left of the graph is for babies). All the results exclude commodities with IESTIs exceeding the ARfD (when calculated with variability factors of 5 and 7).

Results for a range of pesticides and commodities for the age group 2-<5 in Germany are summarised in Figure 14. Note that instead of grouping food items by commodities, in the German models food items were linked directly to the corresponding crops for which field trials were available. Due to limited time it was not practical to incorporate a further classification by commodities. Therefore, in some of the German scenarios, several related commodities were set simultaneously to the MRL, *e.g.* in scenarios for "pome fruits", apples and pears were both set to the MRL. In reality, it is very unlikely that the same group of consumers would eat more than one commodity from batches at the MRL on the same day. Consequently, the results for German intakes at the MRL are conservative and over-estimate the proportions of consumption-days exceeding the ARfD. The implications of this and other uncertainties for the Panel's conclusions are considered in section 7.3.

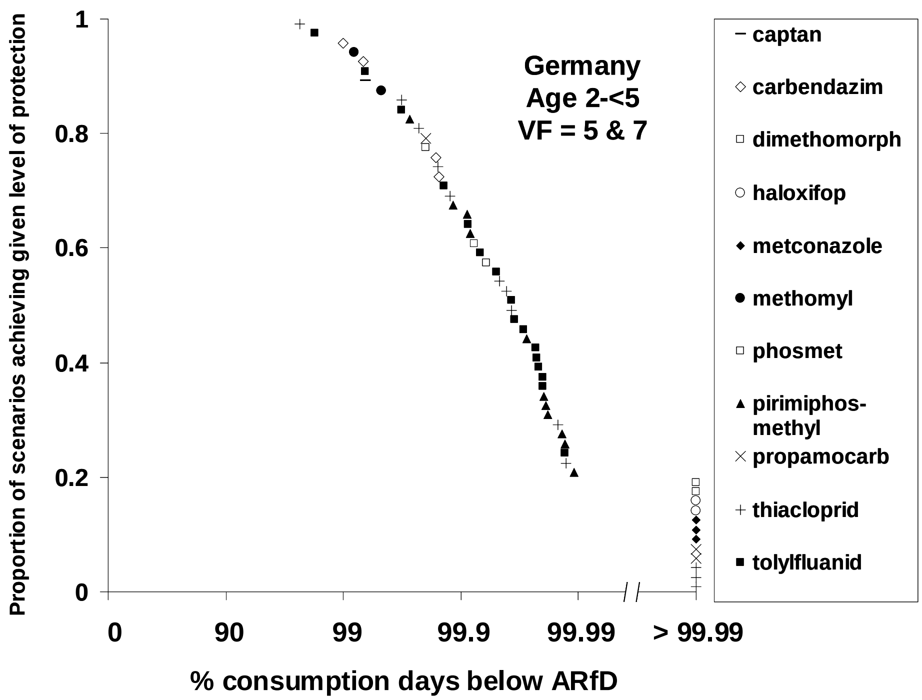

Figure 14: Estimates of the level of protection for people in Germany consuming one commodity or commodity group (*e.g.* pome fruits) containing residues of a pesticide at the MRL and other commodities containing residues of the same pesticide at monitoring levels. All the results exclude commodities with IESTIs exceeding the ARfD (when calculated with variability factors of 5 and 7).

Another way of summarising the results for this section is shown in Table 6, combining the results from both Germany and The Netherlands. The table shows the number of pesticide/commodity/country/age group scenarios that achieve different levels of protection.

Table 6: Number of pesticide/commodity/country/age group scenarios that achieve different levels of protection for consumers of one commodity or commodity group at the MRL and other commodities at monitoring levels. Based on the same results as Figures 13 and 14, combining results for Germany and The Netherlands. The second column from left shows the proportion of scenarios with different percentages of consumption-days below the ARfD. The third and fourth columns show the same for twice and ten times the ARfD, to give an indication of the magnitude of the intakes that are above the ARfD.

% of consumption-days below the given level of intake	Number of pesticide/country/age group scenarios (total=81)		
	1 x ARfD	2 x ARfD	10 x ARfD
0 – 90%	0	0	0
90 – 99%	11	5	0
99 – 99.9%	22	18	5
99.9 – 99.99%	35	27	21
> 99.99%	13	31	55

Note that there are a number of scenarios with levels of protection below 99% in Table 6 (consumers at the MRL) but not in Table 4 (total population). This is because intakes are higher when one commodity is consumed at the MRL than when all are consumed at monitoring levels, and so the percentage of person-days exceeding the ARfD is increased, and the level of protection is decreased. Thus, as would be expected, the level of protection for people who consume one commodity at the MRL and other commodities at monitoring levels, is lower than the level of protection for the population as a whole. However, the magnitude of the difference may be overestimated because of modelling unit-to-unit variation with fixed variability factors of 3, 5 and 6.83.

It can be seen from Figures 13 and 14 that 9 of the 11 scenarios in Table 6 with levels of protection below 99% relate to tolylfluanid in The Netherlands, for several different commodities. Detailed examination of the model output (not shown) suggests that part of the reason for this is that intakes of tolylfluanid at monitoring levels on apples and pears are close to the ARfD for a number of consumers, so assuming that any commodity is at the MRL (plus unit-to-unit variability) takes these consumers above the ARfD. Higher levels of protection at the MRL would be expected for pesticides that have intakes at monitoring levels further below the ARfD. The Panel wishes to emphasise that the results in this section must be interpreted with care:

- the probabilistic estimates of intake are uncertain and the true levels of intake for consumers at the MRL could be either higher or (more probably) lower,
- the results cover a limited range of pesticides, commodities, countries and age groups, and results for other scenarios might be different,
- the level of protection achieved for each pesticide depends in part (although to a lesser extent than the results in section 3.1) on the number of commodities for which the pesticide is approved and the frequency of consumption, neither of which is taken into account by the IESTI equation: therefore the actual level of protection could change over time without being reflected in IESTI estimates,
- the Panel is not certain that all of the MRLs considered in this analysis are current: it is possible that some of the scenarios generating lower levels of protection have been refused MRLs (or had them set equal to the LoD), in which case they should not have been included in the assessment.

The combined effect of these and other uncertainties on the Panel's findings is evaluated in Section 7.3.

4 How might changing the IESTI inputs affect the level of protection?

The Background for this Opinion together with the second and third bullets of the Terms of Reference make clear that the Commission's primary interest is in the choice of inputs for the IESTI equation, especially the values used for the variability factor and the high residue HR.

As explained in section 1.3.4, it is not possible to give reliable predictions for the general performance of the IESTI equations, whether the current inputs are changed or retained. The most important reason is that the level of protection achieved for each pesticide depends in part on the number of commodities with approved uses and the frequency of their consumption, neither of which is reflected by the IESTI equation. The number of commodities treated with each pesticide will change over time as uses are approved or withdrawn, and the frequency of consumption for different commodities may change over time as dietary habits alter. Therefore, the level of protection will change over time but IESTI estimates will remain unchanged: so the level of protection they provide when used for decision-making will change. In addition, despite the efforts made by the Panel to analyse a broad selection of countries and pesticides, these cannot be regarded as a statistically representative sample of all countries and pesticides. The latter problem is especially severe for the results relating to consumers of commodities at the MRL, for which the Panel's sample of scenarios was more limited.

As it is not possible to give reliable predictions for the general performance of the IESTI equations, the best that can be done is to estimate how changing IESTI inputs would alter the performance of the IESTI for the selection of current pesticides analysed by the Panel. Although these should not be regarded as predictions for future pesticides, they are the best indication the Panel can provide of the potential consequences of changing the IESTI inputs.

4.1 Effect of changing the variability factor on levels of protection for the total population

This analysis was possible because some of the pesticides examined by the Panel had some commodities with IESTIs that were above the ARfD, as assessing acute intake was not part of the regulatory procedure when their MRLs were last reviewed. For some of these commodities, the IESTI was above the ARfD when using the current EU variability factors of 5 and 7, but below the ARfD when using a variability factor of 3 (as recently introduced at Codex level by the JMPR). The Panel was therefore able to assess the effect of changing the variability factor by estimating the level of protection with and without the additional commodities. This involved the following steps:

1. Calculate IESTIs with variability factors of 5 & 7, then use probabilistic modelling to estimate intake and level of protection including only those commodities with IESTIs below the ARfD.
2. Recalculate the IESTIs using a variability factor of 3 in place 5 & 7, then rerun the probabilistic modelling to estimate intake and level of protection including the additional commodities with IESTIs below the ARfD.
3. Compare the levels of protection from steps 1 and 2, to determine the effect of changing the variability factors from 5 & 7 to 3.

Note that although different variability factors are used in the IESTIs in steps 1 and 2 above, the variability factors used in the probabilistic modelling are unchanged. This is because the variability factors used in the IESTI calculation are default values which might be changed in order to control the level of protection provided by the IESTI, whereas the variability factors used in the probabilistic modelling are intended to represent actual unit-to-unit variability, which would not be altered by a change in the default values. In other words, deciding to change the variability factor used in the IESTI equation to 3 may change which commodities are given MRLs, but would not change the actual unit-to-unit variation in residues, so the variability factors used in modelling actual intakes should remain unchanged.

Important limitations of this approach are (a) the results are highly influenced by the particular use patterns and ARfDs of the pesticides considered, and hence difficult to extrapolate to other pesticides, (b) it is necessary to assume that commodities with IESTIs exceeding the ARfD are withdrawn, whereas in practice they might be retained in modified form (*e.g.* with reduced application rates to reduce the IESTI).

The impact of other changes to the IESTI inputs (*e.g.* variability factors other than 3, or replacing the HR with the MRL) was not examined because each additional change would require rerunning the probabilistic models for all scenarios, which was not feasible in the time available.

Figure 15 shows an example of a pesticide/country/age group scenario where a change in the default variability factor from 5 and 7 to 3 would lead to uses on additional commodities being permitted. The example is captan/The Netherlands/1-97 age group, which was also used in earlier sections. In Figure 1, it was shown that of the 7 commodities for this scenario, three (peaches, apples and pears) had IESTIs above the ARfD when calculated with the current default variability factor, which is 7 for these commodities. Changing the variability factor to 3 reduces the IESTI for all three commodities: the IESTIs for peaches and apples fall below the ARfD, but the IESTI for pears remains above the ARfD. Therefore, if the default variability factor was changed from 7 to 3, two commodities that would currently not be permissible (peaches and apples) would become permissible. Residues in these two additional commodities would increase the overall intakes in the population. The magnitude of the increase in intakes was estimated using two separate probabilistic intake assessments: first, with all the commodities except peaches, apples and pears (the solid line in Figure 15, with variability factors of 5 and 7) and second, adding peaches and apples but not pears (the dotted line in Figure 15, variability factor 3).[23]

The consequence of changing the variability factor in this scenario is to reduce the level of protection from over 99.99% (the solid curve in Figure 15 does not reach the ARfD) to between 99 and 99.9% (as shown by the gray arrow in Figure 15).

The Panel repeated the analysis shown in Figure 15 for all of the pesticide/country/age group scenarios it modelled. The Panel found that using a variability factor of 3 rather than 5 or 7 to calculate IESTIs increased the number of commodities included (IESTI < ARfD) in 25 of the 78 scenarios. The results are shown in Figure 16. The circles show the levels of protection achieved with variability factors of 5 and 7 (repeated from Figure 8). The triangles show the levels of protection achieved when the variability factor is changed to 3.

[23] If the reader is interested in the further change in intake when pears are also included, this can be seen in Figure 1, which included all commodities for this scenario.

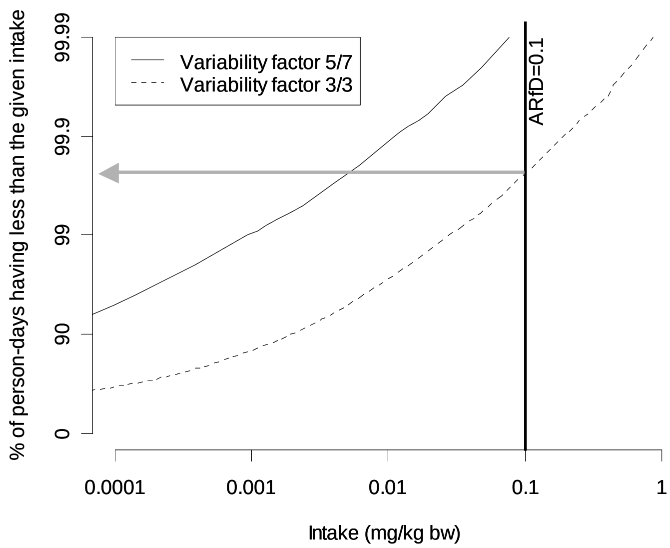

Figure 15: Estimated effect of changing the variability factor, for a single pesticide, country and age group (captan, The Netherlands, ages 1-97). Solid curve shows estimated intake including only those commodities with IESTIs below the ARfD when calculated with the current variability factors of 5 and 7: the level of protection in this case is over 99.99%. When variability factor is reduced to 3, the IESTIs for 2 additional commodities (apples and pears) fall below the ARfD. The dashed curve shows the estimated intake when these commodities are added, and the gray arrow shows the resulting level of protection (between 99 and 99.9%).

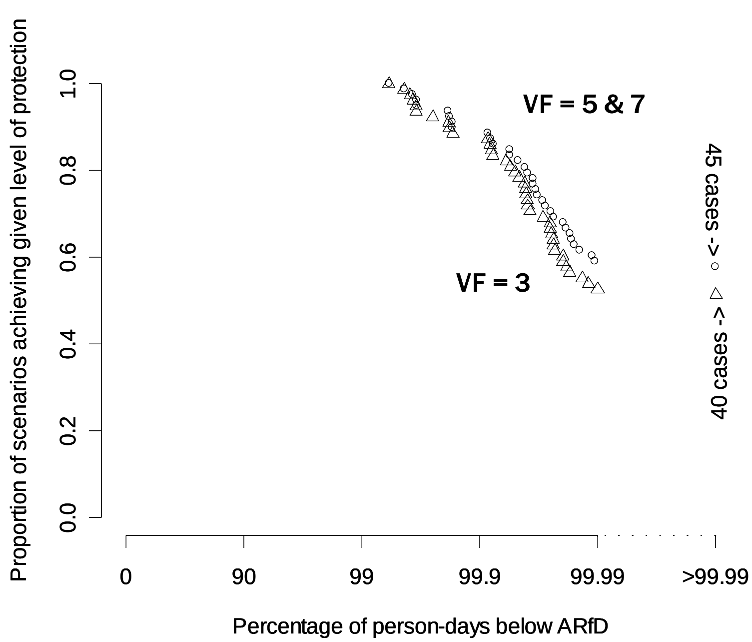

Figure 16: The effect of changing the variability factor from 5 and 7 (circles) to 3 (triangles) on the level of protection achieved for the total population in 78 pesticide/country/age group scenarios, obtained by probabilistic modelling with monitoring data. The difference between the two curves is due to the additional contribution to intakes of commodities that would be authorised with a variability factors of 3 but not with 5 and 7.

Another way of summarising the results for this section is shown in Table 7. This shows the number of pesticide/country/age group scenarios that achieve different levels of protection when compared to the ARfD and also to 2x and 10x the ARfD. The left hand side of the Table is repeated from Table 7 and shows results obtained when commodities are selected using IESTIs calculated with variability factors of 5 and 7, while the right hand side shows results when these variability factors are changed to 3.

Table 7: The effect of changing the variability factor from 5 and 7 to 3 on the proportions of person-days of exceeding 1x, 2x and 10x the ARfD for the total population in 78 pesticide/country/age group scenarios, obtained by probabilistic modelling with monitoring data. Based on the same results as Figure 16.

% of person-days below the given level of intake	Number of pesticide/country/age group scenarios (total=78)					
	Variability factor = 5 or 7			Variability factor = 3		
	1 x ARfD	2 x ARfD	10 x ARfD	1 x ARfD	2 x ARfD	10 x ARfD
0 – 90%	0	0	0	0	0	0
90 – 99%	0	0	0	0	0	0
99 – 99.9%	9	5	0	10	6	0
99.9 – 99.99%	24	20	9	28	23	9
> 99.99%	45	53	69	40	49	69

As the same 78 scenarios have been analysed with different variability factors, it is useful to examine a paired comparison that shows the change in level of protection for each scenario. This is done in Figure 17. Here, each point shows the effect of the change of variability factors on one pesticide/country/age group scenario. The horizontal axis shows the level of protection achieved with variability factors of 5 and 7 (assuming pesticide uses with IESTIs above the ARfD are not authorised), while the vertical axis shows the level of protection when these are changed to 3. Points on the diagonal line represent scenarios for which there is no change in the level of protection – in most cases this is because the change in variability factor did not alter the number of commodities included.

In theory there should be no points above the line in Figure 17, but some do appear above the line due to stochastic variation (random sampling) in the probabilistic modelling process. This was not visible in Figure 16 and Table 7, so the paired comparison in Figure 17 is useful because it indicates that the effect of changing the variability factor from 5 & 7 to 3 is close to the limit of what our models can detect.

The lowest point on the right hand edge of Figure 17 represents the biggest change in the level of protection caused by the change in variability factors, and corresponds to the same scenario as was shown in Figure 15 (captan, The Netherlands, ages 1-97). The other 24 scenarios, for which the change of variability factor altered the number of commodities included, all had levels of protection greater than 99.9%.

It can also be seen from Figure 17 that changes in the level of protection caused by changing the variability factor from 5 & 7 to 3 (indicated by the scatter of points on the right edge of the graph) are smaller than the existing range of variation in the level of protection with the current variability factors of 5 & 7 (as indicated by the range of points on the diagonal line). This suggests that risk managers might be more concerned about the absolute levels of protection achieved in some scenarios using the current variability factors, than about the effect of changing from 5 & 7 to 3.

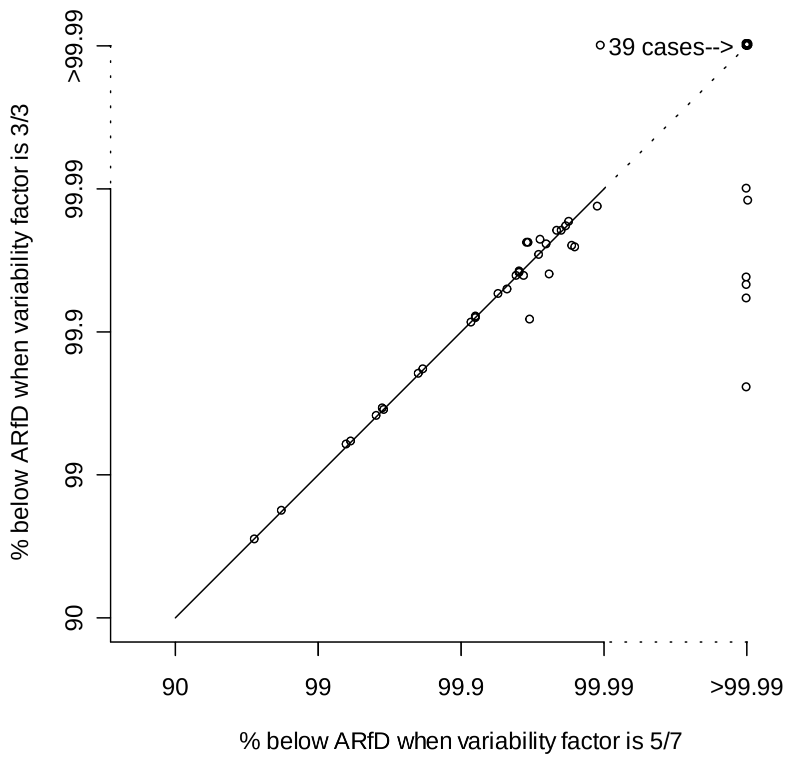

Figure 17: Estimated effect of changing the variability factor from 5 and 7 to 3, for 78 pesticide/country/age group scenarios. Each point represents one scenario. Points close to the diagonal line represent scenarios for which there is no change in the level of protection. Points markedly below and to the right of the line indicate scenarios where changing the variability factor causes an increase in the number of commodities with permissible uses, which leads to a decrease in the level of protection. There is some variation around the line due to stochastic variation in the probabilistic modelling process.

Note that the approach in this section implies an assumption that commodities with IESTIs exceeding the ARfD would no longer be treated with the pesticide concerned, so that their contribution to dietary intake drops to zero. In practice, some uses on these commodities might be allowed to continue with a modified GAP, so that they continue contributing to intake although perhaps at a lower level. This would reduce the impact of changing the variability factor on the level of protection. In addition, the results in this section are affected by the same general uncertainties as those in section 3. Furthermore, the reduced number of pesticides[24] (7) represented in these 25 particular scenarios, where changing the variability factor altered the number of commodities included, is too small to draw general conclusions[25].

[24] Captan, carbendazim, dimethoate, folpet, pirimiphos-methyl, thiacloprid, tolylfluanid (see Table 20 in Appendix Section 8.10).

[25] If any uses of the pesticides modelled by the Panel had already been withdrawn due to their IESTIs exceeding their ARfDs, this might tend to make the results in this section under-estimate the effect of changing the variability factors. However, as far as the Panel is aware, no withdrawals of this sort had occurred prior to the period when the monitoring data used by the Panel was collected.

The results above are an estimate of the effect of changing the variability factor on LoPs for the scenarios modelled by the Panel, and can also be interpreted as an approximate indication of the LoPs that may be achieved for other pesticide/country/age group scenarios that are similar to those modelled by the Panel.

When the IESTI of a commodity is close or equal to the ARfD, the LoP may be lower than for the scenarios modelled by the Panel. The Panel therefore conducted additional assessments to examine the effect of changing the variability factor on estimated minimum LoPs using the same approach as in section 3.1.4, *i.e.* assuming that the ARfD is equal to the highest IESTI of the commodities included in each scenario. The results are shown in Figure 18 and Table 8.

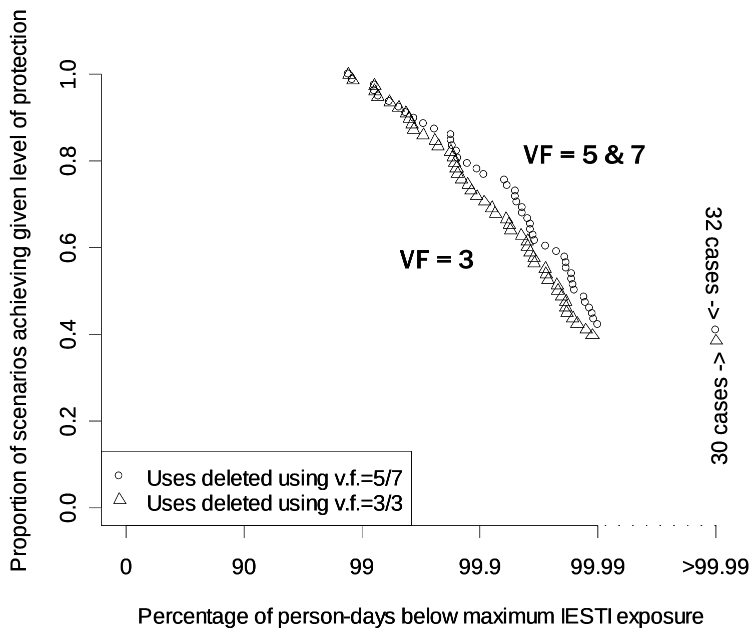

Figure 18: The effect of changing the variability factor from 5 and 7 (circles) to 3 (triangles) on the estimated minimum level of protection achieved in the same 78 pesticide/country/age group scenarios as Figure 16, but assuming the ARfD is reduced to be equal to the highest IESTI in each scenario.

Comparing Figure 17 with Figure 14, and Table 8 with Table 7 it can be seen that changing the variability factor from 5 and 7 to 3 has less effect on the level of protection for these scenarios, than the difference between the actual and minimum levels of protection. This emphasises the need for caution in extrapolating findings for the pesticides modelled by the Panel to other pesticides, for some of which the ARfD will be closer to the IESTI.

Table 8: The effect of changing the variability factor from 5 and 7 to 3 on the estimated minimum level of protection achieved in the same 78 pesticide/country/age group scenarios as Table 7, but assuming the ARfD is reduced to be equal to the highest IESTI in each scenario.

% of person-days below the given level of intake	Number of pesticide/country/age group scenarios (total=78)	
	Estimated minimum level of protection with VF = 5 and 7	Estimated minimum level of protection with VF = 3
0 – 90%	0	0
90 – 99%	2	2
99 – 99.9%	16	21
99.9 – 99.99%	28	25
> 99.99%	32	30

The Panel wishes to emphasise that its results are affected by many sources of uncertainty, so the true effect of changing the variability factor from 5 & 7 to 3 could be either larger or smaller than indicated above. A detailed list of uncertainties identified by the Panel is given in section 7, together with an evaluation of their combined effect on the Panel's conclusions.

4.2 ASSESSING EFFECT OF CHANGING IESTI EQUATION ON LEVEL OF PROTECTION AT THE MRL

Section 4.1 estimated the effect of changing the IESTI equation on the level of protection for all people in the selected age groups, including both consumers and non-consumers of the commodities considered. This was done because the question to the Panel specifically refers to "total population". However, as explained in section 1.3.2, there is also interest in the level of protection achieved for persons who consume a commodity containing residues at the level of the MRL. Therefore, in this section the Panel considers the effect of changing the IESTI equation on the level of protection for consumers of commodities containing residues at the MRL. As in Section 3.2, these assessments include the contributions of other commodities containing residues at monitoring levels. The Panel focused on examining the effect of changing the variability factors of 5 and 7 to 3, and on replacing the HR with the MRL, as time was limiting and it is understood that these are the changes of most interest to risk managers.

This section uses the same approach as section 4.1, but applied to the MRL-level scenarios that were modelled in section 3.2. The results in section 3.2 relate to MRL-level scenarios including all commodities which have IESTIs above the ARfD when calculated with the current default inputs including the HR and variability factors of 5 and 7. For this section, two new sets of model runs were conducted after adjusting the set of commodities by (a) including additional commodities that would have IESTIs below the ARfD if calculated with variability factor 3 (section 4.2.1), and (b) deleting commodities that would have IESTIs above the ARfD if calculated with the HR replaced by the MRL (section 4.2.2).

4.2.1 Effect of changing the variability factor

Results from scenarios for Germany and The Netherlands are initially presented separately. Changing the variability factors of 5 and 7 to 3 did not change the number of commodities with IESTIs below the ARfD in the tolylfluanid/The Netherlands/all ages (1-97) scenario, so the levels of protection for the 8 MRL-level assessments in this scenario were unchanged and remained as shown in Figure 13. However, changing the variability factor to 3 increased the number of commodities with IESTIs below the ARfD for the baby and 1-6 age groups for tolylfluanid in The Netherlands, so the levels of protection changed for these scenarios.

The effect on level of protection for the baby scenario is shown in Figure 19. The right hand curve in this graph is repeated from Figure 13 and shows the levels of protection achieved for this scenario with the current variability factors of 5 and 7. The left hand curve shows the effect of changing the variability factor to 3:

- There is one extra point on the curve, representing the addition of one commodity (pears). This commodity is added because its IESTI was above the ARfD when calculated with a variability factor of 5, but is below the ARfD when calculated with a variability factor of 3.
- The level of protection decreases detectably for 3 other commodities, grapes, potatoes and strawberries (their symbols move leftwards from one curve to the other). The intake from these commodities remains at the MRL and is unchanged, but the total intake increases due to the addition of pears at monitoring levels, so the proportion of consumption-days that are below the ARfD decreases. The addition of pears will also have affected intakes for other commodities, apples, courgette and tomatoes, but these changes are not detectable in the graph due to rounding.

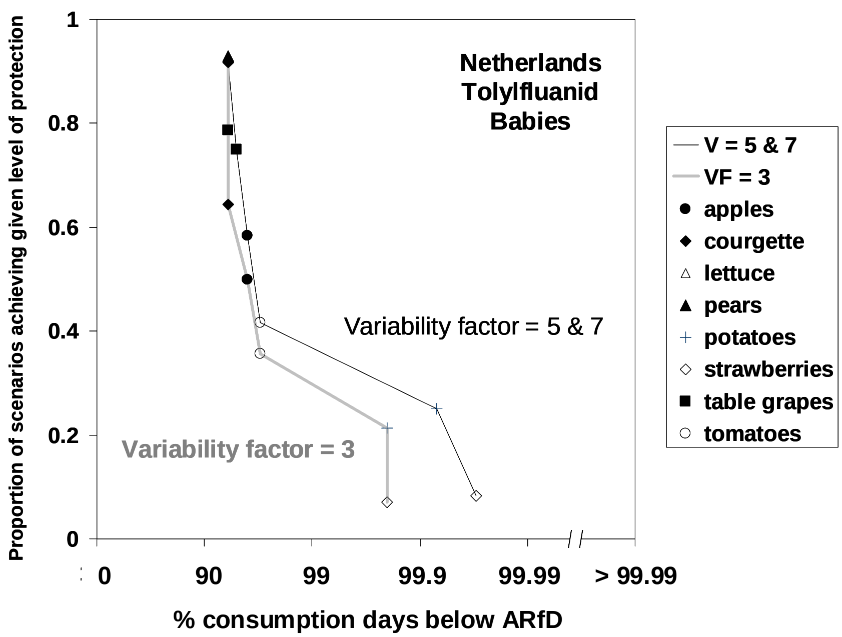

Figure 19: Effect of changing the variability factor on levels of protection for Dutch babies consuming one commodity containing tolylfluanid at the MRL and other commodities at monitoring levels.

Changing the variability factor to 3 also added one commodity to the scenario tolylfluanid/The Netherlands/ages 1-6, although in this case the commodity added was table grapes rather than pears. Changes in levels of protection for the 1-6 age group are not shown but were similar to those for the baby age group. As already mentioned, levels of protection did not change for the 1-97 age group in this scenario. The effect of changing the variability factor on LoPs for tolylfluanid in all three Dutch age groups is summarised together in Figure 20. This shows that changing the variability factor to 3 results in 2 additional commodities having IESTIs below the ARfD for tolylfluanid. As mentioned above, these relate to pears/babies and table grapes/ages 1-6. These are represented by the filled triangles plotted at the right side of Figure 20, showing the level of protection when those commodities are at the MRL and others are at monitoring levels.

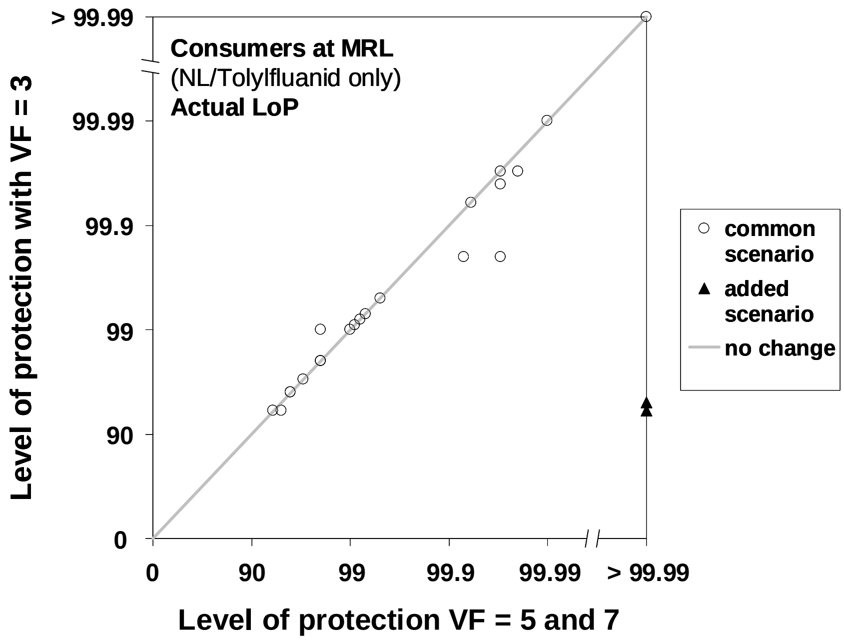

Figure 20: Effect of changing the variability factor from 5 and 7 to 3 on the estimated actual level of protection in MRL-level assessments for all the tolylfluanid/The Netherlands scenarios analysed by the Panel. Points below the line indicate scenarios where changing the variability factor to 3 causes a decrease in the level of protection. Solid triangles on the right edge of the graph represent scenarios that are added when the variability factor is changed to 3.

Figure 21 shows the effect of changing the variability factor on levels of protection for children in Germany consuming one commodity or commodity group (*e.g.* pome fruits) containing residues of a pesticide at the MRL and other commodities containing residues of the same pesticide at monitoring levels.

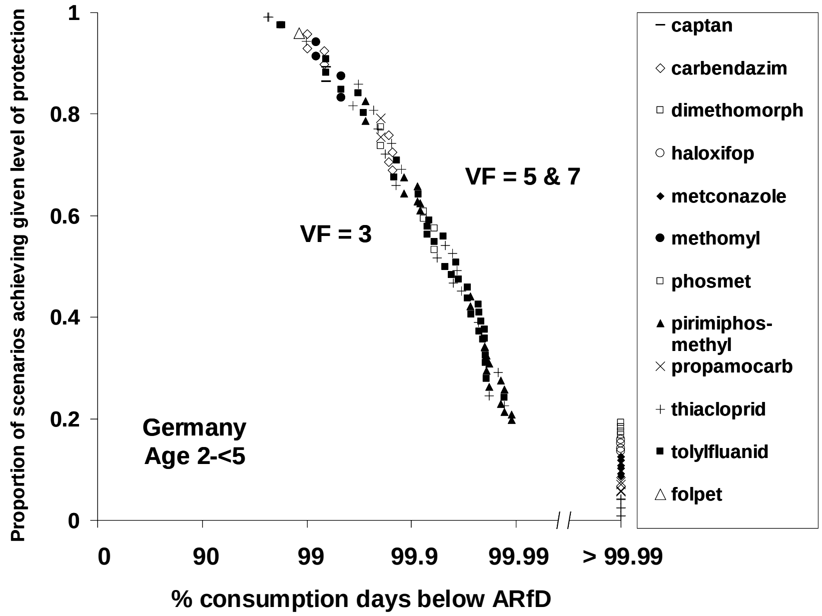

Figure 21: Effect of changing the variability factor on levels of protection for children in Germany consuming one commodity or commodity group (*e.g.* pome fruits) containing residues of a pesticide at the MRL and other commodities containing residues of the same pesticide at monitoring levels.

The main impression from Figure 21 is that the two curves of points are very close together, *i.e.* the effect of changing the variability factors of 5 & 7 to 3 is barely detectable for these scenarios, and much smaller than the range of variation in levels of protection amongst the different scenarios. This is also apparent in the paired comparison plot (Figure 22). For the set of pesticides modelled (listed in Figure 21), changing the variability factor to 3 would result in only 3 additional commodities having IESTIs below the ARfD: these are shown with filled triangles in Figure 22. Two of these are towards the lower end of the range of levels of protection (around 99%). However, in both these cases, nearly all of the intake of the consumers is coming not from the commodity at the MRL, but from one of the other commodities which are at monitoring levels, which were not altered by the change of variability factors. Only the third case (tolylfluanid/grapes) lies away from the diagonal line, indicating a change in level of protection for consumers of that commodity if it is given an MRL as a result of changing the variability factor to 3.

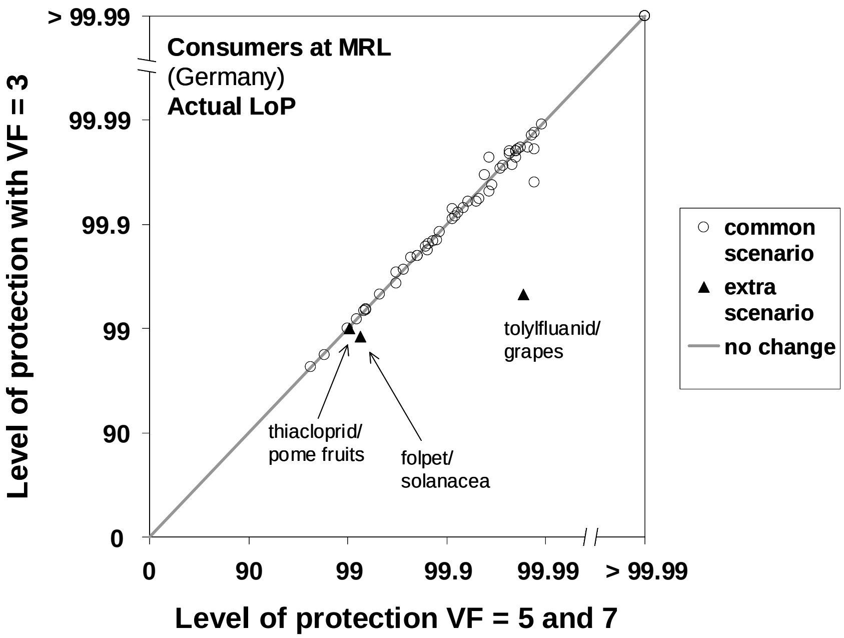

Figure 22: Effect of changing the variability factor from 5 and 7 to 3 on the estimated actual level of protection in MRL-level assessments for the German scenarios analysed by the Panel. Points below the line indicate scenarios where changing the variability factor to 3 causes a decrease in the level of protection. Solid triangles represent scenarios that are added when the variability factor is changed to 3[26]. For these scenarios, pome fruits comprise apples and pears, solanacea comprise tomatoes, peppers and aubergines.

The estimated effects of changing the variability factor from 5 & 7 to 3 are summarised in Table 9, combining both the Dutch and German scenarios. This shows the number of pesticide/country/age group scenarios that achieve different levels of protection when compared to the ARfD and also to 2x and 10x the ARfD. It reflects the results already seen in Figures 19-22: the number of commodity scenarios considered increases by 5 (due to their IESTIs decreasing to below the ARfD), and these additional scenarios tend to have lower levels of protection than the others.

[26] Note that in Figure 20, the solid triangles were on the right margin of the graph, whereas in Figure 22 they are not. This is because the models for Germany estimated the level of protection for these scenarios both with a variability factor of 3 (when the identified commodity was assumed to be at the MRL) and with a variability factor of 5 or 7 (when the identified commodity was assumed not to be granted an MRL so the intake derives only from the other commodities at background level). In other words, the position of the triangle shows the difference in level of protection between consumers of that commodity at its MRL, and the same consumers when no MRL is set for that commodity and intake comes only from the other commodities at monitoring levels.

Table 9: The effect of changing the variability factor from 5 and 7 to 3 on the proportions of person-days of exceeding 1x, 2x and 10x the ARfD for consumers of commodities at the MRL in a selection of pesticide/commodity/age group scenarios for Germany and The Netherlands. Summary of results in Figures 19-22.

% of consumption-days below the given level of intake	Number of pesticide/country/age group scenarios					
	Variability factor = 5 or 7			Variability factor = 3		
	1 x ARfD	2 x ARfD	10 x ARfD	1 x ARfD	2 x ARfD	10 x ARfD
0 – 90%	0	0	0	0	0	0
90 – 99%	11	5	0	15	7	0
99 – 99.9%	22	18	5	25	19	7
99.9 – 99.99%	35	27	21	33	31	24
> 99.99%	13	31	55	13	29	55
Totals	81			86		

The Panel wishes to emphasise again that its results are affected by many sources of uncertainty, so the true effect of changing the variability factor from 5 & 7 to 3 could be either larger or smaller than indicated above. A detailed list of uncertainties identified by the Panel is given in section 7, together with an evaluation of their combined effect on the Panel's conclusions.

4.2.2 Effect of replacing the high residue (HR) with the MRL

Replacing the HR with the MRL did not change the number of commodities with IESTIs below the ARfD in the tolylfluanid/The Netherlands/all ages (1-97) scenario, so the levels of protection for the 8 MRL-level assessments in this scenario were unchanged and remained as shown in Figure 13. However, changing the HR to MRL increased the number of commodities with IESTIs above the ARfD for the baby and 1-6 age groups for tolylfluanid in The Netherlands. If these commodities were not granted MRLs, then (a) exposure of consumers at the MRL for these commodities should not occur, and (b) these commodities would cease to contribute (at monitoring levels) to the intakes of consumers who eat other commodities at the MRL.

The effect on levels of protection for the baby scenario is shown in Figure 23. The right hand curve in this graph is repeated from Figure 13 and shows the levels of protection achieved for this scenario with the HR. The left hand curve shows the effect of changing to the MRL:

- There is one less commodity on the curve (apples). This commodity is omitted because its IESTI was below the ARfD when calculated with the HR, but is above the ARfD when calculated with the MRL.
- The level of protection increases detectably for 2 other commodities, potatoes and strawberries (their symbols move rightwards from one curve to the other). This is because of decreased intakes due to the contribution of apples at monitoring levels, which was excluded when the IESTI was calculated with the HR.

In both Figure 19 and Figure 23, changing the IESTI inputs moves points to the right of the curve more than those to the left. This is partly a consequence of the logarithmic scale of the horizontal axis, but also partly reflects the fact that intake of the commodity at the MRL is smaller for points on the right of the curve, so the change due to monitoring levels of the commodity that is deleted or removed tends to be relatively larger than for points on the left.

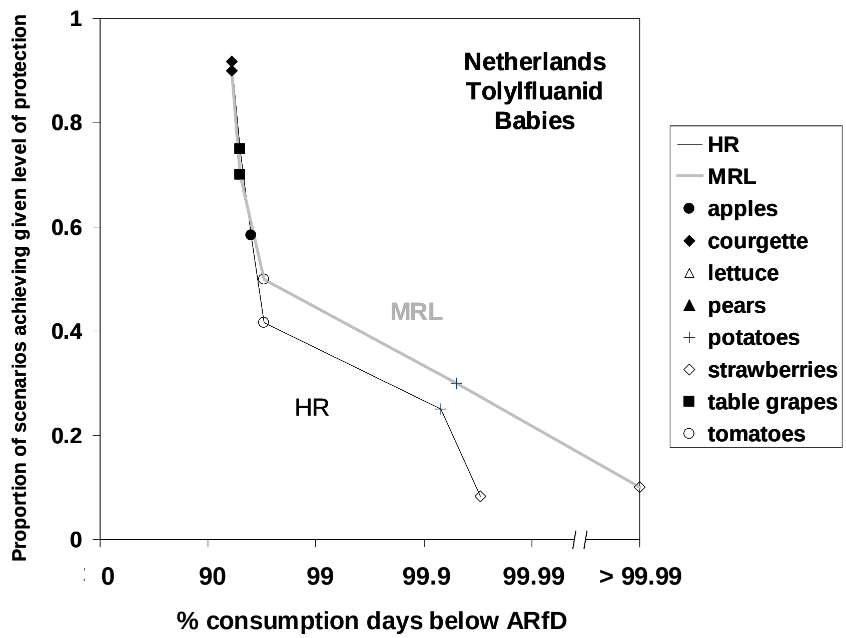

Figure 23: Effect of changing replacing the HR in the IESTI equation with the MRL on levels of protection for Dutch babies consuming one commodity containing tolylfluanid at the MRL and other commodities at monitoring levels.

Replacing the HR with the MRL also removed one commodity from the scenario tolylfluanid/The Netherlands/ages 1-6, although in this case the commodity deleted was lettuce rather than apples. This caused little increase in the level of protection for the 1-6 age group, probably because monitoring levels of tolylfluanid on lettuce were low so the reduction in intake was small (even though the IESTI for lettuce was high). As already mentioned, levels of protection did not change for the 1-97 age group in this scenario. The effect of replacing the HR with the MRL on LoPs for tolylfluanid in all three Dutch age groups is summarised together in Figure 24.

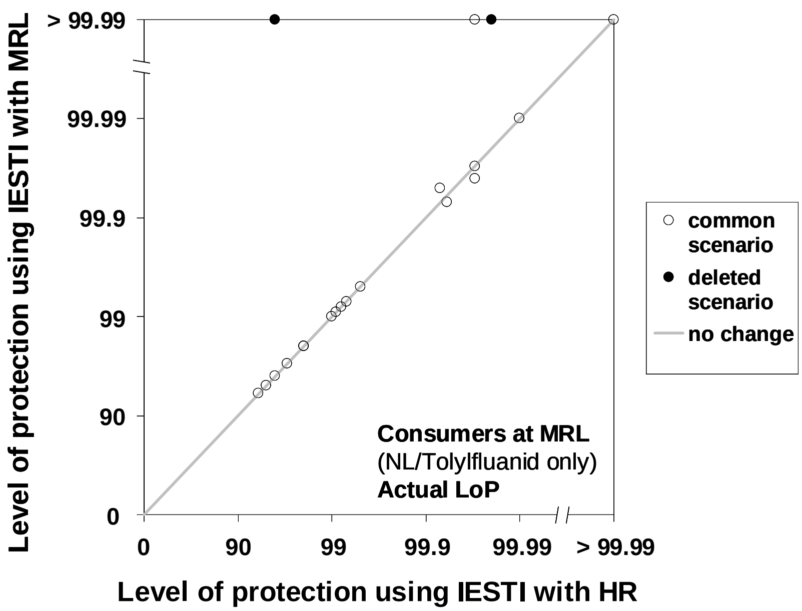

Figure 24: Estimated effect of replacing the HR with the MRL on the estimated actual level of protection in MRL-level assessments for all the tolylfluanid/The Netherlands scenarios analysed by the Panel. Points above the line indicate scenarios where replacing the HR with the MRL causes an increase in the level of protection. Solid circles on the top edge of the graph represent scenarios that are deleted when the HR is replaced with the MRL.

Figure 25 shows the effect of replacing the HR with the MRL on levels of protection for children in Germany consuming one commodity or commodity group (*e.g.* pome fruits) containing residues of a pesticide at the MRL and other commodities containing residues of the same pesticide at monitoring levels.

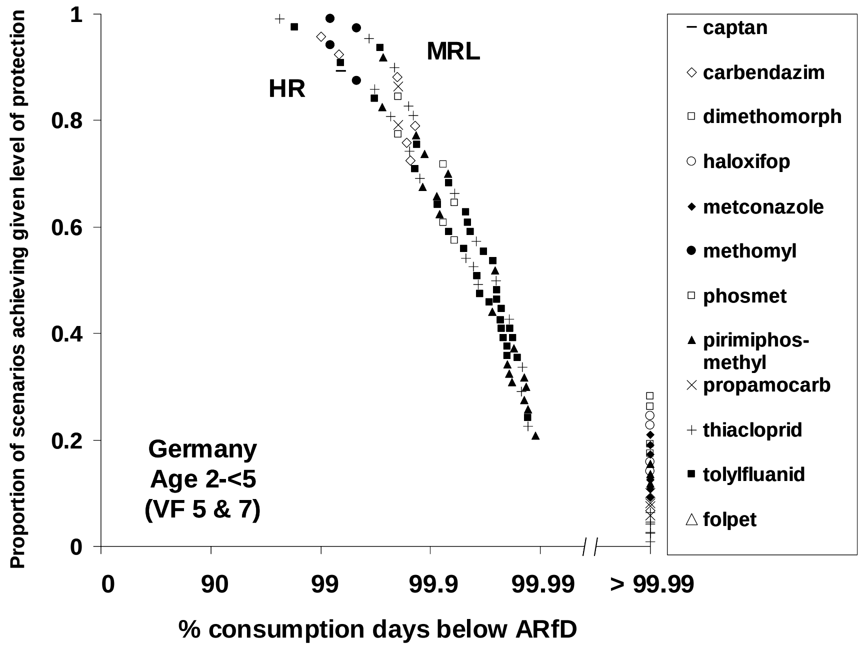

Figure 25: Effect of replacing the HR with the MRL on levels of protection for children in Germany consuming one commodity or commodity group containing residues of a pesticide at the MRL and other commodities containing residues of the same pesticide at monitoring levels.

Whereas changing the variability factor from 5 & 7 had little impact for the German scenarios (Figure 21), replacing the HR with the MRL causes a noticeable increase in the level of protection (Figure 25): the two curves of points are distinguishable although not far apart. Nevertheless, the effect of replacing the HR with the MRL is still much smaller than the range of variation in levels of protection amongst the different scenarios.

The paired comparison plot shows that replacing the HR with the MRL causes the IESTI to rise above the ARfD for 6 commodities (filled triangles in Figure 26), of which 5 show noticeable increases in the level of protection for consumers at the MRL.

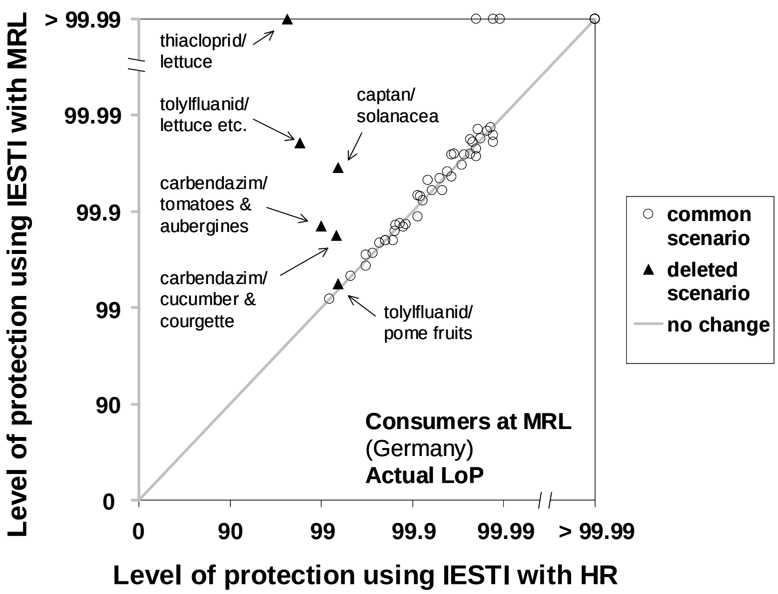

Figure 26: Effect of replacing the HR with the MRL on the estimated actual level of protection in MRL-level assessments for the German scenarios analysed by the Panel. Points above the line indicate scenarios where replacing the HR with the MRL causes an increase in the level of protection. Solid triangles represent scenarios that are added when the HR is replaced with the MRL[27]. For these scenarios, pome fruits comprise apples and pears, solanacea comprise tomatoes, peppers and aubergines.

The estimated effects of replacing the HR with the MRL are summarised in Table 10, combining both the Dutch and German scenarios. This reflects the results already seen in Figures 23-26: the number of commodity scenarios considered decreases by 8 (2 Dutch and 6 German) due to their IESTIs increasing to above the ARfD.

[27] Note that in Figure 24, the solid circles were on the upper margin of the graph, whereas in Figure 26 they are not. This is because the models for Germany estimated the level of protection for these scenarios both when the IESTI is calculated with the HR (when the identified commodity was assumed to be at the MRL) and when the IESTI is calculated with the MRL (when the identified commodity was assumed not to be granted an MRL so the intake derives only from the other commodities at background level).

Table 10: The effect of replacing the HR in the IESTI equation with the MRL on levels of protection achieved for consumers of commodities at the MRL in a selection of pesticide/commodity/age group scenarios for Germany and The Netherlands. Summary of results in Figures 23-26. Note that the current variability factors (including 5 & 7) were used for both sets of scenarios.

% of consumption-days below the ARfD	Number of pesticide/country/age group scenarios	
	Estimated level of protection using the HR in the IESTI equation	Estimated level of protection replacing the HR with the MRL
0 – 90%	0	0
90 – 99%	11	8
99 – 99.9%	22	19
99.9 – 99.99%	35	29
> 99.99%	13	17
Totals	81	73

The Panel wishes to emphasise again that its results are affected by many sources of uncertainty, so the true effect of replacing the HR with the MRL could be either larger or smaller than indicated above. A detailed list of uncertainties identified by the Panel is given in section 7, together with an evaluation of their combined effect on the Panel's conclusions.

5 Contribution of different commodities to aggregate intake

A key feature of the IESTI equations is that they provide a simple estimate of intake calculated for one commodity at a time, whereas in reality most pesticides are used on multiple commodities and the risk to an individual person is determined by their total intake aggregated over all the commodities they consume. Therefore in this section the Panel uses results from probabilistic modelling to analyse the contribution of multiple commodities to overall intakes, and considers how this might influence the performance of the IESTI equations as a regulatory tool. Due to limitations of time the Panel was unable to carry out a comprehensive analysis of this issue, and instead uses selected examples to illustrate the types of patterns that can occur.

It is obvious that the pattern of contributions to overall intake by different commodities will differ between assessments for people who consume one commodity containing residues at the MRL and other commodities at background levels, and total population assessments, which model concentrations for all commodities at monitoring levels and consider both consumers and non-consumers. Therefore these two types of assessment are considered separately in the following sections.

5.1 Contributions to overall intake for the total population

The Panel used the MCRA probabilistic model to examine the contribution of different commodities to overall intake of tolylfluanid by children aged 1-6 in The Netherlands. The model was run repeatedly, starting by including all the commodities for which monitoring data were available and then removing one commodity at a time. Commodities were removed in decreasing order of their IESTIs for tolylfluanid (calculated for this country and age group, with the current variability factors). The results are shown in Figure 27, which shows how the distribution of overall intakes changes as the first 7 commodities are removed from the assessment. The distribution for all commodities just crosses the ARfD for tolylfluanid, with between 99.9 and 99.99% of the population having intakes below the ARfD. Apart from some minor variation in the upper tail (probably largely due to stochastic variation in the model), the distribution of intakes changes very little when the three commodities with the highest IESTIs are removed (grape, lettuce and pear). There is then a marked decrease in intakes when apples, which have the fourth highest IESTI, are removed. Above 90 on the vertical axis, the intake distribution shifts to the left by approximately one log unit on the horizontal axis, implying about a ten-fold reduction in intakes for the top 10% of person-days when apples are removed. The remaining intakes are then little affected by removal of three further commodities with the next highest IESTIs (leek, cucumber, tomato).

Shown in the top left corner of Figure 27 are the percentage contributions of each commodity to total intake, aggregated over all individuals, when all commodities are included. This shows apples as the biggest contributor with 73% of the total intake, which is consistent with the result shown by the curves in the graph.

This example shows that (a) even when the pesticide is present in many commodities, overall intake for the total population can be dominated to a large extent by a single commodity, and (b) the commodity with the highest IESTI is not necessarily the biggest contributor to intakes. Similar results were obtained from a separate analysis of contributions of different commodities to overall intakes of tolylfluanid by Irish children, using the CREMe model.

This behaviour has potentially significant consequences for regulation. In the example in Figure 27, the IESTI for grapes is above the ARfD so in principle would not be authorised, although in practice the contribution of grapes to overall intakes of the total population in this case is very small; whereas the IESTI for apples is below the ARfD, yet this commodity is the main contributor to total population intake and seems mainly responsible for those individuals who are estimated to exceed the ARfD.

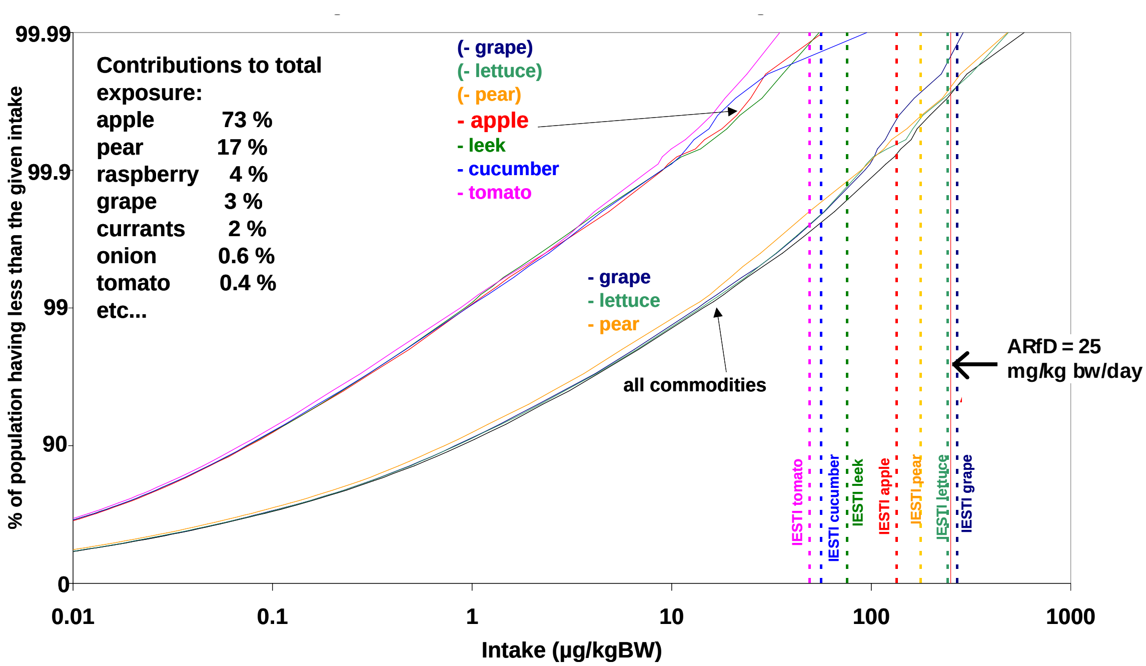

Figure 27: Analysis of the contributions of different commodities to the overall intakes of tolylfluanid by children aged 1-6 in The Netherlands. The curves show how the cumulative distribution for overall intake changes as commodities are removed one at a time from the assessment, in decreasing order of their IESTIs for this scenario. The biggest change occurred when apples (which have the fourth highest IESTI) were removed.

Intake is not always dominated by a single commodity. An example where several commodities contribute similar shares to overall intake is shown in Figure 28. Note that the figure relates specifically to contributions to intakes for individuals in the top 1% of the population considered.

However, this example does resemble the preceding one in another respect: the relative contributions of different commodities to overall intakes do not have a consistent relationship to their IESTIs. Pears and apples are first and 4th contributors to intake of the top 1% of the population in Figure 28, and have the 2nd and 4th highest IESTIs; but tomato and peppers which are 2nd and 3rd contributors to intake are 7th and 10th highest IESTIs. Lettuce has the highest IESTI for this scenario but makes a negligible contribution to intakes.

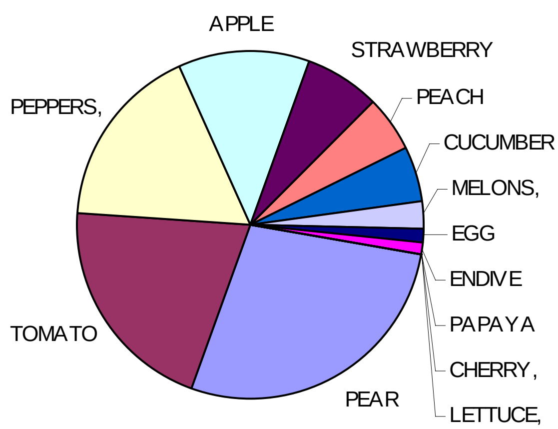

Figure 28: Contributions of different commodities to the top 1% of overall intakes of thiacloprid in the Dutch population, ages 1-97. Estimated using the MCRA model.

Figure 28 shows that several commodities contribute similar shares of intake for the top 1% of the population considered as a group, but it would also be interesting to see whether individual persons derive their intakes mainly from one commodity or from several. The Panel did not investigate this in detail, but as an example, the Panel examined the modelled intakes for the 9 individuals closest to the 99.9th percentile of the intake distribution for thiacloprid in this scenario. For each of these nine individuals, all or virtually all the intake came from a single commodity, although the commodity involved differed between individuals: for 2 it was apple, for another 2 it was peach, and then there was one individual each with strawberry, pear, cucumber, peppers, and tomato. Thus although several commodities contributed to the overall intake of the top 1% of the population, the 9 individuals examined each derived virtually all their intake from a single commodity. If this were a general pattern, then the effect of adding more commodities for a pesticide would be primarily to increase the proportion of the population experiencing high intakes, rather than increasing the level of those intakes. However, a more comprehensive analysis covering a range of pesticides and populations would be required to determine whether this is a general pattern.

Figures 27 and 28 provide contrasting examples: in the first, the population intake was dominated by a single commodity, whereas in the second, several commodities made similar contributions. As a first step towards exploring the relative frequency of these patterns, the Panel analysed the contributions of different commodities in all the “total population” scenarios modelled with MCRA. The results are summarised in Figure 29. This shows that in most scenarios one commodity contributes at least half of the intake, with the median contribution for the first commodity being about 60%. The contribution for the second commodity has a median of about 20%, but in a few scenarios it is close to 50%. Contributions from the third and subsequent commodities tend to be small. These results were calculated over all person-days, but almost identical results were obtained when calculated over only the 1% of person-days with highest intakes.

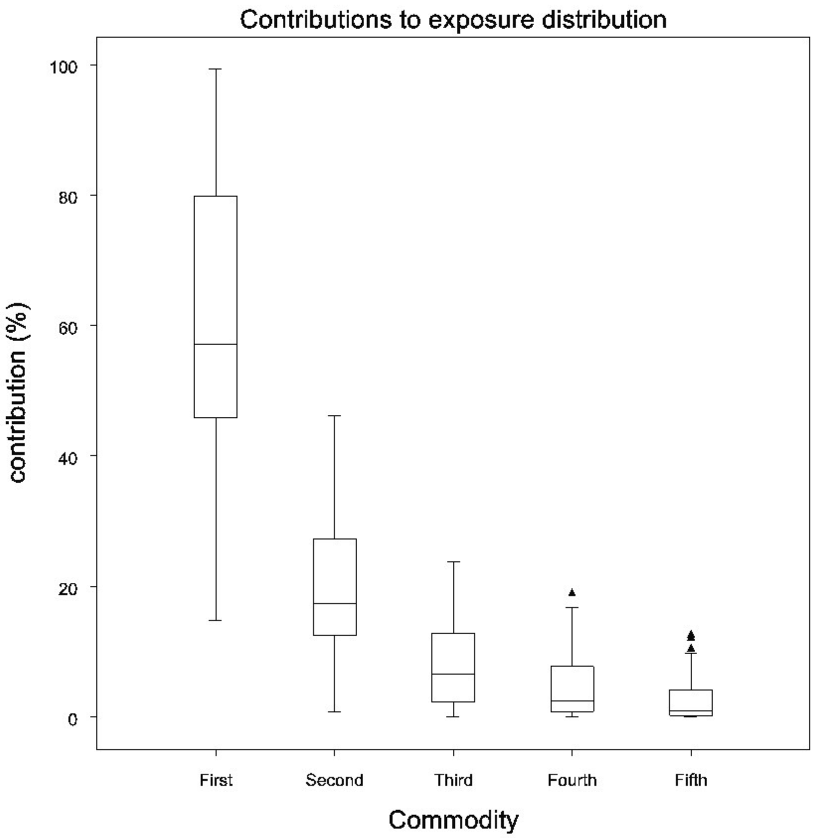

Figure 29: Box and whisker plot for the contribution to overall intake for the first five commodities for each of the total population scenarios modelled with MCRA (ranked by contribution). The boxes show the interquartile range (25th to 75th percentile), the horizontal line shows the median, and the whiskers and symbols show the extreme values.

Apple was the commodity that most often made the dominant contribution to intake in 61 pesticide/country/age group scenarios modelled with MCRA, followed by grapes and pears (Table 11). Perhaps surprisingly, wheat makes a dominant contribution in 3 of the 6 scenarios shown.

Table 11: Contributions of different commodities to overall intake 61 pesticide/country/age group scenarios modelled with MCRA.

	>=10%	10-50%	50-80%	>= 80 %
Apple	43	19	12	12
Grape	16	9	5	2
Wheat	3	0	1	2
Pear	25	21	4	0
Peach	10	9	1	0
Orange	11	11	0	0
Tomato	5	5	0	0
Cucumber	4	4	0	0
Mandarin	3	3	0	0
Other commodities	<=2	<=2	0	0

5.2 Contributions to overall intakes of consumers of commodities at the MRL

The Panel also analysed the contributions of different commodities in the Dutch "MRL" scenarios modelled with MCRA. The results are summarised in Figure 30, and all relate to tolylfluanid. They show that in most scenarios intake is strongly dominated by a single commodity (median contribution over 95%). The contribution for the second commodity has a median of less than 5%, but in a few scenarios it is close to 40%. Contributions from the third and subsequent commodities tend to be very small.

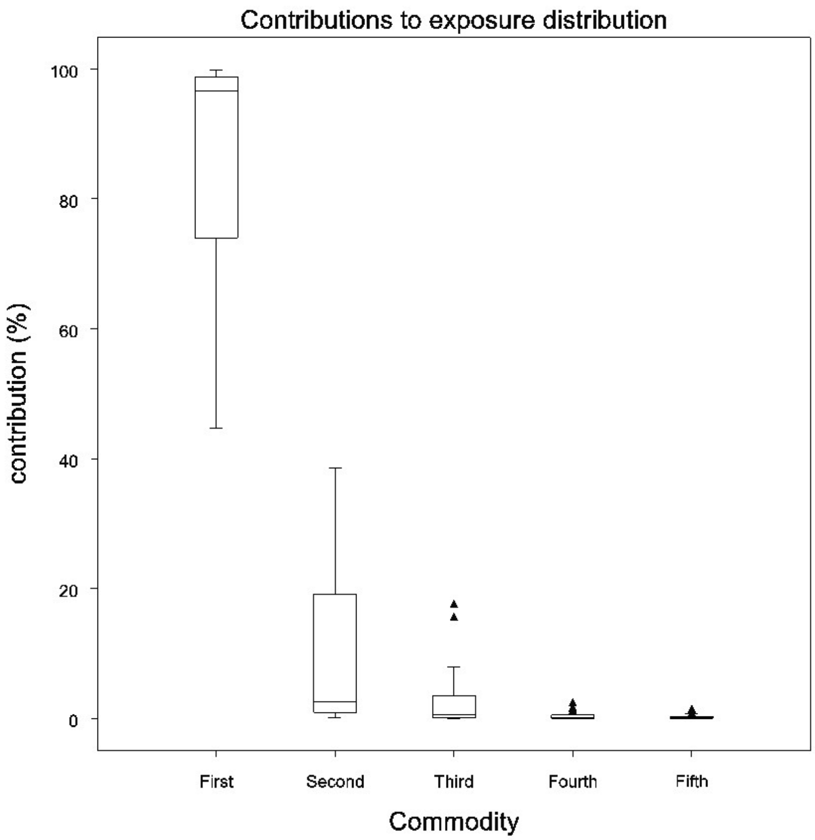

Figure 30: Box and whisker plot for the contribution to overall intake for the first five commodities for the Dutch MRL scenarios modelled with MCRA (ranked by contribution). The boxes show the interquartile range (25th to 75th percentile), the horizontal line shows the median, and the whiskers and symbols show the extreme values.

6 Comparison between measured and modelled intakes

The intake of pesticides has been calculated using different national food consumption databases and residue databases (see Annex), so it is essential to consider how well the modelled intake predicts the real intake. In the European funded project Monte Carlo (QLRT-1999-00155) it was considered that a probabilistic model would be valid or fit for purpose when (a) measured intake was lower than the modelled intake, and (b) the modelled intake was lower than the IESTI approach (Gibney and van der Voet, 2003). Boon *et al.,* (2003) and López *et al.,* (2003) concluded that these criteria were satisfied for the models used in the Monte Carlo project, when compared with measured intakes using duplicate diet studies. The IESTI calculations and probabilistic modelling used monitoring data of the same period in which the duplicate diets were collected. These studies however did not include using field trial data, and the probabilistic models used consumption data from the duplicate diet study (thus increasing the likelihood that they would agree). Furthermore, although the general approach is the same and the CREMe model is essentially the same as the model evaluated by Boon *et al.,* (2003) and López *et al.,* (2003), the MCRA model used in this opinion differs in detail from the model used by Boon *et al*., (2003) and López *et al*., (2003) In this section we therefore compare the measured intakes from the duplicate diet study with predicted intakes for the same pesticides and age group using one of the models used in this opinion, MCRA 5.1. For this only the data collected in the Dutch duplicate diet study were available.

6.1 STUDY POPULATION

The study population consisted of 250 children aged 8-12 months. The infants were recruited in 2000 and 2001. The sampling strategy was designed to include as many children as possible that were fed home-made meals of fruits and vegetables as opposed to manufactured baby food. Children still breast-feeding were excluded from the study due to expected difficulties of collecting breast milk. So the study was representative for Dutch babies given fresh fruit and vegetables, rather than the whole population of babies in The Netherlands.

6.2 DUPLICATE DIET COLLECTION

Carers of the children were requested to prepare a duplicate portion of all meals consumed by the infant during the study day. Duplicate portions were collected in two different clean, leak–proof 1 L polyethylene containers. All fresh vegetables and fruits or food products containing these items were combined in one container and collected separately from other consumed items. In this way possible dilution of pesticides present by food items that do not contain these chemicals was minimised. The containers were placed in cool–boxes with frozen elements or in the participants' refrigerator. At arrival at the institute, containers were homogenised separately[28]. From the fruit and vegetable container an aliquot was collected for laboratory analysis of the pesticides. The samples were stored at −20 °C. Food was collected the whole year round to account for the consumption of all seasonal fruits and vegetables.

6.3 FOOD DIARY

Participants were asked to record food consumption during the day of food collection and to weigh and record the quantities consumed. For this the respondents were supplied with a food diary and a weighing scale (g). The consumption of foods as such was translated into the consumption of raw agricultural commodities (RACs) using the conversion model Primary Agricultural Products (CPAP), developed at the RIKILT–Institute of Food Safety (van Dooren *et al.,* 1995). For example, if a caretaker recorded consumption of 'spaghetti baby food', the model converted this food item into its primary ingredients such as wheat, tomato, pork, vegetable and animal fat, water etc. Body weight was recorded as the weight measured during the last visit at the child health centre prior to the collection day and was corrected for the days between the visit and the measurement.

6.4 PESTICIDE ANALYSES IN DUPLICATE PORTIONS

Samples were analysed for 19 pesticides at a limit of reporting (LOR) of 1 µg/kg, as opposed to 10 µg/kg in methods used in regular monitoring programmes. This low level is important due to dilution of foods containing pesticides with those containing none when collecting duplicate diets. Furthermore, small children consume mainly small amounts of fruits and vegetables after some sort of processing, reducing the probability of detecting pesticide residue levels in duplicate diets.

To achieve such a low LOR, a new method was developed to quantify residue levels as low as 1 µg/kg. Briefly, an extract of the samples was prepared by continuous shaking overnight with acetone, petroleum–ether and dichlormethane. The extract was filtered and after clean–up analysed for pesticides by Large Volume Injection Gas Chromatography. Quality control was performed. The quality of the results of the duplicate diet study is linked to the difficulty of measuring pesticides at the level of 1 µg/kg food. Quality control was performed showing that recovery of residues was rather variable over eight analytical runs, with coefficients of variation

[28] Although for some pesticides, homogenisation at ambient temperatures can cause loss of residues, unpublished information available to the Panel suggests this is unlikely to have occured to a significant extent for the pesticides considered here (Hamey P and van Klaveren JD, personal communications).

between 36% and 38% (Díez *et al.,* 2006). This was due to the sensitivity of the method and its novelty. Intake calculations were corrected for the lower recovery using a run-averaged correction factor for each pesticide.

6.5 RESULTS

In 14% of the Dutch duplicate diets a residue of a pesticide was found. Of the 19 pesticides analysed positive values were reported for chlorfenvinphos (3x), chlorpyrifos (6x), iprodione (4x), methamidophos (3), pirimicarb (9), and pirimiphos-methyl (4). For these six pesticides monitoring results have been extracted from the Dutch residue database for the year 2000/01. For three of the six pesticides reliable field trial data that are more or less representative for Europe during that period could be found.

Results of the model validation are plotted in Figure 31. The distributions for intakes measured in the duplicate diet study are incomplete, due to the limited number of positive values found. It can be assumed that more positive values would have been detected if a lower detection limit could have been established. Also higher values might have been found in duplicate diets if the number of children in the study would have been larger. It is however well recognised that duplicate diet studies are not useful for case finding because of practicalities and costs involved in this type of study (van Klaveren *et al.,* 2000).

Although the duplicate diet study does not provide complete distributions of intakes, Figure 31 shows that, at the 99th percentile, the measured intake is a factor of 10 or more below the modelled intake based on monitoring results, which in turn is lower than the modelled intake using field trial data.

The difference between the measured and modelled intakes in Figure 31 cannot be due to differences in consumption, since the consumption data from the duplicate diet study was also used in the probabilistic modelling (here and in earlier sections of the Opinion). The differences are probably partly be due to assumptions used in the model. Infant food is usually processed very well, and we cannot exclude that the processing factor might have been higher at that time than was assumed when modelling. Also the variability factor used in the model may over-estimate the actual variability of residues in the infants' diets, which may be more mixed than food eaten by adults. The differences might also be partly due to differences between the monitoring data used in the model and the distributions of residues actually present in the fruit and vegetables used in the infant diets. This could arise if the purchasing habits of the parents in the duplicate diet study differed from the general population (*e.g.* if they were more likely to buy organic food).

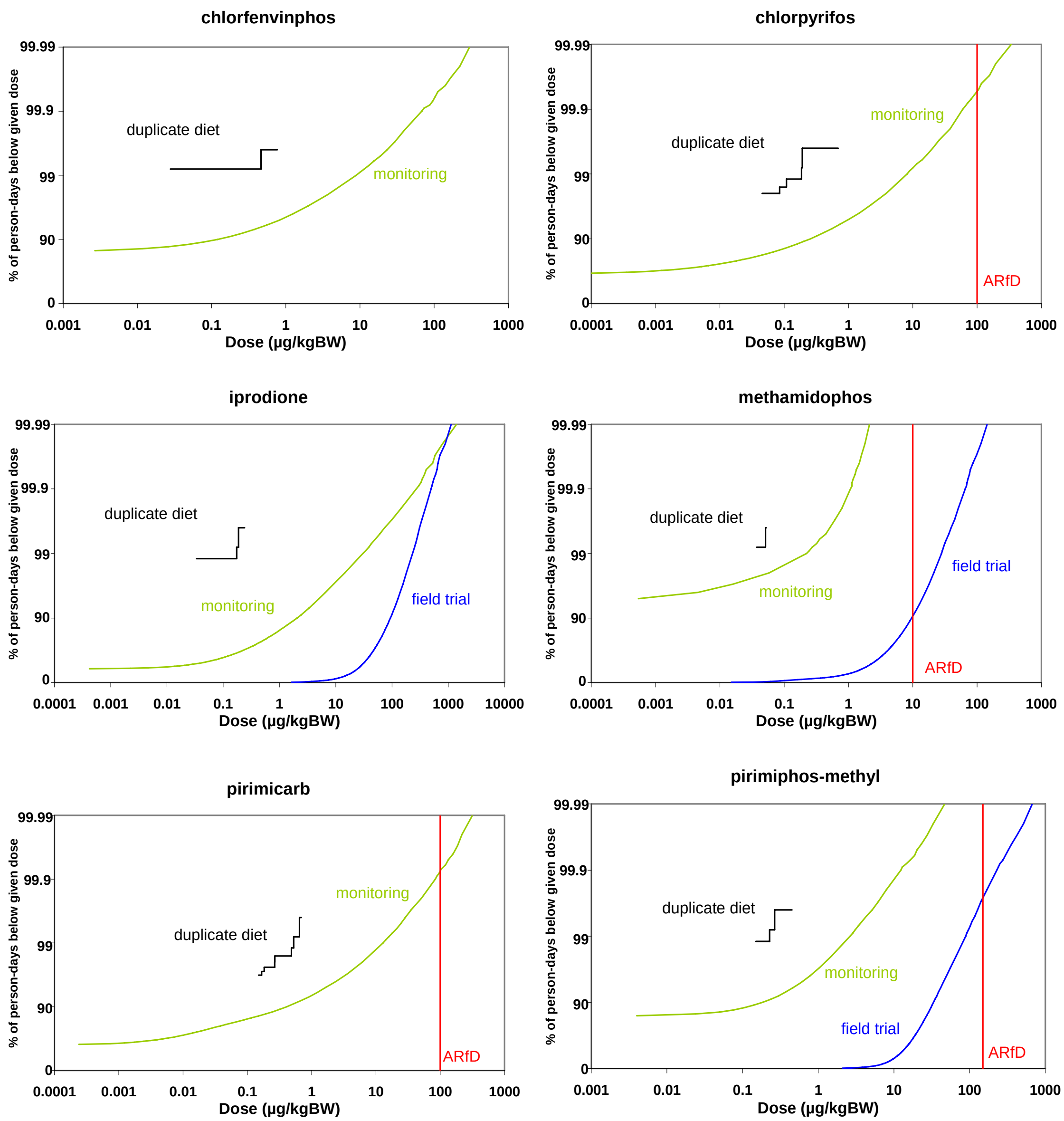

Figure 31: Validation of MCRA modelling results by comparison with empirical distribution from duplicate diet study for six pesticides. The Acute Reference Dose (ARfD) is also shown for comparison. Only a section of the distribution is estimated for the duplicate diet data, due to the limited number of infants studied and limited number of positive residues.

The duplicate diet study was focused on infants because they were assumed to be a vulnerable group (SCF, 1997; NRC, 1993). It was also recognised that the diet of infants is different from that of adults and that consumption data of infants is hardly considered in the risk assessments (SCF, 1997). As mentioned earlier, the duplicate diet study is not representative of all Dutch infants, but of a selected subset which is fed fresh fruit and vegetables. It is not known to what extent the results of this study can be extrapolated to other consumer groups. Infant food might be more mixed than food eaten by adults. However, eating fresh fruit and vegetables was set as an important criterion for selection of participants in the duplicate diet study. Based on those arguments one can speculate that the difference between measured and modelled intake might be smaller for other consumer groups, such as adults which consume more fresh salads where the effect of processing factors is likely to be smaller.

In conclusion, the comparisons in this section provide some support for thinking that probabilistic modelling using concentrations from monitoring programs may tend to over-estimate true intakes. If this were generally true for the modelling in this opinion, it would make the Panel's findings conservative in the sense that levels of protection would be under-estimated. However, the comparisons in this section were done for babies, and there are factors that might make the difference between measured and modelled intake smaller for other age groups. In addition, the comparisons were limited to 6 pesticides in one country and it is uncertain how representative they are of other pesticides and other countries.

7 Uncertainties affecting the assessment (quantified and unquantified)

As has been remarked at many points in this Opinion, the Panel's assessment is affected by a large number of uncertainties. It is essential to take these into account when interpreting the results and/or when using them for decision-making. The aim of this section is therefore to characterise the uncertainties as clearly as possible. This is done in three main parts:

- A few of the uncertainties affecting the probabilistic modelling used in the opinion can be quantified and shown as confidence intervals on model outputs. It was not practical to do this for every model run, so the Panel decided to quantify as many uncertainties as possible for a single scenario (carbendazim/apples/UK toddlers) and use this as an indication of the influence of the same uncertainties on other probabilistic modelling in the opinion. The results of this work are presented in section 7.1.
- Three different probabilistic models developed by 3 different groups are used in the main part of the opinion, and a fourth (the CSL model) is used to model additional uncertainties in section 7.1. The principles of the 4 models are similar but it is possible that differences in methodology or even coding errors might introduce differences or errors in the results. To check for this the Panel applied all 4 models to a single scenario (again carbendazim/apples/UK toddlers), using the same data on consumption and concentrations, and compared the results. This is presented in section 7.2.
- Many other uncertainties affect the assessment, which are not quantified in sections 7.1 or 7.2. Therefore the Panel listed all those uncertainties it identified, together with a qualitative evaluation of their potential impacts on the outcome of the assessment. The results are presented in section 7.3, following the approach recommended in the Scientific Committee's guidance on uncertainties in dietary exposure assessment (EFSA, 2006).

7.1 QUANTIFICATION OF ADDITIONAL UNCERTAINTIES IN THE APPLE/CARBENDAZIM/UK SCENARIO

The Codex Working Principles for Risk Analysis (Codex, 2006) state that "expression of uncertainty or variability in risk estimates may be qualitative or quantitative, but should be quantified to the extent that is scientifically achievable". It was not feasible to quantify uncertainties for every model run, so the Panel decided to quantify as many uncertainties as possible for a single scenario (carbendazim/apples/UK toddlers) and use this as an indication of the influence of the same uncertainties on other probabilistic modelling in the opinion.

Five types of uncertainty in this scenario were quantified by the Panel:

1. sampling uncertainty in the consumption data, caused by the sampling of person-days,

2. sampling uncertainty in the monitoring data, caused by the sampling of batches[29] of raw apples for chemical analysis,
3. further sampling uncertainty in the monitoring data, caused by the sampling of units within the batches of raw apples (*i.e.* the selection of 10 apples from a batch, to form a composite sample),
4. measurement uncertainty in the raw apple residue data, due to variation in calibration of the chemical analysis procedure,
5. uncertainty in the mean and standard deviation of the lognormal distribution for variability factors, which was used in some parts of the modelling.

Uncertainty 1 can be quantified by the MCRA and Uni-HB models, and uncertainty 2 can be quantified by the MCRA and CREMe models: some results for these are shown in the next section (7.2). Note that uncertainties affecting intake via apple juice were not quantified.

In this section, uncertainties 2-5 are quantified using a fourth model (CSL). To quantify uncertainty 4 it was necessary to access the original data from the chemical analysis (chromatogram readings, including calibration runs). This is very laborious, so a single scenario was chosen as an example: intake of carbendazim in apples and apple juice by UK toddlers (age 1.5-4.5 years). The presentation in this section concentrates on results: details of the data and of the methods used to quantify uncertainties 2-5 in the CSL model are given in section 8.8.

The black curves in Figure 32 show the median and 95% probability interval for the intake distribution estimated by the CSL model including all of uncertainties 2-5. The median curve shows the median estimate for each percentile of the intake distribution and the probability interval is a measure of the combined effect of the quantified uncertainties around that value. In the upper tail of the distribution, the 95% probability interval approaches one order of magnitude on the horizontal axis.

The CSL model was then rerun with different subsets of the uncertainties 2-5, in order to gain some insight into the relative importance of these uncertainties in the scenario apples/carbendazim/UK toddlers. The Panel first investigated the effect of ignoring altogether the variability factor and its uncertainty (uncertainty 5 in the list above), *i.e.* all concentrations were fixed at the batch mean level (this is equivalent to setting the variability factor to a fixed value of 1). The result of this is shown by the grey-coloured curves in Figure 32. Notice that when the variability factor is excluded, the width of the probability interval is virtually unchanged. This implies that, in this scenario, uncertainty of the parameters for the distribution of variability factors is small compared to other sources of uncertainty. It is also notable in Figure 32 that, at percentiles above the 92nd (on the vertical axis), the grey curves are shifted to the left compared to the black curves. This implies that excluding the variability factor causes a decrease in intakes in the upper tail of the distribution. The size of this decrease is smaller than might be expected. This is partly because the change of variability factor does not affect that part of the intake that is derived from apple juice, which in this scenario is not negligible. However, it may also be due to an interaction between the variability factor and the uncertainty due to the sampling of units for composite samples[30], which is taken into account by the CSL model.

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[29] Here, a batch refers to a lot or consignment of apples in the market place. Uncertainty 2 arises because data from a limited sample of batches are used to estimate variation between batches in general. Uncertainty 3 arises because, within each batch, a limited number of apples (10) is selected to form a composite sample, which is used to estimate the mean residue in the whole batch.

[30] This interaction occurs because composite samples with high residues may arise due to chance sampling of units with high individual residues: for such samples, the distance between the measured

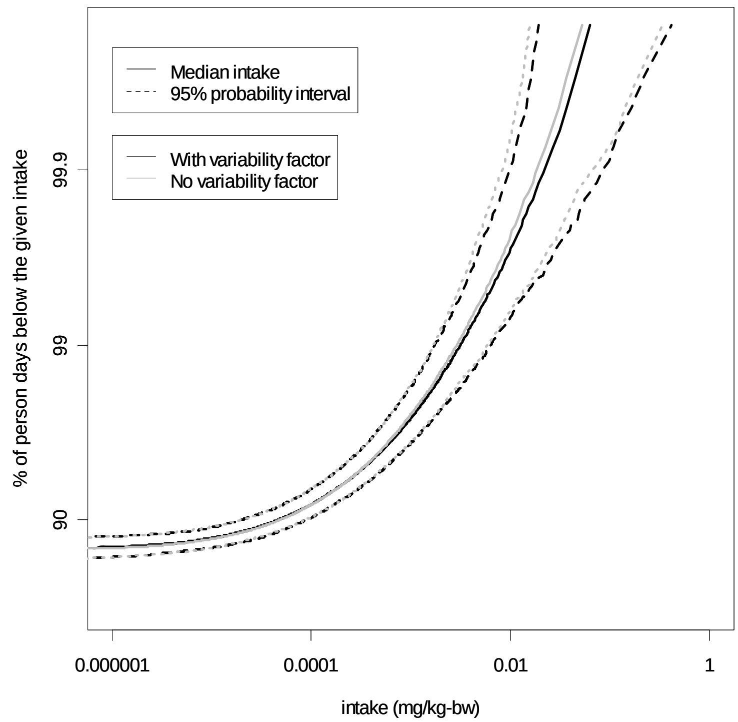

Figure 32: Estimated intakes of carbendazim from apples and apple juice by UK toddlers, aged 1.5-4.5 years. The black curves show results for the CSL model including quantification of four sources of sampling and measurement uncertainty (see text). The grey curves show the effect on the intake distribution of excluding the variability factor for apples (in effect, setting it to a fixed value of 1).

The Panel then tried another variation of the CSL model, in which both measurement error and composite sampling error for raw apple were left out (uncertainties 3 and 4 in the list above). Variability factors, with the associated uncertainty, were kept. Figure 33 shows that again the width of the probability interval is virtually unchanged. This implies that the contribution of measurement error and composite sampling error is small compared to other sources of uncertainty, at least in this case[31]. Again, it is notable that in the upper tail, both the medians and probability intervals shown by the grey curves are shifted to the left. This happens because the inclusion of measurement uncertainties in the full CSL model (black curves) allows for the possibility of higher frequencies of high residues than when the uncertainties are omitted.

mean and the true 97.5^{th} percentile of the lot is less than implied by the variability factor. The converse applies for composite samples with low means. This inter-dependency of the sampling uncertainty for the composite mean and the variability factor is accounted for in the CSL model.

[31] Measurement uncertainty may be more important in other cases as it will vary with chemical, commodity and laboratory.

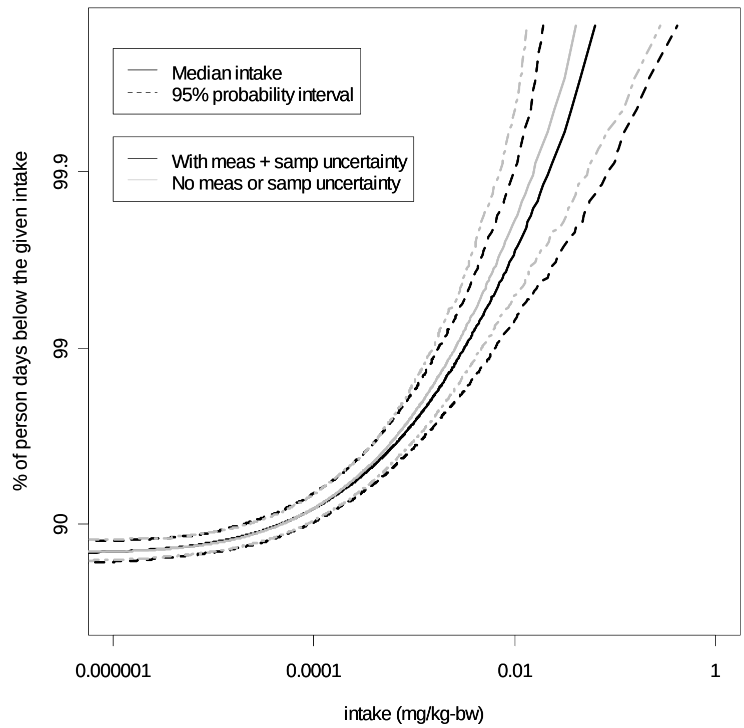

Figure 33: Estimated intakes of carbendazim from apples and apple juice by UK toddlers, aged 1.5-4.5 years. The black curves show results for the CSL model including quantification of four sources of sampling and measurement uncertainty (see text). The grey curves show the effect on the intake distribution of including excluding two types of uncertainty (measurement error and composite sampling error).

The Panel also explored the effect of omitting uncertainty 2 (due to sampling of batches of apples for monitoring) from the CSL model. The results are presented in Figure 34, and show that omitting uncertainty 2 causes a decrease in the median estimates of intakes and also a decrease in the width of the probability intervals. The greater influence of this uncertainty relative to uncertainties 1 (see below), 3, 4 and 5 may reflect that (a) the sample size was much smaller for raw apple batches (n=117) than for consumption data (6868 person-days), and (b) although the sample size for apples within batches was smaller (n=10), errors in estimating batch means would tend to cancel out over multiple batches. In addition, the limited number of apple batches causes sampling uncertainty both in estimating the proportion of true zeroes, and in estimating the mean and variance of positive residues.

The increase in the median estimates of higher percentiles when uncertainty 2 is included probably results from its effect on estimating the proportion of true zeroes. This takes account of the fact that a proportion of the non-detects may be low-level positives, which would increase the variance of the distribution of positives and cause a corresponding increase in the probability of high residues in the upper tail of the distribution. This effect is dependent on the distribution assumed for positive residues, which was lognormal, and should be treated with caution because (a) there are slightly fewer high residues in these data than might be expected for a lognormal distribution (see Appendix section 8.8.4), and (b) a very small fraction of the residues generated by the model seemed improbably far above the highest measured value.

This effect is not present in the MCRA, Uni-HB and CREMe models used to generate the main results of the Opinion[32].

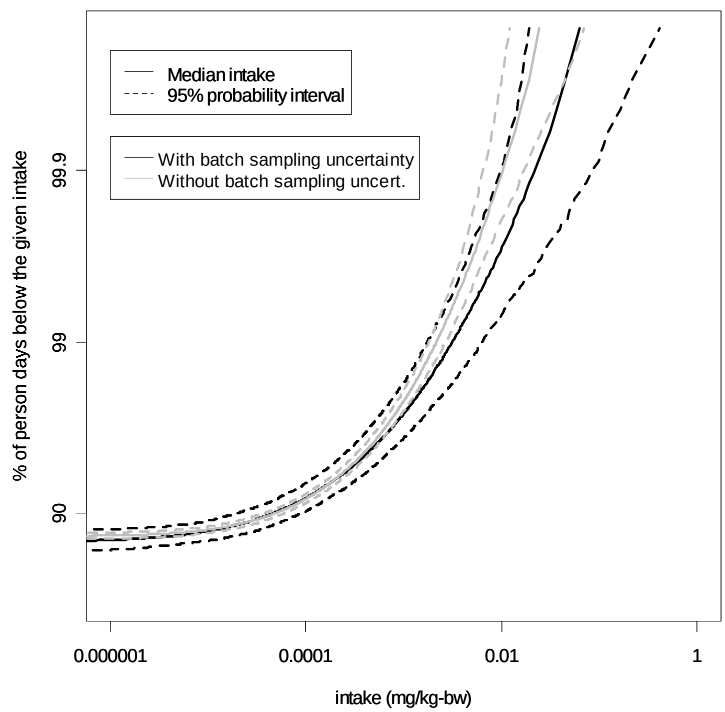

Figure 34: Estimated intakes of carbendazim from apples and apple juice by UK toddlers, aged 1.5-4.5 years. The black curves show results for the CSL model including quantification of four sources of sampling and measurement uncertainty (see text). The grey curves show the effect of excluding sampling uncertainty due to the limited number of residue measurements for batches of raw apples.

Finally, a further variant of the CSL model (not shown) was developed, which used a parametric approach to quantify uncertainty 1 (sampling uncertainty in the consumption data) as well as uncertainties 2-5. This produced results very similar to those shown by the black curves in Figures 32-34 above. This suggests that uncertainty 1 was small relative to other sources for this scenario. This may reflect the relatively large size of the consumption survey (1717 individuals over 4 days) and the relatively high consumption frequency of apples and apple products: uncertainty 1 may be more important for smaller surveys and for less frequently consumed commodities.

The width of the 95% probability interval (including all the quantified uncertainties) at the upper end of the intake distribution (around the 99.9th percentile) is approximately half a log unit on the horizontal axis, *i.e.* about a factor of 3 in intake, and approximately one log unit on the vertical axis (level of protection), *i.e.* a factor of 10 in level of protection. There is less uncertainty at lower percentiles of intake. Note that the most important uncertainty (number 2) accounts for

[32] MCRA and UniHB also assume lognormal distributions but treat all non-detects as true zeroes.

about half of the total width of the probability interval. As the other quantified uncertainties (1 and 3-5) are minor, most of the remaining uncertainty is simulation uncertainty, *i.e.* variation in successive estimates of the intake distribution, caused by the limited number of person-days simulated (6868). This would be reduced by simulating more person days but this was not done because of the high computation time required. This source of uncertainty is reduced in most of the results in the opinion, which simulated larger numbers of person-days (Uni-HB 80,000 and MCRA 100,000), although it will be similar for the Irish scenarios as the CREMe model simulated 10,000 person-days.

In summary:

- It appears that uncertainties 3-5 in the list at the start of this section (residue measurement uncertainty, composite mean uncertainty and uncertainty in the distribution of variability factors) contribute little to uncertainty in estimated intakes for UK/carbendazim/apples, because including or omitting them makes little difference to the width of the probability intervals.
- The influence of uncertainty 1 (sampling uncertainty for consumption) will depend on the size of the dietary surveys available for each country: it is minor for the UK survey with 6868 person-days but will be larger for smaller surveys; it will also be larger in MRL runs for less-frequently eaten commodities with fewer consumption-days.
- Sampling uncertainty for residues (uncertainty 2) is largest of the quantified uncertainties for the UK/carbendazim/apples scenario. This uncertainty will be larger in many of the scenarios modelled by the Panel, as the number of measured residues was frequently much lower than the 117 that were available for UK/carbendazim/apples and the number of positive concentrations was frequently under 10 (see Appendix section 8.5), compared to 58 for UK/carbendazim/apples.
- Results for Ireland and the UK are affected by simulation uncertainty of similar magnitude to uncertainty 2, due to the smaller numbers of person-days simulated.

7.2 COMPARISON BETWEEN THE PROBABILISTIC MODELS USED IN THE OPINION

Four different probabilistic models developed by 4 different groups are used in the opinion: CREMe, MCRA, Uni-HB for the main results, and the CSL model in section 7.1. The principles of the 4 models are similar but it is possible that differences in methodology or even coding errors might introduce differences or errors in the results. To check for this the Panel applied all 4 models to a single scenario (again carbendazim/apples/UK toddlers) and compared the results.

Median estimates of the intake distributions produced by the 4 models for this single scenario are plotted together in Figure 35. The upper percentiles of the distributions differ by about half a log unit overall from the lowest (Uni-HB) to the highest (CSL) on the horizontal axis (intake). Since the underlying data are the same, the differences in outputs are due to differences in the models. The difference between the CSL model and the others is partly due to the quantification of measurement uncertainty and batch sampling uncertainty, which increase the upper tail of the CSL estimates, as was seen in the preceding section. However, the differences between all four models are probably also partly due to differences in the handling of the concentration data: MCRA and CSL use a combination of binomial and lognormal distributions estimated (in different ways) from the full dataset, Uni-HB uses a lognormal distribution estimated from summary statistics of the concentration data[33] and CREMe resamples the raw concentration

[33] The Uni-HB model estimated the distribution from summary statistics of the data because this is the information that was available for the German scenarios modelled by Uni-HB in other sections of the opinion.

data (see Appendix section 8.8 for more detail on differences between the models). For intakes in the top 1% of the distribution, the differences between the four models range over about one log unit on the vertical scale, *i.e.* a factor of 10 in the level of protection.

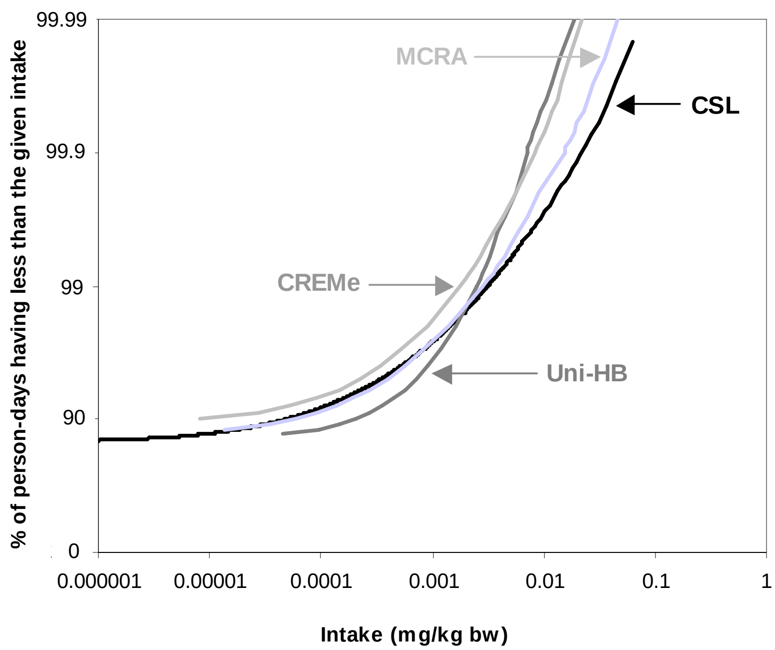

Figure 35: Comparison of median outputs from the four models used in the opinion, when applied to the same input data for the scenario carbendazim/apples/UK toddlers. The curves are cumulative distributions for intake from the 4 models.

Confidence/probability intervals (95%) generated by all 4 models are compared in Figure 36. The confidence intervals for the MCRA, CREMe and Uni-HB models are roughly similar in width and represent batch sampling uncertainties in concentration data (all three models) and consumption (MCRA and Uni-HB). The confidence intervals for the CSL model are somewhat, though not greatly, wider. This is partly due to the smaller number of person-days simulated (6868 compared to 10,000 for the other 3 models in Figure 36), and partly to the different methods used to quantify sampling uncertainty in the concentration data (see Appendix section 8.8 for details).

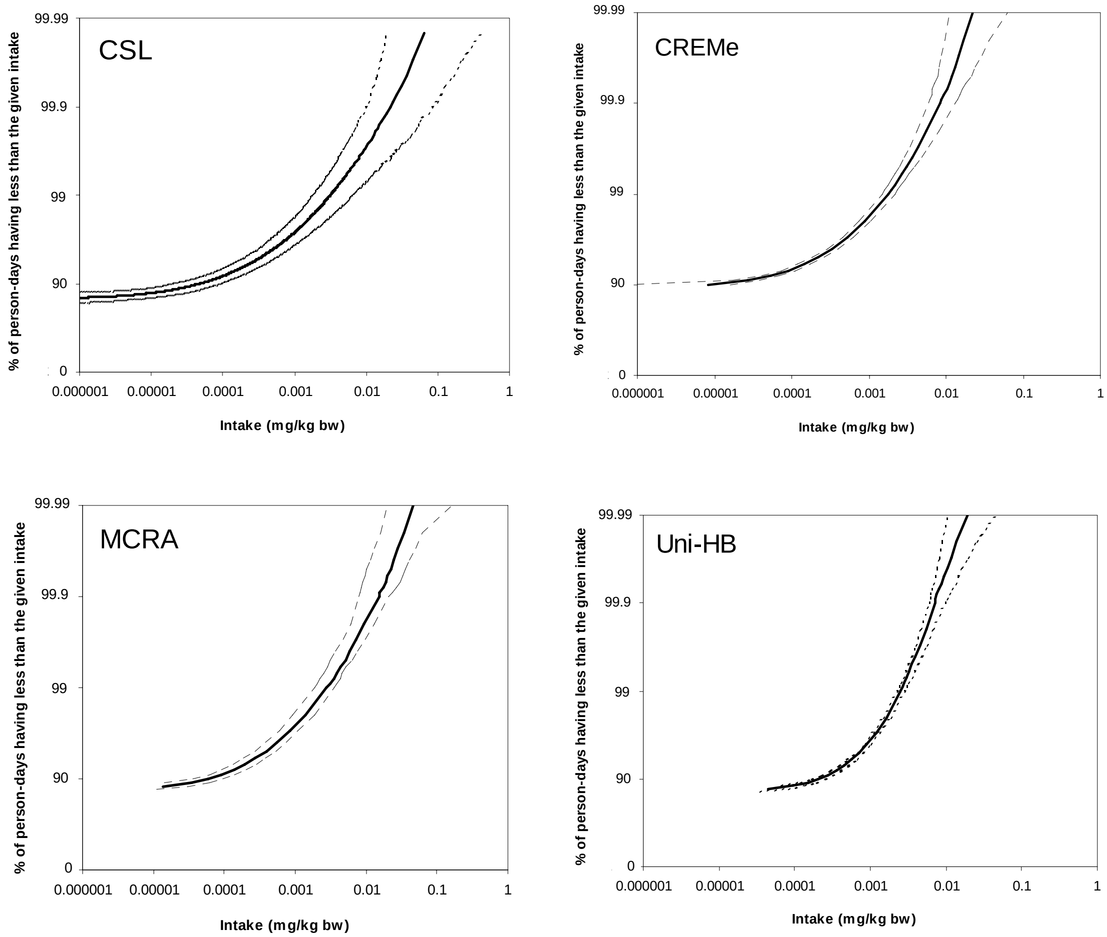

Figure 36: Comparison of 95% confidence intervals from the four models used in the opinion, when applied to the same input data for the scenario carbendazim/apples/UK toddlers.

7.3 EVALUATION OF UNQUANTIFIED UNCERTAINTIES

Many other uncertainties affect the assessment, which are not quantified in sections 7.1 or 7.2. Therefore the Panel lists in Table 12 the major uncertainties it identified, together with a qualitative evaluation of their potential impacts on the outcome of the assessment. The format of Table 12 follows the approach recommended in the Scientific Committee's guidance on uncertainties in dietary exposure assessment (EFSA, 2006).

Additional uncertainties, which the Panel judged to be of lesser magnitude, are listed in Appendix section 8.9.

Note that Table 12 ends with a subjective assessment of the overall impact of the unquantified uncertainties on the outcome of the quantitative assessments. These are considered together with the quantified uncertainties in the following section (7.4).

Table 12: Summary of the uncertainties that are thought most likely to have a significant effect on the assessment outcome, and a subjective evaluation of their individual and combined impact. **Additional uncertainties thought to have less impact are listed in Appendix section 8.9.** The +/- symbols indicate whether each item has the potential to make our estimates of the level of protection (LoP) higher (+) or lower (-) than the true values. The number of symbols provides a subjective relative evaluation of the magnitude of the error (*e.g.* +++ would mean our estimate could be a large over-estimate). If the impact is uncertain or could vary over a range, lower and upper evaluations are given (*e.g.* - / ++).

	Source of uncertainty	**Direction & magnitude**
Concentrations	Monitoring programs do not cover all relevant commodities, and the coverage varies between countries. This will tend to cause underestimation of intake and hence overestimation of LoP, the extent of which will vary between countries.	+ / +++
Concentrations	Sampling uncertainty due to limited monitoring data. Results in section 7.1 suggest this contributes more than other quantified sources of uncertainty, even with a moderately large sample. This uncertainty will be large in many cases, where the number of samples (especially positive samples) is small.	- - - / +++
Concentrations	Choice of lognormal distribution to model variation of positive concentrations in monitoring data (MCRA, Uni-HB and CSL models). The lognormal often fits concentration data reasonably well, but may tend to over-represent high concentrations and therefore underestimate LoP. In some cases the Panel examined, a small fraction of the modelled concentrations were much higher than the highest measured concentration.	- - - / ++ (MCRA, Uni-HB and CSL models)
Concentrations	Use of re-sampling to model variation of positive concentrations in monitoring data (CREMe model). Re-sampling is restricted to the range of observed data and will therefore underestimate high concentrations and overestimate LoP, especially as the number of positive measurements is often very small (see Appendix section 8.5). However, if by chance high concentrations are sampled, the model may overestimate their frequency and hence underestimate LoP.	- - - / +++ (CREMe)
Concentrations	Selection of commodities for monitoring is sometimes targeted on those thought likely to contain high residues. This will tend to overestimate the general distribution of residues and therefore underestimate LoP. In some cases this effect might be large.	-/- - -
Consumption	Nearly all the models presented in this Opinion used raw survey data to model variation in consumption, so consumption levels are limited to those actually observed in the survey data. This will underestimate the highest levels of consumption and intake occurring in the full population, and therefore overestimate the LoP. However, if high consumptions are sampled, the model may overestimate their frequency and hence underestimate LoP. The potential for under- or overestimation is larger for scenarios based on smaller surveys. Slob (2006) recommends a parametric approach, which would model the occurrence of more extreme consumption, but this is not yet feasible for assessments involving multiple foods as in this Opinion. Application of Slob's approach to one scenario showed little difference from the Panel's approach (UK/carbendazim/apples, results not shown), but the consumption survey involved was large and a greater difference might occur in other cases.	- - / +++
Consumption	The consumption data for Dutch babies comes from the duplicate diet study which targeted babies fed fresh fruit and vegetables and avoided breast-fed babies. This will lead to over-estimation of intakes and under-estimation of LoPs for the general Dutch baby population.	Dutch babies - / - - -
Model uncertainty	Simulation uncertainty: repeated runs of the probabilistic models give slightly different results, especially in the extreme tails. In some cases these variations are of similar magnitude to the changes we are trying to assess. In these cases the true magnitude of the change in LoP is very uncertain.	(for extreme percentiles) - - - / +++
MRLs	The Panel is not certain that all of the MRLs used in the analysis of intake at	(for intakes

	the MRL are current: it is possible that some of the scenarios generating lower levels of protection have been refused MRLs (or had them set equal to the LoD), in which case including them will cause over-estimation of intakes and underestimation of LoPs.	at the MRL) - / - - -
MRLs	In some of the German scenarios, several related commodities were set simultaneously to the MRL, *e.g.* in scenarios for "pome fruits", apples and pears were both set to the MRL. In reality, it is very unlikely that the same group of consumers would eat more than one commodity from batches at the MRL on the same day. Consequently, the results for German intakes at the MRL overestimate intakes and underestimate LoPs.	(for German intakes at the MRL) - / - - -
Processing factors	Data on the effects of processing are very limited, so for most foods the Panel followed the common conservative practice of ignoring the effects of processing, which will generally led to overestimation of intake and underestimation of LoP. Where processing factors exist they are approximate and so the degree of under-estimation is uncertain. Factors applied only to part of the food that could be processed. In addition, processing factors are often taken from the literature, with incomplete information on how they were measured. Frequently mean processing factors are estimated from a small number of measurements (*e.g.* 3).	- / - - -
Scenarios	The device of using the maximum IESTI to estimate a minimum level of protection (see section 3.1.4) introduces an important additional uncertainty, because it transforms the real pesticide scenarios used by the Panel into hypothetical ones, which have the same uses, residues, and intake distribution but with IESTIs close to their ARfDs. It is uncertain how well these hypothetical scenarios and their LoPs represent real scenarios with IESTIs close to their ARfDs.	- - - / +++ (for estimates of minimum level of protection)
Scenarios	In models using field trial data, it was assumed that these concentrations apply to 100% of the relevant commodities, *i.e.* 100% of the relevant crops are treated. This is an extreme worst case and will tend to overestimate intakes and underestimate LoP.	- - - (field trial models only)
Variability factors	In much of the modelling, unit-to-unit variability was represented by fixed variability factors of 1, 3, 5 and 6.83 according to the commodity. Variability of this magnitude is reported in at least some market samples (EFSA, 2005). Applying it to every lot probably over-estimates the frequency of higher concentrations. Limited modelling with an alternative assumption (distribution of variability factors derived from EFSA, 2005) indicated that this had little impact on the results for total population intakes. The effect of assuming fixed variability factors when modelling intakes at the MRL was not tested but is likely to overestimate intakes and hence underestimate LoPs, perhaps by a substantial amount.	- - / + (total pop.) - - - / - (intake at the MRL)
<u>Overall assessment.</u> The Panel evaluated 36 unquantified uncertainties (the 15 most important in this table and 21 additional uncertainties listed in Appendix section 8.9). Overall, 15 were judged neutral (equal number of + and -), 16 were judged most likely to be conservative (more – than +, tending to underestimate the LoP), and 5 were judged most likely to be unconservative (more + than -, tending to overestimate the LoP). Only 2 of the latter 5 unconservative effects were judged to be potentially large (+++), compared to 8 of the 16 conservative effects (- - -). In most scenarios, exceedance of the ARfD occurs only in the extreme upper tail of the intake distribution (>99% or >99.9%). This part of the distribution is judged likely to be influenced more by some of the conservative uncertainties, *e.g.* the assumption of lognormal distributions for composite residues. Therefore, on balance the Panel judges that its results are most likely to be conservative, *i.e.* overestimating intakes and underestimating LoPs, although the opposite is also possible. Furthermore, the Panel notes that when estimating the change in LoP resulting from changes to the IESTI equation, the uncertainties in each scenario may tend to cancel out to some extent.		- - - / + for LoPs - - / ++ for changes

7.4 OVERALL ASSESSMENT OF QUANTIFIED AND UNQUANTIFIED UNCERTAINTIES

Five sources of uncertainty were examined quantitatively, in a total population assessment for a selected scenario (UK/carbendazim/toddlers, sections 7.1 and 7.2). In that scenario, the estimated 95% confidence or probability interval for levels of protection in the region of 99.9% was about 99.6% - 99.99%. For levels of protection in the region of 99%, the confidence or probability interval is about 98% - 99.5% (*e.g.* Figure 36)[34]. Wider uncertainty intervals would be expected in many of the other scenarios considered in the main analyses, where either the consumption or concentration datasets are smaller.

Many sources of uncertainty were not quantified and are therefore not included in the confidence/probability intervals shown in sections 7.1 and 7.2. The Panel systematically lists and evaluates these unquantified uncertainties in section 7.3 and Appendix section 8.9. On balance, the Panel judges that its quantitative results are most likely to be conservative, *i.e.* overestimating intakes and underestimating the level of protection, although the opposite is also possible.

Overall, the Panel concludes that its estimates of levels of protection are very uncertain but probably conservative (underestimating the true levels of protection). This is also suggested by the results of the duplicate diet study (section 6), although they are also subject to uncertainty.

The Panel notes that when estimating the change in LoP resulting from changes to the IESTI equation, the uncertainties (both quantified and unquantified) in each scenario may tend to cancel out to some extent. Despite this, many of the estimated changes in LoP (see section 4) are probably smaller than the combined effect of the quantified and unquantified uncertainties affecting the assessment. This does not mean that there is no change in LoP – in principle there must be some change in intakes and hence LoP if changing the IESTI results in more or fewer commodities being granted MRLs – but it means the magnitude of the change is uncertain.

The fact that there are so many substantial uncertainties is an inevitable consequence of the limitations of knowledge in this area of science. Most of the uncertainties could be reduced in the future, by collecting further data. Some of the uncertainties could be reduced without additional data, or at least better characterised, by further modelling[35] if time and resources permitted. The fact that the assessment identifies substantial uncertainty should not be seen as decreasing the usefulness of the Panel's analysis. On the contrary, it is important to be clear about the limits to what science can currently say about the questions posed to the Panel. The Panel is not aware of any alternative scientific approaches that could have given a more certain answer, given the available data and resources.

CONCLUSIONS

The first question from the Commission requests that the conservatism of the IESTI equation should be assessed in terms of the percentage of the total European population that is "protected". The second question implies that the criterion for protection is not exceeding the ARfD, so for the purpose of this Opinion the Panel defined the level of protection (LoP) as the percentage of person-days for which acute dietary intakes are at or below the ARfD.

By referring to the "total population", the first question implies that the assessment should include both consumers and non-consumers of commodities containing a pesticide. Logically,

[34] The figures are very approximate and intended only to give an indication of the magnitude of quantified uncertainties in the range of LoPs encountered in the main analyses. In reading them off the Figures it must be remembered they are shown on an inverted logarithmic scale.

[35] For example, exploring alternative assumptions for key inputs (*e.g.* lognormal distribution for residues).

this should take account of the full range of pesticide residues found in the food supply. However, the Panel is aware that risk managers are also interested in the special case of people who consume a commodity containing residues at the MRL. Therefore the Panel undertook both types of assessment.

In both types of assessment, the Panel estimated the combined intake for all commodities for which residue data are available, because all can contribute to whether the ARfD is exceeded. In the assessments for people who consume one commodity containing residues at the MRL, the contribution of other commodities was based on the levels observed in monitoring programs ("monitoring levels").

Therefore, the Panel undertook two types of assessment:

- "total population assessments", estimating the level of protection for the total population based on the levels of pesticides observed in monitoring programs,
- "MRL-level assessments" for the special case of people who consume one commodity containing residues at the MRL and other commodities at monitoring levels.

The Panel estimated acute dietary intakes by probabilistic modelling. This used data on food consumption and body weight from national surveys, and took account of unit-to-unit variability of residues using variability factors. The Panel evaluated the performance of the models using data from "duplicate diet" studies, where intake was measured directly (Boon *et al*., 2003). Comparison of these data showed that the probabilistic estimates of intakes were higher than measured intakes from the duplicate diet study, which would make the Panel's estimates of levels of protection conservative (*i.e.* underestimates). However, this comparison was possible for only 6 pesticides in one country and one age group and extrapolation to other countries and age groups is uncertain.

It was not possible to conduct analyses for the entire population of the EU, or for all pesticides, due to lack of data. The Panel conducted total population assessments for a number of scenarios representing different combinations of 13 pesticides, 8 countries and a range of age groups from babies to seniors. For example, one scenario considered intake of tolylfluanid by children aged 1-6 years in The Netherlands.

For practical reasons, the MRL–level assessments were based on a reduced range of scenarios, representing only two countries (Germany and The Netherlands) and 11 pesticides.

The Panel's findings are summarised below. For details of methods, data and results please refer to the main text and Appendix.

Question 1. How conservative is the IESTI equation with respect to the percentage of the total European population protected?

To answer this question, the Panel modelled intakes excluding those commodities for which the IESTI exceeded the ARfD, when calculated with the current EU variability factors of 5 and 7[36]. The intake for each scenario was then compared to the ARfD, to determine the percentage of person-days with acute dietary intakes below the ARfD. This estimates the level of protection

[36] The monitoring data used for the assessment included some commodities for which the MRL had not yet been reviewed using the IESTI equations. Therefore it was necessary to exclude those commodities where the IESTI exceeded the ARfD, in order to estimate the intakes that would occur when the IESTI equation is applied.

(LoP) expected when using the IESTI equations with the current EU variability factors of 5 and 7[37].

Figure 37(a) presents results of total population assessments, showing how the LoP varied for the 78 pesticide/country/age group scenarios which were modelled. The Panel refers to these as “estimated actual LoPs” because they are estimated LoPs based on the actual ARfDs of the pesticides considered.

Variation in the LoP is caused by various factors including differences in the number and type of commodities in which residues occur, differences between age groups in intake relative to body weight, and different ARfDs for different pesticides. The results in Figure 37(a) are an estimate of the LoPs for the scenarios analysed by the Panel. They may also provide an indication of the LoPs for other scenarios that are similar to those modelled by the Panel.

When the IESTI of a commodity is close or equal to the ARfD, the LoP may be lower than for the scenarios modelled by the Panel. To examine this situation, the Panel repeated the assessments, assuming that the ARfD is equal to the highest IESTI of the commodities included in each scenario[38]. The Panel refers to LoPs estimated in this way as “estimated minimum LoPs”, because they estimate the minimum LoP that could occur for a theoretical scenario with the same pattern of uses and intakes as the original scenario but a lower ARfD.

Figure 37(b) shows minimum LoPs based on the same 78 scenarios as Figure 37(a). If a risk manager is considering a scenario which is generally similar to those modelled by the Panel but with a smaller margin between its highest IESTI and the ARfD, then Figure 37(b) is more relevant than Figure 37(a) as a guide to the LoP. Figures 37(c) and (d) show results for the same scenarios when the current EU variability factors of 5 and 7 are changed to 3, and are discussed below under Question 2.

Uncertainties affecting these results are discussed below.

[37] Assuming zero intake from a commodity when its IESTI is above the ARfD will underestimate intake in cases where alternative uses of the same pesticide continue on that commodity because they have lower IESTIs. On the other hand, the Panel’s method may have over-estimated intakes where a pesticide use was assumed, but would in fact be disallowed because the IESTI exceeded the ARfD in an age group other than that being modelled. The overall effect of this and other uncertainties affecting the assessment is considered below.

[38] The highest IESTI is used because, if the ARfD were below this, the use that gave rise to that IESTI would not be authorised and therefore the scenario including that use would not exist.

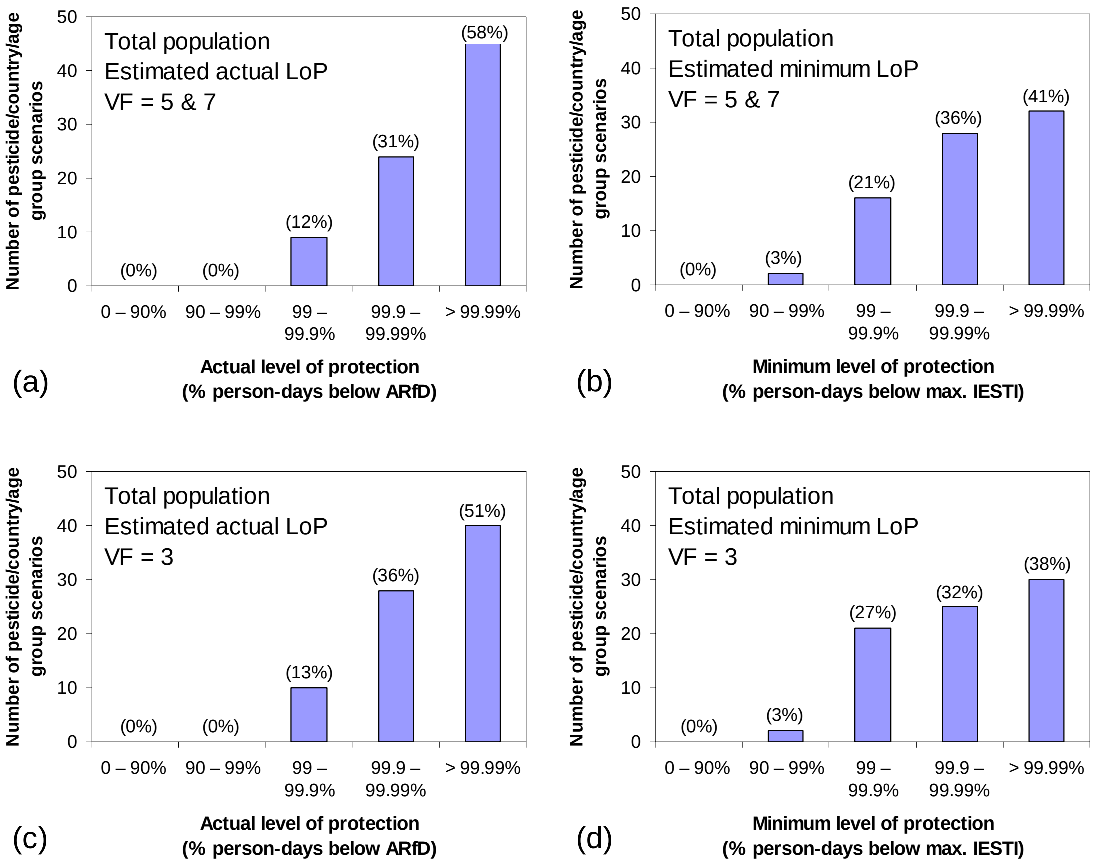

Figure 37: Levels of protection (LoP) for the **total population** in 78 pesticide/country/age group scenarios, estimated by probabilistic modelling: (a) estimated actual LoP with variability factors of 5 and 7, (b) estimated minimum LoP with variability factors of 5 and 7, (c) estimated actual LoP with variability factor of 3, (d) estimated minimum LoP with variability factor of 3. The height of the bars represents the number of scenarios in each range of LoP. The percentage above each bar is the % of all scenarios that lie in that range of LoP.

Figure 38 presents results from the Panel's MRL-level assessments. These estimate LoPs for people consuming one commodity at the MRL and others at monitoring levels. As in Figure 37, intakes are estimated excluding those commodities with IESTIs exceeding the ARfD. As would be expected, these LoPs are lower than those for the total population in Figure 37, because intakes are increased by the commodity with residues at the MRL, and because non-consumers of that commodity are excluded.

The results in Figure 38(a) estimate the actual LoPs for people consuming one commodity at the MRL and others at monitoring levels, in scenarios that qualify for an MRL when the IESTI is calculated with variability factors of 5 & 7. These scenarios relate to a more limited and less balanced selection of pesticides, countries and age groups than those in the total population analysis, so the uncertainty in extrapolating to other scenarios is increased. Figures 38(b) and (c) show results for the same scenarios when the inputs to the IESTI equations are changed, and are discussed below under Questions 2 and 3.

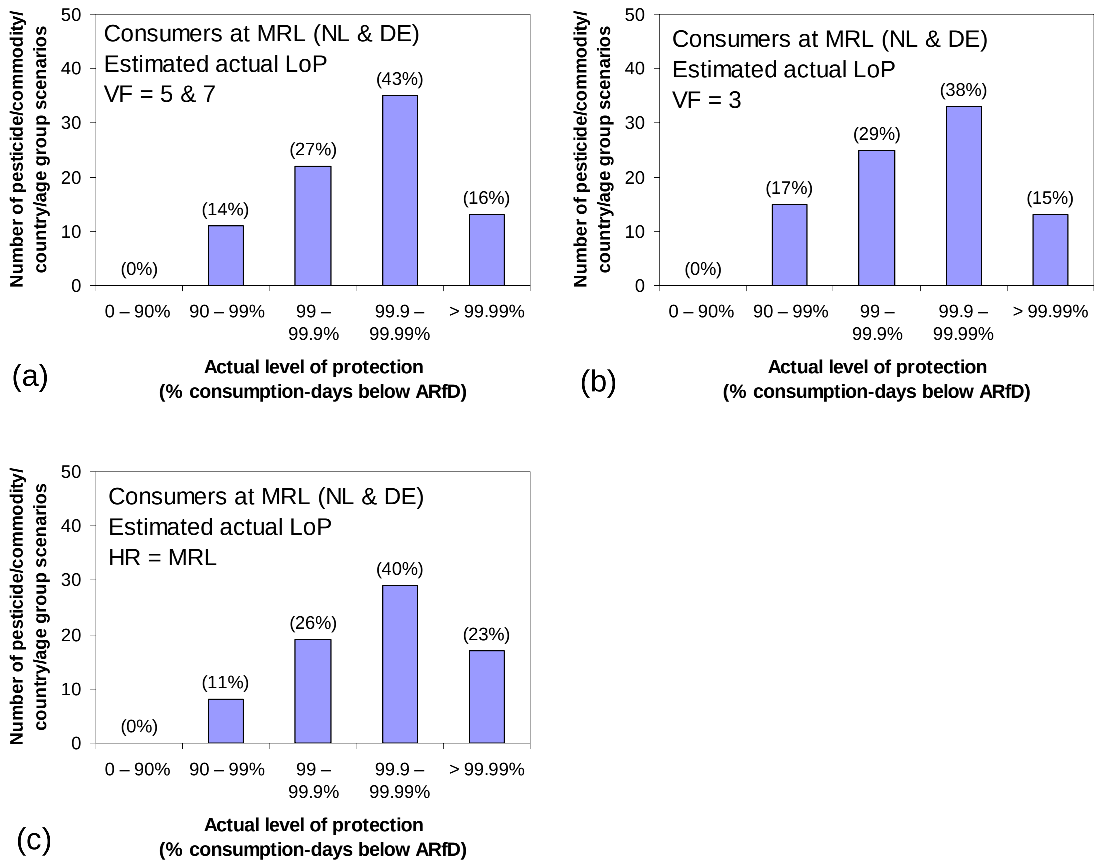

Figure 38: Levels of protection (LoP) for people consuming one commodity at the MRL and others at monitoring levels, estimated by probabilistic modelling: (a) actual LoP with variability factors of 5 and 7, (b) actual LoP with variability factor of 3, (c) actual LoP when the HR is replaced with the MRL. The total number of scenarios differs between the three cases (respectively 81, 86 and 73) because changing the inputs to the IESTI equation changes the number of commodities that are excluded because their IESTIs are above the ARfD.

Question 2. What is the sensitivity - in terms of probability of exceeding the ARfD - to variation and uncertainty in each of the parameters of the IESTI model?

This question could not be answered by a simple sensitivity analysis of the IESTI equation because it asks for sensitivity to be expressed in terms of probability of exceeding the ARfD. The Panel therefore used probabilistic modelling to assess how changes to the IESTI equation might alter the levels of protection achieved. This was done by calculating IESTIs with alternative inputs, modelling intakes for the commodities with IESTIs below the ARfD, and then comparing those intakes with the ARfD to estimate the LoP. These LoPs were then compared with those obtained above for the current IESTI equations.

The Panel focussed on assessing the effect of changing the variability factors for commodities with unit weights over 25g, from the current EU default values of 5 or 7 to the alternative value of 3. This is of particular interest because a default value of 3 has been adopted by the Joint

FAO/WHO Meeting on Pesticide Residues (JMPR). It was not possible, in the time available, to examine the effect of changes to other IESTI parameters except for the HR (Question 3, below).

Results for the LoP in the total population assessments with a variability factor of 3 are shown above in Figure 37(c) (estimated actual LoP) and Figure 37(d) (estimated minimum level of protection). Changing the variability factor to 3 decreased the number of commodities with IESTIs above the ARfD in 25 of the 78 scenarios modelled by the Panel. As in Question 1, the Panel assumed that there was no intake from commodities with IESTIs above the ARfD[39]. Consequently, the estimated intakes increase, and the levels of protection decrease: this can be seen by comparing Figures 37(a) and 37(c).

Comparing all four panels of Figure 37, the difference between the upper and lower graphs is less than the difference between the left and right hand graphs. This implies that the change in total population LoP caused by changing the variability factor is smaller than the difference that occurs when the margin between the highest IESTI and the ARfD is reduced. This reinforces the need for caution in extrapolating the Panel's findings to other scenarios, where the use patterns and intakes as well as the ARfDs will be different.

Results for the LoP in MRL-level assessments are presented in Figure 38. Changing the variability factor to 3 decreased the calculated IESTIs and thus increased the number of pesticide/country/commodities qualifying for MRLs from 81 to 86. Because the proportion of scenarios added is small, the overall distribution of LoPs does not change markedly (compare Figures 38 (a) and (b)). The 5 added scenarios have estimated LoPs at the lower end of the distribution (4 of them at or below 99%), although for at least two of them the LoP appears to be driven by commodities at monitoring levels rather than the commodity at the MRL[40].

Uncertainties affecting these results are discussed below.

Question 3. How does replacing HR with other estimates of highest residues e.g. the MRL (determined either using the EU method –Rber, Rmax-, or an alternative statistical method as the lognormal distribution recently proposed by NAFTA) affect the outcome of the equation?

The Panel examined the effect of replacing the HR with the MRL on the level of protection for MRL-level assessments, using the same approach that was used in Question 2 to assess the change of variability factor. However, due to the large number of probabilistic model runs required for each comparison, the Panel did not have time to evaluate replacing the HR with the MRL for the total population assessments, nor to explore other changes to the IESTI equations.

Results for replacing the HR with the MRL for the MRL-level assessments are shown above, in Figure 38(c). The total number of scenarios is reduced from 81 to 73 because replacing the HR with the MRL generally increases the IESTI, so that more commodities exceed the ARfD. As in Questions 1 and 2, the Panel assumed that there was no intake from commodities with IESTIs above the ARfD.

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[39] In reality, some intake would continue for some of these commodities due to alternative uses of the same pesticides with lower IESTIs. This will tend to cause overestimation of the LoP, as in Question 1. However, it should have less effect when comparing LoPs for different variability factors, because the underestimation of both LoPs will cancel out to some extent. This and other uncertainties are discussed below.

[40] These details can be seen in Figures 20 and 22. In Figure 22, two of the added scenarios fall on the diagonal line, *i.e.* their addition does not change the LoP for consumers of those commodities. This implies the intakes of those consumers derive mainly from other commodities at monitoring levels.

Replacing the HR with the MRL had a slightly larger effect on the overall distribution of LoPs than changing the variability factor (this can be seen more clearly by comparing Figures 21 and 25). The changes occur at the lower end of the distribution: 7 of the eight deleted commodities have LoPs around 99%, although for at least one of them the LoP appears to be driven by commodities at monitoring levels[41].

Magnitude of intakes above the ARfD

The PPR Panel recognises that exceeding the ARfD does not necessarily mean that toxic effects will occur, because of the safety factors that are incorporated in the ARfD. Therefore, it is important to consider not only what percentage of people exceeds the ARfD, but also the amount by which they exceed it. The Panel therefore estimated the percentage of people exceeding the ARfD by a factor of 2, or by a factor of 10, both for the total population and when considering people who consume a single commodity at the MRL and other commodities at monitoring levels. Intakes above 10x ARfD occurred for fewer than 0.1% of person-days in the total population assessments, and for fewer than 1% of consumption-days in the MRL-level assessments[42]. These intakes were in the upper tails of the intake distributions, where the uncertainties affecting the assessment are greatest, so the true prevalence of such cases remains very uncertain.

Relative contributions of different commodities to overall intake

As would be expected, the overall intake of people consuming a single commodity at the MRL and others at monitoring levels is usually dominated by the commodity at the MRL, which often contributes over 90% of the overall intake (summed over all consumption-days). However, there are some cases where other commodities make a significant contribution, and a very few where the commodity at the MRL contributes less than half (for details, see Section 5).

A quite different picture is seen when considering intakes for the total population based on monitoring data. In this case it is common for one commodity to contribute 60-80% of overall intake (summed over all person-days), with significant contributions from 1-2 other commodities. In some cases, overall intake for the population is divided fairly equally between 3-4 commodities, although for individual persons on particular days, intake may still be dominated by one commodity.

An important observation for the performance of the IESTI equation is that even when total population intake is dominated by a single commodity, other commodities for that pesticide may have higher IESTIs. The Panel shows a clear example of this in Figure 27, and did not have time to conduct a systematic assessment of how often this occurs, but suspects it is frequently the case. This means that, if the IESTI were considered as a tool for assessing total population intakes, it would frequently lead to non-authorisation of pesticide uses that, in fact, contributed little to total population intake. The Panel therefore considers that the IESTI is unlikely to be suitable for assessing total population intakes, for which it was not designed.

Precision of the IESTI as an indicator of level of protection

In MRL setting, the magnitude of the IESTI relative to the ARfD – in effect, the ratio of the IESTI to the ARfD – is used as an indicator of the level of protection that will be provided for consumers if a given MRL is set. It is therefore pertinent to consider the precision of the IESTI/ARfD ratio as an indicator of LoP, and how this differs between MRL-level assessments and assessments for the total population. To examine this, the Panel plotted graphs showing

[41] For details see Figures 24 and 26. In Figure 26, one of the deleted scenarios falls on the diagonal line.

[42] For details, see Tables 4.1 and 4.3.

the relationship between the LoP and the IESTI/ARfD ratio (Figures 39 and 40). In both graphs, all of the commodities in each scenario are included, regardless of whether they have IESTIs above the ARfD, as otherwise there would be no indication of how the relationship continues for IESTI/ARfD ratios above 1, which will be encountered in regulatory assessments.

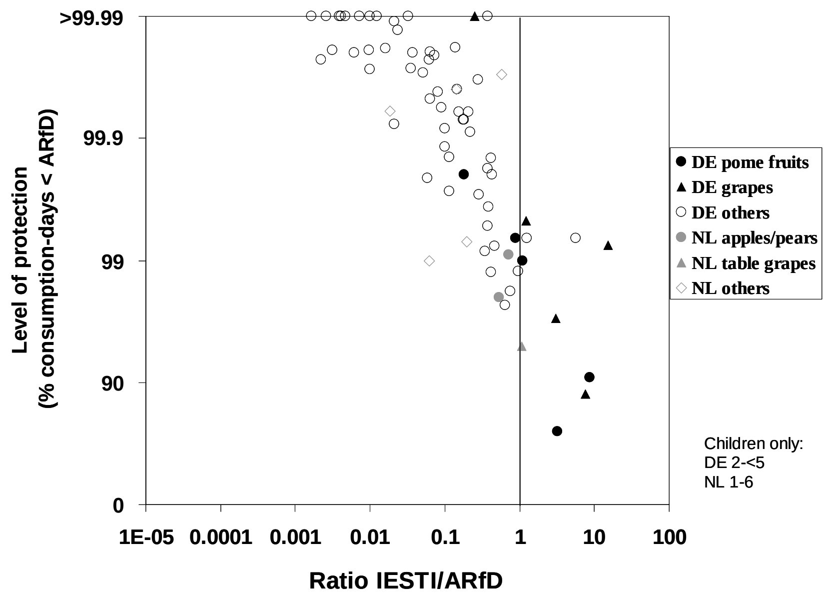

Figure 39: Relationship between the IESTI/ARfD ratio and the level of protection (LoP) for people consuming single commodities or commodity-groups at the MRL and others at monitoring levels. Each point represents a separate pesticide/country/commodity scenario with its own IESTI/ARfD ratio and LoP.

The relationship between the IESTI/ARfD ratio and the LoP is much tighter for consumers at the MRL (Figure 39) than for the total population (Figure 40). This implies that the IESTI provides a much more precise indicator of the level of protection for consumers at the MRL (the purpose for which it was designed) than for total population intakes.

Figure 39 suggests that when the IESTI/ARfD ratio is close to 1, the LoP tends to be around 99%. However, it must be remembered that this estimate is very uncertain, and is probably an under-estimate of the true level of protection (section 7). Furthermore, the results in Figure 39 relate to a limited range of pesticides for one age group (children aged 1-6) in The Netherlands and Germany, and it is uncertain how these relate to LoPs for other pesticides, age groups and countries. It is a risk management question to consider whether, in the light of these estimates and uncertainties, the level of protection provided by the current IESTI equations is appropriate setting MRLs.

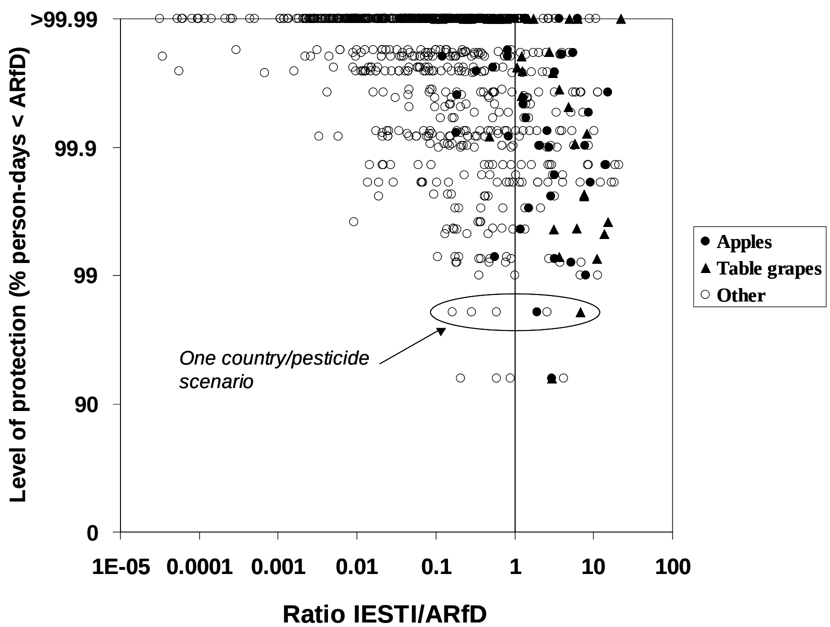

Figure 40: Relationship between the IESTI/ARfD ratio and the level of protection for the total population. Each pesticide/country scenario has a single level of protection but different IESTI/ARfD ratios for different commodities within that scenario, as illustrated by the points circled in the graph. Because the IESTI equation does not take account of the frequencies of consumption or residues, it is a poor indicator of the frequency of exceeding the ARfD.

The wide scatter of points in Figure 40 suggests that the IESTI is a poor indicator of total population intakes, a purpose for which it was not designed. This is because the IESTI takes no account of how many commodities contain the pesticide, of the frequency and distribution of residues in those commodities, or of the frequency with which those commodities are consumed.

It is possible that an alternative deterministic equation could be constructed that would provide a better indicator for total population intake, if desired. This would need to take account of the key factors mentioned above. One possibility might be to use an equation similar to the IESTI but then aggregate this over all the commodities for the pesticide, weighted in a way that reflects their potential contributions. This would require that regulators have ready access to good information on all current uses and MRLs for each pesticide. As the proportion of consumers is omitted in the IESTI equation, this might be considered for use as the weighting factor. This and other possible alternatives could be assessed by calculating them for the scenarios considered by the Panel and replotting Figure 40. However, it is possible that no deterministic model will give a good fit (and it is *a priori* unlikely the fit can be as good as it currently is for the MRL assessments). If so, consideration might need to be given to using probabilistic methods, either as a refinement step or even as the primary method of assessment, if an assessment of total population intakes is wanted.

Uncertainties affecting the Panel's assessment

It is important to be clear about the limits to what science can currently say about the questions posed to the Panel. Acute reference doses are exceeded only at high levels of consumption and residues. Estimating the frequency of such levels is inevitably uncertain, due to the limitations of available data (*e.g.* the extent of residue monitoring and the size of dietary surveys).

Five sources of uncertainty were examined quantitatively, in a total population assessment for a selected scenario. In that one scenario, the estimated 95% confidence or probability interval for levels of protection in the region of 99% was about 98% - 99.5%. Wider uncertainty intervals would be expected in many of the other scenarios considered in the main analyses, where either the consumption or concentration datasets are smaller. Many other sources of uncertainty were evaluated qualitatively (for details see section 7).

Overall, the Panel concludes that its estimates of levels of protection are very uncertain but probably conservative (underestimating the true levels of protection). This is also suggested by the results of the duplicate diet study (section 6), although they are also subject to uncertainty.

When estimating changes in LoP that would result from changes to the IESTI equation (*e.g.* replacing the variability factors of 5 & 7 with 3), the uncertainties in the assessment may cancel out to some extent. Despite this, many of the estimated changes in LoP are smaller than the combined uncertainties affecting the assessment.

Overall conclusion

The Panel assessed the level of protection (LoP) and the effect of changes to the IESTI equation for the total population, and also for consumers exposed to one commodity at the MRL and others at monitoring levels.

For the total population, the Panel's estimates suggest that the LoP provided by the current IESTI equation[43] varies quite widely between different countries, age groups and pesticides. For some pesticide/country/age group scenarios the estimated LoP was between 99 and 99.9%, but most scenarios were above 99.9% and many above 99.99%[44]. The estimates are very uncertain but probably conservative, *i.e.* probably underestimate the true LoPs.

Changing the variability factors of 5 & 7 to 3 would decrease the calculated IESTIs for some commodities. This would result in additional MRLs being set, for commodities where the IESTIs are above the ARfD when calculated with a variability factor of 5 or 7, but below the ARfD when calculated with a variability factor of 3. Granting MRLs to additional commodities would potentially increase intakes and decrease the LoP.

Changing the variability factor to 3 increased the number of commodities qualifying for MRLs in 25 of 78 pesticide/country/age group scenarios in the Panel's total population assessments. The resulting reductions in LoPs were:

- generally much smaller than the existing range of variation in LoPs between the pesticide/country scenarios modelled by the Panel,
- smaller than the effect on LoPs of reducing the margin between maximum IESTI and the ARfD in the scenarios modelled by the Panel,
- for most but not all scenarios, within the range of quantified and unquantified uncertainties affecting the assessment.

[43] "Current" refers here to the IESTI equation as currently applied in the EU, including variability factors of 5 and 7.

[44] Note that these results could equally be expressed in terms of the frequency of person-days exceeding the ARfD, *e.g.* an LoP of 99.9% corresponds to 0.1% or 1 in 1000 person-days exceeding the ARfD.

Changing the way the variability factor was represented in the probabilistic models used by the Panel (fixed factors of 1, 5 and 7 versus distribution) had little effect on the distribution and uncertainty of estimated intakes for the total population. This implies that estimated intakes and LoP for the total population were more strongly influenced by other factors (*e.g.* extreme values in the consumption and residue monitoring data).

The Panel's results suggest that the IESTI is a poor indicator of the LoP for the total population (a purpose for which it was not designed), and of the contribution of individual commodities to the aggregate intake of a pesticide. This is because it considers each commodity separately, and does not take account of key factors such as the frequency of consumption and residues.

For consumers of a single commodity at the MRL and others at monitoring levels, the LoP provided by the current IESTI equation again varies widely between different countries and pesticides, and also between commodities. The Panel estimated LoPs for a total of 92 pesticide/country/commodity scenarios relating to in The Netherlands and Germany, mainly for young children. Eighty-one of these scenarios would qualify for MRLs with the current IESTI equations. For some of these scenarios, the estimated LoP was between 90 and 99%, but most scenarios were above 99% and many above 99.9%. Again, the estimates are very uncertain but probably conservative, *i.e.* probably underestimate the true LoPs.

The Panel's results suggest that the IESTI is a much better indicator of the LoP for consumers of commodities at the MRL (the purpose for which it was designed) than for the total population. On average, the commodity at the MRL contributed over 90% of the intake in these scenarios.

Changing the variability factor from 5 and 7 to 3 increased the number of pesticide/country/commodities qualifying for MRLs from 81 to 86. Because the proportion of scenarios added was small it did not markedly change the overall distribution of LoPs, although 4 of the 5 added scenarios had estimated LoPs at or below 99%.

Replacing the HR with the MRL decreased the number of pesticide/country/commodities qualifying for MRLs from 81 to 73. This had a slightly larger effect on the overall distribution of LoPs than changing the variability factor. Again, the changes occurred at the lower end of the distribution: 7 of the 8 deleted commodities had estimated LoPs around 99%. However, it must be remembered that the estimated LoPs are very uncertain and probably conservative (*i.e.* probably underestimate the true LoPs).

General observations

There is a need for risk managers to decide which measure(s) of the level of protection they consider relevant for which purposes (*e.g.* in MRL-setting versus post-authorisation assessment of monitoring data). The Panel's results suggest that the current IESTI equations are better indicators of the LoP for consumers of commodities at the MRL, for which they were designed, than of the LoP for the total population at monitoring levels. If measures of the LoP for the total population are required, then consideration should be given to modifying the IESTI equations or developing alternatives for this purpose. Based on the Panel's experience, this would require substantial research.

The LoP for consumers at the MRL is of interest because the MRL is a legal limit. The majority of intakes in the general population are well below this level. However, the Panel notes that intake at the MRL should not be considered as a worst case because, although concentrations above the MRL are infrequent (about 5% of monitoring results overall), only a tiny fraction of consignments in trade are monitored and when an exceedance is detected, the affected consignment is not always removed from the market (*e.g.* because it is already sold by the time results are received).

The Panel's assessment quantified levels of protection in terms of the percentage of person-days or consumption days exceeding the ARfD. These measures do not quantify how frequently individual consumers exceed the ARfD over time. If this was required, more complex methods of assessment would be needed.

The Panel notes that it experienced practical difficulties obtaining comprehensive information on current MRLs and residue definitions. As these are also required for other purposes, it might be desirable to consider establishing more coordinated and accessible records or databases.

The high levels of uncertainty encountered in this Opinion are an inevitable consequence of limitations in the data currently available. Most of the uncertainties could be reduced in the future if desired, by collecting further data (*e.g.* larger monitoring programmes, to provide better estimates of the frequency of high concentrations). Some of the uncertainties could also be reduced, or at least better characterised, by further modelling with existing data. Consideration could also be given to conducting more duplicate diet studies covering a wider range of countries and age groups, to provide a better basis for calibrating intake assessment methods (both deterministic and probabilistic) and for evaluating actual LoPs.

DOCUMENTATION PROVIDED TO EFSA

1. Letter, dated 31 July 2006 with reference SANCO/E3/BD/bp (2006)D/530719, from Mrs Paola Testori Coggi from the Health & Consumer Protection Directorate-General of the European Commission, requesting a consultation of the scientific Panel on Plant protection products and their Residues.
2. EC (European Commission) 1999, 2000, 2003.: EU monitoring reports. http://europa.eu.int/comm/food/fs/inspections/fnaoi/reports/annual_eu/index_en.html.
3. World Health Organization (WHO) 1997. Recommendations for the revision of the guidelines for predicting dietary intake of pesticide residues. Report of the FAO/WHO consultation in York. http://www.fao.org/ag/agp/agpp/pesticid/.
4. Joint FAO/WHO Meeting on Pesticide residues (JMPR) Reports 1999, 2000, 2001, 2002, 2003. WHO, Geneva http://www.fao.org/ag/agp/agpp/pesticid/.
5. Short report of an Expert meeting on meeting on short intake of 16 March 2006.

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[45] All legal texts of the EU referenced in this opinion can be found on: http://eur-lex.europa.eu/en/index.htm

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8 Appendix: modelling approaches, inputs and assumptions

SEE SEPARATE DOCUMENT

[46] See also www.cremesoftware.com